NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	218145
Priority or Standard	Priority
Submit Date(s)	November 24, 2025
Received Date(s)	November 24, 2025
PDUFA Goal Date	July 24, 2026
Division/Office	Psychiatry/Office of Neuroscience
Review Completion Date	July 24, 2026
Established/Proper Name	Centanafadine (EB-1020)
(Proposed) Trade Name	Simtriyo
Pharmacologic Class	Norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant
Code name	EB-1020
Applicant	Otsuka Pharmaceutical Development & Commercialization, Inc.
Dosage form	Oral capsule (extended release)
Applicant Proposed Dosing Regimen	Adults: 210 or 280 mg orally once daily Peds (13 to 17 years of age): 280 mg orally once daily Peds (b)(4) to 12 years of age): Based on weight (140 mg, <35 kg; 210 mg, 35 kg to ≤ 50 kg, 210 mg; >50 kg, 280 mg)
Applicant Proposed Indication(s)/Population(s)	Treatment of adults and pediatric patients aged (b)(4) years and older for attention-deficit/hyperactivity disorder (ADHD)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	444613000 | Adult attention deficit hyperactivity disorder (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of ADHD in adults and pediatric patients 6 years of age and older weighing at least 20 kg.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	406506008 | Attention deficit hyperactivity disorder
Recommended Dosing Regimen	Pediatric Patients Aged: • 6 to 12 years: Recommended oral dosage is based on weight. • 13 to 17 years: Recommended dosage is 280 mg orally once daily.

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<td>Adults: Recommended starting dosage is 210 mg orally once daily. Dosage may be increased to maximum daily dosage of 280 mg once daily based on clinical response and tolerability.

Recommended Oral Once Daily Dosage in Pediatric Patients 6 to 12 years of Age by Body Weight

<table>
<tr><th>Body Weight (kg)</th><th>Dose (mg)</th></tr>
<tr><td>20 kg to less than 35 kg</td><td>140 mg</td></tr>
<tr><td>35 kg to 50 kg</td><td>210 mg</td></tr>
<tr><td>Greater than 50 kg</td><td>280 mg</td></tr>
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Signatures

Please refer to uploaded memos for each discipline in DARRTS.

Glossary

5-HT	5-hydroxytryptamine or serotonin
AAP	American Academy of Pediatrics
ADHD	attention deficit/hyperactivity disorder
ADHD-RS-5	ADHD Rating Scale-5
ADHD-RS-IV	ADHD Rating Scale-IV
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AIM-A	ADHD Impact Module - Adult
AISRS	Adult ADHD Investigator Symptom Rating Scale
ALP	alkaline phosphatase
ALT	alanine transaminase
AR	adverse reaction
ASRS	Adult ADHD Self Report Scale
AUC	area under the curve
BA	bioavailability
BP	blood pressure
CBP	child-bearing potential
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression – Change
CGI-S	Clinical Global Impression – Severity
CHO	Chinese hamster ovary
C_{max}	maximum concentration observed
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP	cytochrome P450
DA	dopamine
DBP	diastolic blood pressure
DDD	Division of Dermatology and Dentistry
DMC	data monitoring committee
DPMH	Division of Pediatric and Maternal Health
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EFD	embryofetal development
eGFR	estimated glomerular filtration rate
EOS	end-of-study
EPC	established pharmacologic class
ER	extended release
FAERS	FDA Adverse Event Reporting System
FAS	Full Analysis Set
FEED	fertility and early embryonic development
FDA	Food and Drug Administration
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
HAP	human abuse potential
HEK	human embryonic kidney
hERG	human ether-a-go-go-related gene
HD	high dose
HRQL	Health-Related Quality of Life
HTN	hypertension
IB	investigators brochure
IC_{50}	half maximal inhibitory concentration
ICE	intercurrent event
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medical Product
IND	Investigational New Drug
iPSP	initial pediatric study plan
IRB	institutional review board
ISS	integrated summary of safety
JAS	juvenile animal study
Ki	inhibition constant
LD	low dose
LOE	lack of efficacy
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
MD	mid dose
MDCK	Madin-Darby canine kidney
MDD	major depressive disorder
mITT	modified intent to treat

MI	multiple imputation
MINI	Mini International Neuropsychiatric Interview
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MMRM	mixed model repeated measures
MNAR	missing not at random
NDA	new drug application
NE	norepinephrine
NME	new molecular entity
NMU	nitrosomethylurea
NMT	no more than
NOAEL	no observed adverse effect level
OSI	Office of Scientific Investigation
OTC	over the counter
PD	pharmacodynamics
PedsQL-FIM	Pediatric Quality of Life 2.0 - Family Impact Module
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PND	postnatal day
PPND	pre- and postnatal development
PPSR	proposed pediatric study request
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PWR	pediatric written request
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	Sprague-Dawley
SJS	Stevens-Johnson syndrome
SMWQ	Study Medication Withdrawal Questionnaire
SWMQ-P	Study Medication Withdrawal Questionnaire – Pediatric
SMWQ-PO	Study Medication Withdrawal Questionnaire - Pediatric Observer
SI/B	suicidal ideation and behavior
$T_{1/2}$	terminal elimination half-life
TDD	total daily dose
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
Tg	transgenic
T_{max}	time to reach maximum concentration
TK	toxicokinetics
TTX	tetrodotoxin

ULN	upper limit of normal
WRO	written response only

1 Executive Summary

1.1. Product Introduction

Centanafadine extended-release (ER) capsules (EB-1020; proposed trade name: Simtriyo) is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant developed by the Applicant for the treatment of attention-deficit/hyperactivity disorder (ADHD) under IND 119361. Centanafadine is a new molecular entity (NME) that has not been marketed in the United States or abroad. In this NDA, the Applicant proposes that centanafadine ER capsules be approved for the treatment of ADHD in adults and pediatric patients (b) (4) years of age and older.

The Applicant has developed centanafadine ER in the form of 140-mg, 210-mg, and 280-mg capsules. The Applicant's proposed recommended dosage in pediatric patients (b) (4) to 12 years of age is based on weight. In pediatric patients 13 to 17 years of age, the proposed recommended dosage is 280 mg once daily. In adult patients, the proposed recommended dosage is 210 or 280 mg once daily in the morning. The Applicant proposes that capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled over a tablespoon of soft foods (i.e., applesauce or yogurt) or in 15 mL (one tablespoon) of orange juice.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant demonstrated the effectiveness of centanafadine for the treatment of ADHD in adults in two multi-center randomized controlled trials: 405-201-00013 (Study 13) and 405-201-00014 (Study 14). Studies 13 and 14 tested an earlier formulation of centanafadine at total daily doses of 200 mg and 400 mg in adults with ADHD. The Applicant has provided a pharmacokinetic (PK) bridge between that earlier, twice-daily, tablet formulation used in phase 3 efficacy studies in adults and the to-be-marketed, once-daily formulation of centanafadine ER capsules via a comparative bioavailability (BA) study (405-201-00157).

The Applicant studied centanafadine ER capsules for the treatment of ADHD in pediatric subjects (b) (4) years of age and older in two multi-center randomized controlled trials: 405-201-00016 (Study 16) and 405-201-00021 (Study 21). Study 16 included pediatric subjects 13 to 17 years of age. Study 21 included pediatric subjects 4 to 12 years of age in two cohorts: Cohort 1 (6 to 12 years of age) and Cohort 2 (4 and 5 years of age). In Study 16 and Study 21 Cohort 1, the Applicant demonstrated the effectiveness of 280-mg centanafadine ER capsules in the 13- to 17-year age group and of the weight-based equivalent dose strength in the 6- to 12-year age group.

(b) (4)

Overall, the Applicant has provided substantial evidence of effectiveness for the treatment of ADHD in adults and pediatric patients 6 years of age and older.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant not previously approved or marketed for any Indication in the United States or abroad.

The Applicant submitted four randomized, placebo-controlled, double-blind studies in support of this NDA for the treatment of attention-deficit/hyperactivity disorder (ADHD): 405-201-00013 (Study 13), 405-201-00014 (Study 14), 405-201-00016 (Study 16), and 405-201-00021 (Study 21). In subjects 4 to 12 years old, Study 21 (N=519) tested high and low, weight-based doses of centanafadine ER daily. Study 16 (N=451) tested centanafadine ER 140 and 280 mg daily in subjects 13 to 17 years of age. Studies 13 (N=446) and 14 (N=430) tested an earlier, twice-daily tablet formulation of centanafadine in 200- and 400-mg total daily doses in adults. The Applicant's development program provides substantial evidence of effectiveness for centanafadine for the treatment of ADHD in adults and pediatric patients ages 6 and older.

Adult and pediatric open-label extension studies, 405-201-00015 (Study 15) and 405-201-00017 (Study 17), respectively, provide long-term safety data. At the time of this review, Study 17 is ongoing. As of May 1, 2025, 834 subjects had been exposed to centanafadine for ≥6 months (422 adults and 412 pediatric subjects [4 to 17 years of age]) and 507 subjects had been exposed to centanafadine for ≥1 year (221 adults and 286 pediatric subjects [6 to 17 years of age]). The safety database is consistent with International Council on Harmonisation (ICH) E1 guidance recommendations.

Clinically meaningful improvements in ADHD symptoms were demonstrated for centanafadine ER 280 mg in subjects 12 to 17 years old and the high, weight-based, exposure-equivalent dosage of centanafadine ER in subjects 6 to 12 years old. Lower dosages were also tested: centanafadine ER 140 mg in subjects 12 to 17 years old and a low, weight-based, exposure-equivalent dosage of centanafadine ER in subjects 6 to 12 years old. The 140-mg dosage and weight-based equivalents were not effective (b) (4). In subjects 4- and 5-years of age (Study 21 Cohort 2), neither high, nor low weight-based dosages of centanafadine ER were demonstrated to be effective and safe. Although there was a trend of improvement beyond placebo in the high-dose group, the efficacy results were not clearly convincing; in addition, there were higher incidences of adverse events in 4- and 5-year olds. (b) (4) (b) (4) Although the benefit-risk assessment is favorable for pediatric patients 6 years of age and above, only one of the pediatric subjects in that age group exposed to centanafadine weighed less than 20 kg. Therefore, the data do not support use

of centanafadine in pediatric patients 6 years and older weighing less than 20 kg. A Limitation of Use in product labeling will communicate that centanafadine is not recommended in patients younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than patients 6 years of age and older and centanafadine is not recommended in patients weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss.

The key safety review issues were suicidal ideation and behavior (SI/B), abuse potential, appetite and growth effects, cardiovascular effects, and hypersensitivity reactions. There were higher rates of SI/B with centanafadine ER compared to placebo, but the overall rates were low. This risk can be mitigated through labeling (patients on centanafadine should be monitored for the emergence of SI/B). Centanafadine ER was associated with decreased appetite, weight loss, decreased age-appropriate weight gain, slowing of linear growth, increased blood pressure, and hypersensitivity reactions including rash, angioedema, and anaphylaxis. However, those risks appear no worse than for most approved ADHD treatments (e.g., other CNS stimulants, atomoxetine, and viloxazine), and can be managed by appropriate labeling (e.g., patients should have their weight and vital signs monitored before and during centanafadine ER treatment).

There are no approvability issues with the drug substance, drug product, environmental impact, labeling, or biopharmaceutics information.

In summary, the Applicant has provided substantial evidence of effectiveness of centanafadine ER for the treatment of ADHD in adults and pediatric patients 6 years of age and older weighing at least 20 kg. The benefit of centanafadine ER outweighs the risks for this indication. (b) (4) (b) (4).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Attention deficit hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder that is characterized by hyperactivity, impulsivity, or inattention severe enough to cause functional impairment. • ADHD is the most common neurodevelopmental disorder of childhood. • ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes.	• Effective treatment of ADHD reduces functional impairment in the short-term, and may result in long-term benefits, such as a reduced risk of substance abuse and reduced risk of injuries.
Current Treatment Options	• More than 20 drug products are FDA-approved for the treatment of ADHD. • CNS stimulant medications are the first-line pharmacologic treatment for ADHD. Most of these products contain amphetamine salts or methylphenidate. • Several non-stimulant medications are also approved for the treatment of ADHD (e.g., clonidine extended-release, guanfacine extended-release, atomoxetine, viloxazine). • These products differ in time to therapeutic onset and/or duration of action.	• Stimulant and nonstimulant treatment options are available for ADHD. • Nonstimulant medications are frequently used when patients are unable to tolerate adverse reactions associated with stimulants or when patients prefer a nonstimulant treatment. • These are available as solid or liquid formulations, have different dosing regimens, and allow for different methods of oral administration to accommodate the needs of the individual patient. • Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and CNS stimulant with different pharmacokinetic and pharmacodynamic profiles compared with methylphenidate and amphetamine salts. • Centanafadine will be a useful addition to the treatment armamentarium for ADHD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The Applicant conducted four phase 3 studies to assess the efficacy of centanafadine for the treatment of ADHD in adults (Studies 13 and 14) and pediatric subjects ages 6 years and older (Studies 16 and 21) • The primary efficacy endpoint in pediatric Studies 16 and 21 was the change from baseline in the ADHD Rating Scale-5 (ADHD-RS-5), an 18-question scale that measures the core symptoms of ADHD. The primary efficacy endpoint the adult studies was the change from baseline in the Adult ADHD Investigator Rating Scale (AISRS) total score. A key secondary endpoint in all four studies was the Clinical Global Impression-Severity (CGI-S) scale. • Centanafadine demonstrated statistically significant improvement of ADHD symptoms at the high dose tested in pediatric subjects 6 years of age and older (in Study 16 and Study 21 Cohort 1) on the primary endpoint ADHD-RS-5, but not at the low dose. In Study 16, the placebo-subtracted LS mean difference in ADHD-RS-5 score was -4.35 (95% CI: -6.83, - 1.87). In Study 21 Cohort 1, the LS mean difference was -5.56 (95% CI: -8.78, - 2.33). These results represent clinically meaningful improvement in ADHD. • Centanafadine demonstrated statistically significant improvement of ADHD symptoms at the high (400-mg total daily dose) and low (200-mg total daily dose) doses tested in adults (in Study 13	• Four adequate and well-controlled studies with statistically significant, clinically meaningful results on their primary endpoints, along with a pharmacokinetic bridge, constitute substantial evidence of effectiveness and support approval of centanafadine ER. ○ There is substantial evidence of effectiveness to support approval of the high dosage of weight-based centanafadine ER for the treatment of ADHD in pediatric patients 6 to 12 years of age. ○ There is substantial evidence of effectiveness to support approval of the 280-mg dosage of centanafadine ER for the treatment of ADHD in pediatric patients 13 to 17 years of age. ○ There is substantial evidence of effectiveness to support approval of the 210-mg and 280-mg dosages of centanafadine ER for the treatment of ADHD in adults. • (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and Study 14) on the AISRS. In Study 13, the LS mean difference for the 200-mg total daily dose was -3.15 (95% CI: -5.79, - 0.51) and for the 400-mg total daily dose, -2.74 (95% C: -5.35, -0.14). In study 14, the LS mean difference for the high dose was -4.01 (95% CI: -6.55, - 1.46) and for the low dose, -4.42 (95% CI: -7.02, -1.82). These results represent clinically meaningful improvement in ADHD. • In adults, although the placebo-subtracted reduction in CGI-S score reached statistical significance for both the high and low doses, the difference in LS means did not represent strong, clinically meaningful improvement. In Study 13, the LS mean difference was -0.27 (95% CI: -0.50, -0.04) for the 200 mg total daily dose and -0.28 (95% CI: -0.51, -0.05) for the 400-mg total daily dose. In Study 14, the LS mean difference was -0.33 (95% CI: -0.57, -0.09) for the 200-mg total daily dose and -0.28 (95% CI: -0.53, -0.04) for the 400-mg total daily dose. • Due to the lack of statistical significance for the lower dose of centanafadine in testing of the primary endpoint in Study 16, the key secondary endpoints could not be formally tested. However, descriptive analysis of the CGI-S results demonstrated nominally significant results of LS mean difference of -0.37 (95% CI: -0.61, -0.12). For the same reason, the key secondary endpoints could not be formally tested in Study 21 Cohort 1.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Descriptive analysis of the CGI-S results for Study 21 Cohort 1 demonstrated numerical, but not statistically or nominally significant improvement (LS mean difference of -0.37 [95% CI: -0.61, -0.12]). • Centanafadine did not demonstrate statistically significant improvement in ADHD on the ADHD-RS-5 or CGI-S in pediatric subjects 4 and 5 years of age.	
Risk and Risk Management	• The most common treatment-emergent adverse events (TEAEs) associated with centanafadine in pediatric subjects with ADHD (and occurring more frequently than in placebo-treated subjects) were decreased appetite, nausea, rash, headache, and abdominal pain. • The most common TEAEs associated with centanafadine in adults with ADHD (and occurring more frequently than in placebo-treated subjects) were headache, decreased appetite, insomnia, nausea, dry mouth, and diarrhea. • Centanafadine ER was associated with higher rates of suicidal ideation and behavior in pediatric subjects, increases in blood pressure in pediatric and adult subjects, weight loss and decreased weight gain and linear growth in pediatric subjects, and hypersensitivity reactions including rash, angioedema, and anaphylaxis in pediatric and adult subjects.	• Overall, the safety profile of centanafadine ER has been adequately characterized to support approval in adults and pediatric patients 6 years of age and older weighing at least 20 kg . • Centanafadine is not recommended in pediatric patients younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than patients 6 years of age and older or in patients weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss. These recommendations will be specified in a Limitation of Use in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• In the indicated populations, the most serious safety concerns are risks of suicidal ideation and behavior in pediatric patients; abuse, misuse and addiction; increases in blood pressure in pediatric patients and adults; weight loss, decreased weight gain, and decreased linear growth in pediatric patients; and hypersensitivity reactions including rash, angioedema, and anaphylaxis in pediatric patients and adults. These risks can be adequately managed through labeled Warnings and Precautions.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Section 7
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

1.5. Analysis of Condition

Attention-deficit/hyperactivity disorder (ADHD) is a chronic, neurodevelopmental condition characterized by a persistent pattern of inattention or hyperactivity/impulsivity or by a combination of symptoms from these two domains. ADHD typically presents in childhood with symptoms of difficulty paying attention, hyperactivity, and impulsive behavior. ADHD is the most common neurodevelopmental disorder of childhood. The prevalence in the pediatric population is estimated to be approximately 11% (Reuben 2024). ADHD may persist into adulthood and has a 4% prevalence in adults (Kessler 2006). Pediatric patients with this disorder often experience difficulty with school performance, difficulty interacting with peers, and may engage in dangerous activities due to impulsivity. Adults with ADHD may experience impairment in their workplace, social relationships, and with completing tasks. ADHD has been associated with depression, suicidal behavior, substance abuse, and poor educational and occupational outcomes (Chan et al. 2016). Many individuals with ADHD obtain symptom reduction with appropriate medication treatment resulting in significant decreases in impairment in daily tasks and functioning.

1.6. Analysis of Current Treatment Options

More than 20 drug products are FDA-approved for the treatment of ADHD. These products are classified as CNS stimulants (including methylphenidate, d-methylphenidate, amphetamine, dextroamphetamine, methamphetamine, lisdexamfetamine, and dextroamphetamine) and non-stimulants (e.g., norepinephrine reuptake inhibitors and alpha-adrenergic agonists). Stimulants may be available in immediate-release or extended-release formulations. Once-daily administration of an extended-release product can offer ADHD symptom reduction for an entire day, whereas an immediate release product generally requires dosing at least twice daily. The non-stimulants specifically indicated for ADHD are generally administered once-daily (atomoxetine may be administered once-daily or in evenly divided doses). Once-daily dose administration may increase medication adherence and alleviate the stress associated with dosing during school hours (avoiding interruptions in the school day to have the drug administered by a school nurse).

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Centanafadine has not been approved or marketed for any indication in the United States or abroad.

2.2. Summary of Presubmission/Submission Regulatory Activity

Centanafadine (EB-1020) was developed for ADHD under IND 119361. A previous sponsor (Neurovance, Inc.) opened IND 119361 on August 16, 2013. On September 13, 2013, the Agency issued a May Proceed Letter. Neurovance conducted two phase 2 studies (201 and 202) in adults with ADHD. On June 5, 2017, Neurovance transferred ownership of IND 119361 to Otsuka Pharmaceutical Company, Ltd (the Applicant).

On December 22, 2017, the Division issued a Pediatric Study Plan – Initial Agreement letter. The Agreed iPSP included plans to conduct a pediatric PK trial using a once-daily formulation, centanafadine ER capsules, and two efficacy trials in pediatric subjects (b) (4) (b) (4). The Division agreed that the Applicant did not need to conduct a dedicated adolescent PK study. The Applicant noted they would include some adolescents in the phase 3 trials.

On February 2, 2018, the Applicant requested a Type C meeting to discuss human abuse potential (HAP) assessment. The Applicant described results of a previously completed HAP study, EB-1020-IR-103, which the Applicant interpreted as demonstrating centanafadine to have pharmacologic properties different than classical stimulants. The Applicant proposed to conduct a new HAP study designed based on the recommendations in the FDA guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017) and the Agency's previous feedback on the completed HAP trial (from August 27, 2014). The Applicant also proposed an abuse potential monitoring plan for the phase 3 registration trials. On April 27, 2018, the Agency conveyed preliminary comments in response to the Applicant's request, providing feedback on these proposed plans, as well as the plan for assessment of withdrawal. On May 3, 2018 (following one clarifying question via email), the Applicant indicated no further need for discussion and the meeting was cancelled.

In July 2018, the Applicant submitted protocols for two 6-week studies, 405-201-00013 and 405-201-00014, and on November 5, 2019, the Applicant submitted statistical analysis plans (SAPs) and Interim Analysis Review Committee Charters.

On January 14, 2020, the Applicant requested a meeting to discuss the pediatric program and associated clinical studies. The Agency issued a written response on March 27, 2020, agreeing that two separate pediatric efficacy trials (one targeted at subjects 13 to 17 years of age and one for subjects 4 to 12 years of age) could be conducted in place of the two (b) (4) trials initially proposed in the iPSP. The Division advised that once-daily dosing

would be preferred (b) (4) for the final product development. The Division advised that when the Applicant finalized the pediatric formulation and protocols, they could amend the iPSP to reflect the development plan. The Division also stated that because the safety profile in pediatric patients was unknown, the Applicant should evaluate centanafadine stepwise, first in subjects 9 to 12 years of age and then in subjects 6 to 8 years of age, before determining the dose for 4- and 5-year-olds. The Division stated that if different formulations were planned for adults and children, separate NDAs would be required.

On January 29, 2021, the Applicant submitted a proposed pediatric study request (PPSR) for the indication of ADHD. On May 19, 2021, the Agency issued an Inadequate PPSR letter, explaining that a Written Request could not be issued because the pediatric formulation for centanafadine had not been finalized. The Agency advised that a revised PPSR should also address any other potential indications for which the active moiety may be used in the pediatric population.

On June 30, 2021, the Applicant submitted protocols for two phase 3 pediatric clinical trials, Studies 405-201-00016 and 405-201-00017 (open-label). In August and September 2021, the Agency sent several comments regarding these protocols.

On October 26, 2021, the Applicant requested a meeting to discuss the centanafadine ER capsule dose selection for adolescents in a planned phase 3 study and the proposed strategy to bridge the twice daily tablet formulation studied in the adult phase 3 program with the intended-to-be-marketed once-daily ER capsule formulation. The Agency granted the meeting as a Type C, WRO meeting. On January 27, 2022, the Agency sent a final written response stating that, based on the results of the adult relative BA Study (405-201-00047), the proposed doses of centanafadine ER capsules for adolescents in Studies 16 and 17 appeared reasonable. The Agency agreed that from a safety and PK perspective, dosing of Cohorts 2 and 3 (ages 6 to 8 years) in PK Study 405-201-00046 could proceed but recommended lowering the proposed high dose.

On March 18, 2022, the Applicant submitted a new protocol for a pediatric phase 3 study, 405-201-00021. After discussions with the Agency, the Applicant proposed to limit Study 21 to pediatric subjects 6 to 12 years of age and to add a new cohort of pediatric subjects 4 to 5 years of age. The Division agreed that it might be acceptable for the Sponsor to revise Study 21 study protocol to be conducted in two steps: step 1 (pediatric subjects 6 to 12 years of age) and step 2 (4 to 5 years of age), with two primary analyses and two clinical study reports; however, this would be a matter of review. Dosing would have to be determined for the 4- and 5-year old cohort before that part of the study would be allowed to proceed.

On December 22, 2022, the Applicant requested a WRO meeting to discuss the safety analysis strategy for the integrated summary of safety (ISS). On March 3, 2023, the Agency recommended pooling trials of similar length and design: Adult Short-term Double-blind

Trials, Pediatric Short-term Double-blind Trials, and All Centanafadine Trials. The Agency disagreed with pooling the HAP studies and advised the Applicant to provide CRFs and narratives for all deaths, serious AEs (SAE), and AEs leading to discontinuation. The Agency agreed with the Applicant's proposal to submit an Interim Clinical Study Report for Study 17 (open-label, pediatric safety study) at the time of NDA filing. The Agency advised the Applicant to include enough data to meet ICH exposure recommendations at the time of NDA submission as well as final data on all subjects 6 to 17 years of age by the 120-day update. The Agency told the Applicant to plan to update the interim data for 4- and 5-year-olds at the time of the 120-day update.

On March 29, 2023, the Agency responded to a PPSR submitted December 7, 2022, with a Pediatric Inadequate PPSR letter. The Agency explained that because the Applicant had not determined the dosing of the new formulation in subjects ages 4 to 5 years and because Study 21 remained on hold for subjects ages 4 to 5 years, the Agency could not issue a Pediatric Written Request (PWR). The Applicant would need to resolve the hold issues before FDA could issue a PWR. (b) (4) (b) (4)

On October 24, 2023, the Applicant submitted a Complete Response to the Partial Clinical Hold prohibiting enrollment of 4- and 5-year-olds in Study 21.

On April 15, 2024, the Agency issued an Inadequate PPSR letter in response to the revised PPSR of December 21, 2023. The Agency could not issue a PWR because the plan (b) (4) (b) (4) (b) (4) was inadequate. The Agency stated that the PPSR should describe two adequate and well-controlled studies for pediatric subjects (b) (4) (b) (4). The Agency noted that centanafadine is associated with rash and drug eruption, yet the PPSR revision specified that the studies would not be investigating immunogenicity. The Agency advised that the PPSR should include a plan to evaluate the etiology of rash and drug eruption for centanafadine. On August 2, 2024, the Applicant submitted a revised PPSR, which the review team determined addressed the previous comments adequately. On January 23, 2025, the Agency issued a PWR. The PWR described seven studies to investigate the potential use of centanafadine in the treatment of pediatric patients (b) (4) with ADHD (b) (4) (b) (4).

On June 17, 2025, the Applicant requested a pre-NDA meeting. On September 12, 2025, the Agency sent preliminary responses to the Applicant's questions. In response to the Applicant's question about whether the clinical development program supported the proposed indication statement, the Agency explained that the indication would be a matter of review, including an assessment of whether the benefit-risk analysis supports approval in pediatric patients (b) (4). The Agency noted that other ER stimulant drugs had

been associated with increased rates of AEs in this age group. The Agency would carefully evaluate safety, including growth, in this population. The Agency also noted that of the 62 pediatric subjects 4 and 5 years of age treated with centanafadine in Study 21, 15 (~24%) had dropped out. As of July 7, 2025, of the 55 of the 4- and 5-year-olds enrolled in the open-label safety study (Study 17), 18 (~33%) had dropped out. The Agency requested narratives for the dropouts in this age group. DPMH also provided extensive advice about how the Applicant should evaluate and present laboratory, vital signs, and growth evaluations in pediatric studies. On September 15, 2025, the Applicant withdrew the request, cancelling the meeting.

On August 18, 2025, the Applicant requested that the Agency issue an amendment to the WR issued on January 23, 2025. The Applicant reported that (b) (4) (b) (4) (b) (4) Therefore, the Applicant proposed to amend the PWR to remove the (b) (4) studies.

On November 24, 2025, the Applicant submitted NDA 218145 for "centanafadine for the treatment of adults and pediatric patients aged (b) (4) years and older for attention deficit/hyperactivity disorder (ADHD)." In the cover letter, the Applicant stated that:

> This submission also constitutes a partial response to the Pediatric Written Request (PWR) issued by the Agency on 23 Jan 2025 (Reference ID: 5515655). Full study reports for study 1 (405-201-00046), study 2 (405-201-00016), and study 3 (405-201-00021) are submitted to an NDA for the first time in this application, in alignment with the Agency's PWR letter.

The application received priority review.

3. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Office of Scientific Investigations (OSI)

OSI clinical investigators completed inspections of the study sites of Drs. Valerie Arnold, Howard Rubenstein, Michael Leibowitz, Michael Banov, Nandita Jones, and Divyansu Patel (Sites: 32, 332, 402, 405, 15, and 17). These sites were selected using a risk-based approach primarily based on number of enrolled subjects, treatment effect, protocol deviations, and prior inspection history.

Based on the results of these inspections, OSI concluded that the studies (405-201-00013, 405-201-00014, 405-201-00016 and 405-201-00021) appear to have been conducted adequately, and the clinical data generated by these sites appear acceptable in support of the respective indications. Please refer to the OSI review for a detailed discussion.

3.2. Product Quality

See the separate reviews from the Office of Product Quality for additional information. Based on the review of information submitted, including reviews of drug product, drug substance, biopharmaceutics, process, and facilities, OPQ recommends product approval.

3.3. Clinical Microbiology

No clinical microbiology data were submitted with this application.

3.4. Devices and Companion Diagnostic Issues

No issues related to devices or companion diagnostics were pertinent to this application.

4. Nonclinical Pharmacology/Toxicology

4.1. Executive Summary

This application is approvable from a nonclinical perspective.

The Applicant submitted adequate pharmacology and toxicology data to evaluate the nonclinical safety profile of centanafadine. The relevant pharmacology studies and repeat-dose, genetic, reproductive, development, and carcinogenicity toxicology studies have been fully reviewed under the IND and are summarized below.

Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system (CNS) stimulant. See Section 15.3 for review of established pharmacologic class (EPC).

In repeat-dose toxicology studies of up to 26-weeks in rats and 43-weeks in dogs, clinical signs related to CNS stimulation, reductions in food consumption, and lower body weight and/or body weight gain were observed dose-dependently across studies in both species. The reductions in body weight were dose-limiting in animals and would be monitorable in humans. There were no unmonitorable toxicities observed at doses below those with adverse effects on body weight.

Reproductive and developmental toxicity studies that were conducted included fertility studies in male and female rats, embryofetal development (EFD) studies in rats and rabbits, a pre- and post-natal development (PPND) study in rats, and a juvenile animal study (JAS) in rats. In the rat EFD study, mean maternal body weight gain, absolute maternal body weights, and fetal body weights were decreased at ≥30 mg/kg and correlated with reduced maternal food consumption. Fetal skeletal variations included a significant increase in the litter and fetal incidences of irregularly shaped cervical arches, incompletely ossified cervical arches, and short ribs at 100 mg/kg, which is approximately 4 times the human exposure at the maximum recommended human dose (MRHD) based on AUC. The No Observed Adverse Effect Level (NOAEL) for both maternal toxicity and fetal development was 10 mg/kg/day, which is below the human exposure at the MRHD based on AUC.

In the rabbit EFD study, mean maternal body weight gains were decreased at ≥6 mg/kg/day. There were no effects on embryo-fetal survival, fetal body weights, or fetal external, visceral, or skeletal malformations or variations at any dose. The NOAEL for maternal toxicity was 6 mg/kg/day, which is below the human exposure at the MRHD based on AUC. The NOAEL for fetal development was 15 mg/kg/day, which is below the human exposure at the MRHD of based on AUC.

In the PPND study, mean maternal body weight gain during gestation was decreased at 30 mg/kg and correlated with reduced food consumption. There was a slight increase in the

incidence of pup mortality during the first 4 days after birth in the 30 mg/kg (5% compared to 1% in controls). The NOAEL for both maternal and developmental toxicity was 10 mg/kg/day, which is below the human exposure at the MRHD based on AUC.

In the JAS, a delay in preputial separation and an increase in the proportion of sperm with abnormal morphology were observed in males at 30 mg/kg; however, there were no effects on fertility or reproductive performance. The NOAEL was 30 mg/kg/day, which is below the exposure at the MRHD based on AUC in pediatrics.

Centanafadine was negative in a valid, full battery of genotoxicity studies.

Centanafadine was adequately evaluated in a 6-month transgenic mouse carcinogenicity study and a 2-year rat carcinogenicity study. There was no evidence of drug-related neoplasms in either study.

The Applicant's drug specification proposed a limit for the enantiomer impurity (EB-1070) which was above the qualification threshold recommended in the ICH Q3A(R2)[1] guidance. Based on the toxicology data submitted by the Applicant, the proposed limit for the EB-1070 impurity is considered qualified.

4.2. Referenced NDAs, BLAs, DMFs

None

4.3. Pharmacology

Primary Pharmacology

Mechanism of Action

The mechanism of action of centanafadine in the treatment of ADHD is unclear. Centanafadine inhibits monoamine reuptake at the norepinephrine (NE), dopamine (DA), and serotonin (5-HT) transporters. The potency of reuptake inhibition is greatest for NE followed by DA followed by 5-HT. At clinically relevant doses, centanafadine acts as a central nervous system (CNS) stimulant.

In Vitro Studies
The binding affinities of centanafadine and metabolite EB-10601 were evaluated using human monoamine transporters expressed by transfected cell lines (shown in Table 1). The results for centanafadine indicate the highest affinity is for the NE transporter and affinities for DA and 5-HT transporters are in the range of 4- to 20-fold lower.

[1] Guidance for Industry *Q3A (Revision 2) Impurities in New Drug Substances* (June 2008).

The binding affinities for EB-10601 indicate that this metabolite is unlikely to contribute to the primary pharmacology effects of centanafadine.

Table 1. Binding Affinity at Monoamine Transporters (Human Transfected)

Compound	NE transporter Ki (nM)	DA transporter Ki (nM)	5-HT transporter Ki (nM)	Study Number
Centanafadine	2.24 - 7.5	44 - 57.6	8.82 – 110	(b) (4) 1026454 FR095-0028720-100060199
EB-10601 (metabolite)	4600	810	>10,000	FR095-0028720-100060199

Ki = inhibition constant.
Source: Generated by Reviewer from Applicant data.

The Sponsor investigated the inhibition of reuptake of radio-labelled monoamines into rat brain synaptosomes and transfected cells expressing human monoamine transporters. The resulting IC_{50} values are shown in Table 2**.** Centanafadine inhibited reuptake of all three monoamines with rank order potency for inhibition of NE > DA > 5-HT in both rat synaptosomes and cells expressing human transporters.

Table 2. Inhibition of Monoamine Uptake by Centanafadine in Functional Assays

Assay	NE IC_{50} (nM)	DA IC_{50} (nM)	5-HT IC_{50} (nM)	Study Number
Uptake into rat brain synaptosomes	13	16	25	(b) (4) -13333
Uptake into transfected cells* expressing human transporters	5.4 - 6.3	30.6 - 49.2	65.4 - 107	(b) (4) 1022617 1026456 1026658
Cell line*	MDCK	CHO-K1	HEK-293	

*MDCK = Madin-Darby canine kidney; CHO = Chinese hamster ovary; HEK = human embryonic kidney. IC_{50} = concentration at 50% of maximal effect.
Source: Generated by Reviewer from Applicant Data.

In Vivo Studies

Two microdialysis studies investigated the effects of centanafadine on extracellular monoamine concentrations. Study DOV216419 showed that intraperitoneal doses of 10 and 20 mg/kg centanafadine in Wistar-Han (WH) rats raised NE, DA, and 5-HT levels in the frontal cortex as well as raising DA and 5-HT levels in the striatum.

Study RS2439 showed similar results in freely-moving Sprague-Dawley (SD) rats following oral administration of 3, 10, or 30 mg/kg centanafadine and also tested two comparator drugs, methylphenidate (a CNS stimulant) and bupropion (not labeled as a CNS stimulant). Oral centanafadine dose-dependently increased NE, DA, and 5-HT levels in the prefrontal cortex as well as DA and 5-HT levels in the ventral striatum. A cross-drug comparison with oral 30 mg/kg doses of methylphenidate and bupropion is shown in Table 3. At what is likely

the most clinically relevant dose, 30 mg/kg centanafadine showed similar effects on extracellular NE and DA levels to 30 mg/kg methylphenidate; however, only centanafadine produced large increases in extracellular 5-HT levels. Although the effect of centanafadine on percent change relative to baseline was larger for 5-HT than NE or DA, we cannot infer the relative importance of serotonin transporter activity from this data because the basal levels of 5-HT were approximately 20-fold lower than NE or DA and the effects on post-synaptic neurons were not measured. The rank order magnitude of absolute change in extracellular monoamine levels following 30 mg/kg centanafadine was NE > DA > 5-HT in prefrontal cortex and DA > 5-HT in ventral striatum. The microdialysis results for methylphenidate were consistent with previously published results Rowley et al., 2014).

Table 3. Cross-Drug Comparison of Effects on Extracellular Monoamine Concentrations Via Microdialysis in Freely-Moving Rats

Drug intervention (30 mg/kg p.o.)	Percentage change versus vehicle control (0 – 4 hr time-bin)				
	Prefrontal cortex (PFC)			Ventral striatum (vSTR)	
	Noradrenaline	Dopamine	5-HT	Dopamine	5-HT
Centanafadine	522% ***	210% ***	1013% ***	82% ***	617% ***
Methylphenidate	504% ***	173% ***	±	173% ***	±
Bupropion	42% ***	±	±	61% ***	±

Results taken from the RS2439 Statistical Report.
Vehicle control: n = 7-8 rats/group; Centanafadine, methylphenidate and bupropion: n = 7 rats/group.
*** p<0.001 versus vehicle control; ± = no significant change.

Source: Applicant table; copied from Study RS2439.

Another microdialysis experiment (Study RS1775) in SD rats showed that infusion of the sodium channel blocker, tetrodotoxin (TTX), prevented the elevation of extracellular monoamine levels by intraperitoneal administration of centanafadine. This result is consistent with centanafadine causing presynaptic reuptake inhibition (e.g., like methylphenidate) rather than direct synaptic release (e.g., like amphetamine).

Secondary Pharmacology

Centanafadine and metabolite EB-10601 were screened against a large battery of off-target binding sites across multiple studies with follow-up studies investigating functional activity.

Centanafadine had functional agonist activity below 10 µM at the µ opioid receptor (EC_{50} = 6.6 µM) and 5-HT_{2C} receptor (EC_{50} = 4.2 µM) and functional antagonist activity below 10 µM at the 5-HT_{2A} (IC_{50} = 3.4 µM) and 5-HT_{2B} (IC_{50} = 0.22 µM) receptors, adrenergic alpha 1A (IC_{50} = 3.8 µM) alpha 2A (IC_{50} = 2.7 µM), beta 1 (IC_{50} = 3.2 µM), and beta 2 (IC_{50} = 4.0 µM) receptors, muscarinic M1 (IC_{50} = 5.6 µM) and M3 (IC_{50} = 1.4 µM) receptors.

Metabolite EB-10601 had binding affinity at 5-HT_{2B} (IC_{50} = 1.9 µM), 5-HT_7 (IC_{50} = 8.3 µM), and neurokin 1 (94% at 20 µM) receptors.

No safety concerns are expected from the secondary targets tested for centanafadine or metabolite EB-10601 at clinically relevant doses.

Safety Pharmacology

Table 4. Summary of Safety Pharmacology Studies With Centanafadine

Study	Finding	NOEL
hERG Assay	IC_{50} = 7.9 µM	
CV (Dog)	↑Body temperature; ↑blood pressure; ↑heart rate (1-2 hr post-dose); ↓heart rate (5-7 hr post-dose) at ≥5 mg/kg	1 mg/kg
Respiratory (Rat)	↑Respiratory rate (up to 93%); ↓Tidal volume (up to -35%) at ≥30 mg/kg	10 mg/kg
CNS (Rat)	↓Body temperature; ↑thermal latency response; dilated pupils; exophthalmos at ≥30 mg/kg	10 mg/kg

Source: Generated by Reviewer from Applicant Data.

4.4. ADME/PK

- Oral bioavailability: 18% in rats at 10 mg/kg.
- Absorption:
  - in rats, time of peak concentration (T_{max}) = 0.5-4 hr (T_{max} increases with dose) and half-life ($T_{1/2}$) = 2-8.5 hr;
  - in humans T_{max} = 0.5-2 hr, $T_{1/2}$ = 1-5 hr
- Distribution: Centanafadine preferentially distributed to brain tissue versus plasma in rats, with a mean ratio of 6.6.
- Protein binding: in plasma of rat ~100%, dog ~98%, and human 99%.
- In vitro metabolism: was assessed in mouse, rat, dog, monkey, and human hepatocytes. N-desmethyl, lactam, and lactam of N-desmethyl derivatives of the parent drug were formed in all species.
- In vivo metabolism: 13 metabolites were identified in rat, which were consistent with those formed in vitro in hepatocytes. In dogs, following a single oral dose, there were three major metabolites (two lactams, M1b and M1a, and a third metabolite whose structure is not determined) and two minor metabolites (possible glutathione conjugates).
- There are no unique or disproportionate human metabolites.
- Exposure to the major human metabolite, EB-10601, was covered by toxicology studies in both rat and dog.

- Centanafadine showed significant inhibition of human CYP1A2 and CYP2D6 (IC_{50} =1.9 µM and 5.57 µM, respectively; Study 7DOVP1R1).
- Excretion: In bile duct-intact male and female rats, radioactivity was eliminated by urinary and fecal excretion, which accounted for 53.7% and 37.4% of dose, respectively, in males and for 46.5% and 43.9% of dose, respectively, in females. In male bile duct-cannulated rats, radioactivity was eliminated by urinary and biliary excretion that accounted for 33.2% and 58.2% of dose, respectively, with fecal excretion accounting for 1.95% of the radioactive dose through 168 hours post-dose.

4.5. Toxicology

4.5.1. General Toxicology

Dose Range-Finding Studies

Key Findings

- In rats, oral doses up to 200 mg/kg centanafadine for 5 days were tested. The maximum tolerated dose was 100 mg/kg (deaths occurred at ≥150 mg/kg in females and at 200 mg/kg in males). Clinical signs consisted of behavioral/CNS findings of increased activity in males and increased activity, hyperactivity and/or hyperreactivity to touch in females at all doses. Dose-dependent body weight losses were observed (up to ~10% in males and females).
- In male and female beagle dogs (2/sex), centanafadine was administered at single oral (capsule) doses (0, 10, 15, 20, and 25 mg/kg; escalating dose design with a 2-day washout period) and produced treatment-related clinical signs such as increased activity and emesis in both males and females at doses ≥20 mg/kg. One male dog at 25 mg/kg exhibited circling behavior at 90 min and 4 hr post dose. Subsequently, centanafadine was administered orally (capsule) to 2 male and 2 female beagle dogs at a dose of 20 mg/kg/day for 5 consecutive days. Treatment-related clinical signs consisted of increased activity on Study Days 3 and 4 and emesis throughout the study. Emesis was observed for both males and females as early as 1 hr post-dose on Day 0 and persisted to the 4 h after dosing on Study Day 3 (study (b) (4)451160). Treatment-related body weight losses and lower food consumption were observed in female dogs; on Day 5, body weights were ~6% lower than Day 0 of treatment. Based on the clinical signs of increased activity and emesis observed at 20 mg/kg/day, this dose was considered to be the maximum tolerated dose for both male and female dogs.

Repeat-Dose Toxicity

Table 5. Summary of Repeat-Dose Toxicity Studies With Centanafadine

Species/ Duration	Toxicokinetic parameters	Key Study Findings
Rat 28-day (GLP) Study No. 1961-005	Dose: 10 mg/kg AUC: 1,100 hr*ng/mL C_{max}: 777 ng/mL T_{max}: 0.5 hr Dose: 30 mg/kg AUC: 7380 hr*ng/mL C_{max}: 2,700 ng/mL T_{max}: 0.5 hr Dose: 100 mg/kg AUC: 29,200 hr*ng/mL C_{max}: 4,200 ng/mL T_{max}: 1 hr Day 28, male data shown (females had higher AUC at all doses).	• Oral doses: 0, 10 (LD), 30 (MD), or 100 (HD) mg/kg/day. • Body weight gain reduced at the HD (↓19% for males, ↓14% for females) compared to controls. • Clinical signs included hypersensitivity to touch and vocalization at the HD. • ↑ALP (1.5-fold to 2.8-fold) at the HD in males and at ≥ MD in females; ↑ALT (1.3-fold) at the HD in both sexes. • Liver: minimal centrilobular hepatocellular hypertrophy and centrilobular vacuolation at the HD in males. • The NOAEL* is 30 mg/kg in both sexes based on reduced body weight gain at the HD. At the NOAEL, AUC is lower (~0.5x) than for humans at the MRHD. *We note that this is a different NOAEL than what was identified in the Study Report; however, we consider the body weight loss to be adverse.
Rat 91-day (GLP) Study No. 2271-001	Dose: 10 mg/kg AUC: 1910 hr*ng/mL C_{max}: 932 ng/mL T_{max}: 0.5 hr Dose: 30 mg/kg AUC: 8,790 hr*ng/mL C_{max}: 2,530 ng/mL T_{max}: 0.5 hr Dose: 100 mg/kg AUC: 49,900 hr*ng/mL C_{max}: 7,570 ng/mL T_{max}: 4 hr Day 91, male data shown (females	• Oral doses: 0, 10 (LD), 30 (MD), or 100 (HD) mg/kg/day. • Body weight gain reduced at ≥ MD in males (up to ↓31%) and females (up to ↓32%). • Mortality was seen in one MD main study female and two HD TK males. It is unclear if these deaths were test article related. • Clinical signs were consistent with dose-dependent CNS stimulation, including increased activity, salivation, vocalization, rigid body, and hypersensitivity to touch, all most frequent at the HD. • Liver: increased liver weight, centrilobular hepatocellular hypertrophy, midzonal and centrilobular vacuolation, and increased ALP and ALT were seen primarily in males at the HD. • Decreased prostate gland weight and secretory depletion were observed in males at 100 mg/kg. • The NOAEL is 10 mg/kg in both males (based on reduced body weight gain at ≥ MD) and females (based on mortality at the MD). At the NOAEL, AUC is lower (~0.14x) than for humans at the MRHD.

Species/ Duration	Toxicokinetic parameters	Key Study Findings
	had higher AUC at all doses).	
Rat 26-week (GLP) Study No. 2271-006	Dose: 3 mg/kg AUC: 188 h*ng/mL C_{max}: 80 ng/mL T_{max}: 0.5 hr Dose: 10 mg/kg AUC: 1390 h*ng/mL C_{max}: 856 ng/mL T_{max}: 0.5 hr Dose: 30 mg/kg AUC: 7,260 h*ng/mL C_{max}: 2,640 ng/mL T_{max}: 1 hr Day 180, male data shown (females had higher AUC at all doses).	• Oral doses: 0, 3 (LD), 10 (MD), or 30 (HD) mg/kg/day. • Mortality was observed in one HD male in the main study and one HD male in the TK group. Both animals were in moribund condition prior to euthanasia. The cause was undetermined in each case. • At the HD, absolute mean body weight was reduced in both males (-7%) and females (-9%) compared to controls. • Clinical signs at ≥ MD were consistent with dose-dependent CNS stimulation and similar for both males and females. At ≥ MD, rigid body during handling, hypersensitivity to touch, and vocalization were observed in both sexes. Increased activity and salivation were observed at the HD in both sexes. • ↑ALP at the HD in females. • Liver: centrilobular vacuolation at ≥ MD in males. • The NOAEL is 10 mg/kg for males (based on the moribund condition at the HD) and 30 mg/kg for females. At the NOAEL, male AUC is lower than (~0.1x), and female AUC is approximately equal to (~0.8x), human AUC at the MRHD.
Dog, 28-Day (GLP) Study No. 1961-004	Dose: 1 mg/kg/day AUC: 4,180 h*ng/mL C_{max}: 689 ng/mL T_{max}: 4 hr Dose: 5 mg/kg/day AUC: 21,400 h*ng/mL C_{max}: 5,270 ng/mL T_{max}: 2 hr Dose: 15 mg/kg/day AUC: 50,800 h*ng/mL C_{max}: 13,300 ng/mL T_{max}: 1 hr Day 28, female data shown (males had higher AUC at ≥MD).	• Oral doses: 0, 1 (LD), 5 (MD), or 15 (HD) mg/kg/day. • Decreased body weight at the HD in males (-5% mean body weight loss with one HD male losing 14% body weight) and at the HD in females (-8% mean body weight loss). • Spleen: decreased absolute and relative weight (to body weight and brain weight) at the HD in males (up to 45% lower than controls). • The NOAEL was 5 mg/kg/day based on body weight loss. All adverse effects observed are considered monitorable in humans up to highest dose tested of 15 mg/kg/day. At 15 mg/kg/day, exposure was approximately 3.6 times the human exposure at the MRHD based on AUC.

Species/ Duration	Toxicokinetic parameters	Key Study Findings
Dog, 91-Day (GLP) Study No. 2271-002	Dose: 5 mg/kg/day AUC: 23,600 h*ng/mL C_{max}: 4,670 ng/mL T_{max}: 1 hr Dose: 10 mg/kg/day AUC: 48,300 h*ng/mL C_{max}: 7,570 ng/mL T_{max}: 1 hr Dose: 20 mg/kg/day AUC: 89,700 h*ng/mL C_{max}: 15,900 ng/mL T_{max}: 1 hr Day 91, sex combined data shown.	• Oral doses: 0, 5 (LD), 10 (MD), or 20 (HD) mg/kg/day. • Dose-related clinical observations included increased activity, salivation, red skin, lacrimation, thin body condition, and increased incidence of vomiting and discolored/abnormal feces. • Body weight and body weight gains were decreased relative to controls at all doses in males (up to 20% decreased relative body weight at MD) and at ≥MD in females (up to 20% decreased relative body weight at HD). • Food consumption was decreased at all dose levels in males (up to 36%) and at ≥MD in females (up to 22%) and generally corresponded to reduced body weight gains. • Decreased erythrocytes (up to 21%) and hemoglobin (up to 14%) were observed at ≥MD in both sexes. In males, but not females, this was associated with increased mean corpuscular volume (up to 5%) and mean corpuscular hemoglobin (up to 7.5%). • Decreased albumin (up to 8%) was observed at ≥MD in males. • Liver weight was increased (up to 39% relative to body weight) at ≥MD in males and at all doses in females. Spleen weight was decreased by (up to 48% absolute) at ≥MD in males. • Liver: Hepatocyte vacuolation (consistent with glycogen) was observed with minimal to moderate severity in males at ≥LD (greatest severity at MD) and at all doses (including 3 controls) in females with greatest severity at the HD. This finding was correlated with increased liver weight. Hepatocyte cytoplasmic alteration was observed in one HD male and characterized by condensed eosinophilic foci within the cytoplasm. • Based on the clinical signs, reduced food consumption, and lower body weight, the NOAEL* was the LD of 5 mg/kg/day. All adverse effects observed are considered monitorable in humans up to highest dose tested of 20 mg/kg/day. At 20 mg/kg/day, exposure was approximately 6 times the human exposure at the MRHD based on AUC. *We note that this is a different NOAEL than what was identified in the Study Report; however, we consider the body weight loss to be adverse.
Dog, 26-week (GLP) Study No. 2271-007	Dose: 5 mg/kg/day AUC: 32,700 h*ng/mL C_{max}: 7,290 ng/mL T_{max}: 1 hr	• Oral doses: 0, 5 (LD), 10 (MD), or 20 (HD) mg/kg/day. • Dose-dependent clinical observations (some at LD, many at ≥MD) in both sexes included increased activity, vocalization, panting, hypersensitivity to sound, stereotypy (circling, rearing, head bobbing, forepaw padding, jumping, and

Species/ Duration	Toxicokinetic parameters	Key Study Findings
	Dose: 10 mg/kg/day AUC: 44,900 h*ng/mL C_{max}: 6,450 ng/mL T_{max}: 1 hr Dose: 20 mg/kg/day AUC: 65,800 h*ng/mL C_{max}: 8,500 ng/mL T_{max}: 4 hr Day 180, sex combined data shown.	chatter), and increased incidence of vomiting (tan) and abnormal feces (few, absent, hard, soft, or mucoid). Thin body condition and fissuring of the paws were observed at ≥MD in both sexes. Fissuring of the paws was considered as likely a secondary effect related to increased activity by the Study Director. • Supplemental food was provided at ≥MD throughout the study, potentially confounding food consumption and body weight comparisons. Loss of body weight occurred at the HD during the first two weeks of the study in males (-11%) and females (-16%) compared to +5% and 0% gains in control males and females, respectively. Thereafter body weight gains were similar to controls and group-mean body weights for all dose groups were decreased by 6% compared to controls at the end of dosing. • Decreased hemoglobin (up to 10%) and reticulocyte counts (up to 56%) were observed at the HD in males and ≥MD in females. • Increased cholesterol, decreased albumin, decreased creatinine, decreased phosphorous, and increased chloride were observed at ≥MD in both sexes. Increased globulin was observed at ≥MD in males. Decreased calcium was observed at ≥LD in females. • Urine pH was decreased (up to -23%) at ≥MD in both sexes. • Macroscopic irregular surface of the foot pad (minimal to mild) was observed at ≥MD in males and ≥LD in females and related to microscopic observation of minimal to mild hyperkeratosis. • Increased liver weight (up to 62%) was observed at ≥MD in both sexes. • Minimal to mild cytoplasmic alterations in the liver were observed at ≥MD in males and at the HD in females and consisted of lamellar aggregates (consistent with cell membrane or phospholipid) within cytoplasmic vacuoles. The liver cytoplasmic alterations did not appear to be correlated to the increased liver weight. • Based on the clinical signs and effects on body weight the NOAEL* was the MD of 10 mg/kg/day. All adverse effects observed are considered monitorable in humans up to highest dose tested of 20 mg/kg/day. At 20 mg/kg/day, plasma exposure was approximately 4.7 times the human exposure at the MRHD based on AUC.

Species/ Duration	Toxicokinetic parameters	Key Study Findings
		*We note that this is a different NOAEL than what was identified in the Study Report; however, we consider the body weight loss to be adverse.
Dog, juvenile 43-week (GLP) Study No. 2271-009	Dose: 5 mg/kg/day AUC: 12,000 h*ng/mL C_{max}: 3,570 ng/mL T_{max}: 0.5 hr Dose: 10 mg/kg/day AUC: 47,600 h*ng/mL C_{max}: 13,900 ng/mL T_{max}: 0.5 hr Dose: 20 mg/kg/day AUC: 60,800 h*ng/mL C_{max}: 20,200 ng/mL T_{max}: 0.5 hr Day 306, sex combined data shown.	• Oral doses: 0, 5 (LD), 10 (MD), or 20 (HD) mg/kg/day. • Dogs were approximately 9 weeks of age at the start of dosing. • Dose-dependent clinical signs consistent with CNS stimulant effects were observed in both sexes, including increased activity, stereotypy (e.g., circling, head bobbing, licking), panting, and salivation. • Mean body weight was lower at all doses in males (16 to 19%) and at the LD (7%) and HD (10%) in females, compared to controls, at the end of dosing. • Food consumption was consistently lower at all dose levels in both sexes during the dosing period, compared to controls. During recovery, food consumption was higher in HD females, and there was no difference in males, compared to controls. • Reduced absolute reticulocyte count (up to -45%), erythrocyte count (up to -13%), hemoglobin (up to -11%), and hematocrit (-13%) were observed at the HD in males and at ≥MD in females at the end of the dosing period (none of these findings were seen after recovery). • Decreased creatinine (up to 36%) was observed at ≥MD in both sexes. Increased globulin (up to 16%) and decreased triglycerides (up to 47%) were observed at the HD in both sexes. Only the increased globulin persisted after recovery. • Dose-dependent increases in liver weight (up to 54% absolute/71% relative to body weight) were observed in both sexes at the end of dosing and persisting after recovery. • Microscopic liver findings included minimal to moderate hepatocellular vacuolation in all animals at ≥MD in both sexes and altered cytoplasm at ≥MD in males and at the HD in females observed at the end of dosing. Minimal to moderate hepatocellular vacuolation persisted after recovery. • Based on the clinical signs, reduced food, and lower body weights the NOAEL* is the MD of 10 mg/kg/day. These effects are considered monitorable in humans and no other adverse effects were observed up to highest dose tested of 20 mg/kg/day. At 20 mg/kg exposure is approximately 4.3 times the human exposure at the MRHD based on AUC. *We note that this is a different NOAEL than what was identified in the Study Report; however, we consider the body weight loss to be adverse.

LD = low dose; MD = mid dose; HD = high dose.
Source: Generated by reviewer based on review of Applicant data.

4.5.2. Genetic Toxicology

Centanafadine was negative in a valid, full battery of genetic toxicology assays including a reverse bacterial mutagenicity (Ames) assay, a chromosome aberration assay (CHO cells), and a rat in vivo micronucleus assay.

4.5.3. Carcinogenicity

Centanafadine was adequately evaluated in a 6-month transgenic mouse carcinogenicity study and a 2-year rat carcinogenicity study.

Mouse Carcinogenicity Study

Centanafadine was administered once daily by oral gavage to CByB6F1/Tg rasH2 hemizygous mice at 0 (vehicle: reverse osmosis deionized water), 1, 3, or 10 mg/kg/day for 26 weeks. A positive control group received a single bolus intraperitoneal injection of 75 mg/kg N-nitrosomethylurea (NMU) on the first day of the study.

There was no evidence of drug-related neoplasms in mice treated with centanafadine. There were no clinical signs and a reduction of <10% body weight at the high dose of 10 mg/kg/day centanafadine, consistent with the 28-day dose-range finding study. The absence of tumor findings or effects on survival are supported by the statistical analysis provided by the Agency's statistical reviewer. The positive control (NMU) produced expected tumorigenic effects and reductions in survival.

Rat Carcinogenicity Study

Centanafadine was administered once daily by oral gavage to Sprague Dawley rats at doses of 0 (vehicle; distilled water), 3, 7, or 20 mg/kg/day in males and 0, 3, 10, or 30 mg/kg/day in females.

There was no evidence of drug-related neoplasms in rats treated with centanafadine. The clinical signs and reduction in body weight at 20 mg/kg/day centanafadine in males and ≥10 mg/kg/day in females are consistent with the 13-week and 26-week rat toxicology studies. The absence of tumor findings and lack of effect on survival are supported by the statistical analysis provided by the Agency's statistical reviewer.

4.5.4. Reproductive and Developmental Toxicology

Key Findings

- Fertility and early embryonic development (FEED) was evaluated for male and female rats in two separate studies, each of which evaluated oral doses of 0, 3, 10, and 30 mg/kg centanafadine. In the male FEED study, males were dosed for 70 days prior to cohabitation with untreated females and continuing until necropsy (Day 92 to 95). In the female FEED study, females were dosed for 15 days prior to cohabitation with untreated males and continuing through Gestation Day (GD) 7 prior to necropsy on GD 13.
  - Body weight gains were reduced by ≥20% during the premating period at 30 mg/kg in males and at all doses in females compared to the control groups.
  - For both male and female rats the NOEL for fertility was 30 mg/kg.
- Embryonic and fetal development (EFD) was evaluated in studies in pregnant rats and rabbits.
- In the rat EFD study, pregnant rats were administered oral doses of 0, 10, 30, or 100 mg/kg centanafadine from GD 7 to 17 before cesarean sectioning on GD 21.
  - Mean maternal body weight gain from GD 7 to 21 was reduced by 9% and 34% at the MD and HD, respectively, compared to controls.
  - There were no differences in any ovarian or uterine parameters related to centanafadine.
  - Mean fetal body weights (sex combined) were reduced by 5.3% and 19.8% at the MD and HD, respectively.
  - At the HD, there was increased incidence of the following skeletal variations compared to the control group:
    - Irregularly shaped cervical vertebrae in 41/150 fetuses and 19/24 litters (seen in one control fetus).
    - Incompletely ossified cervical vertebrae in 3 fetuses from 3 litters.
    - Short ribs in 15 fetuses from 7 litters (up to 4 in a single litter).
  - The NOAEL for both maternal toxicity and fetal development was 10 mg/kg based on reduced maternal body weight gain and reduced fetal body weight, respectively, at ≥30 mg/kg.
- In the rabbit EFD study, pregnant rabbits were administered oral doses of 0, 3, 6, or 15 mg/kg centanafadine from GD 7 to 19 before cesarean sectioning on GD 29.
  - Mean maternal body weight gain from GD 7 to 29 was reduced by 8% and 18% at the MD and HD, respectively.
  - There were no differences compared to the control group for any ovarian or uterine parameters or fetal body weights related to centanafadine.
  - There were no differences in incidence of external, visceral, or skeletal abnormalities related to centanafadine.
  - The NOAEL for maternal toxicity was 6 mg/kg based on reduced body weight gain at 15 mg/kg. The NOAEL for fetal development was the high dose of 15 mg/kg.
- Pre- and post-natal development (PPND) was evaluated in a study of offspring of pregnant rats treated with centanafadine.

- In the PPND study, pregnant rats were administered oral doses of 0, 3, 10, and 30 mg/kg centanafadine from GD 6 through delivery and until Lactation Day (LD) 20. The offspring were then followed through maturation and evaluated for behavior and reproductive performance.
  - Maternal body weight gains were reduced at the HD by 11% compared to controls during gestation, from GD 4 to 20.
  - There was a slight increase in incidence of pup mortality from birth through Day 4 at the HD (95%) compared to concurrent controls (99%).
  - Pup body weights were reduced at the HD on PND 1 (birth), by 7.7% in males and 8.2% in females, compared to controls. On PND 21 (weaning), body weights were reduced at the HD by males 5.6% in males and 4.7% in females. No effects of centanafadine were observed on body weights after weaning.
  - There were no effects of centanafadine on pup growth, neurobehavioral assessments, sexual maturation, or reproductive performance.
  - The NOAEL for development was the mid dose of 10 mg/kg due to the slight increase in incidence of early pup mortality.
- A juvenile animal study (JAS) evaluated the effects of centanafadine treatment on developing rats from weaning through the period of adolescence, including evaluations of sexual development, reproductive performance, bone growth and density, and neurobehavior.
- In the JAS, rats were administered oral doses of 0, 3, 10, or 30 mg/kg centanafadine from Postnatal Day (PND) 21 through PND 62.
  - The study protocol was reviewed by the Division and advice was provided, including to base the high dose selection on results from a dose-ranging study in juvenile rats. Based on the reduction in body weight gain of >15% at ≥30 mg/kg in both sexes in the 14-day dose range-finding study, the high dose selection of 30 mg/kg/day is adequate.
  - Body weight gains were reduced at the HD by 8.7% in males and 5.3% in females compared to controls which correlated with reduced food consumption and reduced relative body weights compared to controls (7.3% in males and 3.9% in females).
  - Balano-preputial separation was delayed at the HD in males to PND 45.2 compared to PND 43.2 in controls.
  - There were higher numbers of abnormal sperm morphology at the HD (7.6% compared to 3.0% for controls), including increased incidence of coiled or bent flagellum.
  - Thyroid weights were increased at the HD by 13.4/25.2% (absolute/relative to body weight) in males and 20.3/24.2% (absolute/relative to body weight) in females compared to controls on PND 63 (no differences were observed after 2 weeks recovery period).
  - There were no effects of centanafadine on reproductive performance, bone growth and density, neurobehavior, or histopathology.
  - None of the observed effects were considered adverse as the reduction in body weights and body weight gains were <10%, the male reproductive effects were

minor in magnitude with no differences observed in mating or fertility, and there were no microscopic correlates observed in the thyroid.

- Therefore, the NOAEL in juvenile rats is the high dose of 30 mg/kg.

Table 6. Toxicokinetic Parameters From EFD and JAS Studies

Study	Dose (mg/kg)	C_{max} (ng/mL)	AUC (h*ng/mL)
Rat EFD Data from GD 17	10	1,760	2,310
	30	3,210	9,450
	100	7,550	52,300
Rabbit EFD Data from GD 19	3	313	915
	6	1,030	2,710
	15	2,630	8,330
JAS Data from PND 62*	3	43	102
	10	1,030	1,160
	30	1,710	4,680

*male data shown (females had higher AUC at all doses)
Source: Generated by Reviewer from Applicant data.

4.5.5. Other Toxicology Studies

Evaluation of Impurities

The only proposed impurity limit greater than the ICH Q3A qualification threshold (lesser of 0.15% or 1 mg) is the enantiomer of the drug substance, referred to as EB-1070, which has a proposed limit of NMT (b) (4) %. At the Maximum Recommended Human Dose (MRHD) of 280 mg centanafadine, the maximum daily exposure to EB-1070 would be (b) (4) mg based on the proposed limit.

All pivotal toxicology studies were performed with batches of centanafadine containing ≥ (b) (4) % EB-1070 with the exception of the 28-day repeat-dose studies (both species) and the embryofetal development study in rats.

The Applicant also submitted an in vitro bacterial reverse mutagenicity (Ames) assay for EB-1070 (Study No. 9603796) and a combination 28-day repeat-dose toxicology and an in vivo micronucleus study in rats administered 0.3 mg/kg/day EB-1070 alone and in combination with 30 mg/kg/day centanafadine, with vehicle and 30 mg/kg/day centanafadine alone as controls (Study No. 8003950).

In the 28-day repeat-dose study in rats, some minimal changes in clinical pathology parameters were only observed in groups administered EB-1070. However, no new or exacerbated effects on clinical signs, body weights, or histopathology were observed with the combination of 0.3 mg/kg/day EB-1070 with 30 mg/kg/day centanafadine compared to 30 mg/kg/day centanafadine alone.

Table 7. Summary of 28-Day Repeat-Dose Toxicity Study With EB-1070 (Enantiomer Impurity)

Species/ Duration	EB-1070 Toxicokinetic parameters	Key Study Findings
Rat 28-day (GLP) Study No. 8003950	Dose: 30 mg/kg centanafadine (EB-1070 present as impurity) AUC: 4.23 hr*ng/mL C_{max}: 1.41 ng/mL T_{max}: 0.5 hr Dose: 0.3 mg/kg EB-1070 AUC: 56.8 hr*ng/mL C_{max}: 19.3 ng/mL T_{max}: 1 hr Dose: 30 + 0.3 mg/kg centanafadine + EB-1070 AUC: 67.9 hr*ng/mL C_{max}: 20.1 ng/mL T_{max}: 1 hr Day 28, male data shown (females had higher AUC at all doses)	• Oral doses: 0, 30 mg/kg/day centanafadine, 0.3 mg/kg/day EB-1070, or 30 + 0.3 mg/kg/day centanafadine + EB-1070 (combination). N = 10 rats/sex/group (+5 vehicle and combination for recovery). • Some minimal changes in clinical pathology parameters were only observed in groups administered EB-1070 alone or in combination: ↑ white blood cells (up to 19%) in males after EB-1070 alone and combination. ↑ lymphocytes (up to 14%) in males after EB-1070 alone and combination. ↓ reticulocytes (15%) in females after combination. ↑ urea nitrogen (17%) in females after combination. ↓phosphorous (up to 11%) in females after EB-1070 alone and combination. ↑ glucose (up to 16%) in females after EB-1070 alone and combination. ↑ cholesterol (up to 15%) in males after combination. ↓ urine volume (52%) and ↓ urine pH (9%) in females after combination. • After a 14-day recovery period, only ↑ white blood cells and lymphocytes in males receiving combination persisted. • No effects on clinical signs, body weight, food consumption, macroscopic pathology, organ weights, or microscopic pathology were observed after EB-1070 alone or combination and no increased incidence or severity compared to centanafadine alone were observed. • No adverse effects were observed at any of the doses tested in this study.

Source: Generated by reviewer based on review of Applicant data.

EB-1070 was negative for mutagenicity in the valid in vitro Ames and in vivo micronucleus studies.

Table 8. Summary of Genotoxicity Studies With EB-1070 (Enantiomer Impurity)

Study	Result	Notes
Bacterial Reverse Mutagenicity Assay (Ames) Study No. 9603796	Negative	• Strains: TA1535, TA1537, TA98, TA100, and WP2 uvrA. • Concentrations of up to 5,000 µg/plate EB-1070 were tested using the plate incorporation method with and without metabolic activation by rat S9 liver fraction. • Incomplete or absent background lawns were observed at >500 µg/plate in all strains with and without metabolic activation (except WP2 uvrA which had complete background lawn up to 1581 µg/plate with and without metabolic activation). • No precipitation was observed at <5,000 µg/plate. • All formulation samples were within 7% of nominal concentration. • No significant increases in revertant colonies or dose-response trends were observed for any strain with/without metabolic activation up to ≥500 µg/plate. • The negative controls were within the historic control range for all strains with/without metabolic activation. • Appropriate positive controls induced >3-fold increases in revertant colonies compared to concurrent negative controls for all strains with/without metabolic activation.
In Vivo Micronucleus Rat (GLP) Study No. 8003950	Negative	• Oral doses: 0, 30 mg/kg/day centanafadine, 0.3 mg/kg/day EB-1070, or 30 + 0.3 mg/kg/day centanafadine + EB-1070 for 28 days. • Micronucleus evaluations were performed with peripheral blood collected one day after final dose for N=5 rats/sex/group. • Positive control: N=3 males administered 10 mg/kg cyclophosphamide. • At least 4,000 reticulocytes from each animal were analyzed by flow cytometry. • All treated groups had > 50% relative reticulocytes compared to controls in both sexes. • No treated group had a significantly different percentage of micronucleated reticulocytes compared to same-sex controls. • The positive control group had a robust response with a 12.5-fold increase in % micronucleated reticulocytes compared to control males.

Source: Generated by reviewer based on review of Applicant data.

Based on the available toxicology data, the proposed limit of NMT (b)(4)% EB-1070 is qualified.

Nitrosamine Risk Assessment

The Applicant submitted a nitrosamine assessment that was reviewed by the Office of Pharmaceutical Quality and determined to be adequate for the control of nitrosamine risk.

The Applicant's risk assessment included an evaluation of (b) (4) using a Carcinogenic Potency Categorization Approach (CPCA) as potency category (b) (4) with an acceptable intake (AI) limit of (b) (4) ng/day based on the recommendation published in the Agency guidance document.[2] Independent evaluation by internal Agency experts agreed with the Applicant's evaluation of (b) (4) as potency category (b) (4) Therefore, the AI limit of (b) (4) ng/day (b) (4) is acceptable.

Evaluation of Excipients

The drug product consists of centanafadine in extended release capsules. All excipients are present at levels below those listed in the Agency's inactive ingredient database.

[2] Guidance for Industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (August 2023)*

5. Clinical Pharmacology

5.1. Executive Summary

Otsuka Pharmaceutical Company, Ltd. is seeking approval of centanafadine extended-release (ER) capsules (EB-1020; proposed name: Simtriyo) for the treatment of adults and pediatric patients aged (b) (4) years and older for ADHD. The proposed product is available in dose strengths of 140 mg, 210 mg, and 280 mg free base equivalent to 164.4 mg, 246.6 mg, and 328.8 mg hydrochloride salt, respectively. Centanafadine's mechanism of action involves inhibitory activity at NE, DA, 5-HT reuptake transporters.

Two pivotal phase 3 efficacy and safety trials (Studies 13 and 14) demonstrated favorable effectiveness of 100-mg (low-dose) and 200-mg (high-dose) twice-daily tablet of centanafadine compared to placebo for the treatment of ADHD in adults. Two pediatric efficacy and safety studies (Studies 16 [subjects 13 to 17 years of age] and 21 [Cohort 1: subjects 6 to 12 years of age; Cohort 2: subjects 4 to 5 years of age]) demonstrated effectiveness of an once-daily extended-release (ER) formulation of centanafadine at doses that are approximately equivalent to the high-dose regimen of a twice-daily tablet of centanafadine in adults. However, the once-daily ER formulation of centanafadine at doses that are approximately equivalent to the low-dose regimen of a twice-daily tablet of centanafadine failed to demonstrate effectiveness in pediatric subjects 6 to 17 years of age with ADHD. The safety and effectiveness have not been established in pediatric patients younger than 6 years of age because they had a higher incidence of weight loss than patients 6 years of age and older. This formulation was not studied in subjects weighing less than 20 kg. Additionally, there are two long-term, open-label trials (Studies 15 in adults and 17 in pediatric subjects) that support the safety of centanafadine. Refer to Section 6 and Section 7 for additional information.

The clinical pharmacology package included the following studies that characterized the pharmacokinetics (PK), pharmacodynamics (PD) and safety across healthy adults and pediatric subjects (subjects 4 to 12 years of age, subjects 13 to 17 years of age, adults):

- Single ascending dose (SAD) and multiple ascending dose (MAD) studies
- PK bridging studies to establish a bridge between the once-daily ER capsule and twice-daily tablet formulation used in phase 3 efficacy studies in adults and to establish a bridge between the once-daily ER capsule (clinical trial formulation) used in pediatric efficacy and safety studies and to-be-marketed once-daily ER capsule
- Food effect study
- Human mass balance study
- Organ impairment studies in subjects with moderate hepatic impairment (Child-Pugh Class B) and subjects with severe renal impairment (eGFR <30 mL/min)
- Thorough QT study
- Multi-part drug-drug interaction study evaluating the effects of moderate CYP1A2 inhibitor, ciprofloxacin, strong CYP2D6 inhibitor, quinidine and smoking (moderate

CYP1A2 inducer) on the PK of centanafadine and the effects of centanafadine on the PK of CYP1A2 substrate, caffeine.

The Office of Clinical Pharmacology (OCP) review finds that centanafadine exerts a slightly greater than dose proportional increase in systemic exposures over the dose range of 140 mg to 280 mg. The comparative BA study demonstrated that the scientific bridge between 280 mg of the once-daily ER formulation and 200 mg (high-dose) of a twice-daily tablet used in the phase 3 studies in adults is adequate. Although peak plasma exposures (C_{max}) and area under the plasma concentration-time curve (AUC_{inf}) are similar between 140 mg (equivalent to 164.4 mg centanafadine hydrochloride) of the ER formulation and the 100-mg twice-daily (low-dose) formulation, the post 6-hour exposures of the 140-mg ER formulation are slightly lower than those of a low-dose twice-daily tablet. Therefore, the Applicant performed PK simulations to support an intermediate dose, a 210-mg ER formulation of centanafadine that showed systemic exposures within those observed for 100-mg twice-daily and 200-mg twice-daily tablet demonstrated effectiveness in adults with ADHD. The Applicant-proposed intermediate dose (210 mg once daily) and high dose (280 mg once-daily) ER capsule formulation of centanafadine for the treatment of ADHD in adults are acceptable. The PK bridge between the once-daily ER capsule used in the pediatric efficacy studies and to-be-marketed formulation is adequate. The high-fat meal did not appreciably affect the PK of centanafadine.

Centanafadine is extensively metabolized and approximately 88% of the orally administered dose is excreted in the urine as metabolites and 7% in the feces. The PK of centanafadine was not appreciably changed in subjects with moderate hepatic impairment (Child-Pugh Class B) and subjects with severe renal impairment (eGFR <30 mL/min/1.73m^2; Chronic Kidney Disease Epidemiology Collaboration method) compared to subjects with normal hepatic function and subjects with normal renal function, respectively. Centanafadine did not prolong the QT interval up to two times the maximum recommended dose (280 mg). As centanafadine increased the systemic exposures of a CYP1A2 substrate, caffeine (2-fold increase of area under the plasma concentration-time curve (AUC_{inf}), dosage reduction of concomitantly used CYP1A2 substrates is recommended. No clinically meaningful change in pharmacokinetics of centanafadine was observed with concomitant use of ciprofloxacin (a CYP1A2 inhibitor), quinidine (a CYP2D6 inhibitor), or smoking (a CYP1A2 inducer).

The OCP recommends approval of centanafadine ER formulation for the treatment of ADHD in adults and pediatric patients 6 years of age and older or weighing at least 20 kg.

5.2. Summary of Clinical Pharmacology Assessment

Two adequate and well-controlled phase 3 trials in adult subjects with ADHD (Studies 13 and 14), two phase 3 trials in pediatric subjects with ADHD (Study 16 [subjects 13 to 17 years of age] and Study 21 Cohort 1 [subjects 6 to 12 years of age] and Cohort 2 [subjects 4 to 5 years of age]), two long-term, open-label trials (Studies 15 in adults and 17 in pediatric

subjects), and comparative BA studies (once-daily ER capsule vs. twice-daily tablet studied in the phase 3 studies in adults with ADHD; once-daily ER capsule vs. to-be-marketed once-daily ER capsule) support the dosage recommendations of once-daily ER capsule of centanafadine (i.e., 210 mg and 280 mg once daily for adults with ADHD; 280 mg once-daily ER capsule for pediatric patients 13 to 17 years old with ADHD); weight-based dosage regimens (<35 kg: 140 mg; 35-50 kg: 210 mg and >50 kg: 280 mg) in 6 to 12 years old with ADHD.

The twice-daily tablet formulation of centanafadine (100-mg and 200-mg twice-daily regimens) was used in the pivotal efficacy and safety studies in adults with ADHD and once-daily ER formulation of centanafadine was used in the pediatric efficacy and safety studies. A comparative BA study compared the PK of the 140-mg and 280-mg once-daily ER formulation and 100-mg (low-dose) and 200-mg (high-dose) twice-daily tablet, respectively, under fasted conditions. Although C_{max} and AUC_{inf} are similar between the formulations, the PK profiles of the ER formulation are different. The post-6 hour concentrations of the once-daily ER formulation are lower than those of the twice-daily tablet of centanafadine. As the systemic exposures of 280 mg once-daily ER capsule were within those observed for the low-dose and high-dose of the twice-daily tablet, and both the low-dose and high-dose twice-daily tablet showed a flat dose/exposure-response relationship, the differences in the PK profiles are not expected to have an impact on the effectiveness of 280-mg once-daily ER capsule. Therefore, the scientific bridge between 280-mg once-daily ER capsule and high-dose twice-daily tablet is adequate. Given that 140-mg once-daily ER capsule showed post-6-hour exposures lower than those of low-dose twice-daily tablet, the Applicant performed population PK simulations to support an intermediate dose, a 210-mg once-daily ER capsule that would achieve exposures within of those observed for the low-dose and high-dose twice-daily tablet. A comparative BA study demonstrated an adequate PK bridge between the once-daily ER capsule used in the pediatric efficacy and safety studies and the to-be-marketed once-daily ER capsule formulation. The proposed intermediate dose (210 mg) and high dose (280 mg once-daily ER capsule) for the treatment of ADHD in adults are acceptable.

Food effect: A dedicated food-effect study was conducted using the to-be-marketed once-daily ER capsule to evaluate the effect of a high-fat meal on the PK of centanafadine in 14 healthy adults in a 2-period randomized crossover study. Compared to the fasted conditions, administration with a high-fat meal resulted in a longer t_{max} (5.0-hours vs. 3.5-hours fasted) and increased C_{max} (~29% increase), while the overall exposure (AUC_{inf}) remained comparable. Additionally, a dedicated clinical PK study compared the PK of sprinkling the contents of the capsule on three different types of soft foods (apple sauce, yogurt, and orange juice) and intact capsule administration. The results demonstrated that there was no change in PK of centanafadine between the sprinkling capsule contents over the soft foods and administration of intact capsule.

Renal impairment (RI)/hepatic impairment (HI): A phase 1, open-label, parallel-group, single dose trial in 24 healthy adults evaluated the PK, safety, and tolerability of centanafadine in adults with moderate hepatic and severe renal impairment, compared to matched healthy controls. In adults with moderate hepatic impairment (Child-Pugh Class B) as well as adults with severe renal impairment (eGFR <30 mL/min/1.73m^2, and not undergoing dialysis), centanafadine total plasma exposures were lower (C_{max} reduced by 25 to 30% and AUC_{inf} reduced by 20 to 25%) compared to healthy matched adults. However, the unbound centanafadine levels were higher (i.e., ~10% higher C_{max}, u and AUC_{inf}, u in moderate HI and ~27% higher C_{max}, u and 40% higher AUC_{inf}, u in severe RI). Based on the exposure-response analysis for safety (i.e., skin rash and insomnia; Figure 45 and Figure 46), **Cmax is the significant predictor for safety and approximately 27% increase in Cmax is considered to be clinically not meaningful.**

Drug-Drug Interaction (DDI): A dedicated drug interaction study assessed both the effect of centanafadine as a precipitant as well as an object. The PK of centanafadine (as an object) was minimally impacted by the presence of a strong CYP2D6 inhibitor (quinidine), moderate CYP1A2 inhibitor (ciprofloxacin) or smokers (a moderate CYP1A2 inducer) thus no dose adjustments are warranted in the presence of strong CYP2D6 inhibitor, CYP1A2 inhibitor or smokers. Centanafadine as a precipitant impacted the PK of caffeine (a sensitive CYP1A2 substrate) leading to an approximately 2-fold increase in AUC_{inf} with no change in C_{max}. Therefore, monitoring for adverse reactions and considering dosage reduction of the concomitantly used CYP1A2 substrate is recommended.

5.2.1. Pharmacology and Clinical Pharmacokinetics

The mechanism of action of centanafadine for the treatment of ADHD is unclear; however, its efficacy could be mediated through its activity as a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant. At the plasma concentrations maintained at clinically recommended doses, approximately 80% inhibition of norepinephrine transporter and lower than 50% inhibition for dopamine and serotonin transporters are expected. Refer to Nonclinical Section 4 and Appendix for additional information.

The key clinical pharmacokinetics of centanafadine ER capsule are listed below:

- Following multiple doses of centanafadine ER capsule, exposures (C_{max} and AUC_{inf}) increased slightly greater than dose proportionally across the dose range of 140 to 280 mg following once-daily dosing.
- Steady state concentrations were achieved on Day 2 with minimal drug accumulation (~1.2-fold).
- Peak plasma concentrations were reached at approximately 5 hours post-dose.
- Compared to the fasted conditions, administration of centanafadine ER capsule with a high-fat meal (HFM) resulted in no change in AUC_{inf}, but increased C_{max} (~29%), and delayed time to reach peak plasma concentrations by approximately 1.5 hours.

- Sprinkling the contents of a centanafadine ER capsule on soft foods such as applesauce or yogurt, or in orange juice, had no impact on its PK.
- Centanafadine is highly plasma protein bound with the fraction unbound of centanafadine in the plasma of healthy adults of <0.01 and independent of centanafadine concentrations.
- The apparent volume of distribution (Vd) of centanafadine is approximately ~167 L.
- The mean apparent clearance (CLr) is ~410 mL/min.
- The mean half-life ($T_{1/2}$) of centanafadine ER capsule is ~5.2 hours.
- Centanafadine is primarily metabolized by monoamine oxidase A (MAO-A), with minor pathways of metabolism via CYP1A2 and CYP2D6.
- Following administration of a ^{14}C-centanafadine, 88% of the administered radioactivity was excreted in the urine (mainly as metabolites), and 7% was recovered in the feces (mainly as metabolites).
- The PK of centanafadine (C_{max} and AUC) in pediatric subjects was similar to adults following single and multiple centanafadine doses when the dosage was adjusted for weight.
- In adults with severe renal impairment, total centanafadine exposures were lower (C_{max} reduced by 25% and AUC_{inf} reduced by 20%) compared to healthy matched adults. However, the unbound C_{max} and AUC_{inf} increased by 27% and 40%, respectively, compared to healthy matched adults.
- In adults with moderate hepatic impairment, total centanafadine exposures were lower (C_{max} reduced by 30% and AUC_{inf} reduced by 25%) compared to healthy matched adults. However, the unbound C_{max} and AUC were each increased by approximately 10% compared to healthy matched adults.
- No clinically meaningful change in pharmacokinetics of centanafadine was observed with inhibition of CYP1A2 (by ciprofloxacin), CYP2D6 (by quinidine), or with induction of CYP1A2 (smoking).
- Centanafadine did not have any clinically meaningful effect on the QT interval at two times of the maximum recommended dose (i.e., 280 mg).

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

- The recommended centanafadine doses for the different age groups of patients are: Adults: 210 or 280 mg orally, once daily. Recommended starting dosage is 210 orally once daily. Dosage may be increased to maximum daily dosage of 280 mg once daily based on clinical response and tolerability.
- Adolescents (ages 13 to 17 years): 280 mg, once daily
- Pediatric patients (ages 6 to 12 years): Weight-based dosing as below
  - <35 kg: 140 mg, once daily
  - 35 to 50 kg: 210 mg, once daily
  - >50 kg: 280 mg, once daily

Therapeutic Individualization

- **Concomitant administration with CYP1A2 substrate:** Concomitant administration of centanafadine with a CYP1A2 substrate, caffeine, increased the exposures of caffeine (approximately 2-fold increase in AUC_{inf} and no change in C_{max}) compared to caffeine administration alone. Therefore, monitoring for adverse reactions and considering reducing the dose of CYP1A2 substrates when concomitantly used with centanafadine is recommended.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. Clinical Pharmacology Questions

Are the Proposed Dosage Regimens Appropriate for the General Patient Population for Which the Indication Is Being Sought?

Yes, the proposed dosage regimens are appropriate for the general population for the indication being sought (ADHD). The dosage regimens are consistent with the results from the pivotal phase 3 efficacy and safety trials. Based on the positive results from the phase 3 trials, the proposed dosage regimens for the different age groups are listed below:

- Pediatric patients 6 to 12 years old: Weight-based dosage regimens are shown below.
  - <35 kg: 140 mg, once daily
  - 35 to 50 kg: 210 mg, once daily
  - >50 kg: 280 mg, once daily

  Study 405 201-00021 Cohort 1 (subjects 6 to 12 years of age) demonstrated favorable effectiveness and safety of the above dosage regimens.

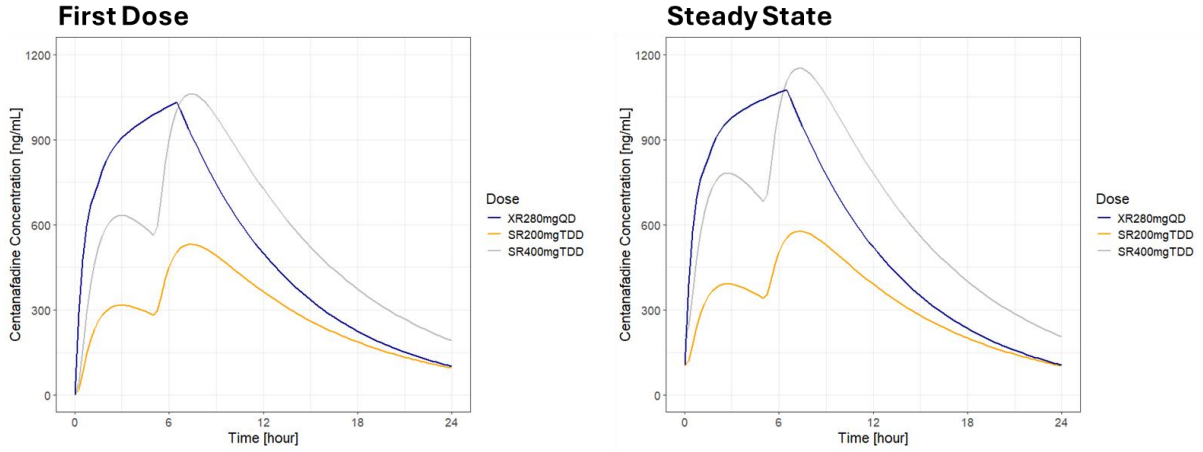
- Pediatric patients 13 to 17 years old: 280 mg, once daily. This is supported by the positive results from Study 16 (subjects 13 to 17 years of age) supported the effectiveness and safety of 280 mg once-daily regimen in pediatric subjects 13 to 17 years of age. However, the low dose of 140 mg failed to demonstrate efficacy in pediatric subjects 13 to 17 years of age.

- Adults (18 years and older): 210 mg once daily as a starting dose. The dose may be increased to 280 mg based on clinical response and tolerability. Two phase 3 efficacy and safety trials in adults with ADHD (Studies 13 and 14) and a PK-bridging study (Study 405-201-00157) support the approval of 210 mg and 280 mg once-daily dosage regimens for the treatment of adults with ADHD. Notably, the efficacy and safety studies were conducted with a twice-daily tablet formulation that was not the final to-be-marketed formulation. However, dedicated PK-bridging studies were conducted to establish a scientific bridge between the twice-daily tablet formulation and once-daily ER capsule formulation (pediatric clinical trial formulation), and the once-daily ER

capsule (pediatric clinical trial formulation) and final to-be-marketed once-daily ER capsule formulation.

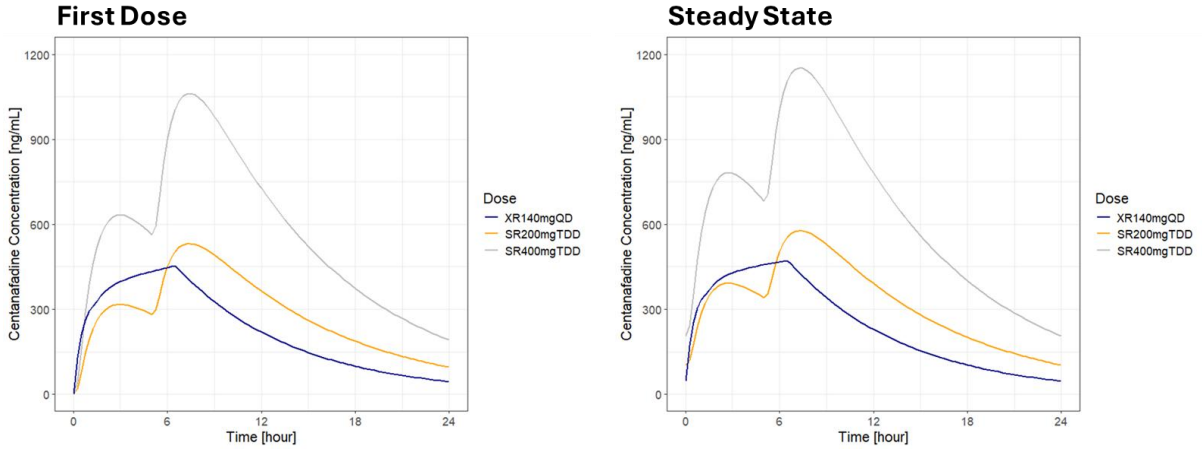
In the pivotal efficacy studies, the twice-daily tablet formulation at both 100 mg and 200 mg twice-daily doses were demonstrated to be efficacious compared to placebo. Therefore, a bracketing approach is utilized, where it is assumed that efficacy will be retained if the exposures are maintained within the PK profiles of low dose (100 mg twice-daily, i.e., 200 mg, total daily dose (TDD)) and high dose (200 mg twice-daily, i.e., 400 mg, TDD) of the twice-daily tablet formulation. Population PK simulation showed that 280-mg once-daily centanafadine ER capsule produced plasma exposures higher than those of 200-mg twice-daily tablet during the first 6 hours after dosing, but thereafter remained within the exposure range associated with 100-mg and 200-mg twice-daily tablet (Figure 1). Notably, the C_{max} of 280 mg centanafadine ER capsule was similar to that of the 400 mg TDD of the twice-daily tablet. In contrast, the 140-mg once-daily ER capsule produced higher exposures during the first 6 hours post-dose followed by lower exposures beginning approximately 6 hours after dosing compared to 200 mg TDD of the twice-daily tablet (Figure 2). The Applicant performed additional PK simulations to support an intermediate dose, 210 mg of centanafadine ER capsule, which produced exposures higher during the first 8 hours followed by relatively similar exposures compared to those of 200 mg TDD of twice-daily tablet after the first dose and at steady state (Figure 3). Overall, the proposed dosage regimens (210 mg and 280 mg once daily) are acceptable for the treatment of adults with ADHD. Considering the dose dependent increase in skin rash, the clinical and clinical pharmacology review teams recommended 210 mg once daily as a starting dose. The dose may be increased to 280 mg once daily based on clinical response and tolerability.

Figure 1. Comparison of the Median PK Profiles Between the 280 mg Once-Daily (QD) Dose of Centanafadine ER Capsule and 200 mg and 400 mg TDD of Centanafadine Twice-Daily Tablet



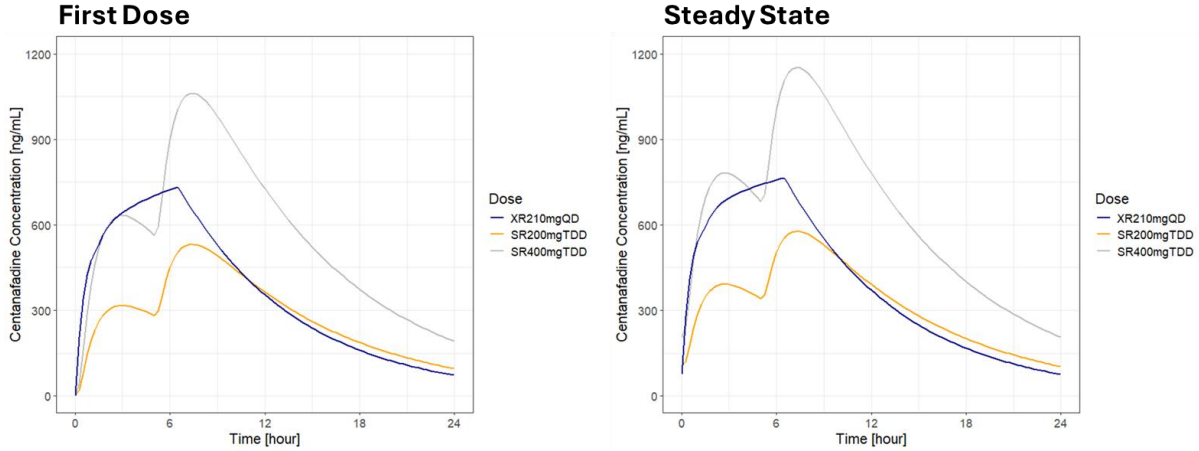
QD XR represents a once-daily extended release (ER) capsule formulation; SR represents a twice-daily sustained-release tablet formulation
TDD = Total daily dose
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Pharmacometrics reviewer's analysis

Figure 2. Comparison of the Median PK Profiles Between the 140 mg QD Dose of Centanafadine ER Capsule and 200 mg and 400 mg TDD of Centanafadine Twice-Daily Tablet



QD XR represents a once-daily extended release (ER) capsule formulation; SR represents a twice-daily sustained release tablet formulation
TDD = Total daily dose
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Pharmacometrics reviewer's analysis

Figure 3. Comparison of the Median PK Profiles Between the 210 mg QD Dose of Centanafadine ER Capsule And 200 mg and 400 mg TDD of Centanafadine Twice-Daily Tablet



QD XR represents a once-daily extended release (ER) capsule formulation; SR represents a twice-daily sustained release tablet formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
TDD = Total daily dose
Source: Pharmacometrics reviewer's analysis

Was the Final "To-Be-Marketed" (TBM) Formulation Used in the Clinical Efficacy/Safety Studies? If Not, Was an Appropriate PK-Bridging Established Between the Clinical and the TBM Formulation?

The adult efficacy trials were conducted with a twice-daily tablet formulation of centanafadine which was different from the once-daily extended-release capsule formulation. Therefore, a dedicated PK-bridging study was conducted to evaluate the scientific bridge between the formulations in a 4-sequence, 4-period design. The results from the PK bridging study demonstrated that the exposures (Cmax and AUCinf) were comparable between the formulations. The 90% confidence intervals (CIs) for the key PK parameters (i.e., Cmax and AUC) were between 0.8 and 1.25.

Although C_{max} and AUC_{inf} are similar between the formulations, the PK profiles of the once-daily ER capsule formulation were different from the twice-daily tablet formulation (Figure 2). The post-6 hour concentrations of the once-daily ER capsule are lower than those of the twice-daily tablet of centanafadine. As the systemic exposures of 280-mg once-daily ER capsule were within those observed for low-dose (200 mg TDD) and high-dose (400 mg TDD) twice-daily tablet, and both the low-dose and high-dose twice-daily tablet showed a flat dose/exposure-response relationship, the differences in the PK profiles are not expected to have an impact on the effectiveness of 280 mg once-daily ER capsule. Therefore, the scientific bridge between 280-mg once-daily ER capsule and high-dose twice-daily tablet is adequate. Given that the 140-mg once-daily ER capsule showed post-6-hour exposures lower than those of low-dose twice-daily tablet, the Applicant performed population PK simulations to support an intermediate dose (210-mg once-daily ER capsule) to achieve exposures within of those observed for low-dose and high-dose twice-daily tablet formulation (Figure 3). The proposed 210-mg once-daily ER capsule produced exposures higher during the first 8 hours followed by relatively similar exposures compared to those of the 200-mg twice-daily tablet TDD after the first dose and at steady state (Figure 3). Overall, the proposed dosage regimens (210 mg and 280 mg once daily) are acceptable for the treatment of adults with ADHD.

Given the dose-dependent increase in skin rash that was observed in the pivotal clinical efficacy and safety studies of centanafadine in adults with ADHD, the clinical and clinical pharmacology review teams recommended 210 mg once daily as a starting dose. The dose may be increased to 280 mg once daily based on clinical response and tolerability.

Table 9. Geometric Mean Ratios and 90% CI for the PK Parameters of the To-Be-Marketed Once-Daily Extended-Release Capsule Formulation of Centanafadine and Twice-Daily Tablet Formulation (Clinical Trial Formulation) of Centanafadine in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1 × 164.4 mg QD XR capsule (test) vs 200 mg TDD SR (reference)	C_{max}	24	0.882	0.8034, 0.9674
	AUC_t	24	0.883	0.8339, 0.9357
	AUC_∞	21	0.888	0.8398, 0.9383
1 × 328.8 mg QD XR capsule (test) vs 400 mg TDD SR (reference)	C_{max}	24	1.094	0.9528, 1.2566
	AUC_t	24	0.915	0.8680, 0.9654
	AUC_∞	21	0.924	0.8703, 0.9810

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval; SR = sustained-release; TDD = total daily dose.

QD XR represents a once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 77

The pediatric efficacy trials were conducted with once-daily ER capsule formulation, which was identical to the to-be-marketed once-daily ER capsule formulation with only a different (b) (4) talc (from a different lot) and no difference in any other key ingredients. However, a PK-bridging study (Study 405-201-00157) was conducted and it established a scientific bridge between the clinical trial formulation (once-daily ER capsule formulation) and to-be-marketed once-daily ER capsule formulation with super-imposable PK profiles. The geometric mean ratio was 1.09 and 1.05 for Cmax and AUCinf, respectively, with the 90% confidence interval between 1.0 and 1.1 for both (details are in section 19).

Table 10. Geometric Mean Ratios and 90% CI for the To-Be-Marketed Centanafadine Once-Daily ER Capsule Compared to the Clinical Trial Formulation (Once-Daily ER Capsules) in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1 × 164.4 mg To-Be-Marketed QD-XR capsule (test) vs Clinical QD XR Capsule (reference)	C_{max}	55	1.021	0.9622, 1.0843
	AUC_t	55	1.034	1.0031, 1.0651
	AUC_∞	43	1.034	0.9987, 1.0705
1 × 328.8 mg To-Be-Marketed QD XR capsule (test) vs 2 × 164.4 mg Clinical QD XR Capsule (reference)	C_{max}	53	1.099	1.0206, 1.1826
	AUC_t	53	1.043	1.0106, 1.0766
	AUC_∞	47	1.050	1.0143, 1.0860

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval.

QD XR represents a once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 80

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No dosage adjustment strategy is recommended for patient subpopulations with organ impairments (i.e., patients with mild (eGFR 60 to <90 mL/min/1.73m^2), moderate (eGFR 30 to <60 mL/min/1.73m^2) and severe renal impairment (eGFR <30 mL/min/1.73m^2) or patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment.

Study 00006 was a phase 1, open-label, multi-center, parallel-group trial designed to assess the PK, safety, and tolerability of oral centanafadine. The objective of this trial was to evaluate the PK of centanafadine in subjects with moderate hepatic impairment (Child-Pugh Class B), and subjects with severe renal impairment (eGFR< 30 mL/min/1.73m^2, and not undergoing dialysis; Chronic Kidney Disease Epidemiology Collaboration method) and comparing their PK to age-, weight-, and sex-matched subjects with normal hepatic and renal function.

The trial population of subjects were evaluated separately as follows:

- Moderate hepatic impairment
- Severe renal impairment
- Age-, weight-, and sex-matched control subjects with normal hepatic and renal function

In adults with moderate hepatic impairment (Child-Pugh Class B) total centanafadine exposures were lower (C_{max} reduced by 30% and AUC_{inf} reduced by 25%) compared to healthy matched adults. Similarly, in adults with severe renal impairment (eGFR <30

mL/min/1.73m^2 and not undergoing dialysis) total centanafadine exposures were lower (C_{max} reduced by 25% and AUC_{inf} reduced by 20%) compared to healthy matched adults.

Furthermore, on correction for the free drug concentrations, the unbound centanafadine $C_{max,u}$ and $AUC_{inf,u}$ were increased approximately 10% and 40% respectively, in subjects with severe renal impairment compared to subjects with normal renal function. Both $C_{max,u}$ and $AUC_{inf,u}$ were increased approximately 10% in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

Table 11. The Geometric Mean Ratios And 90% CI for the Unbound PK Parameters of Centanafadine in Subjects With Moderate Hepatic Impairment and Severe Renal Impairment Compared to Matched Healthy Subjects

Geometric Mean Ratios and 90% Confidence Intervals for Centanafadine Unbound Plasma Pharmacokinetic Parameters		
Parameter	Moderate Hepatic Impairment (N = 8)	Severe Renal Impairment (N = 8)
$C_{max,u}$	1.104 (0.808, 1.508)	1.265 (0.948, 1.689)
$AUC_{t,u}$	1.100 (0.725, 1.670)	1.404 (1.002, 1.967)
$AUC_{\infty,u}$	1.088 (0.736, 1.609)[a]	1.409 (1.006, 1.975)

[a]Ratio reported using data from 5 hepatic impairment and matched healthy subjects.
Source: Clinical Report Synopsis for Protocol 405-201-00006, Page 7

The exposure-response analysis for safety (i.e., skin rash and insomnia; Figure 45 and Figure 46) suggests that C_{max} is the significant predictor for safety and an approximately 27% increase in C_{max} is considered to be clinically not meaningful. Therefore, no dosage adjustment is recommended for patients with mild, moderate, and severe renal impairment or patients with mild and moderate hepatic impairment. As the PK of centanafadine in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied, centanafadine is not recommended in patients with severe hepatic impairment. A post-marketing requirement will be issued study to evaluate the effects of severe hepatic impairment on the PK of centanafadine to inform appropriate dosage recommendation and safe use of centanafadine in patients with severe hepatic impairment.

Are There Clinically Relevant Food-Drug Interactions, and What Is the Appropriate Management Strategy?

High-fat meal (HFM) had a relatively minor effect on the PK of centanafadine and, therefore, centanafadine can be administered without regard to food.

Study 405-201-00157 evaluated the single-dose relative bioavailability of the to-be-marketed centanafadine once-daily ER capsule administered following a HFM relative to fasted conditions in a 2-period randomized crossover design. Fourteen healthy adults were enrolled and randomized into two treatment sequences (fed state vs. fasted state) at the highest dose of 280 mg of centanafadine ER capsule. Administration with a HFM resulted in

a longer t_{max} (5.0-hours vs. 3.5-hours fasted) and increased C_{max} (~29% increase), while the overall exposure (AUC_{inf}) remained comparable.

Table 12. Geometric Mean Ratios and 90% CI for the To-Be-Marketed 280 mg Centanafadine ER Capsule Administered With a High-Fat Meal Compared to the Fasted State in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1×328.8 mg QD XR capsule following a HFM (test) vs fasted state (reference)	C_{max}	14	1.286	1.0976, 1.5056
	AUC_t	14	0.996	0.9240, 1.0730
	AUC_∞	12	0.965	0.8821, 1.0550

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval; HFM = high-fat meal.

QD XR represents a once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report for Protocol 405-201-00157, Page 75

Additionally, Study 405-201-00150, a single dose, open label, 4-treatment, 4-period crossover trial, evaluated the bioavailability of the high dose (280 mg) of the to-be-marketed ER capsule when sprinkled on apple sauce or yogurt, or mixed in orange juice, compared to an intact capsule in 24 healthy adults under fasted state. Sprinkling of centanafadine capsule contents over the soft foods resulted in no appreciable change in the PK of centanafadine (i.e., Cmax and AUCinf changes <20% compared to intact capsule). Therefore, the proposed product can be sprinkled over the soft foods prior to the administration.

Table 13. Geometric Mean Ratios and 90% CIs of PK Parameters of 328.8 mg Centanafadine Once-Daily ER Capsule When Administered Either as Intact Capsule or Sprinkling the Contents of Capsule on Applesauce, Yogurt, or Orange Juice

Comparisons	Parameter	N	Geometric Mean Ratios[a]	90% CI[a]
328.8 mg QD XR capsule sprinkled on applesauce (test) vs intact capsule (reference)	C_{max}	23	1.025	0.931, 1.129
	AUC_t	23	1.033	0.962, 1.110
	AUC_∞	18	1.012	0.933, 1.099
328.8 mg QD XR capsule sprinkled on yogurt (test) vs intact capsule (reference)	C_{max}	23	1.117	1.012, 1.231
	AUC_t	23	1.064	1.006, 1.126
	AUC_∞	16	1.054	0.994, 1.117
328.8 mg QD XR capsule sprinkled in orange juice (test) vs intact capsule (reference)	C_{max}	23	1.067	0.966, 1.178
	AUC_t	23	1.043	0.984, 1.106
	AUC_∞	20	1.026	0.968, 1.088

AUC_∞ = area under the concentration time curve from time zero to infinity; AUC_t = area under the concentration time curve calculated from time 0 to the time of the last observable concentration at time t; CI = confidence intervals; CTN = centanafadine; C_{max} = maximum (peak) plasma concentration of the drug; QD = once daily.

[a]Geometric mean ratio of parameter values following centanafadine QD XR administered sprinkled on applesauce, sprinkled on yogurt, or sprinkled in orange juice over centanafadine administered as an intact capsule in the fasted state. Geometric mean ratio reported using subjects with PK data available for the compared two treatments. Estimates are obtained by exponentiating means and 90% CI based on paired t-test.

QD XR represents a once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00150, Page 67

Both the pediatric efficacy studies (Studies 405 201 00016 and 405 201-00021), conducted with the ER capsule formulation, were also conducted without any restrictions on the type and timing of food.

Overall, considering the relatively minor effect of food on the PK of centanafadine, it is acceptable to administer centanafadine ER capsule without regard to food.

Are There Clinically Relevant Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

Based on the dedicated clinical drug-interaction studies (as an object), centanafadine is unlikely to have clinically relevant drug-interactions with co-administered drugs and thus requires no dose-adjustments. However, as a precipitant, centanafadine increased the systemic exposures of a CYP1A2 substrate, caffeine and thus requires dosage reduction of CYP1A2 substrates when concomitantly administered with centanafadine.

As an object: Study 405-201-00002, a phase 1, open-label, parallel-arm trial in 42 healthy adults, was conducted to evaluate the effect of CYP1A2 inhibition (by the moderate inhibitor ciprofloxacin), the effect of CYP2D6 inhibition (by the strong inhibitor quinidine),

and the effect of moderate CYP1A2 induction (by tobacco smoking) on centanafadine PK. The results indicate that neither of these pathways had any clinically relevant effect on the PK of centanafadine. Therefore, no dose-adjustment is required for centanafadine when concomitantly administered with CYP2D6 or CYP1A2 inhibitors.

Table 14. Geometric Mean Ratios and 90% Confidence Interval for Centanafadine Plasma Pharmacokinetic Parameters in Presence Of CYP1A2 Inhibitor, CYP2D6 Inhibitor & CYP1A2 Inducer

Inhibitor/Inducer	CYP Enzyme	C_{max}	AUC_t	AUC_∞
Ciprofloxacin	CYP1A2 inhibitor	1.101 (0.927, 1.308)	1.124 (1.033, 1.224)	1.115[a] (1.007, 1.235)
Quinidine	CYP2D6 inhibitor	1.271 (1.104, 1.463)	1.173 (1.090, 1.262)	1.189[b] (1.122, 1.260)
Smoking[c]	CYP1A2 inducer	0.935[d] (0.740, 1.183)	0.845[d] (0.711, 1.003)	0.942[e] (0.764, 1.160)

AUC_t: area under the concentration time curve from time 0 to the time of the last measurable concentrations; AUC_∞: area under the concentration time curve from time 0 to infinity; C_{max}: maximal peak plasma concentrations

Note: Geometric mean ratio of parameter values following centanafadine+ Inhibitor/Inducer over centanafadine alone. Geometric mean ratio reported using participants with data in both periods.

[a]Geometric mean ratio reported from 10 participants with data in both periods.

[b]Geometric mean ratio reported from 11 participants with data in both periods.

[c]Geometric mean ratio reported from a cross-arm comparison.

[d]10 smokers and 24 non-smokers.

[e]6 smokers and 22 non-smokers.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 50

As a precipitant: Study 405-201-00002 also evaluated the potential for centanafadine to inhibit or induce CYP1A2 (using caffeine as a sensitive substrate of CYP1A2). Consistent with the in vitro data, centanafadine inhibited the CYP1A2 pathway and increased the AUC_{inf} of caffeine by ~2-fold. However, there was no increase in the C_{max} of caffeine observed. Therefore, monitoring for adverse reactions and considering dosage reduction of the concomitantly used CYP1A2 substrate when concomitantly administered with centanafadine.

Table 15. Geometric Mean Ratios and 90% Confidence Intervals for Caffeine Plasma Pharmacokinetic Parameters With or Without Centanafadine

Day	CYP Substrate	CYP Enzyme	C_{max}	AUC_t	AUC_∞
3	Caffeine	CYP1A2	1.060 (0.995, 1.129)	2.059 (1.893, 2.241)	2.328[a] (2.154, 2.515)
7	Caffeine	CYP1A2	1.093[b] (1.018, 1.174)	1.993[b] (1.819, 2.184)	2.126[b] (1.941, 2.328)

Note: Geometric mean ratio of parameter values following centanafadine+ caffeine over caffeine alone.

[a]Geometric mean ratio reported from 12 subjects (Day 1) and 11 subjects (Day 3).

[b]Geometric mean ratio reported from 9 subjects.

Source: Clinical Study Report 405-201-00002, Page 75

Were There Any QT Prolongation Observed at the Highest Therapeutic Dose or Supratherapeutic Dose?

No significant QTc prolongation effect of centanafadine was detected in the dedicated thorough QT assessment**.** The effect of centanafadine was evaluated in the thorough QT Study 405-201-00001. The highest dose evaluated was 800 mg TDD administered as 400 mg in the morning followed by 400 mg 5 hours later. This dosing regimen provided a 2-fold coverage for the maximum proposed therapeutic dose (280 mg QD-ER, TBM formulation) and an adequate coverage over the highest exposure scenario due to organ impairment (~40% increase in subjects with severe renal impairment). Additionally, the exposure-response analysis did not show a significant QTc prolongation effect (refer to the QT assessment review for centanafadine under IND 119361 from the Cardiac Safety – Integrated Review Team (CS-IRT) archived on May 4, 2020, and the Cardiac Safety IRT Review Memo archived on January 29, 2026, for details).

Was a Validated Bioanalytical Method Established and Utilized for All the Clinical Sample Analysis?

Yes, plasma concentrations of centanafadine and EB-10601 (primary metabolite, pharmacologically inactive) were quantified using a validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) method (Report # (b) (4)-1909-01) and protein precipitation extraction from dipotassium ethylene diamine tetraacetic acid (K2EDTA). Calibration curves ranged from 5.00 to 1500 ng/mL using weighted ($1/x^2$) linear regression of peak area ratios of analyte-to-internal standard over a range of 5.00 ng/mL to 1500 ng/mL. Quality control (QC) samples at three concentrations, as well as the lower limit of quantitation (LLOQ; 5.00 ng/mL) were used to validate the assay. Additionally, to confirm the method reliability and reproducibility, some incurred samples were re-analyzed using the same protocol in separate analytical runs. The reanalysis variability was expressed using the mean of the original and repeat values and were within the acceptance criteria.

The bioanalytical methods satisfied the criteria for “method validation” and “application to routine analysis” set by the guidance for industry, *Bioanalytical Method Development,* and is acceptable.

Does Centanafadine Exert Dose-Proportional PK Characteristics?

No. Following single-dose and multiple-dose (i.e., at steady-state) administration, the exposure parameters (C_{max} and AUC) increased in slightly greater than dose-proportional manner for a dose range of 140 mg to 280 mg centanafadine ER capsule.

Figure 4. Dose Proportionality of 140 mg, 210 mg and 280 mg Centanafadine ER Capsule in Healthy Adults

Parameters (Units)	Estimated Slope (90% CI)
$C_{ss,max}$ (ng/mL)	1.2346 (1.0457, 1.4235)
AUC_τ (ng h/mL)	1.2382 (1.0687, 1.4076)

AUCτ = area under the concentration time curve during the dosing interval at steady state;

$C_{ss,max}$ = maximal peak plasma concentrations at steady state; CI = confidence interval.

Source: Clinical Pharmacology Summary Aid, Page 32

Was the Single And Multiple-Dose PK for Centanafadine ER Capsule Adequately Characterized in Adults?

Yes, dedicated single and multiple-dose PK studies adequately characterized the PK of centanafadine. The PK characteristics remained unchanged from single dose to steady-state. The key PK parameters are listed below.

Table 16. Summary of Single and Multiple Dose PK Parameters for Centanafadine ER Capsule in Adults

Parameter	Single Dose 164.4 to 328.8 mg (% CV range)	Source	Multiple Dose (164.4mg to 328.8 mg)[b] % CV range	Source
C_{max} (ng/mL)	564 - 1380 (32.6 - 40.7%)	405-201-00047 405-102-00074 405-201-00150 405-201-00154 405-201-00157	569 - 1510 (27.5 - 34.7%)	405-201-00154 405-201-00157
AUC (h·ng/mL)[a]	6220 - 14100 (24.6 - 31.0%)		5490 - 14000 (24.6 - 29.9%)	
t_{max} (h)	4.00 - 6.00		4.50 - 6.00	
$t_{1/2,z}$ (h)	6.1 - 6.4 (35.7 - 45.8%)		4.9 - 5.7 (34.1 - 46.3%)	
CL/F (mL/min)	380 - 428 (23.7 - 35.6%)		359 - 449 (24.0 - 26.1%)	

AUC_∞ = area under the plasma concentration time curve from time zero to infinity; C_{max} = maximum (or peak) plasma concentration; CL/F = apparent clearance of drug from plasma after extravascular administration; t_{max} = time to maximum (peak) plasma concentration (C_{max}); $t_{1/2,z}$ = terminal-phase elimination half-life.

[a] AUC_∞ is presented for single dose and AUC_τ for multiple dose.

[b] To-be-marketed QD XR results only are presented for multiple dose.

QD XR represents a once-daily extended release (ER) capsule formulation

Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.

Source: Clinical Pharmacology Summary, Page-23

Was the PK of Centanafadine ER Capsule Adequately Characterized in Children (Ages 4 to 12)?

Yes, dedicated single and multiple-dose PK studies adequately characterized the PK of centanafadine ER capsule in pediatric subjects (4 to 12 years old). The PK characteristics remained unchanged from single dose to steady-state. The comparison of the key PK parameters observed in pediatric subjects administered a dose targeting 400 mg Adult Equivalent Dose (AED) of twice-daily tablet alongside corresponding PK parameters in adults

at 280 mg ER capsule (i.e., equivalent to 328.8 mg hydrochloride salt) and 400 mg TDD of the twice-daily tablet in adults with ADHD is shown in Table 17. Overall, the PK profiles at the high doses are relatively similar between pediatric subjects and adults receiving the ER capsule, as well as between adults receiving a 400 mg TDD of the twice-daily tablet.

Table 17. Centanafadine Plasma Pharmacokinetic Parameters Following Multiple Oral Doses of 400 mg Adult Equivalent Dose of QD ER (in Children 4-12 Years) as Compared to 328.8 mg QD ER in Adults

Parameter	400 mg AED			328.8 mg
	4-to-5-year olds[a] (n=5)	6-to-8-year olds[a] (n=8)	9-to-12-year olds[b] (n=10)	Adults[b] (n=40)
C_{max} (ng/mL)	1590 (910)	1790 (689)	1840 (993)	1510 (525)
t_{max} (h)	6.00 (2.00-6.00)	4.00 (3.00-6.00)	6.00 (3.00-12.00)	5.0 (0.50-10.00)
AUC_{0-24h} (ng·h/mL)	19300 (10200)	18800 (6740)	21700 (6760)	14000 (4190)
$t_{1/2,z}$	3.8 (1.0)[c]	4.2 (1.5)	4.2 (1.8)	5.2 (2.4)
CL/F	400 (257)	347 (152)	300 (150)	359 (93.2)
$R_{ac}C_{max}$	0.95 (0.3)	1.84 (1.13)	1.23 (0.64)	NA
$R_{ac}AUC_{0-24h}$	1.83 (0.69)	1.61 (0.58)	1.39 (0.29)	NA
$R_{ac}C_{24h}$	4.90 (5.49)	1.44 (1.65)	1.19 (0.80)	NA

AED : adult equivalent dose; AUC_{0-24h} : area under the concentration time curve from 0 to 24 hours C_{max} : maximal (peak) plasma concentration; CL/F : apparent clearance from plasma following extravascular administration; CI : confidence interval; NA : not applicable; t_{max} : time to maximum (peak) concentrations; $t_{1/2,z}$: terminal phase elimination half life; R_{ac} : accumulation ratio

[c] n=4

a = Data from clinical study report 405-201-00046

b= Data from clinical studies 405-201-00154 and 405-201-00157

QD XR represents a once-daily extended release (ER) capsule formulation

Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.

Source: Summary of Clinical Pharmacology Studies, Table 1.2.2.6-2, Page 44

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

This 505(b)(1) NDA consists of six main studies: four randomized, placebo-controlled studies and two open label extension studies. See Table 18 for a description of each study.

Table 18. Listing of Clinical Trials Relevant to This NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
405-201-00013		Double-blind, randomized, placebo controlled, parallel-group	• Centanafadine twice-daily tablets (200 mg TDD) • Centanafadine twice-daily tablets (400 mg TDD) • Placebo BID	• AISRS at Day 42 • CGI-S at Day 42	6 weeks	466	Adults with ADHD	45 U.S. sites
405-201-00014		Double-blind, randomized, placebo controlled, parallel-group	• Centanafadine twice-daily tablets (200 mg TDD) • Centanafadine twice-daily tablets (400 mg TDD) • Placebo BID	• AISRS at Day 42 • CGI-S at Day 42	6 weeks	440	Adults with ADHD	48 U.S. sites
405-201-00016		Double-blind, randomized, placebo controlled, parallel-group	• Centanafadine ER 140 mg • Centanafadine ER 280 mg • Placebo	• ADHD-RS-5 • CGI-S-ADHD • Conners 3 Parent Short	6 weeks	459	Pediatric subjects 13 to 17 years with ADHD	47 U.S. sites 1 site in Canada
405-201-00021		Double-blind, randomized, placebo controlled, parallel-group	Cohort 1: • Weight-based low dose centanafadine ER • Weight-based high dose centanafadine ER • Placebo	• ADHD-RS-5 • CGI-S-ADHD • Conners 3 Parent Short	6 weeks	Cohort 1 (6 to 12): 480 Cohort 2 (4 to 5): 94	Pediatric subjects 4 to 12 years with ADHD	Cohort 1: 58 sites, 1 site in Canada and 57 U.S. sites Cohort 2: 23 U.S. sites

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
405-201-00017		Open label	Ages 4 to 12 years (centanafadine dose by weight): • >20 to 35 kg 140 mg ER • 35 to 50 kg 210 mg ER • > 50 kg 328.8 mg ER Ages 13 to 17 years: 280 mg centanafadine ER	Safety	52 weeks	680	Pediatric subjects 4 to 18 years of age with ADHD	74 U.S. sites and 1 in Canada
405-201-00015		Open label	• Centanafadine twice-daily tablets (400 mg TDD)	Safety	52 weeks	662	Adults with ADHD	98 U.S. sites
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
405-201-00198		Randomized, single blind, parallel arm, single-dose crossover	• Centanafadine ER 280 mg • Methylphenidate 36 mg • Lisdexamfetamine 50 mg • Centanafadine ER 280 mg + Methylphenidate 36 mg • Centanafadine ER 280 mg + Lisdexamfetamine 50 mg	PK, Safety	Single dose	40	Male and female healthy participants	Single site

AISRS=Adult ADHD Investigator Symptom Rating Scale; CGI-S=Clinical Global Impression-Severity; ADHD=Attention Deficit Hyperactivity Disorder; ADHD-RS-5=ADHD Rating Scale 5
Source: Reviewer-generated. Adapted from Clinical Study reports

6.2. Review Strategy

The Applicant submitted 39 studies that were conducted as part of the drug development program for centanafadine. The review team considered the potential contribution of each submitted study to the overall approach to the efficacy and safety. Table 18 above tabulates the studies included in the review of efficacy and safety.

Studies 13, 14, 16, and 21 are considered the primary studies for efficacy because they were large, randomized, double-blind, placebo-controlled studies conducted in the population of interest (ADHD). The safety data from these studies in addition to the results from the 52-week open label extension studies, 15 and 17, were considered for the safety review.

The Applicant submitted two phase 2 studies in the centanafadine drug development program: EB-1020-SR-ADHD-201 and NVI-EB-1020-202. These studies were not considered to be pivotal studies supporting the efficacy or safety of centanafadine, as they were exploratory in nature.

The remaining studies were phase 1 studies designed to examine PD, PK, and the safety and tolerability of centanafadine in subjects with ADHD and in special safety populations and healthy volunteers. Phase 1 studies were considered as part of the safety review, when relevant. In particular, Study 405-201-00198 was reviewed for safety findings related to blood pressure and heart rate and to assess the risk of coadministration of centanafadine ER capsules with other CNS stimulants.

We reviewed the Applicant's analyses for the efficacy and safety review. The FDA statistical and clinical review teams conducted independent analyses of the Applicant's submitted data to confirm and supplement the Applicant's analyses, as appropriate.

7. Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

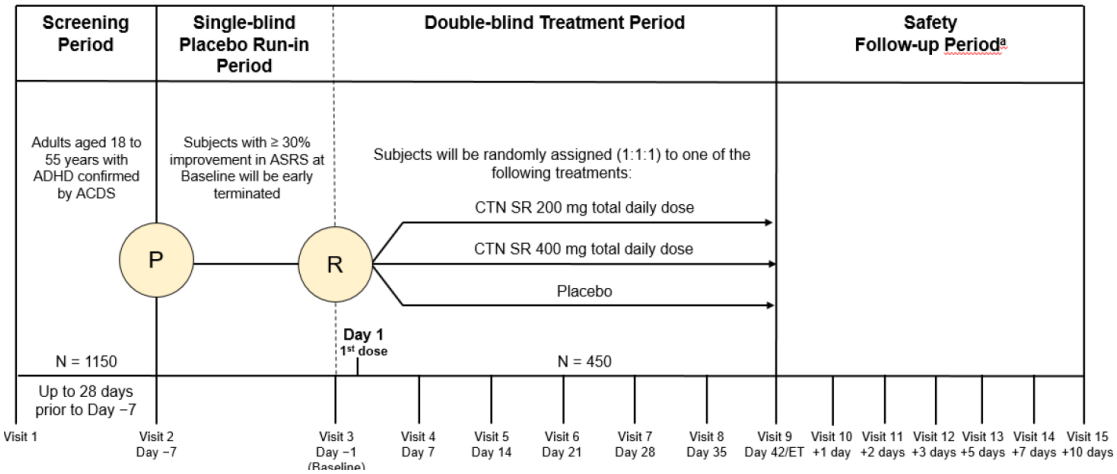
7.1.1. 405-201-00013

7.1.1.1. Trial Design

The primary objective of Study 13 was to evaluate the efficacy of a twice-daily tablet formulation of centanafadine, referred to by the Applicant as "centanafadine SR tablets." The study compared 200 mg or 400 mg TDD to placebo.

Study 13 was a 6-week, multicenter, randomized, double-blind, placebo controlled, parallel-group study in 604 male or female subjects ages 18 to 55 years with ADHD. The study had four periods: screening and washout, 1 week single-blind placebo run-in, 6-week double blind treatment, and 7-day follow-up period. The study design is presented in Figure 5. The study was conducted at 45 sites in the United States.

Figure 5. 405-201-00013 Trial Design Schematic



CTN SR = centanafadine twice-daily sustained release tablets; ET = early termination; P = placebo administration; R = randomization.
[a]All subjects were required to participate in the 7-day follow-up period (follow-up telephone calls at 1, 3, and 5 days after the last dose of study drug, and in-clinic follow-up visits at 2 and 7 days after the last dose of study drug). Subjects who terminated early, decided to not enroll in an open label safety extension study (Trial 405-201-00015), or who were not eligible, were required to participate in an additional follow-up telephone call 10 days after the last dose.
Source: Applicant's Figure 9.1-1, Clinical Study Report 405-201-00013

Individuals 18 to 55 years of age with a current primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, or combined presentations) were eligible to enroll. Those who were not receiving any pharmacological treatment for ADHD had to have an AISRS score of ≥28 at screening. Subjects who were

receiving pharmacological treatment for ADHD at screening had to have an AISRS score of ≥22 at screening. Subjects who were receiving pharmacological treatment for ADHD at Screening were required to have a minimum AISRS score of ≥28 at Baseline (after washout). The AISRS is an 18-item clinical outcome assessment that measures symptoms of inattention, hyperactivity, and impulsivity. Higher scores indicate greater severity of ADHD symptoms. The AISRS contains prompts that refer to adult activities (e.g., ability to remain in seat during meetings, ability to remember appointments and obligations, losing items at work). All subjects were required to have a CGI-S score of ≥4 (≥ moderate impairment) at Baseline. The CGI-S is a clinician-reported, single-item assessment of the severity of a patient's symptoms. Possible responses on the CGI-S are 1=Not at all ill, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=extremely ill.

Key exclusion criteria were:

- Subject had a DSM-5 diagnosis of Other Specified or Unspecified Attention Deficit/Hyperactivity Disorder.
- Subject had initiated, changed, or discontinued receiving psychological interventions (e.g., supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) for ADHD within the 60 days before the screening visit, or were anticipated to start new treatment during the trial. Subjects receiving psychotherapy that was initiated > 60 days before the screening visit were allowed to continue to receive their psychotherapy during the trial only if they agreed to not make any changes in the frequency or nature of their psychotherapy during the course of the trial.
- Subject had a lifetime history of electroconvulsive therapy, or a lifetime history of vagal nerve stimulation or deep brain stimulation for the treatment of depression.
- Subject had a current comorbid psychiatric disorder that either could be expected to require treatment with medications prohibited in the trial, or to confound efficacy or safety assessments (e.g., psychotic disorder (current or lifetime), bipolar disorder (current or lifetime), generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, a current major depressive episode, or posttraumatic stress disorder, as established by the Mini International Neuropsychiatric Interview (MINI)).
- Subjects with a clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, histrionic, narcissistic, avoidant, or dependent personality disorders.
- Subjects who met criteria for Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Items 4 or 5 within the last 6 months prior to screening or subjects who met criteria for any of the five Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) and whose most recent episode meeting criteria for any of these items occurred within the last 2 years prior to screening.
- Subjects who, in the opinion of the investigator, presented a serious risk of suicide.
- Subjects with a history of epilepsy, seizures (other than infantile febrile seizures), syncope, Tourette's disorder, serious neurological disease, history of significant head trauma with clinically significant loss of consciousness, dementia, cerebrovascular

disease, Parkinson's disease, or intracranial lesions.

- Subject had a lifetime history of a pattern of abuse or diversion of stimulants.
- Subject had any current or suspected drug or alcohol use disorder. Subject had met the DSM-5 criteria for a substance use disorder in the past 6 months. Nicotine use disorder was not exclusionary.
- Subjects with a positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (excluding marijuana). Subjects with a positive drug screen for confirmed prescription or over-the-counter (OTC) use of ADHD medications at screening were required to undergo a washout period.
- Subjects who tested positive for marijuana could be enrolled if they had no evidence of a substance use disorder, and if they agreed to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening required explicit approval from the medical monitor.
- Subjects presenting with, or having a history of systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg or symptomatic hypotension, or orthostatic hypotension, defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared with the previous supine blood pressure, OR development of symptoms.
- Subjects with known ischemic heart disease or history of myocardial infarction, congestive heart failure, angioplasty, stenting, coronary artery bypass surgery, or other serious cardiac problems that would place him/her at increased vulnerability to the sympathomimetic effects of a stimulant medication.
- Subjects with history of dermatologic adverse reactions or anaphylaxis secondary to drug exposure.
- In the opinion of the investigator, subject had not derived significant therapeutic benefit from 2 or more ADHD therapies of 2 different classes (e.g., amphetamine and methylphenidate, or amphetamine and atomoxetine) given with an acceptable dose and duration during adulthood (aged 18 years or older). If subject had not derived significant therapeutic benefit due to an inability to tolerate side effects, eligibility could be discussed on case-by-case basis with the medical monitor.

Exclusion Criteria Assessed Prior to Start of the Single-Blind Placebo Run-in

- Subjects with a positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (including marijuana), or a positive drug screen for confirmed prescription or OTC use of ADHD medications were screen failed.
- Subjects with a ≥30% improvement in the (18-item) ADHD Symptoms score of the AISRS compared to the score at screening were screen failed, and not eligible for rescreening.

Exclusion Criteria Assessed at Baseline

- Subjects with a positive alcohol test (via breathalyzer or blood), a positive drug screen for cocaine, or other illicit drugs (including marijuana), or a positive drug screen for confirmed prescription or OTC use of ADHD medications would be early terminated.

- Subjects with a ≥ 30% improvement in the (18-item) ADHD Symptoms score of the AISRS compared to the score at the start of single-blind placebo run-in would be early terminated.
- In the opinion of the investigator, subject unable to adhere to the treatment regimen or other requirements outlined in the protocol.

Treatment was assigned via a computer-generated randomization code provided by the Applicant's Biometrics Department. Applicant personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial. The bioanalytical laboratory was also sent the randomization code. Access to the treatment codes were restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, operating the electronic Case Report Form (eCRF), and reporting SAEs to regulatory agencies. Randomization was stratified by trial site and designed to allocate subjects in a 1:1:1 ratio to centanafadine tablets TDD of 200 mg/day or 400 mg/day or placebo.

Treatment discontinuations could be initiated for withdrawal of informed consent, adverse effect, death, lost to follow-up, rash (regardless of severity or seriousness), pregnancy, or other personal reasons. The trial employed an adherence monitoring platform for all subjects in the trial. The platform used artificial intelligence on smartphones to attempt to confirm investigational medical product (IMP) ingestion. In addition, built-in reminders and a communication system may have allowed real time intervention in case of IMP interruptions. Use of the platform was required for all subjects in the trial. The monitoring platform required that all subjects take each dose of the IMP while using a smartphone. The platform was provided to subjects preloaded on a smartphone, or subjects downloaded the platform onto their own mobile device at the start of the single-blind placebo run-in period (Day -7).

No dietary restrictions were required. As noted above, any medications subjects were taking for ADHD were washed out before the start of the single-blind placebo run-in period (Day -7). The required duration of washout for selected prohibited medications is listed in Table 19. All other prohibited medications were required to be discontinued at least 24 hours before Day -7. Table 20 lists medications prohibited during the trial.

Table 19. List of Medications Prohibited Before the Trial 405-201-00013

Medication		Required Washout Prior to Start of Placebo Run-in Period
1.	Antidepressants Fluoxetine All other antidepressants	 28 days 14 days
2.	Benzodiazepines	7 days
3.	Hypnotics, including non-benzodiazepine sleep aids	7 days
4.	CYP2B6 inhibitors, CYP2D6 inhibitors, CYP2D6 substrates with a narrow therapeutic index, and CYP3A4 inhibitors and inducers	14 days
5.	ADHD medications Stimulants Nonstimulants	 7 days 21 days
6.	Sedating antihistamines (e.g., diphenhydramine, hydroxyzine, chlorpheniramine)	7 days
7.	Antihypertensives Clonidine Propranolol Guanfacine	21 days
8.	Anorexics (weight loss supplements)	7 days
9.	Investigational compounds	7 days

Source: Protocol 405-201-00013 Table 4.1-1

Table 20. List of Medications Prohibited During the Trial 405-201-00013

1.	All psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot formulations b) Anticonvulsants c) Antidepressants d) Mood stabilizers (i.e., lithium) e) Benzodiazepines[a] f) Hypnotics g) All medications intended for the treatment or management of ADHD symptoms (on or off label use), including but not limited to any form of: amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, and methylphenidate h) Opioid analgesics, unless permission is obtained from the medical monitor. Permission for opioid use may be considered for a documented and clinically appropriate indication (e.g., episodic pain condition, tooth extraction) if prescribed at a medically appropriate dose and frequency. i) Nutritional supplements and non-prescription herbal preparations with central nervous system effects (e.g., St. John's Wort, omega-3 fatty acids, melatonin, kava extracts, GABA supplements, etc.) j) Sedating antihistamines (e.g., diphenhydramine, hydroxyzine, chlorpheniramine)
2.	Investigational agents

3.	CYP2B6 inhibitors, CYP2D6 inhibitors, CYP2D6 substrates with a narrow therapeutic index, or CYP3A4 inhibitors and inducers. Selected CYP2B6 inhibitor is: ticlopidine. Selected CYP2D6 inhibitors are: celecoxib, hydroxyzine, chloroquine, methadone, chlorpheniramine, moclobemide, clemastine, paroxetine, clomipramine, pyrilamine, diphenhydramine, quinidine, fluoxetine, terbinafine, halofantrine, tripelennamine. Selected CYP2D6 substrates with a narrow therapeutic index are: thioridazine, pimozide, desipramine, eliglustat, metoprolol, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine, amitriptyline, encainide, imipramine, propafenone, propranolol, tramadol, trimipramine. Selected CYP3A4 inhibitors are: amiodarone, fluvoxamine, amprenavir, indinavir, aprepitant, itraconazole, chloramphenicol, ketoconazole, cimetidine, nefazodone, clarithromycin, nelfinavir, clotrimazole (if used orally), quinupristin/dalfopristin, delavirdine, ritonavir, diltiazem, saquinavir, erythromycin, troleandomycin, fluconazole, verapamil. Selected CYP3A4 inducers are: carbamazepine, oxcarbazepine, phenytoin, dexamethasone, primidone, efavirenz, rifampin, nevirapine, St. John's Wort, phenobarbitol, troglitazone. The medical monitor should be consulted for any questions regarding the potential for PK interactions with concomitant medications used by subjects during the trial.
4.	Barbiturates, except for the treatment of migraine headaches, provided that in the opinion of the investigator the dosing is medically appropriate.
5.	The following antihypertensive medications: propranolol, clonidine, guanfacine
6.	Varenicline or similar medications, excluding nicotine replacement products
7.	Anorexics (weight loss supplements)

[a] Non-benzodiazepine sleep aids (i.e., zolpidem, zaleplon, zopiclone, and eszopiclone only) were permitted for the treatment of insomnia AEs.
Source: Protocol 405-201-00013 Table 4.1-2

The investigational study drug (centanafadine tablets or placebo) was administered twice daily. Treatment could be administered with or without food. Subjects randomized to receive the target TDD of 200 mg centanafadine tablets were started at the target dose on Day 1 of the double-blind treatment period and remained there for the duration of the trial. Subjects randomized to receive a TDD of 400 mg received a TDD of 200 mg on Day 1 of the double-blind treatment period for 7 days before escalating to their target TDD of 400 mg on Day 8. Subjects were instructed to take the first dose at approximately the same time each day, and the second dose 4 to 6 hours after the morning dose.

7.1.1.2. Study Endpoints

The primary efficacy endpoint was the change from Baseline at Day 42 in the AISRS total score.

The key secondary efficacy endpoint was change from Baseline at Day 42 on the CGI-S.

Other efficacy endpoints were:

- Change from baseline in AISRS total score for every scheduled visit;
- Change from baseline in the Inattentive subscale and Hyperactivity-Impulsive subscale scores of the AISRS for every scheduled visit;
- Change from baseline in CGI-S score for every scheduled visit;
- CGI-S change from Baseline score at each scheduled visit;
- Percentage of responders at each post-baseline visit, where a responder was defined as

a subject with a CGI-S change from baseline score of 1 or 2 OR a ≥ 30% improvement in ADHD symptoms compared with baseline as measured by the AISRS total score.

The safety endpoints were adverse events (AEs) including evaluations for rash (an AE of special interest (AESI)), clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital sign measurements, electrocardiograms (ECGs), assessments of withdrawal (Study Medication Withdrawal Questionnaire or SMWQ), and suicidal ideation and behavior (C-SSRS). Abuse-related AEs and AEs involving medication handling irregularities were recorded verbatim on source documentation with detailed narratives.

Table 21 summarizes the schedule of assessment activities in the study. Physical examinations, ECGs, and laboratory assessments were conducted at screening and at end-of-study. Vital sign monitoring, AE tracking, and monitoring for SI/B (using the C-SSRS) were performed at every visit.

Table 21. Schedule of Assessments 405-201-00013

	Screening[a]	PBO Run-in[b]	Double-blind Treatment							Follow-up[c]		
Period	Days −35 to −8	Day −7 ±2 Days	Baseline Day −1 ±2 Days	Day 7 +1 Day	Day 14 ±2 Days	Day 21 ±2 Days	Day 28 ±2 Days	Day 35 ±2 Days	Day 42/ET ±2 Days	Day 44 +1 Day	Day 49 ±2 Days	Day 56 ±2 Days
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed consent	X											
Inclusion/exclusion criteria	X	X	X									
Demography	X											
Concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X	X									
ACDS	X											
Identification of comorbidities using MINI	X											
Psychiatric evaluation	X											
HIV/HBsAg/anti-HCV	X											
Randomization			X									
Urine pregnancy test	X	X	X	X	X	X	X	X	X			
AISRS	X	X	X	X	X	X	X	X	X	X	X	
CGI-S			X	X	X	X	X	X	X			
CGI Change from Baseline				X	X	X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X					X			X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X	X	X		X		X			
Clinical laboratory tests	X	X	X		X				X			
SMWQ								X	X	X	X	X

Period	Screening[a]	PBO Run-in	Double-blind Treatment							Follow-up[b]		
	Days −35 to −8	Day −7 ±2 Days	Baseline Day −1 ±2 *Days	Day 7 +1 Day	Day 14 ±2 Days	Day 21 ±2 Days	Day 28 ±2 Days	Day 35 ±2 Days	Day 42/ET ±2 Days	Day 44 +1 Day	Day 49 ±2 Days	Day 56 ±2 Days
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
UDS/alcohol testing via breathalyzer or blood	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	
PK blood sample				X	X		X		X		X	
Pharmacogenomic and FBR samples			X									
AIM-A		X	X				X		X			
ASRS	X	X	X				X		X			
IMP/placebo dispensing		X	X	X	X	X	X	X				
IMP/placebo return and accountability			X	X	X	X	X	X	X			

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

[a] Screening included a washout period that could range from 7 to 28 days

[b] Completers enrolling in Trial 405-201-00015 had in-clinic follow-up visits at 2 and 7 days after the last dose of IMP before moving over to Trial 405-201-00015. Completers not enrolling in Trial 405-201-00015 or non-completers had in-clinic follow-up visits at 2 and 7 days after the last dose of IMP, and a follow-up phone call 14 days (Visit 12) after the last dose of IMP to assess any withdrawal symptoms (SMWQ), AEs, and changes in concomitant medications.

Source: Protocol 405-201-00013 Table 3.7-1

7.1.1.3. Statistical Analysis Plan

Analysis Populations

- Randomized Sample: All subjects who were randomized in the double-blind treatment period; that is, subject was assigned a treatment group by eSource at the end of the single-blind placebo run-in period. A subject receiving IMP outside of eSource will not be considered randomized, but safety will be reported.
- Safety Sample: All randomized subjects in the double-blind treatment period who received at least one dose of double-blind IMP as indicated on the dosing record. Subjects will be excluded from the safety sample only if there is documented evidence (for example, drug dispensed = drug returned or no IMP dispensed) that the subject did not take IMP. If a subject is dispensed IMP and is lost to follow-up, the subject will be considered to be exposed.
- Efficacy Sample: The full analysis set (FAS), which included all subjects in the safety analysis set, that is who were randomized in the double-blind treatment period and who received at least one dose of double-blind IMP as indicated on the dosing record, and have at least one valid post-randomization efficacy evaluation for AISRS total score within the double-blind treatment period.
- Per Protocol Sample: Subjects in the Efficacy Sample who complete at least the first 2 weeks of double-blind medication ((last day of IMP - first day of IMP + 1) ≥14 days) and have at least one post baseline AISRS measurement on or after Day 14 visit during the double-blind treatment period without major protocol violations deemed by the Applicant to comprise the assessment of efficacy. These major protocol violations include:
    - Subjects who were <80% or >120% compliant with double-blind IMP or missed 7 or more consecutive days of dosing immediately prior to the Day 42/ET AISRS measurement date during the double-blind treatment period according to the subject-reported eCRF compliance data.
    - Subjects who reported concomitant medication use that will impact the primary efficacy endpoint.
    - Subjects who had a major protocol deviation as reported on the protocol deviation eCRF page that will impact the primary efficacy endpoint.
    - Subjects who took the wrong treatment.

Sample Size

For the primary efficacy endpoint of change from baseline to Day 42 in adult ADHD AISRS total score, a sample size of 405 evaluable subjects (135 per treatment arm for each of the centanafadine doses and placebo) was determined to yield at least 90% power to detect a treatment effect at two-tailed alpha of 5%. The sample size was planned based on the results from phase 2 centanafadine trials, with an expected treatment effect of 5 points and standard deviation of 12.5 for mean change from baseline to Day 42 on AISRS total score. The sample size was calculated by the sponsor using PASS 14 (2015) statistical computing

software. Allowing for 10% of subjects to be non-evaluable, the study planned to randomize 450 subjects (150 per treatment arm).

Primary Estimand

The Applicant prespecified the intercurrent event (ICE) of premature treatment discontinuation and proposed handling this ICE with a hypothetical strategy to estimate what the treatment effect would have been if subjects adhered to the treatment by assuming that data arise from a missing at random (MAR) mechanism.

Primary Efficacy Analysis

The primary efficacy outcomes were evaluated using a Mixed-Effect Model for Repeated Measures (MMRM) approach, the model included fixed effect terms for treatment, study center, visit day, and an interaction term of treatment-by-visit day and an interaction term of baseline value AISRS Total score for the double-blind treatment period by visit as a covariate. The parameter calculations assumed that missing data occurred at random and employed restrictive maximum likelihood (REML) estimation methods. To account for correlations within individual subjects, an unstructured variance-covariance matrix as implemented. The Kenward-Roger method was applied to calculate the appropriate denominator degrees of freedom. If the model failed to converge with the unstructured variance-covariance matrix, the following structures other than unstructured were to be used in the following order: 1) heterogenous toeplitz (TOEPH), heterogenous autroregressive of order 1 (AARH1) and heterogenous compound symmetry (CSH). If a structured covariance structure had to be used, the empirical “sandwich” estimator of the standard error of the fixed effects parameters.

Sensitivity Analyses

The Applicant conducted several sensitivity analyses to assess the impact of missing data.

The Applicant conducted the following analyses to assess the sensitivity of the missing at random assumption on the analysis of the primary endpoint. Pattern Mixture Models (PMM) based on Multiple Imputation (MI) were used to explore mixed missing data mechanisms MNAR and/or MAR) to investigate the response profile of subjects who dropped out by reason for dropout under the following three scenarios:

- Dropout reason due to either AE or LOE as MNAR
- Dropout reason due to either AE or LOE or subject withdrew consent as MNAR
- All dropouts are MNAR

For each of the three scenarios, two imputation methods were performed: a delta-adjusted imputation and a placebo-based imputation. The Delta Adjustment Imputation was performed by progressively increasing the delta until the conclusion from the primary analysis is overturned. Delta = 0 is equivalent to MAR, delta >0 is MNAR. For the placebo-

based imputation, missing data for both the placebo and centanafadine groups were imputed based on the imputation model derived from placebo data.

Key Secondary Endpoint Analysis Methods

The key secondary endpoint of change from Baseline to Day 42 in the CGI-S is analyzed in the same manner as the primary endpoint.

Multiplicity

To control the overall type I error for the primary endpoint (AISRS total score) and key secondary endpoint (CGI-S score) across two doses of centanafadine (200 mg TDD and 400 mg TDD), the Applicant pre-specified a fixed sequence strategy using the pre-specified testing order as follows:

1) Change from baseline to Day 42 in the double-blind treatment period in AISRS total score between centanafadine 400 mg TDD and placebo;
2) Change from baseline to Day 42 in the double-blind treatment period in AISRS total score between centanafadine 200 mg TDD and placebo;
3) Change from baseline to Day 42 in CGI-S score between centanafadine 400 mg TDD and placebo;
4) Change from baseline to Day 42 in CGI-S score between centanafadine 200 mg TDD and placebo.

7.1.1.4. Protocol Amendments

The Applicant issued the original protocol on March 8, 2018. The Applicant amended the protocol twice: on May 18, 2018, and January 15, 2020.

Amendment 1 (May 18, 2018) included the following changes:

- Added additional follow-up contacts to be conducted via telephone on 1, 3, and 5 days after the last dose of IMP for all subjects enrolled in Trial 405-201-00013.
- Revised the last day of subject contact from Day +14 to Day +10 for subjects who did not complete Study 13, were not eligible for, or did not rollover to 15.
- Added criteria excluding subjects with HIV seropositive status/acquired immunodeficiency syndrome, seropositive status for hepatitis B (i.e., HBsAg positive), or hepatitis C (i.e., anti-HCV positive and HCV RNA positive).
- Clarified that pregnancy testing at screening should only be performed on females of childbearing potential.
- Added wording in the clinical laboratory table indicating that a CPK reflex for isoenzymes would be conducted if CPK >3 × ULN; serum and urine myoglobin would be collected if CPK >5 × ULN, and that the urine drug screen should include methylphenidate.

- Clarified that SMWQ would be completed by the subject at the site and completed remotely for non-site visits.
- Removed CYP2D6 inhibitors and substrates from the List of Medications Prohibited Before the Trial table and the List of Medications Prohibited During the Trial table.

The Applicant first submitted the protocol for Study 13 to the Agency on July 6, 2018 (along with the protocol for Study 14). In December 2018, the Applicant submitted amendments to these protocols. On August 17, 2019, and November 5, 2019, the Applicant submitted SAPs, interim analyses, and Interim Analysis Review Committee Charters for Studies 13 and 14.

In response to these submissions, the Agency conveyed statistical and clinical comments on November 19, 2019:

> For your ongoing studies 402-201-00013 and 402-201-00014, your primary endpoint and hypothesis test must determine effective doses for a study to be used to support an NDA filing. Your proposed (b) (4) does not fulfill the requirement. (b) (4) (b) (4) .
> You must propose a multiple testing procedure that both establishes an effective dose and controls type I error over both doses.
>
> In addition, you should not plan to terminate either study for early efficacy because you may not have a sufficient safety database for NDA filing.
>
> Additionally, we have the following clinical comments:
>
> We remind you that we have previously advised you to submit information about your primary endpoint, the Adult ADHD Investigator Rating Scale (AISRS). There is no precedence for its use as the primary endpoint in clinical trials for U.S. drug approval in the treatment of ADHD. Because you have proceeded with your study using this scale, whether it is fit-for-purpose will be a review issue if an NDA is submitted.
>
> Please refer to Preliminary Meeting Comments dated April 21, 2017. FDA Response to Question 4i regarding use of the AISRS instead of the ADHD-RS IV as the primary endpoint:
>
> > We have the following comments and recommendations:
> >
> > 1. *You should provide the following materials to the Agency for review and comment:*
> >
> >   a. *Exact copies of the AISRS, CGI-I, and CGI-ADHD-S scales as they will be administered in the planned phase 3 trials (e.g., electronic screen shots)*
> >   b. *AISRS recall period and scoring algorithm to be used for the endpoint score*

c. *AISRS user manual and clinician and site training materials, semi-structured patient interview script, all interview prompts, and all item descriptors to be used by the clinicians when rating the patients*
d. *An exact copy of the ADHD-RS-IV scale, with its user manual, clinician and site training materials, semi-structured patient interview script, all interview prompts, and all item descriptors that clinicians use when rating the patients, if available.*

2. *It is unclear whether a one-category change on the CGI-ADHD-S constitutes a meaningful improvement. The data provided by Spencer and colleagues (2007) suggest that moving from one category to the next on the CGI-ADHD-S may not be a meaningful difference with regard to AISRS mean scores. More specifically, the authors' data yielded no significant difference in mean AISRS scores for patients who were rated as a "1" versus "2" or a "5" versus "6" on the CGI-ADHD-S scale (p=.51 and p=.08, respectively). Provide the Agency with a prespecified responder definition for improvement in AISRS mean scores (i.e., what constitutes a clinically meaningful within-patient improvement) based on anchor-based analyses.*

We also refer to Preliminary Meeting Comments dated April 27, 2018. FDA Response to Question 5:

….We note your intention to use the Adult ADHD Investigator Rating Scale (AISRS) rating for ADHD symptom severity to assess potential "rebound" effects indicative of physical dependence. We agree that the primary endpoint to assess ADHD symptoms and the tool to assess withdrawal after CTN is stopped should be the same. However, we do not have enough information to determine whether the AISRS is fit for purpose to use as the primary endpoint.

On January 17, 2020, the Applicant responded, acknowledging and addressing the comments and recommendations regarding the primary endpoint and the AISRS. The Applicant included Amendment 2 to Study 13 and 14 in this submission. The Applicant also provided a psychometric statistical analysis plan for these studies. Of note, in the time between these interactions with the Applicant and NDA submission, another drug was approved for ADHD in adults based on an AISRS endpoint.

Amendment 2 included the following changes:

- Number of planned screened subjects revised from 900 to 1150.
- Exclusion criteria expanded to prohibit most bariatric surgeries, with the only exception being those where there has been no breach of the gastrointestinal wall (i.e., uncomplicated lap band surgery) AND no sign of malabsorption.
- Exclusion criteria revised to clarify that a drug screen would be assessed prior to Visit 2 and Baseline visit, respectively, and clarification added that the criteria include medications such as opioids or benzodiazepines taken without prescription.
- Interim analysis was removed from multiple sections.

On April 28, 2020, the Agency responded, providing several comments including advice to collapse the CGI-S categories from 7 to 5 options for anchor-based analysis and to use a two-category change, rather than one-category, to define clinically meaningful change.

Due to the COVID-19 pandemic, the Applicant issued guidance to the investigators on March 23, 2020, that subjects who were on treatment were to be withdrawn and early termination procedures were to be conducted within 7 days of notification. Subjects who were in the follow-up period and those who had been withdrawn and were in the early termination period were to continue safety follow-up visits as specified in the protocol unless superseded by local health authority guidance. When in-person visits could not be performed, every effort was to be made to collect information regarding AEs and the use of concomitant medication, and to complete study scales by telephone. Documentation of procedures and deviations were to be recorded. All missing visits and assessments or any assessments completed remotely due to COVID-19 were marked as major deviations and documented as related to COVID-19.

The Applicant submitted an amended statistical analysis plan on March 4, 2020. The FDA sent the following comments on May 8, 2020, regarding the ongoing studies 402-201-00013 and 402-201-00014:

- We remind you that the study must be able to identify effective doses with an adequate control of the overall Type I error rate to support an efficacy claim. Your proposed (b) (4) does not fulfill the requirement. (b) (4) (b) (4). If you fail to demonstrate a statistical significance on the first key secondary endpoint using your pre-specified testing sequence, the trial would not be adequate to support an efficacy claim.
- We recommend that you propose sensitivity analyses to explore the effects of COVID-19 related dropouts. For example, you may wish to consider if patients who drop out with a reason relating to COVID-19 would have dropped out for another reason if the COVID-19 pandemic had not happened and propose a sensitivity analysis to explore this situation.
- In your case report form (CRF), provide instructions and space for clearly documenting COVID-19 related dropout.
- In your proposed pattern mixture model sensitivity analysis, clarify what is meant by "last dropout reason."
- For your proposal to change to remote assessment of the AISRS in study -014, please see Q12 in the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. You should also propose sensitivity analyses to explore the robustness of changes to remote AISRS assessment on the primary endpoint statistical analysis.

The Applicant did not respond to these comments.

7.1.2. 405-201-00014

The primary objective of Study 14 was to evaluate the efficacy of centanafadine twice-daily tablets in total daily doses of 200 mg and 400 mg compared to placebo for ADHD in adults ages 18 to 55 years. Study 14 was identical in design to Study 13 and was conducted in the same time period. The primary and secondary endpoints were also identical. Study 14 included 590 subjects at 48 sites in the United States. The SAP was identical to Study 13 with respect to the sample size assumptions, estimands, analysis of primary and secondary endpoints and description of sensitivity analyses; the SAP for Study 14 does include additional sensitivity analyses to assess the impact of COVID-19, which were not part of the SAP for Study 13.

7.1.3. 405-201-00016

7.1.3.1. Trial Design

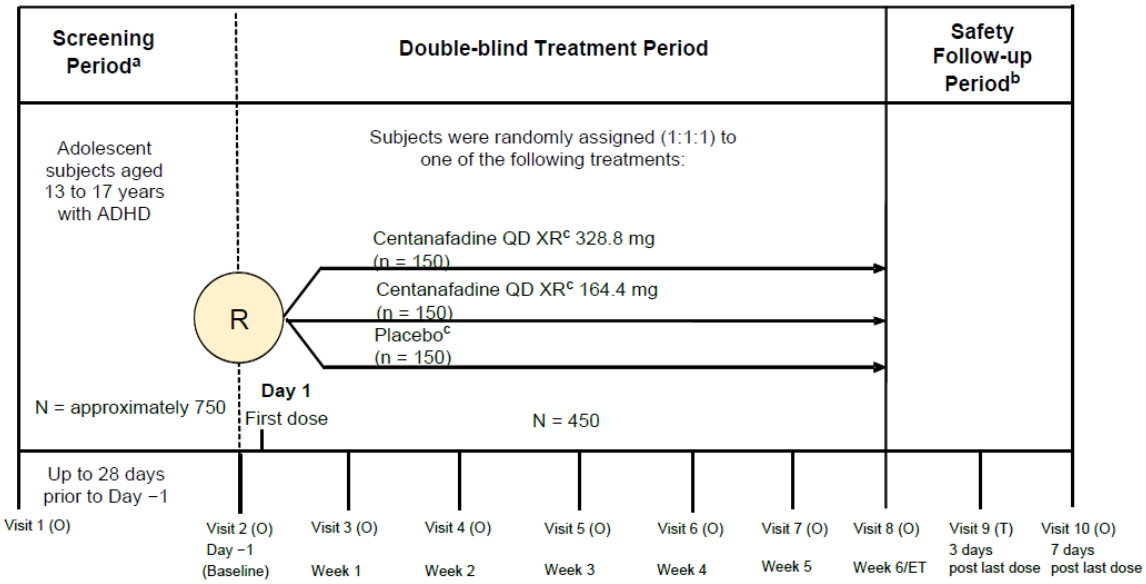
Study 405-201-00016 (Study 16) was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial with the primary objective to determine the efficacy and safety of centanafadine ER capsules for the treatment of pediatric patients 13 to 17 years of age with ADHD.

The study included a screening period (up to 28 days, including a washout period [if needed] of 7 to 28 days), a 6-week, double-blind treatment period, and a 7 (+ 2)-day follow-up period.

Eligible subjects were randomized 1:1:1 at baseline to receive centanafadine ER 280 mg, centanafadine ER 140 mg, or placebo once daily for 6 weeks. Subjects who completed the 6-week double-blind treatment period and the follow-up period of this trial, and who refrained from using prohibited medications, were eligible to roll over into an open-label safety trial (405-201-00017).

The study design is presented in Figure 6. The study was conducted at 48 sites, 1 site in Canada and 47 sites in the United States.

Figure 6. 405-201-00016 Trial Design Schematic



ADHD = attention-deficit/hyperactivity disorder; centanafadine QD XR = centanafadine ER capsules; ET = early termination; IMP = investigational medicinal product; O = office; R = randomization; T = telephone
[a]Included a washout period of 7 to 28 days. The screening period maximum of 28 days could be extended after discussion with the medical monitor.
[b]All subjects were required to participate in a 7-day follow-up period, which consisted of a follow-up telephone call 3 (+ 2) days after the last dose of IMP and an in-clinic follow-up visit 7 (+ 2) days after the last dose of IMP. Subjects were instructed to refrain from using prohibited concomitant medications, including ADHD treatments, until after the follow-up visit 7 (+ 2) days after the last dose of IMP.
[c]Centanafadine ER or placebo was administered daily as 2 capsules.
Source: 405-201-00016 Protocol Figure 1.2-1

Male and female subjects 13 to 17 years of age with primary diagnosis of ADHD based on DSM-5 criteria as confirmed by the MINI-KID were eligible to enroll. In addition, all subjects were required to have a rating of 4 or higher on the CGI-S-ADHD and a minimum symptoms total raw score of ≥28 on the ADHD Rating Scale–5 (ADHD-RS-5) at Baseline. The ADHD-RS-5 is a validated rating scale that assesses symptoms that correspond to the DSM-5 criteria for ADHD. The scale consists of 18 questions, divided into hyperactivity/impulsivity and inattention subscales. Each question assesses the frequency of a symptom on a 4-point Likert scale. Raw scores are converted to percentile scores based on age and [redacted].

Key exclusion criteria were:

- A comorbid diagnosis of Tourette's disorder or other tic disorder (simple, non-Tourette's tics allowed); generalized anxiety disorder severe enough to interfere with study procedures; panic disorder; conduct disorder; psychosis; post-traumatic stress disorder; bipolar disorder; autism spectrum disorder; binge eating disorder; anorexia; bulimia; oppositional defiant disorder severe enough to interfere with study conduct (allowed if not the primary focus of treatment); obsessive-compulsive disorder severe enough to interfere with study conduct (allowed if not the primary focus of treatment); or MDD

with current major depressive episode, required treatment within the 6 months prior to screening or, in investigator's opinion, MDD may worsen or could be expected to require treatment during the course of the trial.

- 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.
- No suitable therapeutic benefit has been derived from adequate courses of 2 classes of therapy for ADHD during the subject's lifetime, in the investigator's opinion.
- Epilepsy or a history of seizures (except for a single episode of febrile seizures [no more than 3]) or a history of severe head trauma.
- Initiated, changed, or discontinued receiving psychological interventions for ADHD (e.g., supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) within the 30 days before the screening visit, or anticipated to start new treatment during the trial. Psychotherapy, including cognitive behavioral therapy, was prohibited if it had not been stable in terms of type, intensity, and frequency, for at least 30 days prior to screening. Changes in the frequency or nature of their psychotherapy could not be made during the course of the trial.
- Use of the Revibe focus watch, the EndevorRx game, or similar digital ADHD or focus therapies at baseline, and/or expected use any of these during the treatment period.
- A history of dermatologic adverse reactions secondary to any drug exposure. Anaphylaxis (or some type of systemic allergic reaction) to any substance.
- A positive drug test for confirmed prescription use of ADHD medications at baseline. Subjects who tested positive at screening were required to undergo a washout period.
- Subjects with a positive alcohol test or a positive drug screen for cocaine or other illicit drugs (excluding marijuana). Subjects testing positive for marijuana could be permitted to be enrolled if they had no evidence of a substance use disorder, and if they agreed to refrain from use for the duration of the trial. Allowance for subjects testing positive for marijuana at screening required explicit approval from the medical monitor.

Treatment assignment was conducted based on a computer-generated randomization code provided by the Applicant's Biostatistics Department. Applicant personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial. Treatment codes were restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, and reporting SAEs to regulatory agencies. The randomization was stratified by trial site and designed to allocate subjects in a 1:1:1 ratio to centanafadine high dose, centanafadine low dose, or placebo.

Individual stopping rules were:

- Resting, supine, and confirmed on 2 readings, SBP >130 mmHg and an increase from baseline by 25 mmHg
- Resting, supine, and confirmed on 2 readings, DBP >90 mmHg and an increase from baseline by 15 mmHg
- Resting, supine, and confirmed on 2 readings, pulse rate >120 bpm and an increase from baseline by 30 bpm
- Skin eruptions classified as severe (defined as the inability to perform normal daily activity) or meeting the criteria for an SAE
- Neutropenia with an absolute neutrophil count < 1.00 × 103/µL.

Treatment could also be discontinued for subject dissatisfaction with treatment, AEs, required treatment with a prohibited medication or therapy, or other issues as determined by the investigator.

Subjects were instructed not to take the study drug with a high fat meal. As noted above, any subjects taking medications for ADHD were washed out before the start of the single-blind placebo run-in period (Day -7). The required duration of washout for selected prohibited medications is listed in Table 22. All other prohibited medications were required to be discontinued at least 24 hours before Day -7. Table 23 lists medications prohibited during the trial.

Table 22. Medications Prohibited Prior to the Trial 405-201-00016

Prohibited Medication	Required Washout Period*
Fluoxetine	24 days
Antidepressants (with the exception of fluoxetine)	14 days
Benzodiazepines	14 days
Hypnotics, including non-benzodiazepine sleep aids	7 days
Any medication to treat ADHD on- or off-label, including but not limited to any form of amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, and methylphenidate	7 days
Sedating anticholinergics and sedating antihistamines (i.e., diphenhydramine, hydroxyzine, chlorpheniramine)	7 days
Weight loss medications/supplements	7 days
Other investigational products	30 days

*Protocol required washout period to be completed by Baseline Visit.
Source: Adapted from Protocol 405-201-00016 Table 6.5.1-1

Table 23. Medications Prohibited During the Trial 405-201-00016

Prohibited/Restricted Medications
Medications affecting CNS and performance
Psychotropic medications including antidepressants, mood stabilizers, anticonvulsants, and antipsychotics
Sedative hypnotics (benzodiazepines, barbiturates, sleep aids)
Sedating anticholinergic and sedating antihistamine medication
Decongestants that have stimulating or sedating effects (saline and corticosteroid nasal sprays are permitted)
Any medication to treat ADHD on- or off-label, including but not limited to any form of amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, and methylphenidate
Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for documented and clinically appropriate indications (i.e., episodic pain condition, tooth extraction) if prescribed at the medically appropriate dose and frequency.
Nonprescription herbal supplements
Melatonin
Weight loss medications/supplements
Other investigational products
Regular use of bronchodilators (for a diagnosis of asthma that has required daily treatment with bronchodilators or nebulizer treatments in the 30 days prior to screening and/or may require daily treatments over the course of the trial). Intermittent use of bronchodilators is not exclusionary.

CNS = central nervous system.
Source: Protocol 405-201-00016 Table 6.5.1-2

The investigational study drug (centanafadine ER capsules or placebo) was administered once daily as intact capsules or capsule contents sprinkled on one tablespoon of applesauce. Treatment could be administered with or without food, but not with a high-fat meal. Subjects randomized to receive placebo took two capsules of placebo. Subjects randomized to receive low-dose centanafadine ER (140 mg) took two capsules, one of 140 mg centanafadine ER and one of placebo. Subjects randomized to high-dose centanafadine ER (280 mg) took two capsules of 140 mg centanafadine ER.

7.1.3.2. Study Endpoints

The primary efficacy endpoint was change from Baseline in the ADHD-RS-5 symptoms total raw score at Week 6.

The key secondary efficacy endpoints were change from Baseline in the CGI-S-ADHD at Week 6 and change from Baseline in the Conners 3 Parent Short T-scores (Hyperactivity-Impulsivity, Inattention, Defiance/Aggression, and Executive Functioning) at Week 6.

The study also included several other efficacy endpoints (e.g., assessing change from Baseline in the ADHD-RS-5 and CGI-S at different time points, assessing changes in ADHD-RS-5 subscales).

Table 24. Schedule of Assessments 405-201-00016

	Screening[a]	BL	Double-Blind Treatment Period							Safety Follow-up	
	Days −28 to −2	Day −1	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) EOT/ ET	3 (+ 2) days post last dose	7 (+ 2) days post last dose
Visit Type	**O**	**O**	**-**	**O**	**O**	**O**	**O**	**O**	**O**	**T**	**O**
ENTRANCE CRITERIA											
Informed consent/assent	X										
Inclusion/ exclusion Criteria	X	X									
Demographics	X										
Concomitant medication(s)	X	X		X	X	X	X	X	X	X	X
Medical and psychiatric history	X										
Psychiatric evaluation and MINI-KID	X										
Pregnancy test	X	X		X	X	X	X	X	X		X
Randomization		X									
EFFICACY											
ADHD-RS-5 (investigator interview with informant)	X	X		X	X	X	X	X	X		X
Conners-3 self-report short		X		X	X	X	X	X	X		X
CGI-S-ADHD	X	X		X	X	X	X	X	X		X
CGI-C-ADHD				X	X	X	X	X	X		X

Conners-3 Parent Short		X		X	X	X	X	X	X		X
PGI-S		X		X	X	X	X	X	X		X
PGI-C				X	X	X	X	X	X		X
SAFETY											
AEs	X	X		X	X	X	X	X	X	X	X
Physical examination		X							X		

	Screen-ing[a]	BL	Double-Blind Treatment Period							Safety Follow-up	
	Days −28 to −2	Day −1	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) EOT/ ET	3 (+ 2) days post last dose	7 (+ 2) days post last dose
Visit Type	**O**	**O**	**-**	**O**	**O**	**O**	**O**	**O**	**O**	**T**	**O**
Height, weight, BMI	X	X			X		X		X		
Tanner puberty staging		X									
Vital signs	X[b]	X		X	X	X	X	X	X		X
12-lead ECG	X[b]	X		X					X		
Clinical laboratory tests	X[b]				X[c]				X		
C-SSRS	X	X		X	X	X	X	X	X	X	X
SMWQ-P/ SMWQ-PO									X	X	X
UDS	X	X		X	X	X	X	X	X		X
Alcohol testing via breathalyzer or blood	X	X[e]									
Daily dosing diary			<- - - - - - - - to be recorded daily- - - - - - - ->								
PHARMACOKINETIC/FUTURE BIOSPECIMEN RESEARCH ASSESSMENTS											
PK blood draws					X				X		
FBR consent/assent	X										
FBR – DNA		X									
FBR – RNA		X			X				X		
FBR – plasma		X			X				X		

OTHER											
IMP dispensing		X		X	X	X	X	X			
IMP administration			X	X	X	X	X	X	X		
IMP return and accountability				X	X	X	X	X	X		
Entry/exit survey		X							X		

BL = baseline; BMI = body mass index; EOT = end of treatment; FBR = future biospecimen research; O = office; PGI-C = Patient Global Impression - Change; PGI-S = Patient Global Impression - Severity; T = telephone; UDS = urine drug screen; Wk = week.

[a] The screening period included a washout period of 7 to 28 days. Screening assessments could be split across multiple visits if necessary. The screening period maximum of 28 days could be extended after discussion with the medical monitor.

Source: Protocol 405-201-00016 Table 1.3-1

7.1.3.3. Statistical Analysis Plan

The Statistical Analysis Plan for Study 16 is similar to Studies 13 and 14. Key differences are primarily due to the change in primary endpoint from AISRS in Studies 13 and 14 to ADHD-RS-5 in Study 16, and inclusion of additional key secondary endpoints in the multiple testing plan. Additional details relevant to the SAP for Study 16 not found in the SAPs for Studies 13 and 14 are presented below.

Analysis Populations

- Efficacy Analysis Set/Full Analysis Set (FAS): The FAS includes all subjects in the safety analysis set, who have a baseline value and at least one valid post-randomization efficacy evaluation for ADHD-RS-5 total score within the double-blind treatment period.

Sample Size

The planned sample size for Study 16 is the same as for Studies 13 and 14, with different assumptions for the expected treatment effect and standard deviation: The sample size was planned based on the results from the adult phase 3 centanafadine trials: Studies 13 and 14, with an expected treatment effect of 4 points and standard deviation of 10 for mean change from Baseline to Week 6 on ADHD-RS-5 total score.

Primary Efficacy Analysis

The primary analysis methods for change from Baseline in the ADHD-RS-5 is largely the same as the methods for the analysis of change from Baseline in the AISRS for Studies 13 and 14. The primary efficacy model for the ADHD-RS-5 includes a fixed effect term for treatment site which is not present in the primary efficacy model for the AISRS: The primary efficacy outcomes were evaluated using a Mixed-Effect Model for Repeated Measures (MMRM) approach, the model included fixed effect terms for treatment, trial site, visit day, and an interaction term of treatment-by-visit day and an interaction term of baseline value ADHD-RS-5 total score for the double-blind treatment period by visit as a covariate. The sensitivity analyses for departures from MAR and for placebo-based imputation are the same as from Studies 13 and 14.

Key Secondary Endpoint Analysis Methods

The key secondary endpoints of change from Baseline to Week 6 in the CGI-S-ADHD and change from Baseline in Conners 3 Parent Short domain T-scores at Week 6 would be analyzed in the same manner as the primary endpoint.

Multiplicity

To control study-wise type I error at the two-sided alpha 0.05 level for the two doses of centanafadine across the primary and key secondary endpoints, the following testing procedure was proposed by the Applicant:

1. The primary endpoint of change from Baseline to Week 6 in the ADHD-RS-5 would first be tested at a global level for the average of the two doses vs. placebo. If the global test reached statistical significance, the low dose and high dose vs. placebo could be tested separately at 2-sided alpha of 0.05. A dose will be considered significant at 2-sided alpha of 0.05 if both the global test and the test for the dose vs. placebo are both significant at 2-sided 0.05.
2. The first key secondary endpoint of change from Baseline to Week 6 in the CGI-S-ADHD could be tested if both comparisons of low dose and high dose centanafadine for the primary endpoint reached statistical significance from the previous step. A similar global test of the average of both doses vs. placebo would first be tested and if this reaches statistical significance, the low dose and high dose vs. placebo can be tested separately at 2-sided 0.05 for change from baseline to Week 6 in the CGI-S-ADHD.
3. The second key secondary endpoint of change from Baseline to Week 6 in the Conners 3 Parent Short can be tested if the primary endpoint and first key secondary endpoint reach statistical significance as outlined in Steps 1 and 2. A global test similar to the one described above will be used and applied to the Conners 3 Parent Short domain T-scores in the order listed below. First a global test will be performed for the average effect of the low dose and high dose for the first domain T score. If this global test is significant, the two doses vs. placebo will be tested at two-sided alpha of 0.05 for the first domain T- score. As with the primary and first key secondary endpoint, a dose comparison can be considered statistically significant for a domain T-score if the global test and the test of that dose vs. placebo are both significant at the 2-sided 0.05 level. The analysis of the subsequent domain T-scores can commence if both the low dose and high dose reach statistical significance for the first domain T score.
    a. Hyperactivity-Impulsivity
    b. Inattention
    c. Defiance/Aggression
    d. Executive Functioning

7.1.3.4. Protocol Amendments

The Applicant issued the original protocol for Study 16 on June 23, 2021. On June 30, 2021, the Applicant submitted the protocol to the Agency, along with the protocol for open label extension Study 17.

On August 3, 2021, the Agency sent the following information request:

> Please clarify if you have conducted a relative bioavailability study comparing the

> pharmacokinetics of centanafadine and any active metabolite(s) after administration of the new XR capsule versus the SR tablet formulations of centanafadine? If conducted, please provide brief results (e.g., the statistical comparison of centanafadine and any active metabolite(s)). Please note, based on iPSP, such a study should be conducted prior to using the new XR formulation in Phase 3 studies.

On August 5, 2021, the Agency sent an additional information request (IR):

> We cannot locate the "Rash/Skin Eruption AESI Workup Instructions" which is mentioned in 8.8.5 of the protocols. Please submit a copy of the "Rash/Skin Eruption AESI Workup Instructions." If already submitted, please tell us its location in the submission.

On August 11, 2021, the Agency sent an additional IR:

> Please confirm if there have been any cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), or other severe or serious cutaneous adverse reactions during any of the studies with centanafadine, considering all of the centanafadine studies conducted to date, including ongoing studies and studies conducted under other INDs. In your response, please include all adverse events (AEs) suggestive of SJS/TEN/DRESS and explain if there were potential cases of SJS/TEN/DRESS that were unable to be ruled out as SJS/TEN/DRESS.

On August 12, 2021, the Agency informed the Applicant that:

> Study 405-201-00047 does not directly compare the [once-daily ER capsule to twice-daily tablet]. Cross studies comparison is not an acceptable method to compare exposures of two formulations to inform dose selection for Phase 3 studies. Based on your iPSP, a bioavailability study should be conducted prior to using the new XR formulation in the Phase 3 studies. You should therefore conduct such a study and submit the data for review to inform dose selection prior to conducting the Phase 3 studies.

On August 25, 2021, the Agency conveyed the following non-hold comments regarding Studies 16 and 17:

1. You do not plan to administer the primary and secondary efficacy measures during the first safety follow-up visit. Please administer their primary and secondary efficacy measures during the first safety follow-up visit, to allow for proper review of the persistence of clinical benefit after the treatment is stopped. Please also confirm that AE monitoring, particularly for withdrawal symptoms (and any withdrawal-related assessments), will be conducted during the first safety follow-up visit.
2. You did not describe trial-stopping criteria. Please specify trial-stopping criteria in your protocol.
3. You have not provided the necessary information for Agency review and comment regarding the Connor-3 Parent Short-derived secondary endpoint;

therefore, we are unable to comment on whether this instrument is fit for purpose for regulatory decision-making.
For any clinical outcome assessment that you propose as a pre-specified efficacy endpoint intended to support labeling claims, we recommend that you provide the Agency with following for review and comment prior to initiation of your clinical trial:

a. Exact copy of the instrument as it will be administered in your trial (e.g., paper form or electronic screen shots)
b. Instrument conceptual framework and scoring algorithm
c. Evidence of content validity from the literature and qualitative research with appropriate stakeholders (e.g., patients/caregivers/ expert clinicians)]
d. Any user manuals and patient and investigator training materials that will be provided in the clinical trial.

To meet diagnostic criteria, patient behaviors need to be demonstrated across more than one environment (e.g., both home and school), not just one or the other. Therefore, in clinical practice, parent-report forms are often used conjunction with teacher-report forms to gather information in both contexts.

Additionally, please explain your intentions for administering the Connor-3 Parent Short.

1. Please submit your informed consent document for review by FDA.
2. Please submitted your revised protocol to FDA for review.

STATISTICAL

1. The protocol states that the 2 intercurrent events “intervention discontinuation for any reason” and “initiation of rescue intervention or change in background intervention (dose and product)” are both addressed by the treatment condition of interest attribute, where the treatment condition is the randomized treatment with or without premature treatment discontinuation or rescue medication (hypothetical strategy). It further states that there are no remaining intercurrent events. This seems to be more in line with the treatment policy strategy instead of the proposed the hypothetical strategy. On the other hand, your proposed analysis with rationale for estimand seems suggest that treatment discontinuation is the only intercurrent event. Please clarify.
2. Your current multiple testing procedure stops statistical testing if the high dose is not statistically significant. We have seen studies fail where there was evidence for the low dose but not the high dose even with preliminary evidence of a dose response. We suggest that you consider a multiple testing procedure that may allow you to have a chance to test the low dose should you fail on the high dose, e.g., the graphical methods introduced by Bretz et al (2009).
3. Please clarify if you plan to screen and randomize additional patients if the non-evaluable patient rate is higher than expected.

On September 17, 2021, the Agency conveyed additional comments on the pediatric protocols from Division of Pediatric and Maternal Health (DPMH) and the Division of

Dermatology and Dentistry (DDD):

1. Please update your protocol to include the full details of your Rash/Skin Eruption AESI Workup Instructions. Your study protocols should contain a specific section describing your complete assessment strategy for skin eruptions. You should include the term "bullous eruption" in the adverse skin reaction workup instructions. Please confirm that you will be conducting skin checks during each physical exam and inquiring about the presence of rash during AE monitoring.
2. We remind you of the Agency advice regarding monitoring for dermatologic reactions, provided April 21, 2017, during the End of Phase 2 meeting. In addition:
    a. Photographs are sufficient for initial documentation but not preferred for evaluation of serious skin eruptions; in-person dermatologist consultation is recommended for evolving skin eruptions, and biopsy of specific lesions are highly recommended to confirm the diagnosis.
    b. With a skin biopsy, direct immunofluorescence evaluation should be considered, particularly if the eruption is characterized by vesicles, bullae, or pustules. Clarify how skin histopathology specimens will be reviewed in your protocol, and whether or not a certified dermatopathologist will review the specimens. We recommend that you include on your Skin Eruption AESI form whether or not a skin biopsy was done, and if so, attach the dermatopathology report for Agency review.
3. You should include a table of blood volumes for each test (or test panel) at each visit and over the course of the study. Please specify that you will use calibrated instruments to measure blood pressure, height, and weight.
4. You should exclude patients with Stage 1 hypertension. Therefore, SBP exclusion should be 130 mmHg and DBP exclusion should be 80 mmHg (for reference, see: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. September 2017. 140(3)).
5. Please revise your withdrawal criteria to include the following criteria for blood pressure:
    - Resting, supine, and confirmed on 2 readings, systolic blood pressure > 130 mmHg, or an increase from baseline by 25 mmHg
    - Resting, supine, and confirmed on 2 readings, diastolic blood pressure > 80 mmHg, or an increase from baseline by 15 mmHg
    - Resting, supine, and confirmed on 2 readings, pulse rate > 120 bpm, or an increase from baseline by 30 bpm.

On October 5, 2021, the Applicant responded to these comments. In response to the request for administration of the efficacy endpoints at the first follow-up visit, the Applicant stated that in Study 13 and Study 14, scores on efficacy endpoints at 7 days post-dosing remained decreased, suggesting a duration of effect beyond the 7-day follow-up window. Based on those data, in addition to the different modality of assessment if ADHD-RS-5 were to be assessed by phone, and the prior in-clinic efficacy assessment being within the 1-week recall period, the Applicant proposed to not add the recommended assessments to the first

safety follow-up phone visit at day 3 post dose.

Regarding the Agency's request for stopping criteria, the Applicant replied that an Independent Data Monitoring Committee (IDMC) would review all SAEs and other safety information during this study. The Applicant noted that the draft IDMC charter outlined specific safety data reviews (both blinded and unblinded) that would be used as the mechanism to potentially modify, suspend enrollment, or discontinue study activity based on a safety signal, a change in risk benefit to study participants or insufficient scientific value of the study. The Applicant stated that protocol stopping rules in Section 7 would be updated to reflect this role of the IDMC.

In response to the comments on the Conners 3 – Parent Short, the Applicant provided a screenshot of the version to be used in the study, as well as a figure illustrating a hypothesized conceptual framework of the Conners 3 – Parent Short. The Sponsor provided additional information and stated that Site training materials were in development and would be submitted when available. Regarding teacher-report forms, the Applicant stated that they did not consider this practical to implement in clinical trials for multiple reasons, including patient confidentiality and logistical concerns.

On October 22, 2021, the Applicant issued Amendment 1, conveying it to the Agency on November 2, 2021. Amendment 1 included multiple clarifications, revision of the estimand, updates to the protocol in response to Agency feedback, and other minor changes.

On October 5, 2022, the Applicant submitted Amendment 2 to the protocol for Study 16, which included several additional changes. The most notable changes are summarized below:

- Removed the eligibility criterion that excluded subjects with a history or dermatologic adverse reactions due to drug exposure and anaphylaxis to any substance.
- Specified that a subject would be considered for discontinuation if that subject met the specified criteria and added the timeframe of assessments, as shown in the following individual subject discontinuation criteria:
    - Resting, supine, and confirmed on 2 readings over 2 consecutive visits, SBP > 130 mmHg and an increase from baseline by 25 mmHg
    - Resting, supine, and confirmed on 2 readings over 2 consecutive visits, DBP > 80 mmHg and an increase from baseline by 15 mmHg
    - Resting, supine, and confirmed on 2 readings over 2 consecutive visits, pulse rate > 120 bpm and an increase from baseline by 30 bpm.
- Specified that the sample size would also provide at least 96% power at a 2-sided alpha level of 0.05 to detect the average effect of low-dose and high-dose centanafadine ER compared to placebo.
- Revised the primary efficacy endpoint analysis to describe the use of a global test and the test of the centanafadine ER dose (low dose or high dose) versus placebo instead of

fixed sequence testing.

- Revised the procedure to control the overall experiment-wise type I error from a fixed sequence testing approach to describe a multiple testing procedure in which the analysis of the first key secondary endpoint would be conducted if both comparisons of low dose versus placebo and high dose versus placebo of the primary endpoint were significant and the analysis of the second key secondary endpoint would be conducted if both comparisons of low dose versus placebo and high dose versus placebo of the primary endpoint and the first key secondary endpoint were significant.

A third amendment was issued on March 28, 2023, and submitted to the Agency on April 4, 2023. For Study 16 and 21, the Applicant revised the eligibility criteria to shorten the timeframe allowed for MDD treatment ("MDD with current major depressive episode, or has required treatment within the 3 months prior to screening or, in investigator's opinion, MDD may worsen or could be expected to require treatment during the course of this trial"). To avoid potential bias of efficacy results, the Agency advised the Applicant to consider requiring that subjects have been stable on their psychiatric medication for at least 3 months.

In the CSR for Study 16, the Applicant stated that they received feedback from the FDA that required further amending of the protocol; however, a new protocol amendment was not possible as trial recruitment was coming to an end. Therefore, the third amendment (dated March 28, 2023) was never implemented for Study 16.

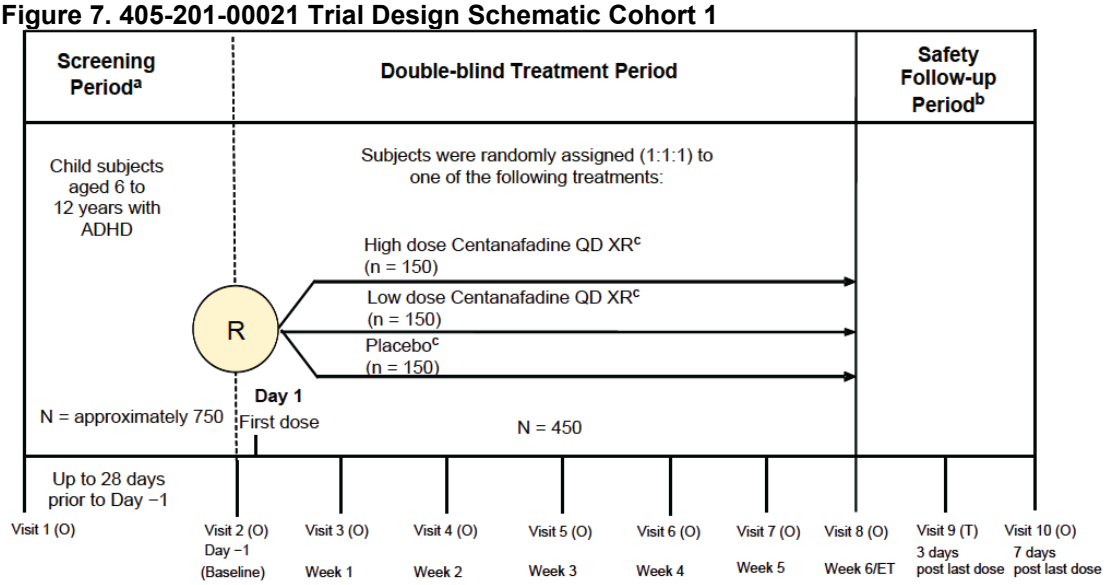
7.1.4. 405-201-00021

7.1.4.1. Trial Design

The primary objective of Study 21 Cohort 1 was to evaluate the efficacy of centanafadine ER capsules versus placebo in the treatment of pediatric subjects 6 to 12 years old with ADHD. The primary objective for Cohort 2 was to evaluate the efficacy of centanafadine ER capsules versus placebo in the treatment of pediatric subjects 4 to 5 years old with ADHD.

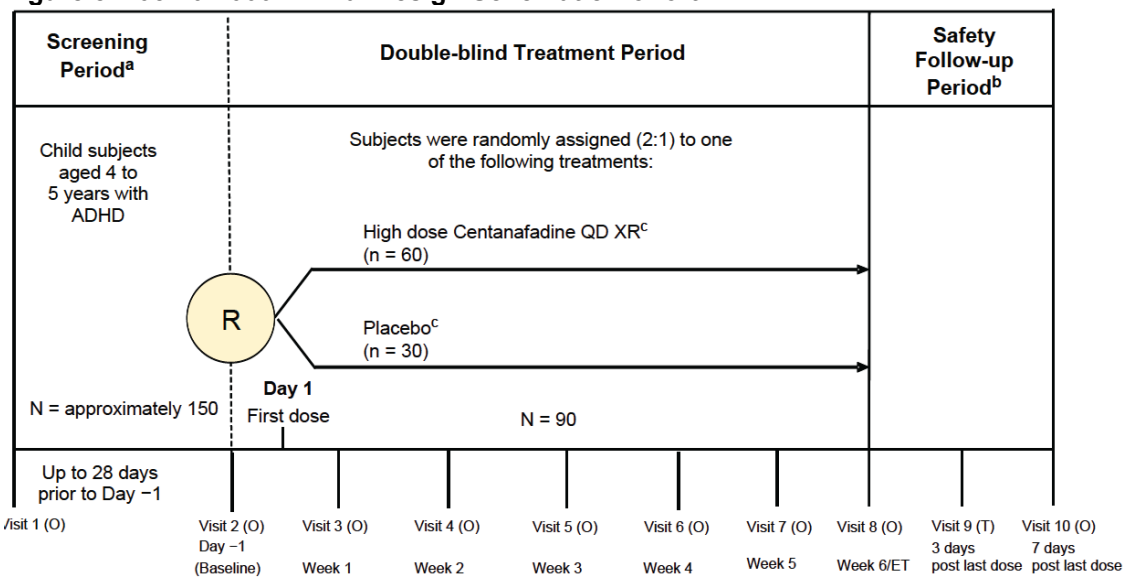
Study 21 was a 6-week, phase 3, multicenter, randomized, double-blind, placebo-controlled trial. The study had three periods: a screening period of up to 4 weeks (28 days), a double-blind treatment period of 6 weeks, and a follow-up period of 7 (+ 2) days. The study designs for Cohort 1 and Cohort 2 are presented in Figure 7 and Figure 8. Cohort 1 was conducted at 58 sites: 1 in Canada and 57 in the United States. Cohort 2 was conducted at 23 sites in the United States.

Figure 7. 405-201-00021 Trial Design Schematic Cohort 1



Source: Applicant's Figure 9.1-1, Clinical Study Report 405-201-00021

Figure 8. 405-201-00021 Trial Design Schematic Cohort 2



Source: Applicant's Figure 9.1-2, Clinical Study Report 405-201-00021

Individuals ages 4 to 12 years (inclusive) at the time of informed consent/assent with a primary diagnosis of ADHD based on DSM-5 diagnosis criteria as confirmed with the MINI-KID were eligible to enroll. In addition, subjects were required to have total raw score of ≥28 on the ADHD-RS-5 and a score of 4 or higher on the CGI-S-ADHD at Baseline. Subjects 4 or 5 years of age were required to have failed adequate psychotherapy or, in the investigator's opinion, to have symptoms severe enough to require pharmacotherapy in the absence of prior psychotherapy.

Key exclusion criteria were generally similar to those of Study 16. Study 21 included specific

exclusion criteria related to BMI and diabetes mellitus. In addition, it included the following age-based vital sign exclusion criteria and a QTcF exclusion criterion:

- Blood Pressure:
  - Subjects 4 to 5 years: SBP ≥ 108 mmHg; DBP ≥ 66 mmHg
  - Subjects 6 to 8 years: SBP ≥ 111 mmHg; DBP ≥ 71 mmHg
  - Subjects 9 to 12 years: SBP ≥ 115 mmHg; DBP ≥ 76 mmHg
- ECG results as follows:
  - QTcF ≥ 450 msec

Treatment assignment was conducted based on a computer-generated randomization code provided by the Applicant's Biostatistics Department. Applicant personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial. The randomization code was sent to the bioanalytical laboratory. Access to the treatment codes was restricted to personnel charged with generating and maintaining randomization files, packaging trial medication, and reporting serious adverse events (SAEs) to regulatory agencies. Randomization was stratified by age group and trial site, allocating subjects in a 1:1:1 ratio to weight-based high dose centanafadine, weight-based low dose centanafadine, or placebo.

Individual subject discontinuation criteria were as follows:

- Resting, supine, and confirmed on 2 readings, SBP >130 mmHg or an increase from baseline by 25 mmHg
- Resting, supine, and confirmed on 2 readings, DBP >80 mmHg or an increase from baseline by 15 mmHg
- Resting, supine, and confirmed on 2 readings, pulse rate >120 beats per minute (bpm) or an increase from baseline by 30 bpm
- Skin eruptions that are classified as severe (defined as the inability to perform normal daily activity) or that meet the criteria for an SAE
- Neutropenia with an absolute neutrophil count <1.00 × 103/µL.

Treatment discontinuations could be initiated for lack of subject satisfaction with the treatment, adverse events, or required treatment with a prohibited medication or therapy, among other reasons. At the start of the double-blind treatment period and through the Week 6/End-of-Treatment visit, subjects with a positive drug screen for any illicit drug (including marijuana) or alcohol were discontinued from the trial. Subjects who had a positive drug screen for prohibited medications (including medications for the treatment of ADHD) could be discontinued from the trial at the investigator's discretion.

As noted above, any subjects taking medications for ADHD were washed out prior to the double-blind treatment period. The required duration of washout for selected prohibited medications is listed in Table 25. Table 26 lists medications prohibited during the trial.

Table 25. List of Medications Prohibited Before the Trial 405-201-00021

Prohibited Medication	Required Washout Period
Fluoxetine	24 days
Antidepressants (with the exception of fluoxetine)	14 days
Benzodiazepines	14 days
Hypnotics, including non-benzodiazepine sleep aids	7 days
Any medication to treat ADHD on- or off-label, including but not limited to any form of amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, methylphenidate, and viloxazine HCl	7 days
Sedating anticholinergics and sedating antihistamines (i.e., diphenhydramine, hydroxyzine, chlorpheniramine)	7 days
Weight loss medications/supplements	7 days
Other investigational products	30 days

Source: Protocol 405-201-00021 Table 6.5.1-1

Table 26. List of Medications Prohibited During the Trial 405-201-00021

Medications affecting CNS and performance
Psychotropic medications including antidepressants, mood stabilizers, anticonvulsants, and antipsychotics
Sedative hypnotics (benzodiazepines, barbiturates, sleep aids)
Sedating anticholinergic and sedating antihistamine medication
Decongestants that have stimulating or sedating effects (saline and corticosteroid nasal sprays are permitted)
Any medication to treat ADHD on- or off-label, including but not limited to any form of amphetamine (mixed salts), atomoxetine, clonidine, dexmethylphenidate, guanfacine, lisdexamfetamine, methylphenidate, and viloxazine HCl
Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for documented and clinically appropriate indications (i.e., episodic pain condition, tooth extraction) if prescribed at the medically appropriate dose and frequency.
Nonprescription herbal supplements
Melatonin
Weight loss medications/supplements
Other investigational products
Regular use of bronchodilators (for a diagnosis of asthma that has required daily treatment with bronchodilators or nebulizer treatments in the 30 days prior to screening and/or may require daily treatments over the course of the trial). Intermittent use of bronchodilators was not exclusionary.

Source: Protocol 405-201-00021 Table 6.5.1-2

Permitted medications are listed in Table 27 below. There were no rescue medications.

Table 27. List of Medications Permitted During the Trial

Non-sedating antihistamine medication.
The following may be used for the treatment of illness or seasonal allergies: saline and corticosteroid nasal sprays.
Stable, intermittent use of bronchodilators.
Opioids, with approval from the medical monitor for documented and clinically appropriate indications (i.e., episodic pain condition, tooth extraction).
Hormonal contraceptives.
Topical numbing agents

Source: Protocol 405-201-00021 Table 6.5.2-1

The investigational study drug (centanafadine ER or placebo) was administered once daily as intact capsules or as capsule contents sprinkled on 1 tablespoon of applesauce. Treatment could be administered with or without food, but not with a high fat meal. Subjects received doses of centanafadine ER intended to match exposures of centanafadine twice-daily tablets administered to adults in 200 mg or 400 mg total daily doses. Centanafadine was provided as 35, 70, and 140 mg capsules; placebo capsules were matching in size and color, dispensed as weekly blister cards with 7 days of dosing plus 2 additional days. All subjects took 2 or 3 capsules per day based on weight per Table 28.

Table 28. Weight-Based Double-Blind Dosing of Centanafadine ER

Subjects	Weight bin	200 mg adult equivalent dose[a]	400 mg adult equivalent dose[a]	Placebo[a]
Children 4 to 12 years of age, inclusive[b]	Bin 1: <20 kg	35 mg (1 × 35 mg capsule (b) (4) + 1 placebo capsule (b) (4))	70 mg (2 × 35 mg capsules (b) (4))	2 placebo capsules (b) (4)
	Bin 2: 20 to <35 kg	70 mg (1 × 70 mg capsule (b) (4) + 1 placebo capsule (b) (4))	140 mg (2 × 70 mg capsule (b) (4))	2 placebo capsules (b) (4)
	Bin 3: 35 to 50 kg	105 mg (1 × 35 mg capsule (b) (4) + 1 × 70 mg capsule (b) (4) + 1 placebo capsule (b) (4))	210 mg (1 × 70 mg capsule (b) (4) + 1 × 140 mg capsule (b) (4) + 1 placebo capsule (b) (4))	1 placebo capsule (b) (4) + 1 placebo capsule (b) (4) + 1 placebo capsule (b) (4)
	Bin 4: >50 kg	140 mg (1 × 140 mg capsule (b) (4) + 1 placebo capsule (b) (4))	280 mg (2 × 140 mg capsules (b) (4))	2 placebo capsules (b) (4)

[a]Capsule strengths of 140, 70, and 35 mg are associated with capsule sizes (b) (4), respectively.
[b]In the case that a subject turned 13 during the trial, that subject would continue taking the dose assigned at randomization
Source: Protocol 405-201-00021 Figure 6.1.1-1

7.1.4.2. Study Endpoints

The primary and secondary efficacy endpoints for Study 21 Cohorts 1 and 2 were the same as for Study 16:

- Primary: change from Baseline in the ADHD-RS-5 symptoms total raw score at Week 6.
- Key secondary: change from Baseline in the CGI-S-ADHD at Week 6 and change from Baseline in the Conners 3 Parent Short T-scores (Hyperactivity-Impulsivity, Inattention, Defiance/Aggression, and Executive Functioning) at Week 6.

Other efficacy endpoints and safety endpoints were also the same as those listed for Study 16 (see Section 7.1.3).

Table 29 summarizes the schedules of assessment activities for Cohort 1 and 2, respectively. Physical examinations, ECGs, and laboratory assessments were conducted at screening and at EOS. Vital sign monitoring, adverse event tracking, and monitoring for suicidal ideation and behavior (using the C-SSRS) were performed at every visit.

Table 29. Schedule of Assessments

	Screening[a]	BL	Double-Blind Treatment Period							Safety Follow-up	
	Days −28 to −2	Day −1	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) EOT/ ET	3 (+ 2) days post last dose	7 (+ 2) days post last dose
Visit Type	**O**	**O**	**-**	**O**	**O**	**O**	**O**	**O**	**O**	**T**	**O**
ENTRANCE CRITERIA											
Informed consent/assent	X										
Inclusion/ exclusion Criteria	X	X									
Demographics	X										
Concomitant medication(s)	X	X		X	X	X	X	X	X	X	X
Medical and psychiatric history	X										
Psychiatric evaluation and MINI-KID	X										
Pregnancy test	X	X[b]		X	X	X	X	X	X		X
Randomization		X									
EFFICACY											
ADHD-RS-5	X	X		X	X	X	X	X	X		X
CGI-S-ADHD	X	X		X	X	X	X	X	X		X
CGI-C-ADHD				X	X	X	X	X	X		X
Conners-3 Parent Short		X		X	X	X	X	X	X		X
PGI-S		X		X	X	X	X	X	X		X
PGI-C				X	X	X	X	X	X		X
PedsQL		X							X		
SAFETY											
AEs	X	X		X	X	X	X	X	X	X	X
Physical examination		X							X		
Height, weight, BMI	X	X			X		X		X		
Tanner puberty staging		X									

Date of last menstrual period	X	X		X	X	X	X	X	X		X
Vital signs	X[c]	X		X	X	X	X	X	X		X
12-lead ECG	X[c]	X		X					X		X[d]

	Screening[a]	BL	Double-Blind Treatment Period							Safety Follow-up	
	Days −28 to −2	Day −1	Day 1	Wk 1 (+ 2 days)	Days −28 to −2	Day −1	Day 1	Wk 1 (+ 2 days)	Days −28 to −2	Day −1	Day 1
Visit Type	**O**	**O**	**-**	**O**	**O**	**O**	**O**	**O**	**O**	**T**	**O**
Clinical laboratory tests	X[c]				X[e]				X		
C-SSRS	X	X		X	X	X	X	X	X	X	X
SMWQ-P/ SMWQ-PO									X	X	X
UDS	X	X		X	X	X	X	X	X		X
Alcohol testing											
PHARMACOKINETIC/ FUTURE BIOSPECIMEN RESEARCH ASSESSMENTS											
PK blood draws[g]					X				X		
FBR consent/assent	X										
FBR - DNA (optional)		X									
FBR - RNA (optional)		X			X				X		
FBR - plasma (optional)		X			X				X		
OTHER											
IMP dispensing		X		X	X	X	X	X			
IMP administration			X	X	X	X	X	X	X		
IMP return and accountability				X	X	X	X	X	X		
Entry/exit survey		X							X		

BL = baseline; BMI = body mass index; EOT = end of treatment; O = office; T = telephone; UDS = urine drug screen; Wk = week.

[a]The screening period included a washout period of 7 to 28 days. Screening assessments could be split across multiple visits if necessary. The screening period

maximum of 28 days could be extended after discussion with the medical monitor.
[b]If a positive urine pregnancy test was observed at baseline and a serum sample was required to be sent to the central lab, the medical monitor was informed before taking any action to screen fail the subject.
[c]If results are exclusionary, a repeat test was performed prior to the baseline visit; the results were verified prior to randomization.
[d]Required for subjects who did not consent to roll over to the open-label trial only.
[e]HbA1c was not assessed at Week 2.
[f]Alcohol testing was performed via breathalyzer only if considered necessary by the investigator.
[g]Two samples were collected at Week 2; two samples were collected at Week 6 and one sample at ET.
Source: Protocol 405-201-00021 Table 1.3-1

7.1.4.3. Statistical Analysis Plan

The SAP for Study 21 is generally similar to the SAPs for Studies 13, 14, and 16. The primary difference is that Study 21 has two age-related cohorts and Cohort 1 is the primary population for efficacy analyses. Efficacy analyses for Cohort 2 are not part of the multiple testing plan. Relevant statistical details important for Study 21 only are summarized below.

Sample Size

Cohort 1: The sample size, underlying assumptions, and power are as described for Study 16.

Cohort 2: A sufficient number of 4- to 5-year-old subjects were to be enrolled into Cohort 2 to reach approximately 90 randomized subjects for the purpose of safety assessment; this study was not powered adequately for assessment of the primary efficacy endpoint.

Primary Efficacy Analysis

The planned primary analysis was carried out separately for Cohort 1 and Cohort 2 using the methods described for Study 16. Of note, sensitivity analyses were only performed for Cohort 1. Additional sensitivity analyses were added for the primary and key secondary endpoints due to a weight-based dosage change for subjects with weight <20 kg in protocol amendment 2; as a result, the Applicant removed subjects who received centanafadine 41.1 mg QD XR from the FAS for these sensitivity analyses.

Type I Error Control

The study-wise type I error was controlled for both doses of centanafadine across the primary and key secondary endpoints for Cohort 1 only. The multiple testing as well as the hierarchy of endpoints was identical to Study 16; however, there was no type I error control over the primary and key secondary endpoints in Cohort 2 or in the combined Cohorts 1 and 2 because Cohort 2 was intended to be informative for safety purposes only.

Changes to Planned Analyses

In the final SAP dated July 24, 2023, the Sponsor added analyses of combined data from Cohort 1 and 2 to be analyzed in an exploratory fashion only. There was a separate SAP dated December 20, 2024, that outlines analyses for Cohort 2 and for the pooled data from Cohorts 1 and 2. In a Type C meeting dated October 25, 2022, the FDA agreed that it might be acceptable for the study protocol to include two age-related cohorts but advised that the analyses for Cohort 1 and Cohort 2 remain separate.

7.1.4.4. Protocol Amendments

The original protocol, which was submitted on March 15, 2022, was amended five times:

- Amendment 1 (September 20, 2022) was the only amendment implemented prior to the completion of Cohort 1.
- Amendment 2 (March 31, 2023) was never implemented due to FDA feedback prior to IRB review, which led to further amending of the protocol (i.e., Amendment 3).
- Amendment 3 (August 23, 2023) was never implemented, due to FDA feedback that required further amending of the protocol; however, a new protocol amendment was not possible as Cohort 1 recruitment was coming to an end.
- Amendment 4 (February 13, 2024) was implemented for Cohort 2, and included the changes described in Amendments 2 and 3.
- Amendment 5 (May 9, 2024) was the last amendment and was implemented for Cohort 2.

Amendment 1 included several updates, including clarifications, refinements of the eligibility criteria, updates to the IDMC procedure, and other changes. The most notable changes are summarized below:

- Revised the exclusionary resting supine SBP and DBP values:
  - For subjects 4 to 5 years: SBP from ≥108 mmHg to ≥122 mmHg and DBP from ≥66 mmHg to ≥80 mmHg
  - For subjects 6 to 8 years: SBP from ≥ 111 mmHg to ≥126 mmHg and DBP from ≥71 mmHg to ≥80 mmHg
  - For subjects 9 to 12 years: SBP from ≥115 mmHg to ≥130 mmHg and DBP from ≥76 mmHg to ≥80 mmHg.
- Removed the eligibility criterion that excluded subjects with a history or dermatologic adverse reactions due to any drug exposure and anaphylaxis to any substance.
- Specified that a subject would be considered for discontinuation if that subject met the specified criteria; changed “or” to “and” and added the timeframe of assessments, as shown in the following individual subject discontinuation criteria:
  - Resting, supine, and confirmed on two readings over two consecutive visits, SBP>130 mmHg and an increase from Baseline by 25 mmHg
  - Resting, supine, and confirmed on two readings over two consecutive visits, DBP>80 mmHg and an increase from Baseline by 15 mmHg
  - Resting, supine, and confirmed on two readings over two consecutive visits, pulse rate >120 bpm and an increase from Baseline by 30 bpm.
- Specified that the sample size would also provide at least 96% power at a 2-sided alpha level of 0.05 to detect the average effect of low dose and high dose centanafadine ER compared to placebo.

- The primary efficacy endpoint analysis was revised to describe the use of a global test and the test of the centanafadine ER dose (low dose or high dose) versus placebo instead of fixed sequence testing.
- The procedure to control the overall experiment-wise type I error was revised from a fixed sequence testing approach to describe a multiple testing procedure in which the analysis of the first key secondary endpoint would be conducted if both comparisons of low dose versus placebo and high dose versus placebo of the primary endpoint were significant and the analysis of the second key secondary endpoint would be conducted if both comparisons of low dose versus placebo and high dose versus placebo of the primary endpoint and the first key secondary endpoint were significant.

Amendment 2 (March 31, 2023) was implemented for Cohort 2 only and included updates to timing of safety and PK assessments, changes to exploratory endpoints, refinements of eligibility criteria and safety assessments, and other changes, the most notable of which were:

- Specified in the synopsis that the primary efficacy analysis for Cohort 2 would be performed similarly to Cohort 1.
- Specified that approximately 150 male and female subjects 4 to 5 years of age, inclusive, with a current diagnosis of ADHD were planned to be screened in order to randomize approximately 90 subjects ages 4 to 5 years.
- Discontinued enrollment into Weight Bin 1 (200 mg adult equivalent dose: 41.1 mg, 400 mg adult equivalent dose: 82.2 mg, placebo).
- Revised the lower weight limit for Weight Bin 2 to < 35 kg.
  - Revised the individual subject discontinuation for pulse rate:
  - >10% increase from Baseline and >144 bpm for 4- to 5-year-old subjects;
  - >10% increase from Baseline and >135 bpm for 6- to 8-year-old subjects;
  - >10% increase from Baseline and >127 bpm for 9- to 12-year-old subjects.
- Separated sample size details for 6- to 12-year-old subjects in Cohort 1 from those for 4- to 5-year-old subjects in Cohort 2.
- Specified that a sufficient number of 4- to 5-year-old subjects would be enrolled into Cohort 2 to achieve approximately 90 randomized subjects (30 subjects in each treatment arm).
- Specified that Cohort 1 (subjects 6- to 12-years-old) and Cohort 2 (subjects 4- to 5-years-old) data would be analyzed independently using the specified analysis sets.
- Specified that inferential statistics and descriptive statistics for appropriate efficacy and safety endpoints would be presented for Cohort 1 (subjects 6 to 12 years of age) and Cohort 2 (subjects 4 to 5 years of age) independently and that sensitivity analyses for the primary efficacy endpoints and key secondary efficacy endpoints would be performed for Cohort 1 only.
- Updated the primary efficacy endpoint analysis to remove age group as a fixed effect term from the model.

- Removed age group as a stratification factor in the sensitivity analyses judgment,
- Revised the individual subject discontinuation for pulse rate:
  - >10% increase from Baseline and >144 bpm for 4- to 5-year-old subjects
  - >10% increase from Baseline and >135 bpm for 6- to 8-year-old subjects
  - >10% increase from Baseline and >127 bpm for 9- to 12-year-old subjects

Amendment 3 (August 23, 2023) was implemented for Cohort 2 only and included the following changes:

- Removed the eGFR exclusion criterion.
- Added a per protocol analysis of only the to-be-marketed doses (i.e., removed subjects who received centanafadine once-daily ER capsules 35 mg).
- Revised the individual subject discontinuation criteria for pulse rate as follows: Resting, supine, and confirmed on two readings with 15 minutes apart, pulse rate:
  - 131 bpm for 4- to 5-year-old subjects
  - >123 bpm for 6- to 8-year-old subjects
  - >115 bpm for 9- to 12-year-old subjects

Amendment 4 (February 13, 2024) was implemented for Cohort 2 only and included the following changes:

- Removed the low dose centanafadine arm in Cohort 2 throughout the protocol.
- Modified the randomization in Cohort 2 to 2:1 ratio and revised the number of subjects randomized to weight-based high dose centanafadine to 60 subjects. Clarified that this cohort is not powered.
- Modified the exclusion criteria for resting supine blood pressure for subjects 4 to 5 years olds: SBP ≥109 mmHg and DBP ≥67 mmHg for 4-year-old subjects and SBP ≥111 mmHg and DBP ≥70 mmHg for 5-year-old subjects.
- Modified the individual subject discontinuation criteria for resting supine blood pressure for subjects 4 to 5 years old: SBP >121 mmHg and DBP >79 mmHg for 4-year-old subjects and SBP >123 mmHg and DBP >82 mmHg for 5-year-old subjects.
- Added information referencing the American Academy of Pediatrics (AAP) HTN Guideline that provides the definition of hypertension for children <13 years of age.

Amendment 5 (May 9, 2024) was implemented for Cohort 2 and included the following changes:

- Revised the exclusion criteria for blood pressure to add tables for blood pressure levels for boys and girls by age and height percentile to align with the AAP HTN Guideline to exclude subjects with Stage I hypertension.
- The individual subject discontinuation criteria for blood pressure were updated in alignment with the AAP HTN Guideline to discontinue subjects with Stage II hypertension.
- Revised the individual subject discontinuation criteria for pulse rate as follows:
  - ≥10% increase from Baseline and ≥131 bpm for 4- to 5-year-old subjects
  - ≥10% increase from Baseline and ≥123 bpm for 6- to 8-year-old subjects
  - ≥10% increase from Baseline and ≥115 bpm for 9- to 12-year-old subjects

7.1.5. Study Results: 405-201-00013

7.1.5.1. Compliance With Good Clinical Practices

The study report attests Study 13 was conducted in compliance with GCP guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by IRB or Independent Ethics Committee at each respective trial center.

7.1.5.2. Financial Disclosure

See Section 15.2.

7.1.5.3. Patient Disposition

The first informed consent document was signed on (b) (6), and the last trial visit was (b) (6). Of the 604 subjects enrolled in the trial, 584 subjects were treated during the placebo run-in period, 466 subjects were randomized into one of the three treatment groups (centanafadine twice-daily tablets 200 mg TDD, n = 154; centanafadine twice-daily tablets 400 mg TDD, n = 156; placebo, n = 156) and 446 subjects were treated during the double-blind treatment period (centanafadine twice-daily tablets 200 mg TDD, n = 149; centanafadine twice-daily tablets 400 mg TDD, n = 149; placebo, n = 148). A total of 348 (74.7%) subjects treated during the double-blind treatment completed and 98 (21.0%) subjects treated during the double-blind treatment discontinued the trial. Overall, the most commonly reported reasons for discontinuation from the double-blind treatment period were protocol deviation (n = 26 [5.6%]), AE (n = 19 [4.1%]), and withdrawal by subject (n = 15 [3.2%]).

Protocol Violations/Deviations

Ninety (20.2%) subjects experienced at least one protocol deviation; 11 of those experienced at least one COVID-19-related deviation during the trial. The most frequently reported deviation was prohibited medications (in 41 or 9.2% of subjects). COVID-19-related deviations included withdrawal per sponsor's instructions, missed visits, missed assessments due to visits completed virtually, and visits completed out of window. Overall, these protocol deviations were distributed relatively evenly between groups and are unlikely to have meaningfully impacted the study results.

7.1.5.4. Table of Demographic Characteristics

Overall, the baseline demographics and disease characteristics were well-balanced in subjects receiving centanafadine and subjects receiving placebo. The studies were conducted entirely in the United States. Greater than 60% of the subjects were male, which is consistent with the [redacted] ratios observed in clinical practice (Ramtekkar et al. 2010). The study population was ethnically diverse, although subjects of Asian, Alaskan Native, Pacific Islander, and Native Hawaiian heritage were underrepresented. Although the study population may differ somewhat from the general clinical population, the treatment groups had similar racial and ethnic compositions, making it unlikely that sociodemographic factors influenced the study results. Table 30 summarizes the baseline demographic characteristics of the primary efficacy population for Study 13.

Table 30. Demographic Characteristics of the Primary Efficacy Analysis - Study 13

Demographic Parameters	**Control Group** (N=156) n (%)	**Treatment Group** (N)		**Total** (N=466) n (%)
		Centanafadine tablets 200 mg TDD (N=154) n (%)	Centanafadine tablets 400 mg TDD (N=156) n (%)	
Sex				
Male	80 (51)	78 (51)	81 (52)	239 (51)
Female	76 (49)	76 (49)	75 (48)	227 (49)
Age				
Mean years (SD)	35.0 (9.9)	36.6 (9.8)	35.3 (10.4)	35.6 (10.0)
Median (years)	34	36	34	35
Min, max (years)	18. 54	18, 55	18, 55	18, 55
Race				
White	130 (83)	126 (82)	123 (79)	379 (81)
Black or African American	21 (13)	19 (12)	23 (15)	63 (14)
Asian	4 (3)	4 (3)	2 (1)	10 (2)
American Indian or Alaska Native	0	0	3 (2)	3 (1)
Native Hawaiian or Other Pacific Islander	0	1 (1)	1 (1)	2 (<1)
Other	1 (1)	4 (3)	4 (3)	9 (2)

Demographic Parameters	**Control Group** (N=156) n (%)	**Treatment Group** (N)		**Total** (N=466) n (%)
		Centanafadine tablets 200 mg TDD (N=154) n (%)	Centanafadine tablets 400 mg TDD (N=156) n (%)	
Ethnicity				
Hispanic or Latino	29 (19)	34 (22)	38 (24)	101 (22)
Not Hispanic or Latino	124 (79)	119 (77)	116 (74)	356 (76)
Other	2 (1)	1 (1)	0	3 (1)
Unknown	1 (1)	0	2 (1)	3 (1)

Source: Reviewer-generated

7.1.5.5. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

There were some differences between treatment groups in psychiatric history. A higher number of subjects in the placebo group (8 subjects or 5.1%) reported a history of anxiety, compared to the centanafadine twice-daily tablets 200 mg TDD group (5 subjects or 3.2%) and the 400 mg TDD group (no subjects). This imbalance is relevant to the safety analyses, given that adverse events of anxiety occurred at a rate of greater than 2% and in more subjects in the centanafadine groups compared with placebo. See Section 7.2.5 for discussion of how the underlying imbalance in anxiety history may lead to underestimation of the risk of anxiety.

There was also an imbalance between groups in terms of history of depression. In the centanafadine twice-daily tablets 200 mg TDD and placebo groups, 9 (5.8%) subjects reported history of major depression, compared with 16 (10.3%) subjects in the 400 mg TDD group. This imbalance is relevant to the safety analyses, given that AEs related to depressed mood occurred in more subjects in the centanafadine groups compared with placebo. See Section 7.2.5 for further discussion.

Importantly, AISRS total score and subscale scores were similar at Baseline of the single-blind placebo run-in period and of the double-blind treatment period between the centanafadine and placebo groups. The same was true of CGI-S scores.

7.1.5.6. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall, based on study drug log data, the majority of subjects were ≥90% adherent during the double-blind treatment period, with similar rates of adherence between treatment groups.

7.1.5.7. Efficacy Results – Primary Endpoint

The statistical review confirmed that Study 13 met its primary objective for both dose levels of centanafadine. Centanafadine twice-daily tablets 200 mg TDD and 400 mg TDD each

demonstrated a statistically significant reduction from Baseline in AISRS total score at Week 42 vs. placebo: 200 mg: LS mean difference -3.15 (95% CI: -5.79, - 0.51); 400 mg: -2.74 (95% C: -5.35, -0.14). Because higher AISRS scores indicate greater severity, the reduction for each dose represents improved ADHD symptoms.

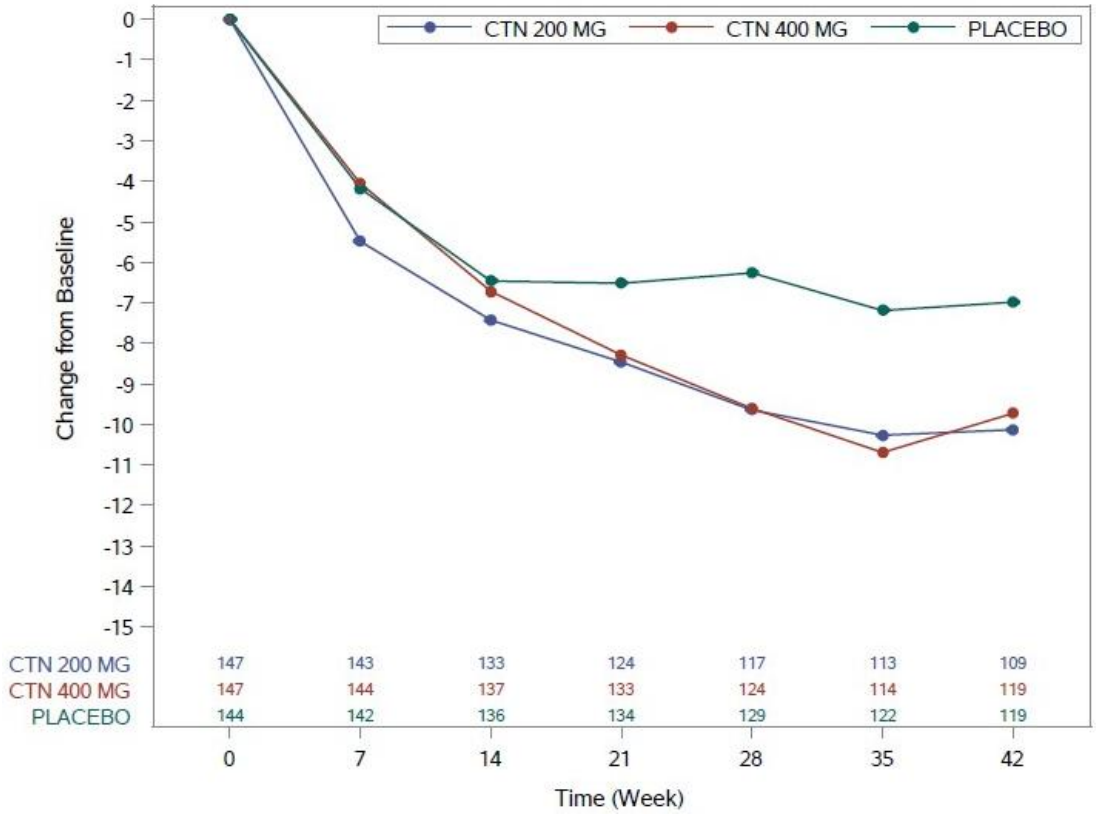
In addition, sensitivity analyses were performed for each dose level of centanafadine vs. placebo to assess the impact of deviations from the MAR assumption used in the primary efficacy analysis on efficacy results. Overall, results of these analyses supported the primary efficacy findings.

Table 31. Study 405-201-00013 Primary Analysis Results on Change From Baseline in AISRS Total Score (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine tablets 200 mg TDD	Centanafadine tablets 400 mg TDD
Baseline			
N	144	147	147
Mean (SD)	39.53 (7.20)	39.6 (6.69)	39.56 (6.82)
Week 42			
n	109	119	119
LS mean (SE)	-6.98 (0.98)	-10.1 (0.99)	-9.73 (0.98)
LS mean difference (SE)		-3.15 (1.34)	-2.74 (1.33)
95% CI for LS mean difference		(-5.79, -0.51)	(-5.35, -0.14)
p-value		0.0193	0.0392

AISRS = Adult ADHD Investigator Symptom Rating Scale; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00013 clinical study report, pages 53, 55, 254, and 255 (Tables 11.2-3, 11.4.1.1-1, and CT-5.2.1.1)

Figure 9. Study 405-201-00013 Least Squares Mean of Change From Baseline in AISRS Total Score by Treatment Arm and Study Week, FAS Population

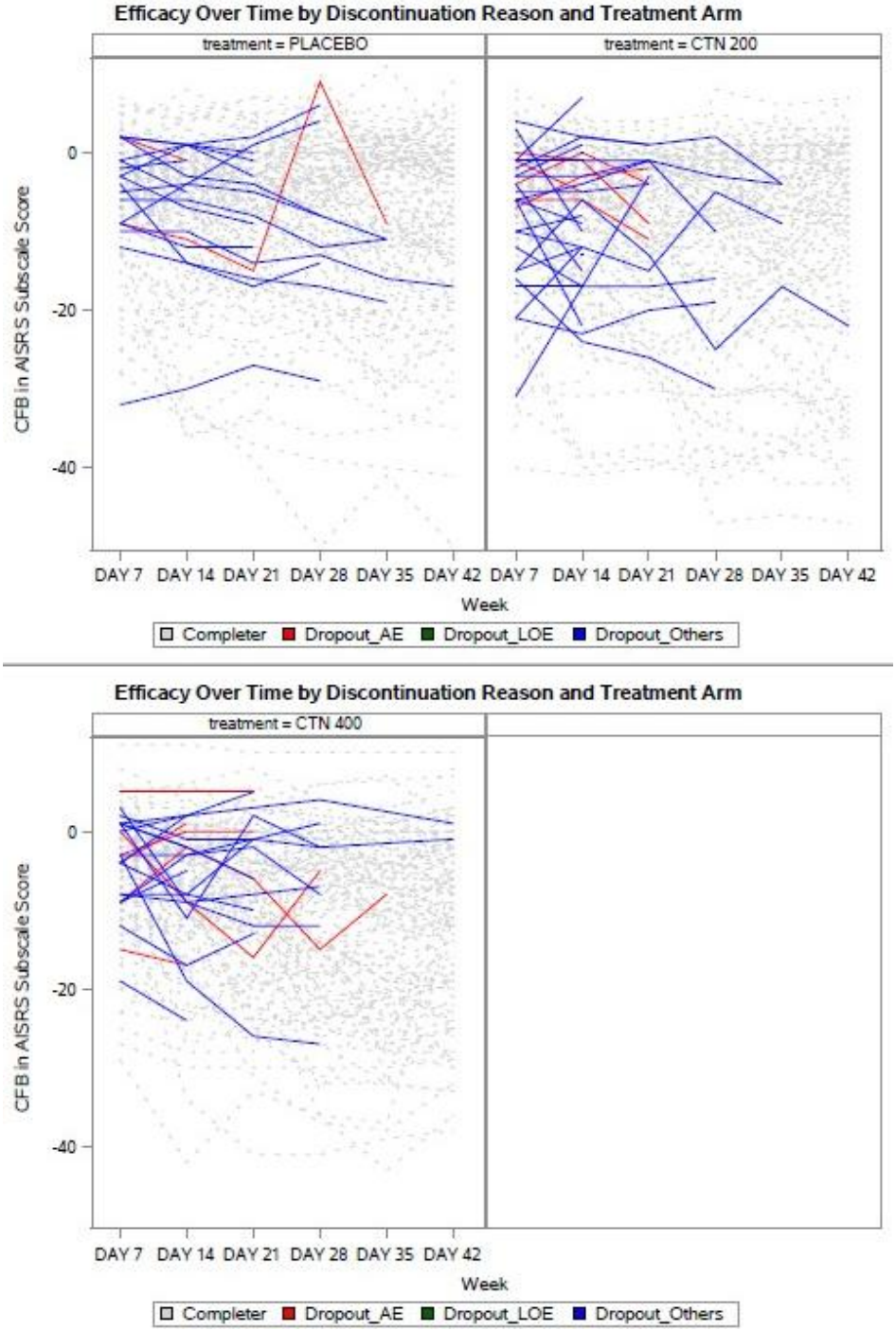


AISRS = Adult ADHD Investigator Symptom Rating Scale; MMRM = Mixed Model for Repeated Measures
Source: Created by statistical reviewer

Graphical Assessment of Dropouts

A graphical assessment of longitudinal trajectories was conducted to explore the plausibility of the MAR assumption in the presence of study dropouts. For each treatment arm, the overall response trajectories of dropouts up to the dropout week do not appear very different from those of the completers, which provides some empirical support for the MAR assumption.

Figure 10. Study 405-201-00013 Change From Baseline in AISRS Total Score Over Time by Discontinuation Reason Within Treatment Arm



AISRS = Adult ADHD Investigator Symptom Rating Scale; MMRM = Mixed Model for Repeated Measures; CFB = change from baseline
Source: Created by statistical reviewer

Data Quality and Integrity

The review team did not identify any concerns regarding data quality or integrity. All datasets and documentation were adequate to complete review of the study.

7.1.5.8. Efficacy Results – Secondary and Other Relevant Endpoints

Both doses of centanafadine showed statistically significant benefits in change from baseline of the CGI-S at Week 42 versus placebo with results verified by the statistical reviewer: twice-daily tablet 200 mg, LS mean difference -0.27 (95% CI: -0.50, -0.04); twice-daily tablet 400 mg, LS mean -0.28 (95% CI: -0.51, -0.05). Of note, although a reduction in CGI-S score does represent an improvement and the results did reach statistical significance at the 2-sided 0.05 level, the differences in LS means for each centanafadine dose versus placebo offer some support for the primary endpoint results.

As for the primary endpoint, sensitivity analyses were performed for each dose level of centanafadine versus placebo to assess the MAR assumption used in the key secondary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings.

Table 32. Study 405-201-00013 Key Secondary Analysis Results for Change From Baseline in CGI-S (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine Tablets 200 mg TDD	Centanafadine Tablets 400 mg TDD
Baseline			
N	144	146	147
Mean (SD)	4.51 (0.55)	4.48 (0.60)	4.53 (0.60)
Week 42			
n	109	119	119
Mean (SD)	3.33 (0.94)	3.17 (1.02)	3.04 (0.93)
LS mean (SE)	-0.52 (0.08)	-0.78 (0.09)	-0.79 (0.08)
LS mean difference (SE)		-0.27 (0.12)	-0.28 (0.12)
95% CI for LS mean difference		(-0.50, -0.04)	(-0.51, -0.05)
p-value		0.0232	0.0162

CGI-S = Clinical Global Impressions – Severity; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00013 clinical study report, pages 53,59, and 254 (Tables 11.2-3, 11.4.1.2-1, and CT-5.1)

Dose/Dose Response

Based on the primary and key secondary efficacy analyses, the treatment effect was similar for centanafadine tablets 200 mg and 400 mg TDD. These results suggest a flat dose-response

relationship for efficacy. However, some exploratory endpoints showed nominally significant results in the higher and not the lower dose group, suggesting some degree of dose-response.

Durability of Response

There was no apparent waning of response over 6 weeks of treatment.

Persistence of Effect

There were no prespecified endpoints assessing persistence of effect beyond drug exposure. As noted above in 7.1.1.4, the Applicant stated in a response to an IR from the Agency that "response at 7 days post-dosing remained decreased, suggesting a duration of effect beyond the 7-day follow-up window." However, the study reports, Summary of Clinical Efficacy, and Integrated Summary of Efficacy do not present post-exposure efficacy data. Overall, despite the Applicant's assertion in the response to IR, this study does not demonstrate persistence of effect beyond centanafadine exposure.

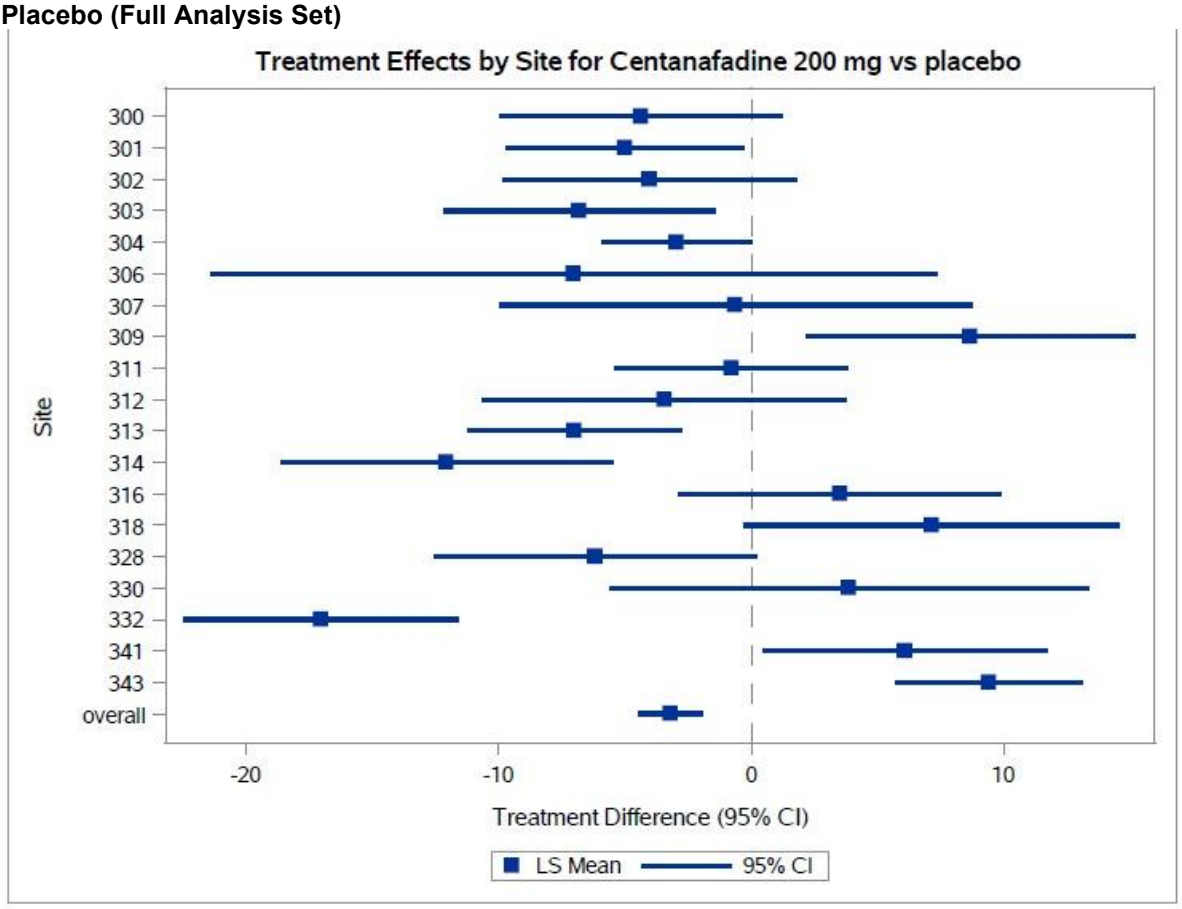
7.1.5.9. Efficacy Results –Exploratory COA Endpoints

The Applicant's exploratory analyses of other endpoints suggested a trend in favor of the high dose when compared with placebo.

7.1.5.10. Additional Analyses Conducted on the Individual Trial

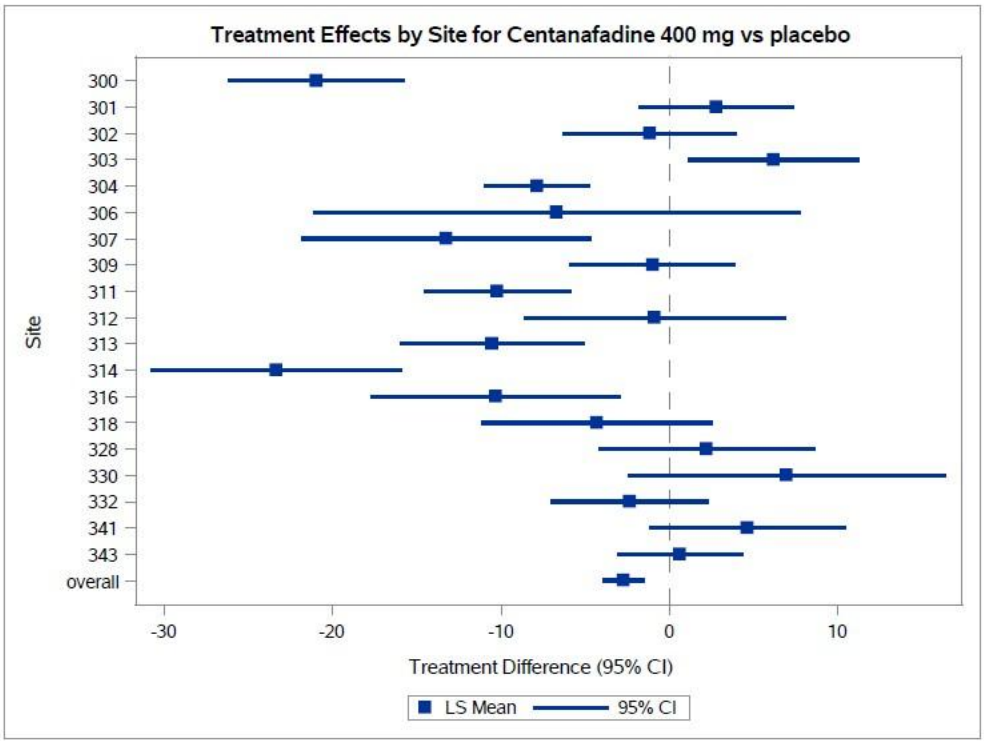
A small number of sites were identified in the course of the review as having extreme values, either with results favoring centanafadine or placebo. The forest plots created by the statistical reviewer show the results for the primary endpoint separately for centanafadine 200 TDD mg vs. placebo and centanafadine 400 mg TDD vs. placebo at individual sites having more than 10 participants enrolled. The sample size at individual sites is small, which makes the power for individual site comparisons low. The extreme values for Sites 332 and 323 in Figure 11 and Sites 300 and 314 in Figure 12 do not meaningfully change the overall conclusion of statistical significance for change from baseline in the AISRS Total Score for both centanafadine dose levels.

Figure 11. Study 405-201-00013 Forest Plot of Treatment Effect by Site for the Primary Endpoint of Change From Baseline in AISRS Total Score for the Comparison of Centanfadine 200 mg vs. Placebo (Full Analysis Set)



AISRS = Adult ADHD Investigator Symptom Rating Scale; LS = Least Squares; CI = Confidence Interval
Source: created by statistical reviewer

Figure 12. Study 405-201-0013 Forest Plot of Treatment Effect by Site for the Primary Endpoint of Change From Baseline in AISRS Total Score for the Comparison of Centanfadine 400 mg vs. Placebo (Full Analysis Set)



AISRS = Adult ADHD Investigator Symptom Rating Scale; LS = Least Squares; CI = Confidence Interval
Source: created by statistical reviewer

7.1.6. Study Results: 405-201-00014

7.1.6.1. Compliance With Good Clinical Practices

The study report attests Study 14 was conducted in compliance with GCP guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by IRB or Independent Ethics Committee at each respective trial center.

However, the Applicant was notified of allegations of GCP noncompliance at Site 407 (Principal Investigator: Eduardo Cifuentes, MD) on June 24, 2020. The Applicant performed a remote directed clinical investigator audit on July 22 through July 24, 2020. The findings of the audit appear to affirm the allegation of sharing Dr. Cifuentes' database authentication for Study 14. These findings were reported to the FDA Office of Compliance, the Division of Psychiatry, and the IRB. Due to this finding, a sensitivity analysis was conducted for the primary and key secondary endpoints. Results are described in Additional Analyses Conducted on the Individual

Trial below.

7.1.6.2. Financial Disclosure

See Section 15.2.

7.1.6.3. Patient Disposition

The first subject informed consent document was signed on (b) (6). The last study visit was on (b) (6). Of the 590 subjects enrolled in the trial, 579 subjects were treated during the placebo run-in period, 440 subjects were randomized into one of the three treatment groups (centanafadine twice-daily tablets TDD 200 mg, n = 147; centanafadine twice-daily tablets TDD 400 mg, n = 147; placebo, n = 146) and 430 subjects were treated during the double-blind treatment period (centanafadine twice-daily tablets 200 mg, n = 145; centanafadine twice-daily tablets 400 mg, n = 143; placebo, n = 142). Of the 430 subjects treated during the double-blind period, 336 (76.4%) subjects completed and 94 (21.4%) discontinued the trial. The most commonly reported reasons for discontinuation from the double-blind treatment period were other (not related to COVID-19) (6.6%), withdrawal by subject (4.5%), and AE (3.0%).

Protocol Violations/Deviations

One hundred seventeen (27.2%) subjects experienced at least one protocol deviation and 71 (16.5%) of these subjects experienced at least one COVID-19-related deviation during the trial. The most frequently reported deviation was “other” (which included all COVID-19-related deviations), occurring in 91 (21.2%) of subjects. COVID-19-related deviations included visit completed remotely, missed visits, missed assessments due to visits completed virtually, visits conducted in-clinic rather than virtually per PI judgment, assessments not completed at onsite visits due to COVID-19, and visits completed out of window. Overall, the number and nature of protocol deviations were similar between treatment arms and are unlikely to have meaningfully impacted study results.

7.1.6.4. Table of Demographic Characteristics

Overall, the baseline demographics and disease characteristics were well-balanced in subjects receiving centanafadine twice-daily tablets and subjects receiving placebo. The studies were conducted entirely in the United States. The majority of subjects were male, which is consistent with the ratios observed in clinical practice (Ramtekkar et al. 2010). The majority were White (78.6%), followed by Black or African American (13.0%); the majority were not Hispanic or Latino (80.7%). Asian, Alaskan Native, Pacific Islander, and Native Hawaiian populations were underrepresented. Although the study population may differ somewhat from the general clinical population, the treatment groups had similar racial and ethnic compositions, making it unlikely that sociodemographic factors influenced the study results. Table 33 summarizes the baseline demographic characteristics of Study 14.

Table 33. Demographic Characteristics of the Primary Efficacy Analysis - Study 14

Demographic Parameters	Control Group (N=146) n (%)	Treatment Group		Total (N=440) n (%)
		Centanafadine tablets 200 mg TDD (N=147) n (%)	Centanafadine tablets 400 mg TDD (N=147) n (%)	
Sex				
Male	80 (55)	76 (52)	77 (52)	233 (53)
Female	66 (45)	71 (48)	70 (48)	207 (47)
Age				
Mean years (SD)	35.2 (9.6)	34.5 (9.7)	35.2 (10.4)	35.0 (9.9)
Median (years)	35	32	33	33
Min, max (years)	18, 54	18, 55	18, 55	18, 55
Race				
White	114 (78)	112 (76)	120 (82)	346 (79)
Black or African American	21 (14)	17 (12)	19 (13)	57 (13)
Asian	6 (4)	10 (7)	2 (1)	18 (4)
American Indian or Alaska Native	2 (1)	0	2 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	0	1 (1)	0	1 (<1)
Other	3 (2)	7 (5)	4 (3)	14 (3)
Ethnicity				
Hispanic or Latino	29 (20)	27 (18)	23 (16)	79 (18)
Not Hispanic or Latino	116 (79)	117 (80)	122 (83)	355 (81)
Other	1 (1)	3 (2)	1 (1)	5 (1)
Unknown	0	0	1 (1)	1 (<1)

Source: Reviewer-generated

7.1.6.5. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Subjects across the three treatment arms generally had similar reported psychiatric comorbidities. However, more subjects in the placebo group (10 subjects or 6.8%) reported a history of depression compared with 4 (2.7%) subjects in the centanafadine twice-daily tablets 200 mg TDD group and 2 (1.4%) subjects in the centanafadine twice-daily tablets 400 mg TDD group. 21 (14.3%) subjects in the centanafadine twice-daily tablets 200 mg TDD group, 14 (9.5%) subjects in the centanafadine twice-daily tablets 400 mg TDD group, and 16 (11.0%) subjects in the placebo group reported a history of MDD.

Subjects across the three treatment arms also had similar AISRS total score and subscale scores at Baseline of the single-blind placebo run-in period and at Baseline of the double-blind treatment period. There were no apparent differences between the treatment arms in CGI-S score at Baseline of the double-blind treatment period.

7.1.6.6. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall, based on study log data, the majority of subjects were ≥90% adherent with dosing during the double-blind treatment period. Adherence was similar between treatment groups.

7.1.6.7. Efficacy Results – Primary Endpoint

The statistical review confirmed that Study 14 met its primary objective for both dose levels of centanafadine. Centanafadine twice-daily tablets 200 mg TDD and 400 mg TDD each demonstrated a statistically significant reduction from Baseline in AISRS total score at Week 42 vs. placebo: 200 mg: LS mean difference -4.01 (95% CI: -6.55, - 1.46); 400 mg: -4.42 (95% CI: -7.02, -1.82). Higher AISRS scores indicate greater severity, thus the reduction for each dose represents improved ADHD symptoms.

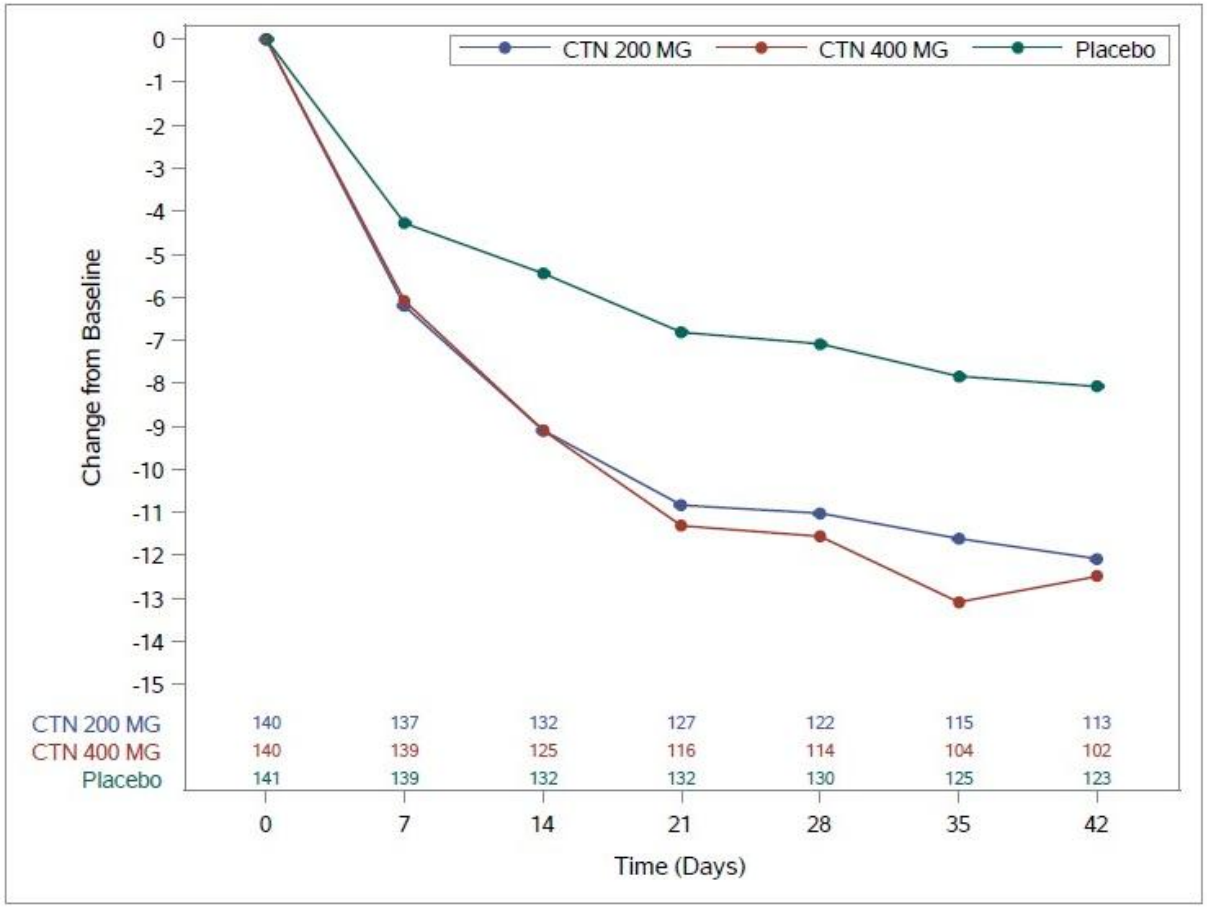
In addition, sensitivity analyses were performed for each dose level of centanafadine vs. placebo to assess the MAR assumption used in the primary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings. The Applicant identified a quality issue at site 407; removing participants from this site did not meaningfully change the results of the primary endpoint.

Table 34. Study 405-201-00014 Primary Analysis Results for Change From Baseline in AISRS Total Score (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine twice-daily tablets 200 mg TDD	Centanafadine twice-daily tablets 400 mg TDD
N	141	140	140
Mean (SD)	37.8 (6.5)	37.6 (6.7)	38.6 (7.0)
Day 42			
n	123	113	102
LS mean (SE)	-8.07 (0.94)	-12.1 (0.96)	-12.5 (0.99)
LS mean difference (SE)		-4.01 (1.29)	-4.42 (1.32)
95% CI for LS mean difference		(-6.55, -1.46)	(-7.02, -1.82)
p-value		0.0021	0.0009

AISRS = Adult ADHD Investigator Symptom Rating Scale; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00014 clinical study report, pages 53 and 55 (Tables 11.2-3 and 11.4.1.1-1)

Figure 13. Study 405-201-00014 Least Squares Mean of Change From Baseline in AISRS Total Score by Treatment Arm and Study Week (Full Analysis Set)

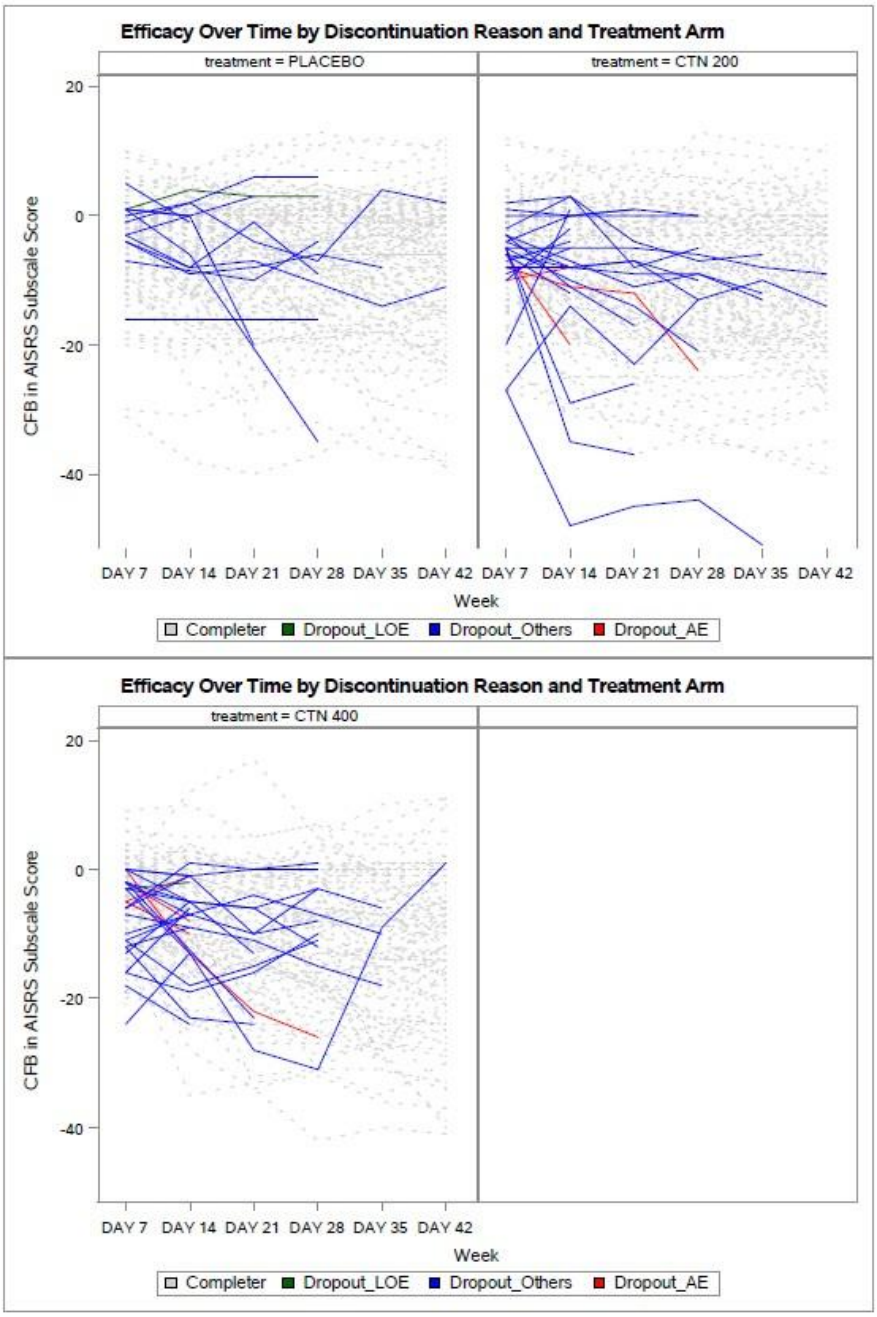


AISRS = ADHD Adult ADHD Investigator Symptom Rating Scale; MMRM = Mixed Model for Repeated Measures
Source: Created by statistical reviewer

Graphical Assessment of Dropouts

A graphical assessment of longitudinal trajectories was conducted to explore the plausibility of the MAR assumption in the presence of study dropouts. For each treatment arm, the overall response trajectories of dropouts up to the dropout week do not appear very different from those of the completers, which provides some empirical support for the MAR assumption.

Figure 14. Study 405-201-00014 Change From Baseline in AISRS Total Score Over Time by Discontinuation Reason Within Treatment Arm



AISRS = ADHD Adult ADHD Investigator Symptom Rating Scale
Source: Created by statistical reviewer Dr. Michelle Marcovitz

Data Quality and Integrity

The review team did not identify any concerns regarding data quality or integrity. All datasets and documentation were adequate to complete review of the study.

7.1.6.8. Efficacy Results – Secondary and Other Relevant Endpoints

Both doses of centanafadine showed statistically significant benefits in change from Baseline of the CGI-S at Week 42 versus placebo with results verified by the statistical review: 200 mg, LS mean difference -0.33 (95% CI: -0.57, -0.09); 400 mg, LS mean -0.28 (95% CI: -0.53, -0.04). As discussed in 7.1.5 for Study 14, the difference in LS means for each centanafadine dose vs. placebo offers some support for the primary endpoint results.

As for the primary endpoint, sensitivity analyses were performed for each dose level of centanafadine vs. placebo to assess the MAR assumption used in the key secondary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings.

Table 35. Study 405-201-00014 Key Secondary Analysis Results for Change From Baseline in CGI-S (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine twice-daily tablets 200 mg TDD	Centanafadine twice-daily tablets 400 mg TDD
N	141	140	140
Mean (SD)	4.52 (0.56)	4.56 (0.57)	4.66 (0.55)
Week 42			
n	122	111	102
LS mean (SE)	-0.68(0.09)	-1.04 (0.09)	-0.99 (0.09)
LS mean difference (SE)		-0.33 (0.12)	-0.28 (0.12)
95% CI for LS mean difference		(-0.57, -0.09)	(-0.53, -0.04)
p-value		0.0073	0.0245

CGI-S = Clinical Global Impressions – Severity; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00014 CSR, pages 53, 61, and 70 (Tables 11.2-3, 11.4.1.2-1, and 11.4.1.3.3.-1)

Dose/Dose Response

Based on the primary and key secondary efficacy analyses, the treatment effect was similar for centanafadine twice-daily tablets 200 mg and 400 mg TDD. These results suggest a flat dose-response relationship for efficacy.

Durability of Response

There was no apparent waning of response over 6 weeks of treatment.

Persistence of Effect

This study did not assess persistence of effect beyond drug exposure.

7.1.6.9. Efficacy Results –Exploratory COA Endpoints

The Applicant's exploratory analyses of other endpoints suggested a trend in favor of the high dose when compared with placebo.

7.1.6.10. Additional Analyses Conducted on the Individual Trial

Sensitivity analyses were performed to assess the impact of COVID-19 on the primary efficacy analysis by excluding efficacy data impacted by COVID-19 at subject level or visit level. For example, one analysis excluded data collected by remote assessment. These sensitivity analyses confirmed the results of the primary efficacy analysis.

An additional sensitivity analysis assessed the impact of Site 407 on the primary efficacy analysis due to the GCP event that occurred at that site. This analysis confirmed the results of the primary efficacy analysis.

7.1.7. Study Results: 405-201-00016

7.1.7.1. Compliance with Good Clinical Practices

The study report attests that the trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.

7.1.7.2. Financial Disclosure

See Section 15.2.

7.1.7.3. Patient Disposition

Overall, 459 subjects were enrolled in the trial and randomized into one of the three treatment groups (centanafadine ER 280 mg, n = 155 subjects; centanafadine ER 140 mg, n = 155 subjects; and placebo, n = 149 subjects). Of 451 subjects treated during the double-blind period, 371 (82.3%) subjects completed and 80 (17.7%) discontinued the trial. The most commonly reported reason for discontinuation was withdrawal by parent or legal guardian (19 of 459 subjects [4.1%]), followed by adverse events and lost to follow-up (17 subjects [3.7%] for each). Discontinuations due to AEs occurred in 12 subjects (7.7%) in the centanafadine ER 240 mg group, 5 subjects (3.2%) in the centanafadine ER 140 mg group, and no subjects in the placebo group.

Protocol Violations/Deviations

Most of the protocol deviations were procedural deviations (e.g., missing follow-up visit, missing assessment, uncertified rater) or prohibited medications. Procedural deviations occurred to a similar extent across the three treatment groups. Deviations due to prohibited medications were most common in the high-dose (280 mg) centanafadine ER group (13 subjects or 8.4%) compared with low dose (140 mg) centanafadine ER (10 subjects or 6.5%) and placebo (8 subjects or 5.4%). There were no protocol deviations due to COVID-19.

There was one trial site with critical audit findings (Site 035, Dr. Lawrence Ginsburg). After completion of the trial, an audit (conducted October 30, 2023, to November 2, 2023) raised concerns about the Investigator's lack of oversight of administration of the efficacy assessments. As a result, the Applicant closed the trial site. A sensitivity analysis was conducted on the primary endpoint excluding this site (see Additional Analyses Conducted on the Individual Trial below).

7.1.7.4. Table of Demographic Characteristics

Overall, the baseline demographics and disease characteristics were well-balanced in subjects receiving centanafadine ER and subjects receiving placebo. The studies were conducted entirely in the United States. The majority of subjects were male, which is consistent with the [redacted] ratios observed in clinical practice (Ramtekkar et al. 2010). The majority were White (70%), followed by Black or African American (25%); the majority were not Hispanic or Latino (72%). Asian, Alaskan Native, Pacific Islander, and Native Hawaiian populations were underrepresented. Although the study population may differ somewhat from the general clinical population, the treatment groups had similar racial and ethnic compositions, making it unlikely that sociodemographic factors influenced the study results. Table 36 summarizes the baseline demographic characteristics of Study 16.

Table 36. Demographic Characteristics of the Primary Efficacy Analysis Study 16

Demographic Parameters	Control Group (N= 149) n (%)	Treatment Group (N= 310)		Total (N= 459) n (%)
		Centanafadine ER 140 mg (N= 155) n (%)	Centanafadine ER 280 mg (N= 155) n (%)	
Sex				
Male	87 (58)	86 (55)	99 (64)	272 (59)
Female	62 (42)	69 (45)	56 (36)	187 (41)
Age				
Mean years (SD)	14.7 (1.3)	14.5 (1.3)	14.7 (1.4)	14.7 (1.3)
Median (years)	15	14	14	14
Min, max (years)	13, 17	13, 17	13, 17	13, 17

Demographic Parameters	Control Group (N= 149) n (%)	Treatment Group (N= 310)		Total (N= 459) n (%)
		Centanafadine ER 140 mg (N= 155) n (%)	Centanafadine ER 280 mg (N= 155) n (%)	
Race				
White	107 (74)	106 (68)	110 (71)	323 (70)
Black or African American	35 (23)	43 (28)	36 (23)	114 (25)
Asian	1 (1)	4 (3)	1 (1)	6 (1)
American Indian or Alaska Native	3 (2)	0	1 (1)	4 (1)
Native Hawaiian or Other Pacific Islander	0	0	1 (1)	1 (<1)
Other[1]	3 (2)	2 (1)	6 (4)	11 (2)
Ethnicity				
Hispanic or Latino	50 (34)	40 (26)	39 (25)	129 (28)
Not Hispanic or Latino	99 (66)	115 (74)	116 (75)	330 (72)

Source: Reviewer-generated

7.1.7.5. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The three treatment arms were generally balanced in terms of height, weight, body mass index (BMI), and Tanner stage. More subjects had comorbid generalized anxiety disorder, major depression, or social anxiety disorder in the centanafadine ER 140 mg group (19 subjects or 13%) and the placebo group (15 subjects or 10%) compared with the centanafadine ER 280 mg group (4 subjects or 3%). More subjects had oppositional defiant disorder in the centanafadine ER 280 mg group (7 subjects or 5%) than in the centanafadine ER 140 mg and placebo groups (2 subjects or 1% in each group). There were more subjects with anxiety in the centanafadine ER 280 mg group (3 subjects) and the placebo group (5 subjects) than in the centanafadine ER 140 mg group (0 subjects). More subjects had insomnia in the centanafadine ER 280 mg group (2 subjects) and the centanafadine ER 140 mg group (3 subjects) than in the placebo group (0 subjects). ADHD-RS-5, Conners 3, CGI-S, and PGI-S scores were similar between the treatment arms.

7.1.7.6. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Because subjects were provided with extra study drug to cover the visit windows, the maximum possible compliance score was 120%. Of 451 subjects:

- 47 (10.4%) were ≥80% to <90% compliant.
- 163 (36.1%) were ≥90% to <100% compliant.
- 234 (51.9%) were ≥100% to <110% compliant.

Compliance was similar across the three treatment groups. No subjects in any treatment group

reported ≥110% compliance with the IMP. Overall, 7 subjects were <80% compliant: 1 of 151 subjects (0.7%) in the centanafadine ER 328.8 mg arm, 4 of 153 subjects (2.6%) in the centanafadine ER 164.4 mg arm, and 2 of 147 subjects (1.4%) in the placebo arm.

7.1.7.7. Efficacy Results – Primary Endpoint

The statistical review confirmed that Study 16 met its primary objective for the 280 mg dose of centanafadine ER for the change from Baseline in ADHD-RS-5 total score at Week 6 vs. placebo: LS mean difference -4.35 (95% CI: -6.83, - 1.87). Higher ADHD-RS-5 scores indicate greater severity, thus the reduction for each dose represents improved ADHD symptoms. The statistical review confirmed the result for the 140-mg dose of centanafadine ER vs. placebo for the same endpoint, which did not reach statistical significance at the two-sided 0.05 level, so it is reported descriptively here: LS mean difference –1.30 (95% CI: -3.77, 1.77).

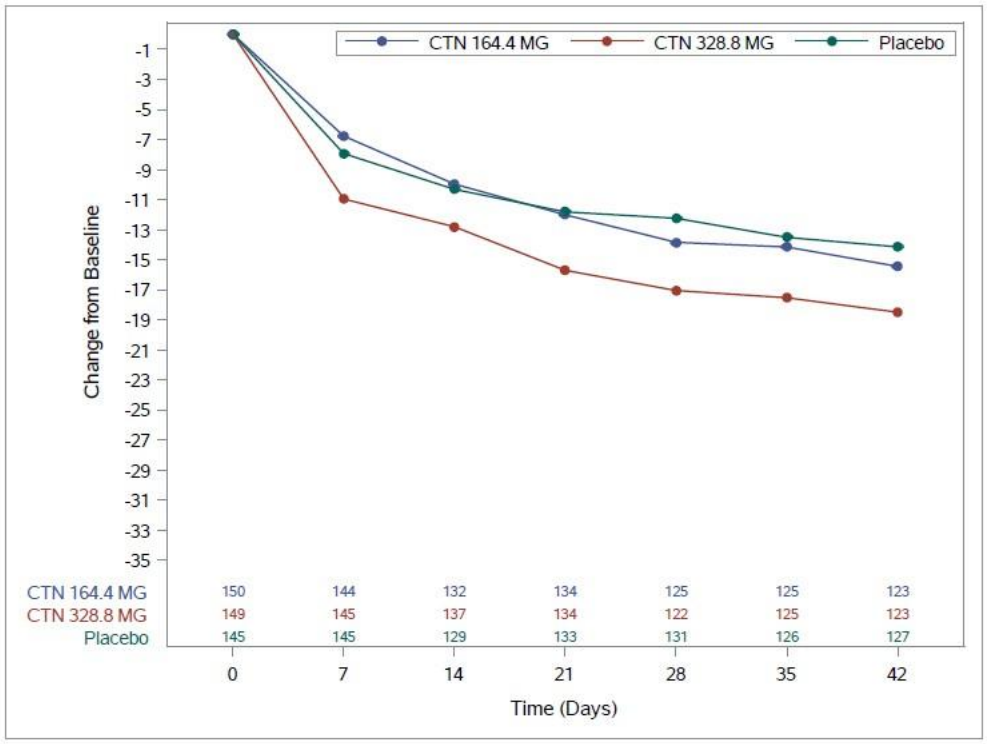
In addition, sensitivity analyses—including two MMRM analyses with a copy placebo multiple imputation (MI) approach 1) MI using MCMC and 2) MI using a monotone approach—and a tipping-point analysis were performed for each dose level of centanafadine vs. placebo to assess the MAR assumption used in the primary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings.

Table 37. Study 405-201-00016 Primary Analysis Results for Change From Baseline in the ADHD-RS-5 (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine ER 140 mg	Centanafadine ER 280 mg	Average (140 mg and 280 mg ER)
N	145	150	149	
Mean (SD)	37.01 (5.73)	37.86 (6.08)	37.87 (6.44)	
Week 6				
n	126	125	125	
LS mean (SE)	-14.15 (0.93)	-15.45 (0.92)	-18.50 (0.93)	
LS mean difference (SE)		-1.30 (1.26)	-4.35 (1.26)	
95% CI for LS mean difference		(-3.77, 1.17)	(-6.83, -1.87)	
p-value		0.3016	0.0006	0.0099

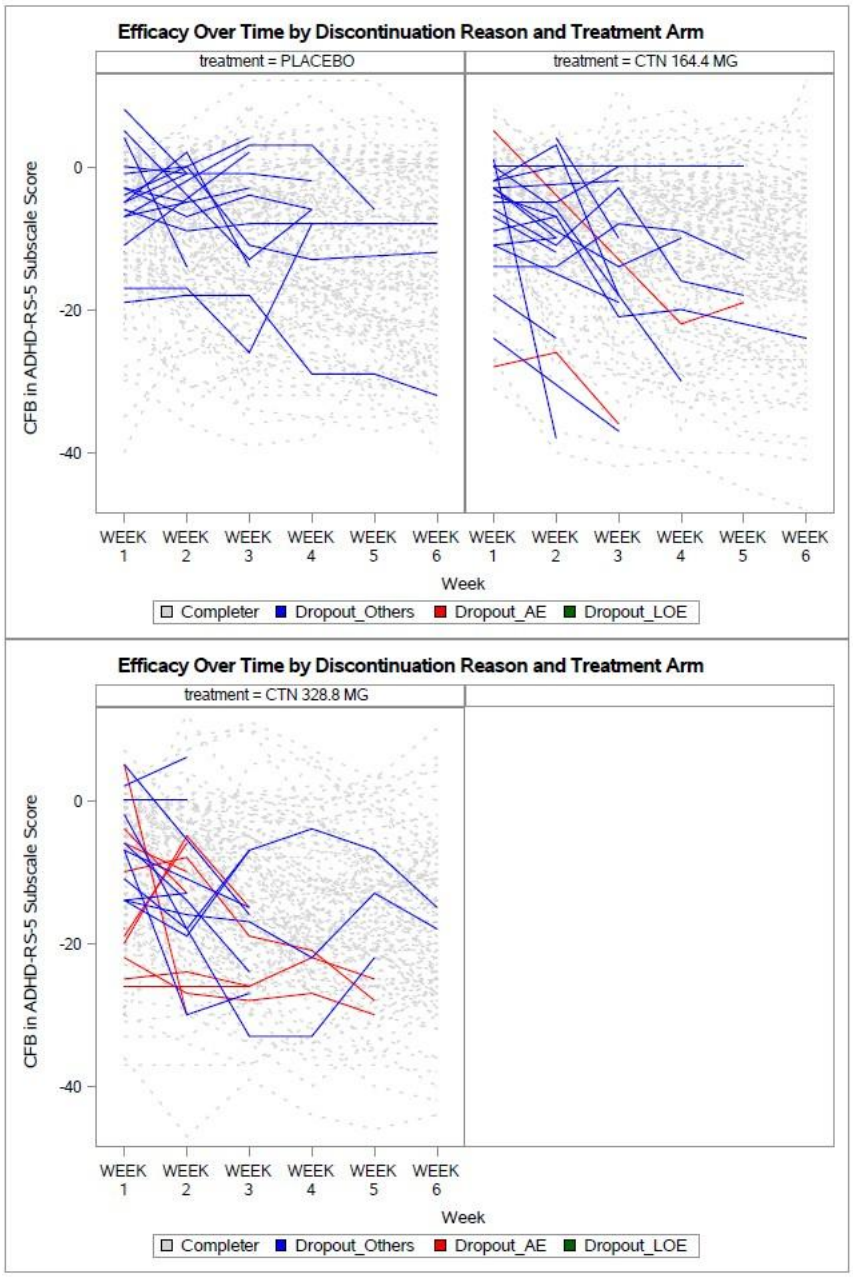
ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00016 clinical study report, pages 65 and 69 (Tables 11.2-3 and 11.4.1.1-1)

Figure 15. Study 405-201-00016 Least Squares Mean of Change From Baseline in ADHD-RS-5 Total Score by Treatment Arm and Study Week (Full Analysis Set)



ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CTN 164.6 mg = centanafadine ER capsules 140 mg; CTN 328.8 mg centanafadine ER capsules 280 mg; MMRM = Mixed Model for Repeated Measures
Source: created by statistical reviewer

Figure 16. Study 405-201-00016 Change From Baseline in ADHD-RS-5 Total Score Over Time by Discontinuation Reason Within Treatment Arm



ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CTN 164.6 mg = centanafadine ER capsules 140 mg; CTN 328.8 mg = centanafadine ER capsules 280 mg
Source: Created by statistical reviewer

Data Quality and Integrity

The review team did not identify any concerns regarding data quality or integrity beyond the audit finding described above regarding Dr. Ginsburg's site. All datasets and documentation were adequate to complete review of the study.

7.1.7.8. Efficacy Results – Secondary and Other Relevant Endpoints

Because of the lack of statistical significance for the 140-mg dose of centanafadine for the primary endpoint, the key secondary endpoints of change from Baseline to Week 6 in the CGI-S-ADHD and the Conners 3 Parent T-scores could not be formally tested. The statistical review has verified results for both key secondary endpoints across both doses of centanafadine, results are provided descriptively here:

Table 38. Study 405-201-00016 Key Secondary Analysis Results on Change From Baseline in CGI-S-ADHD (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine ER 140 mg	Centanafadine ER 280 mg
N	145	150	149
Mean (SD)	4.43 (0.55)	4.49 (0.61)	4.54 (0.62)
Week 6			
n	127	122	123
LS mean (SE)	1.06 (0.09)	-1.15 (0.09)	-1.42 (0.09)
LS mean difference (SE)		-0.09 (0.12)	-0.37 (0.13)
95% CI for LS mean difference		(-0.34. 0.15)	(-0.61, -0.12)
p-value		0.4493	0.0038

CGI-S = Clinical Global Impressions- Severity; CI = confidence interval; LS = least squares; SE= standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00016 clinical study report, pages 72 (Tables 11.2-3, 11.4.1.2-1, and 11.4.1.3.3.-1)

Table 39. Study 405-201-00016 Key Secondary Analysis Results on Change From Baseline in Conners 3 Parent Short T-Scores (Full Analysis Set)

Timepoint Statistic	Placebo	Centanafadine ER 140 mg	Centanafadine ER 280 mg
Hyperactivity/Impulsivity T-Score			
N	141	146	141
Mean (SD)	79.52 (13.44)	78.85 (13.59)	81.42 (12.44))
Week 6			
n	123	118	116
LS mean (SE)	-8.48 (1.09)	-8.56(1.09)	-14.00(1.11)
LS mean difference (SE)		-0.17	-5.52
95% CI for LS mean difference		(-3.06, 2.73)	(-8.44, -2.59)
p-value		0.9108	0.0002
Inattention T-Score			
N	141	146	141
Mean (SD)	82.29 (1.09)	80.32 (10.14)	81.37 (8.62)

Timepoint Statistic	Placebo	Centanafadine ER 140 mg	Centanafadine ER 280 mg
Week 6			
n	123	118	116
LS mean (SE)	-8.08 (1.02)	-9.34 (1.02)	-14.41 (1.04)
LS mean difference (SE)		-1.26	-6.33
95% CI for LS mean difference		(-3.97, 1.45)	(-9.06, -3.60)
p-value		0.3617	<0.0001
Defiance/Aggression T-Score			
N			
Mean (SD)	57.52 (12.46)	59.41 (14.29)	60.55 (15.07)
Week 6			
n	141	146	141
LS mean (SE)	-4.69 (0.88)	-5.13 (0.88)	-5.72 (0.90)
LS mean difference (SE)		-0.44	-1.02
95% CI for LS mean difference		(-2.76, 1.89)	(-3.38, 1.33)
p-value		0.7111	0.3932
Executive Functioning T-Score			
N	141	146	141
Mean (SD)	74.65 (10.40)	74.20 (11.77)	74.50 (10.39)
Week 6			
n	123	118	116
LS mean (SE)	-8.10 (0.99)	-9.56 (0.99)	-13.02 (1.01)
LS mean difference (SE)		-1.46	-4.92
95% CI for LS mean difference		(-4.07, 1.16)	(-7.56, -2.28)
p-value		0.2743	0.0003

CI = confidence interval; Conners 3 = Conners Third Edition; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
Source: Study 405-201-00016 clinical study report, pages 72 (Tables 11.2-3, 11.4.1.2-1, and 11.4.1.3.3.-1)

Dose/Dose Response

Only the 280-mg dose separated from placebo with statistical significance on the primary endpoint. The key secondary endpoints showed a nominally statistically significant difference between the 280-mg dose and placebo, but not for the 140-mg dose.

Durability of Response

There was no evidence of waning drug effect during the double blind treatment period.

Persistence of Effect

Persistence of effect beyond exposure was not studied.

7.1.7.9. Efficacy Results – Secondary or Exploratory COA Endpoints

Subjects treated with centanafadine ER 280 mg demonstrated a nominally statistically significant difference in the mean change from Baseline in the PGI-S-ADHD score compared to subjects in the placebo group starting at Week 3 (LS mean difference: −0.27; 95% CI: −0.50, −0.03; p = 0.0296) and continuing through Week 6 (LS mean difference: −0.29; 95% CI: −0.55, −0.03; p = 0.0282). The centanafadine ER 140 mg arm was not nominally different from placebo in the mean change from Baseline in the PGI-S-ADHD score at any time point.

7.1.7.10. Additional Analyses Conducted on the Individual Trial

Sensitivity analyses were performed for the primary endpoint to exclude data from one trial site (Site 035, Dr. Lawrence Ginsburg) with critical audit findings. Twenty-one subjects were randomized and treated at this site: six subjects in the centanafadine ER 280 mg arm, 7 in the centanafadine ER 140 mg arm, and 8 placebo. The exclusion of data from site 035 had no effect on the primary endpoint results.

7.1.8. Study Results: 405-201-00021

7.1.8.1. Compliance with Good Clinical Practices

The study report attests that the trial was conducted in compliance with Good Clinical Practice guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative. The informed consent form, protocol, and amendments for this trial were submitted to and approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.

7.1.8.2. Financial Disclosure

See Section 15.2.

7.1.8.3. Patient Disposition

In Cohort 1, 480 subjects were enrolled and randomized into three treatment groups: high dose weight-based centanafadine ER(162 subjects), low dose weight-based centanafadine ER (154 subjects), and placebo (164 subjects). Of 480 subjects randomized, 457 subjects were treated and 367 subjects (76.5%) completed the trial. Of the 90 subjects who discontinued 33 were from the high-dose group (20%), 29 from the low dose group (18.8%), and 28 from the

placebo group (17.1%). Discontinuations due to AEs occurred in 16 subjects (3.3%) overall: 10 subjects (6.2%) from the high dose arm, 4 subjects (2.6%) from the low dose arm, and 2 subjects (1.2%) from the placebo arm.

In Cohort 2, 94 subjects were enrolled and randomized into two treatment groups: high dose centanafadine ER (62 subjects) and placebo (32 subjects). All 94 randomized subjects were treated, with 72 subjects (76.6%) completing the trial. Discontinuations were more common in the centanafadine group (15 subjects or 24.2%) than placebo (7 subjects or 21.9%). Three subjects discontinued due to AEs, all of whom were in the high dose centanafadine ER group.

Protocol Violations/Deviations

In Cohort 1, most of the protocol deviations were procedural deviations (e.g., missing assessment, uncertified rater). Procedural deviations occurred at a similar rate between arms. Other protocol deviations were related to prohibited medications, compliance, inclusion/exclusion criteria, or withdrawal criteria. There were no protocol deviations due to COVID-19 in Cohort 1.

In Cohort 2, most of the protocol deviations were related to compliance and were reported in 5 of 62 subjects (8.1%) for high dose centanafadine ER and 3 of 32 subjects (9.4%) for placebo. Other protocol deviations were related to inclusion/exclusion criteria, prohibited medications, and procedural deviations, occurring at similar rates across treatment arms. There were no protocol deviations due to COVID-19 in Cohort 2.

7.1.8.4. Table of Demographic Characteristics

Overall, demographic characteristics of Cohort 1 were fairly representative of the ADHD population. A higher proportion of subjects were male (58.3%) than female (41.7%) subjects, consistent with the epidemiology of ADHD. The mean age was 9.2 years (range: 6 to 12 years). The study population was reasonably diverse. The majority of subjects were White (65.0%); 27%% were Black or African American and 31% were Hispanic or Latino. The baseline demographics and disease characteristics were well-balanced between treatment arms, except that there were more males in the placebo group (106 or 65%) compared with the low- and high-dose centanafadine ER groups (87 in each, or 56.5% and 53.7% respectively). Table 40 summarizes the baseline demographic characteristics of Study 21 Cohort 1.

Cohort 2 was smaller in size and less balanced between treatment arms compared with Cohort 1. The centanafadine group had a higher percentage of male subjects (66%) compared with the placebo group (53%). The racial composition of the groups was also different, with 53% of the placebo group being White and 44% Black or African American compared with the centanafadine group, of which 76% of subjects were White and 18% Black or African American. The proportion of Hispanic or Latino subjects was somewhat higher in the centanafadine group compared with the placebo group (16% versus 12.5%). Table 41 summarizes the baseline demographic characteristics of Study 21 Cohort 2.

Table 40. Demographic Characteristics of the Primary Efficacy Analysis - Study 21 Cohort 1

Demographic Parameters	Control Group (N= 164) n (%)	Treatment Group (N=)		Total (N= 480) n (%)
		Low dose centanafadine ER (N= 154) n (%)	High dose centanafadine ER (N= 162) n (%)	
Sex				
Male	106 (65)	87 (56)	87 (54)	280 (58)
Female	58 (35)	67 (44)	75 (46)	200 (42)
Age				
Mean years (SD)	9.2 (2.1)	9.3 (2.1)	9.1 (2.0)	9.2 (2.0)
Median (years)	9	9	9	9
Min, max (years)	6, 12	6, 12	6, 12	6, 12
Race				
White	105 (64)	102 (66)	105 (65)	312 (65)
Black or African American	44 (27)	40 (26)	47 (29)	131 (27)
Asian	2 (1)	1 (1)	2 (1)	5 (1)
American Indian or Alaska Native	0	2 (1)	1 (1)	3 (1)
Native Hawaiian or Other Pacific Islander	2 (1)	0	0	2 (<1)
Other[1]	11 (7)	9 (6)	7 (4)	27 (6)
Ethnicity				
Hispanic or Latino	45 (27)	54 (35)	50 (31)	149 (31)
Not Hispanic or Latino	119 (73)	100 (65)	112 (69)	331 (69)
Region				
United States	164 (100)	154 (100)	161 (99)	479 (>99)
Canada	0	0	1 (1)	1 (<1)

Source: Reviewer generated

Table 41. Demographic Characteristics of the Primary Efficacy Analysis - Study 21 Cohort 2

Demographic Parameters	Placebo (N=32) n (%)	High dose centanafadine ER (N=62) n (%)	Total (N=94) n (%)
Sex			
Male	17 (53)	41 (66)	58 (62)
Female	15 (47)	21 (34)	36 (38)
Age			
Mean years (SD)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)
Median (years)	5	5	5
Min, max (years)	4, 5	4, 5	4, 5
Race			
White	17 (53)	47 (76)	64 (68)
Black or African American	14 (44)	11 (18)	25 (27)
Asian	0	1 (2)	1 (1)
Other[1]	1 (3)	3 (5)	4 (4)
Ethnicity			
Hispanic or Latino	4 (12.5)	10 (16)	14 (15)

Demographic Parameters	Placebo (N=32) n (%)	High dose centanafadine ER (N=62) n (%)	Total (N=94) n (%)
Not Hispanic or Latino	28 (87.5)	52 (84)	80 (85)

Source: Reviewer-generated

7.1.8.5. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Psychiatric history was generally similar between the three treatment arms in Cohort 1, except that there were 4 subjects (2.4%) in the placebo group with anxiety and compared with 1 subject in each of the centanafadine low and high dose groups (0.6%). ADHD-RS-5 scores and Conners 3 scores were similar between the three treatment arms.

Weight and height were similar between treatment arms in Cohort 1 overall, although BMI was higher in the centanafadine ER low and high dose groups (20.4 and 20.3) compared with placebo (19.8). The weight of the subjects in Cohort 1 was not representative of the U.S. population, particularly in the younger subjects. Only a single subject weighing less than 20 kg was exposed to high dose, weight-based centanafadine ER. Among the 6-year-old subjects who received high dose weight-based centanafadine ER, the mean (SD) weight was 24.2 (3.7) kg for females and 24.7 (4.1) kg for males. The weight of 6-year-olds in the placebo group was lower: 22.7 (1.2) kg for females and 23.6 (4.0) for males. For reference, the 50th percentile weight for 6-year-old girls in the United States is between 20 and 22 kg and for boys between 21 and 23 kg.

Table 42. Height and Weight of 6-Year-Olds in Study 21

		Placebo		Centanafadine ER High Dose*		Centanafadine ER Low Dose*	
		SEX		SEX		SEX	
		F	M	F	M	F	M
WEIGHT	Mean	22.7	23.6	24.2	24.7	25.4	25.5
	Std Dev	1.2	4.0	3.7	4.1	3.3	5.8
HEIGHT	Mean	119.4	119.4	121.0	120.7	121.7	122.1
	Std Dev	4.1	4.2	5.2	3.7	6.0	5.0

*Weight-based

Source: Reviewer-generated

In Cohort 2, the centanafadine ER group was about 2 cm taller and weighed about 2 kg more on average than the placebo group, with a higher mean BMI (17.4 versus 16.2). See Table 43.

In addition to the imbalance in weight between the placebo and centanafadine groups, the weight of the subjects in Cohort 2 was not representative of the U.S. population of pediatric patients 4 to <6 years of age. The mean (SD) weight of 21.3 kg (5.1) in Cohort 2 was considerably greater than the mean weight of the U.S. population of that age group, approximately 18.4 kg for males and 18.0 kg for females. Overall, subjects in Cohort 2 were between 6 and 7 lbs. heavier, on average, than children of their age group in this country.

Table 43. Weight by Treatment Group and Sex in Cohort 2

	Placebo (N=32)			High dose centanafadine ER* (N=62)			Total (N=94)		
Weight (kg)	**Female**	**Male**	**All**	**Female**	**Male**	**All**	**Female**	**Male**	**All**
Mean (SD)	21.2 (4.1)	18.7 (2.6)	19.9 (3.5)	23.2 (8.1)	21.5 (3.4)	22.1 (5.5)	22.4 (6.7)	20.7 (3.5)	21.3 (5.1)
Median	21.4	18.9	19.0	20.0	20.9	20.7	20.2	20.5	20.4
Range	15.8, 29.3	13.5, 23.3	13.5, 29.3	16.4, 51.0	16.6, 34.9	16.4, 51.0	15.8, 51	13.5, 51	13.5, 51.0

*Weight-based
Source: Reviewer-generated

Psychiatric history was similar between the two treatment groups in Cohort 2, except that oppositional defiant disorder was present in 9 of 62 subjects (14.5%) in the centanafadine group and 8 of 32 subjects (25.0%) in the placebo group. ADHD-RS-5 scores and Conners 3 scores were similar between the two treatment arms.

7.1.8.6. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was similar between treatment arms in Cohort 1. There were 21 subjects who were <80% compliant: 8 of 157 subjects (5.1%) for high dose centanafadine ER, 5 of 147 subjects (3.4%) for low dose centanafadine ER, and 8 of 153 subjects (5.2%) for placebo.

In Cohort 2, there were only 3 subjects who were <80% compliant: 2 of 62 subjects (3.2%) in the high dose centanafadine ER group and 1 of 32 subjects (3.1%) in the placebo group.

7.1.8.7. Efficacy Results – Primary Endpoint

The statistical reviewer confirmed that Study 21 met its primary objective for the high dose of centanafadine for the change from Baseline in ADHD-RS-5 total score at Week 6 vs. placebo in Cohort 1: LS mean difference -5.56 (95% CI: -8.78, - 2.33. Higher ADHD-RS-5 scores indicate greater severity, thus the reduction for each dose represents improved ADHD symptoms. The statistical reviewer confirmed the result for the 140-mg dose of centanafadine ER vs. placebo for the same endpoint, which did not reach statistical significance at the two-sided 0.05 level in Cohort 1, so it is reported descriptively here: LS mean difference –2.71 (1.65) (95% CI: -5.97, 0.54). Note, Cohort 2 was not part of the multiplicity plan; the statistical reviewer confirmed the descriptive results for high dose centanafadine ER vs. placebo: LS mean difference – 3.97 (95% CI: -10.22, 2.27).

In addition, sensitivity analyses—including two MMRM analyses with a copy placebo multiple imputation (MI) approach 1) MI using MCMC and 2) MI using a monotone approach—and a tipping-point analysis were performed for each dose level of centanafadine vs. placebo to assess the MAR assumption used in the primary efficacy analysis. Overall, results of these analyses supported the primary efficacy findings.

Table 44. Study 405-201-00021 Primary Analysis Results for Change From Baseline in ADHD-RS-5 Total Score in Cohort 1 (Full Analysis Set)

Timepoint Statistic	Placebo	Low dose centanafadine ER*	High dose centanafadine ER*	Average (Low dose and high dose centanafadine ER*)
Baseline				
N	151	154	143	
Mean (SD)	43.00 (6.70)	43.25 (6.73)	42.91 (6.64)	
Week 6				
n	122	120	115	
LS mean (SE)	-10.8 (1.19)	-13.5 (1.22)	-16.3 (1.19)	
LS mean difference (SE)		-2.71 (1.65)	-5.56 (1.64)	
95% CI for LS mean difference		(-5.97, 0.54)	(-8.78, -2.33)	
p-value		0.1023	0.0008	0.0039

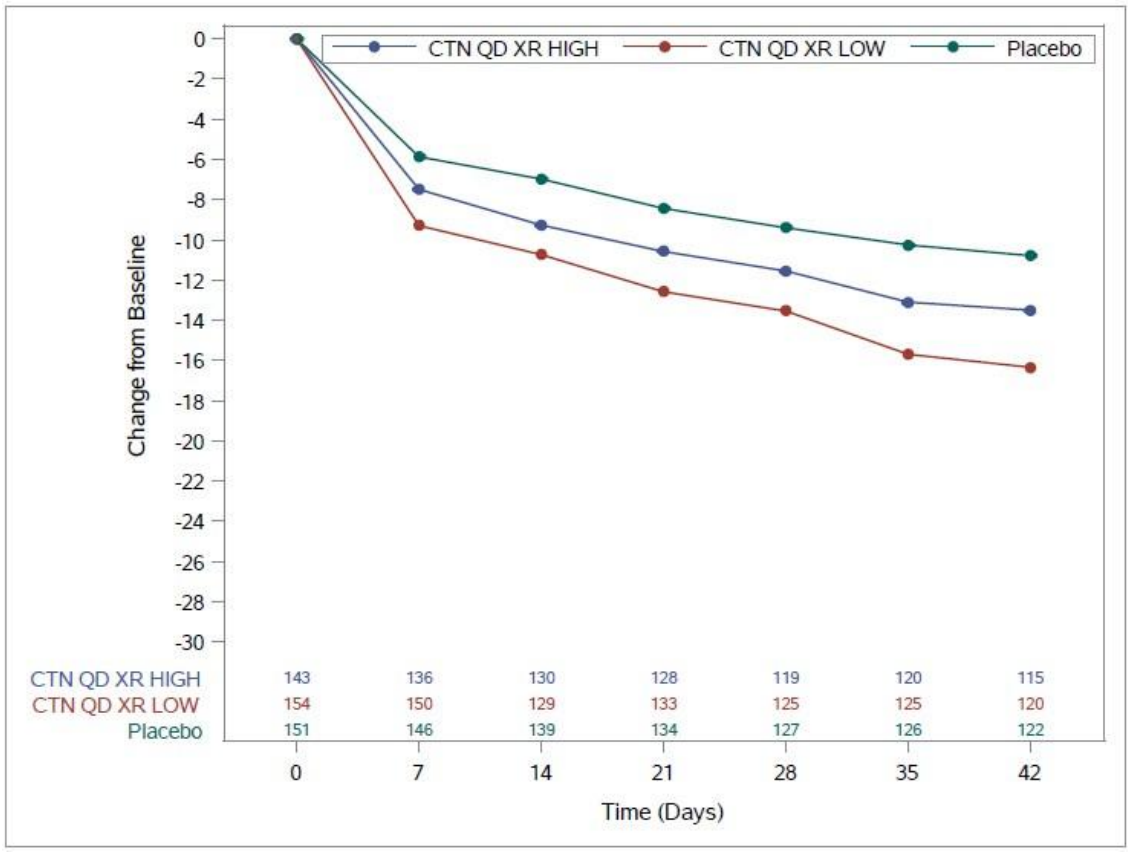
ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages and 107 (Tables 11.2-3 and 11.4.1.1-1)

Table 45. Study 405-201-00021 Primary Analysis Results for Change From Baseline in ADHD-RS-5 Total Score in Cohort 2 (Full Analysis Set)

Timepoint Statistic	Placebo	High dose centanafadine*
Baseline		
N	30	59
Mean (SD)	44.58 (6.58)	45.08 (6.32)
Week 6		
n	24	45
LS mean (SE)	-8.24 (2.58)	-12.21 (1.87)
LS mean difference (SE)		-3.97 (3.12)
95% CI for LS mean difference		(-10.22, 2.27)
p-value		0.2083

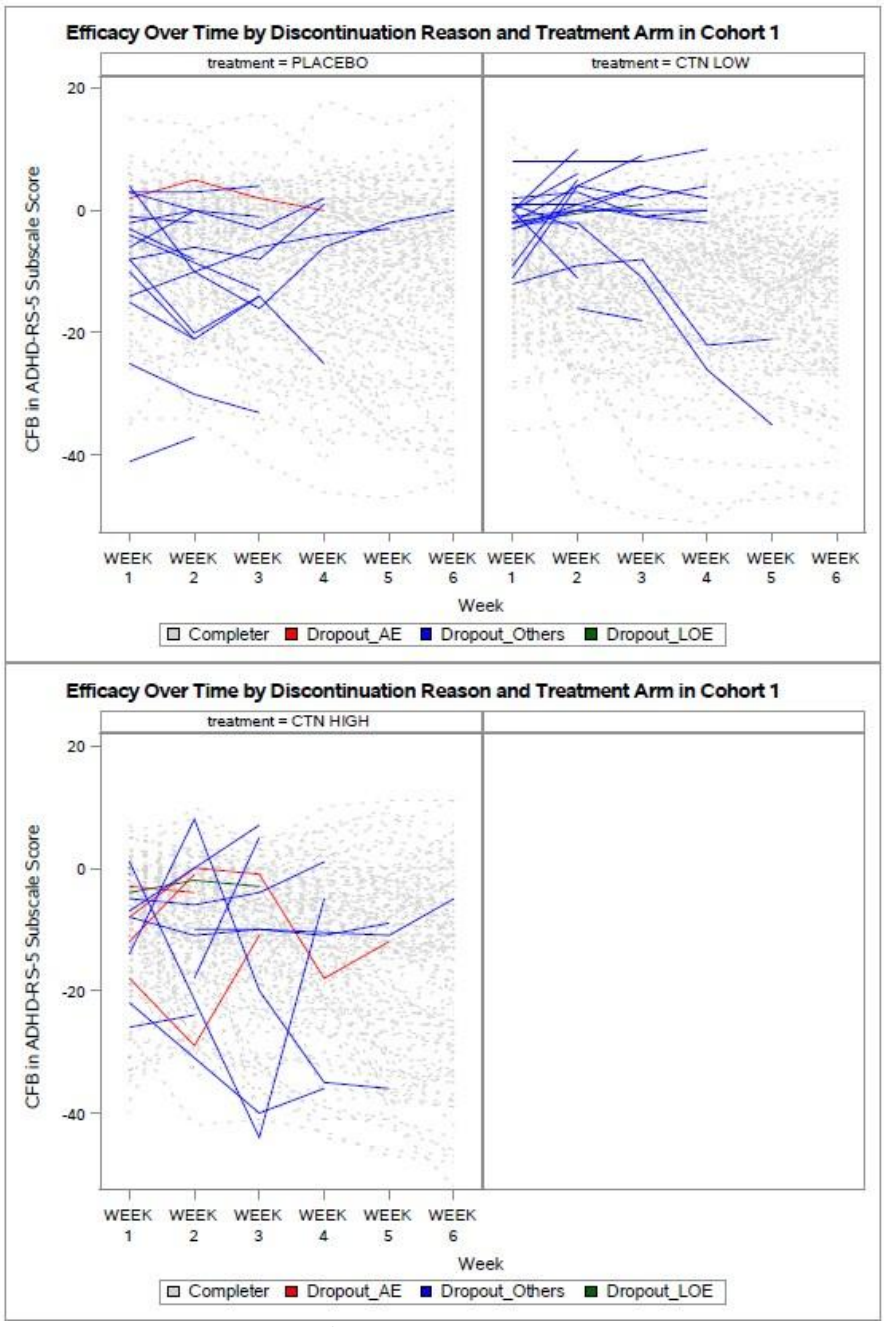
ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages and 107 (Tables 11.2-3 and 11.4.1.1-1)

Figure 17. Study 405-201-00021 Least Squares Mean of Change From Baseline in ADHD-RS-5 Total Score by Treatment Arm and Study Week, Cohort 1 (Full Analysis Set)



ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CTN QD XR HIGH = high dose weight-based centanafadine ER capsules; CTN QD XR LOW = low dose weight-based centanafadine ER capsules; MMRM = Mixed Model for Repeated Measures
Source: created by statistical reviewer

Figure 18. Study 405-201-00021, Change From Baseline in ADHD-RS-5 Total Score Over Time by Discontinuation Reason Within Treatment Arm



ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale Version 5; CTN QD XR HIGH = high dose weight-based centanafadine ER capsules; CTN QD XR LOW = low dose weight-based centanafadine ER; MMRM = Mixed Model for Repeated Measures
Source: created by statistical reviewer

Data Quality and Integrity

The reviewer identified no concerns regarding data quality or integrity. All datasets and documentation were adequate to complete review of the study.

7.1.8.8. Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoint analyses for Cohorts 1 and 2 are presented below:

Table 46. Study 405-201-00021 Key Secondary Analysis Results for Change From Baseline in CGI-S ADHD in Cohort 1 (Full Analysis Set)

Timepoint Statistic	Placebo	Low dose centanafadine*	High dose centanafadine*
Baseline			
N	151	143	154
Mean (SD)	4.87 (0.71)	4.86 (0.69)	4.78 (0.67)
Week 6			
n	122	115	120
LS mean (SE)	-0.89 (0.10)	-1.09 (0.10)	-1.14 (0.10)
LS mean difference (SE)		-0.21	-0.25
95% CI for LS mean difference		(-0.48, 0.07)	(-0.52, 0.02)
p-value		0.1393	0.0705

CGI-S = Clinical Global Impressions - Severity; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages 112 (Tables 11.2-3, 11.4.1.2-1, and 11.4.1.3.3.-1)

Table 47. Study 405-201-00021 Key Secondary Analysis Results for Change From Baseline in CGI-S ADHD, Cohort 2 (Full Analysis Set)

Timepoint Statistic	Placebo	High dose centanafadine*
Baseline		
N	30	59
Mean (SD)	5.13 (0.92)	5.23 (0.78)
Week 6		
n	24	45
LS mean (SE)	-0.65 (0.25)	-1.25 (0.18)
LS mean difference (SE)		-0.60
95% CI for LS mean difference		(-1.20, 0.00)
p-value		0.0516

CGI-S = Clinical Global Impressions - Severity; CI = confidence interval; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages 113 (Tables 11.2-3, 11.4.1.2-2, and 11.4.1.3.3.-1)

Table 48. Study 405-201-00021 Key Secondary Analysis Results for Change From Baseline in Conners 3 Parent Short Form T-Scores, Cohort 1 (Full Analysis Set)

Timepoint Statistic	Placebo	Low dose centanafadine*	High dose centanafadine*
Hyperactivity/Impulsivity T-Score			
Baseline			
N	149	135	147
Mean (SD)	84.67 (9.14)	84.39 (10.23)	83.75 (10.18)
Week 6			
n	119	109	113
LS mean (SE)	-6.93 (1.08)	-7.98 (1.13)	-11.5 (1.10)
LS mean difference (SE)		-1.05	-4.56
95% CI for LS mean difference		(-3.99, 1.88)	(-7.47, -1.64)
p-value		0.4804	0.0022
Inattention T-Score			
Baseline			
N	149	135	147
Mean (SD)	83.30 (9.22)	84.81 (7.68)	83.27 (8.91)
Week 6			
n	119	109	113
LS mean (SE)	-6.42 (1.09)	-9.14 (1.14)	-11.9 (1.10)
LS mean difference (SE)		-2.72	-5.50
95% CI for LS mean difference		(-5.67, 0.23)	(-8.41, -2.59)
p-value		0.0704	0.0002
Defiance/Aggression T-Score			
Baseline			
N	149	135	147
Mean (SD)	67.78 (16.89)	65.59 (17.19)	64.73 (16.84)
Week 6			
n	119	109	113
LS mean (SE)	-6.44 (1.17)	-4.02 (1.22)	-8.55 (1.19)
LS mean difference (SE)		2.42	-2.12
95% CI for LS mean difference		(-0.74, 5.58)	(-5.25, 1.02)
p-value		0.1332	0.1854

Timepoint Statistic	Placebo	Low dose centanafadine*	High dose centanafadine*
Executive Functioning T-Score			
Baseline			
N	149	135	147
Mean (SD)	78.46 (11.17)	79.01 (10.59)	78.44 (11.20)
Week 6			
n	119	109	113
LS mean (SE)	-6.78 (1.11)	-9.30 (1.16)	-11.3 (1.12)
LS mean difference (SE)		-2.52	-4.56
95% CI for LS mean difference		(-5.51, 0.46)	(-7.52, -1.60)
p-value		0.0977	0.0026

CI = confidence interval; Conners 3 = Conners Third Edition; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages 115 (Tables ###, 11.4.1.2.2-1, and 11.4.1.3.3.-1)

Table 49. Study 405-201-00021 Key Secondary Analysis Results for Change From Baseline in Conners 3 Parent Short Form T-Scores, Cohort 2 (Full Analysis Set)

Timepoint Statistic	Placebo	High dose centanafadine*
Hyperactivity/Impulsivity T-Score		
Baseline		
N	27	56
Mean (SD)	89.11 (2.75)	89.16 (2.31)
Week 6		
n	22	42
LS mean (SE)	-6.16 (2.52)	-9.09 (1.84)
LS mean difference (SE)		-2.93
95% CI for LS mean difference		(-9.01, 3.15)
p-value		0.3387
Inattention T-Score		
Baseline		
N	27	56
Mean (SD)	87.59 (6.52)	88.55 (4.42)
Week 6		
n	22	42
LS mean (SE)	-6.41 (2.57)	-9.07 (1.86)
LS mean difference (SE)		-2.66
95% CI for LS mean difference		(-8.88, 3.56)
p-value		0.3957

Timepoint Statistic	Placebo	High dose centanafadine*
Defiance/Aggression T-Score		
Baseline		
N	27	56
Mean (SD)	68.26 (17.72)	72.96 (16.05)
Week 6		
n	22	42
LS mean (SE)	-6.18 (3.02)	-7.05 (2.22)
LS mean difference (SE)		-0.87
95% CI for LS mean difference		(-8.26, 6.51)
p-value		0.8138
Executive Functioning T-Score		
Baseline		
N	27	56
Mean (SD)	79.48 (11.40)	80.13 (10.25)
Week 6		
n	22	42
LS mean (SE)	-5.03 (2.51)	-9.98 (1.83)
LS mean difference (SE)		-4.95
95% CI for LS mean difference		(-11.03, 1.12)
p-value		0.1083

CI = confidence interval; Conners 3 = Conners Third Edition; LS = least squares; SE = standard error of the least squares mean; SD = standard deviation
*Weight-based
Source: Study 405-201-00021 clinical study report, pages 117 (Tables ###, 11.4.1.2.2-2, and 11.4.1.3.3.-1)

Dose/Dose Response

Only the high dose demonstrated a statistically significant difference from placebo on the primary endpoint in Cohort 1. In Cohort 2, only the high dose was tested, and although the results were numerically different from placebo, the difference was not statistically significant. Testing of the key secondary endpoints did not demonstrate statistically significant difference from placebo in any centanafadine group in either cohort.

Durability of Response

There was no evidence of waning effect with time in these short term trials.

Persistence of Effect

Persistence of effect beyond exposure was not assessed.

7.1.8.9. Efficacy Results – Secondary or Exploratory COA Endpoints

Subjects in Cohort 1 treated with high dose centanafadine ER demonstrated a nominally significant difference in the mean change from Baseline in the PGI-S-ADHD score compared to subjects in the placebo group at Week 5 (LS mean difference: −0.30; 95% CI: −0.58, −0.03; p = 0.0279) and Week 6 (LS mean difference: −0.36; 95% CI: −0.65, −0.08; p = 0.0128). In the low dose centanafadine ER group, there was no nominally significant difference in the mean change from Baseline in the PGI-S-ADHD score compared to subjects in the placebo group at any time point.

Subjects in Cohort 2 treated with high dose centanafadine ER did not demonstrate a nominally significant difference in the mean change from baseline in the PGI-S-ADHD score compared to subjects in the placebo group at any time point, although there were numerical differences.

7.1.8.10. Additional Analyses Conducted on the Individual Trial

Sensitivity analyses were performed for Cohort 1 for the primary endpoint to exclude data from one trial site (035) with critical audit findings. There were 4 subjects in Cohort 1 who were randomized and treated at this site; 2 subjects received high dose centanafadine ER and 2 subjects received low dose centanafadine ER. The exclusion of data from site 035 did not have any effect on the primary endpoint results.

7.1.9. Integrated Review of Effectiveness

7.1.9.1. Assessment of Efficacy Across Trials

Primary Endpoints

Testing of the Applicant's prespecified, AISRS-based, primary endpoints demonstrated statistically significant improvement compared with placebo for both the high and low doses of centanafadine tablets tested in both adult phase 3 efficacy trials (Study 13 and Study 14). In Study 13, centanafadine tablets demonstrated statistically significant reductions from Baseline in AISRS total score at Week 42 vs. placebo. For the 200 mg total daily dose, the LS mean difference was -3.15 (95% CI: -5.79, - 0.51); for the 400 mg total daily dose, -2.74 (95% C: -5.35, -0.14). In Study 14, centanafadine tablets at a total daily dose of 200 mg demonstrated a statistically significant reduction from Baseline in AISRS total score at Week 42 vs. placebo, with LS mean difference -4.01 (95% CI: -6.55, - 1.46). For the 400 mg total daily dose, the LS mean difference was -4.42 (95% CI: -7.02, -1.82).

When Studies 13 and 14 were planned and conducted, the AISRS had only been described in labeling to support approval of Concerta for ADHD (one of two randomized double-blind, placebo-controlled multicenter, parallel-group trials in adults included the AISRS as the primary endpoint). Labeling does not include the magnitude of the treatment effect. In April 2022, the Agency expanded the indication for viloxazine ER capsules (Qelbree) from pediatric patients to

include the treatment of ADHD in adults (NDA 211964/S-003). That approval was based on a single, randomized, double-blind, placebo-controlled, flexible dose (viloxazine ER 200 mg to 600 mg) efficacy and safety study in adult subjects with ADHD. The primary efficacy analysis demonstrated a statistically-significant treatment effect in subjects treated with viloxazine ER compared with placebo, with a placebo-subtracted treatment difference of -3.7 points on AISRS total score (95% CI: -6.2, -1.2). The Agency determined that this constituted a clinically-meaningful effect on ADHD symptoms in adults. The primary efficacy endpoint results in Studies 13 and 14 are of a magnitude similar to the results that supported approval of the viloxazine supplement. Although the effect size was slightly smaller in Study 13 compared with the viloxazine study, in Study 14 the effect size was slightly greater. Overall, the results of Studies 13 and 14 were statistically significant and clinically meaningful. Taken together, Studies 13 and 14, along with the pharmacokinetic bridge established with Study 405-201-00157, support the efficacy of the proposed dosages of 210 mg and 280 mg centanafadine ER in adults with ADHD.

In Studies 16 and 21, testing of the Applicant's prespecified, ADHD-RS-5-based primary endpoint demonstrated statistically significant improvement compared with placebo at the high dose tested in pediatric subjects 13 to 17 years of age (280 mg in Study 16) and in 6 to 12 of age (weight-based equivalent in Study 21 Cohort 1). In Study 16, the LS mean difference was -4.35 (95% CI: -6.83, -1.87). In Study 21 Cohort 1, the LS mean difference was -5.56 (95% CI: -8.78, - 2.33). The ADHD-RS-5 supported approval of viloxazine ER capsules for ADHD in pediatric patients 6 to 17 years. Earlier versions (e.g., ADHD Rating Scale-IV) have been described in multiple drug labels to support approvals for pediatric ADHD. Cross-label comparison of effect sizes is challenging, due to differences in study design (many of the pivotal studies for ADHD drugs were conducted decades ago). However, the LS mean differences described above are similar to those for viloxazine ER capsules.

Testing of the primary endpoint for lower doses of centanafadine ER capsules in pediatric subjects 6 to 17 years of age did not demonstrate statistically significant results. In pediatric subjects 4 and 5 years of age (Study 21 Cohort 2), no dose of centanafadine demonstrated statistically significant improvement over placebo.

Secondary and Other Endpoints

In Studies 13 and 14, testing of the key secondary endpoint of CGI-S demonstrated differences that were statistically significant from placebo. In Study 13, the LS mean difference was -0.27 (95% CI: -0.50, -0.04) for centanafadine tablets 200 mg total daily dose and -0.28 (95% CI: -0.51, -0.05) for 400 mg. In Study 14, the LS mean difference was -0.33 (95% CI: -0.57, -0.09) for 200 mg and -0.28 (95% CI: -0.53, -0.04) for 400 mg. This change over placebo does represent a benefit, but the size of the differences are not large enough to independently conclude that the benefit is clinically meaningful. The size of the difference is similar, though slightly smaller, than the effect described in the viloxazine ER label (LS mean difference of -0.4 (95% CI: -0.7, -0.2).]

Subpopulations

The studies submitted with this NDA were not powered to support subgroup analyses.

Additional Efficacy Considerations

None.

7.1.9.2. Integrated Assessment of Effectiveness

The four adequate and well-controlled efficacy studies presented by the Applicant (Studies 13, 14, 16, and 21) provide substantial evidence of effectiveness for centanafadine for the treatment of ADHD in adults and pediatric patients 6 years of age and older. Results from analyses of primary endpoints provide the principal evidence for effectiveness. The effect sizes in these studies provide evidence supporting the clinical meaningfulness of the improvements. These studies, along with the pharmacokinetic bridge established in Study 405-201-00157 support the effectiveness of centanafadine ER capsules for the treatment of ADHD in adults and pediatric patients 6 years of age and older.

The studies did not demonstrate effectiveness for 140 mg centanafadine ER capsules for the treatment of pediatric patients 13 to 17 years of age with ADHD, nor of the corresponding weight-based dosage for the treatment of pediatric patients 6 to 12 years of age. (b) (4) .

7.2. Review of Safety

7.2.1. Safety Review Approach

The focus of this review is the safety of centanafadine for the treatment of adult and pediatric patients with ADHD. This review focuses primarily on safety data submitted from four phase 3 studies (13, 14, 16, and 21). Adverse events were examined for four age groups (ages 4 to 5 years, 6 to 12 years, 13 to 17 years, and adults) and two dose strengths (centanafadine twice-daily tablets total daily dose 200 and 400 mg in adult studies and centanafadine ER capsules 140 mg and 280 mg or weight-based equivalent in pediatric studies). The vital signs, laboratory, electrocardiogram, and C-SSRS databases for the phase 3 trials and select phase 1 trials were also analyzed. See Section 7.2.2 Review of the Safety Database for details.

Study 15 and Study 17, open-label safety extension studies in adults and pediatric subjects, respectively, were the primary sources of long-term safety data. Although these studies did not include controlled data, long-term trends in vital signs, growth parameters, and laboratory assessments were examined.

Safety review issues identified during drug development as requiring particular attention included:

- Suicidal ideation/behavior
- Drug abuse, misuse, and addition
- Increased blood pressure and heart rate
- Orthostatic changes
- Long-term suppression of growth in pediatric patients
- Hypersensitivity reactions including rash

See 7.2.5, Analysis of Submission-Specific Safety Issues for additional details.

The Applicant submitted a thorough QT study, which was reviewed by the IRT consultation team. In addition, the Controlled Substance Staff (CSS) reviewed the data for drug dependence and liability signals.

7.2.2. Review of the Safety Database

Overview

Across the centanafadine development program, 2180 adults (not including subjects in ongoing blinded trials) were exposed to centanafadine in 37 trials conducted in North America, Europe, Australia, and Japan. The program included trials conducted for the treatment of ADHD, binge eating disorder (BED), smoking cessation, and major depressive disorder (MDD). As of the NDA data cutoff date of May 1, 2025, the adult population comprised:

- 1199 subjects in phase 2/3 trials, including 1051 with ADHD in phase 2/3 trials.
- 872 subjects in healthy adult clinical pharmacology trials
- 16 hepatic or renally impaired subjects in Trial 405-201-00006
- 93 recreational drug user subjects (CSR 405-201-00019 and CSR EB-1020-IR-103)

Overall, 1029 pediatric subjects were exposed to centanafadine including:

- 934 subjects (4 to 18 years of age) with ADHD in phase 3 trials
- 95 subjects with ADHD in clinical pharmacology trials

As of May 1, 2025, 834 subjects had been exposed to centanafadine for ≥6 months (422 adults and 412 pediatric subjects [4 to 17 years of age]) and 507 subjects had been exposed to centanafadine for ≥1 year (221 adults, 286 pediatric subjects [6 to 17 years of age]). The size of the safety database is consistent with *ICH E1* recommendations.

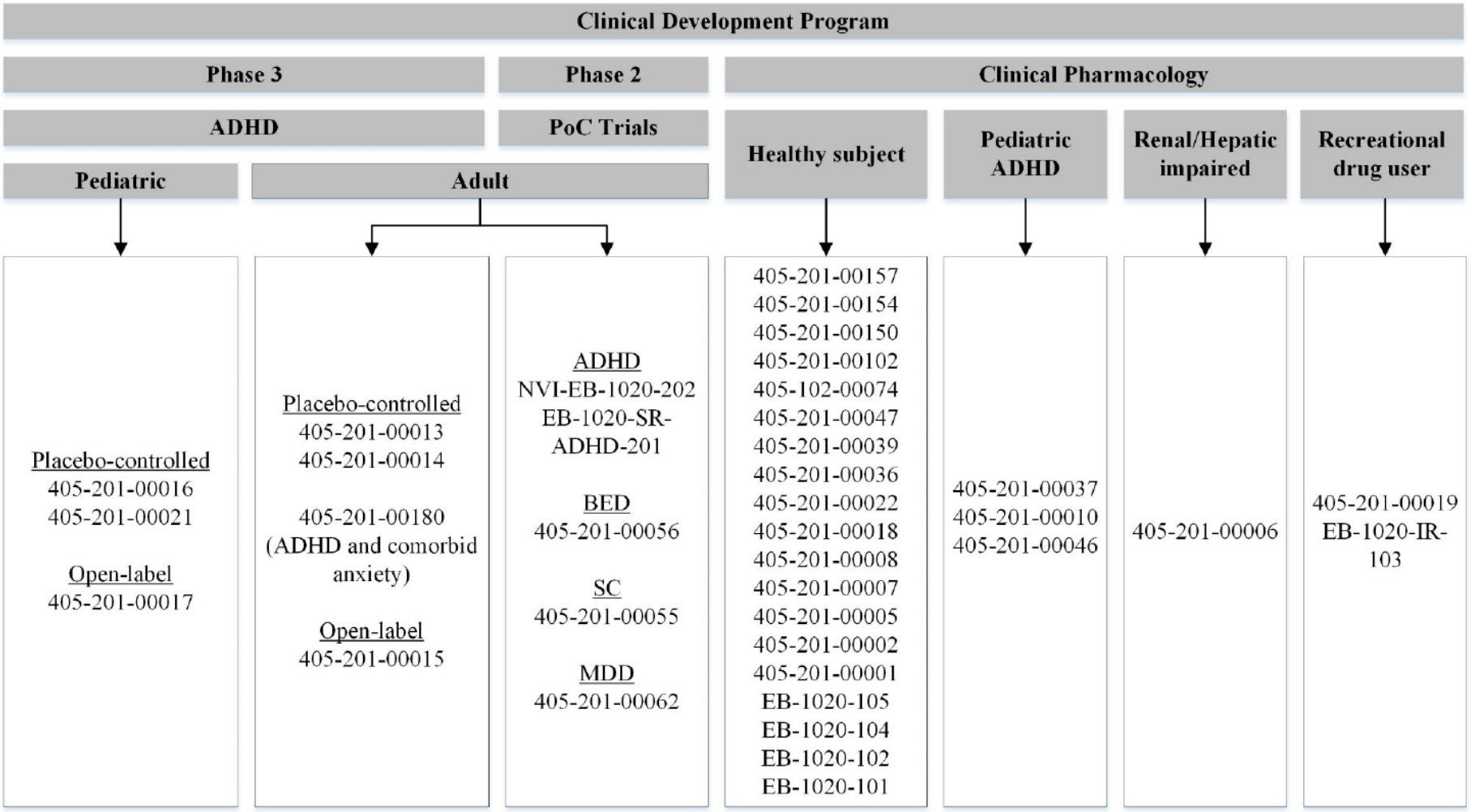
None of the subjects enrolled in centanafadine clinical studies were older adults (age ≥65 years).

As of the NDA cutoff date of May 1, 2025, across all indications over the entire centanafadine development program, 3209 subjects (2133 subjects in phase 2/3 trials and 1076 subjects in clinical pharmacology trials) had been exposed to centanafadine. Over 2180 adults (including 1051 adults with ADHD in phase 2/3 trials) and 1029 pediatric subjects with ADHD (4 to 18 years of age, inclusive; including 934 pediatric subjects in phase 3 trials) had been exposed to centanafadine at the NDA cutoff date. A total of 852 pediatric subjects 6 years and older with ADHD were exposed to centanafadine in phase 3 trials.

In terms of exposure duration, 834 subjects had been exposed to centanafadine for ≥6 months (422 adults and 412 pediatric subjects 4 years and older) and 507 subjects for ≥1 year (221 adults, 286 pediatric subjects 6 years and older). Mean duration of centanafadine exposure was 204.4 days for subjects with ADHD.

Figure 19 outlines the centanafadine development program with studies grouped by subject population. Additional details for individual studies are described and tabulated in 7.1. Refer to Section 5 for additional information on phase 1 studies, including food-effect findings and drug-drug interactions. See CSS review by Dr. Bonson for detailed description of the human abuse potential studies. The protocols for phase 3 studies are described in detail in Section 7.1.

Figure 19. Overview of Trials in Centanafadine Clinical Development Program



ADHD = attention-deficit hyperactivity disorder; BED = binge eating disorder; MDD = major depressive disorder; PoC = proof-of-concept; SC = smoking cessation.
Note: Subjects enrolled in Trials 405-201-00019 and EB-1020-IR-103 were healthy recreational drug users with stimulant experience
Source: Applicant's ISS, Figure 3-1

Table 50. Adult Safety Population, Size and Denominators

	Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review (N=1066)		
Clinical Trial Groups	**New Drug** (n= 1327)	**Active Control** (n= 83)	**Placebo** (n= 426)
Controlled trials conducted for this indication	586	0	290
All other than controlled trials conducted for this indication	480	0	0
Controlled trials conducted for other indications	98 (BED)+163 (MDD)	83 (MDD)	49 (BED)+87 (MDD)

Source: Reviewer-generated

Table 51. Pediatric Safety Population, Size and Denominators

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review (N=1350)			
Clinical Trial Groups	**New Drug** (n=1350)	**Active Control** (n= 0)	**Placebo** (n=332)
Controlled trials conducted for this indication	670	0	332
All other than controlled trials conducted for this indication	680	0	0

Source: Reviewer-generated

Overall Exposure

The number of adults with ADHD who were exposed to ≥ one dose of centanafadine was 586 in short-term placebo-controlled trials (Studies 13 and 14) and 653 in the long-term, open-label trial (Study 15). In Study 15, 422 adult subjects with ADHD were exposed to centanafadine for ≥26 weeks (≥6 months) and 221 subjects were exposed to centanafadine for ≥52 weeks (≥1 year).

In the pediatric short-term placebo-controlled trials, 62 pediatric subjects 4 to 5 years of age and 608 pediatric subjects 6 to 17 years of age with ADHD and were exposed to ≥ one dose of centanafadine. The ongoing long-term, open-label trial (Study 17), exposed 620 pediatric subjects 6 to 17 years of age. In pediatric subjects 6 to 17 years of age with ADHD, 394 subjects were exposed to centanafadine for ≥26 weeks (≥6 months) and 286 subjects were exposed to centanafadine for ≥52 weeks (≥1 year).

In pediatric subjects 4 to 5 years of age with ADHD, at the time of the data cutoff for the NDA submission (May 1, 2025), 18 subjects were exposed to centanafadine for ≥26 weeks (≥6 months) and no subjects were exposed to centanafadine for ≥52 weeks (≥1 year).

Table 52. Treatment Duration and Overall Exposure - Adult ADHD Long-Term Pool (Safety Sample)

	All Centanafadine Doses (N=653)
Treatment duration (days)	
N	653
Mean (SD)	259.2 (141.8)
Min, Max	6.0, 413.0
Treatment duration (cumulative)	
≥ 1 day	653 (100.0)
≥ 1 week	652 (99.8)
≥ 4 weeks	614 (94.0)
≥ 8 weeks	569 (87.1)
≥ 14 weeks	501 (76.7)
≥ 26 weeks	422 (64.6)
≥ 38 weeks	378 (57.8)
≥ 52 weeks	221 (33.8)

Trials: 405-201-00013, 405-201-00014, and 405-201-00015
Note: Percentages are based on the number of subjects in safety sample; includes data from short-term trials (13 and 14) only for centanafadine-treated subjects who entered Trial 15.
Source: ISS, Table 6.2.1.1.1-1.

Table 53. Treatment Duration and Overall Exposure - Pediatric ADHD Long-Term Pool (Safety Sample)

	6 to 18 Years Old (N=611)
Treatment duration (days)	
N	611
Mean (SD)	344.1 (243.9)
Min, Max	2.0, 996.0
Treatment duration (cumulative)	
≥ 1 day	611 (100.0)
≥ 1 week	607 (99.3)
≥ 4 weeks	578 (94.6)
≥ 8 weeks	542 (88.7)
≥ 14 weeks	484 (79.2)
≥ 26 weeks	392 (64.1)
≥ 38 weeks	339 (55.4)
≥ 52 weeks	286 (46.8)
≥ 64 weeks	222 (36.3)
≥ 76 weeks	160 (26.1)
≥ 88 weeks	91 (14.8)
≥ 100 weeks	50 (8.1)
≥ 112 weeks	26 (4.2)
≥ 124 weeks	11 (1.8)
≥ 136 weeks	2 (0.3)

Trials: 405-201-00016, 405-201-00021 (Cohort 1), and 405-201-00017.
Notes: Includes data from short-term trials (16, 21 [Cohort 1]) for centanafadine-treated subjects who entered long-term open-label Trial 17; dose categorization for the Pediatric LT Pool is: All Centanafadine Doses; percentages are based on the number of subjects in safety
Source: ISS, Table 6.3.1.1.1-1sample.

120-Day Safety Update: At the time of NDA submission data cutoff date of May 1, 2025, there were three ongoing trials for centanafadine: Study 17 (pediatric subjects with ADHD), Trial 405-201-00180 (adult subjects with ADHD and comorbid anxiety), and Trial 405-201-00062 (adult subjects with major depressive disorder). The Applicant submitted the 120-day safety update of the ISS on March 19, 2026. The cutoff date for the 120-day safety update was September 12, 2025.

The 120-day update included the following:

- New data from previously enrolled subjects in the Study 17 pediatric open-label extension study
- Data from 197 newly enrolled subjects who received blinded study drug in the phase 3 study 405-201-000180 (ADHD and comorbid anxiety)
- A synoptic clinical study report for the phase 2 MDD study 405-201-00062 in which 81 subjects were treated with centanafadine.

In pediatric subjects 4 and 5 years of age with ADHD, at the time of the data cutoff for the 120-day update, a total of 55 subjects had been enrolled, treated, and analyzed for safety. A total of three subjects (5.5%) completed, and 27 subjects (49.1%) discontinued in the 4- to 5-year-old age group. A total of 25 subjects (45.5%) in the 4- to 5-year-old age group were ongoing in the pediatric long-term trial as of the 120-day update data cutoff date (September 12, 2025). As of that cutoff date, 29 subjects 4 and 5 years of age were exposed to centanafadine for ≥26 weeks (≥6 months) and two subjects were exposed to centanafadine for ≥52 weeks (≥1 year).

Adequacy of the Safety Database

The database includes safety data for a range of centanafadine doses and a range of exposure durations. For adults and pediatric patients ages 6 years and older, the overall exposure meets the *ICH E1A* recommendation for the extent of population exposure to evaluate the safety of drugs intended for the long-term treatment of non-life-threatening diseases.

A major limitation of the safety database was the absence of older adult subjects. The range of ages for adult subjects with ADHD was 18 to 55 years. No subjects over 55 with ADHD were exposed to centanafadine. In the MDD study (405-201-00062), subjects up to 65 years of age were enrolled.

There are also no data on pregnant or lactating women.

Although the pediatric safety database across all ages met the *ICH E1A* guideline recommendations, there is a relative dearth of safety data from 4- and 5-year-olds, in particular longer-term data. This is in part due to low enrollment, but also due to high dropout rates (49.1%) in this age group.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no major issues with safety data quality and no major amendments to the NDA were necessary during the review cycle. The Applicant was responsive to information requests and other communications during the review.

During the review cycle, the clinical review team discovered that the vital signs data from Day 35 were missing for Study 13 and Study 14. On July 2, 2026, the Agency sent an information request to the Applicant regarding the data missing from the ADVS databases for those two studies. On July 6, 2026, the Applicant responded:

> During the database build for these trials there was an issue where the data capture page for Day 35 vitals was not included at study start and was updated during study conduct, thus many subjects did not ultimately have this data collected. The "Day 35 repeat" values reflect the values that were captured after the update. From the Sponsor's review of the ADVS databases there are 53 subjects with Day 35 vital signs data from Study 13 and 44 subjects with Day 35 vital signs data from Study 14.

Although the missing vital sign data creates some degree of uncertainty, the clinical review team was nevertheless able to adequately assess vital sign changes based on the data available from the other 5 weeks of these studies.

The Office of Scientific Investigations (OSI) conducted inspections of the study sites of Drs. Valerie Arnold, Howard Rubenstein, Michael Leibowitz, Michael Banov, Nandita Jones, and Divyansu Patel (site #s: 32, 332, 402, 405, 15, and 17). These sites were selected using a risk-based approach primarily based on number of enrolled subjects, treatment effect, protocol deviations, and prior inspection history.

Based on the results of these inspections, OSI concluded that the studies (Studies 13, 14, 16 and 21) appeared to have been conducted adequately and the data generated by these sites appeared acceptable in support of the application.

Categorization of Adverse Events

The Applicant used standard procedures to collect, code, and analyze the incidence of AEs for all studies described in the ISS. AEs were collected beginning from the time the subject signed the study informed consent document through the last study visit. SAEs were collected for 7 days after the last dose of study drug. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 for the adult short term ADHD trials (Studies 13 and 14), version 24.0 for the adult ADHD open label extension study (Study 15), and version 26.0 for the pediatric ADHD studies. The Applicant defined treatment-emergent adverse events (TEAEs) as AEs that were new in onset or increased in severity following treatment initiation, regardless of causality. For the purpose of this review, quantification of AE frequency and incidence is based on AEs occurring after treatment initiation.

The adae.xpt datafile for the phase 3 studies was examined for the accuracy of translation from verbatim terms (provided by study personnel) to preferred terms. Each unique verbatim term was viewed for Studies 13, 14, 16, and 21 to determine whether the preferred term accurately captured the clinical event described by the verbatim term. Where replacements were indicated, the original verbatim term was deleted and replaced.

Grouping of Preferred Terms: To better assess for the presence and magnitude of safety signals, the clinical review team grouped related preferred terms. Pertinent examples are listed in Table 54.

Table 54. Grouping Terms and Related Preferred Terms

Grouping term	Preferred terms included in grouping term
Abdominal pain	Abdominal discomfort, abdominal pain upper, abdominal tenderness, gastrointestinal pain; abdominal pain lower; abdominal tenderness
Anxiety	Nervousness, panic attack
Blood pressure increased	Blood pressure orthostatic increased, blood pressure diastolic increased, hypertension, orthostatic hypertension
Chest pain	Non-cardiac chest pain, chest discomfort
Depressed mood	Depressive symptom, depression, major depressive disorder, major depression, dysphoria
Dizziness	Lightheadedness, dizziness postural, presyncope
Dyspepsia	Gastrooesophageal reflux disease
Fatigue	Lethargy, asthenia
Headache	Tension headache, cervicogenic headache, migraine with aura, migraine without aura, migraine, head discomfort, sinus headache
Insomnia	Initial insomnia, terminal insomnia, sleep disorder, middle insomnia, poor quality sleep
Parasomnia	Sleep terror, nightmare, abnormal dreams, somnambulism
Rash	Dermatitis, dermatitis contact, rash erythematous, intertrigo, dermatitis atopic, rash maculo-papular, Drug eruption, rash macular, rash morbilliform, rash papular, urticaria, rash pruritic, viral rash
Somnolence	Sedation
Suicidal and self-injurious behaviour	Suicidal behaviour, suicidal ideation, suicide attempt, intentional self-injury
Tachycardia	Sinus tachycardia, supraventricular tachycardia, postural orthostatic tachycardia syndrome, orthostatic heart rate response increased, heart rate increased

Source: Reviewer-generated.

Routine Clinical Tests

Routine clinical tests were performed. Vital signs included supine diastolic and systolic blood pressure, heart rate, orthostatic blood pressure and heart rate measurements, respiratory rate, temperature, height, and weight. Laboratory assessments were collected at Screening, Baseline, at various time points during the treatment periods of studies, at the end of the study/treatment visit, and as applicable, at follow-up and unscheduled visits. For most studies, 12-lead ECGs were obtained at Screening, Baseline, at various time points during treatment periods, and at the end of treatment visit.

In TQT Study 405-201-00001, a continuous ECG signal was obtained up to 16 hours prior to and for 24 hours following dosing.

Details of the timing and collection of routine clinical tests are listed in Section 7.1 for Studies 13, 14, 16, and 21.

7.2.4. Safety Results

Deaths

No deaths have been reported in any centanafadine trials.

Serious Adverse Events

As of the 120-day safety update, 36 SAEs had been reported in 30 subjects: 16 adults with ADHD, 13 pediatric subjects with ADHD, and one adult in the smoking cessation trial.

Pediatric Serious Adverse Events

In pediatric short term trials (Studies 16 and 21), four subjects (0.7%) exposed to centanafadine (one subject in the high dose, three subjects in the low dose group) experienced SAEs compared to no subjects in the placebo group. These SAEs occurred in subjects 10 and 11 years of age in Study 21 Cohort 1. Onset times ranged from Day 11 to 45.

Two subjects experienced SAEs of suicide attempt (one in the low dose centanafadine ER group and one in the high). The subject in the low dose group had already completed Week 6 by the time the SAE was reported, although the event occurred on Day 11. The subject in high dose group experienced the SAE of suicide attempt on Day 17, leading to discontinuation on Day 21. Neither subject had a history of SI/B. Both events occurred in the setting of arguments with family members. Refer to Section 7.2.5 for further discussion of SI/B.

An 11-year-old male subject in the low dose centanafadine ER group experienced an SAE of panic attack on day 45 that was considered serious due to medical significance. According to the subject's mother, he “heard voices and had seen visions of voices that were going to hurt his family.” The panic attack and hallucinations occurred 2 days after his final dose of centanafadine (on Day 43).

A 10-year-old female subject in the low dose centanafadine ER group experienced an SAE of appendicitis. Ten days after the first dose, she experienced rash and began taking 25 mg diphenhydramine three times a day for itching. The drug was discontinued on that day due to the rash. Twelve days after the first dose, she had severe acute abdominal pain and vomiting, was hospitalized for appendicitis, and underwent appendectomy.

In Study 21 Cohort 2, a 4-year-old male subject in the high dose centanafadine group experienced SAEs of seizure and acute respiratory failure, considered serious because they were life threatening and required hospitalization. The subject had no medical history, but did have a family history of seizures. The events occurred on Day 21 and led to discontinuation.

In the long term pediatric trial, eight subjects (1.3%) experienced SAEs. The highest incidence of SAEs were in the SOC Psychiatric Disorders (n=5; 0.8%). One subject experienced an SAE of hallucination, visual. The SAE was moderate in severity and led to discontinuation. Other psychiatric SAEs included suicidal ideation (n=3; 0.5%), hallucination, visual (n=1), and panic attack (n=1, same case as described above, as onset occurred during Study 21). Refer to Section 7.2.5 for further discussion of psychiatric AEs.

Adult Serious Adverse Events

In Studies 13 and 14, three subjects in the lower dose centanafadine group experienced four SAEs of pneumonia, gastroenteritis viral, influenza, and bronchitis. No subjects in the placebo group experienced SAEs.

In Study 15 (the adult open- label safety study), 12 subjects experienced SAEs. SAEs in Study 15 were most frequent in subjects who had been on placebo in the short-term trial (n=7; 3.8%). Three de novo subjects (1.8%) experienced SAEs, compared with one subject each with prior low dose and high dose centanafadine exposure.

Three subjects (0.5%) experienced SAEs in the SOC of Psychiatric Disorders. One subject reported mood swings and suicidal ideation. Two subjects reported intentional self-injury. One of these subjects attempted suicide by ingesting four tablets of tramadol 50 mg and four tablets of ibuprofen 800 mg, drinking alcohol, and ingesting tetrahydrocannabinol (THC) pills. The event occurred on Day 355, resolved by Day 357, and the subject completed the trial on Day 369. The other subject experienced suicidal ideation and self-injurious behavior. She was acutely intoxicated with alcohol and made superficial cuts on her wrist. She was discontinued from the study. Refer to Section 7.2.5 for further discussion of SI/B and other psychiatric adverse events.

One SAE of angioedema in one adult in the smoking cessation trial was considered related to the study drug by both Investigator and Applicant. The SAE was severe in intensity and the drug was discontinued. Angioedema was preceded by drug eruption (verbatim term: dermatitis medicamentosa) 1 day prior. Refer to Section 7.2.5 for further discussion of hypersensitivity reactions.

An SAE of "severe cerebrovascular accident (CVA)" occurred in a phase 2 study, EB-1020-SR-ADHD-201. A 49-year-old Black male subject with ADHD and lisinopril-treated hypertension had been receiving 500 mg of centanafadine tablets (the maximum dose in that study). The SAE reportedly occurred 6 days after completing treatment. The subject experienced CVA presenting as slurred speech and left-sided weakness with inability to stand. A CT scan revealed thrombosis in the brain. He was treated with thrombolytic drug therapy, but the results were not satisfactory and he was transferred to another hospital under the care of a neurosurgeon. An angiogram was performed, and he was then transferred to the intensive care unit. It was reported that after the angiogram, he was responding well to stimuli, was aware of his surroundings and able to speak with slurred speech, and was gaining use of his left arm and leg. However, 1 day later, he developed a brain hemorrhage and increased intracranial pressure and underwent a decompressive craniotomy. The next day, he was removed from the ventilator, responding well to stimuli, aware of his surroundings, and speaking with a slur. He was transferred to a rehabilitation center and lost to follow-up. The subject, who had completed treatment at Week 4, was withdrawn from the trial for this SAE. The Investigator and Applicant assessed the event as unrelated to study drug, attributing the CVA to the subject's underlying hypertension. The subject's BP measurements at trial entry and throughout the trial were: 138/81 mmHg (Screening), 134/84 mmHg (Baseline-1 [placebo run-in]), 123/86 mmHg (Baseline-2), 130/85 mmHg (Treatment Week 1), 118/82 mmHg (Treatment Week 2), 135/78 mmHg (Treatment Week 3), and 123/80 mmHg (Treatment Week 4). However, given the effects of centanafadine on blood pressure and the high dose administered in this study, it is not possible to rule out an association. Refer to Section 7.2.5 for further discussion of blood pressure effects.

Dropouts and/or Discontinuations Due to Adverse Effects

Pediatric Discontinuations

In short-term pediatric studies, 7.1% of subjects in the high dose centanafadine group experienced AEs leading to discontinuation compared with 3.0% of subjects in the low dose group and 0.7% of subjects receiving placebo.

In 4- and 5-year-old subjects (Study 21 Cohort 2), 4.8% (3/62) of in the high dose centanafadine ER group discontinued due to AEs compared with none in the placebo group. AEs leading to discontinuation included lethargy and nausea in one subject, acute respiratory failure and seizure in one subject, and rash in one subject.

Among subjects 6 to 12 years of age (Study 21 Cohort 1), 6.3% (10/157) of those treated with the high, weight-based dosage of centanafadine discontinued due to AEs compared with 2.7% (4/147) of low dose subjects and 1.3% (2/153) of placebo-treated subjects. Among subjects treated with the high dose (the only dose proposed for approval), the most frequently reported AE associated with discontinuation (1% or more and twice rate of placebo) was rash (2.5%). Less frequently reported AEs (less than 1% or less than twice rate of placebo) associated with

discontinuation were altered mood, neutropenia, diarrhea, nausea, increased blood pressure, dizziness, headache, lethargy, irritability, and suicide attempt.

Of subjects 13 to 17 years of age in Study 16, 8% (12/151) treated with 280 mg centanafadine ER capsules discontinued due to AEs compared with 3% (5/153) of subjects treated with 140 mg and 0% (0/147) of placebo-treated subjects. In the 280-mg dose (the only dose proposed for approval in this age group), the most frequently reported AEs (1% or more and twice rate of placebo) associated with discontinuation were rash (2%), decreased appetite (2%), nausea (2%), and somnolence (1%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) associated with discontinuation were abdominal discomfort, hypersensitivity, increased blood creatine phosphokinase, increased blood pressure, increased heart rate, and aggression.

In the long-term safety study (Study 17), there were high rates of discontinuation in all age groups.

A total of 55 subjects 4 and 5 years of age were enrolled and treated. As of the 120-day Safety Update data cutoff date of September 12, 2025, a total of three subjects (5.5%) in the 4- to 5-year-old age group had completed and 27 subjects (49.1%) discontinued. The most frequently reported reasons for discontinuation were lost to follow-up (14.5%), withdrawal by parent/guardian (12.7%), adverse events (5.5%), and lack of efficacy (5.5%). In this group, four subjects (7.3%) experienced AEs leading to discontinuation, which included rash, aggression, agitation, apathy, insomnia, and presyncope. It is possible that some of the subjects lost to follow-up or withdrawn by parent/guardian may have dropped out due to unrecorded AEs.

In the 6- to 12-year-old age group, of 301 subjects enrolled and 299 treated, 143 subjects (47.5%) discontinued. The most frequently reported reasons for discontinuation among subjects in the pediatric long-term trial 6- to 12-year-old age group were withdrawal by parent/guardian (16.9%), lost to follow-up (11.0%), lack of efficacy (6.0%), and TEAEs (3.7%). In this age group, 14 subjects [4.7%] discontinued due to AEs. The AEs leading to discontinuation included irritability (two subjects), hallucination (two subjects), abdominal pain, fatigue, ALT increased, AST increased, CPK increased, electrocardiogram abnormal, weight decreased, insomnia, major depression, mood altered (all in one subject each).

In the 13- to 17-year-old age group, 8.4% of subjects (27/321) discontinued due to AEs. Twelve subjects discontinued due to AEs in the SOC Psychiatric Disorders: three for suicidal ideation, three for depression-related AEs, two for irritability, two for apathy and one each for aggression, anxiety, defiant behavior, and feelings of worthlessness. Other discontinuations included five subjects with nausea; two subjects each with blood pressure increased, headache, fatigue, diarrhea, dry mouth; and one subject each with vomiting, malaise, decreased appetite, muscle spasms, rash, and bromhidrosis.

Adult Discontinuations

In Studies 13 and 14, 6.2% (18/292) of adult subjects treated with the high, 400-mg total daily dose of centanafadine tablets discontinued due to AEs, compared with 4.8% (14/294) of subjects treated with the low (200 mg total daily dose) and 1.4% (4/290) of placebo-treated subjects. The most frequently reported AE associated with discontinuation (1% or more and twice rate of placebo) was rash (2%). Less frequently reported adverse reactions (less than 1% or less than twice rate of placebo) associated with discontinuation were abdominal pain, anxiety, and palpitations.

Significant Adverse Events

Newly acquired, non-traumatic skin eruptions were considered adverse events of special interest (AESIs) and were monitored prospectively in the phase 3 trials through an AESI monitoring plan. Refer to Section 7.2.5 for discussion of hypersensitivity reactions including rash.

Treatment-Emergent Adverse Events and Adverse Reactions

In the placebo-controlled trial in pediatric subjects 4 and 5 years of age (Study 21 Cohort 2), AEs occurred in 21 of 62 subjects (33.9%) in the high dose centanafadine ER group and five of 32 subjects (15.6%) in the placebo group. Decreased appetite and rash each occurred in 4.8% (3/62) of high dose centanafadine subjects and no subjects in the placebo group. Insomnia occurred in 3.2% (2/62) high dose centanafadine subjects and no placebo subjects.

The most common AEs (≥5% and greater than placebo) in the placebo-controlled trial in pediatric subjects 6- to 12-years old (Study 21 Cohort 1) were rash and decreased appetite. In the older pediatric subjects 13- to 17-years old (Study 16), the most common AEs were decreased appetite, nausea, rash, headache, and abdominal pain. In the placebo-controlled trials in adults (Studies 13 and 14), the most common AEs were headache, decreased appetite, insomnia, nausea, dry mouth, and diarrhea.

Table 55 presents AEs reported in 2% or more of pediatric subjects 6 to 12 years of age treated with the high, weight-based dosage of centanafadine ER capsules in Study 21 Cohort 1 (and more frequently than in placebo).

Table 55. AEs in ≥2% of Pediatric Subjects 6 to 12 Years of Age Treated With Centanafadine and Greater Than Placebo in Study 21 Cohort 1

	Placebo (N=153)	**Centanafadine Low dose*** (N=147)	**Centanafadine High dose*** (N=157)
Rash[a]	0%	7%	9%
Decreased appetite	3%	4%	8%
Fatigue[b]	0%	2%	4%
Abdominal pain[c]	2%	1%	4%

	Placebo (N=153)	Centanafadine Low dose* (N=147)	Centanafadine High dose* (N=157)
Nausea	1%	2%	3%
Pharyngitis streptococcal	2%	0%	3%
Diarrhea	0%	0%	2%
Influenza	0%	1%	2%

*Weight-based equivalent dose (targeting adult exposures at 280 mg/day)
[a]Rash includes: drug eruption, macular rash, maculo-papular rash, morbilliform rash, papular rash, and other related terms
[b]Fatigue includes: lethargy
[c]Abdominal pain includes: upper abdominal pain, abdominal discomfort
Source: Reviewer-generated

Table 56 presents AEs reported in ≥2% of pediatric subjects 13 to 17 years of age treated centanafadine ER capsules 280 mg in Study 21 Cohort 1 and more frequently than placebo.

Table 56. AEs in ≥2% of Pediatric Subjects 13 to 17 Years of Age Treated With Centanafadine and Greater Than Placebo in Study 16

	Placebo (N=147)	Centanafadine ER capsules 140 mg/day (N=153)	Centanafadine ER capsules 280 mg/day (N=151)
Decreased appetite	2%	6%	15%
Nausea	3%	5%	10%
Rash[a]	1%	2%	8%
Headache[b]	6%	8%	7%
Abdominal pain[c]	0%	3%	5%
Somnolence[d]	3%	3%	4%
Fatigue[e]	1%	2%	3%
Dizziness	0%	2%	3%
Nasopharyngitis	1%	1%	3%
Insomnia[f]	1%	1%	3%
Irritability	1%	1%	3%
Dry mouth	0%	1%	2%
Weight decreased	1%	0%	2%

[a]Rash includes: drug eruption, macular rash, maculo-papular rash, morbilliform rash, papular rash, and other related terms.
[b]Headache includes: migraine
[c]Abdominal pain includes: abdominal discomfort, upper abdominal pain, abdominal tenderness, gastrointestinal pain; lower abdominal pain; abdominal tenderness
[d]Somnolence includes: sedation
[e]Fatigue includes: lethargy
[f]Insomnia includes: initial insomnia
Source: Reviewer-generated

Table 57 presents AEs reported in ≥2% of adults treated with centanafadine twice-daily tablets in Studies 13 and 14 and more frequently than placebo.

Table 57. AEs in ≥2% of Adults Treated With Centanafadine and Greater Than Placebo in Studies 13 and 14

	Placebo (N=290)	Centanafadine tablets 200 mg total daily dose (N=294)	Centanafadine tablets 400 mg total daily dose (N=292)
Headache[a]	7%	5%	8%
Decreased appetite	2%	5%	7%
Insomnia[b]	4%	5%	7%
Nausea	2%	2%	7%
Dry mouth	0%	3%	6%
Diarrhea	1%	2%	5%
Irritability	2%	3%	4%
Rash[c]	2%	2%	4%
Abdominal pain[d]	1%	2%	4%
Parasomnias[e]	1%	1%	3%
Tachycardia[f]	1%	1%	2%
Depressed mood[g]	0%	3%	2%
Anxiety[h] Upper respiratory tract infection	1% 2%	2% 5%	2% 2%

[a] Headache includes: cervicogenic headache, migraine with aura, migraine without aura, sinus headache, head discomfort, tension headache, migraine, and other related terms
[b] Insomnia includes: initial insomnia, middle insomnia, poor quality sleep, terminal insomnia, and other related terms.
[c] Rash includes: erythematous rash, maculo-papular rash, morbilliform rash, papular rash, pruritic rash, and other related terms.
[d] Abdominal pain includes: abdominal discomfort, upper abdominal pain, lower abdominal pain, abdominal tenderness, gastrointestinal pain, and other related terms.
[e] Parasomnias includes: abnormal dreams, sleep terror, nightmare, somnambulism, and other related terms.
[f] Tachycardia includes: sinus tachycardia, supraventricular tachycardia, postural orthostatic tachycardia syndrome, increased orthostatic heart rate response, increased heart rate, and other related terms.
[g] Depressed mood includes: depressive symptom, depression, major depressive disorder, major depression, dysphoria, and other related terms.
[h] Anxiety includes: nervousness, panic attack, and other related terms.
Source: Reviewer-generated

Laboratory Findings

No clinically meaningful differences in mean laboratory values were observed in centanafadine-treated subjects, as compared to placebo. Most laboratory values in the phase 3 controlled studies remained within the reference ranges for age.

In the placebo-controlled trials in adults (Studies 13 and 14), potentially clinically relevant

elevations of alanine transaminase (ALT) occurred in 0.4% in both the all centanafadine doses group and placebo group. Potentially clinically relevant AST elevations occurred in 0.4% of the all centanafadine doses group and placebo group. Potentially clinically relevant bilirubin elevations occurred in 0.5% in the all centanafadine doses group and 0.4% in the placebo group. There were no Hy's Law cases (ALT or aspartate aminotransferase (AST) ≥3× upper limit of normal (ULN) and Total Bilirubin ≥2× ULN).

Table 58. Incidence of Hepatic Laboratory Test Abnormalities (≥3X ULN) in Studies 13 and 14

		Placebo		Centanafadine 200 mg TDD		Centanafadine 400 mg TDD		All Centanafadine Doses	
Parameter (Units)		**N[a]**	**n(%)[b]**	**N[a]**	**n(%)[b]**	**N[a]**	**n(%)[b]**	**N[a]**	**n(%)[b]**
Alanine Aminotransferase (U/L)	High	285	1 (0.4)	284	1 (0.4)	286	1 (0.3)	570	2 (0.4)
Aspartate Aminotransferase (U/L)	High	285	1 (0.4)	284	2 (0.7)	286	0 (0.0)	570	2 (0.4)
Alkaline Phosphatase (U/L)	High	285	0 (0.0)	284	0 (0.0)	286	0 (0.0)	570	0 (0.0)
Bilirubin (mg/dL)	High	272	1 (0.4)	275	2 (0.7)	279	1 (0.4)	554	3 (0.5)

Trials: 405-201-00013 and 405-201-00014.
[a]N is the total number of subjects with at least one post-baseline numeric result for the given laboratory parameter.
[b]n is the number of subjects with laboratory value of potential clinical relevance.
Source: Applicant's Integrated Summary of Safety

In the short-term trials, four adults subjects in the centanafadine groups experienced ALT or AST values ≥3× ULN. Three experienced AEs associated with hepatic function (two in the low dose group, one in the high dose).

- One subject receiving the high dose of centanafadine tablets (total daily dose of 400 mg) had an ALT value ≥5× ULN (182 U/L) on Day 28. This subject had an AE of ALT increased which was considered moderate in severity.
- One subject receiving the low dose of centanafadine tablets (total daily dose of 200 mg) had an ALT value ≥3× ULN (165 U/L) on Day 15. No associated AE was reported.
- One subject receiving the low dose of centanafadine tablets had an AST value ≥5× ULN (314 U/L) on Day 15. This subject had an AE of aspartate aminotransferase increased, which was considered moderate in severity, related to the IMP by the Investigator, and nonserious. The subject had a concurrent AE of blood creatine phosphokinase increased.
- One subject receiving the low dose of centanafadine tablets had an AST value ≥3× ULN (178 U/L) on Day 14. This subject had an AE of liver function test increased which was considered moderate in severity, related to IMP by the investigator, and nonserious.

In the long-term adult study (Study 15), two subjects experienced ALT or AST values ≥10× ULN:

- One subject who had received the low dose of centanafadine in the short-term trial had an ALT value ≥10× ULN (509 U/L) and an AST value of 268 U/L on Day 117. This subject had an AE of hepatitis A on Day 117 which was considered moderate in severity, not related to centanafadine by the Investigator, and nonserious. The subject was discontinued from centanafadine on Day 125 and discontinued from the trial on Day 187 due to the event of

hepatitis A.
- One subject who had received the high dose of centanafadine in the short-term trial had an AST value ≥10× ULN (383 U/L) and an ALT value of 165 U/L on Day 107. The subject had an AST of 152 U/L on Day 105. This subject had an AE of blood creatine phosphokinase increased on Day 105 which was considered mild in severity, not related to centanafadine by the investigator, and nonserious. The subject had a creatine kinase value of 10730 U/L on Day 105, 20721 U/L on Day 107, and 1386 U/L on Day 110. According to the listings in ISS Appendix 3, the verbatim term was "ELEVATED CREATINE PHOSPHOKINASE RELATED TO INCREASE IN PHYSICAL EXERCISE."

The first case of ALT or AST values ≥10× ULN was due to Hepatitis A infection and is unlikely to have been related to centanafadine. The second case appears consistent with rhabdomyolysis. Based on the verbatim term, this was likely to have been exercise-induced and unlikely to have been related to centanafadine.

Overall, there were no clinically meaningful differences in laboratory abnormalities between centanafadine and placebo.

Vital Signs

Refer to 7.2.5 for analysis of vital signs.

Electrocardiograms (ECGs)

Differences in HR are discussed in Analysis of Submission-Specific Safety Issues (Section 7.2.5). No other clinically meaningful differences in changes in ECG parameters were noted between the groups in the controlled study. Refer to IRT review for detailed analyses.

QT

Refer to IRT review for full assessment of potential for QT prolongation. No concerning trends towards changes in QTcF interval changes were observed for centanafadine exposed subjects in the controlled trials or open-label safety studies.

Immunogenicity

Refer to Section 7.2.5.6 for assessment of hypersensitivity reactions.

7.2.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues included suicidal ideation and behavior (SI/B), abuse potential, psychiatric adverse events, changes in blood pressure and heart rate, long-term suppression of growth in pediatric patients, and hypersensitivity reactions. Newly acquired, non-traumatic skin eruptions were considered adverse events of special interest (AESIs) and were monitored prospectively in the phase 3 trials through an AESI monitoring plan (see Section 2.2 Summary of Presubmission/Submission Regulatory Activity).

7.2.5.1. Suicidal Ideation and Behavior

The review team evaluated the data related to SI/B from the controlled clinical studies (Studies 16 and 21) and the open label long-term safety study (Study 17). SI/B was prospectively monitored at each study visit as assessed by the C-SSRS and were also reported by some subjects as AEs.

AEs: In Study 21, two subjects from Cohort 1 receiving centanafadine experienced AEs of suicide attempt (2/304; 0.7%) compared with no subjects in the placebo group. One subject was receiving low dose, weight-based centanafadine; the other was receiving high-dose, weight-based centanafadine. In the pediatric long-term, open-label study (Study 17), AEs of suicidal ideation were reported in 0.7% (5/675) of subjects, leading to discontinuation in 0.6% (4/675).

C-SSRS: SI/B was reported via the C-SSRS in three subjects in Study 21 Cohort 1 during the treatment period: one subject who received high dose centanafadine ER experienced suicidal behavior and suicidal ideation (also reported as a serious AE of suicide attempt), one subject who received low dose centanafadine ER experienced suicidal behavior, and one subject who received low dose centanafadine ER experienced suicidal ideation (neither subject in the low dose group had any reported AEs related to SI/B).

Pediatric subjects who received centanafadine ER capsules were more likely than subjects who received placebo to experience SI/B. Pediatric patients with ADHD may be more likely to experience SI/B than the general pediatric population. Any increased risk of suicidal ideation and behavior associated with centanafadine ER should be characterized and described in labeling to allow healthcare professionals to assess the benefit-risk for each individual patient.

7.2.5.2. Abuse Potential

Refer to CSS review by Dr. Bonson for evaluation of abuse potential and scheduling recommendation. Refer also to Section 15.3 for the review of the established pharmacological class. Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and CNS stimulant.

In clinical studies for ADHD, safety signals emerged that may relate to abuse potential. In particular, affect lability, aggression, agitation, anxiety, depression, hallucinations, irritability, mood changes, mood swings, and somnolence may be relevant to abuse potential. In the long-term open label adult study (Study 15), AEs of feeling jittery, feeling abnormal, mood altered, mood swings, and mania occurred, which may relate to abuse potential.

In addition, in a healthy volunteer study, an AE occurred that is particularly concerning for abuse potential. The subject was a 37-year-old healthy white female enrolled in Study 405-201-00154. On Day 6 of treatment, the subject experienced euphoric mood (the reported term was “felt high”). The event occurred following the first dose of centanafadine ER 246.6 mg, subsequent to several days of receiving a lower dose. The subject reported that she felt high,

had a heavy head, and started to sweat 1 hour after dosing. The subject was at baseline when she woke up the next morning. No further information is available about this event. In total, seven subjects exposed to centanafadine in healthy adult clinical pharmacology trials experienced AEs with the PT "euphoric mood."

In the long-term open-label extension in adults (Study 15), three subjects had medication handling irregularities that involved suspected or known abuse or diversion of study drug. Suspected or known abuse or diversion of centanafadine was reported at Week 8 in one subject with prior high-dose centanafadine exposure (reported as second occurrence of lost or stolen IMP with strong evidence in support of diversion) and at early termination in two de novo subjects (one subject took all 30 tablets in 9 days and one subject dropped 10 tablets down the drain after knowing he would be early terminated due to positive urine drug screen).

Overall, the totality of evidence from animal studies, human abuse potential studies, and from the clinical studies indicates that centanafadine has a potential for abuse and misuse.

7.2.5.3. Psychiatric Adverse Events

Pediatric Subjects

Across all pediatric age groups in the short-term, placebo-controlled studies 16 and 21, Psychiatric Disorder AEs occurred in 9.4% of the high dose centanafadine group, 7.0% of the low dose centanafadine group, and 6.0% of the placebo group. The most common Psychiatric Disorder AEs across all age groups in the short-term studies were somnolence, insomnia, irritability, and anxiety.

In the long-term study (Study 17), 13.1% of subjects reported at least one AE in the Psychiatric Disorders SOC. Irritability and insomnia were the most common psychiatric AEs. Irritability occurred in 18 subjects (2.9%). AEs related to insomnia (including initial insomnia and poor quality sleep) occurred in 17 subjects (2.8%). There were several psychiatric SAEs, including irritability, mood altered, aggression, and agitation.

Five AEs associated with hallucination occurred in a total of four subjects in the pediatric short-term and long-term studies. An AE of hallucination was reported in one subject (0.2%) in the high dose centanafadine group in Study 21 and in three subjects in Study 17. One subject in Study 17 experienced an SAE of hallucination, visual and an AE of hallucination, auditory.

Table 59 shows all AEs in the SOC Psychiatric Disorders by age group and treatment group.

Table 59. Psychiatric AEs in Pediatric Placebo-Controlled Trials

	Age Group 4 to 5 Years		Age Group 6 to 12 Years			Age Group 13 to 17 Years		
	Placebo N=32 n (%)	**CTN ER High Dose** N=62 n (%)	**Placebo** N=153 n (%)	**CTN ER Low Dose** N=147 n (%)	**CTN ER High Dose** N=157 n (%)	**Placebo** N=147 n (%)	**CTN ER 140 mg** N=153 n (%)	**CTN ER 280 mg** N=151 n (%)
Psychiatric disorders (SOC)	0	6 (9.7)	6 (3.9)	9 (6.1)	6 (3.8)	5 (3.4)	8 (5.2)	13 (8.6)
Tic	0	1 (1.6)	1 (0.7)	0	0	0	0	0
Suicide attempt	0	0	0	1 (0.7)	1 (0.6)	0	0	0
Suicidal ideation	0	0	0	0	0	1 (0.7)	1 (0.7)	1 (0.7)
Suicidal behaviour	0	0	0	0	0	1 (0.7)	0	0
Somnambulism	0	0	0	1 (0.7)	0	0	0	0
Panic attack	0	0	0	1 (0.7)	0	1 (0.7)	0	1 (0.7)
Onychophagia	0	1 (1.6)	0	0	0	0	0	0
Nervousness	0	0	0	0	0	0	0	1 (0.7)
Mood swings	0	0	0	0	0	0	0	1 (0.7)
Mood altered	0	0	0	1 (0.7)	0	0	0	0
Irritability	0	1 (1.6)	1 (0.7)	0	1 (0.6)	2 (1.4)	2 (1.3)	4 (2.6)
Insomnia	0	2 (3.2)	0	2 (1.4)	2 (1.3)	1 (0.7)	1 (0.7)	3 (2.0)
Initial insomnia	0	0	1 (0.7)	0	0	0	1 (0.7)	1 (0.7)
Hallucination	0	0	0	0	0	0	0	1 (0.7)
Emotional disorder	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Dermatillomania	0	1 (1.6)	0	0	0	0	0	0
Depression	0	0	1 (0.7)	0	0	1 (0.7)	0	0
Anxiety	0	0	0	1 (0.7)	0	0	1 (0.7)	0
Agitation	0	0	1 (0.7)	0	0	0	0	0
Aggression	0	0	1 (0.7)	0	0	1 (0.7)	1 (0.7)	0
Affect lability	0	1 (1.6)	2 (1.3)	1 (0.7)	2 (1.3)	0	0	0

Source: Clinical Data Scientist-generated

The incidence of AEs in the SOC of Psychiatric Disorders was higher in the centanafadine group compared with placebo in pediatric subjects 4 and 5 years of age (9.7% versus 0%). The most common psychiatric AE in this age group was insomnia, with an incidence of 3.2% (2/62 subjects). Irritability, affect lability, onychophagia, and dermatillomania each occurred in one subject in the centanafadine group (1.6%) and no subjects in the placebo group. In the long-term safety study (Study 17), AEs of aggression, agitation, apathy, and insomnia each led to discontinuation in this age group in one subject.

In pediatric subjects 6 to 12 years of age, AEs in the Psychiatric Disorders SOC occurred in 3.8% of subjects who received the high weight-based dose of centanafadine, 6.1% of subjects who received the low dose, and 3.9% of placebo subjects. Two subjects experienced AEs of suicide attempts: one each in the high-dose and one in the low-dose centanafadine group (compared with none who received placebo. Two subjects in the high- and low-dose centanafadine group (1.3 and 1.4%) experienced AEs related to insomnia, compared with one in the placebo group (0.7%). Two subjects in the low-dose centanafadine group experienced anxiety-related AEs (anxiety and panic attack). In the long-term safety study (Study 17), AEs in the Psychiatric Disorder SOC led to discontinuation in 6 subjects (2%) in this age group. Two subjects discontinued for irritability (0.7%), and one subject each (0.3%) for hallucination auditory, hallucination visual, major depression, mood altered, and suicidal ideation.

In pediatric subjects 13 to 17 years of age, AEs in the Psychiatric Disorder SOC occurred in a dose-dependent manner, in 8.6% of subjects in the 280-mg group, 5.2% in the 140-mg group, and 3.4% in the placebo group. Irritability and insomnia were the most common psychiatric AEs. Irritability occurred in four subjects (2.6%) in the 280-mg group compared with two subjects (1.3%) in the 140-mg group and two subjects (1.4%) in the placebo group. Insomnia AEs (including “initial insomnia”) occurred in four subjects (2.7%) in the 280-mg group, two subjects (1.4%) in the 140-mg group, and one subject (0.7%) in the placebo group. In the long-term safety study (Study 17), AEs in the Psychiatric Disorder SOC led to discontinuation in 12 subjects (3.7%) in this age group. Three subjects (0.9%) discontinued for suicidal ideation; three (0.9%) for AEs related to depression; two (0.6%) for irritability; two (0.6%) for apathy; and one subject each (0.3%) for aggression, anxiety, defiant behavior, and feelings of worthlessness.

Adults

In the placebo-controlled short-term adult ADHD studies (13 and 14), AEs in the SOC of Psychiatric Disorders occurred at a higher rate in centanafadine treated subjects compared with placebo and in a dose-dependent manner. Of subjects treated with the high dose of centanafadine twice-daily tablets, 15.8% experienced AEs in the SOC Psychiatric Disorders, compared with 13.6% in the low dose centanafadine group at 8.3% in the placebo group. The most frequent psychiatric AEs in adults were related to insomnia, irritability, parasomnias, depressed mood, and anxiety.

Centanafadine was associated with insomnia in a dose-dependent manner: 7% of subjects who received the high total daily dose of 400 mg experienced AEs related to insomnia, compared

with 5% of the low, 200-mg total daily dose and 4% of subjects who received placebo. Irritability occurred in 4% of subjects who received the high dose, 3% of low-dose subjects, and 2% of placebo. Three percent (3%) of subjects experienced AEs related to parasomnia (e.g., abnormal dreams, sleep terror, nightmare, and somnambulism) in the high-dose centanafadine group, compared with 1% of low-dose and placebo subjects. Subjects in the low and high dose groups experienced AEs related to depressed mood with an incidence of 3% and 2%, compared to no subjects in the placebo group. AEs related to anxiety occurred in 2% of subjects in each of the centanafadine groups, compared with 1% of placebo subjects.

No events of psychosis or psychosis-associated TEAEs were observed in the adult phase 3 ADHD trials.

7.2.5.4. Changes in Blood Pressure and Heart Rate

Centanafadine was associated with elevations in blood pressure and heart rate. Although on a population level, the mean elevations over placebo were mild, subpopulations experienced clinically relevant increases in blood pressure including new onset hypertension. Refer to Division of Pediatric and Maternal Health (DPMH) Pediatric Team Consult Memo for additional discussion of pediatric vital sign data.

Blood Pressure in Pediatric Subjects 4 to 5 Years of Age

In the short-term placebo-controlled study, mean absolute changes in SBP and DBP were similar between 4- and 5-year-olds treated with centanafadine and those treated with placebo. However, a subset of these subjects experienced clinically relevant increases in blood pressure.

Among pediatric subjects 4 and 5 years old treated with high dose, weight-based centanafadine in Study 21 Cohort 2, 8.2% (5/61) developed new-onset hypertension[3] compared with 6.5% (2/31) of the placebo group. In the long-term safety study (Study 17), 3.9% (2/51) subjects 4 and 5 years of age developed new-onset hypertension and 2% (1/51) developed severe hypertension.[4] Of the subjects who developed new onset hypertension in Study 21 and rolled over into Study 17, 25% (1/4) had persistence of hypertension[5] in Study 17.

[3] New-onset hypertension defined as at least two post-baseline SBP or DBP measurements at or above the stage I hypertension range or one SBP or DBP measurement at or above the stage II hypertension range in trial patients with a baseline SBP and DBP in the normal or elevated BP category for age, sex, and height percentile as per AAP HTN Guidelines.
[4] Severe hypertension defines as at least one post-baseline SBP or DBP measurements at or above the stage II hypertension range in trial patients with a baseline SBP and DBP in the normal, elevated BP, or stage I HTN category for age, sex, and height percentile as per the AAP HTN Guidelines.
[5] Persistence of HTN defined as two or more consecutive or non-consecutive measured SBP and/or DBP after the baseline visit at or above the stage I HTN range based on age, sex, and height percentile as per the AAP HTN Guidelines.

Blood Pressure in Pediatric Subjects 6 to 12 Years of Age

Compared to placebo, short-term (6-week) treatment (Study 21, Cohort 1) with high dose weight-based centanafadine in pediatric subjects 6 to 12 years of age was associated with differences ranging from +0.1 to +2.8 mmHg in the mean absolute change from baseline systolic blood pressure (SBP) and with differences ranging from +0.2 mmHg to +1.6 mmHg in the mean absolute change from baseline diastolic blood pressure (DBP). Pediatric subjects enrolled in the long-term open-label study had mean absolute changes in baseline SBP ranging from +0.7 to +2.5 mmHg and in baseline DBP ranging from +0.5 to +2.8 mmHg through Week 88. In this age group, the incidences of new onset hypertension and severe hypertension were similar between centanafadine and placebo.

In Study 21, one subject in Cohort 1 treated with high dose centanafadine ER experienced a TEAE of blood pressure increased, which was moderate in severity and led to the discontinuation of centanafadine.

Blood Pressure in Pediatric Subjects 13 to 17 Years of Age

In a short-term, placebo-controlled trial (Study 16), the proportion of subjects 13 to 17 years of age treated with 280 mg centanafadine ER capsules who developed new-onset hypertension was 10.7% compared to 8.9% treated with placebo. Compared to placebo, short-term (6-week) treatment with centanafadine in subjects 13 to 17 years of age was associated with differences, ranging from +0.5 to +1.3 mmHg, in the mean absolute change from baseline SBP and with differences, ranging from +0.6 mmHg to +1.5 mmHg, in the mean absolute change from baseline DBP. Subjects in this age group enrolled in the long-term open-label study had mean absolute changes in baseline SBP ranging from +0.9 to +3.2 mmHg and in baseline DBP ranging from +1.7 to +3.1 mmHg through Week 88. Two subjects in this age group discontinued the long-term safety study due to AEs of increased blood pressure.

Blood Pressure Elevations in Adults

In Study 13, centanafadine was associated with dose-dependent increases in blood pressure. Subjects in the high-dose centanafadine group experienced the greatest mean changes in SBP, peaking at Day 35 with mean increase of 3.5 mmHg compared with decreases in the other two groups at that timepoint. In contrast, in Study 14, subjects in the low-dose centanafadine group experienced greater increases in SBP than those in either the high-dose group or placebo.

Table 60. SBP Mean Change From Baseline - Study 13 (mmHg)

	Placebo	Centanafadine Twice-Daily Tablets 200 mg	Centanafadine Twice-Daily Tablets 400 mg
DAY 7	1.7	0.14	0.69
DAY 14	0.63	0.037	0.64
DAY 21	1.6	1.3	1.9
DAY 28	1.5	0.91	2.0
DAY 35*	-0.7	-4.8	3.5
DAY 42	1.7	0.11	2.4

*Refer to discussion of missing Day 35 vital sign data in Adequacy of Applicant's Clinical Safety Assessments.
Source: Reviewer-generated

Table 61. SBP Mean Change From Baseline - Study 14 (mmHg)

	Placebo	Centanafadine Twice-Daily Tablets 200 mg	Centanafadine Twice-Daily Tablets 400 mg
DAY 7	-0.61	1.4	0.26
DAY 14	-2	2.2	1.2
DAY 21	-0.10	2.1	0.86
DAY 28	-1.7	2.9	0.69
DAY 35*	0.63	4.2	3.9
DAY 42	-0.97	3.1	1.8

*Refer to discussion of missing Day 35 vital sign data in Adequacy of Applicant's Clinical Safety Assessments.
Source: Reviewer-generated

Although the mean SBP changes were small in magnitude, the mean change obscures the more extreme effects. A greater subpopulation of centanafadine-treated subjects experienced clinically significant increases in blood pressure compared with placebo-treated subjects. In placebo-controlled studies in adults 18 to 55 years of age with ADHD (Studies 13 and 14), increases in SBP of ≥20 mmHg occurred in 7% (19/292) of subjects treated with the high dose of centanafadine tablets, 10% (29/294) of subjects treated with the low dose, and 6% (18/290) of placebo. The Applicant provided frequencies in the draft label that demonstrated a higher frequency of shifts in each group. The review team analyzed the data and determined the Applicant was using all post-baseline visits, including post-treatment visits after the study drug had been discontinued. Although these numbers are different, the review team determined that the Applicant's analyses conveyed the same qualitative pattern of differences between groups and were, therefore, acceptable for inclusion in labeling.

Table 62. Subjects With Vital Sign Shifts - Studies 13 and 14

	Placebo N=290 n(%)	**Centanafadine Twice-Daily Tablets 200 mg** N=294 n(%)	**Centanafadine Twice-Daily Tablets 400 mg** N=292 n(%)
SBP Shift of 20mmHg or Greater	18 (6)	29 (10)	19 (7)
DBP Shift of 15mmHg or Greater	20 (7)	22 (7)	21 (7)
HR Shift of 20 BPM or Greater	25 (9)	25 (9)	36 (12)

Source: Reviewer-generated

In the long-term safety study in adults with ADHD (Study 15), a higher proportion of subjects treated with high dose centanafadine experienced clinically relevant shifts in SBP compared with those in the short-term trial (15% [95/653]).

In contrast, DBP shifts occurred at similar rates across all groups in Studies 13 and 14 (7%). In the long-term adult open label extension (Study 15), 13% (85/653) experienced DBP shift of 15 mmHg or greater.

Table 63 summarizes the mean change from Baseline in diastolic blood pressure (DBP) in mmHg by treatment group at each time point in Study 13. After 6 weeks of treatment, subjects receiving high dose centanafadine experienced a mean change in DBP of 1.7 mmHg, compared with 1.0 mmHg in subjects receiving centanafadine twice-daily tablet 200 mg (TDD) and 1.1 mmHg in subjects receiving placebo.

Table 63. DBP Mean Change From Baseline - Study 13 (mmHg)

	Placebo	**Centanafadine Twice-Daily Tablets 200 mg**	**Centanafadine Twice-Daily Tablets 400 mg**
DAY 7	2.0	0.81	0.41
DAY 14	1.2	0.037	0.31
DAY 21	1.5	0.94	2.0
DAY 28	0.62	0.75	0.98
DAY 35*	-0.41	-0.77	-0.89
DAY 42	1.1	1.0	1.7

*Refer to discussion of missing Day 35 vital sign data in Adequacy of Applicant's Clinical Safety Assessments.
Source: Reviewer-generated

Table 64 summarizes the mean change from Baseline in DBP in mmHg by treatment group at each time point in Study 14. After 6 weeks of treatment, subjects receiving high dose centanafadine experienced a mean change in DBP of 1.4 mmHg, compared with 1.6 mmHg in

subjects receiving centanafadine twice-daily tablet 200 mg (TDD) and -0.027 mmHg in subjects receiving placebo.

Table 64. DBP Mean Change From Baseline - Study 14 (mmHg)

	Placebo	Centanafadine Twice-Daily Tablets 200 mg	Centanafadine Twice-Daily Tablets 400 mg
DAY 7	0	0.058	-0.71
DAY 14	-0.082	0.27	0.53
DAY 21	0.14	0.58	0.54
DAY 28	-0.98	0.36	0.65
DAY 35*	2.7	-1.5	2.8
DAY 42	-0.027	1.6	1.4

*Refer to discussion of missing Day 35 vital sign data in Adequacy of Applicant's Clinical Safety Assessments.
Source: Reviewer-generated

Heart Rate Changes in Pediatric Subjects

At the Agency's request, the Applicant identified potentially clinically relevant (PCR) changes in HR from Study 16 and Study 21 as defined by either a decrease or increase in HR from Baseline by at least 10% and resulting in a measured HR below the 1st percentile or above the 99th percentile.

Among younger pediatric subjects (4 and 5 years of age in Study 21 Cohort 2 and 6 to 12 years in Cohort 1), HR decreases with centanafadine were more common than HR increases. A higher proportion (6/61; 9.8%) of subjects 4 to less than 6 years of age taking high-dose centanafadine developed decreases in HR of at least 10% leading to a measured heart rate below the first percentile for age compared to placebo (1/31; 3.2%). In 6- to 12-year-olds, 5/156 (3.2%) taking high-dose centanafadine experienced PCR decreases in HR compared with 1/152 (0.7%) of placebo subjects. In the pediatric open-label safety study (Study 17), 4/51 (7.8%) of 4- and 5-year olds experienced PCR decreases in HR.

However, some younger pediatric subjects did experience increases in HR. In Study 21, one subject in Cohort 1 treated with high dose centanafadine ER experienced an AE of tachycardia, compared with none treated with placebo.

In contrast, older pediatric subjects were more likely to experience increases in heart rate. The rates of PCR changes in HR were similar between centanafadine and placebo groups for 13- to 17-year-olds in Study 16. However, 13- to 17-year-olds exposed to 280 mg centanafadine ER experienced increases in mean HR that peaked at 4.5 bpm at Week 4 compared with no mean change in heart rate for placebo subjects at that timepoint (and decreases at other time points). In the pediatric open-label safety study (Study 17), 5/317 (1.6%) of subjects experienced PCR increases in HR.

In Study 16, two subjects in the high-dose centanafadine group experienced AEs related to increased heart rate (one subject experienced elevated heart rate and another tachycardia), compared with none in the placebo group. The increased heart rate AE was moderate in intensity and led to discontinuation of centanafadine.

Heart Rate Changes in Adults

In the short-term, placebo-controlled trials in adults with ADHD (Studies 13 and 14), mean changes in HR were only mildly elevated in the centanafadine groups compared with placebo (increases of between 1 to 3 BPM over placebo).

Table 65. Heart Rate (BPM) Mean Change From Baseline - Study 13

	Placebo	Centanafadine Twice-Daily Tablets 200 mg	Centanafadine Twice-Daily Tablets 400 mg
DAY 7	0.49	2.1	0.78
DAY 14	0.67	1.9	1.1
DAY 21	1.9	2.5	2.0
DAY 28	0.50	3.0	2.5
DAY 35	1.3	2.3	3.7
DAY 42	0.86	1.8	2.3

Source: Reviewer-generated

Table 66. Heart Rate Mean Change From Baseline - Study 14

	Placebo	Centanafadine Twice-Daily Tablets 200 mg	Centanafadine Twice-Daily Tablets 400 mg
DAY 7	0.69	1.3	1.5
DAY 14	1.2	0.66	2.1
DAY 21	1.6	2.4	2.9
DAY 28	0.64	1.2	1.8
DAY 35	1.3	1	4.3
DAY 42	1.8	0.89	3.2

Source: Reviewer-generated

However, as with SBP, although mean HR increases over placebo were relatively mild, a greater subpopulation of subjects treated with high-dose centanafadine experienced clinically significant increases in HR compared with placebo-treated subjects. In Studies 13 and 14, increases in heart rate ≥20 beat per minute (bpm) occurred in 12% (36/292) of subjects on the high dose of centanafadine tablets compared with 8.5% (25/294) of the low dose and 8.6% (25/290) of placebo. See Table 62 above for summary of vital sign shifts.

In the long-term safety study (Study 17), a greater proportion of subjects treated with high-dose centanafadine experienced clinically relevant shifts in HR: 17% (110/653).

In addition to the elevations in HR associated with centanafadine in clinical studies in ADHD, healthy volunteer studies demonstrated dose-dependent increases in HR.

In Study 405-201-00001, a double-blind, randomized, placebo- and active-controlled, three period crossover thorough QT study in healthy volunteers, the mean increase in heart rate was 8 bpm at total daily doses of centanafadine tablets of 800 mg TDD (expected to lead to exposures two times that of the approved 280-mg dose). Four subjects reported TEAEs of palpitations, tachycardia, or orthostatic heart rate increases. Four subjects had at least one occurrence of HR >100 bpm.

In Study 405-201-00154, a phase 1, open label study of dose proportionality of centanafadine ER once daily at steady state in 16 healthy volunteers, centanafadine ER capsules caused dose-dependent increases in heart rate. Vital signs were collected at 4-hours post-dose. Table 67 lists the mean change from Baseline in HR on the day of each dose increase. On Day 1, at 4 hours after the first administration of centanafadine ER at a dose of 140 mg, subjects experienced a mean increase in heart rate of 4.75 beats per minute (BPM) from baseline. On Day 6, 4 hours after the first dose of 210 mg (increased from 140 mg the previous day), subjects experienced a mean increase in heart rate of 5.6 BPM. On Day 11, 4 hours after the first dose of 280 mg (increased from 210 mg the previous day), subjects experienced a mean increase in heart rate of 8.8 BPM from baseline.

Table 67. Heart Rate Mean Change From Baseline - Study 154

VISIT	Treatment	Mean change (BPM)
DAY 1	Centanafadine ER 1 x 140 mg	4.8
DAY 6	Centanafadine ER 1 x 210 mg	5.6
DAY 11	Centanafadine ER 1 x 280 mg	8.8

Source: Reviewer-generated

Orthostatic Changes

Treatment with centanafadine was not associated with orthostatic changes in adult or pediatric subjects. Refer to DPMH Consult Memo and consult addendum for further details of the analyses in pediatric subjects.

7.2.5.5. Long-term Suppression of Growth in Pediatric Patients

Refer to the DPMH Pediatric Team Consult Memo by Dr. Tuchman for full evaluation of long-term suppression of growth in pediatric patients.

In short-term pediatric studies (Studies 16 and 21), centanafadine was associated with weight loss. In contrast, pediatric subjects receiving placebo generally gained weight (as expected based on development).

A greater proportion of subjects 4 and 5 years of age (Study 21 Cohort 2) experienced reductions in mean baseline weight z-score and BMI z-score with short-term (6-week) centanafadine treatment compared with older pediatric subjects. The mean baseline weight z-score decreased by at least 0.5 in 8.5% of centanafadine-treated subjects in this youngest age group compared to none of the placebo-treated subjects at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 25.5% of centanafadine-treated subjects compared to 4.2% placebo-treated subjects at Week 6. In the long-term open-label study (Study 17), no subjects in this age group at the latest timepoint (Week 26, the longest any subject had been exposed) had a change from baseline weight leading to a decrease in weight z-score by at least 1 and 14.3% had a decrease in BMI z-score by at least 1. Because no subjects in the 4- to less than 6-year-old age cohort had reached 52 weeks of follow-up in the trial, height z-score was not analyzed for this age group.

In subjects 6 to 12 years of age, short-term treatment with centanafadine (Study 21 Cohort 1) was associated with a mean change from baseline weight of -0.6 kg compared to +0.8 kg in placebo-treated subjects at Week 6. The mean baseline weight z-score decreased by at least 0.5 in 0.8% of centanafadine-treated subjects compared to none in placebo-treated subjects at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 7.3% of centanafadine-treated subjects compared to 3.2% of placebo-treated subjects at Week 6. In the long-term open-label study (Study 17), 2.2% of subjects in this age group had a change from baseline weight leading to a decrease in weight z-score by at least 1, 2.2% had a decrease in BMI z-score by at least 1, and 15.6% had a decrease in height z-score by at least 1 at Week 88.

In subjects 13 to 17 years of age, short-term treatment with centanafadine (in Study 16) was associated with a mean change from baseline weight of -1.2 kg compared to +0.6 kg in placebo-treated subjects at Week 6. The mean baseline weight z-score decreased by at least 0.5 in 2% of centanafadine-treated subjects compared to none in placebo at Week 6. The mean baseline BMI z-score decreased by at least 0.5 in 4.9% of centanafadine treated subjects compared to none in placebo at Week 6. In the long-term open-label study, 4.6% of subjects had a change from baseline weight leading to a decrease in weight z-score by at least 1, 4.6% had a decrease in BMI z-score by at least 1, and 1.5% had a decrease in height z-score by at least 1 at Week 88.

The etiology of weight loss and reduced growth may have been multifactorial. Reduced appetite occurred across all age groups with centanafadine. Among 4- and 5-year-olds in Study 21 Cohort 2, 4.8% (3/62) experienced reduced appetite with centanafadine compared with no subjects in the placebo group. In 6- to 12-year-olds, reduced appetite occurred in a dose-dependent manner, affecting 3% of subjects in the placebo group, 4% of subjects in the low-dose centanafadine group, and 8% of subjects in the high-dose centanafadine group (the only dose proposed for approval). A similar pattern of dose-dependent decrease in appetite was seen in the 13- to 17-year age group: 2% of placebo subjects, 6% of centanafadine 140 mg subjects, and 15% of centanafadine 280 mg subjects (the proposed dose for approval).

Of subjects 13 to 17 years of age in Study 16, 2% in the 280-mg dose group discontinued due to decreased appetite. In the long-term safety study, 1 subject in the 6- to 12-year-old age group discontinued due to weight decreased. In the 13- to 17-year-old age group, 1 subject discontinued due to decreased appetite.

In addition to reduced appetite, AEs of nausea, vomiting, and abdominal pain were relatively common and may have contributed to weight loss and suppression of long term growth (see Section 7.2.4 for frequency of AEs across pediatric age groups.

7.2.5.6. Hypersensitivity Reactions

Refer to the Division of Dermatology Consult Memo for full evaluation of hypersensitivity reactions including rash.

Rash was identified as a safety signal early in the centanafadine development program. Newly acquired, non-traumatic skin eruptions were considered adverse events of special interest (AESIs) and were monitored prospectively in the phase 3 trials through an AESI monitoring plan. The formal Rash and Skin Eruption AESI Monitoring Plan included:

- "Rash/Skin Eruption AESI Workup Instructions," instructions distributed to the study sites.
- "Centanafadine Skin AESI Worksheet for Local/tele Dermatologist" emailed or delivered to a local dermatologist / tele dermatologist if such a consult is required (as per Plan). Moderate, severe, or SAE skin-based AESIs require evaluation by either a local dermatologist or the study teledermatology service. An appointment should be made as soon as possible.

Rash was one of the most common TEAEs, associated with centanafadine in a dose-dependent pattern across all studies and age groups. In 4- and 5-year-olds, AE related to rash occurred in 4.8% (3/62) of high-dose centanafadine subjects and no subjects in the placebo group. In 6- to 12-year-olds, rash AEs occurred in 9% of high dose centanafadine subjects, 7% of low dose subjects, and no placebo subjects. In subjects 13 to 17 years of age, rash AEs occurred in 9% of subjects receiving 280 mg centanafadine, 2% of subjects receiving 140 mg of centanafadine, and 1% of placebo. In adults, rash occurred in 4% of subjects in the high-dose centanafadine group compared with 2% of subjects in the low-dose group and 2% of placebo.

Of 62 subjects 4 and 5 years of age in Study 21 Cohort 2, one discontinued centanafadine due to rash. Among subjects 6 to 12 years of age treated in Study 21 Cohort 1, 2.5% discontinued due to rash. Similarly, 2% of subjects 13 to 17 years of age in Study 16 discontinued due to rash. In the long-term safety study (Study 17), two subjects discontinued due to rash (one in the 4 to 5-year-old age group and one in the 13 to 17-year-old age group). In adults with ADHD enrolled in short-term, placebo-controlled trials (Studies 13 and 14), the most frequently reported AE associated with discontinuation (1% or more and twice rate of placebo) was rash (2%).

The risk of rash may actually be underestimated based on these studies because the protocols initially explicitly excluded subjects with "A history of dermatologic adverse reactions secondary to any drug exposure" and "anaphylaxis (or some type of systemic allergic reaction) to any substance." Although it is usual practice to exclude subjects with a history of hypersensitivity reactions to the drug being tested, it is not typical to exclude subjects with any history of adverse reactions to any drug. Between 10 and 25% of children/parents may report a drug rash, although the number of true drug allergies is actually much lower, based on immunologic testing (Prosty 2022; Segal 2007).

Although there were no SAEs of rash in the studies submitted with this NDA, three SAEs of rash occurred in other studies with centanafadine.

In the smoking cessation study, an SAE of angioedema occurred in an adult female. Angioedema was preceded by drug eruption (verbatim term: dermatitis medicamentosa) 1 day prior. The SAE was severe in intensity and the drug was discontinued.

Two other SAEs related to hypersensitivity and rash were reported during the NDA review cycle. On April 8 and April 16, 2026, DP received FAERS 7-day reports under IND 119361 describing cases of "anaphylaxis" that occurred in studies of centanafadine for ADHD.

The first case (b) (6) concerned a 28-year-old Asian male subject enrolled in an ADHD study in Japan (Study 405-102-00112: "A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-controlled, Trial to Evaluate the Efficacy and Safety of EB-1020 Once Daily Extended Release (XR) Capsules Administered Orally at Low or High Dose in Adults With Attention-deficit/Hyperactivity Disorder"). He experienced rash and fever 8 days after the first dose of centanafadine. He was treated in an emergency hospital with adrenaline for "anaphylaxis." He had leukocytosis (11,800/mm3). Leukocyte differential revealed a relative decrease in lymphocyte proportion. There were no atypical lymphocytes (5% or more), and no eosinophilia (1500/mm3 or more).

The second case concerned a 45-year-old Asian male enrolled in an ADHD study in Japan (Study 405-102-00113: "A Multicenter, Open-label, Uncontrolled, Long-term Trial to Study Evaluate the Safety and Efficacy of Long-term Administration of EB-1020 Once Daily Extended Release (XR) Capsules in Adults With Attention Deficit/ Hyperactivity Disorder." Nine days after the first dose, at around 4:00 am, the subject became aware of closed sensation of throat, face edema, swelling of the eyes and lips, and rash on the palms, soles, both hands and arms, and both thighs. He presented to an internal medicine clinic. Vital signs were not taken. He was instructed to take fexofenadine hydrochloride tablets from his own supply, which he did.

Refer to Division of Dermatology consultation memo for their analysis of these three cases. Labeling will include a warning about the risk of serious hypersensitivity reactions, including angioedema and anaphylaxis requiring emergency treatment.

7.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Refer to Section 7.2.5.1 for discussion of C-SSRS results.

7.2.7. Safety Analyses by Demographic Subgroups

No clinically meaningful differences for the safety of centanafadine by sex and race were identified in adults or pediatrics subjects with ADHD.

7.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted a protocol for a new phase 1 study 405-201-00198 (Study 198) to IND 119361 on August 5, 2025 (SDN 376). Study 198 was entitled, "A Phase 1, Single-blind, Parallel-arm Trial to Assess the Potential for Pharmacodynamic Interaction of Centanafadine when Co-administered with Stimulants in Healthy Adults."

Study 198 had two arms. In each arm, healthy participants were randomized to one of three treatment sequences for three dosing periods separated by 96-hour washout:

- Sequence 1 (n = up to 7): ABC
- Sequence 2 (n = up to 7): BCA
- Sequence 3 (n = up to 7): CAB

In Arm 1, participants were administered centanafadine 280 mg alone (A), 36 mg methylphenidate alone (B), and 280 mg centanafadine co-administered with 36 mg methylphenidate (C) in a crossover design with dosing on Days 1, 5 and 9.

In Arm 2, participants were administered centanafadine 280 mg alone (A), lisdexamfetamine 50 mg alone (B), and centanafadine 280 mg co-administered with lisdexamfetamine 50 mg (C) in a crossover design with dosing on Days 1, 5, and 9.

The study drug was administered in the morning following a minimum 10-hour fast. All doses were administered with approximately 240 mL of water. No additional water was permitted for 1 hour before and after morning dosing. A meal was provided after the 4-hour PK blood draw.

The 36-mg dose strength of methylphenidate and 50-mg dose strength of lisdexamfetamine are below the maximum approved dose strengths for those products (72 mg/day for methylphenidate and 70 mg/day for lisdexamfetamine). However, the Division recognized that the combination of these stimulants with centanafadine, another stimulant, would be expected to have additive effects. Nevertheless, the Division concluded that, given that higher doses of methylphenidate and lisdexamfetamine are approved and doses of 800 mg of the twice-daily formulation of centanafadine had been studied (e.g., in phase 1 QT study 405-201-00001), it would be acceptable to administer these drugs together in this study.

After reviewing the protocol, the Division sent the following non-hold comments to the Applicant on October 10, 2025:

> We note that there are no subject-level or study-level stopping criteria for hypertension or tachycardia. You should devise subject- and study-level stopping criteria that include both objective measures (vital signs) and subjective measures (symptoms), given that subjects will be exposed to two stimulants at once.

On December 15, 2025, the Applicant submitted a protocol amendment for Study 198. The Applicant amended the protocol to include study level stopping criteria including both objective (vital signs) and subjective (symptoms) measures for tachycardia and bradycardia, per the Agency's request. The Applicant added the following study level stopping criteria will be applied to vital sign and adverse events assessed within 24 hours of dosing:

> The trial will be stopped if any of the following is observed in one arm and within 24 hours after each dosing:
>
> - Three participants with resting heart rate in a seated position > 120 bpm or an increase of > 30 bpm from baseline and accompanied by symptoms (e.g., dizziness, chest pain, etc.) in a seated position over 2 consecutive sets of triplicate measurements taken 5 minutes apart.
> - Three participants with resting systolic blood pressure in a seated position of > 180 mmHg or resting diastolic blood pressure in a seated position of > 110 mmHg over 2 consecutive sets of triplicate measurements taken 5 minutes apart.
> - Three participants with resting systolic blood pressure > 140 mmHg or resting diastolic blood pressure> 90 mmHg in a seated position, with any of the following symptoms: chest pain, dyspnea, syncope, palpitations or other medically relevant symptoms deemed by the investigator to be related to elevated blood pressure or heart rate.

The Applicant did not add subject-level stopping criteria, stating that because a given subject will only receive simultaneous dosing of centanafadine and an approved stimulant one time during the trial, subject-level stopping criteria would not provide additional safety for subjects.

On April 30, 2026, the Applicant submitted a letter (eCTD 0397) to IND 119361 informing CDER's Office of Compliance of a reported serious non-compliance for Trial 405-201-00198 that occurred at the ICON site of Principal Investigator Dr. Ahad Sabet, in Salt Lake City, UT between February 5, 2026, and March 24, 2026. The letter alerted the Agency to protocol deviations that occurred in Arm 1 of Trial 405-201-00198 where the site failed to take repeat vital signs measurements in eight subjects, at one or more time points, who demonstrated elevations in HR. This requirement for repeat vital sign measurements was part of the stopping criteria assessment for the trial required based on the Agency's comments.

In response to these site deviations, a Corrective and Preventive Action required the trial site staff to undergo retraining on these elements prior to permitting dosing of Arm 2 to ensure compliance, consistent with the requirements of 21 CFR 312.56(b). The protocol deviations

were also submitted to the governing IRB. Arm 2 proceeded dosing following the retraining; however, further deviations were seen where repeated vital signs measurements were not taken for two subjects at one or more time points. This was again reported to the IRB who approved continuation of the trial on April 1, 2026, and cited that they considered this to be a reportable, serious noncompliance issue. All subject dosing was complete at that time and there were no safety risks to subjects.

On May 18, 2026, in response to the notification of the noncompliance, the Agency sent an information request requesting all available safety information from Trial 405-201-00198, including the datasets. On May 21, the Applicant responded, providing the requested information. Although the clinical study report is not yet available for Study 198, the clinical review team conducted multiple safety analyses in order to inform labeling for the NDA under review.

Overall, centanafadine was associated with elevations in SBP and DBP to a similar degree to methylphenidate. Centanafadine had a smaller effect on heart rate compared with methylphenidate, although a large proportion (43%) of subjects experienced an increase of 20 BPM or more after a single dose. Lisdexamfetamine caused a greater proportion of subjects to experience shifts in SBP (95%) compared with centanafadine (55%) and methylphenidate (57%). Table 68 shows the proportion of subjects who experienced significant shifts in vital signs following single doses of study drug.

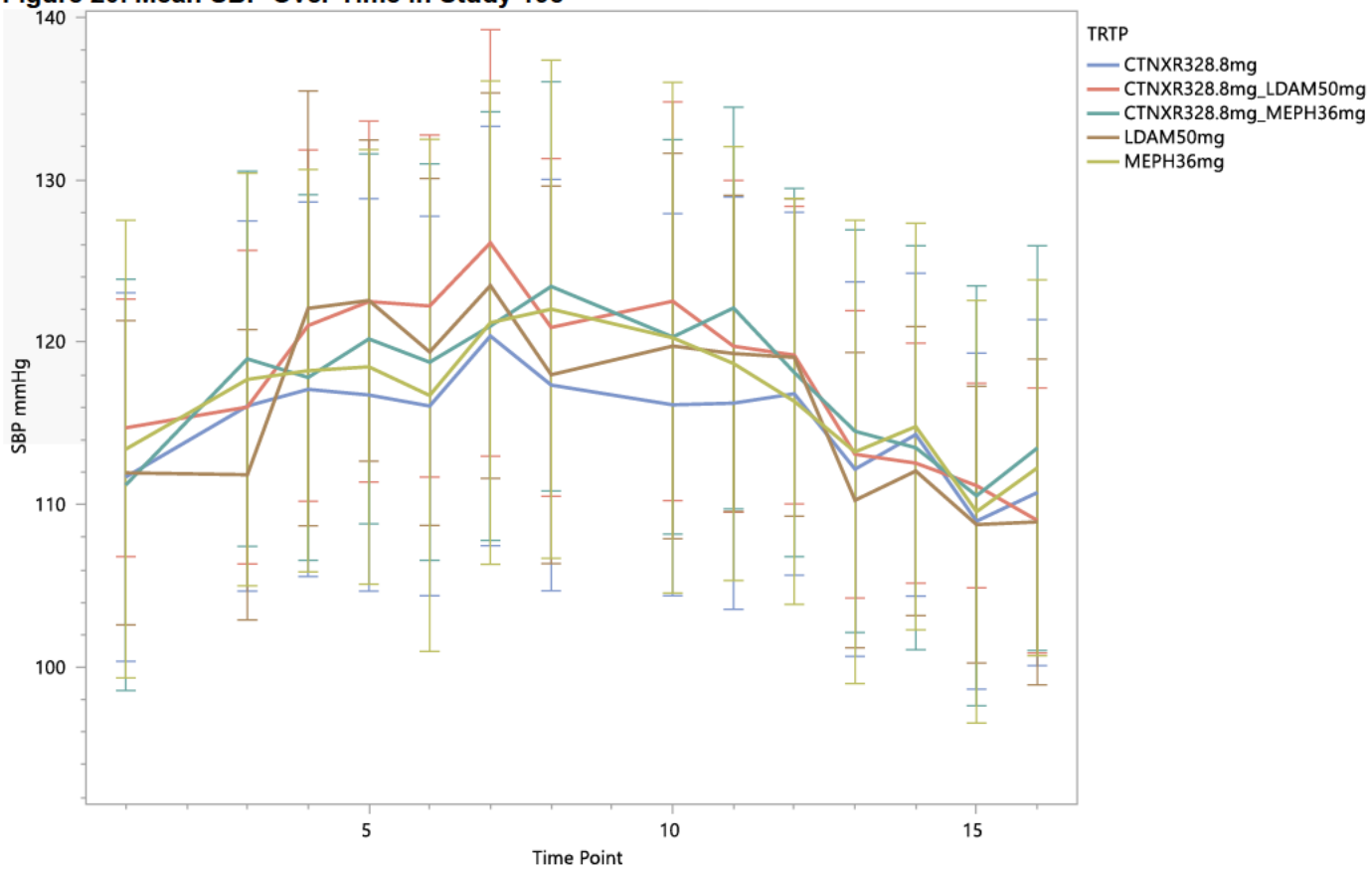
Table 68. Vital Sign Shifts in Study 198

	Centanafadine 280 mg N=40	Centanafadine 280 mg+ lisdexamfetamine 50 mg N=19	Centanafadine 280 mg+ methylphenidate 36 mg N=21	Lisdexamfetamine 50 mg N=18	Methylphenidate 36 mg N=21
SBP Change >=20 mmHg	22 (55%)	12 (63%)	20 (95%)	16 (89%)	12 (57%)
DBP Change >=20 mmHg	19 (48%)	9 (47%)	9 (43%)	9 (50%)	6 (29%)
HR Change >=20 bpm	17 (43%)	11 (58%)	15 (71%)	13 (72%)	19 (90%)

Source: Reviewer-generated

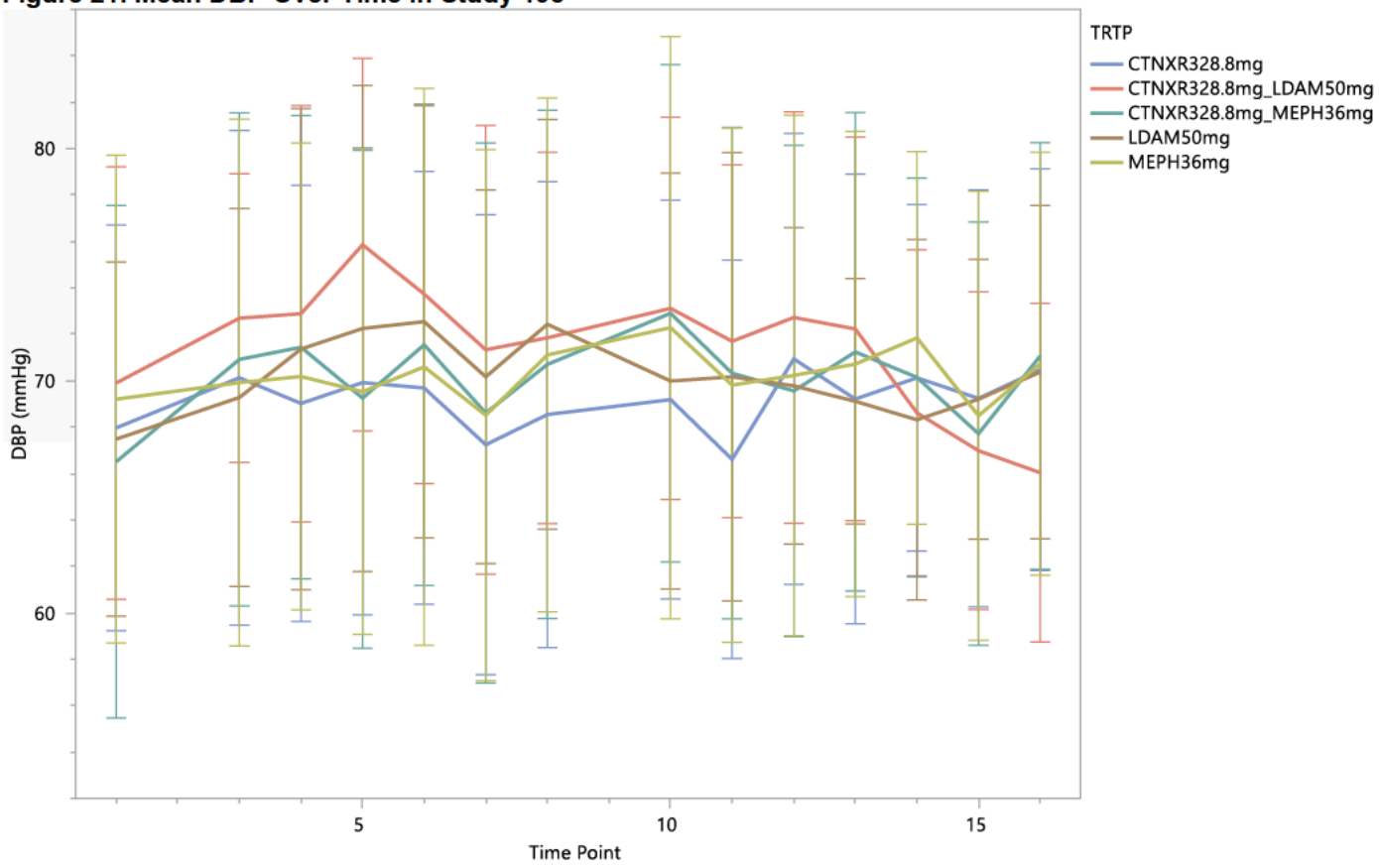
Figure 20, Figure 21, and Figure 22 show mean SBP, DBP, and heart rate over time following single doses of study drug. The effects on blood pressure and heart rate of centanafadine, methylphenidate, and lisdexamfetamine demonstrate different time courses, based on their different pharmacokinetic profiles. The greatest increases in SBP and DBP are seen following the administration of the combination of centanafadine and lisdexamfetamine. The data suggest an additive effect for these two drugs on blood pressure.

Figure 20. Mean SBP Over Time in Study 198



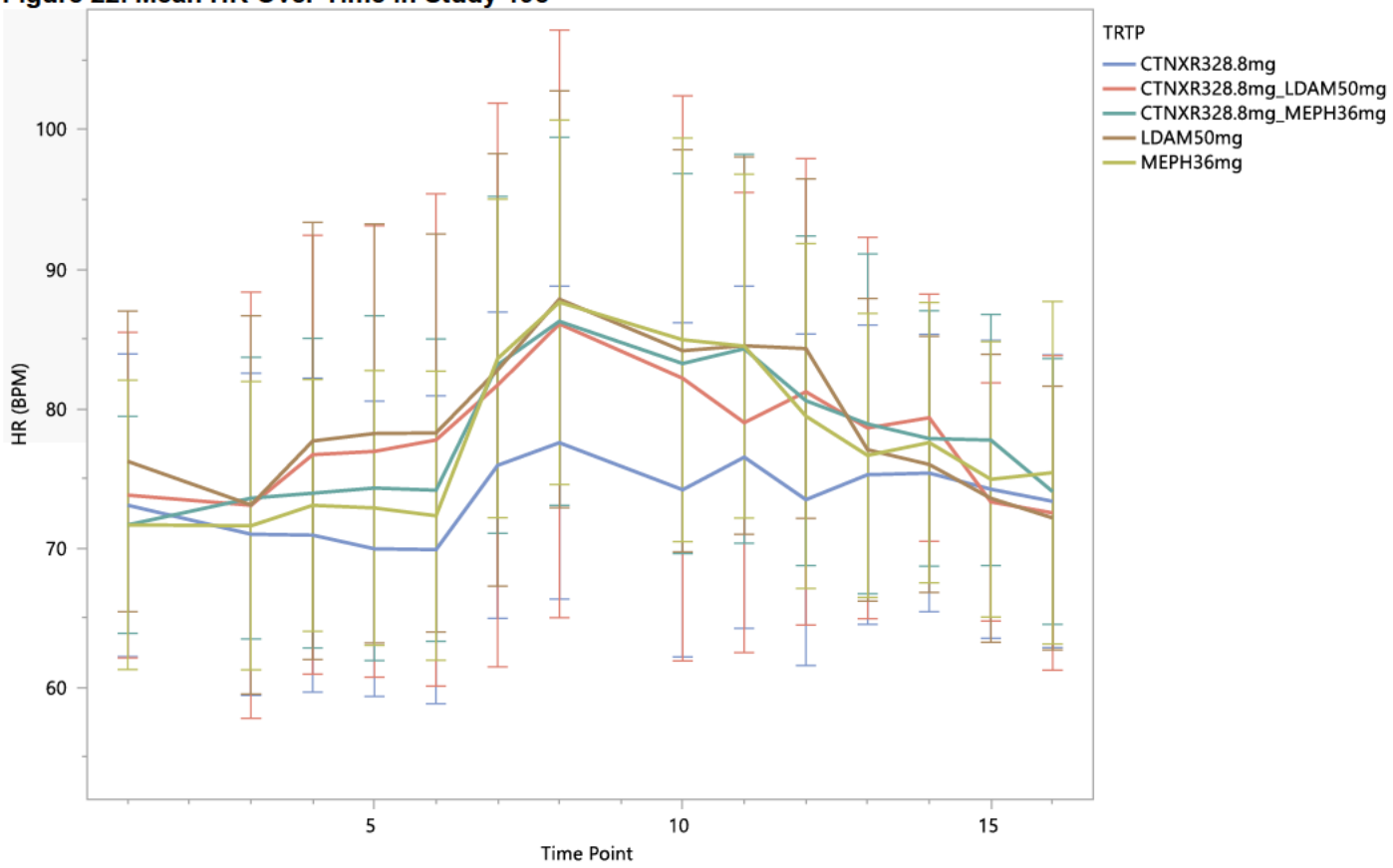
Error bars represent one standard deviation.
Source: Reviewer-generated

Figure 21. Mean DBP Over Time in Study 198



Error bars represent one standard deviation.
Source: Reviewer-generated

Figure 22. Mean HR Over Time in Study 198



Error bars represent one standard deviation.
Source: Reviewer-generated

Overall, this study demonstrates increases in blood pressure with centanafadine similar to methylphenidate. In addition, there are clinically relevant additive effects on blood pressure when centanafadine and lisdexamfetamine are coadministered.

7.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The available safety data did not raise concern about carcinogenicity associated with centanafadine ER capsules.

Human Reproduction and Pregnancy

Refer to the DPMH Maternal Health Review for full details regarding the information related to human reproduction, pregnancy, and lactation. Refer to Section 12 for details of the necessary pregnancy- and lactation-related PMRs.

Pediatrics and Assessment of Effects on Growth

Refer to Section 7.2.5.5 above and to the DPMH Pediatrics consult by Dr. Tuchman for assessment of the risk of long-term growth suppression in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Refer to CSS review by Dr. Bonson.

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Centanafadine has never been marketed in the United States or abroad.

Expectations on Safety in the Postmarket Setting

The Applicant submitted sufficient safety information to adequately characterize centanafadine's safety profile to support the initial regulatory approval decision. However, as with most clinical trials to support regulatory submissions, the centanafadine trials had eligibility criteria that would have likely excluded many patients who could be prescribed centanafadine in clinical practice. It is possible that patients with more medical comorbidities or concomitant medication use will experience adverse reactions to a greater extent than observed in the development program. In particular, the exclusion of adults over age 55 years limits the generalizability of the study results to the real world population, which includes patients over age 55 years with ADHD. Older adults are also more likely to have medical comorbidities and to be prescribed multiple medications. The risk of adverse reactions with centanafadine is likely to be higher among older patients. It is also possible that off-label use of higher doses of centanafadine may increase the risk of abuse.

PMRs will be issued to assess a signal of a serious risk of changes in exposure in patients with severe hepatic impairment; assess a signal of a serious risk of exposure of infants to centanafadine during breastfeeding; and to identify any serious risks of adverse maternal, fetal, and infant outcomes associated with centanafadine exposure during pregnancy.

An additional risk in the postmarket setting stems from fact that only the high dose (280 mg or weight-based equivalent) will be approved for pediatric patients 6 and older. Given that 140, 210, and 280 mg capsules will be available and that two dose strengths (210 and 280 mg) will be approved in adults, lower doses that have not been demonstrated to be effective may be prescribed off-label to pediatric patients. To resolve this issue, the Agency proposed a postmarketing commitment (PMC) to conduct a randomized, double-blind, placebo-controlled efficacy and safety study to evaluate a centanafadine dose strength between 140 mg and 280 mg in pediatric subjects 13 to 17 years of age with attention-deficit hyperactivity disorder (ADHD) and the weight-based equivalent dose in pediatric subjects 6 to 12 years of age with ADHD. However, the Applicant declined. See Section 12 for additional details including the Applicant's rationale.

The rate of hypersensitivity reactions may also be higher in the postmarket setting, because individuals with history of dermatologic adverse reaction to any drug were initially excluded from the centanafadine trials, making the study population significantly lower in risk for hypersensitivity reactions than the general population.

7.2.11. Integrated Assessment of Safety

Centanafadine is a new molecular entity with no prior approval in the United States or abroad. As such, the Applicant conducted numerous studies focused on evaluating potential safety concerns with this drug, as described in this review. The overall exposure meets the *ICH E1A* recommendation for the extent of population exposure to evaluate the safety of drugs intended for the long-term treatment of non-life-threatening diseases. There were no deaths reported during the drug development program.

Overall, centanafadine was well-tolerated in most adults and pediatric subjects ages 6 years and older with ADHD. However, several important safety signals have emerged during the development program. Risks include SI/B, abuse and misuse, psychiatric AEs, changes in blood pressure and heart rate, long-term suppression of growth in pediatric patients, and hypersensitivity reactions including rash.

Centanafadine was not well-tolerated in pediatric subjects 4 and 5 years of age. Subjects in this age group had a higher incidence of weight loss than subjects 6 years of age and older.

A higher proportion of subjects 4 to less than 6 years of age developed changes in mean baseline weight z-score and BMI z-score with short-term (6-week) centanafadine treatment compared to older pediatric subjects. The mean baseline weight z-score decreased by at least 0.5 in 8.5% of centanafadine-treated subjects compared to none of the placebo-treated subjects at Week 6. The mean baseline BMI z-score decreased by at least 1 in 25.5% of centanafadine-treated subjects compared to 4.2% placebo-treated subjects at Week 6. With short- and long-term centanafadine treatment, a higher proportion of subjects 4 to less than 6 years of age also experienced decreases in HR of at least 10% leading to a measured HR below the first percentile for age compared to pediatric subjects 6 years of age and older.

Centanafadine was not studied in pediatric subjects 6 years of age and older weighing less than 20 kg. Only a single pediatric subject 6 years of age or older with ADHD weighing less than 20 kg was exposed to the high dose strength of centanafadine proposed for approval. Based on the increased rates of adverse reactions seen in 4- and 5-year-olds, smaller pediatric patients may be more vulnerable to weight loss and long term growth suppression due to potentially higher exposures. Based on the available safety data, centanafadine is not recommended in pediatric patients younger than 6 years of age or weighing less than 20 kg.

In adults and pediatric subjects 6 years of age and older, the most common adverse reactions were rash, decreased appetite, nausea, headache, abdominal pain, insomnia, dry mouth, and diarrhea. Psychiatric adverse reactions as a group were relatively frequent compared to other SOCs and included anxiety, irritability, and depressed mood. Other rare, but clinically important psychiatric adverse reactions included suicidal ideation/behavior, hallucinations, agitation, and aggression in pediatric subjects.

An important area of uncertainty is the safety of centanafadine in older adults. No adults over the age of 55 years were studied in the ADHD trials. A recent MDD trial included subjects up to 65 years of age. Given that medical comorbidities and concomitant medications are more common in older adults, there may be a higher risk of adverse reactions to centanafadine in these populations. In particular, older adult patients may be more vulnerable to hypertension and tachycardia. This risk can by mitigated through labeling, including recommendations for screening and monitoring for cardiovascular effects.

The safety of centanafadine in pregnant patients and lactating women has not been established. Post-marketing studies are being required to characterize the safety of centanafadine in settings of pregnancy and lactation.

An important issue in this NDA review has been whether centanafadine is a CNS stimulant. In the Introduction to NDA 218145 (Module 2.2), the Applicant calls centanafadine a “first-in-class treatment for ADHD with inhibitory activity at norepinephrine (NE), dopamine (DA), and serotonin (5 hydroxytryptamine [5-HT]) reuptake transporters.” In Section 11 of the Applicant’s draft labeling, the Applicant calls centanafadine a “norepinephrine-dopamine-serotonin reuptake inhibitor (NDSRI),” creating a new EPC for centanafadine. In the clinical overview, the Applicant contrasts centanafadine with CNS stimulants, highlighting perceived differences in cardiovascular effects, abuse potential, and “stimulant-associated AEs such as irritability, weight loss, and dizziness.” The Applicant interprets the safety data as differentiating centanafadine from CNS stimulants.

The review team carefully examined the available safety data and made a different determination. The review team agreed that “norepinephrine-dopamine-serotonin reuptake inhibitor” is an accurate description of the primary pharmacology of centanafadine. However, the review team also concluded, based on shared pharmacology, clinical effect profile, and abuse potential, that centanafadine is also a CNS stimulant. Therefore, the team recommends EPCs for centanafadine of norepinephrine-dopamine-serotonin reuptake inhibitor *and* central nervous system stimulant. Refer to Section 15.3 for additional discussion.

An EPC is a pharmacologic class associated with an approved indication of an active moiety that FDA has determined to be scientifically valid and clinically meaningful. In the case of centanafadine for ADHD, identifying centanafadine as a CNS stimulant is clinically meaningful and important from a safety perspective, because it alerts prescribers to important risks including abuse potential, psychiatric adverse reactions, blood pressure and heart rate effects,

and effects on appetite and growth. Centanafadine demonstrates all of these effects, as detailed in Section 7.2.5. The safety data from Study 198 described in Section 7.2.8 demonstrate the variability in cardiovascular effects between drugs within the CNS stimulant class (i.e., different effects of methylphenidate versus lisdexamfetamine), based on different pharmacokinetic and pharmacodynamic profiles. Those data also show that centanafadine has similar effects on blood pressure to methylphenidate as well as potentially additive effects on blood pressure when combined with other CNS stimulants.

Patients, families, and prescribers who want to avoid CNS stimulants due to concerns about abuse, misuse, diversion, cardiovascular effects, negative effects on appetite and growth, and psychiatric adverse effects need to know that centanafadine carries all of these risks. Identifying centanafadine as a CNS stimulant will, therefore, communicate important clinical information that can be used to mitigate risk.

In summary, the safety findings in the centanafadine ADHD development program appear generally consistent with the existing FDA-approved CNS stimulants. Additional concerns here are the risks of SI/B in pediatric patients and hypersensitivity reactions in all ages. Product labeling should inform clinicians and patients about the potential for these adverse reactions, as well as the other safety signals discussed above.

7.3. Statistical Issues

Refer to Section 7.1 for detailed analysis of the statistical approach. Concerns include the limitations of interpreting findings associated with the key secondary endpoints. However, these concerns are consistent with many drug development programs and do not undermine the clinically meaningful, statistically significant effects seen on the primary endpoints in the pivotal trials. No specific statistical issues were identified that influence the overall conclusions of benefit-risk assessment for centanafadine.

7.4. Conclusions and Recommendations

Substantial evidence of effectiveness for centanafadine as a treatment for ADHD in adults and pediatric patients 6 years of age and older was generated in four adequate and well-controlled studies: Studies 13, 14, 16, and 21. The primary efficacy endpoint in the adult ADHD studies (Studies 13 and 14) was change from Baseline in AISRS total score at Day 42. Both studies demonstrated clinically and statistically significant changes from Baseline compared with placebo on the primary endpoint for both the high and low doses of the formulation of centanafadine tested. Testing of the key secondary endpoint of CGI-S demonstrated statistically significant change in severity from Baseline compared with placebo. Although the magnitude of the CGI-S change over placebo is not considered clinically significant on its own, it does represent a benefit and provides some context and support for the results on the primary endpoint. Sensitivity analyses also support the robustness of the primary efficacy results. In addition, the Applicant has provided an adequate pharmacokinetic bridge between the twice-

daily tablet formulation tested in Studies 13 and 14 and the to-be-marketed formulation of centanafadine ER capsules.

The primary efficacy endpoint in the pediatric ADHD studies (Studies 16 and 21) was change from Baseline in ADHD-RS-5 symptoms total raw score at Week 6 (Day 42). Both studies demonstrated clinically and statistically significant changes from Baseline compared with placebo on their primary endpoints for the high dose of centanafadine tested (280 mg ER capsules in Study 16 and the weight-based equivalent in Study 21 Cohort 1). The key secondary endpoints of CGI-S-ADHD and Conners 3 Parent T-scores could not be formally tested due to the failure of the lower dose of centanafadine to meet the criteria for statistical significance, aborting the testing hierarchy for multiplicity. Exploratory analyses of these endpoints demonstrated nominally statistically significant results indicating some degree improvement. However, these results are not great in magnitude (e.g., do not cross diagnostic severity thresholds). Nevertheless, these exploratory secondary endpoint analyses indicate a benefit, providing context and some support for the positive results on primary endpoint.

In Study 21 Cohort 2, statistical testing did not demonstrate significant results on any of the endpoints in 4- and 5-year-old pediatric subjects with ADHD. (b) (4)).

The Applicant submitted sufficient information to adequately assess centanafadine's safety profile. The Agency's main concerns are risks of SI/B, abuse and misuse, psychiatric adverse events, changes in blood pressure and heart rate, long term suppression of growth in pediatric patients, and hypersensitivity reactions. Some of these concerns are expected based on findings in other CNS stimulant drugs; others appear more drug-specific. Overall, these risks can be addressed and mitigated through labeling. Patients, caregivers, and prescribers will need to weigh the risks and benefits of centanafadine prior to starting treatment. Patient selection and monitoring are strategies that can be used to minimize potential adverse reactions for centanafadine in the treatment of ADHD.

Unfortunately, in pediatric patients dose adjustment will not be an option for mitigation of adverse reactions, given that only the high dose of centanafadine will be approved. With lower dose strengths (i.e., 140 and 210 mg) being available for prescription, there is concern that some pediatric patients may be prescribed lower doses that have not been demonstrated to be effective in order to prevent or mitigate adverse reactions. Therefore, the Division recommended a postmarketing commitment (PMC) to study the efficacy and safety of an intermediate dose (between the approved dose of 280 mg and the failed dose of 140 mg in pediatric subjects 13 to 17 years of age and the equivalent, weight-based dosage in pediatric subjects 6 to 12 years of age). However, the Applicant did not agree to the PMC. The Applicant asserted that there were no safety concerns that would require a lower dosage to be available to pediatric patients; that, in their assessment of the data, there was no compelling evidence that a lower dose would provide efficacy in pediatric patients and that addition of a lower dose

strength to labeling would not prevent healthcare professionals from prescribing dosing regimens that are not described in the label.

Centanafadine has not been studied in individuals with severe hepatic impairment or pregnant or lactating individuals. Postmarketing requirements will address these gaps.

Considering the prevalence of ADHD in the United States, the seriousness of the condition, and the risks and benefits of centanafadine, the review team recommends approval for the treatment of ADHD in in adults and pediatric patients 6 years of age and older weighing at least 20 kg. Additional studies are not needed prior to marketing to further characterize safety concerns. Postmarketing requirements will address gaps in severe hepatic impairment data and pregnancy and lactation data.

Refer to Section 1.3 for a more detailed overview of the benefit-risk assessment for centanafadine in the treatment of ADHD.

8. Advisory Committee Meeting and Other External Consultations

The Division did not identify questions or concerns requiring discussion by external consultants, the Psychopharmacologic Drugs Advisory Committee, or the Drug Safety and Risk Management Advisory Committee.

9. Pediatrics

The centanafadine ER development program has evaluated safety and efficacy in pediatric patients 4 to 17 years of age.

As described in Section 2.2, the Applicant submitted an amended agreed initial Pediatric Study Plan (iPSP) on April 14, 2023, that described plans to request a partial waiver for conducting studies in patients 0 to 3 years of age with ADHD because necessary studies are impossible or highly impracticable given the absence of clear diagnostic criteria in that age group. The amended agreed iPSP also described a plan to request deferral of studies in 4- and 5-year-olds until additional safety or effectiveness data had been collected and for an assessment in pediatric patients 6 years of age and older. The Division concurred with the Applicant's rationale and plans to request the partial waiver and deferral, issuing an Amended Agreed iPSP letter on July 5, 2023.

The actual content of the NDA 218145 submission was somewhat different from what the Amended Agreed iPSP described. Instead of requesting a deferral in pediatric subjects 4 and 5 years of age, the Applicant included an assessment in this age group (Study 21 Cohort 2). Although the long-term, pediatric safety extension study (Study 17) was ongoing at the time of NDA submission, at the Late Cycle Meeting on May 19, 2026, the Applicant confirmed that the trial conduct had completed and the study report submission was anticipated by the end of 2026.

During the NDA review, the Agency identified an issue with the approval of only a single, high dose strength in pediatric subjects ages 6 and older (compared with adults, in whom both a high and low dose will be approved). Given that 140 and 210 mg capsules will be manufactured and two dose strengths (210 and 280 mg) will be approved in adults, lower doses that have not been demonstrated to be effective may be prescribed off-label to pediatric patients to avoid or mitigated dose-dependent adverse reactions. Refer to Section 7.2.10 for further discussion of this risk. Details of the study to be requested are presented in Section 12, Postmarketing Requirements and Commitments.

After discussing with DPMH, PeRC, and ORP, the Division determined that PREA postmarking requirement (PMR) could not be issued because the Applicant already demonstrated efficacy in the pediatric population and identified an effective and safe dosage for pediatric patients. A safety PMR was also not possible, because, despite the safety implications described above, the desired data were primarily efficacy data. The Agency proposed a postmarketing commitment (PMC) to conduct a randomized, double-blind, placebo-controlled efficacy and safety study to evaluate a centanafadine dose strength between 140 mg and 280 mg in pediatric subjects 13 to 17 years of age with ADHD and the weight-based equivalent dose in pediatric subjects 6 to 12 years of age with ADHD. DP also determined that it might be possible to revise the current PWR to include such a study (see 2.2 for details of the current PWR and the Applicant's previous request for an amendment). However, the Applicant declined. See Section 7.4 for further

details including the Applicant's rationale for not conducting an additional efficacy study in pediatric patients.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

The table below summarizes high-level, significant changes to the proposed prescribing information made by FDA.

Section	Proposed Labeling	Approved Labeling
1. Indications and Usage	(b) (4)	SIMTRIYO is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant indicated for the treatment of ADHD in adults and pediatric patients 6 years of age and older weighing at least 20 kg. <u>Limitations of Use</u> The use of SIMTRIYO is not recommended in pediatric patients: • Younger than 6 years of age because this pediatric subpopulation had a higher incidence of weight loss than patients 6 years of age and older (8.4) • Weighing less than 20 kg because of a lack of data for this subpopulation and the risk of weight loss (8.4).
2. Dosage and Administration		Prior to initiating SIMTRIYO, assess (2.1): • Risk of abuse, misuse, and addiction (5.2) • For presence of cardiac disease (5.3) • Heart rate and blood pressure (5.4) • Risk for developing a manic episode (5.6) • Family history of tics or Tourette syndrome and clinically evaluate patients for

	(b) (4)	motor or verbal tics or Tourette syndrome (5.11)
		• Pediatric Patients Aged: (2.2)
		  ○ 6 to 12 years: Recommended oral dosage is based on weight.
		  ○ 13 to 17 years: Recommended dosage is 280 mg orally once daily.
		• Adults: Recommended starting dosage is 210 mg orally once daily. Dosage may be increased to maximum daily dosage of 280 mg once daily based on clinical response and tolerability. (2.2)
		• Administer in the morning with or without food, at approximately the same time each day. (2.3)
		• Capsules may be swallowed whole or opened and entire contents sprinkled on applesauce or yogurt, or in orange juice. (2.3)

3. Dosage Forms and Strengths		Extended-release capsules: 140 mg of centanafadine: capsules with light orange opaque cap (imprinted with “C140”) and white opaque body (imprinted with “Otsuka”) 210 mg of centanafadine: capsules with yellow opaque cap (imprinted with “C210”) and white opaque body (imprinted with "Otsuka”) 280 mg of centanafadine: capsules with powder blue opaque cap (imprinted with “C280”) and white opaque body (imprinted with “Otsuka”)
4. Contraindications		SIMTRIYO is contraindicated in patients: • With known hypersensitivity to centanafadine or any of the excipients of SIMTRIYO.

	(b) (4)	• Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with SIMTRIYO [see Adverse Reactions (6.1)]. • Taking, or within 14 days of stopping, MAOIs due to the risk of serious and possibly fatal drug interactions, including hypertensive crisis and serotonin syndrome [see Warnings and Precautions (5.10) and Drug Interactions (7)].
5. Warnings and Precautions		This section was revised according to class labeling considerations for CNS stimulants and findings from the clinical review. The following Warnings will be included: 5.1 Suicidal (b) (4) and Behaviors in Pediatric Patients 6 Years of Age and Older 5.2 Abuse, Misuse, and Addiction 5.3 Risks to Patients with Serious Cardiac Disease 5.4 Increased Blood Pressure and Heart Rate 5.5 Psychiatric Adverse Reactions 5.6 Hypersensitivity Reactions 5.7 Long-Term Suppression of Growth in Pediatric Patients 5.8 Peripheral Vasculopathy Including Raynaud's Phenomenon 5.9 Serotonin Syndrome 5.10 Motor and Verbal Tics, and Worsening of Tourette's Syndrome 5.11 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5
6. Adverse Reactions	(b) (4)	The most common adverse reactions (≥5% and greater than placebo) were presented by age group as follows: • Pediatric Patients Aged 6 to 12 Years: rash, decreased appetite.

	(b) (4)	• Pediatric Patients Aged 13 to 17 Years: decreased appetite, nausea, rash, headache, abdominal pain. • Adults: headache, decreased appetite, insomnia, nausea, dry mouth, diarrhea. For all common (≥2%) adverse reactions tables, (b) (4) was removed. Adverse reactions were grouped under a single preferred term when appropriate. Separate common adverse reactions tables were created for pediatric patients 6 to 12 years and 13 to 17 years of age. Adverse reactions were grouped under a single preferred term when appropriate. Data on (b) (4) was removed from the tables (b) (4) (b) (4) The most common adverse events leading to discontinuation (≥1%) in the pediatric and adult double-blind clinical trials were presented as rash, decreased appetite, nausea, and somnolence. References to (b) (4) were replaced with "another centanafadine formulation" to avoid confusion. Additional information about the following risks described in Section 5 Warnings and Precautions was

		provided and presented by age group: • Suicidal (b) (4) and Behavior in Pediatric Patients Aged 6 Years and Older • Blood Pressure and Heart Rate • Psychiatric Adverse Reactions • Hypersensitivity Reactions • Effects on Growth in Pediatric Patients 6 Years of Age and Older
7. Drug Interactions	(b) (4)	Drug interaction potential with all of the following were added: MAOI's Alcohol CYP1A2 substrates CNS stimulants Serotonergic drugs All information presented in a tabular format.
8. Use in Specific Populations		The language was simplified and updated according to current labeling standards. Pregnancy section was edited to base all exposure margins for centanafadine described on AUC. Pediatric use section was revised to provide a summary of the basis of approval in the approved pediatric population, and to reflect risks associated with use of SIMTRIYO in the approved and unapproved pediatric populations. Because the PK of centanafadine in patients with severe hepatic impairment (HI) was not studied, a recommendation to not use SIMTRIYO in patients with severe HI was added. Hepatic impaired patients: No dose adjustments for mild and moderate

		HI patients. Centanafadine is not recommended for patients with severe HI.
9. Drug Abuse and Dependence	(b) (4)	Based on the human abuse potential studies, the review team determined that SIMTRIYO has the potential for abuse, misuse, and dependence. Therefore, these sections were added to describe the data and risks.
10. Overdosage		Minor edits were made to this section.
11. Description		The EPC was updated to reflect that centanafadine is consistent with the CNS stimulant pharmacologic class. A combination EPC is warranted to communicate both the full pharmacologic profile and CNS stimulant effects: SIMTRIYO is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant.
12. Clinical Pharmacology		All the key ADME characteristics presented consistent with the current OCP/FDA label guidance.
13. Nonclinical Toxicology		This section was revised to base all safety margins for centanafadine on AUC exposure. (b) (4)

14. Clinical Studies	(b) (4)	The Agency requested that the Applicant reorganize the content of Section 14 to present pediatric data first (6 to 12 years of age, followed by 13 to 17 years of age) and then adult data. A statement that there are no expected differences in effectiveness of the low and high doses of the other centanafadine formulation compared to SIMTRIYO 210 mg and 280 mg once daily, respectively, for the treatment of ADHD was added to link the dosages of the other centanafadine formulation to the recommended SIMTRIYO dosages in adults. The Agency requested that the Applicant edit Figures 1 and 2 to include the number of participants for each treatment group at each visit. The Agency recommended that, for each figure, the Applicant should consider increasing the font size of the legend, footnotes, and other figure text to improve readability. The Agency also requested that the Applicant update the legends at the top of the Figure 1 and 2 to follow the order and terminology used in the preceding table, i.e., (b) (4) (b) (4) (b) (4) (b) (4) The Agency edited this section to only include the numerical results for the primary endpoint in the labeling if statistically significant. The Agency removed (b) (4) . The

		Agency removed (b) (4) , in keeping with labeling policy. The Agency removed (b) (4) from the efficacy table for pediatric patients 13 to 17 years of age (b) (4) . The Agency requested that the Applicant revise the figures to do the same. (b) (4)
16. How Supplied/ Storage and Handling	(b) (4)	Only one minor change was made to this section to reflect current labeling practices.
17. Patient Counseling		The Agency requested that the Applicant revise Section 17 based on revisions to Section 5 to reflect information a health care provider should convey to a patient (or caregiver) during a counseling discussion.
Medication Guide		The Medication Guide was updated to reflect changes in other sections of Full Prescribing Information. In particular, changes were made to reflect the revised SI/B warning. Consultative input received from the patient labeling team was incorporated.

11. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues necessitating a Risk Evaluation and Mitigation Strategy have been identified.

12. Postmarketing Requirements and Commitment

After completing the safety and efficacy review for centanafadine for the treatment of ADHD, the following postmarketing requirements (PMRs) were issued to the Applicant:

12.1. Maternal, Fetal, and Infant Outcomes of Centanafadine Exposure

The following three post-marketing studies will be required to assess risk of exposure of infants to centanafadine during breastfeeding and to identify any serious risks of adverse maternal, fetal, and infant outcomes associated with centanafadine exposure during pregnancy:

1. Perform a lactation study in lactating women who have received therapeutic doses of centanafadine to evaluate the pharmacokinetics of centanafadine and its major metabolites in breast milk, using a validated assay. Evaluate the effects of centanafadine on the breastfed infant, if available, based on study population.

   Rationale: Based on centanafadine's characteristics, including its low molecular weight, centanafadine is likely to transfer into breastmilk. Because attention-deficit hyperactivity disorder (ADHD) is a condition commonly seen in females of reproductive potential, it is likely this product will be used in lactating women. These data are critical to inform labeling, support benefit-risk assessments and guide healthcare providers and patients regarding the safe use of centanafadine during lactation.

2. Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct pregnancy registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women exposed to drug name regardless of indication during pregnancy with unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry should identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

   Rationale: Because centanafadine is systemically absorbed, it is likely that the drug will transfer to the fetus. ADHD is a condition commonly seen in females of reproductive potential, and it is likely this product will be used in females who could become pregnant.

3. Conduct a pregnancy study using claims or electronic health record data with medical chart validation that is adequately powered to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in

women exposed to centanafadine during pregnancy compared to appropriate comparator population(s).

Rationale: Because centanafadine is systemically absorbed, it is likely that the drug will transfer to the fetus. ADHD is a condition commonly seen in females of reproductive potential, and it is likely this product will be used in females of reproductive potential who could become pregnant.

12.2. Severe Hepatic Impairment

The Applicant will be required conduct the following post-marketing study to assess the risk of changes in exposure in patients with severe hepatic impairment:

4. Perform a dedicated study to assess the effect of “severe” hepatic impairment on the pharmacokinetics of centanafadine

   Rationale: Centanafadine is extensively metabolized by monoamine oxidase A and ~90% of administered dose is excreted via urine primarily as metabolites. The results from a dedicated pharmacokinetics and safety study conducted in subjects with moderate hepatic impairment (Child-Pugh Class B) suggest that the moderate hepatic impairment did not appreciably affect the PK of centanafadine. However, the impact of severe hepatic impairment (Child-Pugh Class C) on the PK of centanafadine is not known. A PK and safety study in subjects with severe hepatic impairment is required to understand whether the systemic exposures of centanafadine are increased in patients with severe hepatic impairment. This information is required to provide appropriate dosage adjustment recommendations and adequately inform product labeling to support the safe use of centanafadine in patients with severe hepatic impairment.

13. Division Director (DP) Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

14. Deputy Office Director (Designated Signatory Authority) Comments

This review reflects my edits and feedback. I agree with the findings as described by the review team and concur with the approval decision.

15. Appendices

15.1. References

1. Chan E, Fogler JM, Hammerness PG. Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents: A Systematic Review. JAMA. 2016 May 10;315(18):1997-2008. doi: 10.1001/jama.2016.5453. PMID: 27163988.

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15.2. Financial Disclosure

The Applicant submitted forms for the following covered clinical studies: Study 13, 14, 15, 16, 17, and 21. Six principle investigators were required to disclose financial interests. Three of the investigators were from Site (b) (6). They were associated with the following sites that participated in the Applicant's phase 3 trials: (b) (6). In all six forms, the box was checked for "Significant equity interest held by investigator in Sponsor of covered study." The Applicant provided details of the disclosable financial interests/arrangement as well as descriptions of the steps taken to minimize potential bias provided. The Investigators had all received (b) (6) from the Applicant.

Covered Clinical Study (Name and/or Number): 405-201-00013, 405-201-00014, 405-201-00015, 405-201-00016, 405-201-00017, 405-201-00021

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 51, 53, 131, 61, 77, 68		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: 6		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology – Review of Established Pharmacologic Class (EPC)

Executive Summary

The Applicant has proposed norepinephrine-dopamine-serotonin reuptake inhibitor as the established pharmacologic class (EPC) for centanafadine. This would create a new EPC for centanafadine. Although the proposed new EPC provides an accurate description of the primary pharmacology of centanafadine, the nonclinical, clinical, and CSS review teams evaluated whether the existing EPC of central nervous system stimulant could also be appropriate for centanafadine based on shared pharmacology, clinical effect profile, and abuse potential compared with other compounds from this class indicated for treatment of ADHD. The Agency recommends an EPC for centanafadine of norepinephrine-dopamine-serotonin reuptake inhibitor *and* central nervous system stimulant. The Agency's review has determined that this combination EPC is warranted for centanafadine as it will provide the most clinically meaningful information for prescribers.

Background

Products currently marketed with an indication for treatment of ADHD generally fall into one of two categories, central nervous system (CNS) stimulants or non-stimulants. CNS stimulants act to increase norepinephrine and dopamine signaling in the CNS. Examples of CNS stimulants include norepinephrine and dopamine releasing agents (e.g., dextroamphetamine) and norepinephrine and dopamine reuptake inhibitors (e.g., methylphenidate). Non-stimulant drugs indicated for treatment of ADHD include selective norepinephrine reuptake inhibitors (e.g., atomoxetine) and central alpha-2 adrenergic agonists (e.g., guanfacine).

Because of the overlapping effects on norepinephrine signaling, CNS stimulants and the non-stimulants indicated for ADHD share a variety of clinical effects. However, there are major distinctions between these two categories. Clinically, the two most important differences are the greater reduction in growth (as ADHD is a common pediatric indication) and the potential for misuse and abuse that are each associated with CNS stimulants. Whether centanafadine is or is not labeled as a CNS stimulant is likely to impact expectations regarding these safety concerns for both prescribers and patients.

The pharmacology, clinical effect profile, and potential for misuse and abuse are summarized below.

Pharmacology

- Centanafadine binds to monoamine transporters with relative affinity for norepinephrine (NE) > dopamine (DA) > serotonin (5-HT) and inhibits reuptake into presynaptic terminals with the same relative order of potency, NE > DA > 5-HT.

- Due to the relative potency, lower doses of centanafadine primarily inhibit NE reuptake while higher doses increasingly inhibit DA and 5-HT reuptake.

- Clinical signs consistent with CNS stimulation (including increased activity, hyperactivity, body weight loss, and/or lower food consumptions) were observed dose-dependently in rats and dogs in toxicology studies. In both species, reduced body weight and food consumption were dose-limiting for repeat-dose studies of durations ≥28-days. In a 26-week repeat-dose toxicology study in dogs, irregular thickened footpads characterized by hyperkeratosis, secondary to increased activity, were observed at ≥5 mg/kg/day in females and ≥10 mg/kg/day in males.

- At the plasma concentrations associated with treatment at the recommended clinical doses, the reuptake inhibition effects on NE, DA, and 5-HT are all expected to be clinically meaningful.

- Compared to methylphenidate (a CNS stimulant indicated for ADHD), at clinically relevant plasma concentrations centanafadine is expected to have similar occupancy of the NE transporter, lower occupancy of the DA transporter, and greater occupancy of the serotonin transporter.

- Pharmacologically, centanafadine is similar to cocaine which acts as a norepinephrine-dopamine-serotonin reuptake inhibitor and is considered as a canonical psychostimulant by pharmacologists.

- See primary pharmacology review in Section 4 of the Unireview for additional information.

Clinical Effect Profile

The clinical effects of CNS stimulants are generally related to increased sympathetic nervous system activity. CNS stimulants are associated with increases in blood pressure and heart rate, increased wakefulness, appetite suppression, weight loss, and abuse potential. CNS stimulants are also associated with a spectrum of psychiatric adverse reactions ranging from anxiety and irritability to agitation, delirium, and psychotomimetic symptoms (e.g., hallucinations, delusions).

Centanafadine's clinical profile is similar to other CNS stimulants:

- Centanafadine is associated with dose-dependent increases in blood pressure. Centanafadine is also associated with dose-dependent increases in heart rate in pediatric patients 13 years and older and in adults. Refer to Section 7.2.5 for further details regarding changes in blood pressure and heart rate.

- Centanafadine is associated with increased wakefulness. Among subjects 4 and 5 years of age, 5% experienced insomnia with high-dose centanafadine compared to none with placebo. In 6- to 12-year-olds, two subjects exposed to high-dose centanafadine (1.3%) and two subjects exposed to low-dose centanafadine (1.4%) experienced insomnia compared with none exposed to placebo. In pediatric subjects 13 to 17 years of age, insomnia occurred at a higher frequency with high-dose centanafadine than with placebo (3% versus 1%). Insomnia occurred in a dose-dependent manner in adults, affecting 7% of high-dose centanafadine subjects, 5% of low-dose centanafadine subjects, and 4% of placebo subjects. Although somnolence also occurred, this is not unexpected, given that subjects may experience increased somnolence later in the day when centanafadine drug levels fall. In addition, persistent insomnia can be associated with daytime sleepiness. Insomnia and somnolence are not mutually exclusive as AEs, in the sense that a single subject could experience both in the course of a day. The presence of somnolence-related AEs with centanafadine does not negate the increase in wakefulness demonstrated by these insomnia AEs.

- Centanafadine is associated with appetite suppression and weight loss. In pediatric subjects 4 and 5 years of age, 7% exposed to high-dose centanafadine ER experienced decreased appetite, compared with no subjects exposed to placebo. In a 6-week study (Study 21 Cohort 2), mean baseline weight z-score decreased by at least 0.5 in 8.5% of centanafadine-treated subjects compared to none of placebo at Week 6. Mean baseline BMI z-score decreased by at least 1 in more than a quarter (25.5%) of centanafadine-treated subjects compared to 4.2% of placebo at Week 6. Decreased appetite was also common in older pediatric subjects, occurring in 8% of high dose centanafadine-treated 6- to 12-year olds and 15% of 13- to 17-year-olds versus 3% and 2% of placebo in those age groups, respectively. Decreased appetite occurred in a dose-dependent manner in adults, affecting 7% of high-dose centanafadine subjects, 5% of low dose centanafadine subjects, and 2% of placebo subjects. Refer to Section 7.2.5.5 Long-term Suppression of Growth in Pediatric Patients for further details.

- Centanafadine was determined to have abuse potential. See discussion of human abuse potential (HAP) studies below. In total, 7 healthy subjects exposed to centanafadine in clinical pharmacology trials experienced AEs with PT “euphoric mood” and there were 5 AEs of hallucination associated with centanafadine in this development program. Other AEs associated with centanafadine more than placebo that may relate to abuse potential include mood swings, mood altered, agitation, aggression, and affect lability. In the long-term open-label adult study (Study 15), AEs of feeling jittery, feeling abnormal, mood altered, mood swings, and mania occurred, which may also relate to abuse potential. Importantly, in that same study, three subjects had medication handling irregularities that involved suspected or known abuse or diversion of study drug (n = 3). Suspected or known abuse or diversion of centanafadine was reported at Week 8 in one subject with prior high-dose centanafadine exposure (reported as second occurrence of lost or stolen IMP with strong evidence in support of diversion) and at early termination in two de novo subjects

(one subject took all 30 tablets in 9 days and one subject dropped 10 tablets down the drain after knowing he would be early terminated due to positive urine drug screen).

- Centanafadine is associated with psychiatric adverse reactions. Refer to Section 7.2.5.3, Psychiatric Adverse Events, for details. Across all pediatric age groups in the short-term, placebo-controlled studies 16 and 21, Psychiatric Disorder AEs occurred in a dose-dependent manner, in 9.4% of the high dose centanafadine group, 7.0% of the low dose centanafadine group, and 6.0% of the placebo group. In the long term study (Study 17), 13.1% of subjects reported at least one AE in the Psychiatric Disorders SOC. Refer to Table 59 for all psychiatric AEs across pediatric age groups. In the placebo-controlled short-term adult ADHD studies (13 and 14), AEs in the SOC of Psychiatric Disorders were associated with centanafadine in a dose-dependent manner. Of subjects treated with the high dose of centanafadine twice-daily tablets, 15.8% experienced AEs in the SOC Psychiatric Disorders, compared with 13.6% in the low dose centanafadine group at 8.3% in the placebo group. The most frequent psychiatric AEs in adults were related to insomnia, irritability, parasomnias, depressed mood, and anxiety.

- In Study 198, which assessed the potential for pharmacodynamic interaction of centanafadine and co-administered stimulants, centanafadine was associated with effects on systolic and diastolic blood pressure similar to methylphenidate. When centanafadine was coadministered with another CNS stimulant (lisdexamfetamine) in that study, there were clear, additive cardiovascular effects. Refer to Section 7.2.8 for additional details about these study results.

In summary, the safety findings in the centanafadine ADHD development program appear generally consistent with the existing FDA-approved CNS stimulants. Patients, families, and prescribers who want to avoid CNS stimulants due to concerns about abuse, misuse, diversion, cardiovascular effects, negative effects on appetite and growth, and psychiatric adverse effects need to know that centanafadine carries all of these risks. Identifying centanafadine as a CNS stimulant will therefore communicate important clinical information that can be used to mitigate risk.

Abuse Potential

CSS reviewed the nonclinical and clinical abuse-related data submitted in NDA 218145 for centanafadine and concluded that the drug has abuse potential and should be recommended for placement in Schedule III of the CSA, if the NDA for centanafadine is approved as a drug product. This conclusion is based on the data described below:

- In mechanism of action studies, centanafadine was shown to be a monoamine reuptake inhibitor at norepinephrine, serotonin, and dopamine transporters (inhibition constant [Ki] = 2 to 8 nM, 9 to 110 nM, and 44 to 58 nM, respectively), which produced increased extracellular concentrations of these neurotransmitters in rat brain. This mechanism of action is similar to that of cocaine. In a human brain imaging study, centanafadine produced

occupancy at the transporters for norepinephrine (82%), dopamine (47%), and serotonin (44%).

- In a self-administration study in rats trained with cocaine, centanafadine produces rewarding properties that sustain reinforcement, as evidenced by self-administration of the drug. Rats in this study similarly self-administered cocaine and methylphenidate, scheduled stimulants with known abuse potential. These data show that centanafadine has rewarding properties that are sufficient to produce positive reinforcement.

- In a drug discrimination study in rats trained to discriminate amphetamine from placebo, centanafadine produced full generalization to the amphetamine stimulus cue. This demonstrates that centanafadine produces interoceptive cues (drug responses) that are similar to amphetamine. Full generalization to the amphetamine cue was also produced by methylphenidate and phentermine. These data show that centanafadine produces stimulant effects.

- Two HAP studies were conducted with centanafadine. The first HAP study showed that centanafadine at supratherapeutic doses (2X and 4X; 400 and 800 mg) produced increases on positive subjective measures that were statistically greater than placebo. However, the data do not demonstrate that centanafadine produced statistically significantly less positive subjective responses compared to the positive control drugs, amphetamine (40 mg) and lisdexamfetamine (150 mg). In the second HAP study, supratherapeutic doses of centanafadine (2X and 4X) produced Drug Liking that was statistically greater than placebo but statistically lower than that from either dose of the positive control drug, amphetamine (15 and 30 mg). Subjects also indicated overall drug disliking to the supratherapeutic doses of centanafadine and no interest in taking the drug again. This is in contrast to the responses to both doses of amphetamine, which produced a high degree of overall drug liking and a high interest in taking the drug again. In both studies, supratherapeutic doses of centanafadine produced negative subjective responses and adverse events. Although it is clear from these two HAP studies that centanafadine has abuse potential, the ability of the drug to produce negative responses is likely to limit its abuse potential relative to the positive control drugs, amphetamine and lisdexamfetamine.

- Centanafadine produced an adverse event (AE) profile in phase 1 and phase 3 studies that is representative of a stimulant. The AEs observed with an incidence $\geq$2% and in at least 2 subjects in phase 1 studies include mood altered, insomnia, tachycardia, chest discomfort, and decreased appetite. In phase 3 studies, the AEs observed with an incidence $\geq$2% and at least 2 subjects include anxiety, insomnia, irritability, and decreased appetite.

- The ability of centanafadine to produce physical dependence in rats was evaluated in two studies. However, neither study is valid to evaluate physical dependence because the doses used did not produce plasma levels that are equivalent to those produced in humans during clinical studies. In contrast, physical dependence in humans was evaluated at the conclusion

of centanafadine administration at the therapeutic doses and a 2X dose (200 and 400 mg/day) for 42 days in two phase 3 studies in adults with ADHD. During the 10-day drug discontinuation period, patients did not endorse symptoms of withdrawal on a questionnaire developed to assess amphetamine withdrawal. These data demonstrate that centanafadine does not produce a withdrawal syndrome indicative of physical dependence following chronic drug administration and abrupt drug discontinuation.

Conclusion

As detailed above, the pharmacology of centanafadine is similar to existing products labeled as CNS stimulants that are indicated for treatment of ADHD with the additional presence of serotonin reuptake inhibition. The profile of clinical effects and potential for misuse and abuse are consistent with CNS stimulants. Thus, centanafadine fits into the EPC of CNS stimulant and should be labeled as such in order to accurately inform prescribers of the expected clinical effects and abuse potential. Because the 5-HT reuptake inhibition by centanafadine is not described for other CNS stimulants, but may contribute to both the efficacy and safety profiles of centanafadine, a combination EPC is warranted to also communicate this primary pharmacological effect. Therefore, the Agency recommends an EPC for centanafadine of norepinephrine-dopamine-serotonin reuptake inhibitor central nervous system stimulant. A combination EPC similar to the Agency's recommended EPC for centanafadine (albeit for a different indication and not as a CNS stimulant) previously existed for products containing sibutramine (now withdrawn). Sibutramine was labeled as a norepinephrine, serotonin, and dopamine reuptake inhibitor anorectic indicated for assistance with weight loss in obesity.

15.4. Clinical Pharmacology

15.4.1. In Vitro Data

Protein Binding

Study Method: Ultrafiltration method using rat, dog, and human plasma at concentrations of 1 and 10 µM. For the metabolite EB-10601, ultrafiltration was performed in human plasma only.
Moieties Tested:
- Centanafadine & EB-10601 (major metabolite)

Results:
- Centanafadine showed extensive binding (>98%) to plasma proteins across all species tested: Human plasma: 99.5 to 99.9% bound, Dog plasma: 98.1 to 99.9% bound, Rat plasma: 99.3 to 100% bound
- EB-10601 showed high binding in human plasma: >97.9% at 1 µM and 98.8% at 10 µM

In Vitro Metabolism

Study Method: Multiple approaches were used for evaluating the in vitro metabolism including:
- CYP reaction phenotyping using recombinant human CYP Supersomes (1A2, 2B6, 2C8, 2C9,

2C19, 2D6, and 3A4), hepatocyte incubations (mouse, rat, dog, monkey, and human), human liver microsomes (HLM) and mitochondria studies, monoamine oxidases (MAO-A and MAO-B) studies

Moieties Tested:
- Centanafadine (parent compound) & EB-10601 (primary metabolite)
Enzymes Tested: CYP enzymes: 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, MAO-A, and MAO-B, Non-CYP enzymes in hepatocytes
Results:
- Centanafadine was metabolized primarily by MAO-A and minor via CYP2D6 and CYP1A2
- EB-10601 formation was NADPH-independent and mediated by MAO-A (not MAO-B). The formation of EB-10601 in the HLM and human liver mitochondria incubations was inhibited by the MAO-A inhibitor, clorgyline. Additionally, the formation rates of EB-10601 decreased with increasing clorgyline concentrations.
- MAO-A parameters for centanafadine: Km = 2.65 ± 0.124 µM, CLint = 5546 µL/min/mg
- Km and Vmax values: CYP1A2 (Km = 0.200 ± 0.0151 µM, CLint = 321 µL/min/mg), CYP2D6 (Km - 0.283 ± 0.0400 µM, CLint = 6824 µL/min/mg)
- In hepatocytes, approximately 80% of centanafadine remained unchanged after 4 hours in human hepatocytes
Clinical Implications: Centanafadine is primarily metabolized by monoamine oxidase A (MAO-A) mediated oxidation, leading to the formation of a lactam metabolite, EB-10601. CYP enzymes play very minor role in the metabolism of centanafadine.

CYP Inhibition

Study Method: Direct inhibition studies using human liver microsomes with probe substrates; Time-dependent inhibition (TDI) studies with pre-incubation ± NADPH; Recombinant CYP Supersomes using fluorogenic substrates

Moieties Tested:
- Centanafadine & EB-10601
Enzymes Tested: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4

Results:
Centanafadine concentration that achieves 50% of maximal inhibition (IC_{50}) values:
- CYP1A2: 0.28 µM (most potent inhibition)
- CYP2B6: 1.60 µM
- CYP3A4: 4.56 µM
- CYP2D6: 12.4 µM
- CYP2C19: 99.3 µM
- CYP2C8, 2C9: >100 µM

EB-10601 IC_{50} values:
- CYP1A2: 5.45 µM

- CYP2C19: 54.0 µM
- Other CYPs: >100 µM

Clinical Implications: Based on R-values calculated using clinical C_{max} concentrations, centanafadine exceeded FDA thresholds for CYP1A2 (R value for CYP1A2 inhibition was 1.52; FDA threshold is 1.02), warranting clinical drug-drug interaction (DDI) evaluation for CYP1A2 inhibition. Clinical studies confirmed centanafadine is a moderate CYP1A2 inhibitor (2-fold increase in caffeine's AUC_{inf}).

CYP Induction

Study Method: In vitro CYP mRNA induction assay using cryopreserved human hepatocytes from 3 donors incubated with centanafadine (0.10-32 µM) for 72 hours. Quantitative polymerase chain reaction (PCR) analysis was performed for CYP1A2, 2B6, and 3A4 mRNA expression.

Moieties Tested: Centanafadine only
Enzymes Tested: CYP1A2, 2B6, and 3A4

Results:
- At 32 µM, centanafadine showed 2.4 to 3.6-fold increase in CYP1A2 mRNA compared to control in all 3 donors. However, less than 2-fold decrease in CYP3A4 and CYP2B6 mRNA was seen across all 3 donors compared to control.

Clinical Implications: Despite centanafadine at high concentration (32 µM) showing 2.4- to 3.6-fold increase in CYP1A2 mRNA in vitro, the clinical study with a CYP1A2 substrate (caffeine) demonstrated that centanafadine increased rather than decreased the exposures of CYP1A2 substrate, caffeine at clinically relevant concentration (~4 µM). This increase in caffeine exposure is likely due to the concurrent inhibition of CYP1A2 by centanafadine.

Transporter Interaction

Study Method: Multiple cell-based assays using transfected cell lines: MDCKII cells expressing P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) for substrate assessment, Various cell lines (MDCK-MDR1, LLC-PK1, Caco-2, and HEK293) for inhibition studies.

Moieties Tested:
- Centanafadine & EB-10601

Transporters Tested:
Efflux transporters: P-gp, BCRP and bile salt export pump (BSEP)
Uptake transporters: Organic anion transporting polypeptide (OATP1B1 and OATP1B3), organic anion transporter (OAT1 and OAT3), organic cation transporter (OCT1 and OCT2) and multidrug and toxin extrusion protein (MATE1 and MATE2-K).

Results:
Centanafadine:
- Not a substrate of P-gp or BCRP (efflux ratios <1.5)
- Not a substrate of OATP1B1 or OATP1B3
- Mild inhibition IC_{50} values: OCT2 (5.36 µM), OCT1 (5.81 µM), MATE1 (25.0 µM), MATE2-K (65.7 µM), BSEP (92.75 µM)
- P-gp inhibition: IC_{50} >30-100 µM depending on assay
- BCRP inhibition: IC_{50} >30-100 µM
EB-10601:
- Mild inhibition IC_{50} values: OAT3 (11.0 µM), OATP1B1 (45.2 µM), MATE1 (58.8 µM), BCRP (66.1 µM)
- P-gp, OATP1B3, OAT1, OCT2, MATE2-K: IC_{50} >100 µM

Clinical Implications: Based on predicted unbound clinical concentrations (0.02 µM), the C_{max},u/IC_{50} ratios were well below thresholds of clinical concern (typically <0.1) for all transporters tested. Therefore, centanafadine is unlikely to cause clinically meaningful transporter-mediated drug interactions. The lack of P-gp and BCRP substrate activity suggests minimal risk for drug interactions involving these major efflux transporters.

15.4.2. Individual Clinical Studies

Food Effect, Dose Strength Equivalency & PK-Bridging Study (Study 405-201-00157)

Title

A multiple-arm, phase 1, open-label trial to determine dose strength equivalence and effect of food on the to-be-marketed once-daily, centanafadine extended-release (ER) capsules, bioequivalence between the clinical trial formulation and to-be-marketed ER capsules and relative bioavailability (BA) of the to-be-marketed ER capsules to twice-daily tablets in healthy adults

Objectives

- Arm 1: To evaluate the dose strength equivalence of 2 × 164.4 mg to-be-marketed centanafadine ER capsules to a 1 × 328.8 mg to-be-marketed centanafadine ER capsule in healthy adults.
- Arm 2: To evaluate the relative BA of 328.8 mg to-be-marketed centanafadine ER capsule administered following a high-fat meal (HFM) relative to the fasted state in healthy adults.
- Arm 3: To evaluate the relative BA of centanafadine twice-daily SR [twice-daily] tablets (clinical trial formulation) to the to-be-marketed centanafadine ER capsules in healthy adults.
- Arm 4: To evaluate the bioequivalence (BE) of centanafadine ER capsules (clinical trial formulation) to the to-be-marketed centanafadine ER capsules in healthy adults.

Design

Arm 1 evaluated the dose strength equivalence of the to-be-marketed 2 × 164.4 mg centanafadine ER capsules compared with the to-be-marketed 1 × 328.8 mg centanafadine ER capsule in a 2-period randomized crossover design. The 164.4 and 328.8 mg dose strengths represent the lowest and highest dose strengths of centanafadine ER capsule (to be marketed formulations as single capsules). Fifty-six healthy adults were enrolled and randomized into 2 treatment sequences on Day 1; 28 participants were administered 2 × 164.4 mg centanafadine ER capsules while the other 28 participants were administered 1 × 328.8 mg centanafadine ER capsule on Day 1. Both the 2 × 164.4 mg and 1 × 328.8 mg doses of centanafadine ER capsule were administered in the fasted state and blood samples for pharmacokinetic (PK) analysis were collected for 48 hours postdose. On Day 4, participants were crossed over to the other treatment and blood samples were collected for 48 hours postdose.

Arm 2 evaluated the relative BA of the to-be-marketed centanafadine ER capsule administered following a HFM relative to fasted conditions in a two-period randomized crossover design. Fourteen healthy adults were enrolled and randomized into two treatment sequences on Day 1; 7 participants were administered 1 × 328.8 mg centanafadine ER capsule under fasted conditions, while the other 7 participants were administered 1 × 328.8 mg centanafadine ER capsule following a HFM and blood samples for PK analysis were collected for 48 hours postdose. On Day 4, participants were crossed over to the other treatment and blood samples were collected for 48 hours postdose.

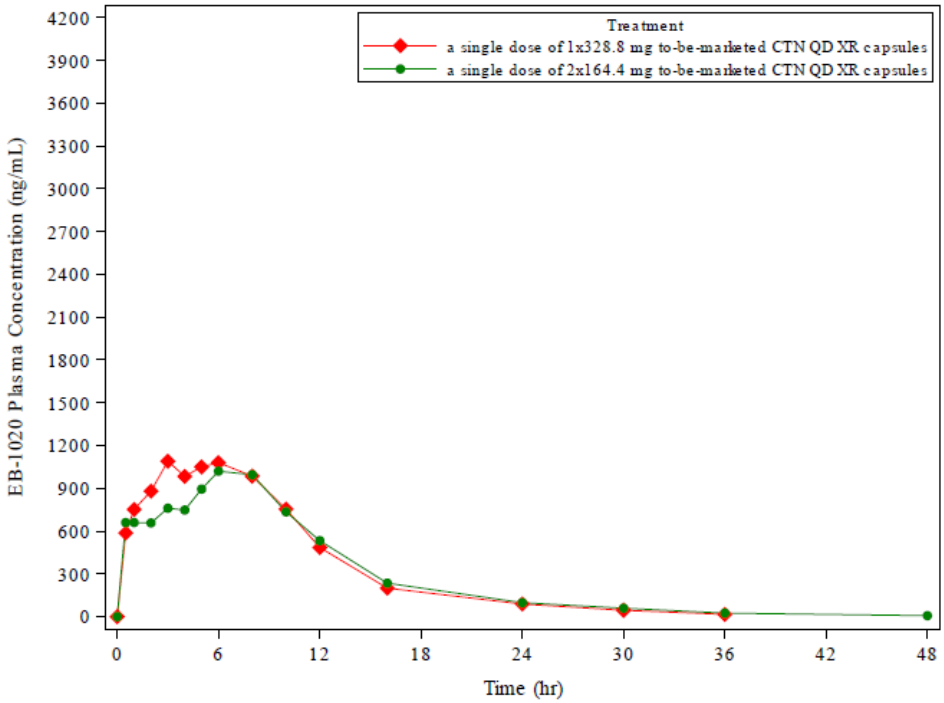
Arm 3 evaluated the relative BA of the to-be-marketed centanafadine ER capsule to the centanafadine twice-daily tablet in a 4-sequence, 4-period design. Twenty-four healthy adults were enrolled and randomized into 1 of 4 sequences (6 participants per sequence). In each sequence, participants were administered 200 mg total daily dose (TDD) centanafadine twice-daily tablet (1 × 100 mg tablet twice daily, 5 hours apart [q5h], 1 × 164.4 mg centanafadine ER capsule (to-be-marketed capsule), 400 mg TDD centanafadine twice-daily tablet (2 × 100 mg tablets twice daily, q5h), and 1 × 328.8 mg centanafadine ER capsule (to-be-marketed capsule) on Days 1, 4, 7, and 10. All investigational medicinal products (IMPs) were administered after a 10-hour overnight fast (except for the second dose of twice-daily tablets). Serial PK samples were collected for the determination of centanafadine and metabolite concentrations in plasma over the 48-hour period following administration.

Arm 4 used a similar 4-sequence, 4-period cross-over trial design as Arm 3 but evaluated the BE of the to-be-marketed centanafadine ER capsule to the clinical centanafadine ER capsule. Fifty-six healthy adults were enrolled and randomized into 1 of 4 sequences (14 participants per sequence). In each sequence, participants were administered 1 × 164.4 mg ER capsule (clinical trial formulation), 1 × 164.4 mg ER capsule (to-be-marketed capsule), 2 × 164.4 mg once-daily ER capsule (QD XR; clinical trial capsules), or 1 × 328.8 mg QD XR (to-be-marketed capsule) on Days 1, 4, 7, and 10. All IMP was administered after a 10-hour overnight fast. Serial PK samples were collected for the determination of centanafadine and metabolite concentrations in plasma over the 48-hour period following administration.

Results

For Arm 1 (Dose-Strength Proportionality), Centanafadine geometric mean ratios (GMRs) of C_{max}, AUC_t, and AUC_∞ were between 1.005 to 1.076 with 90% CIs within the 0.80 to 1.25 BE range for the comparison of to-be-marketed 1 × 328.8 mg to 2 × 164.4 mg QD XR capsules. Therefore, the overall PK parameters and PK profile were established to be similar for the 328.8 mg vs. 2 capsules of 164.4 mg XR capsule.

Figure 23. Arm-1: Centanafadine Plasma Concentrations Following Administration of Single Doses of the To-Be-Marketed 1 × 328.8 mg and 2 × 164.4 mg Centanafadine Once-Daily ER Capsules in Healthy Adults



CTN = centanafadine; QD XR: represents a once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 64

Table 69. Geometric Mean Ratios and 90% CIs for the To-Be-Marketed 1 × 328.8 mg Centanafadine Once-Daily ER Capsules Compared to 2 × 164.4 mg ER Capsules in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1 × 328.8 mg QD XR capsule (test) vs 2 × 164.4 mg OK6339-15 (reference)	C_{max}	55	1.076	1.0108, 1.1452
	AUC_t	55	1.008	0.9833, 1.0331
	AUC_∞	49	1.005	0.9787, 1.0318

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval.

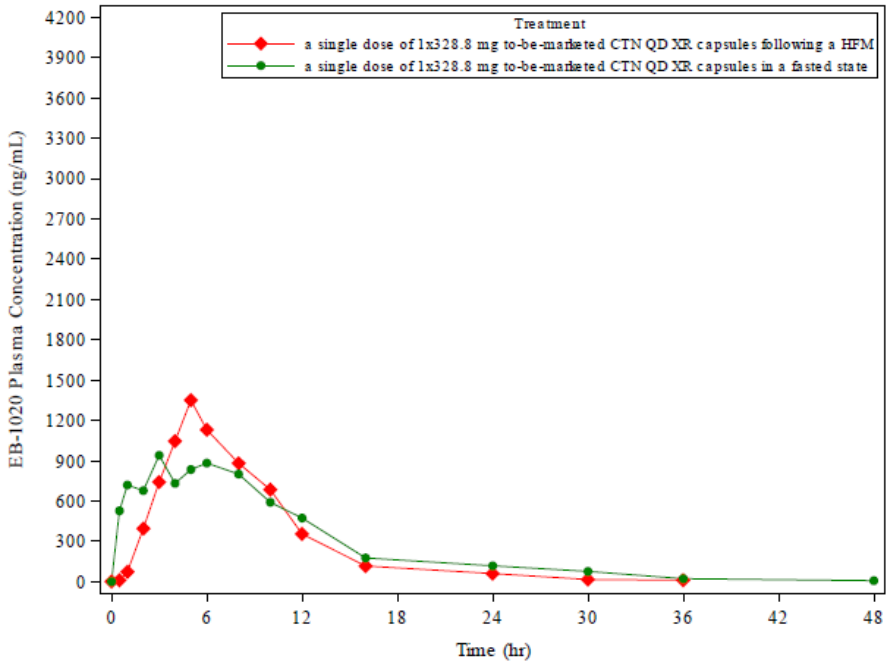
QD XR = once-daily extended release (ER) capsule formulation

Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.

Source: Clinical Study Report 405-201-00157, Page 74

For Arm 2 (Food -Effect), centanafadine AUC_{inf} remained unchanged but the C_{max} increased ~29% with a corresponding delay of ~1.5 hrs in T_{max} in the presence of high-fat meal compared to the fasted state.

Figure 24. Arm-2: Median Centanafadine Plasma Concentration-Time Profiles (Single Dose of 1 × 328.8 mg Centanafadine Once-Daily ER Capsule) Following Administration of a High-Fat Meal or in the Fasted State in Healthy Adults



CTN = centanafadine; QD XR = once-daily extended release (ER) capsule formulation

Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.

Source: Clinical Study Report 405-201-00157, Page 66

Table 70. Summary of Centanafadine Plasma Pharmacokinetic Parameters Following Administration of Single Doses of the To-Be-Marketed 1 × 328.8 mg Centanafadine ER Capsule Administered With a High-Fat Meal or in the Fasted State in Healthy Adults

Parameter[a]	1 × 328.8 mg QD XR with a HFM (N = 14)	1 × 328.8 mg QD XR in the Fasted State (N = 14)
C_{max} (ng/mL)	1490 (505)	1140 (290)
t_{max} (h)	5.00 (3.00-24.00)	3.50 (0.50-8.00)
AUC_t (ng·h/mL)	12300 (2740)	12400 (2780)
AUC_∞ (ng·h/mL)	12400 (2960)[b]	12700 (2940)
CL/F (mL/min)	427 (95.0)[b]	429 (99.2)
Vz/F (L)	197 (101)[b]	275 (186)
$t_{1/2,z}$ (h)	5.4 (2.7)[b]	7.6 (5.2)

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CL/F = apparent clearance of drug from plasma after extravascular administration; HFM = high-fat meal; SD = standard deviation; $t_{1/2,z}$ = half-life of drug elimination during terminal phase; t_{max} = time to maximum (peak) plasma concentration; V_z/F = apparent volume of distribution after extravascular drug administration.

[a]Values are mean (SD) except for t_{max}, which shows median (minimum-maximum).

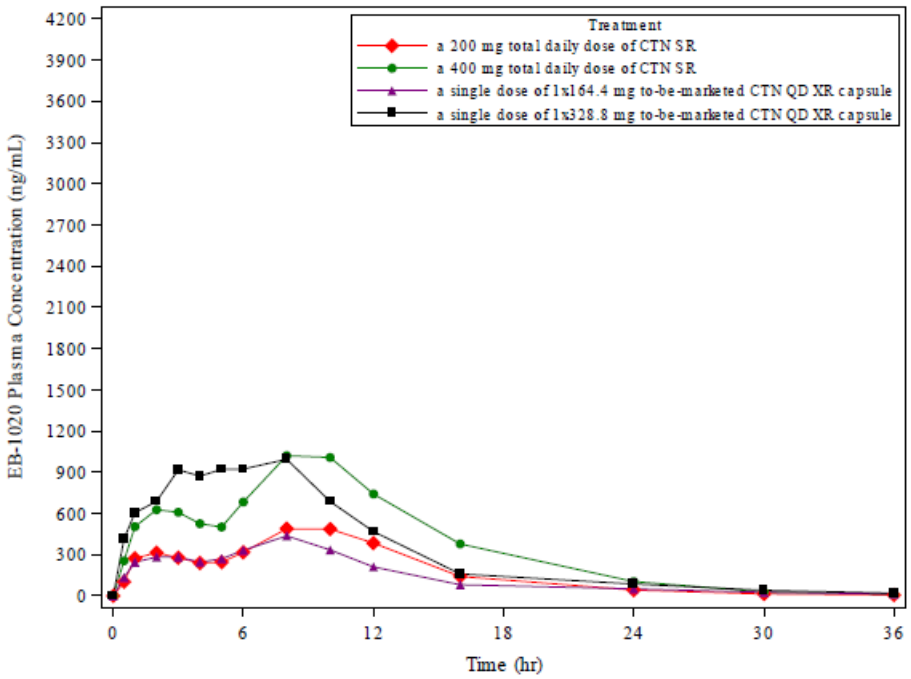
QD XR = once-daily extended release (ER) capsule formulation

Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively. Source: Clinical Study Report 405-201-00157, Page 74

For Arm 3 (PK bridging of the twice-daily formulation to the TBM-ER formulation): Centanafadine GMRs of C_{max}, AUC_t, and AUC_∞ were between 0.882 to 0.888, with the 90% CIs within the 0.80 to 1.25 BE range following single dose administration of 164.4 mg to-be-marketed ER capsule compared to 200 mg TDD of the twice-daily tablet.

Centanafadine GMRs of C_{max}, AUC_t, and AUC_∞ were between 0.915 to 1.094; with the 90% CI meeting the acceptance criteria for AUC_∞ for 1 × 328.8 mg to-be-marketed ER capsule compared to 400 mg TDD of the twice-daily tablet. The upper bound of the 90% CI for C_{max} was 1.26 instead of 1.25 (which was deviation of less than 1%).

Figure 25. Arm-3: Median Centanafadine Plasma Concentration-Time Profiles Following Administration of Single Doses of the To-Be-Marketed 1 × 164.4 mg or 1 × 328.8 mg Once-Daily ER Capsules and 200 mg or 400 mg TDD Twice-Daily Tablets in Healthy Adults



CTN = centanafadine; QD XR = once-daily extended release (ER) capsule formulation; SR = twice-daily tablet formulation; TDD = Total daily dose
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 67

Table 71. Geometric Mean Ratios and 90% CI for the To-Be-Marketed Centanafadine Once-Daily ER Capsule Compared to Centanafadine Twice-Daily Tablet in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1 × 164.4 mg QD XR capsule (test) vs 200 mg TDD SR (reference)	C_{max}	24	0.882	0.8034, 0.9674
	AUC_t	24	0.883	0.8339, 0.9357
	AUC_∞	21	0.888	0.8398, 0.9383
1 × 328.8 mg QD XR capsule (test) vs 400 mg TDD SR (reference)	C_{max}	24	1.094	0.9528, 1.2566
	AUC_t	24	0.915	0.8680, 0.9654
	AUC_∞	21	0.924	0.8703, 0.9810

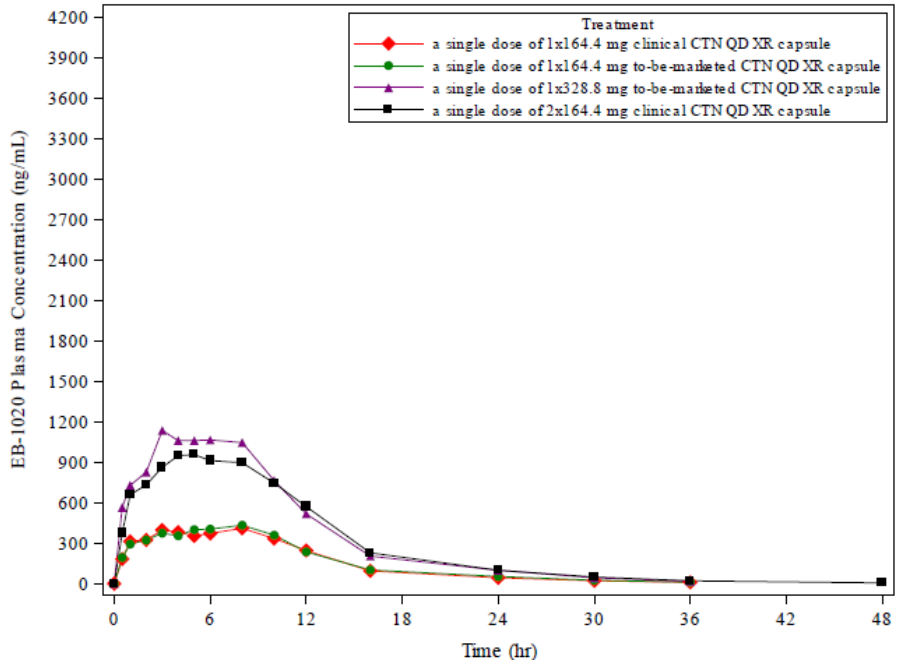
AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval; SR = sustained-release; TDD = total daily dose.

QD XR = once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 77

For Arm 4 (PK bridging between the ER capsule (clinical trial formulation) and TBM-ER capsule formulation): The GMRs of C_{max}, AUC_t, and AUC_∞ were between 1.021 and 1.034 (for 164.4 mg

to-be-marketed to 164.4 mg clinical trial formulation comparison) and between 1.043 and 1.099 (for 328.8 mg to-be-marketed formulation to 328.8 mg clinical trial formulation) 90% CIs were within the 0.80 to 1.25 BE range for comparisons at both dose strengths.

Figure 26. Arm-4: Centanafadine Plasma Concentration-Time Profiles Following Administration of a Single Dose of the To-Be-Marketed 1 × 164.4 mg and 1 × 328.8 mg Centanafadine Once-Daily ER Capsule and 1 × 164.4 mg and 1 × 328.8 mg Centanafadine Once-Daily ER Capsule (Clinical Trial Formulation)



CTN = centanafadine; QD XR = once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 69

Table 72. Geometric Mean Ratios and 90% CI for the To-Be-Marketed Centanafadine Once-Daily ER Capsule Compared to the Clinical Trial Formulation (Once-Daily ER Capsules) in Healthy Adults

Comparisons	Parameter	N	Geometric Mean Ratio	90% CI
1 × 164.4 mg To-Be-Marketed QD-XR capsule (test) vs Clinical QD XR Capsule (reference)	C_{max}	55	1.021	0.9622, 1.0843
	AUC_t	55	1.034	1.0031, 1.0651
	AUC_∞	43	1.034	0.9987, 1.0705
1 × 328.8 mg To-Be-Marketed QD XR capsule (test) vs 2 × 164.4 mg Clinical QD XR Capsule (reference)	C_{max}	53	1.099	1.0206, 1.1826
	AUC_t	53	1.043	1.0106, 1.0766
	AUC_∞	47	1.050	1.0143, 1.0860

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; AUC_t = area under the plasma concentration-time curve from time zero to time of the last observable concentration at time t; C_{max} = maximum (or peak) plasma concentration; CI = confidence interval.

QD XR = once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00157, Page 80

Drug Interaction Study (Study 405-201-00002)

A phase 1, open-label, parallel-arm trial in 42 healthy adults evaluated the effects of (1) a moderate CYP1A2 inhibitor (ciprofloxacin), (2) a strong CYP2D6 inhibitor (quinidine), (3) under conditions of moderate CYP1A2 induction (by smoking) on the PK of 200 mg TDD of centanafadine twice-daily tablet; and (4) the potential for centanafadine to inhibit or induce CYP1A2 (using caffeine as a substrate).

Figure 27. Trial Design and the Dose Levels of Precipitant and Object Drug

Trial Day	Arm 1: Ciprofloxacin as Inhibitor	Arm 2: Quinidine as Inhibitor	Arm 3: Smoking as Inducer	Arm 4: Centanafadine as Inhibitor/Inducer
−32 to −10	Screening	Screening	Screening	Screening
−1	Clinic check-in	Clinic check-in	Clinic check-in	Clinic check-in
1	200 mg TDD centanafadine[a]	200 mg TDD centanafadine[a]	200 mg TDD centanafadine[a]	200 mg caffeine
2				
3	750 mg ciprofloxacin BID	200 mg TDD centanafadine[a] + 324 mg quinidine gluconate QD	Discharge 48 h post-morning dose Day 1	200 mg caffeine + 400 mg TDD centanafadine[b]
4	750 mg ciprofloxacin BID	324 mg quinidine gluconate QD		400 mg TDD centanafadine[b]
5	750 mg ciprofloxacin BID	Discharge 48 h post-morning dose Day 3		400 mg TDD centanafadine[b]
6	750 mg ciprofloxacin BID			400 mg TDD centanafadine[b]
7	200 mg TDD centanafadine[a] + 750 mg ciprofloxacin BID			200 mg caffeine + 400 mg TDD centanafadine[b]
8	750 mg ciprofloxacin BID			400 mg TDD centanafadine[b]
9	Discharge 48 h post-morning dose Day 7			
10				Discharge 48 h post-morning dose Day 8
Varied	Follow-up phone call, Day 37	Follow-up phone call, Day 33	Follow-up phone call, Day 31	Follow-up phone call, Day 38

BID: twice daily (or 2 times a day); QD: once daily; TDD: total daily dose.
[a]The 200 mg TDD of centanafadine was given as a split dose with 100 mg in the morning and 100 mg 5 hours later.
[b]The 400 mg TDD of centanafadine was given as a split dose with 200 mg in the morning and 200 mg 5 hours later.

Source: Clinical Study Report 405-201-0002, Page 30

Dose and Dosage Regimen

- Arm 1: 200 mg TDD centanafadine administered on Days 1 and 7 + 750 mg ciprofloxacin tablet BID, every 12 hours (q12h), administered on Days 3 through 8
- Arm 2: 200 mg TDD centanafadine administered on Days 1 and 3 + 324 mg quinidine gluconate tablet QD, administered on Days 3 and 4
- Arm 3: 200 mg TDD centanafadine administered to smokers on Day 1
- Arm 4: 200 mg caffeine administered as 400 mg caffeine citrate solution (20 mL of 20 mg/mL) on Days 1, 3, and 7 + 400 mg TDD centanafadine administered on Days 3 to 8

Blood samples for PK analysis of centanafadine and the major metabolite were collected up to 48 hours post-dose (pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 hrs) on days centanafadine was administered alone as well as on the day administered concomitantly with the precipitant drug.

Results

A summary of geometric mean ratios (GMR) and 90% CIs of PK parameters for centanafadine (as an object) with ciprofloxacin, quinidine and in smokers is presented below. The results indicate that CYP1A2 and CYP2D6 inhibition did not have meaningful effects on the PK of centanafadine, as demonstrated by GMRs that were either at or just above 1. Additionally, the induction of CYP1A2 activity by smoking did not produce any clinically meaningful change in the PK of centanafadine.

Table 73. Geometric Mean Ratios and 90% Confidence Interval for Centanafadine Exposure in Presence of Inhibitors and Inducers

Inhibitor/Inducer	CYP Enzyme	C_{max}	AUC_t	AUC_∞
Ciprofloxacin	CYP1A2 inhibitor	1.101 (0.927, 1.308)	1.124 (1.033, 1.224)	1.115[a] (1.007, 1.235)
Quinidine	CYP2D6 inhibitor	1.271 (1.104, 1.463)	1.173 (1.090, 1.262)	1.189[b] (1.122, 1.260)
Smoking[c]	CYP1A2 inducer	0.935[d] (0.740, 1.183)	0.845[d] (0.711, 1.003)	0.942[e] (0.764, 1.160)

AUC_t: area under the concentration time curve from time 0 to the time of the last measurable concentrations; AUC_∞: area under the concentration time curve from time 0 to infinity; C_{max}: maximal peak plasma concentrations

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 50

Centanafadine's effects (as a precipitant) on the PK of caffeine (200 mg) were assessed after both single and multiple doses of 400 mg TDD twice-daily tablet. Although the C_{max} of caffeine remained largely unchanged, AUC_t increased approximately 2-fold (C_{max}=4940 ng/mL [caffeine alone] to 5530 [caffeine with centanafadine] and AUC_t=47000 h·ng/mL [caffeine alone] to 96200 h·ng/mL [caffeine with centanafadine].

Conclusions: CYP1A2 or CYP2D6 inhibition, and CYP1A2 induction, had no clinically meaningful effect on the PK of centanafadine. Therefore, no dose adjustments are recommended when centanafadine is concomitantly administered with CYP 1A2 or CYP2D6 inhibitors or CYP1A2 inducers. As centanafadine is a moderate CYP1A2 inhibitor (leading to a 2-fold increase in caffeine AUC_{inf}), consider reducing the dose of concomitantly administered CYP1A2 substrates by one-half.

Effect of Renal and Hepatic Impairment (Study 405-201-00006)

Study Title: A phase 1 trial to evaluate the pharmacokinetics, safety, and tolerability of centanafadine in subjects with moderate hepatic impairment or severe renal impairment compared to age-, weight-, and sex-matched subjects with normal hepatic and renal function

Design/Methodology

Phase 1, open-label, multi-center, parallel-group trial designed to evaluate the PK, safety, and tolerability of oral centanafadine. The trial evaluated three distinct populations in parallel:

Subjects with moderate hepatic impairment (Child-Pugh B classification), subjects with severe renal impairment (eGFR <30 mL/min/1.73m^2, and not undergoing dialysis), and age, weight, and sex-matched control subjects with normal hepatic and renal function. All subjects were administered centanafadine twice-daily tablets (400 mg TDD) on Day 1 as 200 mg in the morning under fasted conditions (minimum of 10 hour fast) and then 200 mg 5 hours later. All tablets were ingested orally with 240 mL water. Blood samples for PK analysis were collected predose and for up to 30 hours post-dose.

Results

Total concentrations were lower in adults with moderate hepatic impairment and adults with severe renal impairment. In adults with moderate hepatic impairment (Child Pugh B), total centanafadine exposures were lower (C_{max} reduced by 30% and AUC_{inf} reduced by 25%) compared to healthy matched adults. Similarly, in adults with severe renal impairment (eGFR <30 mL/min/1.73m^2, and not undergoing dialysis), total centanafadine exposures were lower (C_{max} reduced by 25% and AUC_{inf} reduced by 20%) compared to healthy matched adults.

However, the fraction unbound (fu) of centanafadine increased by approximately 1.66-fold and 1.87-fold, respectively, resulting in higher unbound concentrations in organ impairment subjects. A summary of GMR and 90% CI for the unbound PK parameters in adults with moderate hepatic or severe renal impairment compared to matched healthy adults is presented below.

Table 74. Geometric Mean Ratios and 90% CI for Centanafadine Unbound Plasma Pharmacokinetic Parameters

Parameter	Moderate Hepatic Impairment (N=8)	Severe Renal Impairment (N=8)
$C_{max,u}$	1.104 (0.808, 1.508)	1.265 (0.948, 1.689)
$AUC_{t,u}$	1.100 (0.725, 1.670)	1.404 (1.002, 1.967)
$AUC_{\infty,u}$	1.088 (0.736, 1.609)[a]	1.409 (1.006, 1.975)

$AUC_{t,u}$: unbound area under the concentration time curve from time 0 to the time of the last measurable concentrations; $AUC_{\infty,u}$: unbound area under the concentration time curve from time 0 to infinity; $C_{max,u}$: unbound maximal unbound peak plasma concentrations; CI : confidence interval.

Source: 2.7.2 Summary of Clinical Pharmacology Studies, Page 48

Conclusions

Total centanafadine concentrations were lower in adults with moderate hepatic or severe renal impairment; however, the mean unbound fraction were higher (with <40% increase in systemic exposures). Based on the exposure-response analysis for safety (i.e., skin rash and insomnia) and efficacy, the minimal increase in C_{max} and AUC_{inf} in adults with moderate hepatic impairment and adults with severe renal impairment is not expected to have clinically meaningful effects on safety and efficacy of centanafadine. Therefore, no dosage adjustment is recommended in adults with mild and moderate hepatic impairment and adults with mild, moderate and severe renal impairment.

Mass Balance Study (Study 405-201-00005)

Title: A phase 1 trial to evaluate the mass balance and pharmacokinetics of a single oral administration of ^{14}C-centanafadine in healthy subjects

Design/Methodology

This was a single-center, open-label, single-dose administration design.
Dosing was conducted in a single cohort of 8 subjects. The trial included a screening period (Days −28 to −3), an in-clinic treatment period (Days 1 to 10). Blood samples (venous) were collected to determine the total radioactivity in whole blood and plasma, and for the determination of centanafadine and metabolite EB-10601 concentrations in plasma. Urine was collected in 12-hour intervals on Day 1 and 24-hour intervals thereafter until discharge/early termination (ET). Feces for mass balance determination were collected in 24-hour intervals following dosing, until discharge/ET.

Results

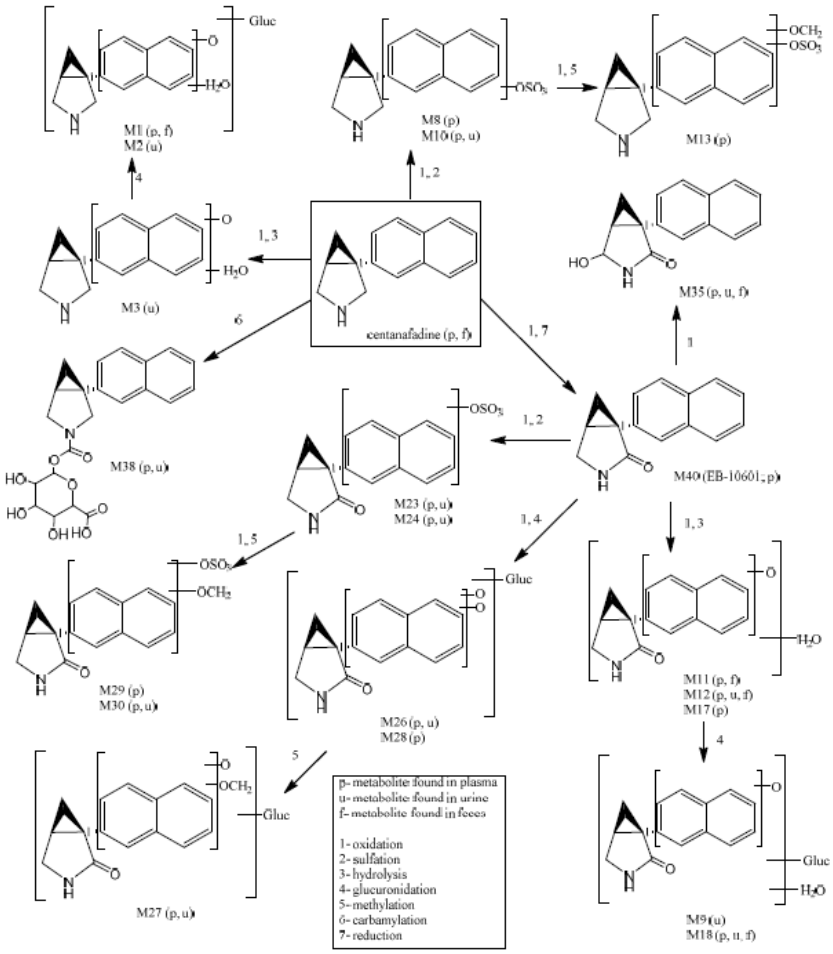
Overall, the mean radioactivity recovered in urine and feces was 95% over a collection period of 144 hours post-dose, with 87.6% of radioactivity eliminated in the urine, compared to 6.83% in feces. In plasma, the main circulating moiety is the parent- centanafadine (~32%), with the major metabolite EB-10601 (~21%), which is pharmacologically inactive. Neither centanafadine nor EB-10601 was excreted unchanged in urine, indicating complete metabolism prior to renal excretion. Other urine metabolites represented less than 5%. Centanafadine and 16 metabolites were quantified in fecal samples; however, none of the component peaks were greater than 0.7% of the dose. The mean C_{max} and AUC_{∞} values of 200 mg ^{14}C-centanafadine were 3820 (1020) ng/mL and 11200 (2750) h·ng/mL, respectively. Neither centanafadine nor its metabolites were quantifiable at 36 hours post-dose in plasma indicating all moieties have rapid elimination.

Table 75. Total Radioactivity in Pooled Plasma Samples Derived From Healthy Male Adults Following Oral Administration of 200 mg ^{14}C-Centanafadine (300 µCi)

Analyte	Proposed Chemical Name	Retention Time (min)	%Total Radioactivity AUC
Centanafadine	Centanafadine	33.00 - 33.67	31.4
EB-10601	Lactam centanafadine	44.33 - 45.00	21.2
M13	Methoxy centanafadine sulfate	18.50 - 18.67	8.35
M12	Dihydro-dioxy-EB-10601-2		
M11	Dihydro-dioxy-EB-10601-1	17.83 - 18.17	6.00
M24	EB-10601-sulfate-2	25.67 - 26.00	4.20
M27	Methoxy-EB-10601 glucuronide	26.83 - 27.33	3.14
M28	Dioxy-EB-10601 glucuronide-2		
M29	Methoxy-EB-10601 sulfate-1		
M23	EB-10601-sulfate-1	25.33 - 25.50	2.68

AUC = area under the curve.
Note: Retention time ranges are from profiling analyses of plasma.
Source: Clinical Pharmacology Summary Aid, Page 28

Figure 28. Proposed Biotransformation Pathways of 14C-Centanafadine in Humans



Source: Clinical Study Report 405-201-00005, Page 69

Conclusions

Centanafadine (31.4%) and EB-10601 (21.2%) accounted for the highest percentage of radioactivity in pooled plasma; all other metabolites were ≤10% of the total radioactivity AUC. Following oral administration, 87.6% of radioactivity was recovered in urine and 6.83% in feces. Centanafadine and EB-10601 were not recovered unchanged in the urine, indicating complete metabolism prior to renal excretion. Fecal excretion was minimal, with no individual component peak exceeding 0.7% of the dose.

PK of Centanafadine ER Capsule Following Administration of the Contents of Capsule Sprinkled Over the Soft-Foods (#405-201-00150)

Title: A phase 1, open-label, randomized trial to evaluate the relative bioavailability of centanafadine ER capsules in healthy adults.

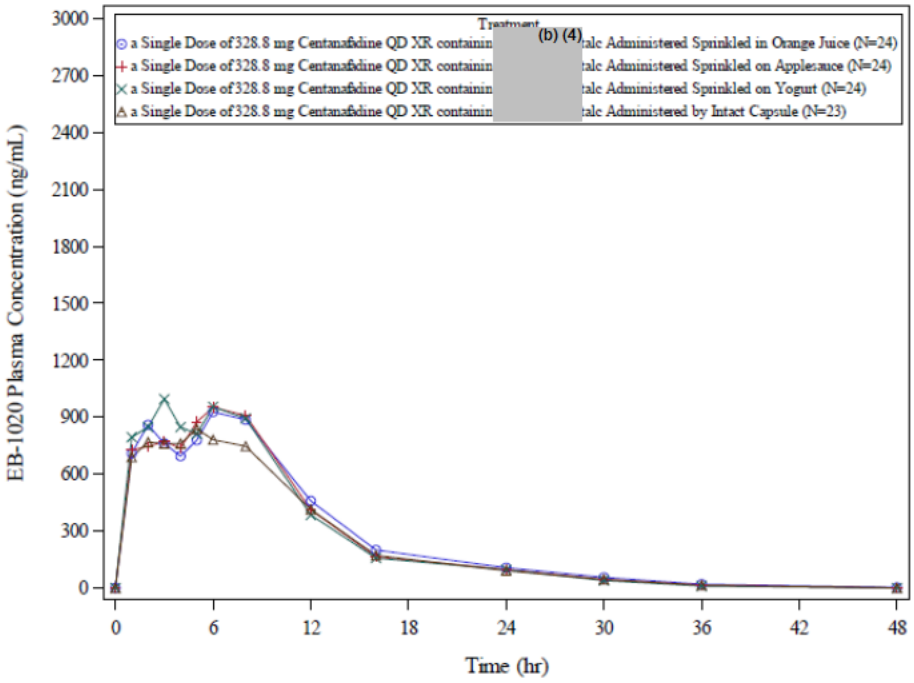
Design

In this multi-arm study, Arm-4 was single doses of 328.8 mg centanafadine ER capsule (i.e., to-be-marketed ER capsule) administered in soft foods (either sprinkled on 15 mL of apple sauce, 15 mL of yogurt, or in 15 mL of orange juice) compared to administration as intact capsule. The drug product was administered after a 10-hr overnight fast.

Results

The key PK parameters and PK profiles of centanafadine remained unchanged when centanafadine ER capsule was administered either as intact or sprinkled the contents of capsule over soft-foods such as apple-sauce, yogurt or in orange juice.

Figure 29. Median Centanafadine Plasma Concentrations Following Administration of a Single Daily Dose of 328.8 mg Centanafadine QD ER as an Intact Capsule, Sprinkled on Applesauce or Yogurt or Orange Juice to Healthy Adults



QD XR = once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00150, Page 57

Table 76. Geometric Mean Ratios and 90% CIs of PK Parameters of 328.8 mg Centanafadine Once-Daily ER Capsule When Administered Either as Intact Capsule or Sprinkling the Contents of Capsule on Applesauce, Yogurt, or Orange Juice

Comparisons	Parameter	N	Geometric Mean Ratios[a]	90% CI[a]
328.8 mg QD XR capsule sprinkled on applesauce (test) vs intact capsule (reference)	C_{max}	23	1.025	0.931, 1.129
	AUC_t	23	1.033	0.962, 1.110
	AUC_∞	18	1.012	0.933, 1.099
328.8 mg QD XR capsule sprinkled on yogurt (test) vs intact capsule (reference)	C_{max}	23	1.117	1.012, 1.231
	AUC_t	23	1.064	1.006, 1.126
	AUC_∞	16	1.054	0.994, 1.117
328.8 mg QD XR capsule sprinkled in orange juice (test) vs intact capsule (reference)	C_{max}	23	1.067	0.966, 1.178
	AUC_t	23	1.043	0.984, 1.106
	AUC_∞	20	1.026	0.968, 1.088

AUC_∞ = area under the concentration time curve from time zero to infinity; AUC_t = area under the concentration time curve calculated from time 0 to the time of the last observable concentration at time t; CI = confidence intervals; CTN = centanafadine; C_{max} = maximum (peak) plasma concentration of the drug; QD = once daily.

[a]Geometric mean ratio of parameter values following centanafadine QD XR administered sprinkled on applesauce, sprinkled on yogurt, or sprinkled in orange juice over centanafadine administered as an intact capsule in the fasted state. Geometric mean ratio reported using subjects with PK data available for the compared two treatments. Estimates are obtained by exponentiating means and 90% CI based on paired t-test.

QD XR = once-daily extended release (ER) capsule formulation
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Clinical Study Report 405-201-00150, Page 67

Conclusions

The geometric mean ratios (Sprinkling the contents/Intact capsule) and 90% CIs for C_{max}, AUC_t, AUC_∞ were within the bioequivalence range of 0.80 to 1.25. This suggests that sprinkling the contents of 328.8 mg of ER capsule on applesauce, yogurt, or in orange juice did not affect the PK of centanafadine ER capsule. Therefore, sprinkling the contents of capsule over those soft foods are acceptable alternative methods of administration of a centanafadine ER capsule.

Single and Multiple- Ascending Dose PK in Pediatric Subjects 4 to 12 Years of Age (Study 405-201-00150)

Title: A phase 1b, multicenter, open-label, multiple ascending dose trial to evaluate the pharmacokinetics, safety, and tolerability of centanafadine extended-release capsules after oral administration in pediatric subjects (4 to 12 years, inclusive) with attention-deficit hyperactivity disorder.

Design

This was a phase 1b, multicenter, open-label, multiple ascending dose trial in pediatric subjects (4 to 12 years of age, inclusive) with a confirmed diagnosis of ADHD. This trial consisted of a

screening period (including washout period), check-in on Day −1, a 14-day treatment period, and a safety follow-up phone call after the last dose. The total duration of the trial was up to approximately 51 days for each subject. The trial population of subjects ages 4 to 12 years of age was evaluated separately in 3 subgroups:

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

Weight-adjusted doses (based on allometric scaling and population pharmacokinetic modeling) of centanafadine ER capsule that were expected to produce exposures similar to 400-mg adult centanafadine twice-daily tablet doses were evaluated in separate cohorts of subjects 9 to 12 years of age. Similarly, weight-adjusted doses of centanafadine once-daily ER capsule that are expected to produce exposures similar to 200 and 400 mg adult centanafadine twice-daily tablet doses were evaluated in separate cohorts of subjects 6 to 8 years of age and subjects 4 to 5 years of age. Safety and tolerability were also reviewed for each cohort.

The exact dose levels for the different weight categories of the subjects were:
20 kg to <35 kg: 140 mg; 35 to 50 kg: 210 mg, and >50 kg: 280 mg.

Figure 30. Study Schematic for PK in Pediatric Subjects

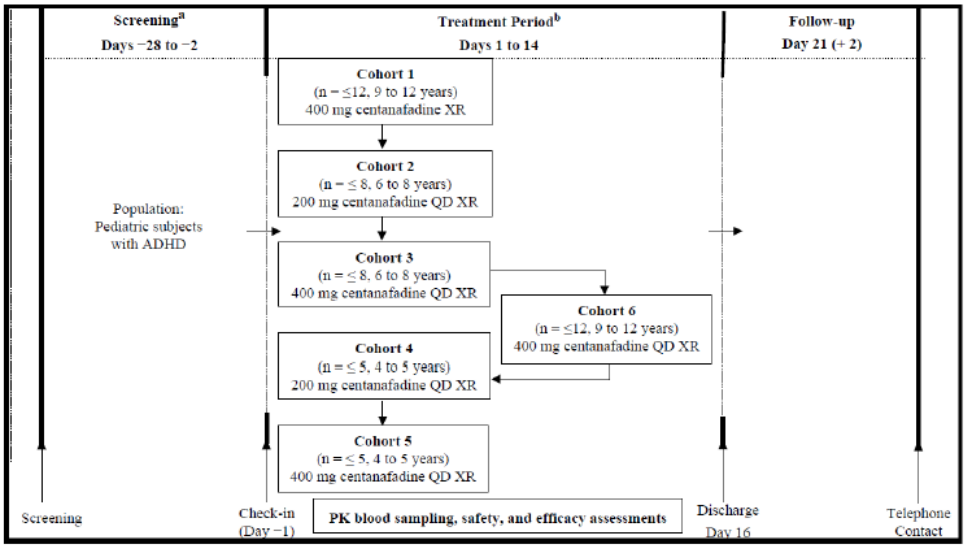


Figure 9.1-1 Trial Design Schematic

ADHD = attention-deficit/hyperactivity disorder; PK = pharmacokinetic(s); QD = once daily; XR = extended release.
Note: Cohorts 1 through 3 were dosed sequentially, followed by Cohort 6, then Cohorts 4 and 5. The safety and tolerability of each cohort was reviewed before dosing was started in the next cohort.
All doses of centanafadine XR and QD XR were equivalents by body weight that were predicted to produce exposures similar to 200 mg or 400 mg centanafadine sustained-release tablets in adults.
Source: Clinical Study Report 405-201-00046, Page-31

Table 77. Centanafadine PK in Subjects 9 to 12 Years of Age With ADHD

Parameter[a]	400 mg AED Centanafadine QD XR	
	Single (Day 1) Dose (n=12)	Multiple (Day 14) Dose (n=10)
C_{max} (ng/mL)	1320 (725)	1840 (993)
t_{max} (h) [a]	5.00 (1.00-8.00)	6.00 (3.00-12.00)
AUC_{0-24h} (ng·h/mL)	12600 (6910)	21700 (6760) [b]
C_{24h} (ng/mL)	98.9 (75.4)	124 (86.8) [b]
CL_{ss}/F (mL/min)	—	300 (150) [b]
Vz/F (L)	—	113 (80.9) [b]
$t_{1/2,z}$ (h)	—	4.2 (1.8) [b]
$R_{ac,}C_{max}$		1.23 (0.64) [c]
$R_{ac,}AUC_{0-24h}$		1.39 (0.29) [b,c]
$R_{ac,}C_{24h}$		1.19 (0.80) [b,c]

[a]Values are mean (SD) except for t_{max} which shows median (minimum-maximum).

[b]n = 9.

[c]Accumulation ratios were calculated using values on Day 14 over Day 1.

AED = Adult equivalent dose; QD XR = once-daily extended release (ER) capsule formulation
Source: Synopsis, Clinical Study Report 405-201-00046, Page 11

Table 78. Centanafadine PK in Subjects 6 to 8 Years of Age With ADHD

Parameter[a]	200 mg AED QD XR		400 mg AED QD XR	
	Single (Day 1) Dose (n=8)	Multiple (Day 14) Dose (n=7)	Single (Day 1) Dose (n=8)	Multiple (Day 14) Dose (n=8)
C_{max} (ng/mL)	775 (363)	850 (418)	1200 (576)	1790 (689)
t_{max} (h) [a]	6.00 (4.00 - 6.00)	6.00 (4.00-6.00)	6.00 (4.00-8.00)	4.00 (3.00-6.00)
AUC_{0-24h} (ng·h/mL)	6700 (3530)	6630 (3180)	12400 (5070)	18800 (6740)
C_{24h} (ng/mL)	26.9 (23.6)	21.3 (16.1)	148 (140)	133 (147)
CL_{ss}/F (mL/min)	—	529 (276)	—	347 (152)
Vz/F (L)	—	234 (238)	—	134 (115)
$t_{1/2,z}$ (h)	—	4.5 (2.0)	—	4.2 (1.5)

AED = Adult equivalent dose; QD XR = once-daily extended release (ER) capsule formulation
Source: Synopsis, Clinical Study Report 405-201-00046, Page 8

Table 79. Centanafadine PK in Subjects 4 to 5 Years of Age With ADHD

Parameter[a]	200 mg AED QD XR		400 mg AED QD XR	
	Single (Day 1) Dose (n=5)	Multiple (Day 14) Dose (n=5)	Single (Day 1) Dose (n=5)	Multiple (Day 14) Dose (n=5)
C_{max} (ng/mL)	466 (138)	516 (390)	1620 (827)	1590 (910)
t_{max} (h)[a]	6.00 (4.00-24.00)	6.00 (3.00-8.00)	4.00 (1.00-6.00)	6.00 (2.00-6.00)
AUC_{0-24h} (ng·h/mL)	4700 (1480)	5930 (4570)	12100 (8100)	19300 (10200)
C_{24h} (ng/mL)	12.6 (9.46)	45.1 (25.5)	60.6 (68.5)	249 (190)
CL_{ss}/F (mL/min)	—	888 (819)	—	400 (257)
Vz/F (L)	—	371 (296)	—	104 (73.7)[b]
$t_{1/2,z}$ (h)	—	5.0 (0.8)	—	3.8 (1.0)[b]
R_{ac},C_{max}	—	1.15 (0.87)[c]	—	0.95 (0.3)[c]
R_{ac},AUC_{0-24h}	—	1.30 (0.85)[c]	—	1.83 (0.69)[c]
R_{ac},C_{24h}	—	4.41 (3.93)[c]	—	4.90 (5.49)[b,c,d]

[a]Values are mean (SD) except for t_{max} which shows median (minimum-maximum).

[b]n = 4.

[c]Accumulation ratios were calculated using values on Day 14 over Day 1.

AED = Adult equivalent dose; QD XR = once-daily extended release (ER) capsule formulation
Source: Synopsis, Clinical Study Report 405-201-00046, Page 10

Table 80. Centanafadine Plasma Pharmacokinetic Parameters Following Multiple Oral Doses of 400 mg Adult Equivalent Dose of Once-Daily ER Capsule (in Children 4-12 Years) as Compared to 328.8 mg Once-Daily ER Capsule in Adults

Parameter	400 mg AED			328.8 mg
	4-to-5-year olds[a] (n=5)	6-to-8-year olds[a] (n=8)	9-to-12-year olds[b] (n=10)	Adults[b] (n=40)
C_{max} (ng/mL)	1590 (910)	1790 (689)	1840 (993)	1510 (525)
t_{max} (h)	6.00 (2.00-6.00)	4.00 (3.00-6.00)	6.00 (3.00-12.00)	5.0 (0.50-10.00)
AUC_{0-24h} (ng·h/mL)	19300 (10200)	18800 (6740)	21700 (6760)	14000 (4190)
$t_{1/2,z}$	3.8 (1.0)[c]	4.2 (1.5)	4.2 (1.8)	5.2 (2.4)
CL/F	400 (257)	347 (152)	300 (150)	359 (93.2)
$R_{ac}C_{max}$	0.95 (0.3)	1.84 (1.13)	1.23 (0.64)	NA
$R_{ac}AUC_{0-24h}$	1.83 (0.69)	1.61 (0.58)	1.39 (0.29)	NA
$R_{ac}C_{24h}$	4.90 (5.49)	1.44 (1.65)	1.19 (0.80)	NA

AED : adult equivalent dose; AUC_{0-24h} : area under the concentration time curve from 0 to 24 hours C_{max} : maximal (peak) plasma concentration; CL/F : apparent clearance from plasma following extravascular administration; CI : confidence interval; NA : not applicable; t_{max} : time to maximum (peak) concentrations; $t_{1/2,z}$: terminal phase elimination half life; R_{ac} : accumulation ratio

[c]n=4

a= Data from clinical study report 405-201-00046
b= Data from clinical study report 405-201-000154 and 405-201-000157
Dose strengths of 164.4 mg, 246.6 mg, and 328.8 mg centanafadine hydrochloride salt are equivalent to 140 mg, 210 mg, and 280 mg free base, respectively.
Source: Summary of Clinical Pharmacology Studies, Table 1.2.2.6-2, Page 44

Conclusions

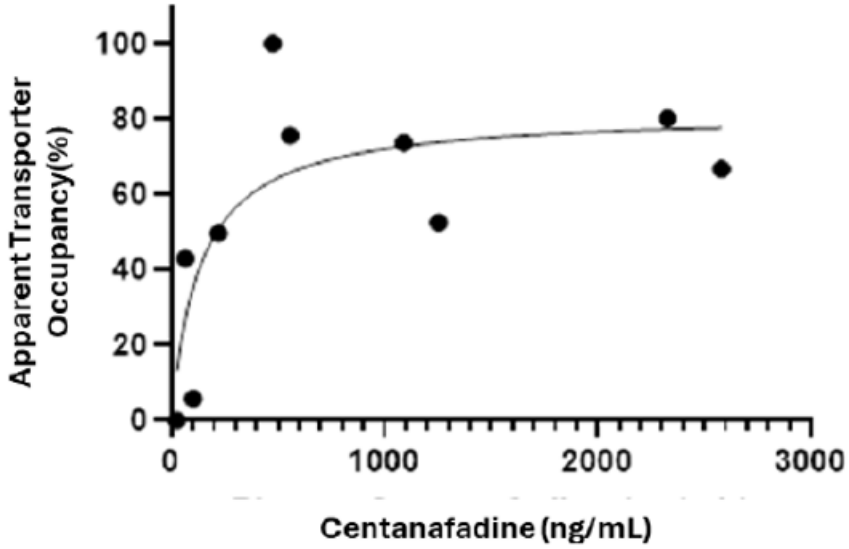
Using the weight-based dosing strategy, the key PK parameters (e.g., C_{max} , AUC_{0-24h}, CL/F etc.) were similar across all pediatric age categories (4 to 5 years of age, 6 to 8 years of age, and 9 to 12 years of age) following single and multiple doses of 400 mg adult equivalent dose (AED) of centanafadine once-daily ER capsule. Mean CLss/F and Vz/F were similar across all pediatric subjects administered multiple doses of 400 mg AED centanafadine QD XR, demonstrating that there is no effect of age on PK of centanafadine once-daily ER capsule. Additionally, the exposures observed in the entire pediatric age category (i.e., 4 to 12 years of age) were also generally similar to the exposure in adults. Therefore, the weight-based dosing strategy implemented for selecting the dose in the pediatric efficacy and safety studies was an acceptable strategy.

Evaluation of Norepinephrine, Dopamine, and Serotonin Transporter Occupancy by Positron Emission Tomography (PET) Imaging (Study # 405-201-00022)

A phase 1, open-label trial evaluated the occupancies of norepinephrine, dopamine, and serotonin transporters in the human brain using PET imaging after administration of centanafadine. Ten healthy male adults were enrolled and randomized into two cohorts. In Cohort 1, six participants received a 400 mg TDD of centanafadine (given as twice/daily) over 4 days with PET imaging on Days 4 and 5. In Cohort 2, four participants received an 800 mg TDD of centanafadine (given as twice/daily) on Day 1, with PET imaging performed Day 1 and Day 2.

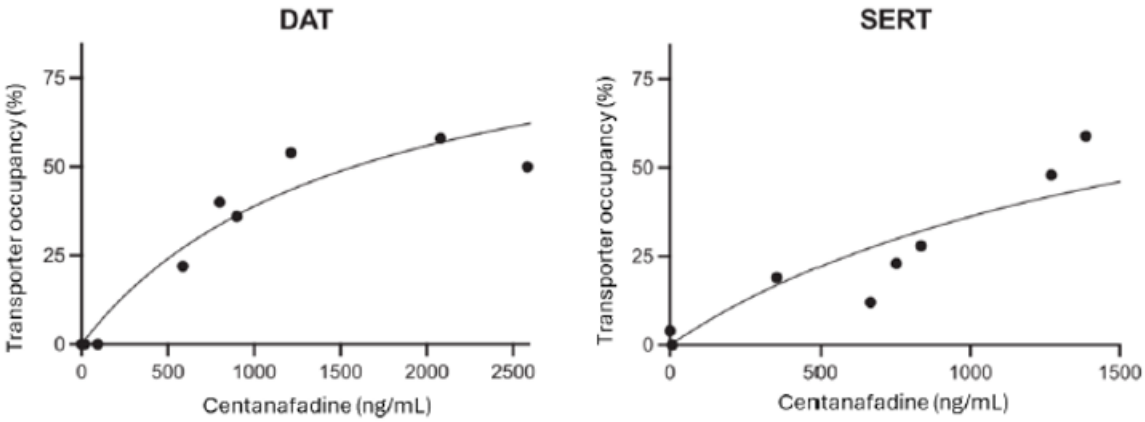
Centanafadine has a greater affinity for norepinephrine transporter (IC_{50} ~135 ng/mL), than for dopamine (IC_{50} ~1580 ng/mL) or serotonin (IC_{50} ~1760 ng/mL) transporter. Norepinephrine transporter occupancy appeared to plateau at plasma concentrations >500 ng/mL; however, no plateau was observed for either dopamine or serotonin transporter. At the plasma concentrations maintained at clinically recommended doses, approximately 80% inhibition of norepinephrine transporter and lower than 50% inhibition for dopamine and serotonin transporters are expected.

Figure 31. Relationship Between Plasma Concentrations and Transporter Occupancy for Norepinephrine



Source: Summary of Clinical Pharmacology Studies, Page 56

Figure 32. Relationship Between Plasma Concentrations and Transporter Occupancy for Dopamine (DAT) and Serotonin (SERT)



Source: Summary of Clinical Pharmacology Studies, Page 55

15.5. Pharmacometrics

Executive Summary

The question of interest (QOI) and model risk assessment for pharmacometrics analysis is shown in Table 81.

Table 81. Model Risk Assessment for Pharmacometrics Analysis

Question of Interest	Is the 210-mg once-daily centanafadine ER capsule appropriate for adult patients with ADHD?
Context of Use	Population PK analyses were conducted to bridge the PK of the proposed 210-mg centanafadine once-daily ER capsule to that of the studied 200 mg TDD and 400 mg total daily dose (TDD) of twice-daily tablet. Exposure-response analyses were conducted to provide supportive evidence for the benefit-risk assessment of the proposed dosing regimen, 210-mg once-daily centanafadine ER capsule.
Model Influence	High. No clinical efficacy data was generated for ER 210 mg QD in adult patients with ADHD.
Consequence of Wrong Decision	Low. In study 405-201-00157, centanafadine once-daily ER capsule at 140 mg and 280 mg doses demonstrated comparable C_{max} and AUC_{inf} to those of 200 mg TDD and 400 mg TDD of the twice-daily tablet (clinical trial formulation in adults), respectively, to support the bridge between the formulations. The pivotal efficacy and safety trials demonstrated favorable efficacy and safety of 200 mg TDD and 400 mg TDD of the twice-daily tablet compared to placebo. Furthermore, the efficacy of 200 mg TDD and 400 mg TDD of twice-daily tablet are comparable. As the proposed model-based intermediate dosing regimen, 210 mg once-daily centanafadine ER capsule's PK profiles are within the range of 200 mg TDD and 400 mg TDD of twice-daily tablet, the wrong decision is unlikely to result in a lack of efficacy or unexpected safety concerns for the proposed dosing regimen, 210 mg centanafadine ER capsule.
Model Risk	Moderate. By combining the high model influence and low consequence of wrong decision, the overall model risk is moderate.

Source: Pharmacometric reviewer's analysis

In the pivotal trials (Studies 13 and 14), the efficacy and safety of 200 mg and 400 mg TDD of twice-daily tablet were established in adults with ADHD. Study 405-201-00157 demonstrated comparable C_{max} and AUC_{inf} values between 200 mg TDD of twice-daily tablet (clinical trial formulation) and 140-mg once-daily ER capsule as well as between 400 mg TDD of twice-daily tablet and 280-mg once-daily ER capsule to support the PK bridge between the formulations. Although C_{max} and AUC_{inf} were comparable between twice-daily tablet and ER capsule formulations, population PK simulations demonstrated that 280-mg once-daily ER capsule yielded higher exposure than 400 mg TDD of twice-daily tablet during the first 6 hours post-dose, but remained within the range of 200 mg TDD and 400 mg TDD exposure of twice-daily tablet thereafter (Figure 1). Conversely, 140-mg once-daily ER capsule produced higher exposures during the first 6 hours post-dose followed by lower exposures beginning approximately 6 hours after dosing compared to 200 mg twice-daily tablet TDD (Figure 2). The

Applicant performed additional PK simulations to support an intermediate dose, 210 mg of centanafadine ER capsule, which produced exposures higher during the first 8 hours followed by relatively similar exposures as those of 200 mg twice-daily tablet TDD after the first dose and at steady state (Figure 3). Increased PK exposures were predicted to be associated with increased probability of rash/skin eruptions and insomnia. However, the incidence differences between the proposed once-daily 210-mg and 280-mg ER capsule regimens are expected to be relatively small, based on both model predictions and observed dose-response relationships. Notably, the 210-mg ER capsule is expected to have an incidence rate falling between those observed for 200 mg and 400 mg TDD of twice-daily tablet.

In summary, the 210-mg ER QD capsule regimen is appropriate for adult patients with ADHD.

Population PK Analysis

The population PK model for twice-daily tablet formulation included a total of 5277 evaluable centanafadine plasma concentrations from 782 subjects in six phase 1, one phase 2b, and two phase 3 clinical trials in adults. Demographic characteristics and other covariates evaluated in this population PK analysis were summarized in Table 82 for continuous covariates and in Table 83 for categorical covariates.

Table 82. Descriptive Statistics of Continuous Covariates for Subjects Involved in the Population PK Model Development for Twice-Daily Tablet

Covariate	All Subjects (N= 782)						
	Min	5th Percentile	25th Percentile	Median	75th Percentile	95th Percentile	Max
Age (year)	18	21	26	33	43	53	72
Weight (kg)	41.0	57.1	69.4	80.2	92.7	113	152
BMI (kg/m^2)	18.0	20.4	23.9	27.1	30.5	37.2	40.0
eGFR ($mL/min/1.73m^2$)	50.6	75.4	91.6	105	118	127	134
Serum creatinine level (mg/dL)	0.5	0.6	0.8	0.9	1.0	1.2	1.6
ALT (IU/L)	4	9	13	19	26	47	92

ALT = alanine transaminase; BMI = weight (kg)/height $(m)^2$; eGFR = estimated glomerular filtration rate (derived using the 2021 CKD-EPI creatinine equation)
Source: 405-23-201-report-body, Table 4.1.2-1

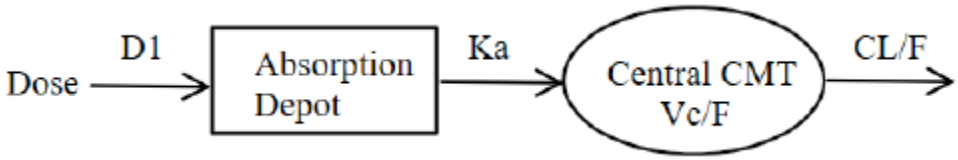
Table 83. Descriptive Statistics of Categorical Covariates for Subjects Involved in the Population PK Model Development for Twice-Daily Tablet

Covariate	Categories	All Subjects (N=782) n (%)
Sex	Male	440 (56.3 %)
	Female	342 (43.7 %)
Race	White/ Caucasian	608 (77.7 %)
	Black/ African American	111 (14.2 %)
	American Indian/ Alaska Native	27 (3.5 %)
	Asian	6 (0.8 %)
	Native Hawaiian or other Pacific Islander	3 (0.4 %)
	Unknown/ Other	27 (3.5 %)
Smoking Status	Non-smoker	622 (79.5 %)
	Smoker	97 (12.4 %)
	Unknown	63 (8.1 %)

Source: 405-23-201-report-body, Table 4.1.2-2

The proposed structural model is a one compartment (CMT) model with a sequential zero-then-first order absorption with inter-individual variability (IIV) on apparent clearance (CL/F), apparent central volume of distribution (Vc/F), and first order absorption rate constant (Ka). Weight was retained as a significant covariate on both CL/F and Vc/F with the allometric scaling exponents fixed to the standard values. A combined proportional and additive error model, separate for phase 3 data (vs. phase 1 and 2b data), was used to account for the residual variability. A schematic drawing of the structural model is presented in Figure 33. Parameter estimates of the final twice-daily tablet model are presented in Table 84.

Figure 33. Schematic Diagram of Model Structure for the Population PK Model for Twice-Daily Tablet



CL/F = apparent clearance; CMT = compartment; D1 = duration of zero-order process; Ka = first order absorption rate constant; Vc/F = apparent central volume of distribution
Source: 405-23-201-report-body, Figure 4.2.2-1

Table 84. Parameter Estimates of the Final Population PK Model for Twice-Daily Tablet

Parameter	Unit	Estimate	RSE%	Shrinkage (%)
CL/F	$L \cdot h^{-1}$	22.9	1.6	-
Vc/F	L	152	3.1	-
D1	h	0.402	9.1	-
Ka	h^{-1}	0.998	7.6	-
θ_{weight} on CL/F[a]	-	0.75 FIX	-	-
θ_{weight} on Vc/F[b]	-	1 FIX	-	-
Random effect: variance (CV)				
CL/F	-	0.121 (34.8%)	12%	17
Covariance CL/F-Vc/F	-	0.00352	432%	-
Vc/F	-	0.185 (43.0%)	16%	37
Covariance CL/F-Ka	-	-0.0484	67%	-
Covariance Vc/F-Ka	-	0.302	20%	-
Ka	-	0.676 (82.2%)	20%	36
Random effect parameters: variance				
Proportional (phase 1 and 2b)	-	0.113	5%	6.5
Additive (phase 1 and 2b)		19	62%	6.5
Proportional (phase 3)	-	0.214	5%	12.4
Additive (phase 3)		170	28%	12.4

θ_{weight} = covariate effect of body weight; CL/F = apparent clearance; D1 = duration of zero-order process; Ka = first order absorption rate constant; Vc/F = apparent central volume of distribution; RSE = relative standard error

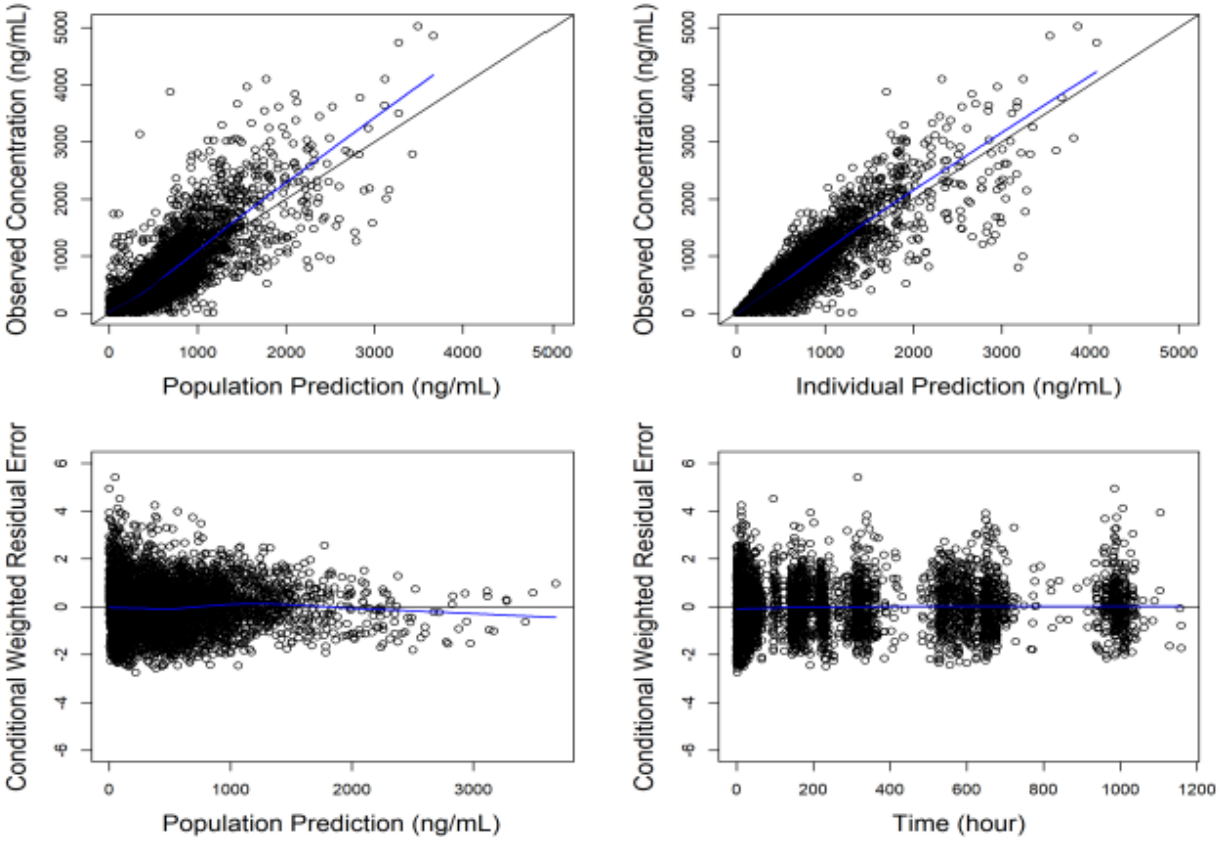
[a]CL/Fi = CL/F * (Weighti/70)^θ_{weight}

[b]Vc/Fi = Vc/F * (Weighti/70)^θ_{weight}

No major bias was observed based on goodness-of-fit plots (Figure 34). Overall, the model's predictive capability appeared to be reasonable (Figure 35).

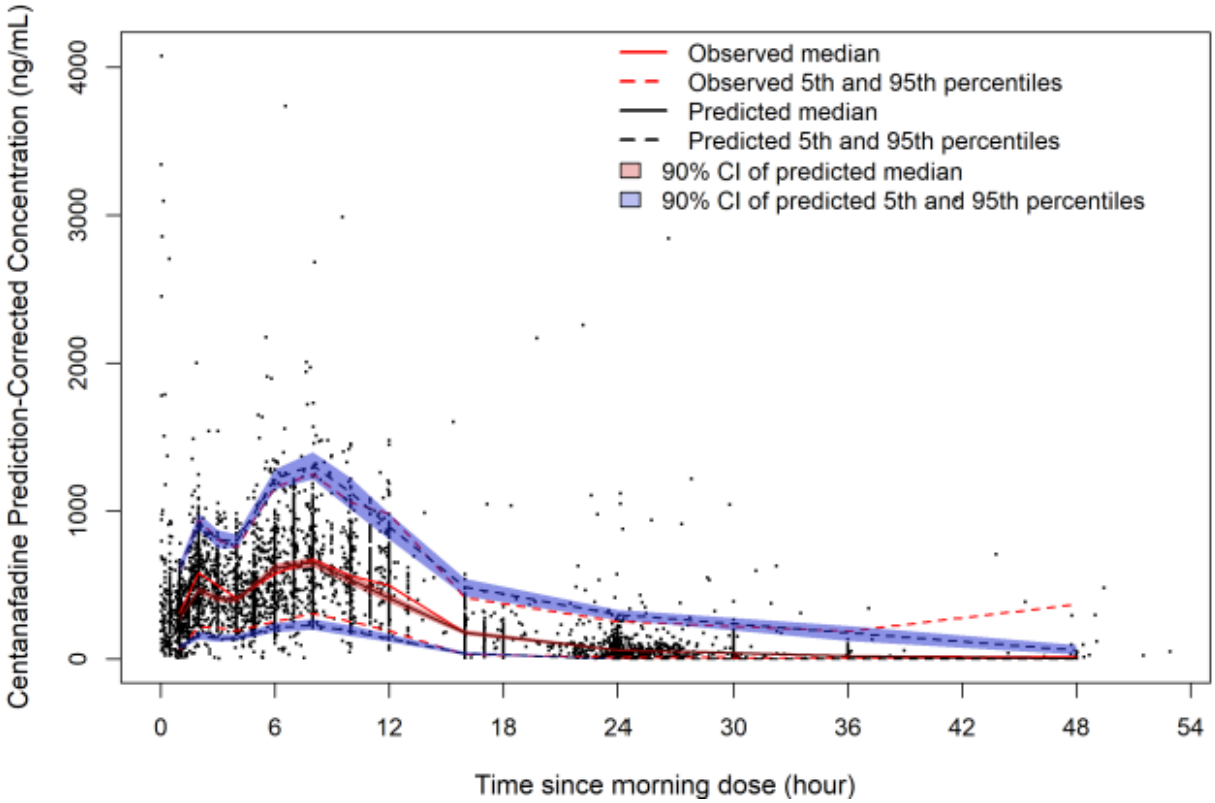
Source: 405-23-201-report-body, Table 4.2.4.1-1

Figure 34. Goodness-of-Fit Plots for the Population PK Model for Twice-Daily Tablet



Source: 405-23-201-report-body, Figure 4.2.4.3.1-1

Figure 35. Prediction-Corrected Visual Predictive Check for the Population PK Model for Twice-Daily Tablet



Source: 405-23-201-report-body, Figure 4.2.4.3.1-1

A separate population PK model was proposed for the once-daily centanafadine ER capsule. In total, 10263 evaluable centanafadine plasma concentrations from 328 subjects from 405-201-00046, 405-201-00047, 405-201-00150, and 405-201-00157 were included in the model development. Demographic characteristics and other covariates evaluated in this population PK analysis were summarized in Table 85 for continuous covariates and in Table 86 for categorical covariates.

Table 85. Descriptive Statistics of Continuous Covariates for Subjects Involved in the Population PK Model Development for ER Capsule

	405-201-00046 (N=26)	405-201-00047 (N=32)	405-201-00150 (N=96)	405-201-00157 (N=174)	**Overall (N=328)**
Age (Years)					
Median (5%, 95%)	8 (6, 12)	35 (20, 52)	36 (23, 50)	33 (21, 51)	33 (9, 50)
Mean (SD)	8 (2)	36 (11)	36 (9)	34 (9)	33 (11)
Range	(6, 12)	(19, 55)	(18, 54)	(18, 55)	(6, 55)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weight (kg)					
Median (5%, 95%)	28 (20, 71)	74 (51, 98)	76 (57, 95)	75 (53, 99)	74 (33, 98)
Mean (SD)	34 (16)	75 (14)	76 (12)	76 (13)	72 (17)
Range	(18, 78)	(49, 107)	(49, 104)	(46, 108)	(18, 108)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Height (cm)					

	405-201-00046 (N=26)	405-201-00047 (N=32)	405-201-00150 (N=96)	405-201-00157 (N=174)	**Overall (N=328)**
Median (5%, 95%)	131 (114, 168)	171 (154, 189)	170 (156, 184)	171 (155, 188)	169 (137, 186)
Mean (SD)	135 (17)	170 (10)	171 (9)	171 (10)	168 (14)
Range	(112, 179)	(152, 191)	(146, 195)	(150, 202)	(112, 202)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Creatinine (mg/dL)					
Median (5%, 95%)	0.40 (0.30, 0.60)	0.88 (0.60, 1.28)	0.82 (0.59, 1.14)	0.85 (0.60, 1.18)	0.82 (0.50, 1.16)
Mean (SD)	0.43 (0.13)	0.91 (0.20)	0.83 (0.17)	0.86 (0.18)	0.82 (0.21)
Range	(0.20, 0.80)	(0.55, 1.31)	(0.52, 1.18)	(0.49, 1.30)	(0.20, 1.31)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ALT (IU/L)					
Median (5%, 95%)	14 (10, 33)	15 (9, 36)	21 (9, 42)	17 (9, 43)	17 (9, 41)
Mean (SD)	16 (9)	18 (12)	23 (13)	21 (10)	21 (11)
Range	(7, 50)	(8, 72)	(7, 78)	(6, 60)	(6, 78)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BMI (kg/m^2)					
Median (5%, 95%)	16.8 (13.5, 24.3)	26.3 (20.4, 31.5)	26.3 (21.1, 31.1)	25.8 (20.5, 31.1)	25.7 (17.0, 31.1)
Mean (SD)	17.7 (3.9)	26.0 (3.6)	26.1 (3.1)	25.7 (3.2)	25.2 (4.0)
Range	(13.5, 30.3)	(20.2, 31.5)	(20.4, 31.9)	(19.3, 31.6)	(13.5, 31.9)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
eGFR ($mL/min/1.73m^2$)					
Median (5%, 95%)	167 (148, 211)	101 (69, 123)	105 (82, 123)	104 (77, 124)	105 (78, 165)
Mean (SD)	173 (23)	97 (17)	104 (14)	103 (15)	108 (25)
Range	(136, 251)	(67, 125)	(74, 130)	(65, 135)	(65, 251)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

ALT = alanine transaminase; BMI = weight (kg)/height $(m)^2$; eGFR = estimated glomerular filtration rate (derived using the 2021 CKD-EPI creatinine equation)
Source: 405-201-00213-report-body, Table 4.1.2-1

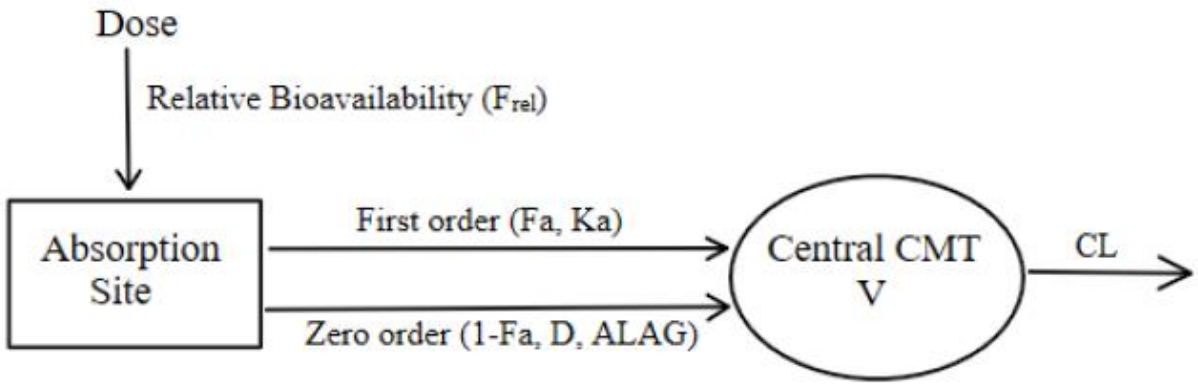
Table 86. Descriptive Statistics of Categorical Covariates for Subjects Involved in the Population PK Model Development for ER Capsule

	405-201-00046 (N=26)	405-201-00047 (N=32)	405-201-00150 (N=96)	405-201-00157 (N=174)	**Overall (N=328)**
Sex					
Female	13 (50%)	14 (44%)	48 (50%)	87 (50%)	162 (49%)
Male	13 (50%)	18 (56%)	48 (50%)	87 (50%)	166 (51%)
Race					
White	8 (31%)	12 (38%)	49 (51%)	111 (64%)	180 (55%)
Black or African American	16 (62%)	19 (59%)	36 (38%)	50 (29%)	121 (37%)
American Indian or Alaska native	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (0.6%)
Asian	0 (0%)	0 (0%)	5 (5.2%)	6 (3.4%)	11 (3.4%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	1 (1.0%)	1 (0.6%)	2 (0.6%)
Other	2 (7.7%)	1 (3.1%)	5 (5.2%)	4 (2.3%)	12 (3.7%)
Ethnicity					
Hispanic or Latino	4 (15%)	1 (3.1%)	23 (24%)	47 (27%)	75 (23%)
Not Hispanic or Latino	22 (85%)	31 (97%)	73 (76%)	127 (73%)	253 (77%)

Source: 405-201-00213-report-body, Table 4.1.2-2

The proposed structural model was a one-compartment model with parallel first-order and zero-order absorption, including a lag time (ALAG) on the zero-order absorption. A fraction of absorption parameter (Fa) was included to estimate the fraction of the dose absorbed through each process and a duration (D) was estimated for the zero-order absorption. Relative bioavailability (Frel) was fixed to 1, and IIV on Frel was estimated. IIV was also included on clearance (CL), volume of distribution (V), and the first-order absorption rate constant (Ka). A combined proportional and additive error model was used to account for residual variability. A schematic of the model structure is shown in Figure 36. Parameter estimates of the final ER capsule model are presented in Table 87.

Figure 36. Schematic Diagram of Model Structure for the Population PK Model for ER capsule



Frel = relative bioavailability, Fa= Fraction absorbed through first-order process, Ka = first-order absorption rate constant (1/h), D = duration (h), ALAG= Lag time (h), CMT= compartment, V = apparent volume of distribution of the central compartment (L), CL = apparent clearance from the central compartment (L/h)
Source: 405-201-00213-report-body, Figure 4.2.2-1

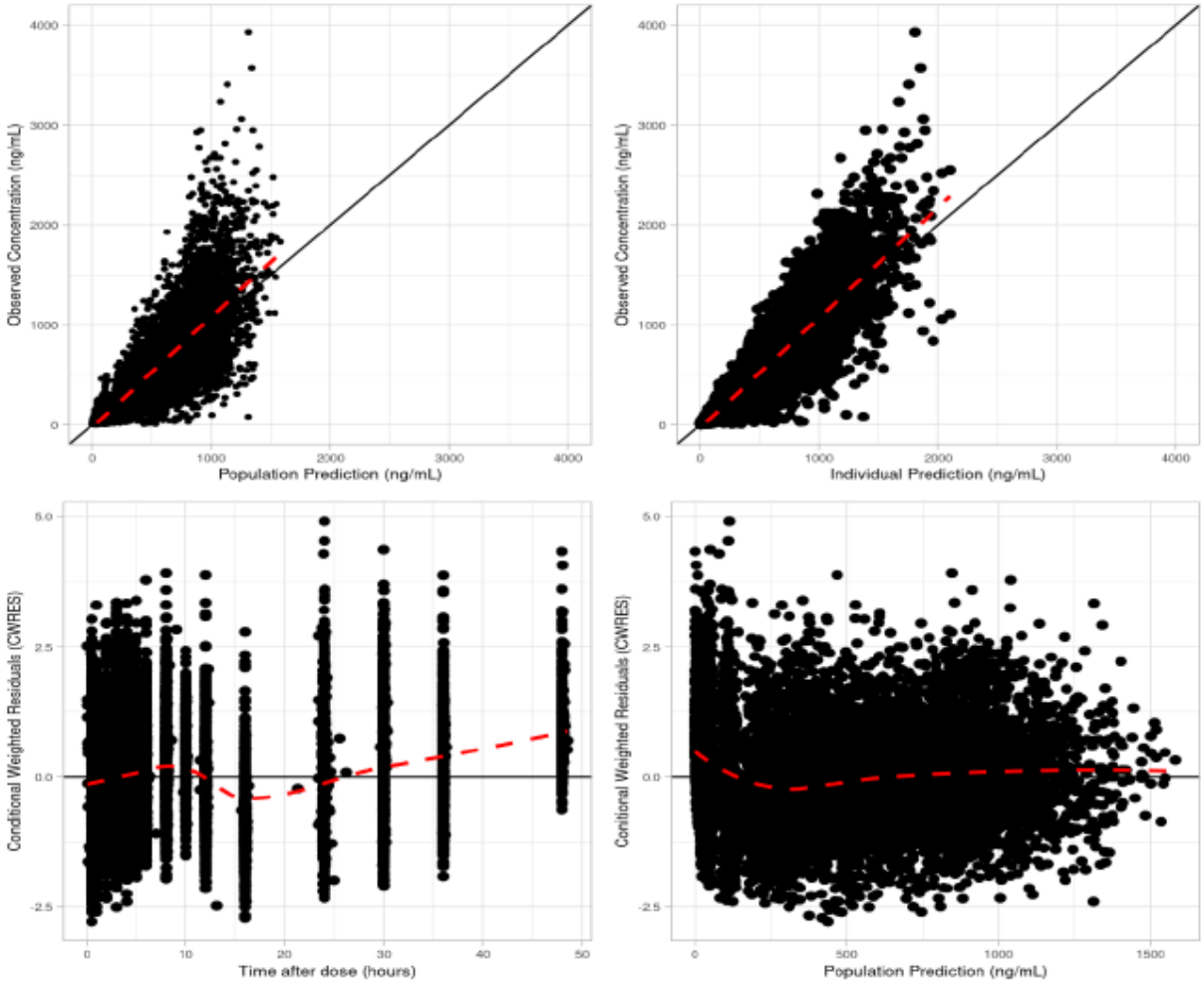
Table 87. Parameter Estimates of the Final Population PK Model for ER Capsule

Parameter	Unit	Estimate	RSE%	Shrinkage (%)
Ka	1/h	1.58	5.95	-
Fa	-	0.538	2.88	-
CL	L/h	22.9	1.34	-
F_{rel}	-	1 (fixed)		-
V	L	174	1.96	-
D	h	5.47	3.39	-
ALAG	h	1.56	8.93	-
Weight effect on KA	-	0.636	16.4	-
Dose effect on F_{rel}	-	0.211	6.43	-
Allometric exponent on CL	-	0.873	4.98	-
Inter-Individual Variability (CV%)				
ωKa	-	66.0	12.3	19.5
ωCL	-	8.75	40.3	47.9
ωV	-	18.7	13.4	13.2
ωF_{rel}	-	19.6	12.3	12.2
Residual Variability				
σProportional (CV%)	-	36.2	2.75	3.3
σAdditive (Variance)	-	57.8	14.1	3.3

Source: 405-201-00213-report-body, Table 4.2.4-1

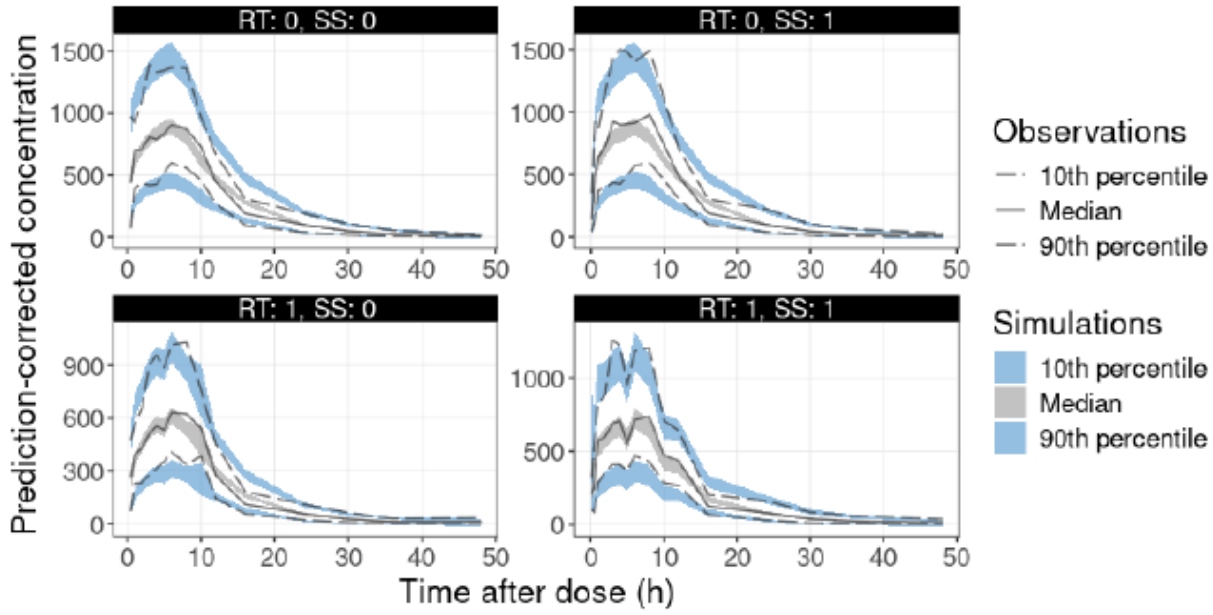
The proposed model appeared to underestimate C_{max}, with a noticeable pattern in the residual plots (Figure 37). Overall, the model's predictive capability appeared to be reasonable, though some deviations between predictions and observations remained (Figure 38).

Figure 37. Goodness-of-Fit Plots for the Population PK Model for ER Capsule



Source: 405-201-00213-report-body, Figure 4.2.6-1

Figure 38. Prediction-Corrected Visual Predictive Check for the Population PK Model for ER Capsule



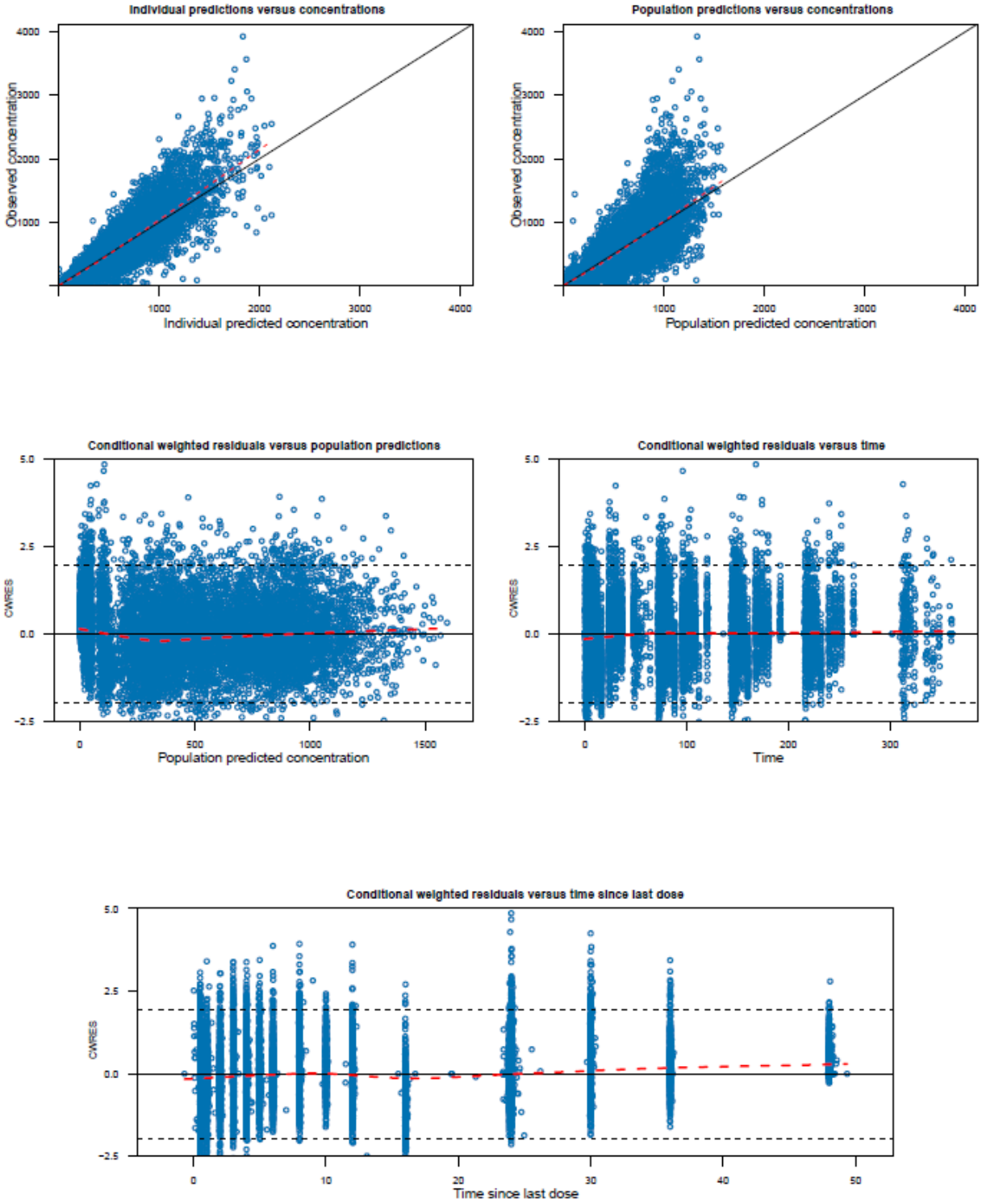
RT = Reference Talc (0 represents to-be-marketed talc and 1 represents clinical talc), SS = Steady State (0 represents not at steady state and 1 represents at steady state).
Note: The prediction-corrected observed concentrations against time after last dose are represented by black lines (median, 10th and 90th percentiles). The prediction-corrected simulated concentrations based on the analysis population (n = 500 simulations) are represented by the grey ribbon (median and 95% CI of the median, respectively), and the blue shaded ribbons (95% CI of the 10th and 90th percentiles, respectively).
Source: 405-201-00213-report-body, Figure 4.2.6-2

Overall, the proposed population PK models for the twice-daily tablet and ER capsule appear reasonable.

For the twice-daily tablet model, the Applicant used a full OMEGA matrix for the random effects associated with CL/F, Vc/F, and Ka. The pharmacometric reviewer conducted a sensitivity analysis by fitting a simplified model using a diagonal OMEGA matrix. The estimates of CL/F, Vc/F, and Ka were reasonably close to those from the Applicant's model.

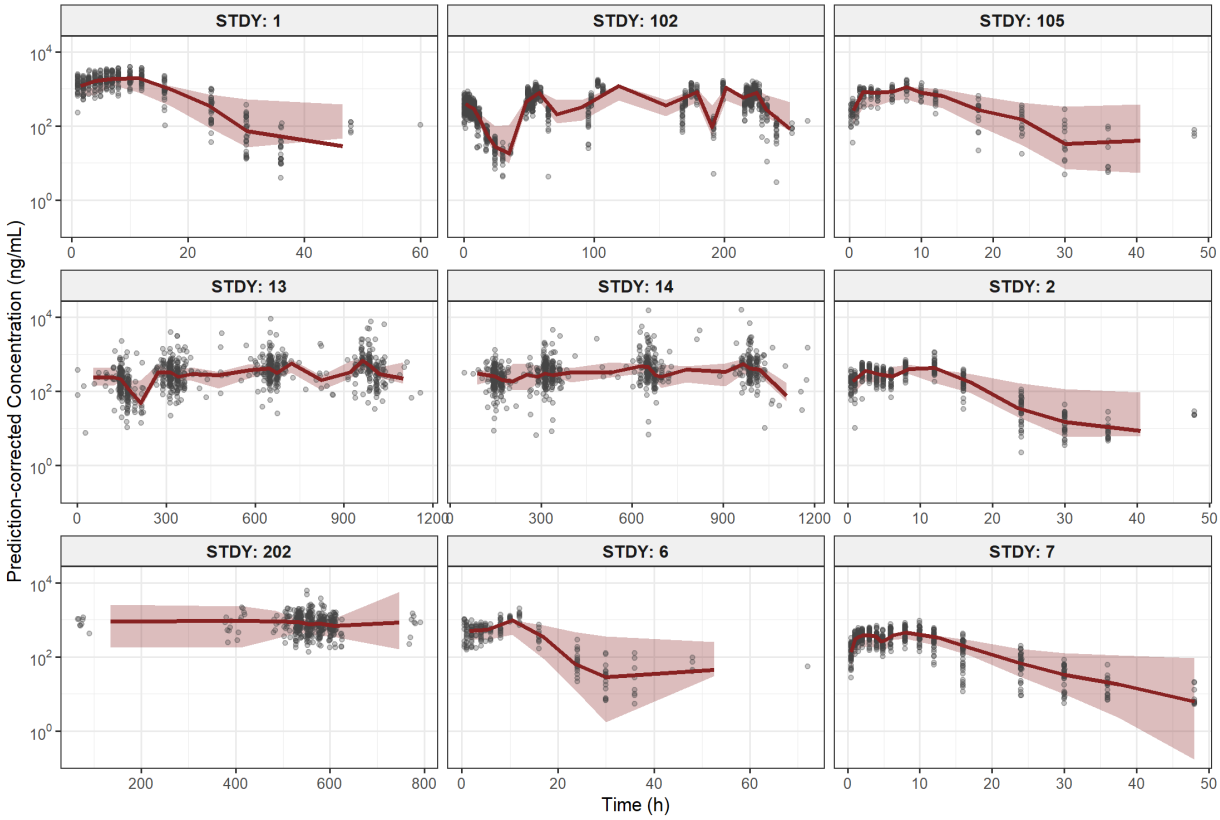
For the ER model, the Applicant's model showed noticeable bias based on the goodness-of-fit plots (Figure 37). However, the pharmacometrics reviewer's reproduced model did not show a comparable level of bias (Figure 39). The pharmacometrics reviewer further conducted a sensitivity analysis by fitting the ER capsule data in log-transformed space and making minor revisions to the residual error model as appropriate (i.e., modeled in log domain). The parameter estimates from this sensitivity analysis were reasonably consistent with those from the Applicant's original model.

Figure 39. Goodness-of-Fit Plots for the Pharmacometrics Reviewer-Reproduced Population PK Model for ER Capsule



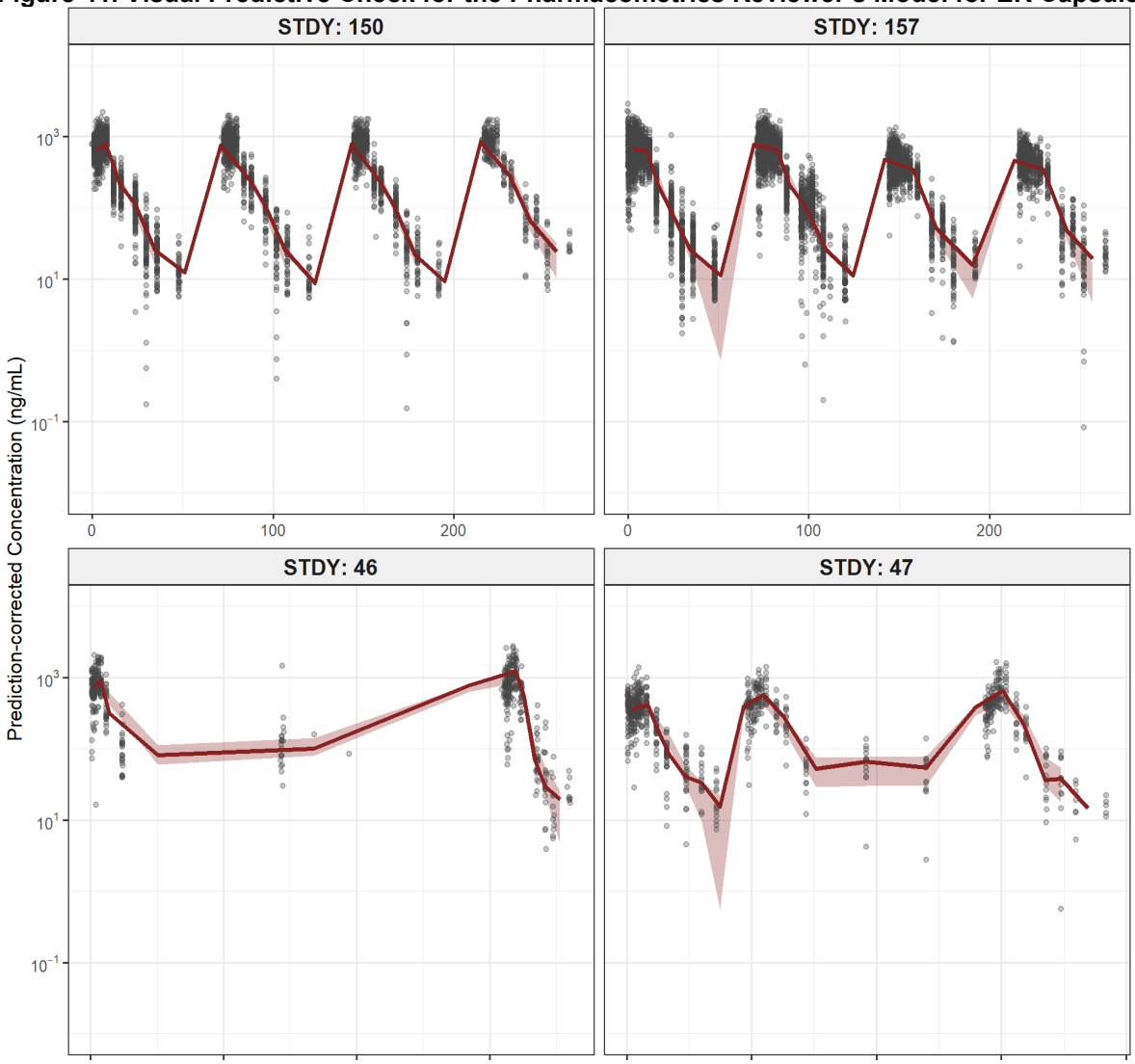
Horizontal dashed lines: -2 and +2; red *dashed line: loess regression*
Note: The y-axis were truncated for residual plots to match Applicant's plots. Regressions were conducted with full data set.
Source: Pharmacometric reviewer's analysis

Figure 40. Visual Predictive Check for the Pharmacometric Reviewer's Model for Twice-Daily Tablet



Black dots = observations; red line = observed median; shaded area = 95% predictive confidence interval for median
STDY = study; STDY 1 = Study 405-201-00001; STDY 102 = Study EB-1020-102; STDY 105 = NVI-EB-1020-105 Part A; STDY 13 = Study 405-201-00013; STDY 14 = Study 405-201-00014; STDY 2 = Study 405-201-00002; STDY 202 = NVI-EB-1020-202; STDY 6 = Study 405-201-00006; STDY 7 = Study 405-201-00007
Source: Pharmacometric reviewer's analysis

Figure 41. Visual Predictive Check for the Pharmacometrics Reviewer's Model for ER Capsule



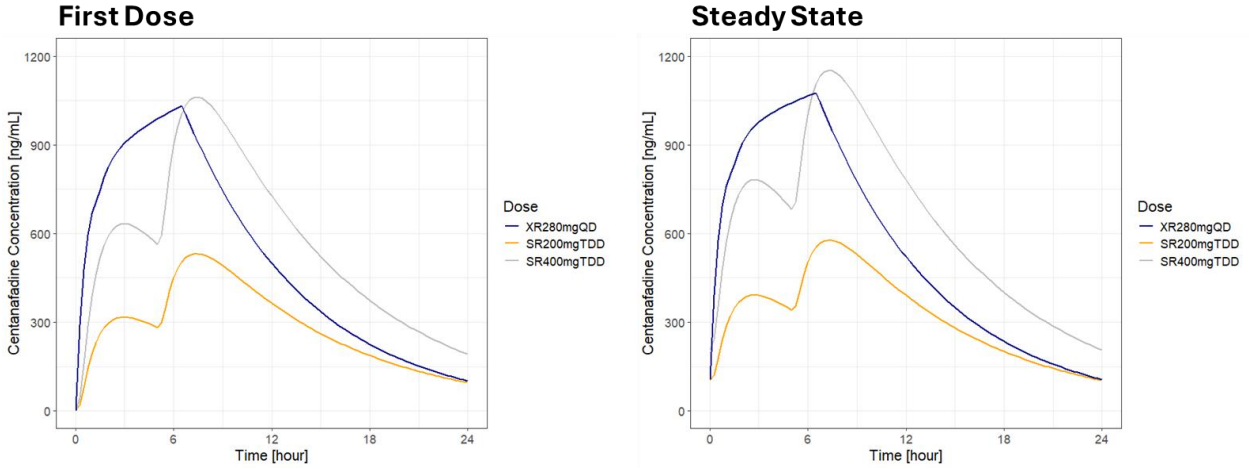
Black dots = observations; red line = observed median; shaded area = 95% predictive confidence interval for median
STDY = study; STDY 150 = Study 405-201-00150; STDY 157 = Study 405-201-00157; STDY 46 = Study 405-201-00046; STDY 47 = Study 405-201-00047
Source: Pharmacometric reviewer's analysis

Overall, the twice-daily tablet and ER capsule models developed in the pharmacometric reviewer's sensitivity analyses adequately described the population-level PK profiles (Figure 40 and Figure 41). Therefore, subsequent evaluations of the proposed dosage regimens were conducted using the models developed by the pharmacometric reviewer.

In the pivotal trials for adults, 200 mg and 400 mg TDD of twice-daily tablet demonstrated comparable efficacy. Although the pivotal trials evaluated the twice-daily tablet formulation, the Applicant proposed the once-daily ER capsule for adult patients. In the bridging study,

systemic exposures, as measured by AUC_{inf} and C_{max}, were comparable between 200 mg TDD of twice-daily tablet administered with doses separated 4 to 6 hours apart and 140-mg ER capsule administered as a single dose. Comparable exposures were also observed between 400 mg TDD of twice-daily tablet administered with doses separated 4 to 6 hours apart and 280-mg ER capsule administered as a single dose. However, the PK shape of twice-daily tablet and once-daily ER capsule is different and post-6 hours exposures of 140-mg and 280-mg ER capsule were lower than those of 200 mg and 400 mg TDD of twice-daily tablet. The exposures of 280-mg ER capsule are within the range of exposures of 200 mg and 400 mg TDD of twice-daily tablet but 140-mg ER capsule's exposures are slightly lower than those of 200 mg TDD of twice-daily tablet. The Applicant proposed an intermediate dose, once-daily 210-mg and high dose, 280-mg ER capsule, rather than 140-mg and 280-mg ER capsule in the proposed label. To evaluate the appropriateness of the proposed ER capsule dosing regimens, the pharmacometrics reviewer conducted PK simulations using the Reviewer-developed models. The simulations showed that 280-mg once-daily ER capsule produced comparable C_{max} but higher exposure during the first 6 hours after dosing than 400 mg TDD of twice-daily tablet, but thereafter the exposures of 280-mg ER capsule remained within the exposure range associated with 200 to 400 mg TDD of twice-daily tablet (Figure 42 and Table 88). In contrast, 140-mg once-daily ER capsule produced lower exposure than 200 mg TDD of twice-daily tablet beginning approximately 6 hours after dosing (Figure 43 and Table 89). The exposures of the proposed intermediate dose, 210-mg once-daily ER capsule, were within the range associated with 200 to 400 mg TDD after the first dose and at steady state (Figure 44 and Table 90). The simulations using Applicant's original models showed similar results (data not shown).

Figure 42. Comparison in Median PK Profiles Between the 280-mg Once-Daily ER Capsule and 200 mg and 400 mg TDD of Twice-Daily Tablet (Clinical Trial Formulation)



Lines: median PK profile
Source: *Pharmacometric reviewer's analysis*

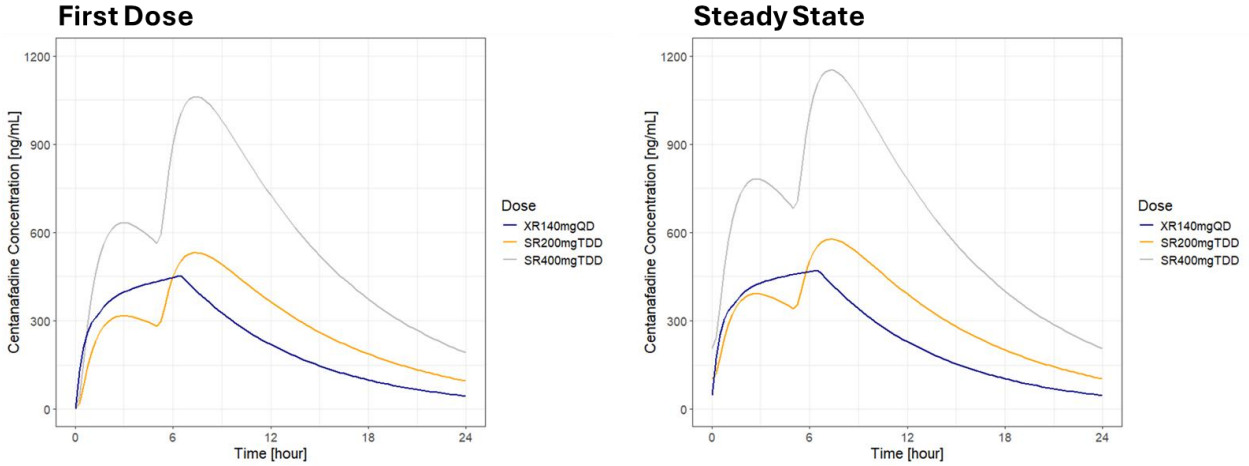
Overall, the simulation results support the acceptability of the Applicant's proposed dosage regimens of 210 mg and 280 mg once-daily ER capsule for the treatment of ADHD in adults.

Table 88. Simulated Median Plasma Concentration at 3 Hours (C3h), 7 Hours (C7h), 12 Hours (C12h), and 15 Hours (C15h) Post Dosing for 200 mg and 400 mg TDD of Twice-Daily Tablet, and 280-mg Once-Daily ER Capsule

Concentration	C3h		C7h		C12h		C15h	
Time	1st dose	SS	1st dose	SS	1st dose	SS	1st dose	SS
SR 200 mg	317	391	528	575	364	391	262	281
SR 400 mg	633	780	1053	1147	727	781	522	561
XR 280 mg	906	977	970	1012	500	521	336	350

Unit for plasma concentration: ng/mL
SS = steady state; SR200 mg = 100 mg twice-daily sustained-release tablet; SR 400 mg = 200 mg twice-daily sustained-release tablet; TDD = total daily dose; XR280 mg = once-daily extended-release (ER) capsule
Source: Pharmacometric reviewer's analysis

Figure 43. Comparison of Median PK Profiles Between the 140-mg Once-Daily ER Capsule and 200 mg and 400 mg TDD of Twice-Daily Tablet (Clinical Trial Formulation)



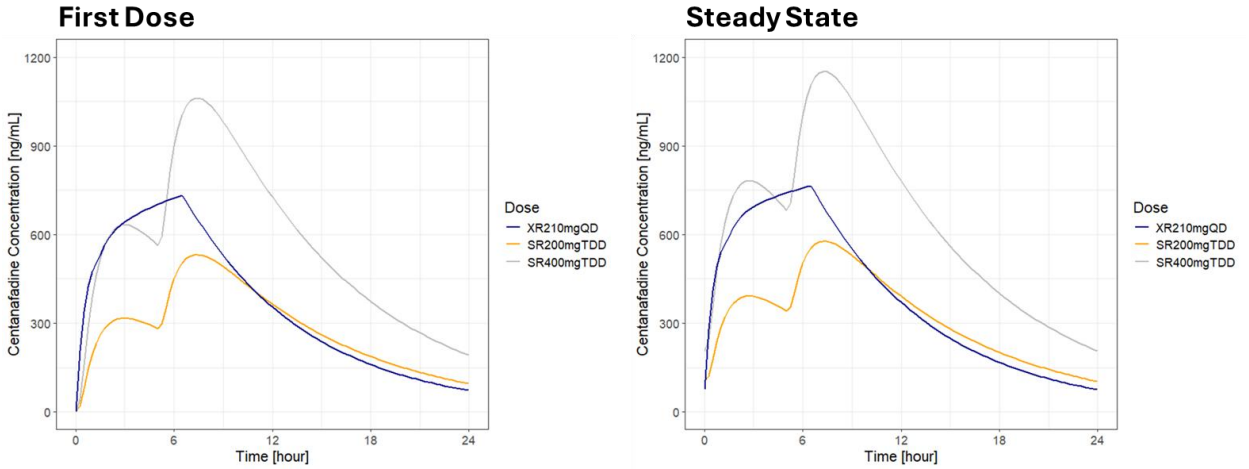
SR200 mg = 100 mg twice-daily tablet; SR 400 mg = 200 mg twice-daily tablet; TDD = total daily dose; XR280 mg = once-daily extended-release (ER) capsule
Source: Pharmacometric reviewer's analysis

Table 89. Simulated Median Plasma Concentration at 3 Hours (C3h), 7 Hours (C7h), 12 Hours (C12h), and 15 Hours (C15h) Post Dosing for 200 mg and 400 mg TDD of Twice-Daily Tablet, and 140-mg Once-Daily ER Capsule

Concentration	C3h		C7h		C12h		C15h	
Time	1st dose	SS	1st dose	SS	1st dose	SS	1st dose	SS
SR 200 mg	317	391	528	575	364	391	262	281
SR 400 mg	633	780	1053	1147	727	781	522	561
XR 140 mg	398	429	426	444	220	229	147	154

Unit for plasma concentration: ng/mL
SS = steady state; SR200 mg = 100 mg twice-daily tablet; SR 400 mg = 200 mg twice-daily tablet; TDD = total daily dose; XR280 mg = once-daily extended-release (ER) capsule
Source: Pharmacometric reviewer's analysis

Figure 44. Comparison of Median PK Profiles Between the 210-mg Once-Daily ER Capsule and 200 mg and 400 mg TDD of Twice-Daily Tablet (Clinical Trial Formulation)



SR200 mg = 100 mg twice-daily tablet; SR 400 mg = 200 mg twice-daily tablet; TDD = total daily dose; XR280 mg = once-daily extended-release (ER) capsule
Source: Pharmacometric reviewer's analysis

Table 90. Simulated Median Plasma Concentration at 3 Hours (C3h), 7 Hours (C7h), 12 Hours (C12h), and 15 Hours (C15h) Post Dosing for 200 mg and 400 mg TDD of Twice-Daily Tablet, and 210 mg Once-Daily ER Capsule

Concentration	C3h		C7h		C12h		C15h	
Time	1st dose	SS	1st dose	SS	1st dose	SS	1st dose	SS
SR 200 mg	317	391	528	575	364	391	262	281
SR 400 mg	633	780	1053	1147	727	781	522	561
XR 210 mg	644	694	689	719	355	371	239	249

Unit for plasma concentration: ng/mL
SS = steady state; SR200 mg = 100 mg twice-daily tablet; SR 400 mg = 200 mg twice-daily tablet; TDD = total daily dose; XR280 mg = once-daily extended-release (ER) capsule
Source: Pharmacometric reviewer's analysis

Both the low dose (200 mg TDD of twice-daily tablet) and high dose (400 mg TDD of twice-daily tablet) demonstrated efficacy in pivotal trials for the treatment of ADHD in adults. In pediatric subjects 6 years of age and older; however, only the high dose of centanafadine once-daily ER capsule, corresponding to the 400 mg TDD of twice-daily tablet (i.e., adult equivalent dose), demonstrated a statistically significant treatment effect. To assess whether the apparent difference in dose response could be attributed to lower PK exposure in pediatric patients, the PK in pediatric subjects 4 to 12 years of age (Study 405-201-00046) was compared to adults (Studies 405-201-00154 and 405-201-00157). The results suggest that systemic exposures are relatively similar between pediatric patients 4 to 12 years of age and adults (Table 17). Therefore, the observed differences in dose responses between pediatric subjects 6 years and older and adult subjects with ADHD were not due to the lower systemic exposures in pediatric subjects 6 to 17 years of age than adults with ADHD.

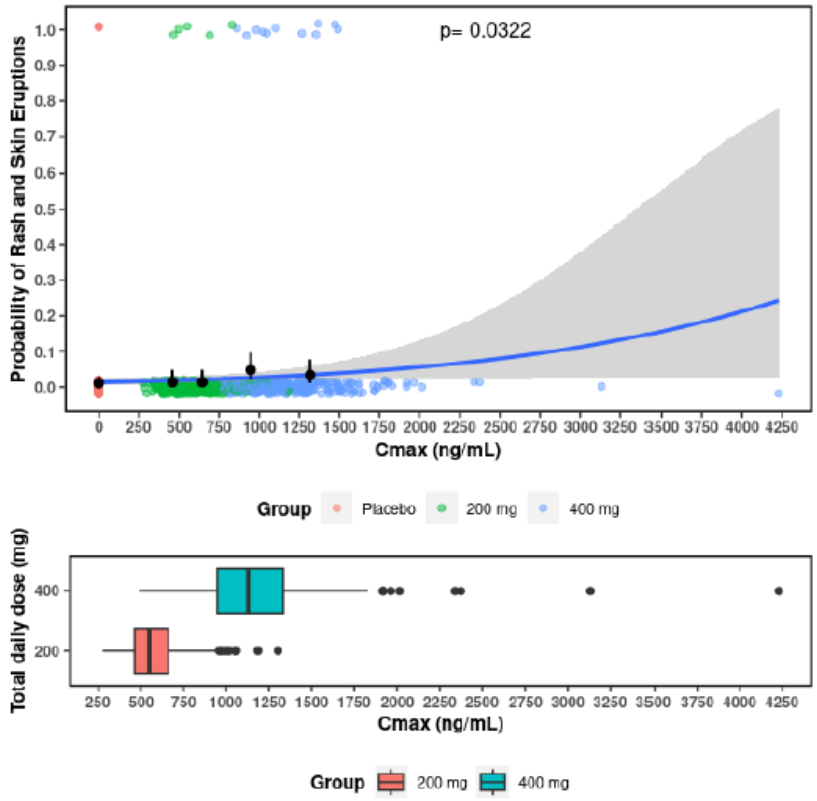
Exposure-Response (ER) Analyses

ER analyses were conducted for both efficacy and safety based on data collected from Study 13 and Study 14. A total of 829 subjects were included in the exposure-efficacy analysis with 285 subjects on placebo, 272 on 200 mg TDD (100 mg twice daily) and 272 on 400 mg TDD (200 mg twice daily) of centanafadine twice-daily tablet. A total of 6,127 AISRS total score observations were recorded in the double-blind period. A total of 876 subjects were included in the exposure-safety analysis, with 290 on placebo, 294 on 200 mg TDD and 292 on 400 mg TDD of centanafadine twice-daily tablet. The measures of exposure (average plasma concentration at steady state [Cavg], maximum plasma concentration at steady state [Cmax] and minimum plasma concentration at steady state [Cmin]) were derived from the final population PK model for centanafadine twice-daily tablets.

For efficacy, the longitudinal trend in AISRS total score was characterized by a disease drug model where a linear function was used to capture worsening of AISRS total score, and a placebo-response model with a binary on/off treatment effect was used to describe the improvement in AISRS total score. The on/off treatment effect model was chosen over the Cavg and Cmin effects models based on its superior ability at describing the data by estimating plausible and interpretable parameters, maintaining numerical stability, and offering robust fits across various profiles, which suggested no ER within the treated subjects.

For safety, logistic regression and time-to-event analyses were conducted for each safety outcome, including rash and skin eruptions, insomnia, and somnolence. Neither the logistic regression analyses nor the time-to-event analyses using Cox proportional hazards models identified a statistically significant association ($p \geq 0.05$) between centanafadine exposure metrics and somnolence. However, both the logistic regression and time-to-event analyses identified Cmax as a statistically significant predictor ($p < 0.05$) for rash and skin eruptions (Figure 45) and for insomnia (Figure 46). Cavg and Cmin were not correlated with any safety outcomes. Based on the logistic regression analysis, the predicted probabilities of rash and skin eruptions were 1.29%, 1.94%, and 2.98% for subjects treated with placebo (Cmax = 0 ng/mL), 200 mg TDD (median Cmax = 546 ng/mL), and 400 mg TDD (median Cmax = 1127 ng/mL) of centanafadine twice-daily tablets, respectively. The corresponding predicted probabilities of insomnia were 3.47%, 4.64%, and 6.27%, respectively.

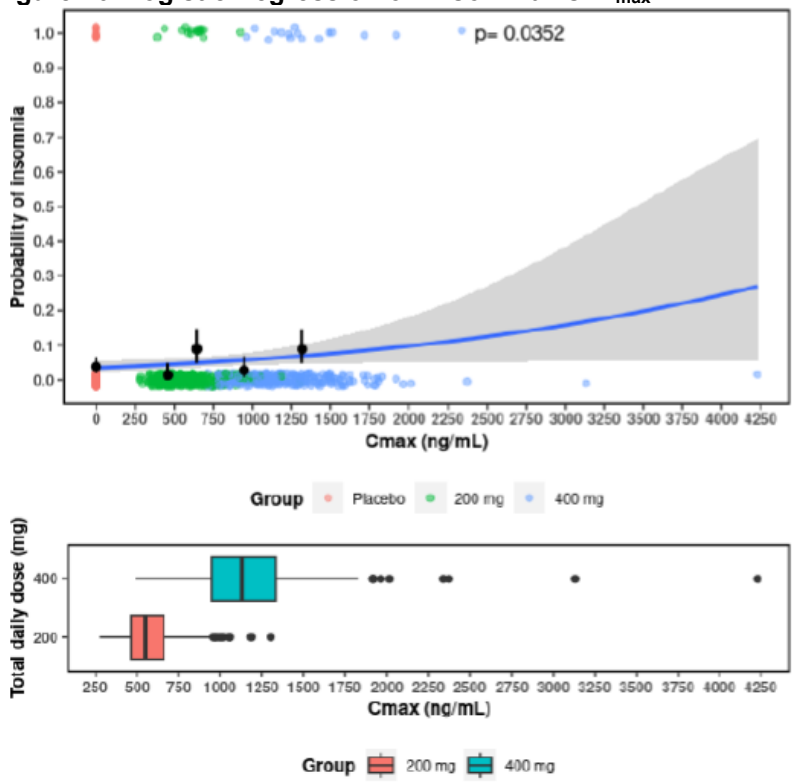
Figure 45. Logistic Regression on Rash and Skin Eruptions vs. C_{max}



Source: 405-23-202-report-body, Figure 17

The top graph illustrates the logistic regression plot comparing probability of events across Cmax. In this plot, the red, green, and blue points show individual observations for the placebo, 200 mg TDD and 400 mg TDD groups, respectively. The black dots and error bars indicate the mean and 95% confidence intervals of the observed event probability for placebo and each Cmax quartile. The blue line and shaded area correspond to the mean and 95% confidence interval of the predicted event probability. The lower panel presents boxplots for Cmax distribution.

Figure 46. Logistic Regression on Insomnia vs. C_{max}



Source: 405-23-202-report-body, Figure 18

The top graph illustrates the logistic regression plot comparing probability of events across C_{max}. In this plot, the red, green, and blue points show individual observations for the placebo, 200 mg TDD and 400 mg TDD groups, respectively. The black dots and error bars indicate the mean and 95% confidence intervals of the observed event probability for placebo and each C_{max} quartile. The blue line and shaded area correspond to the mean and 95% confidence interval of the predicted event probability. The lower panel presents boxplots for C_{max} distribution.

Overall, the Applicant's exposure-response analyses for efficacy in adults with ADHD appears reasonable. The lack of an apparent ER relationship among treated adult subjects was consistent with the comparable efficacy responses observed between the two studied doses in the pivotal trials. Because limited PK samples were collected from pediatric subjects, an ER analysis for efficacy could not be adequately conducted in the pediatric population. In addition, because the primary efficacy endpoints differed between the adult and pediatric pivotal trials, the ER or dose-response relationships could not be directly compared between pediatric subjects and adults with ADHD.

The proposed ER analyses identified positive relationships between centanafadine PK exposure and the risk of rash/skin eruptions and insomnia. These findings were directionally consistent with the numerical differences observed between the two studied doses in the pivotal trials (Table 91). However, the ER model appeared to numerically underestimate the incidence of rash/skin eruptions in subjects receiving 400 mg TDD of twice-daily tablet and overestimate the

incidence in subjects receiving 200 mg TDD of twice-daily tablet (Table 91). In contrast, the ER model numerically overestimated the incidence of insomnia in subjects receiving either dose of twice-daily tablet (Table 91). Overall, the incidence differences in rash/skin eruptions and insomnia are expected to be relatively small between the proposed 210 mg and 280 mg once-daily ER capsule, based on both model predictions and observed dose-response relationships. Notably, 210 mg once-daily ER capsule is expected to have an incidence rate falling between those observed for 200 mg TDD and 400 mg TDD of twice-daily tablet.

Table 91. Observed Incidence Rate for Certain Safety Outcomes in Studies 405-201-00013 and 405-201-00014

Study	405-201-00013		405-201-00014		Total	
Arm	SR 200 mg	SR 400 mg	SR 200 mg	SR 400 mg	SR 200 mg	SR 400 mg
N	149	149	145	143	294	292
TEAE	64 (43%)	73 (49%)	59 (40.7%)	71 (49.7%)	123 (41.8%)	144 (49.3%)
Severe TEAE	2 (1.3%)	0 (0%)	2 (1.4%)	4 (2.8%)	4 (1.4%)	4 (1.4%)
Discontinuation due to AE	8 (5.4%)	10 (6.7%)	6 (4.1%)	8 (5.6%)	14 (4.8%)	18 (6.2%)
Rash	2 (1.3%)	5 (3.4%)	2 (1.4%)	6 (4.2%)	4 (1.4%)	11 (3.8%)
Insomnia	5 (3.4%)	5 (3.4%)	3 (2.1%)	8 (5.6%)	8 (2.8%)	13 (4.5%)

N (%); SR = twice-daily sustained-release tablet; Doses 200 mg and 400 mg represents total daily dose (i.e., 100 mg and 200 mg twice-daily dose, respectively)
Source: Pharmacometric reviewer's analysis

15.5.1. CSS Appendices

See archived CSS review.

15.5.2. Additional Clinical Outcome Assessment Analyses

None.

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