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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Centanafadine for ADHD Treatment in Children: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND AND OBJECTIVES: Centanafadine (CTN) is a first-in-class norepinephrine, dopamine, serotonin reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder (ADHD). This randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy, safety, and tolerability of CTN vs placebo in children with ADHD.

METHODS: Children aged 6 to 12 years (inclusive) with a primary diagnosis of ADHD were randomized to weight-based low-dose CTN, weight-based high-dose CTN, or placebo once daily for 6 weeks. The primary endpoint was the change from baseline in the ADHD Rating Scale, version 5 (ADHD-RS-5) symptoms total raw score at week 6.

RESULTS: Of 480 participants randomized (low-dose CTN, n = 154; high-dose CTN, n = 162; placebo, n = 164), 457 received at least 1 dose of study drug and 367 (76%) completed the trial. At week 6, improvements in ADHD-RS-5 symptoms total raw score were significantly greater with high-dose CTN than with placebo (–16.3 [1.2] vs –10.8 [1.2], $P < .001$). High-dose CTN showed separation from placebo as early as week 1, the first postbaseline time point, with the effect maintained throughout the study period. Low-dose CTN did not show statistical significance in the primary endpoint. Treatment-emergent adverse events (TEAEs) occurred in 52/147 (35%) participants in the low-dose CTN group, 61/157 (39%) in the high-dose CTN group, and 39/153 (25%) in the placebo group. The most common TEAEs were decreased appetite (23/457 [5%]), rash (14/457 [3%]), and vomiting (13/457 [3%]). All TEAEs were of mild or moderate severity.

CONCLUSIONS: High-dose CTN was efficacious for treatment of ADHD in children. Both CTN doses were safe and well tolerated.

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Dr Ward conceptualized and designed the study, supervised data collection, and conducted the analysis and data interpretation. Dr Wilens conceptualized and designed the study and assisted with the interpretation of findings. Ms Jin performed data analyses and interpretation of results. Dr Turkoglu designed the study, supervised data collection, and assisted with the interpretation of findings. Dr Skubiak supervised data collection and assisted with the interpretation of findings. Dr Childress conceptualized and designed the study, performed and supervised data collection, conducted the analysis, enrolled participants, and assisted with the interpretation of findings. All authors had access to the full data presented here. All authors critically reviewed and/or revised the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. To submit inquiries related to Otsuka clinical research or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, (Continued)

WHAT'S KNOWN ON THIS SUBJECT: Centanafadine (CTN) is an investigational norepinephrine, dopamine, serotonin reuptake inhibitor that had demonstrated efficacy, safety, and tolerability in adults with attention-deficit/hyperactivity disorder (ADHD) at sustained-release, daily doses of 200 or 400 mg.

WHAT THIS STUDY ADDS: Once-daily doses of CTN resulting in plasma levels equivalent to the 400-mg daily adult dose improved ADHD symptoms in children aged 6 to 12 years with ADHD and were safe and well tolerated in this population.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects ~7.6% of children globally[1] and is a leading cause of childhood disability.[2] ADHD, characterized by persistent symptoms of inattention and hyperactivity/impulsivity,[3,4] can interfere with functioning and/or development.[5] Although psychoeducation and behavioral management can improve symptoms and functioning in children living with ADHD,[6–8] not all children respond to or tolerate currently available pharmacologic options.[9] Psychostimulants are recommended as first-line or accompaniments to nonpharmacologic approaches[8,10–12]; however, side effects (eg, appetite suppression, insomnia, nausea) and concerns on growth and adverse cardiovascular effects prohibit use in some children.[8] Nonstimulants (atomoxetine, guanfacine, clonidine) are generally less effective than stimulants and typically reserved for patients in whom stimulant medications are not effective/poorly tolerated or in cases of comorbidity.[6–8] These pharmacologic interventions are believed to exert their effects by enhancing dopamine and norepinephrine activity.[12]

Although the effects of dopamine and norepinephrine are well recognized in the neurobiology of ADHD, the role of serotonin is still emerging. Serotonin is a modulator of many neuropsychological processes[13] and is involved with different functions and behaviors relevant to ADHD including attention, impulsivity, hyperactivity, emotional regulation, and executive function. Due to this, serotonin and its receptor system are thought to contribute to the neurobiology of ADHD alongside dopamine and norepinephrine.[14,15] Centanafadine (CTN) is a norepinephrine, dopamine, serotonin reuptake inhibitor (NDSRI)[16,17] in development for the treatment of ADHD in adults, children, and adolescents. Studies completed in adults with ADHD established the efficacy, safety, and tolerability of sustained-release, once-daily CTN 200 or 400 mg.[18,19] The objective of this trial was to evaluate the efficacy, safety, and tolerability of once-daily, extended-release low- or high-dose CTN vs placebo in the treatment of children aged 6 to 12 years with ADHD. Our aim was to evaluate the change in ADHD symptoms as rated by the ADHD Rating Scale, version 5 (ADHD-RS-5) symptoms total raw score after 6 weeks of CTN treatment compared with placebo with the hypothesis that CTN would be more effective.

Methods

Study Design

This phase 3, randomized, double-blind, placebo-controlled trial was conducted at 58 sites (57 in the United States, 1 in Canada) and was completed in compliance with the study protocol, US Food and Drug Administration regulations, International Council for Harmonisation Good Clinical Practice Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. The protocol, amendments, and informed consent form were reviewed/approved by the governing institutional review board or independent ethics committee for each investigational site/country; at screening, written informed consent was obtained from all parents/legal guardians and assent from participants older than 7 years (in line with the requirement of the central institutional review board). The trial was ~11 weeks in duration, comprising a less-than-or-equal-to-4-week screening period, a 6-week double-blind treatment period, and a 7 (+2)-day follow-up period (Supplemental Figure 1). Participants were separated into 2 cohorts based on age, 6 to 12 years and 4 to 5 years (inclusive), with the 6- to 12-year-old cohort initiating first. An additional Independent Data Monitoring Committee meeting occurred to review safety data once at least 20 CTN-treated children aged 6 to 12 years completed 4 weeks of treatment and prior to the start of enrollment of children aged 4 to 5 years. The 4- to 5-year-old cohort began once sufficient supportive data were collected. This cohort is ongoing and will be analyzed/reported separately.

Participants taking ADHD medications at screening underwent a washout period. After, if a participant still tested positive for ADHD medications (methylphenidate or amphetamine; nonstimulants were not tested), they were considered a screening fail and not permitted to rescreen. The first informed consent form was signed July 1, 2022, and the last visit for the last participant of the 6- to 12-year-old cohort was August 18, 2023. This trial is registered at ClinicalTrials.gov (NCT05428033).

Participants

Eligible participants were children aged 6 to 12 years (inclusive) with a primary diagnosis of ADHD based on *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) criteria[5] as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[20] All participants required a rating of greater than or equal to 4 (moderately ill) on the Clinical Global Impression of Severity, modified to address the severity of ADHD (CGI-S-ADHD) and a minimum symptoms total raw score of greater than or equal to 28 on the ADHD-RS-5 at baseline.[21]

Children with a comorbid diagnosis of Tourette syndrome, panic disorder, conduct disorder, psychosis, posttraumatic stress disorder, bipolar disorder, autism spectrum disorder, or major depressive disorder (with current major depressive episode) were excluded. Also excluded were those with generalized anxiety disorder, oppositional defiant disorder, or obsessive-compulsive disorder severe enough to interfere with trial procedures (determined by the MINI-KID). A complete list of inclusion/exclusion criteria is provided in Supplemental Table 1.

For the sponsor, race and ethnicity are collected in all trials to define baseline characteristics of participants; this

information is not required. In this trial, race was self-reported with categories consistent with the US Census, including white, Black/African, American Indian/Alaska Native, Asian, Native Hawaiian/other Pacific Islander, or other. The "other" category was used for participants who did not self-identify with any category and/or identified with more than 1 category. Race and ethnicity are considered social constructs and not genetic/biological categories.

Randomization and Masking

Participants were randomized 1:1:1 to weight-based, once-daily, extended-release low-dose CTN, high-dose CTN, or placebo. The sponsor generated the allocation sequence, and the study sites enrolled participants. The participants who met eligibility criteria were assigned to their groups by the Interactive Response Technology system stratified by study site and age group. Due to the ongoing trial at the time of writing, block size cannot be disclosed in this publication.

Participants, site personnel, principal investigator, and all sponsor staff were blinded (ie, everyone administering the intervention and assessing the outcomes). Only the Independent Data Monitoring Committee was unblinded (ie, they reviewed the safety of the ongoing trial). The blind was not broken in this study.

Treatments

CTN once-daily, extended-release capsules (41.1 mg, 82.2 mg, and 164.4 mg) or matching placebo capsules were administered as intact capsules or capsule contents sprinkled on 1 tablespoon of applesauce. There was no initial titration, as safety and tolerability data from the adult trials indicated that a titration is not necessary. Study drugs were administered once daily for 6 weeks, with less than or equal to 240 mL of water at approximately the same time each morning. Weight-based doses were calculated to match exposures observed in adults treated with CTN sustained-release tablets 200 mg or 400 mg daily. Low-dose CTN was defined as 41.1 mg, 82.2 mg, 123.3 mg, and 164.4 mg in children weighing less than 20 kg, 20 to less than 35 kg, 35 to 50 kg, and more than 50 kg, respectively. High-dose CTN was defined as 82.2 mg, 164.4 mg, 246.6 mg, and 328.8 mg in children weighing less than 20 kg, 20 to less than 35 kg, 35 to 50 kg, and more than 50 kg, respectively.

Outcomes

Efficacy Assessments

The primary efficacy endpoint was mean change from baseline in ADHD-RS-5 symptoms total raw score at week 6.[21] Key secondary efficacy endpoints were change from baseline in the CGI-S-ADHD[22] and change from baseline in the Conners 3-Parent Short content scale T-scores at week 6 (content scales included Inattention, Hyperactivity/Impulsivity, Defiance/Aggression, and Executive Functioning).[23]

Secondary endpoints were percentage of responders up to week 6, with response defined by reduction in ADHD-RS-5 (≥30%, ≥40%, and ≥50% improvement of ADHD symptoms) and/or a Clinical Global Impression of Change, modified to address ADHD (CGI-C-ADHD) score of 1 (very much improved) or 2 (much improved) up to week 6. A post hoc analysis evaluated the percentage of participants with a clinically meaningful within-patient change in ADHD-RS-5 symptoms total raw score (≥18-point reduction [data on file]) at week 6. Details on these scales and additional efficacy endpoints are in the Supplemental Methods section.

Safety Assessments

Safety assessments included adverse event (AE) monitoring, clinical laboratory testing, physical examination, vital signs measurement, and electrocardiograms. Suicidality was monitored using the Columbia-Suicide Severity Rating Scale.[24] Assessment of withdrawal was performed at week 6 and throughout the safety follow-up period (1, 2, 3, and 7 days following the last dose of study medication) using questionnaires derived from the Study Medication Withdrawal Questionnaire used in the adult CTN study,[25] modified to obtain both participant and caregiver input.

Data Collection and Management

Trial sites were responsible for collecting and reporting data, including some collected data provided directly from caregivers. Additional details are in the Supplemental Methods.

Statistical Analysis

Sample Size Considerations

A sample size of 405 evaluable children (135/treatment arm) was selected to yield greater than or equal to 90% power to detect the treatment effects at a 2-tailed significance level of .05 (assuming a treatment difference of 4 points with an SD of 10 in the mean change from baseline to the week 6 visit in the ADHD-RS-5 symptoms total raw score in either CTN dose-group compared with placebo). The selected sample size provided greater than or equal to 96% power at a 2-sided alpha level of .05 to detect the average effect of low-dose and high-dose CTN compared with placebo.

Randomization of 450 children (150/treatment arm) was targeted to allow for less than or equal to 10% nonevaluable participants in the double-blind treatment period. To ensure 405 evaluable participants, the number of nonevaluable participants was monitored in a blinded manner on an ongoing basis during the trial.

Details on analyses populations are in the Supplemental Methods.

Endpoint Analyses

Primary and key secondary efficacy endpoints for low-dose and high-dose CTN vs placebo were analyzed using a mixed model for repeated measures (MMRM), with trial site, treatment group, visit, and treatment group-by-visit interaction as factors and baseline-by-visit interaction as a covariate. Each MMRM used an "unstructured" covariance.

Percentage of responders and percentage of participants meeting the threshold (≥18 point reduction) of clinically meaningful within-patient change in ADHD-RS-5 symptoms total raw score at week 6 were evaluated using the Cochran-Mantel-Haenszel general association test, controlling for trial site, in the last observation carried forward analysis set.

To control the overall experiment-wise type I error at the .05 level, a global test of the average effect of both CTN groups was conducted, then individual comparison of low-dose CTN or high-dose CTN with placebo was performed, in a parallel way, if the global test was statistically significant. The fixed-sequence testing approach was planned for key secondary efficacy endpoints after both the global test and the 2 individual comparisons were significant for the primary efficacy endpoint at an alpha level of .05.

Because low-dose CTN did not demonstrate a statistically significant effect on the primary endpoint, all other *P* values were not controlled for multiplicity. For other prespecified outcomes, nominal *P* values are provided.

All analyses were conducted using SAS software (SAS Institute) Version 9.4 and SAS/STAT 15.2.

Results

Altogether, 480 children were randomized: 154 to low-dose CTN, 162 to high-dose CTN, and 164 to placebo; 457 (95%) received at least 1 dose of study drug and 367 (76%) completed the study (Figure 1). Mean age across treatment groups was 9.2 years, and mean body mass index was 20.1 kg/m^2. There were more male (58%) than female (42%) children, and 65% of participants were white. The mean (SD) baseline ADHD-RS-5 symptoms total raw score was 43.1 (6.7). Of participants in this trial, 47.3% (216/457; safety analysis set) used more than 1 ADHD medication and 26.0% (125/480; randomized analysis set) previously used a stimulant. Demographic and baseline clinical characteristics were generally similar across treatment groups (Table 1).

At week 6, mean (SE) changes from baseline in the ADHD-RS-5 symptoms total raw score were −13.5 (1.2), −16.3 (1.2), and −10.8 (1.2) for low-dose CTN, high-dose CTN, and placebo groups, respectively (Figure 2A). Mean (SE) change from baseline in ADHD-RS-5 total raw score vs placebo at week 6 was statistically significant for high-dose CTN ($P < .001$), but not for low-dose CTN (mean difference: −2.7; 95% CI, −6.0 to 0.5; $P = .10$). High-dose CTN showed separation from placebo as early as week 1, the first postbaseline time point, with the effect maintained throughout the study. Improvements were observed on the ADHD-RS-5 inattention and hyperactivity/impulsivity subscales (Supplemental Table 2).

At week 6, the mean (SE) changes from baseline in CGI-S-ADHD were −1.1 (0.1; $P = .14$ vs placebo), −1.1 (0.1; $P = .07$ vs placebo), and −0.9 (0.1) for the low-dose CTN, high-dose CTN, and placebo groups, respectively (Figure 3; Supplemental Table 2). At week 6, significant improvements in ADHD symptoms of inattention (mean difference: −5.5; 95% CI, −8.4 to −2.6; $P < .001$), hyperactivity/impulsivity (mean difference: −4.6; 95% CI, −7.5 to −1.7; $P = .002$), and executive functioning (mean difference: −4.6; 95% CI, −7.5 to −1.6; $P = .003$) were observed for high-dose CTN vs placebo on the Conners 3-Parent Short content scales (Figure 2B).

Up to week 6, the percentage of participants with greater than or equal to 30%, greater than or equal to 40%, or greater than or equal to 50% improvement on the ADHD-RS-5 symptoms total raw score and percentage of participants with a CGI-C-ADHD score of 1 or 2 were significantly greater ($P < .05$) for high-dose CTN vs placebo (Supplemental Figure 2). The proportion of participants at week 6 that met the clinically meaningful within-patient change threshold for ADHD-RS-5 symptoms total raw score was 34% for low-dose CTN, 34% for high-dose CTN, and 23% for the placebo group ($P < .05$ for both doses vs placebo) (Supplemental Figure 3).

Safety and Tolerability

A total of 457 children received at least 1 dose of study treatment and were included in the safety analysis set. Durations of exposure were 5351 days (low-dose CTN), 5554 days (high-dose CTN), and 5591 days (placebo). Treatment-emergent adverse events (TEAEs) occurred in 52/147 (35%) for the low-dose CTN, 61/157 (39%) for high-dose CTN, and 39/153 (25%) for placebo; TEAEs occurring in greater than or equal to 2% of children in either CTN group and greater than placebo are presented in Table 2.

The most common TEAEs were decreased appetite (23/457 [5%]), rash (14/457 [3%]), and vomiting (13/457 [3%]). Decreased appetite and rash each occurred in greater than or equal to 5% in any CTN group and at a greater incidence than placebo. All TEAEs were of mild/moderate severity, except 1 severe TEAE (appendicitis) in the low-dose CTN group. This event resolved and was deemed as serious and not related to CTN.

A total of 16 children discontinued study medication due to an AE, 4 (3%) in the low-dose CTN group, 10 (6%) in the high-dose CTN group, and 2 (1%) in the placebo group. Out of 457 participants, 21 (5%) were less than 80% compliant with taking the study drug(s), 49 (11%) were greater than or equal to 80% to less than 90% compliant, 150 (33%) were greater than or equal to 90% to less than 100% compliant, and 237 (52%) were

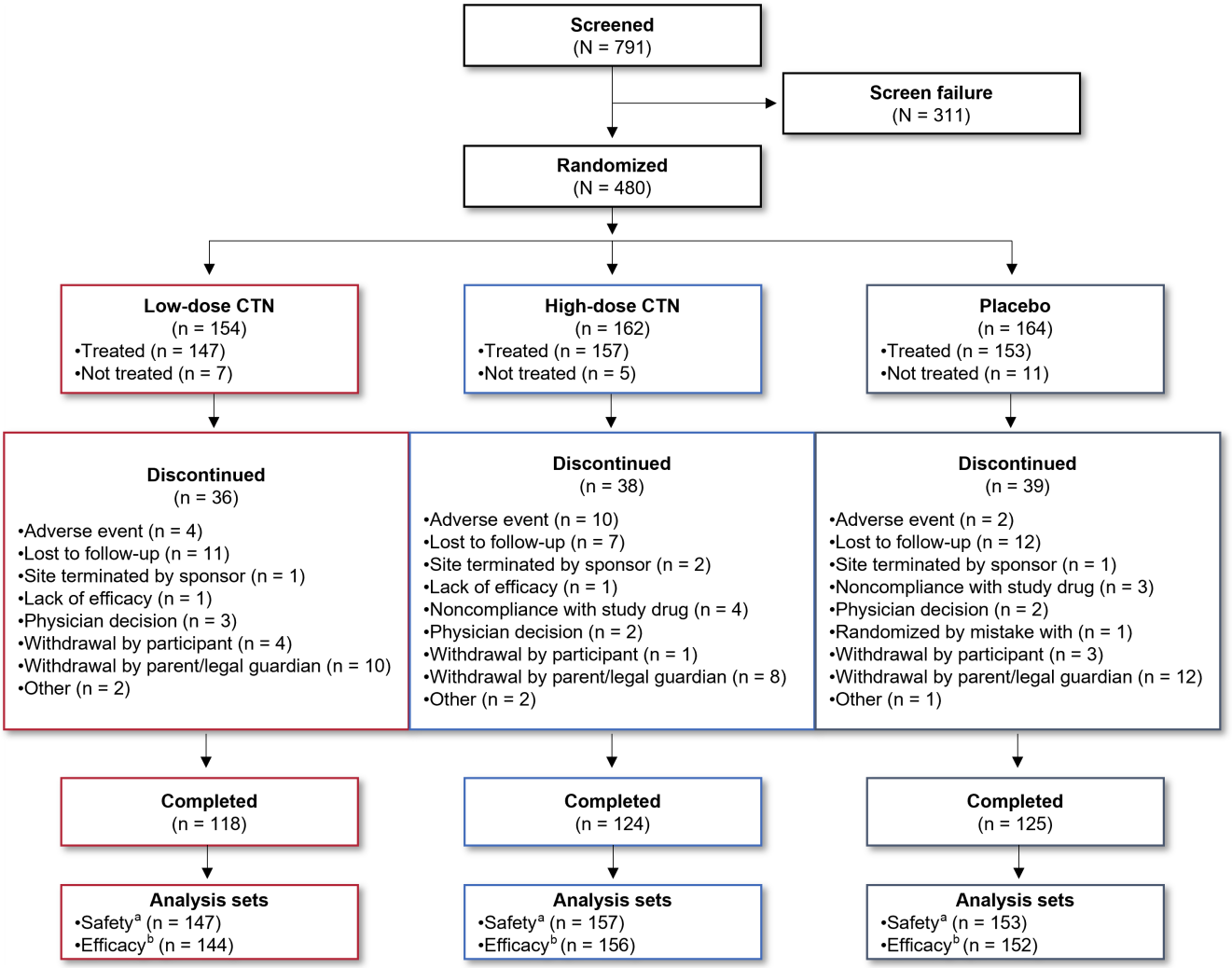

FIGURE 1. Participant disposition.
[a]Participants who received at least 1 dose of study medication.
[b]Participants who received at least 1 dose of study medication in the double-blind treatment period and had both baseline and at least 1 postrandomization ADHD-RS-5 symptoms total raw score during the double-blind treatment period.
Abbreviations: ADHD-RS-5, Attention-Deficit/Hyperactivity Disorder Rating Scale, version 5; CTN, centanafadine.

greater than or equal to 100% to less than 110% compliant. Serious events occurred in 3 (2%) children in the low-dose CTN group (suicide attempt [n = 1], panic attack [n = 1], and appendicitis [n = 1]) and 1 (1%) in the high-dose CTN group (suicide attempt). The AE profile indicated a low likelihood of abuse. No serious events were deemed by the investigator to be related to study treatment, and no deaths were reported.

Discussion

This 6-week randomized, double-blind, placebo-controlled trial demonstrated the short-term efficacy, safety, and tolerability of CTN in children aged 6 to 12 years with ADHD. High-dose CTN demonstrated a statistically significant difference at week 6 in the primary endpoint (change from baseline in ADHD-RS-5 symptoms total raw score) vs placebo, with separation from placebo as early as week 1, and the effect maintained throughout the full 6-week treatment. Similarly, the response rate of greater than or equal to 30% improvement on the ADHD-RS-5 symptoms total raw score was significantly greater for high-dose CTN compared with placebo. The Conners 3-Parent Short data highlight that when compared with placebo at week 6, high-dose CTN had an impact not only on the core symptoms of ADHD but also on executive functioning, suggesting that CTN may be efficacious in treating associated features of ADHD. In this trial, 47% of participants had previously used more than 1 ADHD medication and 26% had previously used a stimulant,

TABLE 1. Baseline Demographic and Clinical Characteristics

	Low-Dose CTN N = 154	High-Dose CTN N = 162	Placebo N = 164
Age, mean (min, max), y	9.3 (6, 12)	9.1 (6, 12)	9.2 (6, 12)
Sex at birth, n (%)			
Male	87 (56)	87 (54)	106 (65)
Female	67 (44)	75 (46)	58 (35)
Weight, mean (SD), kg	41.9 (15.4)	40.8 (15.2)	40.8 (16.0)
BMI, mean (SD), kg/m^2	20.4 (4.8)	20.3 (4.9)	19.8 (4.5)
Race, n (%)[a]			
White	102 (66)	105 (65)	105 (64)
Black	40 (26)	47 (29)	44 (27)
American Indian or Alaska Native	2 (1)	1 (1)	0
Asian	1 (1)	2 (1)	2 (1)
Native Hawaiian or Other Pacific Islander	0	0	2 (1)
Other	9 (6)	7 (4)	11 (7)
Tanner stage, n (%)			
Stage 1 (preadolescent)	86 (55.8)	99 (61.1)	92 (56.1)
Stage 2	36 (23.4)	37 (22.8)	40 (24.4)
Stage 3	23 (14.9)	21 (13.0)	23 (14.0)
Stage 4	9 (5.8)	5 (3.1)	8 (4.9)
Stage 5	0	0	1 (0.6)
Used 1 or more ADHD medication, n (%)[b]	69 (46.9)	70 (44.6)	77 (50.3)
Number of previous ADHD medications, mean (SD)	1.4 (0.7)	1.7 (1.5)	1.7 (0.8)
Previously took stimulants, n (%)			
Yes	39 (25.3)	40 (24.7)	46 (28.0)
No	115 (74.7)	122 (75.3)	118 (72.0)
ADHD-RS-5 total score, mean (SD)	43.1 (6.8)	42.9 (6.6)	43.2 (6.8)
CGI-S-ADHD, mean (SD)	4.9 (0.7)	4.8 (0.7)	4.9 (0.7)
Conners 3-Parent Short, mean (SD)[c]			
Inattention	84.8 (7.7)	83.1 (9.4)	83.5 (9.0)
Hyperactivity/impulsivity	84.5 (10.1)	83.5 (10.5)	85.0 (8.9)
Defiance/aggression	65.4 (17.2)	64.9 (16.9)	68.2 (16.9)
Executive function	78.9 (10.9)	78.1 (11.5)	78.8 (11.0)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-5, ADHD Rating Scale, version 5; BMI, body mass index; CGI-S-ADHD, Clinical Global Impression of Severity, modified to address the severity of ADHD; CTN, centanafadine; max, maximum; min, minimum.

[a] Race was self-reported.

[b] n = 147, 157, and 153 for low-dose CTN, high-dose CTN, and placebo groups, respectively.

[c] n = 147, 156, and 161 for low-dose CTN, high-dose CTN, and placebo groups, respectively.

suggesting that CTN is safe and effective in children with ADHD and previous pharmacological treatment and not only in medication-naive children. Results in this trial were similar to another trial of CTN in adolescents, which demonstrated efficacy with high-dose CTN and safety and tolerability with both doses.[26]

The placebo response in the current trial compares to the average placebo response across other clinical trials that investigated pharmacological interventions for ADHD, in which there was a 23.1% reduction in symptoms with placebo when compared with baseline.[27] In this current trial, at week 6, 34% of participants in the high-dose CTN group met the clinically meaningful within-patient change threshold for the ADHD-RS-5 symptoms total raw score compared with 23% for the placebo group. This 11%-point difference represents a ~50% increase in the likelihood of response with CTN treatment (relative risk: 1.48).

Although this was not a head-to-head study, similar to stimulant and nonstimulant medications for ADHD treatment, significant improvements in ADHD symptom severity were observed.[28] Matching-adjusted indirect comparison (MAIC) analyses using data from the adult CTN clinical trials compared CTN's efficacy and safety with already established ADHD treatments[29] and showed that the efficacy of CTN was lower than with lisdexamfetamine but comparable to methylphenidate. CTN had a significantly better short-term safety profile than lisdexamfetamine, and similarly, CTN showed significantly lower incidence of several AEs when compared with methylphenidate.[29] MAIC studies have yet to be performed with pediatric clinical trial data.

Whereas the roles of dopamine and norepinephrine in the neurobiology of ADHD are more defined, the role of serotonin in the neurobiology and treatment of ADHD is emerging. Research indicates that dysregulation of dopamine, norepinephrine, and serotonin contributes to the core symptoms of ADHD and associated features like aggression, executive function deficits, emotional dysregulation, and frequently co-occurring conditions like depression and anxiety.[30] Serotonin is a well-established modulator in a wide range of neuropsychological processes.[13] Depletion of serotonin in the orbitofrontal cortex results in deficits in inhibition and emotional regulation, and reduced serotonin in the striatum can lead to reduced impulse control.[31] Genetic changes in the serotonin transporter (5-HTT) have been associated with ADHD,[31,32] as well as genetic changes in serotonin receptors (5-HT$_{1B}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{5A}$),[31] all of which affect concentrations of serotonin in the brain. CTN is an NDSRI that is thought to treat ADHD symptoms by reducing the reuptake of norepinephrine, dopamine, and serotonin via interaction with each of their transporters with varying affinities (half-maximal inhibitory concentration for each transporter: norepinephrine = 6 nM, dopamine = 38 nM, and serotonin = 83 nM)[16]; however, the clinical impact of the broader mechanism of action of CTN relative to currently established ADHD agents remains to be fully elucidated.

In this trial, both doses of CTN were well tolerated, with serious events and discontinuation due to TEAEs being

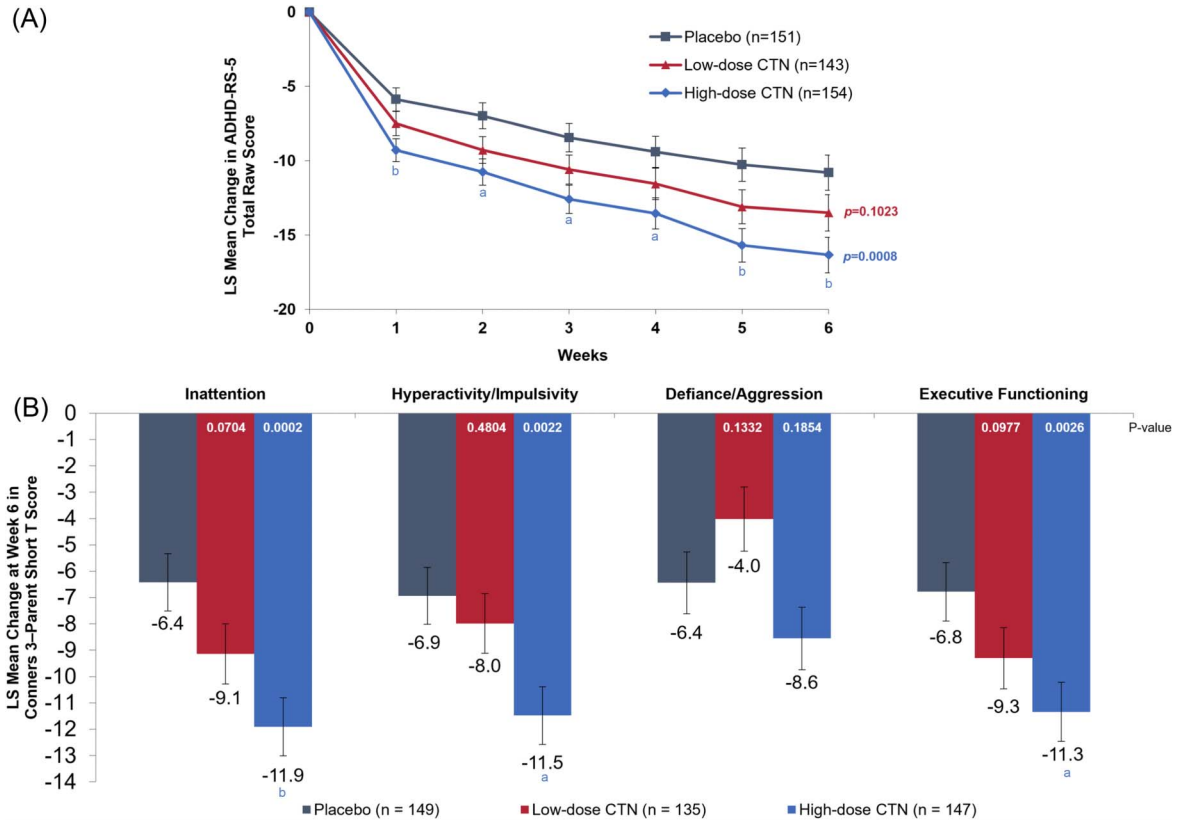

FIGURE 2. Mean change from baseline in ADHD-RS-5 symptoms total raw score over weeks 1 to 6 (A), and Conners 3-Parent Short Inattention, Hyperactivity/Impulsivity, Defiance/Aggression, and Executive Functioning content scale T-scores at week 6 (B). Mean change is derived from MMRM. Error bars are standard error of the means.

[a]*P* value <.01.

[b]*P* value <.001.

Abbreviations: ADHD-RS-5, Attention-Deficit/Hyperactivity Disorder Rating Scale, version 5; CTN, centanafadine; LS, least squares; MMRM, mixed model for repeated measures.

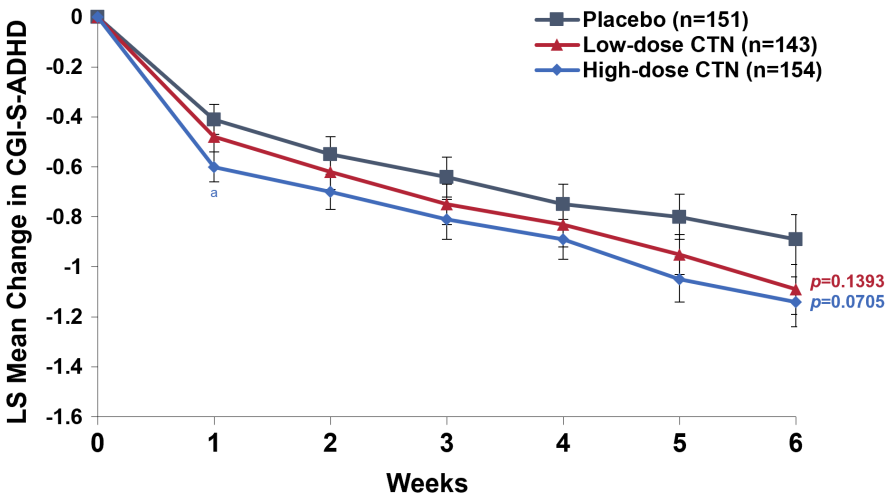

FIGURE 3. Mean change from baseline in CGI-S-ADHD over weeks 1 to 6.

[a]*P* < .05 vs placebo.

Abbreviations: CTN, centanafadine; CGI-S-ADHD, Clinical Global Impression of Severity, modified to address the severity of ADHD.

TABLE 2. Summary of TEAEs

	Low-Dose CTN N = 147	High-Dose CTN N = 157	Placebo N = 153
Participants with any TEAE, n (%)	52 (35)	61 (39)	39 (25)
Participants with serious TEAEs, n (%)	3 (2)	1 (1)	0
Participants with severe TEAEs, n (%)	1 (1)	0	0
Participants discontinued study drug due to an adverse event, n (%)	4 (3)	10 (6)	2 (1)
Death, n (%)	0	0	0
TEAEs occurring in ≥2% of either CTN group and at a greater rate than placebo, n (%)			
Decreased appetite	6 (4)	12 (8)	5 (3)
Rash	5 (3)	9 (6)	0
Vomiting	5 (3)	4 (3)	4 (3)
Upper respiratory tract infection	5 (3)	3 (2)	4 (3)
Fatigue	3 (2)	6 (4)	0
Nausea	3 (2)	5 (3)	1 (1)
Upper abdominal pain	1 (1)	6 (4)	2 (1)
Streptococcal pharyngitis	0	5 (3)	3 (2)
Somnolence	3 (2)	2 (1)	2 (1)
Pyrexia	4 (3)	1 (1)	1 (1)
Cough	3 (2)	0	1 (1)

Abbreviations: CTN, centanafadine; TEAE, treatment-emergent adverse event.

uncommon. The most frequently reported potentially CTN-related TEAEs were rash and decreased appetite. Of the 14 incidences of rash, all events resolved and were assessed by the investigator as related to CTN, except for 1 event of rash that was assessed as not related. Most of the rash events were assessed as mild in severity, except for 1 rash and 1 rash maculopapular event that were moderate in severity. Similar rates of appetite suppression and rash were reported in phase 3 clinical trials of CTN in adults.[18] Rates of rash observed for methylphenidate[33] and lisdexamfetamine have been reported to be between 2% and 5.7%.[34] Systematic reviews have shown that treatment-related insomnia and appetite suppression can be problematic among children and adolescents receiving methylphenidate or lisdexamfetamine.[35–37] In this current trial, appetite suppression occurred in 4% to 8% of children receiving CTN; insomnia was only reported for 2 participants receiving CTN (1%). Low incidences of insomnia and decreased appetite were observed in phase 3 adult CTN studies (5.8% and 6.0%, respectively).[18]

Trial limitations included the absence of an active comparator, which prevents direct comparisons of safety and efficacy relative to other ADHD treatments. The population studied was restricted by study center locations (North America only) and by the exclusion of many comorbidities, further limiting the generalizability of this study's results. Moreover, the occurrence of distinctive symptoms after initiation of the study drug, such as rash or fatigue, and the process of acquiring consent/assent by participants including comprehensive information about potential AEs had potential to confound blinding. Lastly, the study was short duration; long-term studies are needed to confirm safety, tolerability, and maintenance of effect with continued use.

Conclusion

The NDSRI CTN was found to be safe and well tolerated for the treatment of ADHD in children aged 6 to 12 years. This study found that the high dose was efficacious for the short-term treatment of ADHD in the population studied. Additional long-term studies can be performed to assess long-term safety, tolerability, and efficacy.

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ADHD-RS-5: ADHD Rating Scale, version 5
AE: adverse event
CGI-C-ADHD: Clinical Global Impression of Change, modified to address ADHD
CGI-S-ADHD: Clinical Global Impression of Severity, modified to address the severity of ADHD
CTN: centanafadine
DSM-5: *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)
MAIC: matching-adjusted indirect comparison
MINI-KID: Mini International Neuropsychiatric Interview for Children and Adolescents
MMRM: mixed model for repeated measures
NDSRI: norepinephrine, dopamine, serotonin reuptake inhibitor
TEAE: treatment-emergent adverse event

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