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Centanafadine for Attention-Deficit/Hyperactivity Disorder in Adolescents: A Randomized Clinical Trial

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Objective: This randomized, double-blind, placebo-controlled trial evaluated the efficacy, safety, and tolerability of centanafadine—a norepinephrine, dopamine, serotonin reuptake inhibitor—in the treatment of attention-deficit/hyperactivity disorder (ADHD) in adolescents.

Method: Adolescents (aged 13-17 years, inclusive) with a primary diagnosis of ADHD were randomized to once-daily centanafadine 164.4 mg, 328.8 mg, or placebo for 6 weeks. Dosing was not titrated. The primary endpoint was change from baseline in the ADHD Rating Scale, version 5 (ADHD-RS-5) symptoms total raw score at week 6. This trial is registered with ClinicalTrials.gov (NCT05257265).

Results: Of 459 participants (centanafadine 164.4 mg, n = 155; 328.8 mg, n = 155; placebo, n = 149), 451 received ≥1 dose of study drug and 371 (80.8%) completed the trial. At week 6, improvements in ADHD-RS-5 symptoms total raw score were significantly greater with centanafadine 328.8 mg than with placebo (–18.50 [0.93] vs –14.15 [0.93]; $p = .0006$); centanafadine 164.4 mg did not meet the primary endpoint. Centanafadine 328.8 mg showed separation from placebo at week 1, the first postbaseline timepoint, with the effect maintained throughout the study. Treatment-emergent adverse events (TEAEs) occurred in 48 of 153 (31.4%, 164.4 mg), 76 of 151 (50.3%, 328.8 mg), and 35 of 147 (23.8%, placebo) participants. The most common (≥5% any group) TEAEs were decreased appetite, nausea, headache, and rash. Most TEAEs were of mild or moderate severity; 3 events were severe: liver function test increase (n = 1, 164.4 mg); aggression (n = 1, 164.4 mg); and somnolence (n = 1, placebo).

Conclusion: Centanafadine 328.8 mg was efficacious for ADHD treatment in adolescents. Both doses were generally safe and well tolerated.

Plain language summary: Centanafadine is a drug under investigation for the treatment of attention-deficit/hyperactivity disorder (ADHD). This clinical trial tested how well centanafadine worked in treating symptoms of ADHD in adolescents (ages 13 to 17 years) when compared to placebo. A total of 459 adolescents participated in this clinical trial. Adolescents treated with higher-dose centanafadine (328.8 mg) had greater improvement in ADHD symptoms at 6 weeks compared to those treated with placebo or centafadine at lower dose (164.4 mg). Centanafadine was generally safe and generally well tolerated in adolescents.

Clinical Trial Registration Information: A Trial of Centanafadine Efficacy and Safety in Adolescents With Attention-Deficit/Hyperactivity Disorder; https://clinicaltrials.gov/study/NCT05257265

Diversity & Inclusion Statement: We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. We worked to ensure that the study questionnaires were prepared in an inclusive way. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. One or more of the authors of this paper self-identifies as living with a disability. We actively worked to promote sex and gender balance in our author group. The author list of this paper includes contributors from the location and/or community where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

Key words: attention-deficit/hyperactivity disorder; centanafadine; efficacy; safety; adolescent

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common pediatric neurodevelopmental disorders, affecting ~5.6% of adolescents globally,[1] and is a leading cause of disability in adolescents worldwide.[2] The disorder is characterized by persistent symptoms of inattention and hyperactivity/impulsivity that can interfere with functioning or development,[3,4] with more than 50% of children or adolescents diagnosed with ADHD continuing to have significant and impairing symptoms in adult life.[5,6]

As children age into adolescence and begin to gain more autonomy, treatment adherence and/or diversion can arise, creating challenges for treating ADHD in this age group.[7] Some reasons for individuals with ADHD to choose not to take their medication can be side effects and/or tolerability. In previous stimulant trials, school-aged children have reported that they "stopped feeling like him/herself" as a reason to discontinue a medication.[8] Additional studies for newer treatments with improved tolerability and fewer side effects that target a wide range of

symptoms could help increase adherence in the adolescent population with ADHD.

Psychostimulants are commonly prescribed as first-line treatments; however, the presence of comorbidities and/or limiting adverse events such as appetite suppression, insomnia, potential stimulant misuse, and adverse cardiovascular effects may preclude their use in some adolescents.[9] Nonstimulants, including atomoxetine, guanfacine, viloxazine XR, and clonidine, are also used for ADHD but appear to be less effective than stimulants for core ADHD symptoms.[9-12] Stimulant medications primarily enhance the activity of both dopamine and norepinephrine, whereas nonstimulant medications act primarily on norepinephrine alone.[13]

Although the neurobiology of ADHD is not fully understood, the effects of dopamine and norepinephrine are well recognized. Emerging data have linked serotonin and its receptor system to ADHD because of their association with neuropsychological processes and behaviors relevant to ADHD such as attention, impulsivity, hyperactivity, emotional regulation, and executive function.[14,15]

Centanafadine, a norepinephrine, dopamine, and serotonin reuptake inhibitor (NDSRI),[16,17] has demonstrated efficacy, safety, and tolerability in adults with ADHD and is currently in development for the treatment of ADHD in adults, children, and adolescents.[18,19] In 2 randomized, double-blind, placebo-controlled, 6-week trials, the administration of centanafadine sustained-release tablets of 200 or 400 mg total daily dose was associated with significant improvement in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score at the trial endpoint.[18] The objective of this trial was to evaluate the efficacy, safety, and tolerability of centanafadine vs placebo in the treatment of adolescents with ADHD. We hypothesized that centanafadine would be more effective than placebo in the Attention-Deficit/Hyperactivity Disorder Rating Scale, version 5 (ADHD-RS-5) symptoms total raw score after 6 weeks of treatment in adolescents with ADHD.

METHOD

Study Design

This phase 3, randomized, double-blind, placebo-controlled trial was conducted from February 2022 to October 2023 at 48 sites (47 in the United States and 1 site in Canada). The trial was conducted in compliance with the 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 (CIOMS) guidelines, and applicable local laws and regulations. Recruitment methods included searches of sites' databases, centralized patient recruitment campaigns (including online and social media advertisements), and local advertising by the sites (such as local media). All participant facing materials were reviewed and approved by an institutional review board. Prior to study start, the governing institutional review board or independent ethics committee for each investigational site or country reviewed and approved the protocol, any amendments, and the informed consent form. Written informed consent was obtained from all parents/legal guardians prior to screening, and assent from all participants was obtained prior to any trial procedures. Participants/caregivers were not paid for participation but were reimbursed for the cost of travel and meals, with reimbursement amounts fixed per study site. The trial is registered with ClinicalTrials.gov (identifier: NCT0525726).

The trial was ~11 weeks in duration and comprised a ≤4-week screening period (which included a 7- to 28-day washout period), a 6-week double-blind treatment period, and a 7 (+2)–day follow-up period (Figure S1, available online). Participants taking ADHD medications at screening were required to undergo washout. After the allotted washout period, if a participant still tested positive for ADHD medication, they were considered a screening fail, and not permitted to rescreen.

Participants

Eligible participants included adolescents 13 to 17 years of age (inclusive) with a primary diagnosis of ADHD based on *DSM-5* criteria.[20] The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) was used to confirm ADHD diagnosis and to exclude comorbid conditions.[21] To be eligible, at baseline participants required a rating of ≥4 (moderate impairment) on the Clinical Global Impression of Severity scale modified to address ADHD (CGI-S–ADHD)[22] and a minimum symptoms total raw score of ≥28 on the ADHD-RS-5.[23-25]

Participants were excluded if they had a comorbid diagnosis of Tourette syndrome, panic disorder, conduct disorder, psychosis, posttraumatic stress disorder, bipolar disorder, autism spectrum disorder, binge eating disorder, anorexia, or bulimia; had a comorbid diagnosis that was severe enough to interfere with trial conduct/procedures, including generalized anxiety disorder, oppositional defiant disorder (allowed if not the primary focus of treatment), or obsessive-compulsive disorder (allowed if not the primary focus of treatment); or had a comorbid diagnosis of major depression disorder and were in a current major depressive

episode that required treatment within the 3 months prior to screening, or, in investigator's opinion, may worsen or could be expected to require treatment during the course of the trial. Also excluded were participants who in their lifetime did not respond to 2 classes of therapy for ADHD. A complete list of inclusion and exclusion criteria are provided in Table S1 (available online).

Investigators informed participants that normal consumption of caffeine was permitted, and age-appropriate instruction was given to participants to refrain from drinking alcoholic beverages or using illicit drugs (including marijuana) during the trial. The investigator could request a blood or urine drug screen at any time during the trial if there was suspicion of illicit drug use. Alcohol testing was performed at screening via breathalyzer or blood alcohol test. Participants with a positive alcohol test (via breathalyzer or blood) or positive drug screen for illicit drugs (excluding marijuana) were not eligible to be retested or rescreened and were considered a screen failure. Participants who tested positive for marijuana were 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. Participants who tested positive for amphetamine or methylphenidate at baseline were considered a screen failure, and those who tested positive during the trial may have been discontinued.

Regarding potential pregnancy, the investigator (or appropriate site staff) instructed participants on the risk of pregnancy while participating in the trial as well as ensuring that participants understood how pregnancies occur and can be avoided. Urine or serum pregnancy testing for participants as appropriate was performed during the trial. No pregnancies were reported in this trial.

Race and ethnicity were self-reported in this trial to define the baseline characteristics of participants; this information was not required. The categories included American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian/other Pacific Islander, White, or other and are consistent with the categories in the US Census. The "other" race category was used for any participants who did not self-identify with any of the presented categories. Efficacy endpoints analyzed by race and/or ethnicity will be presented in subsequent publications.

Randomization and Masking

Adolescents were randomized 1:1:1 to centanafadine 164.4 mg, centanafadine 328.8 mg, or placebo via a computer-generated randomization system. Randomization was stratified by study site. Treatment was double-blind in which neither the investigator nor the participant had knowledge of the treatment assignment. Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the randomization code during the trial. The bioanalytical laboratory had access to the randomization code as well as any personnel charged with generating and maintaining randomization files, packaging trial medication, and reporting serious adverse events (SAEs) to regulatory agencies.

Treatments

Centanafadine 164.4-mg extended-release, once-daily capsules and matching placebo capsules were used for this study. Doses were calculated to match exposures observed in adults treated with centanafadine sustained-release tablets 200 mg or 400 mg total daily dose.[18,19] This calculation was informed by a review in which 87 of 92 (94.5%) unique products with $\geq$1 adolescent indication concordant with an adult indication had equivalent dosing for adults and adolescent patients.[26] Using the concentration data obtained from the clinical trial in adults,[18] it was determined that 328.8 mg of centanafadine extended release administered as capsules would produce centanafadine exposures similar to 400 mg of the sustained release tablet used in the adult trial. The lower dose of centanafadine was half of the high dose, with exposures matching the 200-mg sustained release tablet used in adult trials. All participants received 2 capsules per day (164.4-mg group: 1 centanafadine 164.4-mg capsule and 1 placebo capsule; 328.8-mg group, 2 centanafadine 164.4-mg capsules; placebo group, 2 placebo capsules). Doses were administered once daily for 6 weeks, without an initial titration period, at approximately the same time each morning with $\leq$240 mL of water as intact capsules or capsule contents sprinkled on 1 tablespoon of applesauce.

Outcomes

The primary efficacy endpoint was the change from baseline in the ADHD-RS-5 symptoms total raw score at week 6.[23] This assessment was done via an investigator interview with an informant. The informant was the same throughout the trial and was either a parent/guardian or caregiver who lived with the participant. Key secondary efficacy endpoints were the change from baseline in CGI-S–ADHD at week 6[22,27] and the change from baseline in Conners 3–Parent Short content scale *T* scores of Inattention, Hyperactivity/Impulsivity, Defiance/Aggression, and Executive Function at week 6.[28]

Other prespecified efficacy endpoints presented here include the percentage of participants who obtained a $\geq$30%, $\geq$40%, or $\geq$50% reduction (improvement) in ADHD-RS-5 symptoms total raw score at week 6, and the

percentage of participants who obtained a Clinical Global Impression of Change scale modified to address ADHD (CGI-C-ADHD) score of 1 (very much improved) or 2 (much improved) at week 6. A post hoc analysis evaluated the percentage of participants who obtained a clinically meaningful within-patient change in ADHD-RS-5 symptoms total raw score (defined as a ≥18-point reduction [data on file]) at week 6. Additional details on the scales used and a list of additional efficacy endpoints can be found in Supplement 1, available online.

In this trial, safety was monitored using standard assessments, which included adverse event monitoring (weekly), clinical laboratory testing (weeks 2 and 6), physical examination (baseline and week 6), vital signs measurement (weekly), and electrocardiography (ECG; weeks 1 and 6). Suicidality was monitored weekly during the trial via the Columbia–Suicide Severity Rating Scale.[29] Withdrawal assessment was performed using the self-report Study Medication Withdrawal Questionnaire–Pediatric (based on a similar questionnaire in adult centanafadine studies[18]) at week 6 and during the safety follow-up period on days 1, 2, 3, and 7 following the last dose of study medication.

Trial sites collected and reported all data, including data provided by caregivers. Additional details on data collection can be found in Supplement 1, available online.

Statistical Approach

Assuming a treatment difference of 4 points with a standard deviation of 10 in the mean change in the ADHD-RS-5 symptoms total raw score (from baseline to week 6) in either centanafadine dose group (164.4 mg or 328.8 mg) compared to the placebo group, a sample size of 405 evaluable adolescents (135 per treatment arm) was selected to provide ≥96% power at a 2-sided alpha level of 0.05 to detect the average effect of centanafadine 164.4 mg or 328.8 mg compared to placebo. To allow for 10% non-evaluable participants in the double-blind treatment period, randomization of 450 adolescents was targeted. To ensure 405 evaluable participants, the number of non-evaluable participants was monitored in a blinded manner on an ongoing basis during the trial.

The safety analysis set comprised all randomized participants who received ≥1 dose of study drug in the double-blind treatment period. The efficacy analyses used data from all participants in the safety analysis set who had a baseline value ≥1 valid postrandomization efficacy evaluation for ADHD-RS-5 in the double-blind treatment period.

The primary efficacy endpoint and key secondary endpoints were analyzed using a mixed-effect model for repeated measures, with trial site, treatment group, visit week, and treatment group-by-visit week interaction as factors, baseline-by-visit week interaction as a covariate, and an "unstructured" variance–covariance structure was used. The percentage of responders and percentage of participants meeting the threshold (≥18-point reduction) for 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.

To control the overall experiment-wise type I error at the 0.05 level, a global test of the average effect of both centanafadine groups was conducted first; then, after the global test was statistically significant, individual comparisons of centanafadine 164.4 mg or 328.8 mg to placebo were performed in a parallel way. 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 0.05.

Because centanafadine 164.4 mg did not demonstrate a statistically significant effect on the primary endpoint, all other p values were not controlled for multiplicity and are considered descriptive. For other prespecified outcomes, nominal p values are provided.

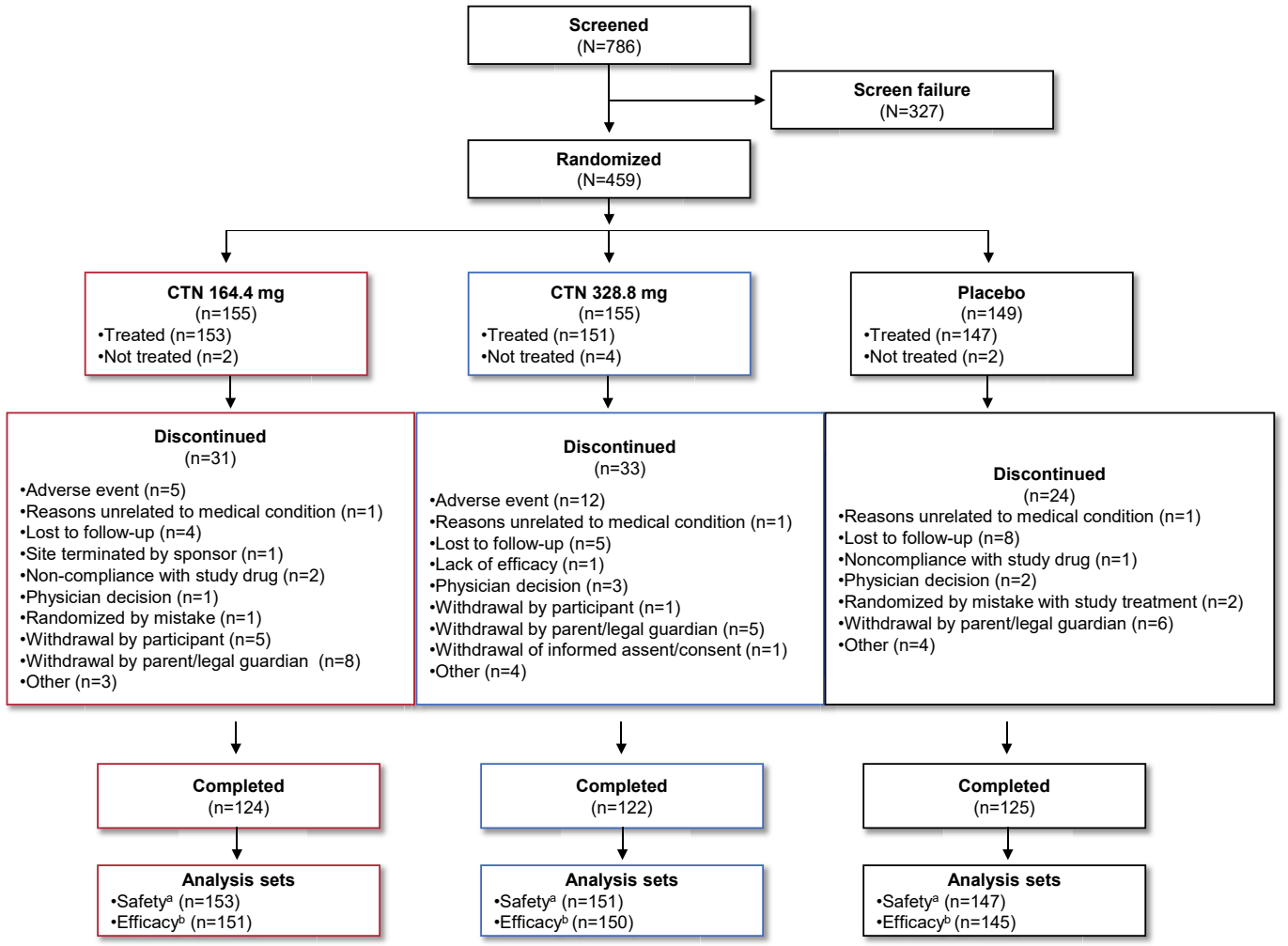
All analyses were conducted using SAS software (SAS Institute) Version 9.4 and SAS/STAT 15.2.

RESULTS

Study population

A total of 459 adolescents were randomized to study treatment (centanafadine 164.4 mg, n = 155; centanafadine 328.8 mg, n = 155; placebo, n = 149); 451 (98.3%) received ≥1 dose of study drug and 371 (80.8%) completed the study. For participants that discontinued, the majority discontinued because of withdrawal by a parent/legal guardian (19 of 459 [4.1%]), an adverse event (17 of 459 [3.7%]), or being lost to follow-up (17 of 459 [3.7%]) (Figure 1). No noticeable differences between those who completed the trial or discontinued were observed for demographic characteristics, primary diagnosis, or baseline severity (Tables S2-S4, available online). The mean (SD) age of all study participants was 14.7 (1.3) years; in the overall population, there were more participants who identified as male than as female (59.3% and 40.7%, respectively), and more than two-thirds (70.4%) of the participants were White. The mean (SD) baseline ADHD-RS-5 symptoms total raw score was 37.5 (6.1), and the mean (SD) GCI-S-ADHD score was 4.5 (0.6), which is considered "moderately ill." Demographic and baseline clinical characteristics were generally similar across

FIGURE 1 Participant Disposition



Note: *ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale, version 5; CTN = centanafadine.*

[a]*Participants who received ≥1 dose of study medication.*

[b]*Participants who received ≥1 dose of study medication in the double-blind treatment period and had both baseline and ≥1 postrandomization ADHD-RS-5 symptoms total raw score during the double-blind treatment period.*

the 3 treatment groups, except that there were more participants that identified as male enrolled in the centanafadine 328.8-mg group than in the centanafadine 164.4-mg and placebo groups, and more Hispanic or Latino participants enrolled in the placebo group than in centanafadine group (Table 1).

Efficacy

At week 6, the mean (SE) changes from baseline in the ADHD-RS-5 symptoms total raw score were –15.5 (0.92), –18.5 (0.93), and –14.2 (0.93) for the centanafadine 164.4-mg, centanafadine 328.8-mg, and placebo groups, respectively (Figure 2A). The change from baseline in ADHD-RS-5 symptoms total raw score vs placebo at week 6 was statistically significant for centanafadine 328.8 mg (p = .0006) but not for centanafadine 164.4 mg; thus, all subsequent p values are not controlled for multiplicity and are considered descriptive. Centanafadine 164.4 mg was numerically favored when compared to placebo at week 6 (p = .3016). Centanafadine 328.8 mg showed separation from placebo as early as week 1, with the effect maintained throughout the study period (p = .001) (Table S5, available online). Compared to placebo, the Cohen d values for centanafadine 164.4 mg and centanafadine 328.8 mg were –0.12 and –0.40, respectively.

Relative to placebo, adolescents who received centanafadine 164.4 mg demonstrated a significant difference in the mean change from baseline in the ADHD-RS-5

TABLE 1 Baseline Demographic and Clinical Characteristics of Study Participants

	CTN 164.4 mg n = 155	CTN 328.8 mg n = 155	Placebo n = 149
Age, y, mean (min, max)	14.5 (1.3)	14.7 (1.4)	14.7 (1.3)
Sex at birth, n (%)			
Male	86 (55.5)	99 (63.9)	87 (58.4)
Female	69 (44.5)	56 (36.1)	62 (41.6)
Weight, kg, mean (SD)	65.4 (17.6)	69.0 (19.7)	67.5 (16.9)
BMI, kg/m^2, mean (SD)	23.7 (5.5)	24.3 (5.6)	24.2 (5.3)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.6)	3 (2.0)
Asian	4 (2.6)	1 (0.6)	1 (0.7)
Black or African American	43 (27.7)	36 (23.2)	35 (23.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.6)	0
White	106 (68.4)	110 (71.0)	107 (71.8)
Other	2 (1.3)	6 (3.9)	3 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	40 (25.8)	39 (25.2)	50 (33.6)
Not Hispanic or Latino	115 (74.2)	116 (74.8)	99 (66.4)
ADHD presentation, n (%)[a]			
ADHD combined presentation	106 (68.4)	109 (70.3)	99 (66.4)
ADHD predominantly inattentive	39 (25.2)	43 (27.7)	43 (28.9)
ADHD predominantly hyperactive	1 (0.6)	1 (0.6)	2 (1.3)
ODD diagnosis, n	2 (1.3)	7 (4.5)	2 (1.3)
No. of previous ADHD medications, mean (SD)[b]	1.6 (1.1)	2.3 (1.9)	1.7 (1.5)
Previous received stimulants, n (%)			
Yes	61 (39.4)	64 (41.3)	68 (45.6)
No	94 (60.6)	91 (58.7)	81 (54.4)
ADHD-RS-5 symptoms total raw score, mean (SD)	37.7 (6.1)	37.8 (6.4)	37.0 (5.7)
CGI-S-ADHD, mean (SD)	4.5 (0.6)	4.5 (0.6)	4.4 (0.5)
Conners 3—Parent Short, mean (SD)[c]			
Inattention	80.1 (10.3)	81.5 (8.7)	82.2 (8.7)
Hyperactivity/Impulsivity	78.9 (13.5)	80.8 (13.1)	79.8 (13.3)
Defiance/Aggression	59.9 (14.6)	60.0 (14.9)	57.8 (12.8)
Executive function	74.1 (11.7)	74.4 (10.4)	74.5 (10.5)

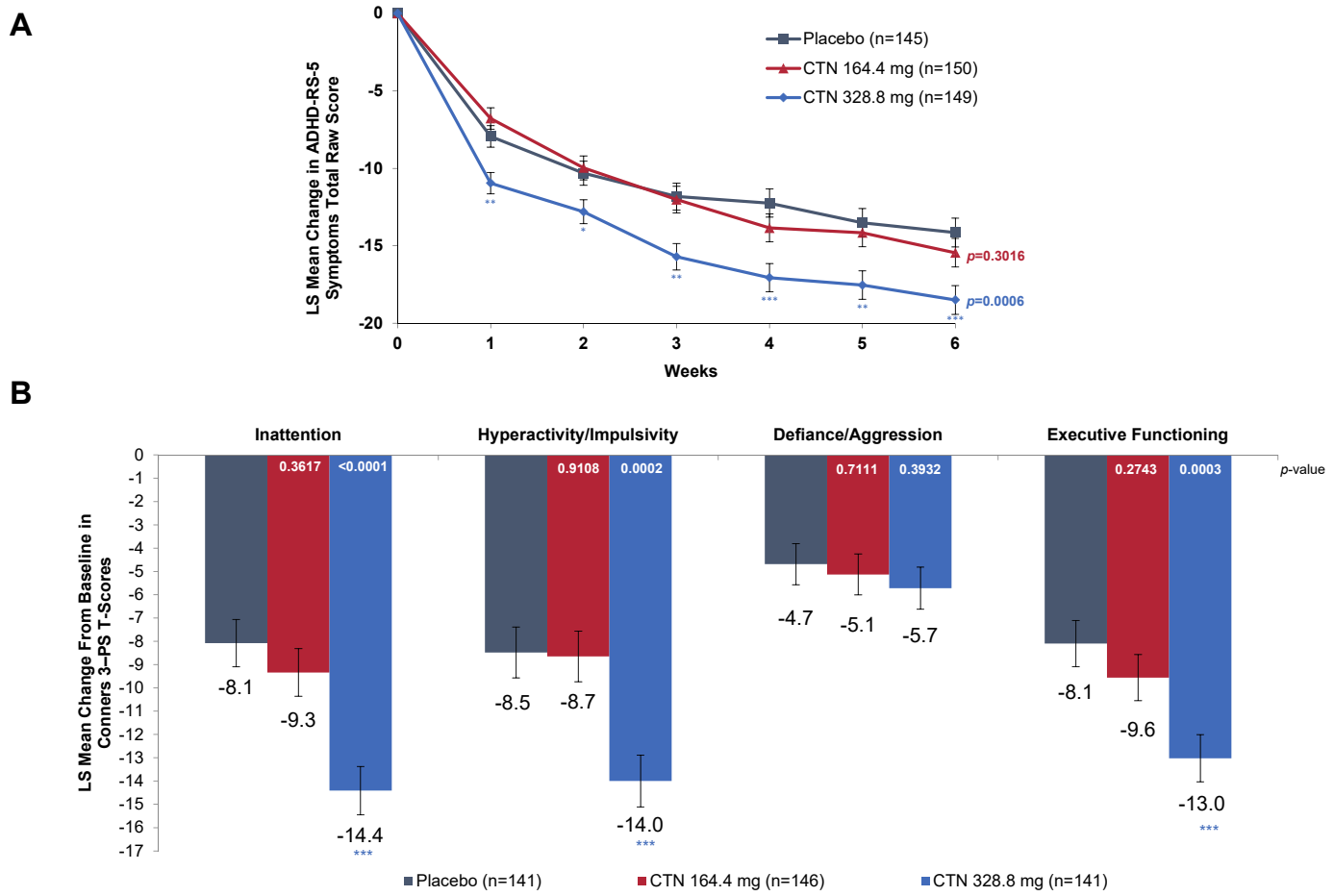
Note: ADHD-RS-5 = Attention-Deficit/Hyperactivity Disorder Rating Scale, version 5; BMI = body mass index; CGI-S-ADHD = Clinical Global Impression of Severity scale modified to address ADHD; CTN = centanafadine; ODD = oppositional defiant disorder.
[a]*Assessed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).*
[b]*n Values are 61, 64, and 70 for the CTN 164.4-mg, CTN 328.8-mg, and placebo groups, respectively.*
[c]*n Values are 152, 149, and 146 for the CTN 164.4-mg, CTN 328.8-mg, and placebo groups, respectively.*

Inattention subscale score compared to participants in the placebo group at week 4 (mean difference = –1.47; 95% CI = –2.94, –0.01; p = .0492), but not at week 6. However, those treated with centanafadine 328.8 mg demonstrated a significant difference starting at week 1 (mean difference = –2.07; 95% CI = –3.21, –0.92; p = 0.0005) and continuing through week 6 (mean difference = –2.74; 95% CI = –4.28, –1.21; p = 0.0005) (Table S5, available online).

In all treatment groups, improvements in CGI-S-ADHD were observed at week 1 with mean [SE] changes from baseline of –0.39 [0.06], –0.71 [0.06], and –0.50 [0.06] in the centanafadine 164.4-mg, centanafadine 328.8-mg, and placebo groups, respectively. Increasingly greater improvements were observed over weeks 1 to 6. At week 6, the mean (SE) changes from baseline were –1.15 (0.09), –1.42 (0.09), and –1.06 (0.09) for the centanafadine 164.4-mg, centanafadine 328.8-mg, and placebo groups, respectively. The mean change from baseline in CGI-S-ADHD at week 6 was significantly greater in the centanafadine 328.8-mg group than in the placebo group at this timepoint (p = .0038) (Table S5, available online).

At week 6, on the Conners 3–Parent Short content scale T scores, significant improvements in the ADHD

FIGURE 2 Mean Change From Baseline in ADHD Rating Scale, version 5 (ADHD-RS-5) Symptoms Total Raw Score Over Weeks 1–6 (A) and Conners 3–Parent Short Inattention, Hyperactivity/Impulsivity, Defiance/Aggression, and Executive Functioning Content Scale *T* scores at Week 6 (B)



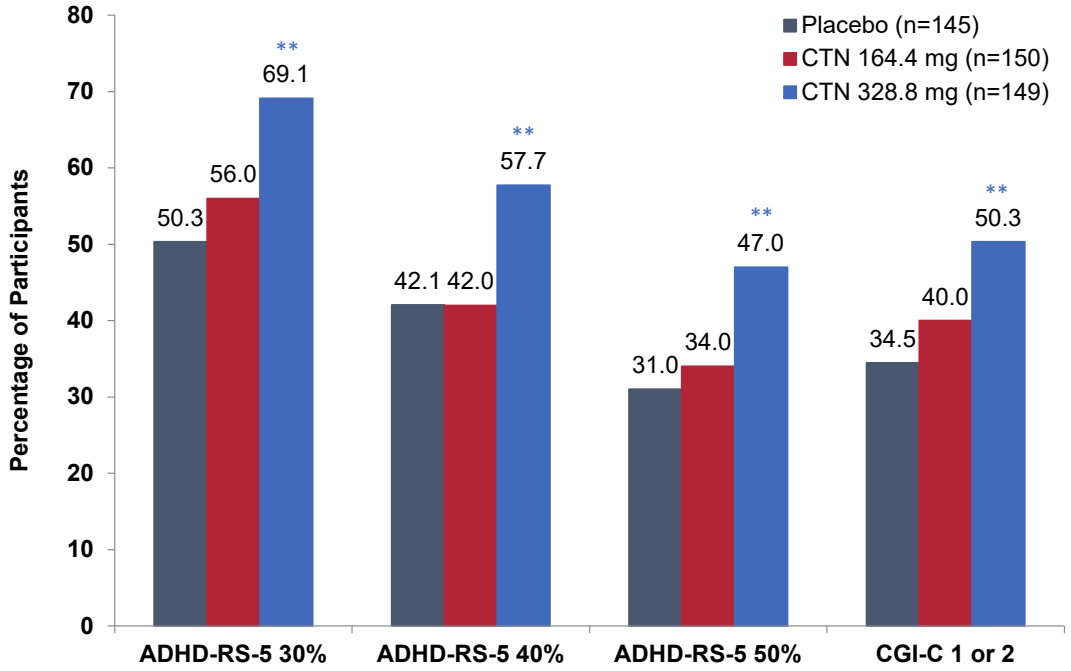
Note: *Mean change is derived from a mixed-effect model for repeated measures. Error bars are standard error of the mean. Conners 3–PS = Conners 3–Parent Short; CTN = centanafadine; LS = least squares.*
**p < .05; **p < .01; ***p < .001 vs placebo.*

symptoms of inattention (mean difference: −6.63; 95% CI = −9.06, −3.60; $p < .0001$), hyperactivity/impulsivity (mean difference: −5.52; 95% CI = −8.44, −2.59; $p = .0002$), and executive functioning (mean difference: −4.92; 95% CI = −7.56, −2.28; $p = .0003$) were observed for centanafadine 328.8 mg vs placebo (Figure 2B).

At the week 6 endpoint, the percentage of responders defined as having a ≥30%, ≥40%, and ≥50% improvement in ADHD-RS-5 symptoms total raw score was significantly greater ($p < .01$) for centanafadine 328.8 mg compared to placebo, as was the percentage of responders with a CGI-C-ADHD score of 1 or 2 (Figure 3). At week 6, the proportions of responders who met the clinically meaningful within-patient change threshold for the ADHD-RS-5 symptoms total raw score were 36.0% for centanafadine 164.4 mg ($p = .4570$), 47.7% for centanafadine 328.8 mg ($p = .0039$), and 31.7% for the placebo group (Figure S2, available online).

Relative to placebo, adolescents who received centanafadine 164.4 mg demonstrated a significant difference in the mean change from baseline in the ADHD-RS-5 Hyperactivity/Impulsivity subscale score compared to participants in the placebo group at week 1 (mean difference = 1.36; 95% CI = 0.40, 2.32; $p = .0054$). Adolescents treated with centanafadine 328.8 mg demonstrated a significant difference in the mean change from baseline in the ADHD-RS-5 Hyperactivity/Impulsivity subscale score starting at week 3 (mean difference = –1.49; 95% CI = –2.65, –0.33; $p = .0118$) and at week 4 (mean difference = –1.59; 95% CI = –2.78, –0.41; $p = .0085$) and week 6 (mean difference = –1.52; 95% CI = –2.70, –0.34; $p = .0120$) (Table S5, available online).

FIGURE 3 ADHD Rating Scale, Version 5 (ADHD-RS-5) and Clinical Global Impression of Change Scale Modified to Address ADHD (CGI-C-ADHD) Responders at Week 6 (Last Observation Carried Forward [LOCF])



Note: *Analyzed via Cochran–Mantel–Haenszel general association test. CTN = centanafadine.*
***p < .01 vs placebo.*

Safety and Tolerability

A total of 451 adolescents received ≥1 dose of study treatment and were included in the safety analysis set (centanafadine 164.4 mg, n = 153; centanafadine 328.8 mg, n = 151; placebo, n = 147). Treatment-emergent adverse events (TEAEs) occurred in 48 of 153 (31.4%) adolescents in the centanafadine 164.4-mg group, 76 of 151 (50.3%) in the centanafadine 328.8-mg group, and 35 of 147 (23.8%) in the placebo group (Table 2). Most TEAEs were of mild or moderate severity. The most common (≥5% any group and greater than placebo) TEAEs were decreased appetite, nausea, headache, and rash (Table 2). Of the 13 rash events (6% [9 of 151] centanafadine 328.8 mg; 2% [3 of 153] centanafadine 164.4 mg; 0.7% [1 of 147] placebo), the duration was ∼4 to 17 days, except for 1 event that lasted for ∼2 months. A total of 11 events were assessed by the investigator as related to the study drug; all were mild in severity except 1 event, which was moderate. All events resolved by the follow-up visit. Three of the rash events led to study discontinuation (1.3 % [2 of 151] centanafadine 328.8 mg; 0.7% [1 of 153] centanafadine 164.4 mg).

A total of 3 participants experienced 1 severe event: liver function test increased (n = 1, centanafadine 164.4 mg; led to study discontinuation), aggression (n = 1, centanafadine 164.4 mg; led to study discontinuation), and somnolence (n = 1, placebo); all of these were assessed by the investigator as related to study treatment. The event of liver function test increased (high alanine aminotransferase and aspartate aminotransferase levels at week 2 and the end-of-treatment visit) was ongoing at the follow-up visit 7 days after the last dose; the other 2 events had resolved by the follow-up visit. The participant who experienced the event of liver function test increase also experienced events of blood creatine phosphokinase increase (moderate) and hepatitis (moderate), both of which resolved.

There were no trends and no meaningful differences in vital sign parameters between the 3 treatment groups. One participant treated with centanafadine 164.4 mg had a vital sign abnormality that was reported as a TEAE: postural orthostatic tachycardia syndrome (mild, related, resolving by the 7-day posttreatment follow-up visit). Four participants treated with centanafadine 328.8 mg had vital signs abnormalities that were reported as TEAEs: blood pressure increase (mild, related, led to study drug discontinuation), heart rate increase (moderate, related, led to study drug discontinuation), hypertension (mild, unrelated, resolved), and

TABLE 2 Summary of Treatment-Emergent Adverse Events

	CTN 164.4 mg n = 153	CTN 328.8 mg n = 151	Placebo n = 147
Participants with any TEAE, n (%)	48 (31.4)	76 (50.3)	35 (23.8)
Participants with serious TEAEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Participants with severe TEAEs, n (%)	2 (1.3)	0 (0.0)	1 (0.7)
Participants discontinued study drug because of an adverse event, n (%)	5 (3.3)	12 (7.9)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs occurring in ≥2% of either CTN group and at a greater rate than with placebo, n (%)			
Decreased appetite	9 (5.9)	23 (15.2)	3 (2.0)
Headache	12 (7.8)	9 (6.0)	8 (5.4)
Nausea	8 (5.2)	15 (9.9)	4 (2.7)
Rash	3 (2.0)	9 (6.0)	1 (0.7)
Somnolence	2 (1.3)	6 (4.0)	4 (2.7)
Fatigue	3 (2.0)	4 (2.6)	1 (0.7)
Irritability	2 (1.3)	4 (2.6)	2 (1.4)
Abdominal pain, upper	2 (1.3)	5 (3.3)	0 (0.0)
Dizziness	3 (2.0)	4 (2.6)	0 (0.0)
Nasopharyngitis	0 (0.0)	4 (2.6)	1 (0.7)
Time to onset of TEAEs occurring in ≥5% of either CTN group and at a greater rate than placebo, mean (SD) days[a]			
Decreased appetite	8.6 (8.2)	9.2 (10.5)	10.3 (15.3)
Headache	11.8 (8.1)	12.3 (15.2)	14.5 (15.5)
Nausea	8.9 (8.6)	7.2 (8.3)	27.3 (18.6)
Rash	30.0 (24.8)	8.9 (2.0)	4.0 (0.0)
Duration of TEAEs occurring in ≥5% of either CTN group and at a greater rate than placebo, mean (SD) days[b]			
Decreased appetite	20.6 (17.9)	24.1 (16.6)	35.3 (28.4)
Headache	6.2 (8.0)	4.7 (6.0)	5.8 (7.5)
Nausea	11.3 (13.1)	15.6 (15.6)	3.3 (2.2)
Rash	28.0 (29.3)	10.1 (4.0)	8.0 (0.0)

Note: CTN = centanafadine; TEAE = treatment-emergent adverse event.
[a]*Time to onset is considered as time to first occurrence of specific TEAE.*
[b]*Duration of TEAE for each participant was calculated as duration for single occurrence of TEAEs or sum of durations for multiple occurrences of specific TEAEs in the trial.*

tachycardia (moderate, related, ongoing at 7-day posttreatment follow-up visit). Occasional changes from baseline in ECG values were reported during the trial; however, no meaningful differences in values between the treatment groups were observed, and no ECG abnormalities were recorded as TEAEs.

Six participants had decreases or increases in weight that were recorded as TEAEs. A weight gain of ≥7% at week 6 was reported in 0.0% of participants for centanafadine 328.8 mg, 1.6% for centanafadine 164.4 mg, and 3.2% for placebo. A weight loss of ≥7% at week 6 was reported in 4.9% of participants for centanafadine 328.8 mg, 0.0% for centanafadine 164.4 mg, and 0.8% for placebo. To account for normal growth in a pediatric population, age- and gender-adjusted Z scores for weight and body mass index were derived, and were used to compare the participants' weight and BMI to the average for their age and gender. A Z score of ≥0.5 or of −0.5 or less was considered clinically relevant. The percentage of participants with a change in weight Z scores of ≥0.5 or of −0.5 or less at week 6 was <3% for all treatment groups, and the percentage of participants with a change in body mass index Z scores of ≥0.5 or of −0.5 or less at week 6 was <5% for all treatment groups. Of note, a 6-week trial is not sufficient to

identify any trends in growth as the Food and Drug Administration draft guidance recommendation is that growth is assessed for a minimum of 12 months.[30]

Overall, 4 participants reported TEAEs related to suicidality (n = 1, centanafadine 328.8 mg; n = 1, centanafadine 164.4 mg; n = 2, placebo), which were deemed positive for suicidal ideation per the C-SSRS. Of the 5 events reported, only 1 was considered related to the study drug by the investigators, in the centanafadine 328.8-mg group. All events were mild to moderate in severity and resolved with no changes made regarding the study drug; no differences among treatment groups were observed.

The mean Study Medication Withdrawal Questionnaire—Pediatric scores were generally low and similar among all 3 treatment groups, indicating that there was no evidence of withdrawal following discontinuation of centanafadine at the last visit and in the follow-up period.[30] Moreover, the adverse event profile indicated a low likelihood of abuse.

DISCUSSION

The results of this study demonstrate the general tolerability and clinical benefits of centanafadine, an NDSRI, in the treatment of ADHD in an adolescent population and support the hypothesis proposed. Specifically, the higher dose tested (centanafadine 328.8 mg) demonstrated a statistically significant difference in the primary endpoint of change from baseline in ADHD-RS-5 symptoms total raw score vs placebo at week 6. The onset of this effect was rapid, with significant benefit observed as early as the first time point measured (week 1). The higher dose also demonstrated significant improvements when compared to placebo in the key secondary endpoints of change from baseline in CGI-S-ADHD and in the Conners 3–Parent Short content scale *T* scores for Inattention, Hyperactivity/Impulsivity, and Executive Functioning. The Conners 3–Parent Short data show that centanafadine has an impact not only on the core symptoms of ADHD, but also on executive functioning, suggesting that centanafadine may also be effective in addressing associated features of ADHD. Results in this trial were similar to those of a trial in children, which also demonstrated efficacy with the higher centanafadine dose and safety/tolerability with both doses.[31]

Centanafadine was generally well tolerated at both doses tested. The most commonly reported (≥5% any treatment group) TEAEs were decreased appetite, headache, nausea, and rash (all reported as mild or moderate). Similar events were also observed in phase 3 adult studies.[18] Severe events were uncommon, with a single participant in the centanafadine 164.4-mg group experiencing an increased liver function test result and another in the same group experiencing severe aggression; both events led to study drug discontinuation. Of note, the participant who reported a liver function test increase also reported a nonserious TEAE of hepatitis. Overall, for this participant population, the mean changes from baseline to the last visit in alanine aminotransferase, aspartate aminotransferase, and bilirubin values were not clinically meaningful and were similar between the centanafadine and placebo groups. Therefore, from these findings, it does not seem there are any safety issues regarding liver abnormalities due to centanafadine.

The safety and efficacy of centanafadine relative to established ADHD treatments have been compared using matching-adjusted indirect comparison using data from adult clinical trials.[32] These analyses showed that centanafadine had a significantly better short-term tolerability profile than lisdexamfetamine, atomoxetine, and viloxazine ER and showed a significantly lower incidence of several adverse events when compared to methylphenidate. In these studies, the efficacy of centanafadine was lower than with lisdexamfetamine but was comparable (ie, nondifferent) with atomoxetine, viloxazine ER, and methylphenidate. While matching-adjusted indirect comparison analyses have yet to be performed with centanafadine in the pediatric population, the literature has shown that both stimulant and non-stimulant medications have consistently demonstrated significant improvements in symptom severity,[33] with stimulants generally being associated with greater efficacy vs placebo (odds ratio = 6.21, 95% CI = 4.89, 7.96) for stimulants vs odds ratio = 3.95 (95% CI = 3.13, 5.07) for non-stimulants), but have also been found to have tolerability concerns.[10] For instance, in a meta-analysis of the efficacy and safety of medications for pediatric ADHD, the non-stimulant atomoxetine was found to have superior efficacy for ADHD core symptoms as rated by clinicians when compared to placebo, albeit not when based on teachers' ratings.[34] However, atomoxetine use was associated with weight and blood pressure changes in pediatric patients, both of which should be monitored similarly as if a patient were taking a stimulant.[34]

For core ADHD symptoms, the effect size of centanafadine 328.8 mg was −0.40 in this adolescent population, which is similar to previously published data from an adult population with ADHD treated with centanafadine (effect sizes vs placebo were −0.28 for 200 mg/d and −0.24 for 400 mg/d in study 1 and −0.37 for 200 mg/d and −0.40 for 400 mg/d in study 2).[18] The effect size in this trial is within range of the effect sizes observed with nonstimulants.[35,36]

Neurobiological and pharmacological research on ADHD has focused primarily on the roles of norepinephrine and dopamine.[37,38] However, emerging evidence suggests that serotonin may also contribute to the disorder, as serotonergic activity interacts with dopaminergic and noradrenergic pathways, both of which are well established in the neurobiology of ADHD.[15,39] Moreover, serotonin levels have been shown to influence processes related to mood (including anxiety and depression), executive function, sleep, and memory—all of which are linked to core symptoms, associated features, and comorbid conditions commonly observed in ADHD, such as inattention, impulsivity, deficits in emotional regulation and executive function, anxiety, and depression.[14,39,40] The NDSRI centanafadine offers a broader mechanism of action compared to existing ADHD treatments, as it affects serotonergic neurotransmission in addition to dopamine and norepinephrine pathways.[16] The full impact of this broader mechanism is still yet to be fully elucidated, but it suggests that centanafadine may have an impact on a wide range of symptoms associated with ADHD.

There were some methodological limitations in this study. The population studied may not be representative of the entire population of adolescents with ADHD, as enrollment was restricted by study center locations (North America only) and the inclusion and exclusion criteria. Thus, limited variability in comorbidities, symptom severity, and treatment history may have influenced the outcomes observed. In addition, because of practical constraints, teacher ratings were excluded, limiting perspective and its potential impact on the study findings. Moreover, this trial did not include an active comparator; therefore, conclusions regarding the safety and efficacy relative to other ADHD treatments cannot be drawn. Finally, the study was of short duration; long-term studies are needed to confirm the safety, tolerability, and maintenance of effect with continued use.

In this clinical trial, several steps were taken to avoid potential biases, including independent oversight, in which the trial was overseen by an independent data monitoring committee that was responsible for monitoring the safety and integrity of the trial data. In addition, the study used a double-blind, randomized controlled design, ensuring that both participants and investigators were unaware of the treatment assignments. This blinding procedure helped to minimize any potential influence on the outcomes due to preconceived notions or biases. Moreover, the study protocol, including the statistical analysis plan, was preregistered and will be publicly accessible after marketing approval in global markets or beginning 1 to 3 years after article publication. There is no end date to the availability of the data, ensuring transparency and reducing the potential for selective reporting or data manipulation. Finally, all authors disclosed any potential conflicts of interest in the study, and the guidelines set forth by the International Committee of Medical Journal Editors regarding transparency in funding and potential biases were fully adhered to.

In summary, the NDSRI centanafadine was safe and generally well tolerated in adolescents with ADHD at both doses tested, with the higher dose (328.8 mg once daily) being efficacious for the treatment of ADHD in adolescents. In combination with studies in adults[18,19] and children,[31] these results demonstrate efficacy across the lifespan. Studies are needed on longer-term outcomes, treatment of ADHD with comorbid conditions, and comparative efficacy with other agents used for ADHD treatment.

CRediT authorship contribution statement

Caroline L. Ward: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Ann C. Childress:** Writing – review & editing, Writing – original draft, Visualization, Resources, Conceptualization. **Na Jin:** Writing – review & editing, Writing – original draft, Formal analysis. **Osman Turkoglu:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Taisa Skubiak:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Timothy E. Wilens:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization.

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Data Sharing Statement: To submit inquiries related to Otsuka clinical research or to request access to individual participant data (IPD) associated

with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

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