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EFFICACY, SAFETY, AND TOLERABILITY OF CENTANAFADINE SUSTAINED-RELEASE TABLETS IN ADULTS WITH ADHD: RESULTS OF TWO PHASE 3, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED TRIALS

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INTERACTIVE POSTER
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INTRODUCTION

- Centanafadine is an inhibitor of norepinephrine, dopamine, and serotonin re-uptake transporters[1] currently under investigation for attention-deficit/hyperactivity disorder (ADHD) treatment[2]
- Objective: The efficacy, safety, and tolerability of centanafadine sustained-release (SR) tablets 200 mg/day or 400 mg/day were assessed vs placebo in adults with ADHD in two Phase 3 trials (Study 1: NCT03605680; Study 2: NCT03605836)

METHODS

Study design

- Study 1 and Study 2 were randomized, double-blind (DB), multicenter, placebo-controlled trials comprising four study periods (**Figure 1**)
- Eligible subjects (**Table 1**) in the centanafadine 200 mg/day and 400 mg/day groups received 200 mg total daily dose (TDD) from DB Day 1. The 400 mg/day dose group escalated to 400 mg on Day 8

Endpoints

- Primary efficacy endpoint: Change from baseline at Day 42 in Adult ADHD Investigator Symptom Rating Scale (AISRS) total score
- Key secondary efficacy endpoint: Change from baseline at Day 42 in Clinical Global Impression-Severity of Illness Scale (CGI-S) score
- Safety assessments included the following: Adverse events (AEs); clinical laboratory tests; physical examinations; vital signs; electrocardiograms; Study Medication Withdrawal Questionnaire; and Columbia-Suicide Severity Rating Scale

Statistical analysis

- Efficacy analyses included all randomized subjects who received ≥1 dose of centanafadine or placebo and had both baseline and ≥1 post-randomization efficacy evaluation in the DB period
- Safety analyses included any randomized subject who received ≥1 dose of centanafadine or placebo during the DB period

Figure 1. Design for Centanafadine Study 1 and Study 2 in Adults With ADHD

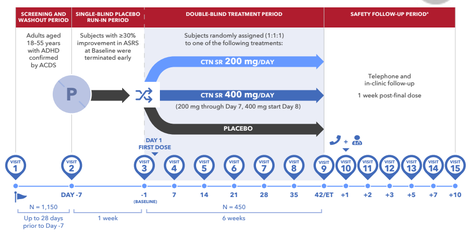


Table 1. Key Inclusion/Exclusion Criteria for Centanafadine Study 1 and Study 2

KEY INCLUSION CRITERIA	KEY EXCLUSION CRITERIA
ADHD (DSM-5 criteria)	Other specified or unspecified ADHD diagnosis
– No pharmacological ADHD treatment: AISRS score of ≥28 at screening and baseline	Comorbid psychiatric disorder requiring prohibited medications or confounding assessments
– Pharmacological ADHD treatment: AISRS score of ≥22 at screening and ≥28 at baseline	No benefit from ≥2 ADHD therapies of two different classes
Discontinuation of prohibited psychotropic medications	Positive alcohol test or drug screen
CGI-S score of ≥4	

Figure 2. CONSORT Flow Diagram for Centanafadine Study 1 and Study 2 (Randomized Sample)

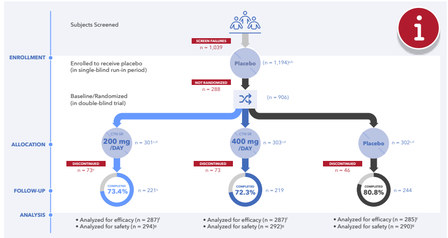


Table 2. Subject Demographics and Baseline Characteristics for Centanafadine Study 1 and Study 2

	CTN SR 200 mg/day (n = 301)	CTN SR 400 mg/day (n = 303)	Placebo (n = 302)	Total (N = 906)
Mean age, y (SD)	35.6 (9.5)	35.3 (10.4)	35.1 (9.7)	35.3 (10.0)
Gender, n (%)				
Female	147 (48.8)	145 (47.1)	142 (47.0)	434 (47.9)
Male	154 (51.2)	158 (52.1)	160 (53.0)	472 (52.1)
Race, n (%)				
White	238 (79.1)	243 (80.2)	244 (80.8)	725 (80.0)
Black or African American	36 (12.0)	42 (13.9)	42 (13.9)	120 (13.2)
Asian	14 (4.7)	4 (1.3)	10 (3.3)	28 (3.1)
American Indian or Alaska Native	0 (0.0)	5 (1.7)	2 (0.7)	7 (0.8)
Native Hawaiian or Other Pacific Islander	2 (0.7)	1 (0.3)	0 (0.0)	3 (0.3)
Other	11 (3.7)	8 (2.6)	4 (1.3)	23 (2.5)
Ethnicity, n (%)				
Hispanic or Latino	61 (20.3)	61 (20.1)	58 (19.2)	180 (19.9)
Mean weight, kg (SD)	82.7 (18.2)	83.0 (18.3)	81.0 (17.9)	82.2 (18.1)
Mean BMI, kg/m² (SD)	28.0 (5.3)	28.1 (5.2)	27.5 (5.2)	27.9 (5.2)
Mean AISRS Total Score (SD)	38.7 (6.8)	39.0 (6.9)	38.6 (6.8)	38.7 (6.8)
Mean AISRS Inattentive Subscale Score (SD)	21.5 (3.6)	21.4 (3.8)	21.7 (3.3)	21.5 (3.6)
Mean AISRS Hyperactive-Impulsive Subscale Score (SD)	17.2 (4.7)	17.6 (4.9)	16.9 (5.0)	17.2 (4.9)
Mean ASRS Total Score of 18 Items (SD)	50.7 (10.2)	50.6 (10.2)	51.0 (10.5)	50.8 (10.3)
Mean CGI-S Score (SD)	4.5 (0.6)	4.6 (0.6)	4.5 (0.6)	4.5 (0.6)

RESULTS

Subject disposition and baseline demographics (combined results)

- 906 subjects were randomized across both studies (centanafadine 200 mg n = 301; centanafadine 400 mg n = 303; placebo n = 302; **Figure 2**)
- Baseline demographics and clinical characteristics were balanced between study groups (**Table 2**)
- Most subjects reported moderate-to-severe ADHD symptoms at baseline (AISRS)

Primary endpoint (efficacy)

- In both studies, the primary endpoint of statistically significant improvement in AISRS total score at Day 42 was achieved for centanafadine 200 mg/day and 400 mg/day compared with placebo (**Figures 3 and 4**)
- Statistically significant differences in AISRS total scores were seen as soon as Day 7 in Study 1 and Day 28 in Study 2 and were maintained until the end of treatment

Key secondary endpoint (efficacy)

- In both studies, centanafadine 200 mg/day and 400 mg/day demonstrated statistically significant improvements in CGI-S score vs placebo (**Figures 5 and 6**)

Figure 3. Least Squares Mean Change from Baseline to Day 42 in AISRS Total Score (Primary Endpoint) for Study 1

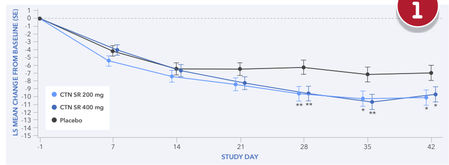


Figure 4. Least Squares Mean Change from Baseline to Day 42 in AISRS Total Score (Primary Endpoint) for Study 2

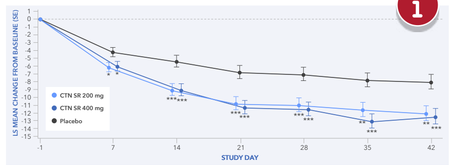


Figure 5. Least Squares Mean Change from Baseline to Day 42 in CGI-S Score (Secondary Endpoint) for Study 1

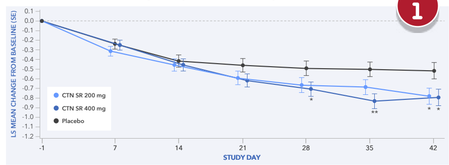
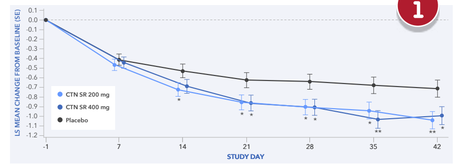


Figure 6. Least Squares Mean Change from Baseline to Day 42 in CGI-S Score (Secondary Endpoint) for Study 2



Safety (combined results)

- 738 treatment-emergent adverse events (TEAEs) were experienced by 360 (41.1%) of the 876 subjects who received ≥1 dose of study treatment in the DB period (**Table 3**)
- The most common TEAEs reported by subjects who received centanafadine were headache and decreased appetite
- Most TEAEs were considered mild or moderate
- No deaths were reported during either study
- Three subjects reported serious AEs (SAEs; all centanafadine 200 mg/day group); no SAE was considered by investigators to be related to the study drug
  - All SAEs resolved and no changes were made to centanafadine treatment
- Across both studies, 36 subjects (4.1%) discontinued study medication due to TEAEs:
  - Centanafadine 200 mg/day: n = 14 (4.8%); centanafadine 400 mg/day: n = 18 (6.2%); placebo: n = 4 (1.4%)
  - Reasons for withdrawal due to TEAEs: Psychiatric disorders (n = 12; 1.4%), skin and subcutaneous disorders (n = 11; 1.3%); rash (n = 10; 1.1%); and erythematous rash (n = 1; 0.1%)

Table 3. Incidence of TEAEs During the Double-blind Treatment Period Reported by ≥2% in Any Centanafadine Group and Greater Than Placebo in Study 1 and Study 2

	CTN SR 200 mg/day (n = 294)	CTN SR 400 mg/day (n = 292)	Placebo (n = 290)	Total (N = 876)
Subject with any TEAE[a,b]	74 (25.2)	93 (31.8)	51 (17.6)	218 (24.9)
Gastrointestinal disorders	23 (7.8)	45 (15.4)	10 (3.4)	78 (8.9)
Constipation	6 (2.0)	2 (0.7)	3 (1.0)	11 (1.3)
Diarrhea	5 (1.7)	15 (5.1)	2 (0.7)	22 (2.5)
Dry mouth	9 (3.1)	17 (5.8)	1 (0.3)	27 (3.1)
Nausea	6 (2.0)	19 (6.5)	6 (2.1)	31 (3.5)
Infections and infestations	15 (5.1)	5 (1.7)	7 (2.4)	27 (3.1)
Upper respiratory tract infection	15 (5.1)	5 (1.7)	7 (2.4)	27 (3.1)
Metabolism and nutrition disorders	15 (5.1)	20 (6.8)	5 (1.7)	40 (4.6)
Decreased appetite	15 (5.1)	20 (6.8)	5 (1.7)	40 (4.6)
Nervous system disorders	12 (4.1)	19 (6.5)	16 (5.5)	47 (5.4)
Headache	12 (4.1)	19 (6.5)	16 (5.5)	47 (5.4)
Psychiatric disorders	30 (10.2)	35 (12.0)	18 (6.2)	83 (9.5)
Abnormal dreams	2 (0.7)	7 (2.4)	2 (0.7)	11 (1.3)
Anxiety	7 (2.4)	5 (1.7)	3 (1.0)	15 (1.7)
Depressed mood	8 (2.7)	2 (0.7)	1 (0.3)	11 (1.3)
Insomnia	8 (2.7)	13 (4.5)	7 (2.4)	28 (3.2)
Irritability	10 (3.4)	12 (4.1)	5 (1.7)	27 (3.1)
Skin and subcutaneous tissue disorders	4 (1.4)	11 (3.8)	2 (0.7)	17 (1.9)
Rash	4 (1.4)	11 (3.8)	2 (0.7)	17 (1.9)

CONCLUSIONS

These two Phase 3 trials were the first large-scale studies demonstrating the efficacy profiles of centanafadine-SR 200 mg/day and 400 mg/day in adults with ADHD. Centanafadine met the primary endpoint of reduction in ADHD symptoms at Day 42, as assessed by change in AISRS total score from baseline, in both studies. It also achieved the key secondary endpoint of statistically significant improvements in CGI-S score vs placebo

Centanafadine demonstrated favorable safety and tolerability profiles in combined study results

The results of these trials demonstrate the value of centanafadine's unique mechanism of action, targeting three neurotransmitters involved in behavioral and mood disorders, including ADHD

Trials examining the long-term profile of centanafadine are in progress (NCT03605849; NCT05279313)

DISCLOSURES

Dr. Adler: Received grant and research support from Sunovion Pharmaceuticals, Shire/Takeda Pharmaceuticals, and Otsuka Pharmaceuticals; served as a consultant to Bracket, Sunovion Pharmaceuticals, Shire/Takeda Pharmaceuticals, Otsuka Pharmaceuticals, SUNY, the National Football League, and Major League Baseball; and has received loyalty payments (as inventor) since 2004 from NYU for license of adult ADHD scales and training materials. Drs. Adams, Madera, Hobart, Chang, and McQuade, and Mr. Angelicola: Employees of Otsuka Pharmaceutical Development & Commercialization. Dr. Liebowitz: Otsuka Pharmaceutical Company.

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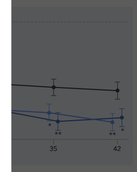

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Table 2. Subject Demographics and Baseline Characteristics for Centanafadine Study 1 and Study 2

- Baseline demographics and clinical characteristics were balanced between study groups
- Most subjects reported moderate-to-severe ADHD symptoms at baseline (AISRS)

	CTN SR 200 mg /DAY	CTN SR 400 mg /DAY	Placebo	TOTAL
	N = 301	N = 303	N = 302	N = 906
MEAN AGE	35.6 years old (9.5 SD)	35.3 years old (10.4 SD)	35.1 years old (9.7 SD)	35.3 years old (10.0 SD)
GENDER	51.2% n = 154 ♂ / 48.8% n = 147 ♀	52.1% n = 158 ♂ / 47.1% n = 145 ♀	53.0% n = 160 ♂ / 47.0% n = 142 ♀	52.1% n = 472 ♂ / 47.9% n = 434 ♀
RACE	White (238); Black or African American (36); Asian (14); American Indian or Alaska Native (0); Native Hawaiian or Other Pacific Islander (2); Other (11)	White (243); Black or African American (42); Asian (4); American Indian or Alaska Native (5); Native Hawaiian or Other Pacific Islander (1); Other (8)	White (244); Black or African American (42); Asian (10); American Indian or Alaska Native (2); Native Hawaiian or Other Pacific Islander (0); Other (4)	White (725); Black or African American (120); Asian (28); American Indian or Alaska Native (7); Native Hawaiian or Other Pacific Islander (3); Other (23)
ETHNICITY	20.3% Hispanic or Latino (N = 61); 79.7% Non-Hispanic or Latino	20.1% Hispanic or Latino (N = 61); 79.9% Non-Hispanic or Latino	19.2% Hispanic or Latino (N = 58); 80.8% Non-Hispanic or Latino	19.9% Hispanic or Latino (N = 180); 80.1% Non-Hispanic or Latino
WEIGHT	82.7 MEAN WEIGHT (KG) (18.7 SD); 28.0 MEAN BMI (KG/M²) (5.3 SD)	83.0 MEAN WEIGHT (KG) (18.3 SD); 28.1 MEAN BMI (KG/M²) (5.2 SD)	81.0 MEAN WEIGHT (KG) (17.9 SD); 27.5 MEAN BMI (KG/M²) (5.2 SD)	82.2 MEAN WEIGHT (KG) (18.1 SD); 27.9 MEAN BMI (KG/M²) (5.2 SD)
TEST SCORES	50.7 MEAN ASRS TOTAL SCORE OF 18 ITEMS (10.2 SD); 38.7 MEAN AISRS TOTAL SCORE (6.8 SD); 4.5 MEAN CGI-S SCORE (0.6 SD); 17.2 MEAN AISRS HYPERACTIVE-IMPULSIVE SUBSCALE SCORE (4.7 SD); 21.5 MEAN AISRS INATTENTIVE SUBSCALE SCORE (3.6 SD)	50.6 MEAN ASRS TOTAL SCORE OF 18 ITEMS (10.2 SD); 39.0 MEAN AISRS TOTAL SCORE (6.9 SD); 4.6 MEAN CGI-S SCORE (0.6 SD); 17.6 MEAN AISRS HYPERACTIVE-IMPULSIVE SUBSCALE SCORE (4.7 SD); 21.4 MEAN AISRS INATTENTIVE SUBSCALE SCORE (3.8 SD)	51.0 MEAN ASRS TOTAL SCORE OF 18 ITEMS (10.5 SD); 38.6 MEAN AISRS TOTAL SCORE (6.8 SD); 4.5 MEAN CGI-S SCORE (0.6 SD); 16.9 MEAN AISRS HYPERACTIVE-IMPULSIVE SUBSCALE SCORE (5.0 SD); 21.7 MEAN AISRS INATTENTIVE SUBSCALE SCORE (3.3 SD)	50.8 MEAN ASRS TOTAL SCORE OF 18 ITEMS (10.3 SD); 38.7 MEAN AISRS TOTAL SCORE (6.8 SD); 4.5 MEAN CGI-S SCORE (0.6 SD); 17.2 MEAN AISRS HYPERACTIVE-IMPULSIVE SUBSCALE SCORE (4.9 SD); 21.5 MEAN AISRS INATTENTIVE SUBSCALE SCORE (3.6 SD)

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; ASRS, Adult ADHD Self-Report Scale; BMI, body mass index; CGI-S, Clinical Global Impression-Severity of Illness Scale; CTN SR, centanafadine sustained release; SD, standard deviation.

DISCLOSURES

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Table 3. Incidence of TEAEs During the Double-blind Treatment Period Reported by ≥2% in Any Centanafadine Group and Greater Than Placebo in Study 1 and Study 2

STUDY 1
One subject experienced moderate pneumonia, which resulted in hospitalization and study withdrawal. One subject experienced severe viral gastroenteritis and moderate influenza, which led to hospitalization

STUDY 2
One subject was hospitallzed with moderate bronchitis

All SAEs resolved and no changes were made to centanafadine treatment

[a]All adverse events that started after start of trial drug treatment; or if the event was continuous from baseline and was serious, study-drug related, or resulted in death, discontinuation, interruption, or reduction of study therapy.

[b]Subjects were counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

CTN SR, centanafadine sustained release; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

All rash and erythematous rash TEAEs resulting in discontinuation were of mild-to-moderate severity except one rash (centanafadine 400 mg/day group). In seven subjects who discontinued due to rash, the rash resolved with treatment; four subjects who discontinued due to rash were not treated for rash

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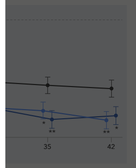

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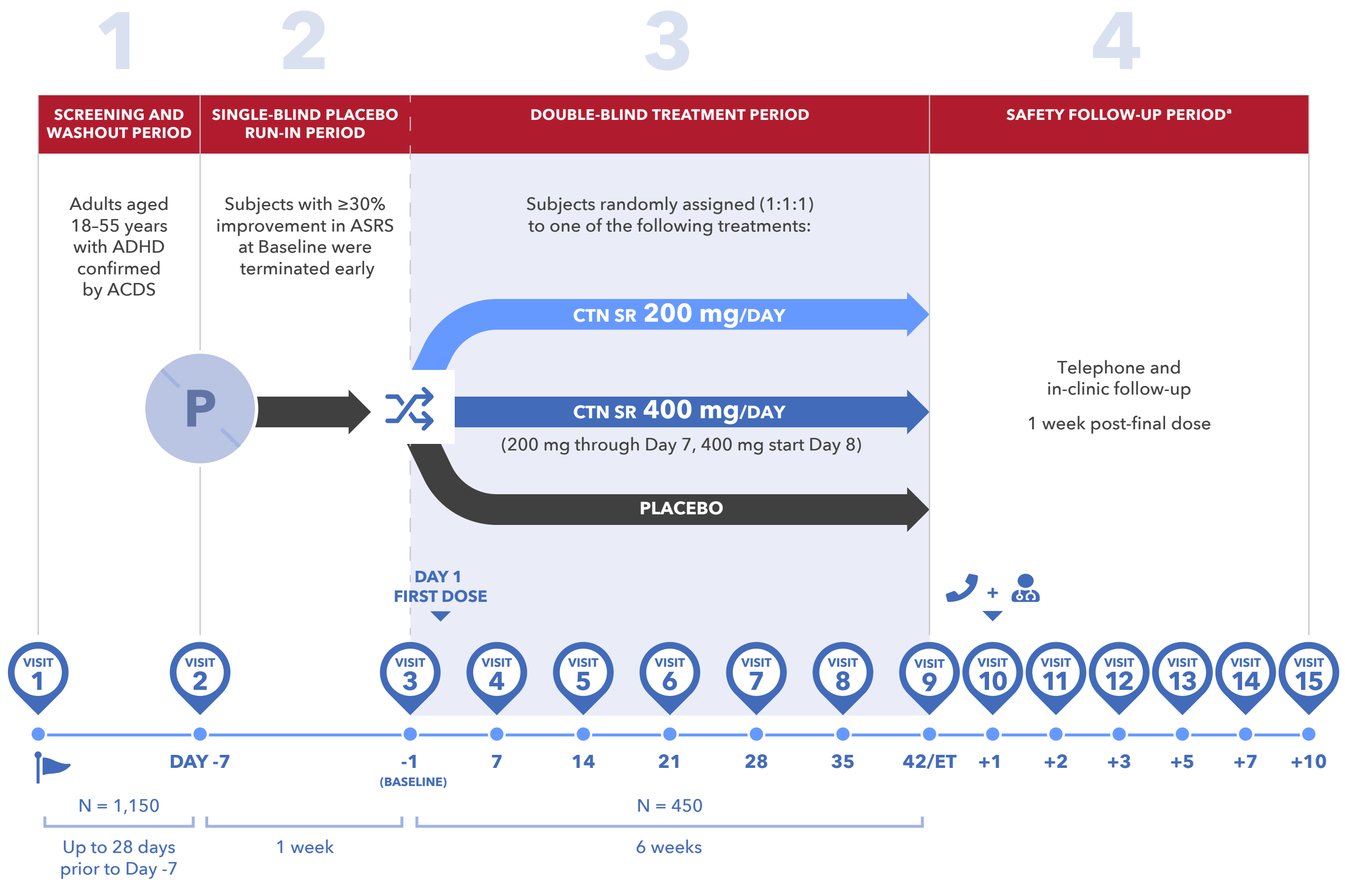
Figure 1. Design for Centanafadine Study 1 and Study 2 in Adults With ADHD

- Study 1 and Study 2 were randomized, double-blind (DB), multicenter, placebo-controlled trials comprising four study periods



[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 treatment, and in-clinic follow-up visits at 2 and 7 days after the last dose of study treatment).

Subjects who terminated early, who decided to not enroll in the long-term open-label safety and tolerability study, or who were not eligible to enroll were also required to participate in an additional follow-up telephone call 10 days after the last dose of centanafadine or placebo.

ACDS, Adult ADHD Clinical Diagnostic Scale; ADHD, attention-deficit/hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale; CTN, centanafadine; ET, early termination; P, placebo; SR, sustained release.

DISCLOSURES

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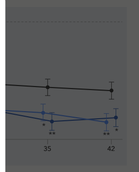

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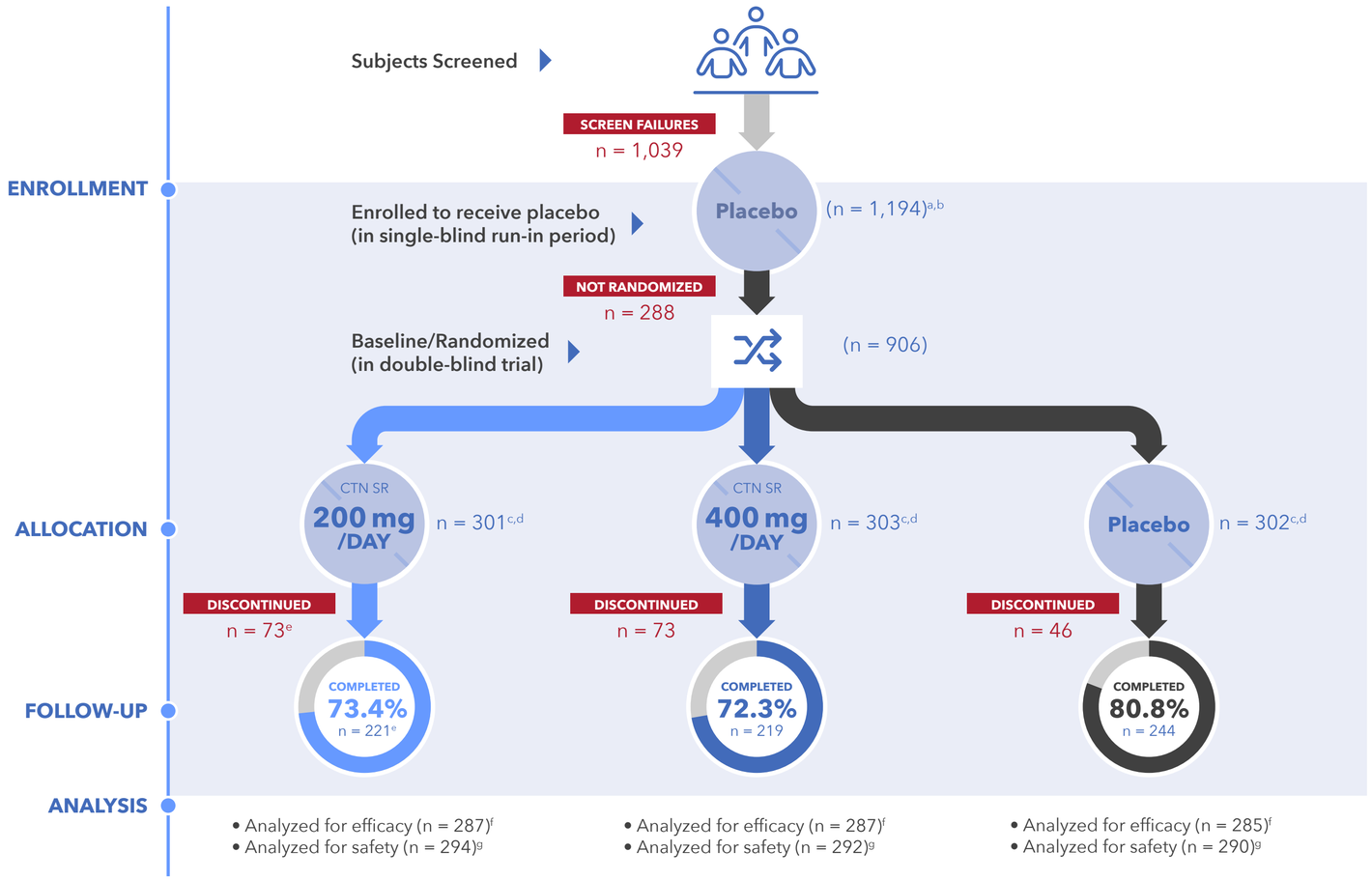
Figure 2. CONSORT Flow Diagram for Centanafadine Study 1 and Study 2 (Randomized Sample)

- 906 subjects were randomized across both studies (centanafadine 200 mg n = 301; centanafadine 400 mg n = 303; placebo n = 302)



[a]Subjects receiving at least one dose of study medication during the single-blind placebo period/double-blind period. [b]Subjects who signed an informed consent form for the trial and enrolled into the single-blind placebo run-in period. [c]Subjects who were randomized and received study medication during the double-blind period or were not randomized and received study medication during the single-blind placebo period. [d]One subject who was enrolled in the trial did not receive study medication in the placebo run-in period. [e]One subject in the CTN SR 200 mg/day group was included in the discontinued subject count in error but completed all trial visits to be considered a completer. [f]Randomized subjects who received at least one dose of double-blind study medication and had a baseline and post-baseline value for AISRS total score. [g]Subjects receiving at least one dose of study medication during the double-blind treatment period are included in the safety analysis.

AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN, centanafadine; SR, sustained release.

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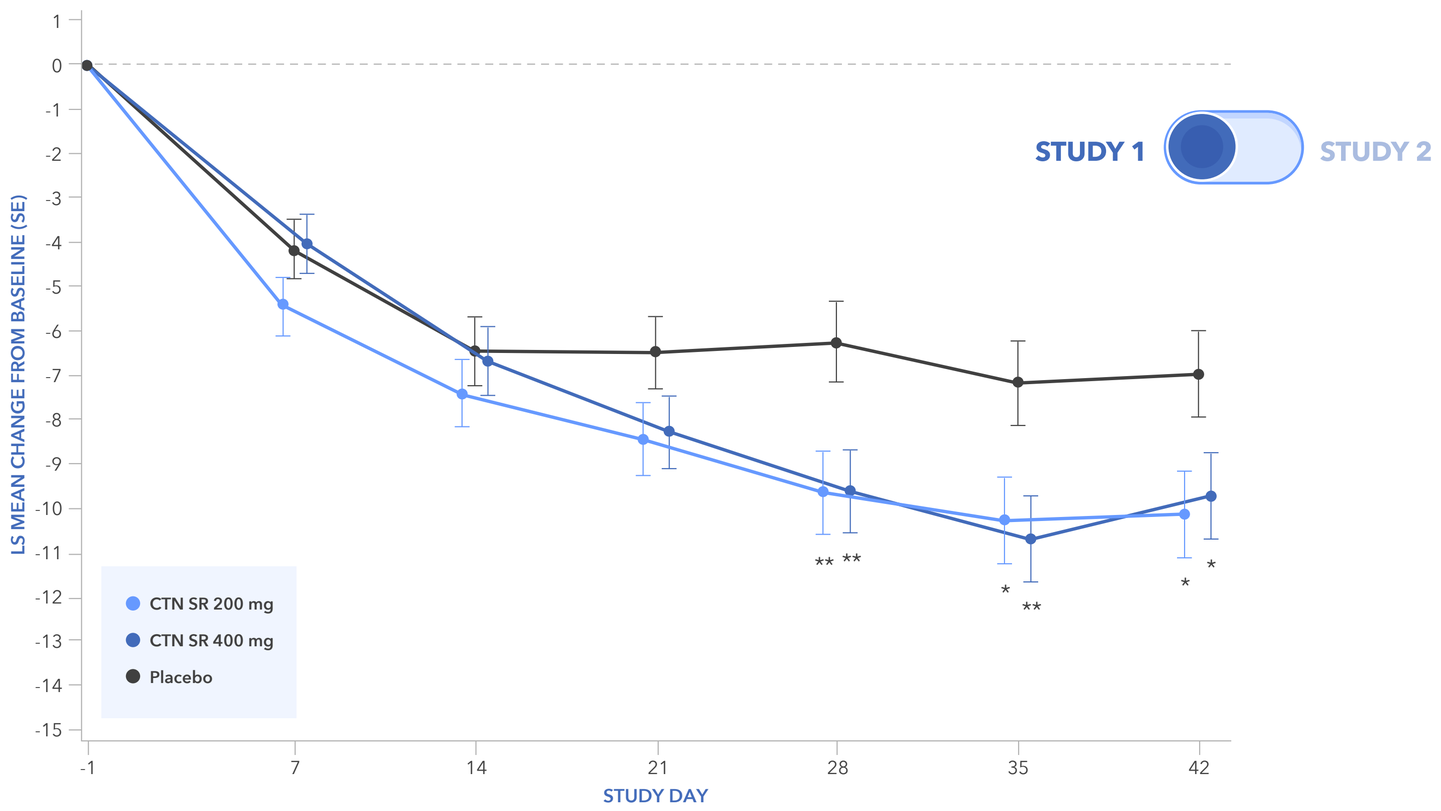
Figure 3. Least Squares Mean Change from Baseline to Day 42 in AISRS Total Score (Primary Endpoint) for Study 1

- AISRS total scores at Day 42 were reduced by:
  - STUDY 1: centanafadine 200 mg/day 25.5%; centanafadine 400 mg/day 24.6%; placebo 17.7%
  - STUDY 2: centanafadine 200 mg/day 32.2% for subjects in the centanafadine 200 mg/day and the centanafadine 400 mg/day dose groups, and 21.4% for subjects in the placebo group



LS MEAN DIFFERENCE FROM BASELINE (SE)

CTN SR 200 mg/day	-5.48 (0.66)	-7.43 (0.76)	-8.46 (0.81)	-9.65 (0.93)	-10.27 (0.96)	-10.13 (0.99)
CTN SR 400 mg/day	-4.05 (0.67)	-6.72 (0.77)	-8.29 (0.82)	-9.61 (0.93)	-10.69 (0.96)	-9.73 (0.98)
Placebo	-4.18 (0.67)	-6.46 (0.78)	-6.52 (0.82)	-6.26 (0.93)	-7.19 (0.95)	-6.98 (0.98)

*P value < 0.05; **P value < 0.01.

Note: Error bars are LS mean ± one SE. Data are based on an MMRM analysis for AISRS total score using an unstructured variance-covariance structure based on the observed cases data set. Model included fixed class effect terms for treatment, trial center, visit day, and an interaction term of treatment-by-visit day. Treatment differences were calculated based on the difference in LS mean changes vs placebo for MMRM.

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN SR, centanafadine sustained release; LS, least squares; MMRM, mixed-effect model repeated measure; SE, standard error.

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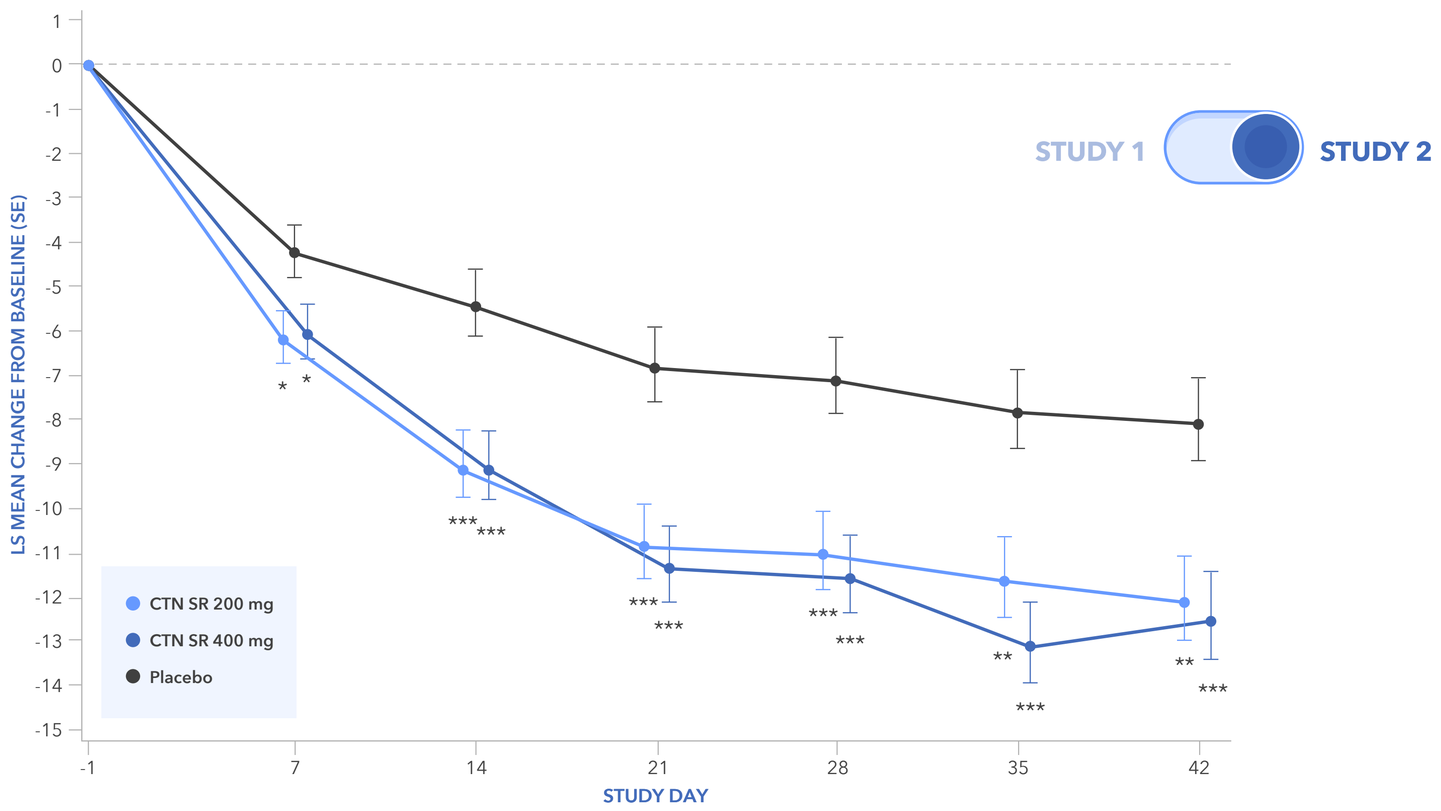
Figure 4. Least Squares Mean Change from Baseline to Day 42 in AISRS Total Score (Primary Endpoint) for Study 2

- AISRS total scores at Day 42 were reduced by:
  - STUDY 1: centanafadine 200 mg/day 25.5%; centanafadine 400 mg/day 24.6%; placebo 17.7%
  - STUDY 2: centanafadine 200 mg/day 32.2% for subjects in the centanafadine 200 mg/day and the centanafadine 400 mg/day dose groups, and 21.4% for subjects in the placebo group



LS MEAN DIFFERENCE FROM BASELINE (SE)

CTN SR 200 mg/day	-6.21 (0.62)	-9.09 (0.76)	-10.83 (0.82)	-11.02 (0.86)	-11.61 (0.91)	-12.08 (0.96)
CTN SR 400 mg/day	-6.09 (0.62)	-9.09 (0.78)	-11.31 (0.84)	-11.56 (0.89)	-13.09 (0.93)	-12.49 (0.99)
Placebo	-4.28 (0.61)	-5.44 (0.76)	-6.81 (0.81)	-7.08 (0.85)	-7.84 (0.89)	-8.07 (0.94)

*P value < 0.05; **P value < 0.01.

Note: Error bars are LS mean ± one SE. Data are based on an MMRM analysis for AISRS total score using an unstructured variance-covariance structure based on the observed cases data set. Model included fixed class effect terms for treatment, trial center, visit day, and an interaction term of treatment-by-visit day. Treatment differences were calculated based on the difference in LS mean changes vs placebo for MMRM.

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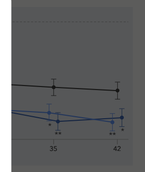

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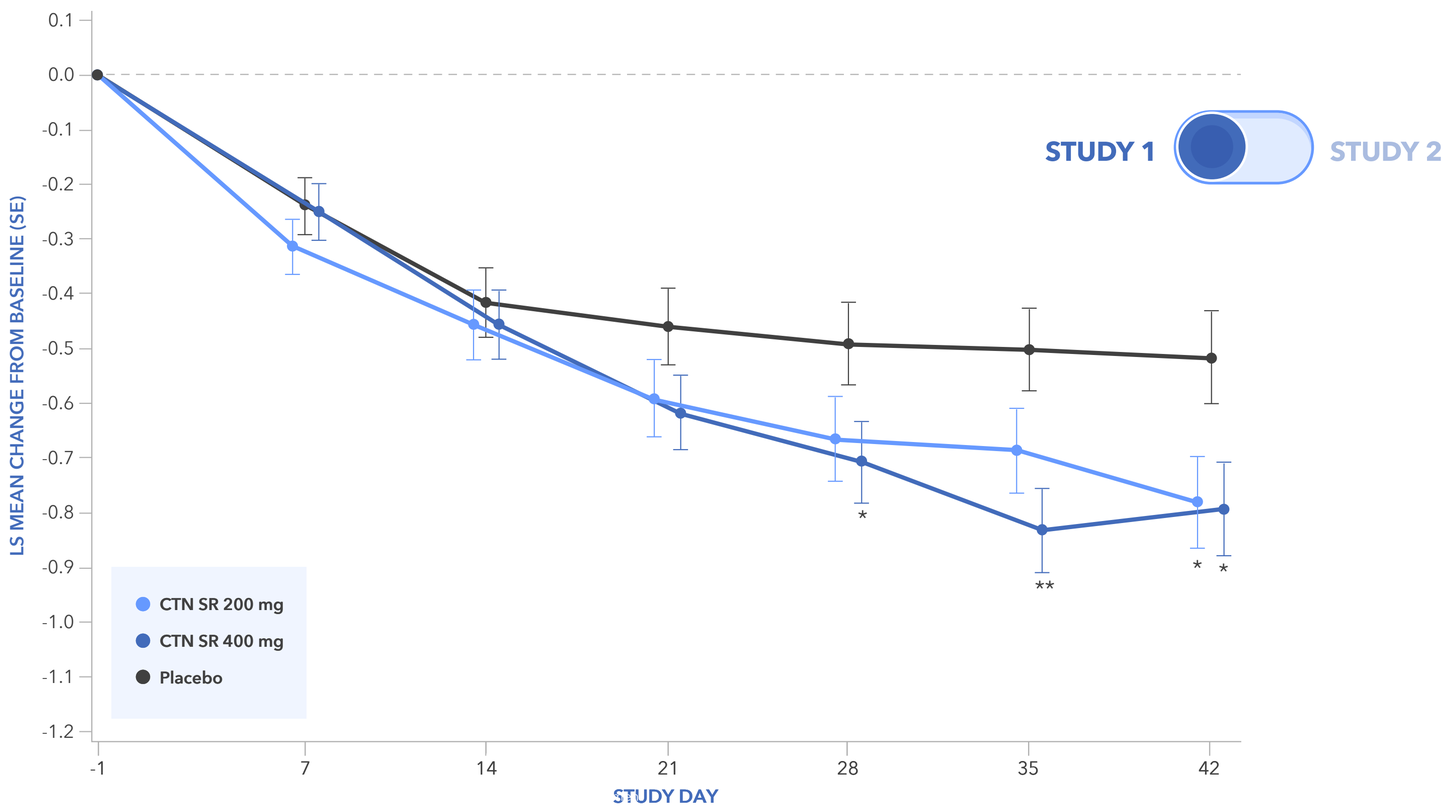
Figure 5. Least Squares Mean Change from Baseline to Day 42 in CGI-S Score (Secondary Endpoint) for Study 1

- In Study 1, statistically significant differences in CGI-S scores were seen as soon as Day 28 and were maintained to the end of treatment for the centanafadine 400 mg/day group
- In Study 2, statistically significant differences in CGI-S scores were seen as soon as Day 14 for centanafadine 200 mg/day and Day 21 for centanafadine 400 mg/day. Improvements were maintained to the end of the study



LS MEAN DIFFERENCE FROM BASELINE (SE)

CTN SR 200 mg/day	-0.32 (0.05)	-0.46 (0.06)	-0.59 (0.07)	-0.67 (0.08)	-0.69 (0.08)	-0.78 (0.09)
CTN SR 400 mg/day	-0.25 (0.05)	-0.46 (0.06)	-0.62 (0.07)	-0.71 (0.08)	-0.83 (0.08)	-0.79 (0.08)
Placebo	-0.24 (0.05)	-0.41 (0.06)	-0.46 (0.07)	-0.49 (0.08)	-0.50 (0.08)	-0.52 (0.08)

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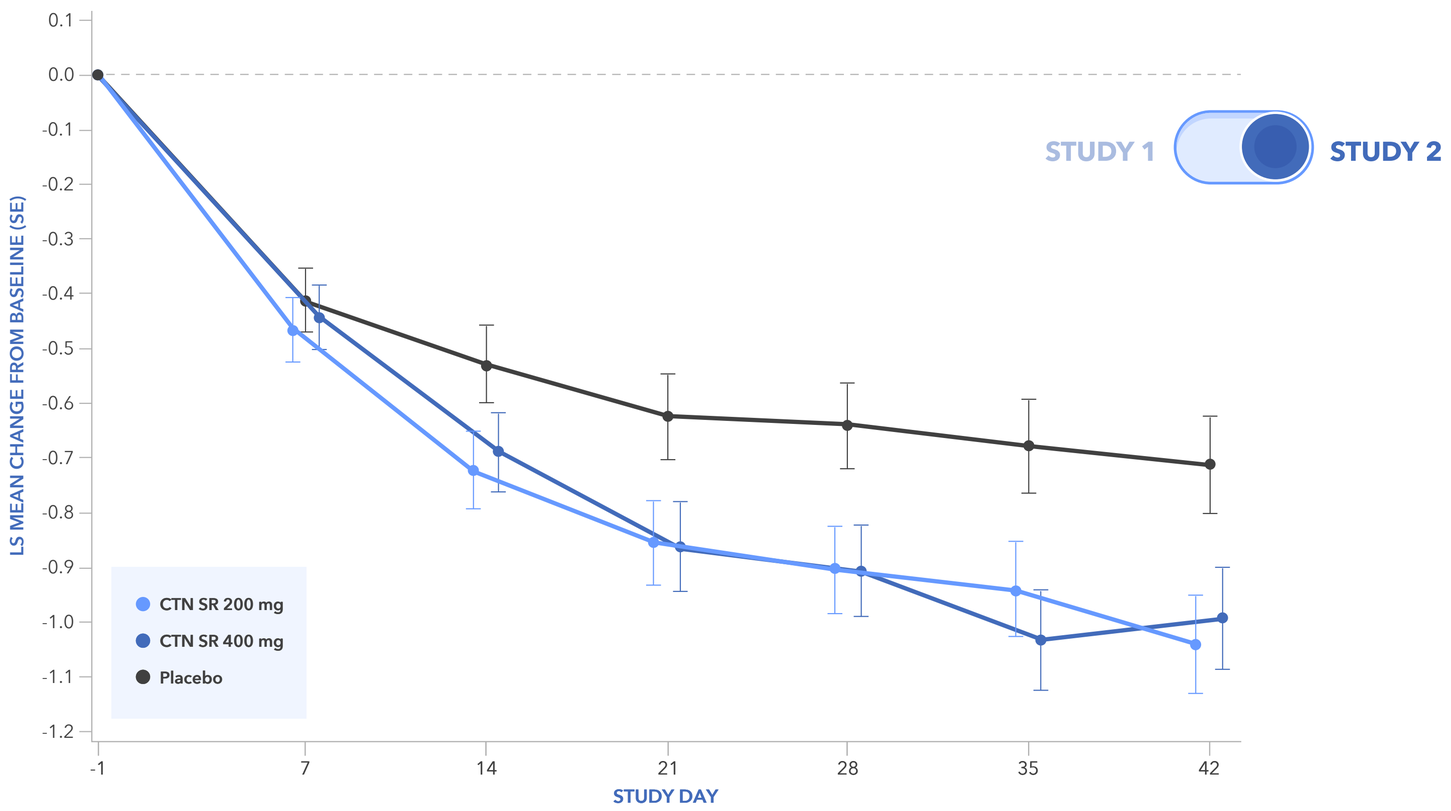
10 (3.4)	78 (8.9)
3 (1.0)	11 (1.3)
2 (0.7)	22 (2.5)
1 (0.3)	27 (3.1)
6 (2.1)	31 (3.5)
7 (2.4)	27 (3.1)
7 (2.4)	27 (3.1)
5 (1.7)	40 (4.6)
5 (1.7)	40 (4.6)
16 (5.5)	47 (5.4)
16 (5.5)	47 (5.4)
18 (6.2)	83 (9.5)
2 (0.7)	11 (1.3)
3 (1.0)	15 (1.7)
1 (0.3)	11 (1.3)
7 (2.4)	28 (3.2)
5 (1.7)	27 (3.1)
2 (0.7)	17 (1.9)
2 (0.7)	17 (1.9)

Figure 6. Least Squares Mean Change from Baseline to Day 42 in CGI-S Score (Secondary Endpoint) for Study 2

- In Study 1, statistically significant differences in CGI-S scores were seen as soon as Day 28 and were maintained to the end of treatment for the centanafadine 400 mg/day group
- In Study 2, statistically significant differences in CGI-S scores were seen as soon as Day 14 for centanafadine 200 mg/day and Day 21 for centanafadine 400 mg/day. Improvements were maintained to the end of the study



LS MEAN DIFFERENCE FROM BASELINE (SE)

CTN SR 200 mg/day	-0.46 (0.06)	-0.72 (0.07)	-0.85 (0.08)	-0.90 (0.08)	-0.94 (0.09)	-1.04 (0.09)
CTN SR 400 mg/day	-0.44 (0.06)	-0.69 (0.07)	-0.86 (0.08)	-0.91 (0.08)	-1.03 (0.09)	-0.99 (0.09)
Placebo	-0.41 (0.06)	-0.53 (0.07)	-0.62 (0.08)	-0.64 (0.08)	-0.68 (0.09)	-0.71 (0.09)

*P value < 0.05; **P value < 0.01.

Note: Error bars are LS mean ± one SE. Data are based on an MMRM analysis for AISRS total score using an unstructured variance-covariance structure based on the observed cases data set. Model included fixed class effect terms for treatment, trial center, visit day, and an interaction term of treatment-by-visit day. Treatment differences were calculated based on the difference in LS mean changes vs placebo for MMRM.

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness Scale; CTN SR, centanafadine sustained release; LS, least squares; MMRM, mixed-effect model repeated measure; SE, standard error.

DISCLOSURES

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