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Enclosure:

POSTER: Oberdhan D, Ward CL, Skubiak T, et al. Presented at: Psych Congress 2024; October 29–November 2, 2024; Boston, MA, USA.

Efficacy and Safety of Sustained-Release Centanafadine for the Treatment of ADHD in Adults: A Pooled Analysis of Two Phase 3 Trials

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INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in children and adults, characterized by symptoms of inattention, hyperactivity, and impulsivity—all of which can affect overall quality of life for patients and their families[1]
- Centanafadine (CTN)—a norepinephrine, dopamine, serotonin reuptake inhibitor (NDSRI)—was studied in two phase 3 trials for the treatment of ADHD in adults aged 18–55 years[2]
- The two phase 3 trials were the first large-scale studies to demonstrate the efficacy profiles of CTN in adults with ADHD, meeting the primary (change from baseline in Adult ADHD Investigator Symptom Rating Scale [AISRS] total score), and key secondary endpoint (change from baseline in Clinical Global Impression-Severity for ADHD (CGI-S-ADHD), at Week 6[2]

OBJECTIVE

- To assess the efficacy and safety of CTN for the treatment of ADHD in the pooled adult population

METHODS

- **Study:** Pooled analysis of two identically designed phase 3, multicenter, randomized, double-blind, placebo-controlled trials conducted in the US (NCT03605680 and NCT03605836) (**Figure 1**)
- **Eligible patients:** Adults (18–55 years) with a primary diagnosis of ADHD (of any presentation) according to *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria, as confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS)
- **Treatment:** Patients were randomized (1:1:1) to receive CTN 200 mg, CTN 400 mg, or placebo for up to 6 weeks
- **Primary endpoint:** Change from baseline to Week 6 in the AISRS total score
- **Key secondary endpoint:** Change from baseline to Week 6 in the CGI-S-ADHD score
- **Other efficacy endpoints:** Change from baseline to Week 6 in the mean AISRS Inattentive and Hyperactive/Impulsive (H/I) subscale scores
- **Analysis:** Mixed-effect model for repeated measures, with trial site, treatment group, visit, and treatment group-by-visit interaction as factors and baseline-by-visit interaction as a covariate; used "unstructured" covariance matrix
  - Only the primary and key secondary endpoints were controlled for multiplicity, with all other *P*-values descriptive.
- **Other outcomes:** Safety and tolerability

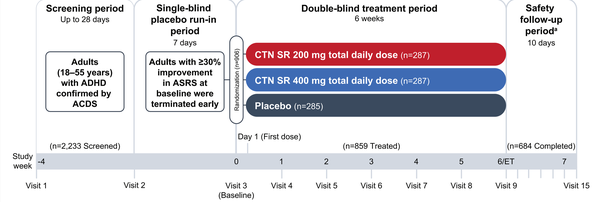
RESULTS

- Of the 906 adults in the pooled population randomized, 684 (75.5%) completed the study; 51.6% were male at birth and 48.4% were female at birth, with a mean age of 35.4 years (**Figure 2**)
- At Week 6, both doses of CTN demonstrated statistically significant improvement in the AISRS total score versus placebo with a mean difference of −3.56 (95% confidence interval [CI]: −5.34, −1.77) for CTN 200 and −3.59 (95% CI: −5.32, −1.85) for CTN 400 mg (both *P*<0.0001), and effect sizes of 0.33 and 0.34, respectively (**Figure 3**)
- Numerically greater improvements were observed for CTN in the AISRS Inattention and H/I subscale scores at Week 6 (**Figure 4**)
- Statistically significant reductions in ADHD symptom severity per CGI-S were also demonstrated by CTN with mean differences of −0.30 (95% CI: −0.46, −0.13) for CTN 200 and −0.28 (95% CI: −0.45, −0.12) for 400 mg, and effect sizes of 0.30 and 0.28, respectively, at Week 6 (**Figure 5**)

Safety and tolerability

- The incidence of treatment-emergent adverse events (TEAEs) was 45.6% in the pooled CTN population compared to 32.1% in the placebo group; majority were mild to moderate (**Table 1**)
- The most common TEAEs (≥2% of adults in CTN and greater than placebo) are presented in **Table 1**

Figure 1. Study design



[a]All patients were required to participate in the 7-day follow-up period, with follow-up telephone calls at days 1, 3, and 5 after the last dose of trial treatment, and in-clinic follow-up visits at days 2 and 7 after the last dose of trial treatment. Patients who terminated early, decided to not enroll, or were not eligible to enroll in the open label trial were required to participate in an additional follow-up telephone call 10 days after the last dose of trial treatment. ACDS, Adult ADHD Clinical Diagnostic Scale; ADHD, attention-deficit/hyperactivity disorder; ASRS, Adult ADHD Self Report Scale; CTN SR, centanafadine sustained release; ET, end of treatment.

Figure 2. Baseline demographics and clinical characteristics of the pooled population (N=859)

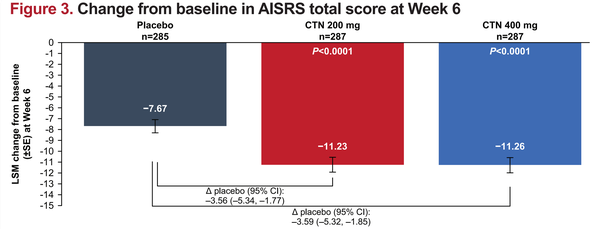
SEX AT BIRTH	MEAN WEIGHT	MEAN AISRS TOTAL SCORE
♂ **51.6%** male (n=443)	**82.3 (18.1)** kg	**38.8 (6.8)** (moderately ill)
MEAN AGE	**MEAN BMI**	**MEAN CGI-S-ADHD SCORE**
35.4 (9.9) years	**27.9 (5.3)** kg/m^2	**4.5 (0.6)** (moderately/markedly ill)

RACE

80.3% White (n=690) **0.8%** American Indian / Alaskan Native (n=7)
12.8% Black (n=110) **0.3%** Native Hawaiian / Other Pacific Islander (n=3)
3.0% Asian (n=26) **2.7%** Other (n=23)

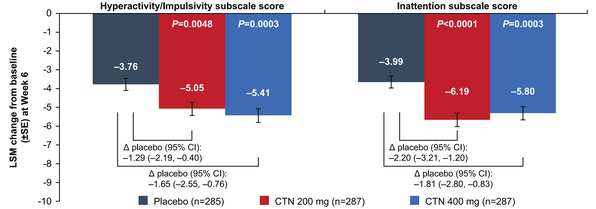
Means are presented with standard deviations. AISRS, Adult ADHD Investigator Symptoms Rating Scale; BMI, body mass index; CGI-S-ADHD, Clinical Global Impression-Severity for ADHD.

Figure 3. Change from baseline in AISRS total score at Week 6



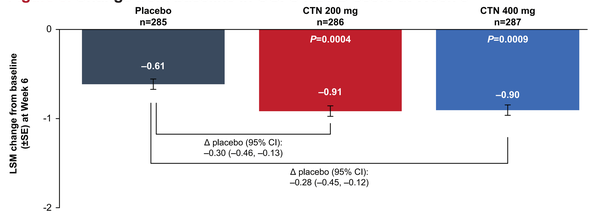
Δ placebo, change from placebo; CI, confidence interval; CTN, centanafadine; LSM, least squares mean; SE, standard error.

Figure 4. Change from baseline in AISRS H/I and Inattention subscale scores at Week 6



Δ placebo, change from placebo; CI, confidence interval; CTN, centanafadine; H/I, hyperactivity/impulsivity; LSM, least squares mean; SE, standard error.

Figure 5. Change from baseline in CGI-S-ADHD score at Week 6



Δ from PBO, change from placebo; CI, confidence interval; CGI-S-ADHD, Clinical Global Impression-Severity for ADHD; CTN, centanafadine; LSM, least squares mean; SE, standard error.

Table 1. Treatment-emergent adverse events

	CTN 400 mg	CTN 200 mg	CTN Pooled	Placebo
Patients treated	292	294	586	290
Patients with AEs, n (%)	144 (49.3)	123 (41.8)	267 (45.6)	93 (32.1)
Adverse events	333	248	581	180
Patients with TEAEs, n (%)	144 (49.3)	123 (41.8)	267 (45.6)	93 (32.1)
TEAEs*	318	245	563	175
Patients with serious TEAEs, n (%)	0 (0.0)	3 (1.0)	3 (0.5)	0 (0.0)
Patients with non-serious TEAEs, n (%)	144 (49.3)	122 (41.5)	266 (45.4)	93 (32.1)
Patients with severe TEAEs, n (%)	4 (1.4)	6 (2.0)	10 (1.7)	2 (0.7)
Patients discontinued due to AE, n (%)	18 (6.2)	14 (4.8)	32 (5.5)	4 (1.4)
Patient deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs ≥2% in CTN and greater than placebo, n (%)				
Decreased Appetite	20 (6.8)	15 (5.1)	35 (6.0)	5 (1.7)
Dry Mouth	17 (5.8)	9 (3.1)	26 (4.4)	1 (0.3)
Nausea	19 (6.5)	6 (2.0)	25 (4.3)	6 (2.1)
Irritability	12 (4.1)	10 (3.4)	22 (3.9)	5 (1.7)
Anxiety	5 (1.7)	7 (2.4)	12 (2.0)	3 (1.0)
Insomnia	13 (4.5)	8 (2.7)	21 (3.6)	7 (2.4)
Diarrhea	15 (5.1)	5 (1.7)	20 (3.4)	2 (0.7)
Upper Respiratory Infection	5 (1.7)	15 (5.1)	20 (3.4)	7 (2.4)
Rash	11 (3.8)	4 (1.4)	15 (2.6)	2 (0.7)

*Adverse events were counted once, per subject and term, for the most severe of multiple occurrences of a specific MedDRA preferred term. AEs, adverse events; TEAEs, treatment-emergent adverse events; CTN, centanafadine.

CONCLUSIONS

- In the pooled adult population with ADHD, CTN demonstrated statistically significant reductions in ADHD symptoms, per AISRS total score, and numerically greater improvements versus placebo in AISRS Inattention and Hyperactivity/Impulsivity subscale scores, at Week 6
- Treatment with CTN resulted in statistically significant improvements from baseline in ADHD symptom severity per CGI-S versus placebo at Week 6
- CTN demonstrated a favorable safety and tolerability profile in adults with ADHD
- CTN, a first-in-class NDSRI, was effective and generally safe and well tolerated in the pooled adult population with ADHD

References

1. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013:59-66.
2. Adler LA, et al. *J Clin Psychopharmacol*. 2022;42(5):429-39.

Acknowledgements

Medical writing and poster development support were provided by The Medicine Group, LLC (New Hope, PA, USA) in accordance with Good Publication Practice guidelines.

Funding

This study and poster development support were sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, NJ, USA).

Disclosures

DO, CLW, TS and **ZZ** are all full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **LAA** received grant/research support to NYU Grossman School of Medicine from Corium, Otsuka, Shire/Takeda; was a consultant for Bracket/Signant, Major League Baseball, National Football League, Neurocentria, Otsuka, SUNY, and Supernus; and received royalty payments (as inventor) from NYU Grossman School of Medicine for license of adult ADHD scales and training materials since 2004.

Poster presented at the
Psych Congress 2024; October 29–November 2, 2024; Boston, MA, United States