Request for Copy of Published Material

Please note, this is an investigational product and is not approved by the US Food and Drug Administration (FDA).

Enclosure:

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

Effect of Centanafadine on AISRS Over 6 Weeks of Treatment in Adults with ADHD: A Pooled Analysis of Two Phase 3 Trials

Dorothee Oberdhan[1a], Caroline L. Ward[1a], Taisa Skubiak[1b], Zhen Zhang[1b], Lenard A. Adler[2]

[1]Otsuka Pharmaceutical Development & Commercialization Inc., [a]Rockville, MD, and [b]Princeton, NJ, United States; [2]NYU Grossman School of Medicine, New York, NY, United States

Scan the QR code to receive a PDF of the poster

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]
- ADHD is associated with significant humanistic and economic burden on the patient and society, especially in adults, even after remission of some symptoms[2-5]
- 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[6]
- The two phase 3 trials presented here 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[6]

OBJECTIVE

- To evaluate the effect of CTN over 6 weeks of treatment of ADHD in a pooled adult population

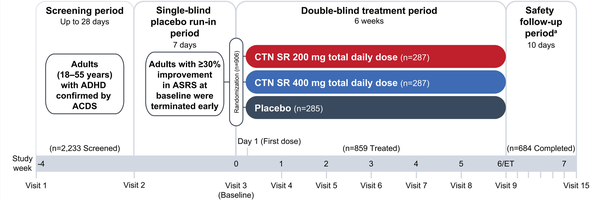
METHODS

- **Study:** 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
- **Other efficacy endpoints:** Change from baseline in the AISRS total score, Inattention and Hyperactivity/Impulsivity (H/I) subscale scores, and CGI-S-ADHD score over 6 weeks of treatment
- **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
  - Endpoints were not controlled not for multiplicity, and all *P*-values are therefore descriptive

RESULTS

- Of the 906 adults 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**)
- Numerically greater improvements in the AISRS total score versus placebo were observed as early as Week 1 for CTN 200 mg (effect size: 0.23) and Week 2 for 400 mg (effect size: 0.24), and maintained effect through 6 weeks of treatment (effect size: 0.33 and 0.34, respectively) (**Figure 3**)
- Similar numerical improvements were observed for CTN in the AISRS H/I subscale (**Figure 4**) and Inattention subscale scores (**Figure 5**), with early benefits which were maintained throughout 6 weeks of treatment
- Numerically greater improvements in ADHD symptom severity per CGI-S were first observed for CTN at Week 3 and remained significant through Week 6, with effect sizes ranging from 0.22–0.24 at Week 3 to 0.28–0.30 at Week 6 (**Figure 6**)

Figure 1. Study design



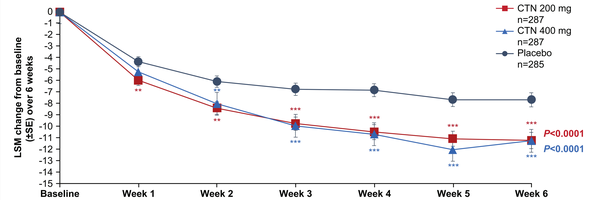
[a]All patients were required to participate in the 7-day follow-up period, with follow-up telephone calls at Days 1, 3, and 5 after the last dose of trial treatment, and in-clinic follow-up visits at Days 2 and 7 after the last dose of trial treatment. Patients who terminated early, decided to not enroll, 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/m²	**4.5 (0.6)** (moderately/markedly ill)
RACE	**80.3%** White (n=690) **12.8%** Black (n=110) **3.0%** Asian (n=26)	**0.8%** American Indian / Alaskan Native (n=7) **0.3%** Native Hawaiian / Other Pacific Islander (n=3) **2.7%** Other (n=23)

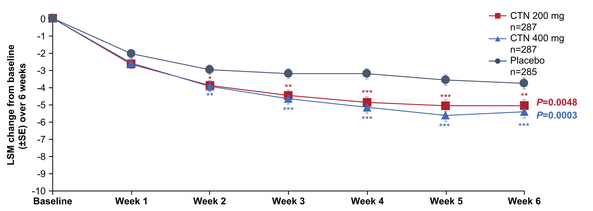
Means are presented with standard deviations. AISRS, Adult ADHD Investigator Symptoms Rating Scale; BMI, body mass index; CGI-S-ADHD, Clinical Global Impression-Severity for ADHD.

Figure 3. Change from baseline in AISRS total score over 6 weeks



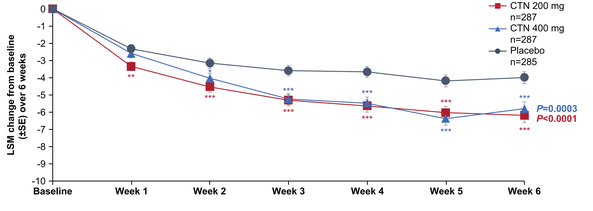
**P<0.01, ***P<0.001 vs placebo; with the exception of the Week 6 time point (primary efficacy endpoint), *P*-values were not controlled for multiplicity and are descriptive. The LSM change from baseline was analyzed using a mixed-effect model for repeated measures. AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN, centanafadine; LSM, least squares mean; SE, standard error.

Figure 4. Change from baseline in AISRS H/I subscale over 6 weeks



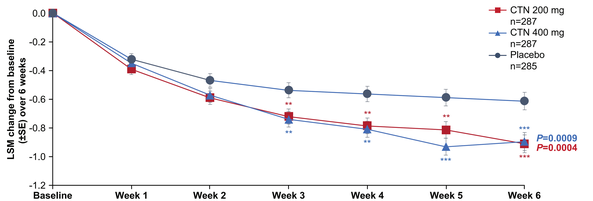
*P<0.05, **P<0.01, ***P<0.001 vs placebo. *P*-values were not controlled for multiplicity and are descriptive. The LSM change from baseline was analyzed using a mixed-effect model for repeated measures. AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN, centanafadine; H/I, hyperactivity/impulsivity; LSM, least squares mean; SE, standard error.

Figure 5. Change from baseline in AISRS Inattention subscale over 6 weeks



*P<0.05, **P<0.01, ***P<0.001 vs placebo; with the exception of the Week 6 time point (primary efficacy endpoint), *P*-values were not controlled for multiplicity and are descriptive. The LSM change from baseline was analyzed using a mixed-effect model for repeated measures. AISRS, Adult ADHD Investigator Symptom Rating Scale; CTN, centanafadine; LSM, least squares mean; SE, standard error.

Figure 6. Change from baseline in CGI-S-ADHD score over 6 weeks



**P<0.01, ***P<0.001 vs placebo; with the exception of the Week 6 time point (key secondary efficacy endpoint), *P*-values were not controlled for multiplicity and are descriptive. The LSM difference vs placebo from baseline was analyzed using a mixed-effect model for repeated measures. CGI-S-ADHD, Clinical Global Impression-Severity for ADHD; CTN, centanafadine; LSM, least squares mean; SE, standard error.

CONCLUSIONS

- In the pooled adult population with ADHD, CTN demonstrated greater improvements in core ADHD symptoms versus placebo, as assessed by the AISRS total score, as early as Week 1, with statistically significant improvements at Week 6
- CTN demonstrated numerically greater improvements in the AISRS Hyperactivity/Impulsivity and Inattention subscale scores as early as Week 2
- Improvements in ADHD symptom severity versus placebo, as assessed by CGI-S, were evident by Week 3 with CTN and maintained effect through Week 6

References

1. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association; 2013:59-66.
2. Thapar A. *Lancet*. 2016;387(10024):1240-50.
3. Volkow JD, et al. *NEJM*. 2013;369(20):1935-44.
4. Doshi JA, et al. *JAACAP*. 2012;51(10):990-1002.e2.
5. Schein J, et al. *JMCP*. 2022;28(2):168-79.
6. 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