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Enclosure:

POSTER: Hebert C, Childress AC, Strawn JR, et al. Presented at: Psych Congress 2026, September 15-19, 2026; New Orleans, LA, USA.

Effects of Centanafadine Across Core and Expanded ASRS Symptom Domains in Adults With ADHD and Comorbid Anxiety Disorders

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in adults that can substantially impair daily functioning and quality of life[1-3]
- Psychiatric comorbidities are common in adults with ADHD, with anxiety disorders among the most prevalent and contributing to a greater symptom burden and functional impairment[4-6]
- In addition to core symptoms of inattention, hyperactivity, and impulsivity, adults with ADHD often experience associated features such as executive dysfunction and emotional dysregulation, which can further contribute to functional impairment and treatment complexity[4,6]
- Centanafadine, a norepinephrine-dopamine-serotonin reuptake inhibitor (NDSRI) and central nervous system stimulant, was recently approved for the treatment of ADHD in children, adolescents, and adults[7]

Objective

- This phase 3b trial evaluated the effect of centanafadine on patient-reported core ADHD symptoms and associated features in adults with ADHD and comorbid anxiety disorders

Methods

- **Study:** A phase 3b, multicenter, randomized, double-blind, 8-week, placebo-controlled trial conducted in the US (NCT06973577)
- **Participants:** Adults (18–65 years) with ADHD (of any presentation) and diagnosed anxiety disorders (generalized and/or social), according to *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, Text Revision, (*DSM-5-TR*) criteria
- **Treatment:** Patients were randomized (1:1) to receive once-daily centanafadine extended-release 328.8 mg or placebo for up to 8 weeks
- **Secondary efficacy endpoints:** Change from baseline in the adult ADHD Self-Report Scale (ASRS) Expanded Version scores at Week 8, including ASRS 18-item total score and Hyperactivity/Impulsivity, Inattention, Executive Function (EF), and Emotional Dyscontrol (ED) subscale scores
  - The ASRS is a validated, self-administered questionnaire used to screen for and assess ADHD symptoms and symptom severity and consists of 31 items, including 18 assessing the frequency of DSM-5 symptoms of ADHD, 9 assessing executive function deficits, and 4 assessing emotional dyscontrol[8]
  - Response choices consist of 0 (never), 1 (rarely), 2 (sometimes), 3 (often), and 4 (very often)[8]
- **Analysis:** Secondary efficacy endpoints were analyzed using a 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
  - No adjustment was made for multiplicity; therefore, *P*-values are nominal and should be interpreted descriptively

Results

- Of the 315 adults (mean age 38 years, 64% female) randomized to centanafadine (n=157) or placebo (n=158), 241 (76.5%) completed the trial
- Mean ± standard deviation baseline ASRS scores were 51.5 ± 9.9 for the ASRS 18-item total score and 23.9 ± 6.1, 27.7 ± 4.9, 26.5 ± 5.4, and 10.4 ± 3.2 for Hyperactivity/Impulsivity, Inattention, Executive Function, and Emotional Dyscontrol subscales, respectively, consistent with significant symptom burden (**Figure 1**)
- At Week 8, centanafadine demonstrated greater improvements in the patient-reported ASRS 18-item total score (P=0.0002) and in the Hyperactivity/Impulsivity (P=0.0009) and Inattention (P=0.0002) subscales than placebo (**Figures 2 and 3**)
- Consistent with improvements in core symptoms, greater improvements were observed with centanafadine than placebo in both the Executive Function (P<0.0048) and Emotional Dyscontrol (P<0.0484) subscales (**Figures 4 and 5**)

Figure 1. Baseline demographics and clinical characteristics

SEX AT BIRTH
64.4% female (n=203)
35.6% male (n=112)

MEAN AGE
38.1 (11.3) years

MEAN WEIGHT
80.4 (17.5) kg

ANXIETY TYPE
94.0% GAD (n=296)
14.6% SAD (n=46)

RACE
0.6% American Indian/Alaskan Native (n=2)
5.7% Asian (n=18)
17.1% Black or African American (n=54)
9.2% Other (n=29)
67.0% White (n=211)

MEAN ASRS 18-ITEM TOTAL SCORE
51.5 (9.9) (severe)

MEAN ASRS H/I SCORE
23.9 (6.1) (moderate)

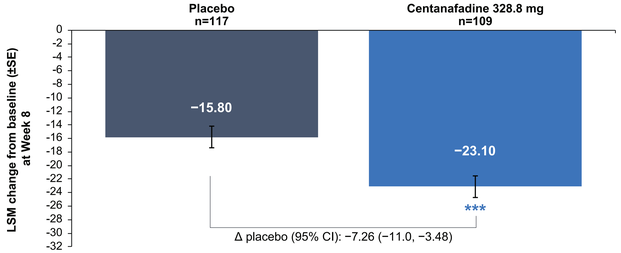
MEAN ASRS INATTENTION SCORE
27.7 (4.9) (severe)

MEAN ASRS EF SCORE
26.5 (5.4) (severe)

MEAN ASRS ED SCORE
10.4 (3.2) (severe)

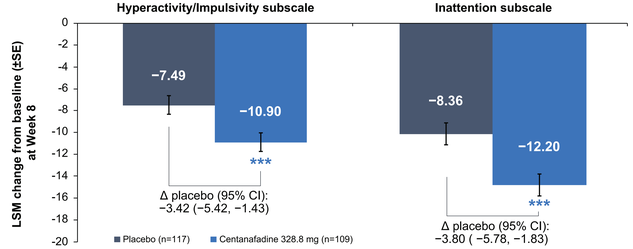
Baseline demographics and clinical characteristics are reported for the randomized population (N=315). Means are presented with standard deviations.
ADHD, attention-deficit/hyperactivity disorder; ASRS, adult ADHD Self-Report Scale; ED, Emotional Dyscontrol; EF, Executive Function; GAD, generalized anxiety disorder; H/I, Hyperactivity/Impulsivity; SAD, social anxiety disorder.

Figure 2. Change from baseline in the ASRS 18-item total score at Week 8



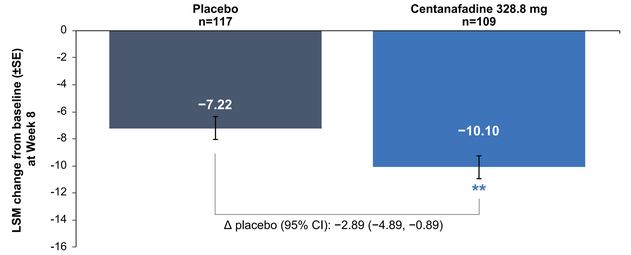
Efficacy analyses were conducted in the full analysis set (N=308).
***P<0.001.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; LSM, least squares mean; SE, standard error.

Figure 3. Change from baseline in the ASRS Hyperactivity/Impulsivity and Inattention subscales at Week 8



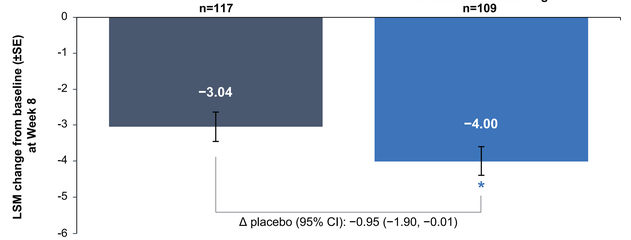
Efficacy analyses were conducted in the full analysis set (N=308).
***P<0.001.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; LSM, least squares mean; SE, standard error.

Figure 4. Change from baseline in the ASRS Executive Function subscale at Week 8



Efficacy analyses were conducted in the full analysis set (N=308).
**P<0.01.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; LSM, least squares mean; SE, standard error.

Figure 5. Change from baseline in the ASRS Emotional Dyscontrol subscale at Week 8



Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05.
Δ placebo, change from placebo; ASRS, adult ADHD Self-Report Scale; CI, confidence interval; LSM, least squares mean; SE, standard error.

Conclusions

- **Centanafadine demonstrated greater improvements than placebo across patient-reported ASRS measures of core ADHD symptoms and associated impairments, including executive dysfunction and emotional dysregulation, in adults with ADHD and comorbid anxiety disorders**
- **These findings support further investigation of centanafadine's potential to address not only core ADHD symptoms but also the emotional and cognitive impairments frequently experienced by adults with ADHD and comorbid anxiety disorders**

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Acknowledgements

The study and poster development support were sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, United States. Medical writing and poster development support were provided by The Medicine Group, LLC (New Hope, PA, United States) in accordance with Good Publication Practice guidelines.

At Otsuka, we hold a deep respect for the value of every mind. We will not rest until mental illnesses and brain diseases are approached with the same priority and urgency as our physical health and recognized as chronic diseases that warrant early, equitable, and accessible intervention for patients and caregivers everywhere.

Disclosures

CH has been an advisory board member for GSK, Ironshore (Collegium), Otsuka, Rhodes, Supernus, and Teva; and has been on a speaker bureau for GSK, Ironshore (Collegium), Otsuka, Rhodes, and Supernus. **ACC** has been a consultant for Aardvark, Alora, Arbor, Attentiv, Aytu, Corium, Ironshore, Lumos, Neos Therapeutics, Neurocentria, Noven, Otsuka, Purdue, Rhodes, Sky, Sunovion, Supernus, Tris, and Zevra Therapeutics Inc.; has participated on speakers' bureaus for Collegium (Ironshore), Supernus, Takeda, and Tris; has received research support from Aardvark, Adlon, Akili, Allergan, Arbor, Emalex, IntraCellular Therapies, Collegium (Ironshore), Lumos, Neos Therapeutics, Otsuka, Purdue, Rhodes, Servier, Sunovion, Supernus, Suven, Syndeio, Takeda, Tris, and Zevra Therapeutics Inc.; has received writing support from Arbor, Collegium (Ironshore), Neos Therapeutics, Purdue, Rhodes, Sunovion, Takeda, and Tris; and has participated on advisory boards for Adlon, Akili, Arbor, Cingulate, Corium, Collegium (Ironshore), Otsuka, Purdue, Sunovion, Supernus, and Tris. **JRS** has received research support from the National Institutes of Health, PCORI Abbvie, and Definium; has received material support from Myriad Genetics; has consulted for AbbVie, Alkermes, Collegium, Definium, Newleos, Otsuka, Supernus, Sensorium, Vistagen, and Genomind; has served on the speaker's bureau for Abbvie, Collegium, Supernus, and Myriad Genetics; receives royalties from Springer Publishing and Cambridge University Press; receives honoraria from the Neuroscience Education Institute; serves as an author for UpToDate; and serves a member of a data safety monitoring board for Eli Lilly. **GM** serves as a speaker for Alkermes, Allergen Ironshore, Janssen, Lundbeck, Otsuka, Sunovion, and Takeda; serves as a consultant for Akili, Alkermes, Allergan, Axsome, Ironshore, Intra-Cellular, Ironshore, Janssen, Lundbeck, Otsuka, Neos, Purdue, Rhodes, Sage, Sunovion, Takeda, and Teva; and is a researcher for Akili, Alkermes, Allergan, Axsome, Boehringer, Janssen, Lundbeck, Medgenics, NLS-1 Pharma AG, Otsuka, Reckitt Benckiser, Roche, Sage, Sunovion, Supernus, Takeda, and Teva. **AJC** has been a consultant or advisory board member for AbbVie, Acadia, Actinogen, Alfasigma, Alkermes, Anavex Life Sciences, Arrivo BioVentures, Autobahn, Axsome, Aytu, Bristol Myers Squibb, Collegium, Definium, 4M, Helus, Incannex Healthcare, J&J Innovative Medicine, Jazz, Knight, Kye, Kuvatris Therapeutics, LivaNova, Lundbeck, Luye, MapLight, Mentavi, Neumora, Neurocrine Biosciences, Noven, Otsuka, Sensorium, Sirtsei, Supernus, Teva, Thynk, Transneural, Tris, Vanda, and Vistagen; has been on a speaker bureau for AbbVie, Alfasigma, Alkermes, Axsome, Aytu, Bristol Myers Squibb, Collegium, J&J Innovative Medicine, Knight, Kye, Lundbeck, Luye, Neurocrine, Noven, Otsuka, Supernus, Teva, Tris, and Vanda; was on a data safety monitoring board for Compass Pathways; and has stock options/equity in EMA Wellness, Evolution Research Group, 4M, Jupiter Neuroscience, Sensorium, and Transneural. **ZZ, LL,** and **CLW** are all full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **EB** was a former employee of Otsuka Pharmaceutical Development & Commercialization, Inc.

Poster Number: 217

Poster presented at Psych Congress 2026; September 15–19, 2026; New Orleans, LA, United States.