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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.

Efficacy and Safety of Centanafadine in Adults With ADHD and Comorbid Anxiety Disorders: A Randomized, Double-Blind, Placebo-Controlled Trial

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in adults, characterized by core symptoms of inattention, hyperactivity, and impulsivity, along with associated features such as emotional dysregulation and executive dysfunction, that can further contribute to impaired daily functioning and quality of life[1-3]
- Psychiatric comorbidities are common in adults with ADHD, with anxiety disorders among the most prevalent comorbidities, affecting 25-50% of individuals with ADHD[4-6]
- Co-occurring anxiety disorders are associated with greater symptom burden and functional impairment and may complicate ADHD treatment[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 efficacy and safety of centanafadine in adults with ADHD and comorbid anxiety disorders

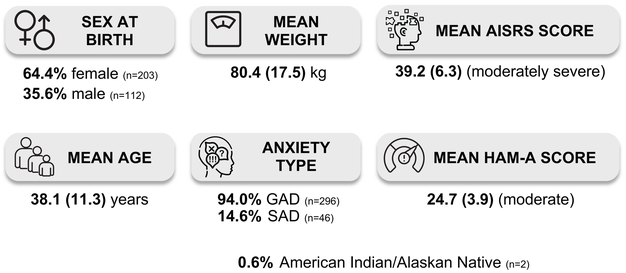
Methods

- **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
- **Efficacy endpoints:** The primary and key secondary efficacy endpoints were the change from baseline to Week 8 in the adult ADHD Investigator Symptom Rating Scale (AISRS) total score and Hamilton Anxiety Rating Scale (HAM-A) total score, respectively; secondary efficacy endpoints included change from baseline in the AISRS Inattention and Hyperactivity/Impulsivity subscale scores
  - The AISRS is an 18-item clinician-rated scale that assesses the severity and functional impact of ADHD symptoms from 0 (none) to 3 (severe), yielding a total score of 0–54, with higher scores indicating greater symptom severity[8]
  - The HAM-A is a 14-item clinician-rated scale that assesses the severity of psychic (mental agitation and psychological distress) and somatic (physical complaints related to anxiety symptoms) anxiety; each item is rated from 0 (not present) to 4 (very severe), yielding a total score of 0–56, with higher scores indicating greater anxiety severity[9]
- **Other outcomes:** Safety and tolerability
- **Analysis:** 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
  - Only the primary and key secondary endpoints were controlled for multiplicity, with all other *P*-values being descriptive
  - Effect sizes were calculated using Cohen's d method based on mixed models for repeated measures estimates

Results

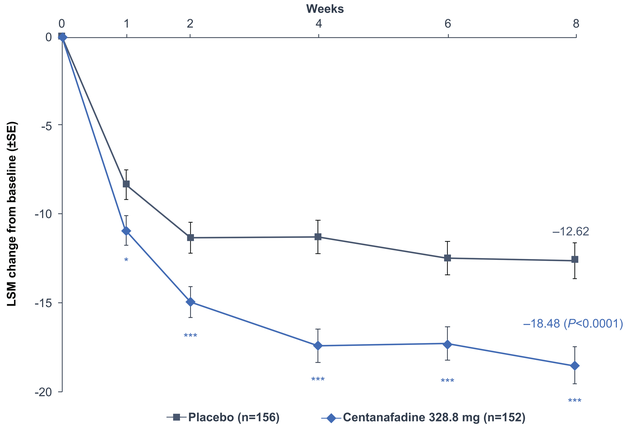
- Of the 315 adults (mean age 38 years, 64% female) randomized to centanafadine (n=157) or placebo (n=158), a total of 241 (76.5%) completed the trial
- Baseline mean ± standard deviation AISRS and HAM-A scores were 39.2 ± 6.3 and 24.7 ± 3.9, respectively (**Figure 1**)
- At Week 8, centanafadine demonstrated significantly greater improvement than placebo on the AISRS total score (change from baseline: −18.48, treatment difference: −5.87; *P*<0.0001), with an effect size of 0.50, and improvements evident as early as Week 1 (**Figure 2**)
- Similarly, centanafadine demonstrated significantly greater improvement than placebo on the HAM-A total score (change from baseline: −12.55, treatment difference: −1.92; *P*=0.0244) at Week 8 and as early as Week 4 (**Figure 3**)
- AISRS Inattention and Hyperactivity/Impulsivity subscale scores improved as early as Week 1, with improvements observed through Week 8 (change from baseline: –9.31 and –9.23, respectively; both *P*<0.0001)
- Overall, 111 (70.7%) centanafadine-treated participants experienced a treatment-emergent adverse event (TEAE), with majority being mild to moderate in severity (**Table 1**)
- The most common TEAEs for centanafadine versus placebo were nausea, decreased appetite, and diarrhea
- One centanafadine-treated participant experienced a serious TEAE (suicide attempt), which was deemed not treatment-related

Figure 1. Baseline demographics and clinical characteristics



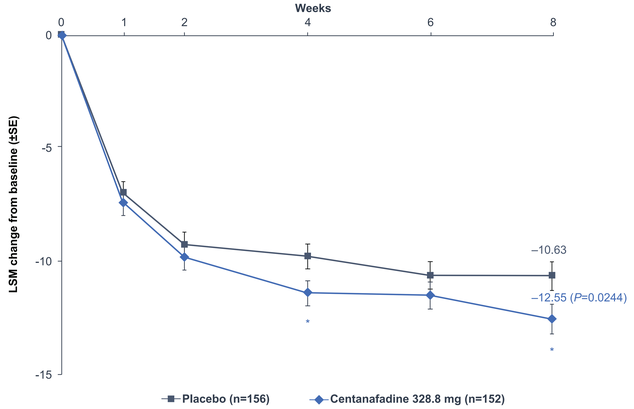
Baseline demographics and clinical characteristics are reported for the randomized population (N=315). Means are presented with standard deviations.
ADHD, attention-deficit/hyperactivity disorder; AISRS, adult ADHD Investigator Symptom Rating Scale; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; SAD, social anxiety disorder.

Figure 2. Change from baseline in the AISRS total score across 8 weeks



Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05, ***P<0.001.
AISRS, adult ADHD Investigator Symptom Rating Scale; LSM, least squares mean; SE, standard error.

Figure 3. Change from baseline in the HAM-A across 8 weeks



Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05.
HAM-A, Hamilton Anxiety Rating Scale; LSM, least squares mean; SE, standard error.

Table 1. Summary of treatment-emergent adverse events

	Centanafadine 328.8 mg n=157	Placebo n=158
Participants with TEAEs, n (%)	111 (70.7)	80 (50.6)
Serious TEAEs	1 (0.6)[a]	0
Severe TEAEs	5 (3.2)	3 (1.9)
Discontinuations due to TEAEs, n (%)	17 (10.8)	5 (3.2)
Deaths, n (%)	0	0
Abuse potential-related TEAEs, n (%)	7 (4.5)	6 (3.8)
Dizziness	6 (3.8)	5 (3.2)
Somnolence	1 (0.6)	1 (0.6)
AEs of special interest: rash, n (%)	10 (6.4)	4 (2.5)
Rash	4 (2.5)	3 (1.9)
Maculo-papular rash	2 (1.3)	1 (0.6)
Morbilliform rash	1 (0.6)	0
Papular rash	2 (1.3)	0
Pruritic rash	1 (0.6)	0
TEAEs with an incidence ≥5% in centanafadine-treated participants and greater than placebo, n (%)		
Nausea	27 (17.2)	9 (5.7)
Decreased appetite	21 (13.4)	5 (3.2)
Diarrhea	16 (10.2)	5 (3.2)
Insomnia	14 (8.9)	7 (4.4)
Dry mouth	13 (8.3)	1 (0.6)
Vomiting	9 (5.7)	2 (1.3)
Initial insomnia	8 (5.1)	0

TEAEs are summarized for the safety population (N=315).
[a]Suicide attempt, deemed not related to study treatment.
AEs, adverse events; TEAEs, treatment-emergent adverse events.

Conclusions

- **Centanafadine significantly improved ADHD and anxiety symptoms in adults with ADHD and comorbid anxiety disorders**
- **Centanafadine was generally well tolerated, with a safety profile consistent with previous studies**

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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**, **ST**, 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: 215

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