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Enclosure:

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Effects of Centanafadine on Clinician- and Patient-Rated Global Impressions 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 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, functional impairment, and treatment complexity[4-6]
- Evaluating treatment response both from clinician and patient perspectives can provide complementary insight into changes in overall ADHD and anxiety symptom severity[7]
- 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[8]

Objective

- This phase 3b trial evaluated the effects of centanafadine on clinician- and patient-rated global impressions of ADHD and anxiety symptom severity and change 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:** Endpoints included change from baseline at Week 8 in Clinical Global Impression–Severity (CGI-S) and the corresponding patient-reported version, Patient Global Impression–Severity (PGI-S), and Clinical Global Impression–Change (CGI-C), modified for ADHD and anxiety scores at each post-baseline visit
  - CGI-S was rated from 1 (normal, not at all ill) to 7 (among the most extremely ill)[9]
  - PGI-S scores ranged from 1 (no symptoms) to 7 (severe symptoms)[9]
  - CGI-C was rated from 1 (very much improved) to 7 (very much worse)[9]
- **Analysis:** CGI/PGI-S were analyzed using a mixed-effects 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); CGI-C was analyzed using Cochran Mantel Haenszel (last-observation-carried-forward) without adjusting for multiplicity

Results

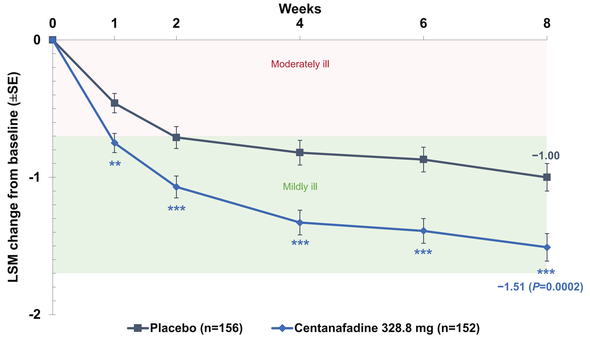
- A total of 315 adults (mean age 38 years, 64% female) were randomized to centanafadine (n=157) or placebo (n=158), and 241 (76.5%) completed the trial
- Baseline mean ± standard deviation ADHD and anxiety symptom severity scores were 4.7 ± 0.6 and 4.4 ± 0.6, respectively, consistent with moderate to marked symptom severity (**Figure 1**)
- At Week 8, improvement in ADHD severity was observed from both clinician and patient perspectives, with treatment differences versus placebo of −0.51 (95% CI, −0.77, −0.24) on the clinician-rated CGI-S-ADHD and −0.50 (95% CI, −0.83, −0.17) on the patient-reported PGI-S-ADHD; mean clinician-rated severity decreased from a moderate range at baseline to mildly ill at Week 8, with improvements observed as early as Week 1 on both measures (**Figures 2 and 3**)
- A similar pattern was observed in anxiety severity at Week 8, with treatment differences versus placebo of −0.29 (95% CI, −0.55, −0.04) on the clinician-rated CGI-S-anxiety and −0.38 (95% CI, −0.71, −0.04) on the patient-reported PGI-S-anxiety; mean clinician-rated severity decreased from a moderate range at baseline to borderline ill at Week 8, with improvements on both measures observed beginning at Week 4, consistent with the onset of improvement on the Hamilton Anxiety Rating Scale (HAM-A) (**Figures 4 and 5**)
- At Week 8, clinicians rated greater overall improvement with centanafadine than placebo on the CGI-C for both ADHD and anxiety; mean scores with centanafadine were 2.51 versus 2.90 (P=0.0003) for ADHD and 2.49 versus 2.76 (P=0.0352) for anxiety, respectively, indicating improvement on both domains

Figure 1. Baseline demographics and clinical characteristics

SEX AT BIRTH	MEAN AGE	MEAN WEIGHT	ANXIETY TYPE	MEAN CGI-S-ADHD SCORE	MEAN CGI-S-ANXIETY SCORE	MEAN PGI-S-ADHD SCORE	MEAN PGI-S-ANXIETY SCORE	RACE
64.4% female (n=203) **35.6%** male (n=112)	**38.1 (11.3)** years	**80.4 (17.5)** kg	**94.0%** GAD (n=296) **14.6%** SAD (n=46)	**4.7 (0.6)** (moderately ill)	**4.4 (0.6)** (moderately ill)	**5.3 (1.0)** (moderately severe)	**4.8 (1.1)** (moderately severe)	**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)

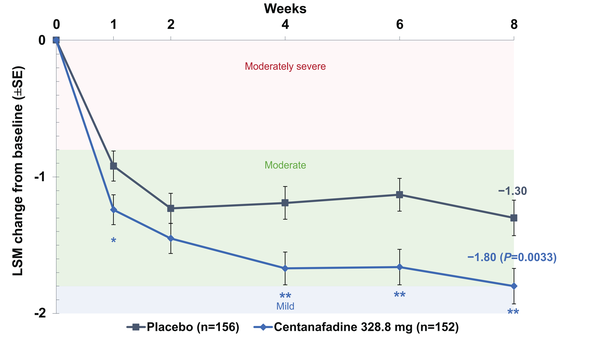
Baseline demographics and clinical characteristics are reported for the randomized population (N=315). Means are presented with standard deviations.
CGI-S-ADHD, Clinical Global Impression-Severity modified for ADHD; CGI-S-anxiety, Clinical Global Impression-Severity modified for anxiety; GAD, generalized anxiety disorder; PGI-S-ADHD, Patient Global Impression-Severity modified for ADHD; PGI-S-anxiety, Patient Global Impression-Severity modified for anxiety; SAD, social anxiety disorder.

Figure 2. Clinician-reported mean change from baseline in ADHD severity across 8 weeks



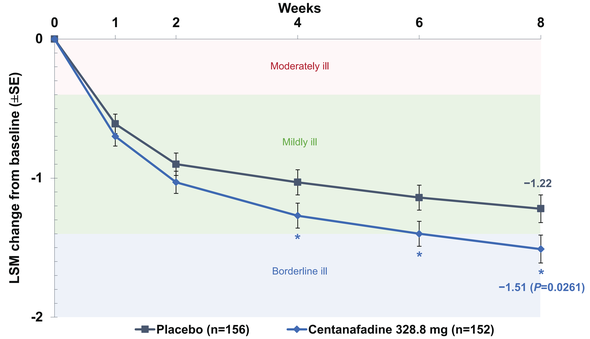
Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05, **P<0.01, ***P<0.001.
Shaded bands indicate approximate CGI-S-ADHD severity categories based on the mean baseline scores and are provided for contextual interpretation of mean change from baseline; they do not represent individual participant shifts in severity.
LSM, least squares mean; SE, standard error.

Figure 3. Patient-reported mean change from baseline in ADHD severity across 8 weeks



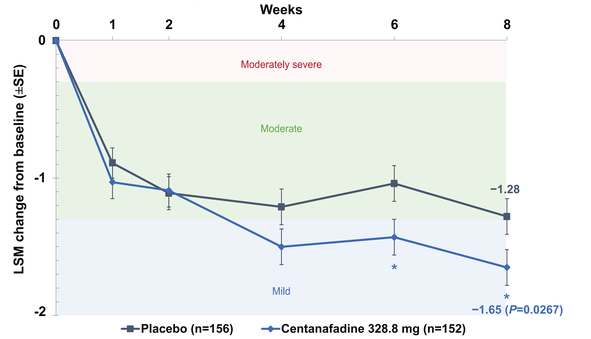
Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05, **P<0.01.
Shaded bands indicate approximate PGI-S-ADHD severity categories based on the mean baseline scores and are provided for contextual interpretation of mean change from baseline; they do not represent individual participant shifts in severity.
LSM, least squares mean; SE, standard error.

Figure 4. Clinician-reported mean change from baseline in anxiety severity across 8 weeks



Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05.
Shaded bands indicate approximate CGI-S-anxiety severity categories based on the mean baseline scores and are provided for contextual interpretation of mean change from baseline; they do not represent individual participant shifts in severity.
LSM, least squares mean; SE, standard error.

Figure 5. Patient-reported mean change from baseline in anxiety severity across 8 weeks



Efficacy analyses were conducted in the full analysis set (N=308).
*P<0.05.
Shaded bands indicate approximate PGI-S-anxiety severity categories based on the mean baseline scores and are provided for contextual interpretation of mean change from baseline; they do not represent individual participant shifts in severity.
LSM, least squares mean; SE, standard error.

Conclusions

- **In adults with ADHD and comorbid anxiety disorders, improvements were observed across clinician- and patient-rated global measures of both ADHD and anxiety, supporting a consistent treatment effect across multiple clinically meaningful assessments**
- **ADHD improvements were evident as early as Week 1, while anxiety improvements emerged beginning at Week 4 across global measures and HAM-A, consistent with the time course generally reported for the anxiolytic effects of serotonergic therapies used to treat anxiety disorders[10]**

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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, Attenliv, 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, Allergan 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**, **TS**, and **CLW** are all full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **EB** was a former employee of Otsuka Pharmaceutical Development & Commercialization, Inc.

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