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Enclosure:

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Impact of Centanafadine on Sleep in Adults With ADHD: Safety Assessments Pooled From Two Phase 3 Trials

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INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic and prevalent neurodevelopmental disorder in 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 in adults is associated with substantial burden, including impaired quality of life, reduced daily functioning, and increased healthcare and societal costs. Sleep disturbances—such as fluctuating quality and duration of sleep—are commonly reported and may result from the disorder itself or its treatment[2-7]
- Given that prevalence of sleep disturbances in adults with ADHD, it is important to consider that pharmacologic treatments—despite their efficacy—may also contribute to sleep-related adverse events[6,7]
- Centanafadine—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[8]
- Large-scale studies have demonstrated the efficacy and safety profiles of centanafadine in adults with ADHD[8]

OBJECTIVE

- This pooled analysis evaluated the impact of centanafadine on sleep, as assessed through safety outcomes, in adults with ADHD

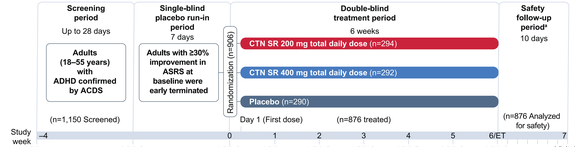
METHODS

- **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 centanafadine sustained-release twice daily formulation 200 mg, 400 mg, or placebo for up to 6 weeks
- **Safety:** Sleep outcomes, analyzed in all participants treated (Safety Sample), included treatment-emergent adverse events (TEAEs) related to sleep disturbances, defined as:
  - Subtopic: Somnolence
    - Hypersomnia, Microsleep, Sedation, Sleep attacks/inertia, Somnolence, Sudden onset of sleep
  - Subtopic: Insomnia
    - Abnormal sleep-related event, Advanced/Delayed/Irregular sleep phase, Behavioral induced insufficient sleep syndrome, Circadian rhythm sleep disorder, Dyssomnia, Hyposomnia, Initial/Middle/Terminal/Paradoxical/Psychophysiologic insomnia, Insomnia, Irregular sleep-wake rhythm disorder, Non-24-hour sleep-wake disorder, Parasomnia, Poor quality sleep, Sleep deficit, Somniphobia
  - Subtopic: Other sleep disturbances
    - Rapid eye movement sleep abnormal/behavior disorder, Sleep disorder, Sleep paralysis/sex/talking, Sleep-related eating disorder, Somnambulism
- **Analysis:** All sleep-disturbance-related treatment emergent adverse events (TEAEs) were coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA version 26.0) preferred term

RESULTS

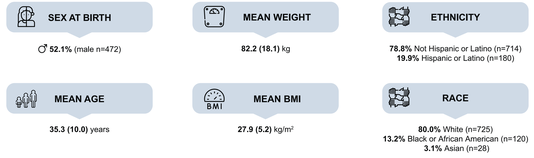
- Baseline demographics and characteristics of the pooled randomized population are presented in **Figure 2**
- In the pooled centanafadine-treated group, insomnia-related TEAEs were reported in 6.0% of participants versus 3.8% in the placebo group, while somnolence-related TEAEs in 1.0% and 1.4%, respectively (**Table 1**); none of these events were considered serious
- No participants reported other sleep disturbances
- Most sleep-disturbance-related TEAEs were mild to moderate in severity, with only 3 events considered severe within the subtopic of Insomnia; day of onset and range of durations of these events were variable with no apparent trends observed (**Table 2**)
- Overall, only 3 participants in the pooled centanafadine group discontinued due to a sleep-disturbance-related TEAE; 2 due to insomnia and 1 due to somnolence

Figure 1. Study design



*All participants 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. Participants 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 randomized population (N=906)



Means are presented with standard deviations. BMI, body mass index.

Table 1. Incidence of sleep-disturbance-related TEAEs

	CTN 200 mg (N=294)	CTN 400 mg (N=292)	All CTN (N=586)	Placebo (N=290)
All TEAEs, n (%)	123 (41.8)	144 (49.3)	267 (45.6)	93 (32.1)
Sleep disturbance TEAEs, n (%)				
Subtopic: Insomnia	16 (5.4)	19 (6.5)	35 (6.0)	11 (3.8)
Initial insomnia	2 (0.7)	3 (1.0)	5 (0.9)	4 (1.4)
Insomnia	8 (2.7)	13 (4.5)	21 (3.6)	7 (2.4)
Middle insomnia	2 (0.7)	1 (0.3)	3 (0.5)	0
Poor quality sleep	1 (0.3)	2 (0.7)	3 (0.5)	0
Terminal insomnia	4 (1.4)	0	4 (0.7)	0
Subtopic: Somnolence	1 (0.3)	5 (1.7)	6 (1.0)	4 (1.4)
Sedation	0	1 (0.3)	1 (0.2)	1 (0.3)
Somnolence	1 (0.3)	4 (1.4)	5 (0.9)	3 (1.0)
Subtopic: Other sleep disturbances	0	0	0	0
All treatment-related TEAEs, n (%)	72 (24.5)	95 (32.5)	167 (28.5)	46 (15.9)
Initial insomnia	1 (0.3)	3 (1.0)	4 (0.7)	3 (1.0)
Insomnia	7 (2.4)	10 (3.4)	17 (2.9)	3 (1.0)
Middle insomnia	2 (0.7)	1 (0.3)	3 (0.5)	0
Poor quality sleep	1 (0.3)	1 (0.3)	2 (0.3)	0
Terminal insomnia	4 (1.4)	0	4 (0.7)	0
Sedation	0	0	0	1 (0.3)
Somnolence	0	4 (1.4)	4 (0.7)	1 (0.3)

Under the topic of interest (sleep-disturbance-related TEAEs) preferred terms are organized by subtopic of interest (insomnia, somnolence, or other). Participants were counted once per preferred term, once per subtopic, and once per overarching topic.
CTN, centanafadine; TEAEs, treatment emergent adverse events.

Table 2. Summary of characteristics for sleep disturbance TEAEs

	CTN 200 mg (N=294)	CTN 400 mg (N=292)	All CTN (N=586)	Placebo (N=290)
All severe TEAEs, n (%)	6 (2.0)	4 (1.4)	10 (1.7)	2 (0.7)
Insomnia	0	2 (0.7)	2 (0.3)	0
Middle insomnia	1 (0.3)	0	1 (0.2)	0
All discontinuations due to TEAEs, n (%)	14 (4.8)	18 (6.2)	32 (5.5)	4 (1.4)
Insomnia	1 (0.3)	1 (0.3)	2 (0.3)	0
Somnolence	0	1 (0.3)	1 (0.2)	0

Under the topic of interest (sleep-disturbance-related TEAEs) preferred terms are organized by subtopic of interest (insomnia, somnolence, or other). Participants were counted once per preferred term, once per subtopic, and once per overarching topic.
Table includes only severe sleep disturbance–related TEAEs and those resulting in participant discontinuation. Mild to moderate events are not shown.
CTN, centanafadine; TEAEs, treatment emergent adverse events.

CONCLUSIONS

- Centanafadine was generally well tolerated over 6 weeks, with a low incidence of sleep disturbances as TEAEs
- Sleep-disturbance-related TEAEs were generally mild to moderate
- Discontinuations due to sleep disturbances were infrequent, with only three participants discontinuing in the pooled adult population
- In adults, centanafadine showed a favorable sleep-related tolerability profile, with notably lower rates of insomnia (6.0% vs 15–23.0%) and somnolence (1.0% vs 6–8.0%) compared to approved non-stimulant therapies in trials lasting 6 to 25 weeks[9,10]

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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.

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