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Enclosure:

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Characterization of Adverse Event Timing and Duration With Centanafadine in Children and Adolescents With ADHD: Pooled Results From Two Phase 3 Trials

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Introduction

- Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous stimulant approved as a once-daily extended-release (QD XR) formulation for the treatment of attention-deficit/hyperactivity disorder (ADHD) in pediatric and adult populations[1]
- Centanafadine was shown to be generally safe, well tolerated, and efficacious in treating core symptoms and associated features of ADHD in two Phase 3 trials for the treatment of ADHD in children aged 6–12 years[2] and adolescents aged 13–17 years[3]

Objective

- To characterize the timing of adverse event (AE) onset, emergence, and duration in children and adolescents treated with centanafadine.

Methods

- **Studies:** Two phase 3, multicenter, randomized, double-blind, placebo-controlled trials conducted in the United States and Canada (children[2]: NCT05428033; adolescents[3]: NCT05257265)
- **Participants:** Post hoc analyses included pooled data from children (6–12 years) and adolescents (13–17 years) from each trial 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 Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
- **Treatment and dosing:** Participants included in this analysis received centanafadine 328.8 mg QD XR (or a weight-based equivalent) without titration, or placebo, for 6 weeks
- **Outcomes:**
  - Safety and tolerability
    - Onset time and duration of common AEs (≥5% for centanafadine and greater than placebo)
    - AE categories reported are consistent with the centanafadine label.[1] Reported percentage of rash AEs used composite criteria, which includes skin eruptions and other related terms

Results

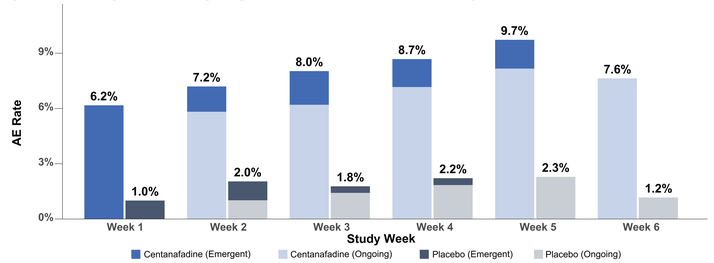
- Overall, 608 participants were included in this analysis (centanafadine, n=308; placebo, n=300)
- The most common AEs reported in the centanafadine group and occurring more frequently than with placebo were decreased appetite, rash (pruritic or non-pruritic), nausea, and headache (**Table 1**)
- For decreased appetite, the most newly emergent cases occurred during Week 1 (6.2%), with few new cases occurring in Weeks 2 and 3 (**Figure 1**)
- For nausea, most newly emergent cases occurred in Week 1 (4.5%), with fewer emergent cases occurring in the weeks thereafter (**Figure 2**)
- For rash, in Week 1, there was a 1.3% emergent rate, which rose to 7.9% in Week 2. Only one new rash event occurred after Week 2—a maculo-papular rash with onset on Day 16 (**Figure 3**)
- Most rash cases were simple maculopapular exanthema (pruritic or non-pruritic) with no associated systemic symptoms, mild in severity, and resolved within 2 weeks
- There were no serious cases, no occurrences of severe cutaneous adverse reactions (SCAR), no deaths reported, and most participants (73.1%) continued treatment despite rash symptoms (**Table 1**)
- Headache, nausea, and rash are predominantly early-treatment events, with a median duration typically limited to 1–2 weeks; whereas decreased appetite persists over a longer duration compared to other AEs for both centanafadine and placebo groups

Table 1. Summary of adverse events in children and adolescents

	Centanafadine (n=308)	Placebo (n=300)
Overall adverse events, n (%)		
Any TEAE	137 (44.5%)	74 (24.7%)
Any serious TEAE	1 (0.3%)[a]	0 (0.0%)
Any severe TEAE	0 (0.0%)	1 (0.3%)[b]
TEAE leading to discontinuation of centanafadine or placebo	22 (7.1%)	2 (0.7%)
Deaths	0 (0.0%)	0 (0.0%)
TEAEs occurring in ≥5% of participants in the centanafadine group, n (%)		
Decreased appetite	35 (11.4%)	8 (2.7%)
Rash and Skin Eruptions	26 (8.4%)	1 (0.3%)
Nausea	20 (6.5%)	5 (1.7%)
Headache (including migraine)	17 (5.5%)	18 (6.0%)
Rash-related adverse events		
Participants with rash, n (%)	26 (8.4%)	1 (0.3%)
Total incidences of rash	28	1
Rash TEAE leading to discontinuation of study drug, n (%)	7 (2.3%)	0 (0.0%)
Deaths from rash TEAE, n (%)	0 (0.0%)	0 (0.0%)
Rash severity, n (%)		
Any mild rash TEAE	23 (88.5%)	1 (100%)
Any moderate rash TEAE	5 (19.2%)	0 (0.0%)
Any serious rash TEAE	0 (0.0%)	0 (0.0%)

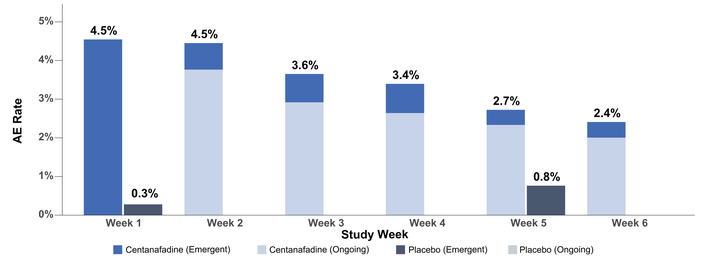
TEAE, treatment-emergent adverse event. [a]Suicide attempt (deemed not-related to study drug by investigator) [b]Somnolence (deemed related to study drug by investigator). For "Rash-related adverse events," the percentages are relative to total population in the header. For "Rash severity," the percentages are relative to participants with rash.

Figure 1. Emergent and ongoing decreased appetite events by treatment week



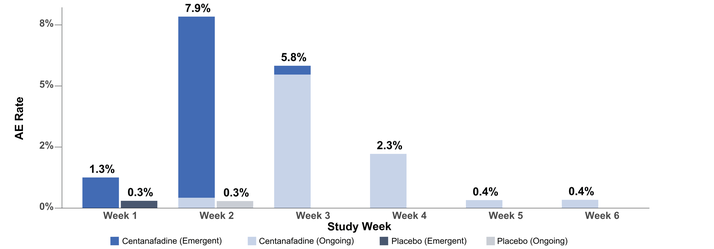
AE, adverse event.

Figure 2. Emergent and ongoing nausea events by treatment week



AE, adverse event.

Figure 3. Emergent and ongoing rash and skin eruption events by treatment week



Rash includes: drug eruption, macular rash, maculo-papular rash, morbilliform rash, papular rash, and other related terms. AE, adverse event.

Conclusions

- **Most AEs were mild or moderate in severity, transient, and occurred during the first 2 weeks of centanafadine treatment**
- **Most rash cases were simple maculopapular exanthema, with no associated systemic symptoms, mild in severity, and resolved within 2 weeks**
- **The low occurrence of headache, nausea, and rash after the first 2 weeks suggests these AEs are less likely to occur later in patients who tolerate treatment initiation**

References

1. SIMTRIYO® (centanafadine) extended-release capsules [prescribing information]. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; 2026.
2. Ward CL, et al. *Pediatr. Open Sci.* 2025;1(3):1–11.
3. Ward CL, et al. *J Am Acad Child Adolesc Psychiatry.* 2026;65(6):805-817.

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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

CC has served as a consultant for AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Corium, Intra-Cellular, Janssen, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, and Teva; has served on advisory boards for AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Idorsia, Intra-Cellular, Janssen, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, and Teva; advisory board (spouse): Karuna and Otsuka; has served on speakers bureaus for AbbVie, Acadia, Alkermes, Axsome, Bristol Myers Squibb, Corium, Intra-Cellular, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, and Teva; and has received research and/or grant support from Acadia, Axsome, Harmony, Neurocrine, and Teva. **OT**, **ZZ**, **GSP**, **MH**, and **CLW** are full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **ACC** has been a consultant for Aardvark, Arbor, Attentive, Aytu, Lumos, Neurocentria, Noven, Otsuka, Purdue, Sky, Sunovion, Tris Pharma, Zevra Therapeutics Inc. (previously KemPharm Inc.), Supernus, Corium, and Lumos; has participated on speakers bureaus for Collegium (Ironshore), Supernus, Takeda (Shire), and Tris Pharma; has received research support from Adlon, Akili, Allergan, Arbor, Collegium (Ironshore), Lilly, Lumos, Otsuka, Sunovion, Supernus, Suven, Syndeio Biosciences, Takeda Shire, Tris Pharma, Vanda, and Zevra Therapeutics Inc. (previously KemPharm Inc); has received writing support from Arbor, Ironshore, Neos Therapeutics, Otsuka, Takeda Shire, Purdue, Rhodes, Sunovion, and Tris Pharma; and participated on advisory boards for Akili, Corium, (Collegium) Ironshore, Otsuka, Sunovion, Supernus, Takeda (Shire), and Tris Pharma. **GWM** discloses that in the past 3 years he received consultant fees or honoraria from AbbVie, Acadia, Alkermes, Avanir, Axsome, Boehringer Ingelheim, Eisai, Emalex, Ironshore, Intra-Cellular Therapies, Janssen, Lundbeck, Medgenics, Neos, Neurocrine, NLS-1 Pharma AG, Otsuka, Redax, Rhodes, Roche, Sage, Shire, Sunovion, Supernus, Takeda, Teva, and Tris Pharma.

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