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Enclosure:

POSTER: Cotero-Lefevre V, Piacentino D, Hogan M, et al. Presented at: Psych Congress 2026, September 15-19, 2026; New Orleans, LA, USA.

Coadministration of Centanafadine With Methylphenidate or Lisdexamfetamine in Healthy Adults: Results From a Phase 1 Single-Dose Crossover Trial

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Introduction

- Although stimulants are commonly used to treat attention-deficit/hyperactivity disorder (ADHD)—a chronic and prevalent neurodevelopmental disorder—incomplete response, tolerability limitations, or persistent comorbid symptoms may lead to use of combination pharmacotherapy[1-3]
- Understanding the safety and tolerability of coadministered ADHD treatments is important when combination pharmacotherapy is used in clinical practice[2,3]
- 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[4]

Objective

- This study evaluated the cardiovascular risk potential of coadministering of centanafadine with methylphenidate or lisdexamfetamine in adults

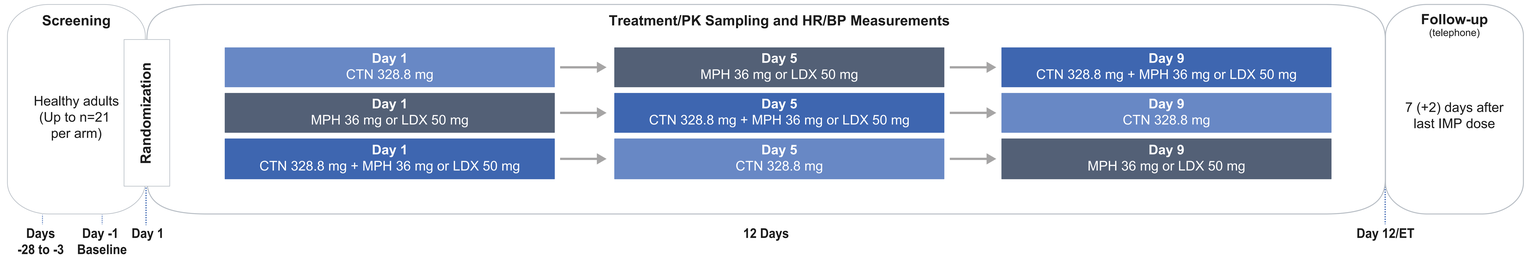
Methods

- **Study:** A phase 1 single-blind, randomized, crossover study (NCT07314333)
- **Participants:** Healthy adults (aged 18–55 years)
- **Treatment:** Participants were assigned to 1 of 2 treatment arms evaluating centanafadine 328.8 mg with methylphenidate 36 mg or lisdexamfetamine 50 mg
  - In each arm, participants received centanafadine alone, methylphenidate or lisdexamfetamine alone, and centanafadine coadministered with methylphenidate or lisdexamfetamine in a 3-period Williams design, with a 4-day washout between periods (**Figure 1**)
- **Efficacy endpoints:** Triplicate heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurements, collected through 72 hours postdose; key drug–drug interaction contrasts compared baseline-corrected changes in HR, SBP, and DBP with coadministration versus methylphenidate or lisdexamfetamine alone during the co-exposure window
  - Prespecified thresholds for potentially clinically meaningful double-corrected increases were +10 bpm for HR, +20 mmHg for SBP, and +10 mmHg for DBP
  - Double-corrected BP and HR accounted for day-to-day and time-of-day variability by subtracting the corresponding baseline change from the postdose change, providing an estimate of treatment-related effects.
- **Analysis:** Endpoints were analyzed using a linear mixed-effects model with treatment, timepoint, treatment-by-timepoint interaction, period and sequence as fixed effects and subject as a random effect

Results

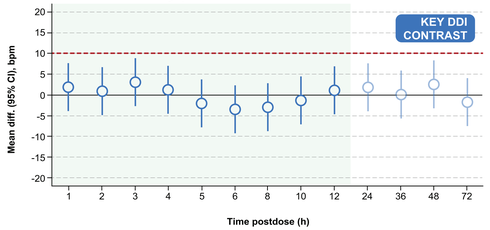
- During the co-exposure window, coadministration of centanafadine did not produce clinically meaningful increases in HR beyond those observed with methylphenidate or lisdexamfetamine alone (**Figures 2 and 3**)
- Similarly, SBP and DBP changes remained comparable to those observed with methylphenidate or lisdexamfetamine alone, with no clinically meaningful additional increases during coadministration (**Figures 4, 5, 6, and 7**)
- All key drug–drug interaction contrasts remained below prespecified clinical thresholds across the methylphenidate and lisdexamfetamine treatment arms and cardiovascular endpoints
- Peak HR increases with methylphenidate and lisdexamfetamine were 13.7 and 10.8 bpm greater, respectively, than with centanafadine, consistent with the expected increases in HR with methylphenidate and lisdexamfetamine and minimal HR change with centanafadine over the same interval
- Peak SBP and DBP increases were 3.0 and 2.3 mmHg greater with methylphenidate than with centanafadine and 8.6 and 7.1 mmHg greater with lisdexamfetamine than with centanafadine; the larger differences with lisdexamfetamine reflected its greater BP increase, while the BP response to centanafadine was similar across arms
- No new safety findings were observed

Figure 1. Study design



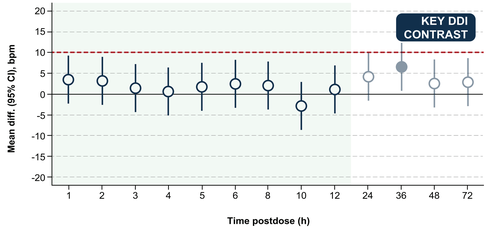
BP, blood pressure; CTN, centanafadine; ET, end of treatment; HR, heart rate; IMP, investigational medicinal product; LDX, lisdexamfetamine; MPH, methylphenidate; PK, pharmacokinetic.

Figure 2. Baseline-corrected change in HR across 72 hours: centanafadine + methylphenidate



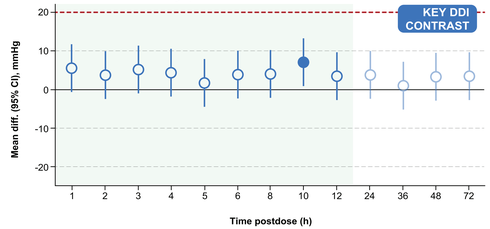
Key DDI contrast: centanafadine + methylphenidate versus methylphenidate alone.
BPM, beats per minute; CI, confidence interval; DDI, drug–drug interaction; HR, heart rate.

Figure 3. Baseline-corrected change in HR across 72 hours: centanafadine + lisdexamfetamine



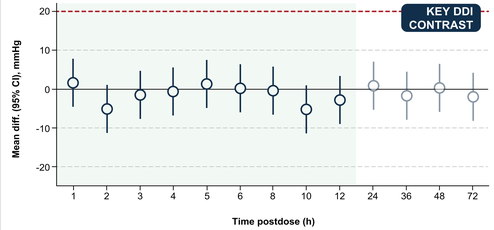
Key DDI contrast: centanafadine + lisdexamfetamine versus lisdexamfetamine alone. Filled circles indicate timepoints at which the 95% CI for the baseline-corrected mean treatment difference excludes 0.
BPM, beats per minute; CI, confidence interval; DDI, drug–drug interaction; HR, heart rate.

Figure 4. Baseline-corrected change in SBP across 72 hours: centanafadine + methylphenidate



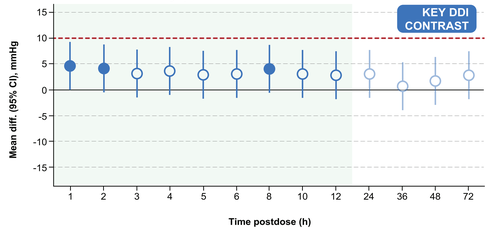
Key DDI contrast: centanafadine + methylphenidate versus methylphenidate alone. Filled circles indicate timepoints at which the 95% CI for the baseline-corrected mean treatment difference excludes 0.
CI, confidence interval; DDI, drug–drug interaction; SBP, systolic blood pressure.

Figure 5. Baseline-corrected SBP across 72 hours: centanafadine + lisdexamfetamine



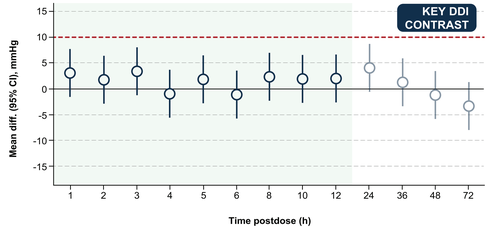
Key DDI contrast: centanafadine + lisdexamfetamine versus lisdexamfetamine alone.
CI, confidence interval; DDI, drug–drug interaction; SBP, systolic blood pressure.

Figure 6. Baseline-corrected change in DBP across 72 hours: centanafadine + methylphenidate



Key DDI contrast: centanafadine + methylphenidate versus methylphenidate alone. Filled circles indicate timepoints at which the 95% CI for the baseline-corrected mean treatment difference excludes 0.
CI, confidence interval; DBP, diastolic blood pressure; DDI, drug–drug interaction.

Figure 7. Baseline-corrected DBP across 72 hours: centanafadine + lisdexamfetamine



Key DDI contrast: centanafadine + lisdexamfetamine versus lisdexamfetamine alone.
CI, confidence interval; DBP, diastolic blood pressure; DDI, drug–drug interaction.

Conclusions

- **Coadministration of centanafadine with methylphenidate or lisdexamfetamine did not increase acute heart rate, systolic blood pressure, or diastolic blood pressure responses beyond those observed with methylphenidate or lisdexamfetamine alone**

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Text Revision. American Psychiatric Association; 2022.
2. Adler LA, et al. *Curr Psychiatry Rep*. 2006;8(5):409-15.
3. Treuer T, et al. *J Child Adolesc Psychopharmacol*. 2013;23:179-93.
4. SIMTRIYO® (centanafadine) extended-release capsules [prescribing information]. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; 2026.

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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

VCL, **DP**, **MH**, **GSP**, **CLW**, **KW**, and **OT** are all full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

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