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Enclosure:

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Abuse Potential Assessment of Centanafadine in Healthy Adults: Results From a Single-Dose, Randomized, Placebo- and Active-Controlled Crossover Study

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Introduction

- Attention-deficit/hyperactivity disorder (ADHD) is a chronic, prevalent neurodevelopmental disorder associated with functional impairment across the lifespan[1-3]
- While stimulants are established treatments for ADHD, misuse, abuse, and diversion remain recognized concerns in this medication class[4,5]
- For new ADHD pharmacotherapies, characterizing abuse potential is an important component of clinical development and can inform assessment of abuse-related risks[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 study assessed the human abuse potential of centanafadine in healthy recreational drug users with stimulant experience

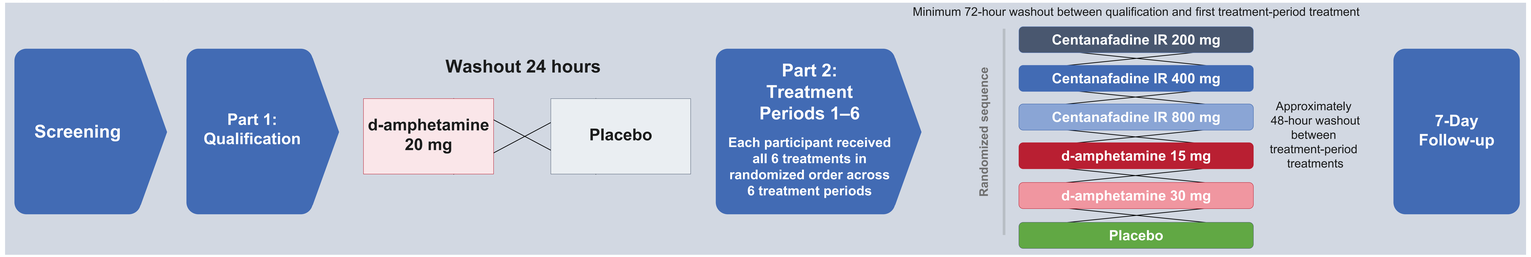
Methods

- **Study:** A phase 1 single-dose, randomized, double-blind, placebo- and active-controlled crossover study
- **Participants:** Healthy recreational drug users aged 18–55 years with stimulant experience (N=45 per treatment arm)
- **Treatment:** After a qualification phase (Part 1) confirming discrimination of d-amphetamine 20 mg from placebo, participants then received a single-dose (Part 2) of the following 6 treatments in randomized, double-blind, crossover manner with a 48-hour washout period in-between: centanafadine immediate-release capsule 200, 400, or 800 mg; d-amphetamine 15 or 30 mg; or placebo (**Figure 1**)
- **Efficacy endpoints:** Primary endpoint was the maximum effect (E_{max}; "at this moment") for Drug Liking Visual Analog Scale (VAS) score; key secondary endpoints included maximum effect for Take Drug Again, Overall Drug Liking, Good Effects, Bad Effects, and Nausea VAS scores
  - VAS endpoints were scored on a 0 to 100 scale
  - Bipolar VAS endpoints (Drug Liking and Overall Drug Liking) used 50 as the neutral point
  - Unipolar VAS endpoints ranged from 0 (Not at all) to 100 (Extremely)
- **Analysis:** Efficacy endpoints were analyzed using linear mixed-effects models; per the SAP, abuse-potential comparisons were evaluated using a prespecified one-sided significance level of α=0.05; reported *P*-values are 2-sided unless otherwise specified; pharmacokinetics were summarized using descriptive statistics

Results

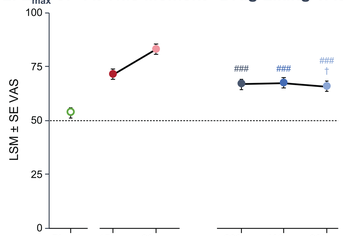
- Centanafadine immediate-release produced supratherapeutic exposures (C_{max} 3.8- to 6.2-fold higher than the once-daily extended-release commercially available formulation [SIMTRIYO®]) and significantly higher maximal Drug Liking VAS scores versus placebo (*P*<0.0001)
- However, Drug Liking E_{max} was significantly lower for all centanafadine doses versus d-amphetamine 30 mg and for centanafadine 800 mg versus d-amphetamine 15 mg; centanafadine 200 and 400 mg were numerically lower versus d-amphetamine 15 mg (**Figure 2**)
- Within 1 hour postdose, mean Drug Liking VAS scores for centanafadine fell below neutral, indicating dose-dependent drug disliking before modest liking, primarily associated with nausea and vomiting (**Figure 3**)
- Whereas d-amphetamine produced dose-related increases in Take Drug Again, centanafadine produced dose-related decreases, with lowest scores at 800 mg (**Figure 4**)
- Similarly, d-amphetamine produced dose-related increases in Overall Drug Liking, with significantly higher scores compared to centanafadine across all doses
- Additionally, centanafadine was also associated with significant disliking relative to placebo and d-amphetamine, with dose-related responses in Bad Effects and Nausea across all doses, but most prominent with the 800 mg dose (**Figures 5 and 6**)
- The most common adverse events reported in the centanafadine treatment groups were nausea, vomiting, and euphoric mood

Figure 1. Study design



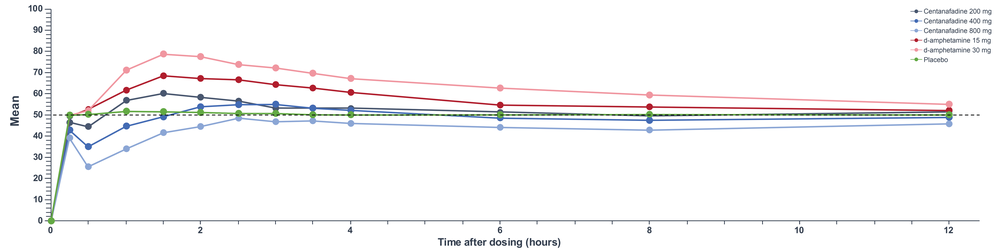
IR, immediate-release.

Figure 2. E_{max} of "At This Moment" Drug Liking VAS



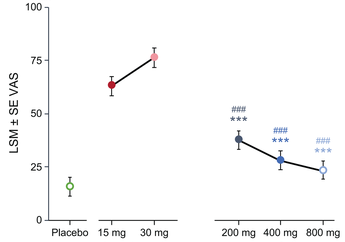
0=strong disliking, 50=neutral, 100=strong liking.
The † and # symbols indicate significant differences versus d-amphetamine 15 mg and 30 mg, respectively, with one, two, and three symbols corresponding to *P*<0.05, *P*<0.01, and *P*<0.001; † denotes a comparison that met significance based on the prespecified one-sided α=0.05 criterion; filled circles indicate significant differences versus placebo (*P*<0.05).
E_{max}, maximum effect; LSM, least squares mean; SE, standard error; VAS, visual analog scale.

Figure 3. "At This Moment" Drug Liking VAS scores over time



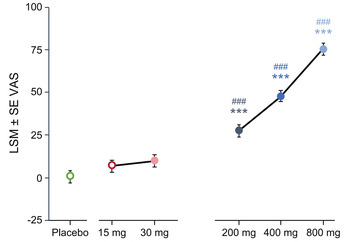
0=strong disliking, 50=neutral, 100=strong liking.
VAS, visual analog scale.

Figure 4. E_{max} of Take Drug Again VAS scores



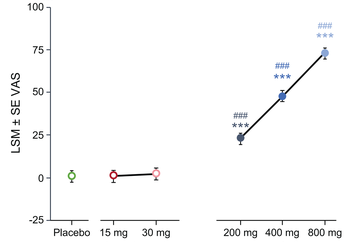
The * and # symbols indicate significant differences versus d-amphetamine 15 mg and 30 mg, respectively, with one, two, and three symbols corresponding to *P*<0.05, *P*<0.01, and *P*<0.001; filled circles indicate significant differences versus placebo (*P*<0.05).
E_{max}, maximum effect; LSM, least squares mean; SE, standard error; VAS, visual analog scale.

Figure 5. E_{max} of Bad Effects VAS scores



The * and # symbols indicate significant differences versus d-amphetamine 15 mg and 30 mg, respectively, with one, two, and three symbols corresponding to *P*<0.05, *P*<0.01, and *P*<0.001; filled circles indicate significant differences versus placebo (*P*<0.05).
E_{max}, maximum effect; LSM, least squares mean; SE, standard error; VAS, visual analog scale.

Figure 6. E_{max} of Nausea VAS scores



The * and # symbols indicate significant differences versus d-amphetamine 15 mg and 30 mg, respectively, with one, two, and three symbols corresponding to *P*<0.05, *P*<0.01, and *P*<0.001; filled circles indicate significant differences versus placebo (*P*<0.05).
E_{max}, maximum effect; LSM, least squares mean; SE, standard error; VAS, visual analog scale.

Conclusions

- **Centanafadine immediate-release demonstrated higher maximal Drug Liking than placebo but lower Drug Liking than d-amphetamine 30 mg across all doses and than d-amphetamine 15 mg at the highest centanafadine dose**
- **Dose-dependent disliking preceded modest Drug Liking and occurred alongside nausea and vomiting**
- **Drug disliking was accompanied by dose-dependent increases in Bad Effects and Nausea, suggesting a profile not consistent with abuse-related reinforcement**

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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, **CLW**, **DC**, **MH**, and **GSP** are all full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc. **BB** is an independent consultant.

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