The aim of this exploratory human abuse potential assessment of centanafadine, a novel triple reuptake inhibitor of dopamine (DA) and serotonin (5HT) with half-maximal inhibition concentration \( (IC_{50}) \) values of 6, 38, and 84, respectively, is to modulate symptoms of induction, impulsivity, and hyperactivity in ADHD.

Since TRIs increase DA in the nucleus accumbens, the potential for drug liking and recreational abuse should be considered.

The aim of the exploratory study was to evaluate the abuse potential of single doses of CTN immediate-release (IR) compared with placebo, atomoxetine (AMP-IR), and lisdexamfetamine (LDX-IR) in recreational drug users.

This was a single site, single-blind, randomized, placebo- and active-controlled, 3-way crossover study performed at Vince and Associates Clinical Research (Figure 1).

Subjects: Healthy adult males, aged 18-55 years with a history of recreational use of CNS stimulant drugs, who provided written informed consent.

Treatments: Single oral doses of CTN IR (600 mg, 830 mg) were compared with that of placebo, AMP-IR (400 mg, 800 mg) were compared with that of placebo and LDX-IR (400 mg, 800 mg) were compared with that of placebo.

Methods: Subjective measures included visual analog scales (VAS) and Addiction Research Center Inventory (ARCI) subscales to evaluate the abuse potential of CTN IR compared with placebo, AMP-IR, and LDX-IR, indicating significant effects. As shown in Figure 2, mean peak drug effect occurred within 15–30 minutes of CTN IR administration, whereas mean peak drug effect was delayed, up to 2 to 3 hours.

Figure 2. Early Time Course of “at the moment” Drug Liking VAS Scores

Figure 4. The median drug similarity VAS scores for the drug similarity assessment: centanafadine (CTN), atomoxetine (AMP), lisdexamfetamine (LDX), ecstasy, and other substances.

Figure 5a. Time Course of ARCI A Scale Scores

Figure 5b. Time Course of ARCI B Scale Scores

Figure 6. Median Drug Similarity VAS Scores

Results (continued)

• Bad Effects VAS \( E_{max} \) was significantly higher for CTN relative to placebo and \( E_{max} \) for CTN 800 mg was also higher compared to AMP-IR 400 mg (Figure 4). The results of the present exploratory study indicate that the subjective effects profile of CTN differs from that of AMP and LDX, and supports a lower abuse potential compared with these typical stimulants.

Discussion

• AMP and LDX were significantly liked compared with placebo, confirming study validity. Subjects identified these treatments as stimulant-like, with minimal negative effects.

• Overall, the pharmacodynamic results showed a unique profile of subjective effects for CTN compared with AMP and LDX. While CTN was associated with stimulant-like effects, it was also associated with significant substantial and negative effects. The prominent negative effects at 800 mg indicate that there would be little incentive to escalate the dose.

• CTN was not overly reward-associated as a stimulant, which could in part be related to its prominent NE and 5HT action modulating the expression of dopamine by 5HT activity.

• The observed pattern of subjective effects has been observed with other drugs, such as atomoxetine, stilbamidine, modafinil and phenethylamine, which are either uncontrolled or Schedule IV, and show low or no abuse potential.

• The results of the present exploratory study indicate that the subjective effects profile of CTN differs from that of AMP and LDX, and supports a lower abuse potential compared with these typical stimulants.

REFERENCES


RESULTS (continued)

Safety

• The most common adverse events (those occurring in at least 3 subjects in any treatment group) in the treatment arms were nausea (16.1%), headache (9.7%), and insomnia (6.5%). These effects were considered primarily due to drug class and were dose-related.

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