EXPLORATORY HUMAN ABUSE POTENTIAL ASSESSMENT OF CENTANAFADINE, A NOVEL TRIPLE REUPTAKE INHIBITOR

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INTRODUCTION and AIM

- Stimulants, such as methylphenidate and amphetamines, are considered first line pharmacotherapy for attention deficit hyperactivity disorder (ADHD). The usefulness of stimulants is limited in some patients by side effects, including increases in blood pressure and pulse, appetite suppression, insomnia, and abuse liability[1] (risk of abuse, dependence).
- Centanafadine (CTN) is a triple reuptake inhibitor (TRI) under development as a sustained release formulation for the treatment of ADHD. CTN inhibits reuptake of norepinephrine (NE), dopamine (DA) and serotonin (5-HT) with half-maximal inhibitory concentration (IC_{50}) values of 6, 38, and 84, respectively, neurotransmitters known to mediate symptoms of inattention, impulsivity and hyperactivity in ADHD.[2]
- Since TRIs increase DA in the nucleus accumbens, the potential for drug liking and recreational abuse should be considered.
- The aim of this exploratory human abuse potential study was to evaluate the abuse potential of single doses of CTN immediate-release (IR) compared with placebo, *d*-amphetamine (*d*-AMP), and lisdexamfetamine (LDX) in recreational stimulant users.

METHODS

This was a single site, single-dose, randomized, double-blind, placebo- and active-controlled, 5-way crossover study performed at Vince and Associates Clinical Research (**Figure 1**).

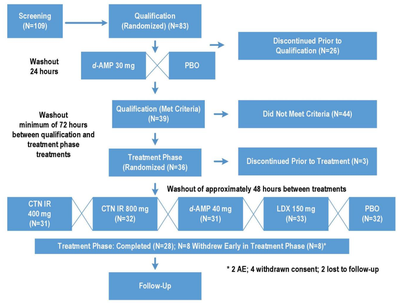
Subjects: Healthy adult males, aged 18-55 years with a history of nontherapeutic use of CNS stimulant drugs, who provided written informed consent.

Treatments: Single oral doses of CTN IR (400 mg, 800 mg) were compared with that of placebo, *d*-AMP 40 mg, and LDX 150 mg.

Measures: Subjective measures included visual analog scales (VAS) and Addiction Research Center Inventory (ARCI) subscales to evaluate balance of effects (e.g., Drug Liking VAS), positive, negative, stimulant (e.g., ARCI Amphetamine) and other effects were administered over 24 hours following study drug administration. Standard safety assessments were included. Pharmacokinetic samples were also taken to confirm exposure (data not shown).

Analysis: A mixed effects model for a crossover study was used to compare pharmacodynamic endpoints. The model included treatment, period, sequence, and first order carryover effect as fixed effects, and subject nested within treatment sequence as random effect. Baseline (predose) measurement was included as a covariate, where applicable. If the carryover effect was found to be nonsignificant at the 25% level, then the term was dropped from the model. If not normally distributed, parameters were analyzed nonparametrically.

Figure 1. Study Design and Subject Disposition



AE=adverse event; CTN=centanafadine; *d*-AMP=*d*-amphetamine; LDX=lisdexamfetamine; PBO=placebo.

Although CTN will be developed as a sustained-release formulation, the original IR formulation was administered in this study, in accordance with current FDA guidance, to evaluate the drug substance and to represent a "worst-case" scenario by inducing the most rapid onset and greatest extent of exposure.

RESULTS

Subjective Measures

- Drug Liking VAS (**Figures 2 and 3**) maximum effect (E_{max}) was significantly higher for *d*-AMP and LDX compared with placebo, confirming study validity.
- Drug Liking E_{max} scores were significantly higher for CTN IR compared with placebo, but not significantly different from *d*-AMP or LDX.
- Drug Liking minimum effect (E_{min}) scores were significantly lower for CTN compared with placebo, *d*-AMP and LDX, indicating significant disliking. As shown in **Figure 2**, mean peak disliking occurred within 15 - 30 minutes of CTN IR administration, whereas mean peak liking was delayed, up to 2 to 3 hours.

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

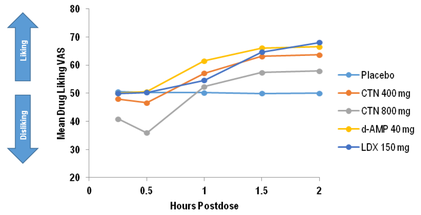
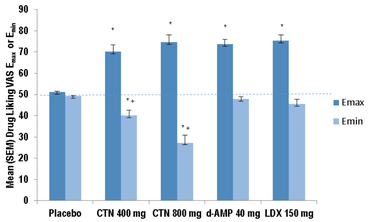
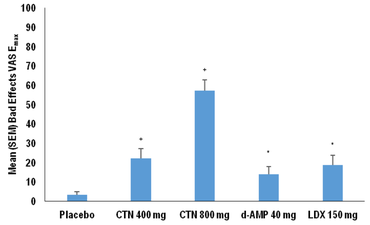


Figure 3. Mean E_{max} and E_{min} of "at the moment" Drug Liking VAS



*p<0.002 vs. placebo; +p<0.02 vs. d-AMP and LDX

Figure 4. Mean E_{max} of Bad Effects VAS



*p<0.01 vs. placebo; +p<0.001 vs. placebo, d-AMP and LDX

Abbreviations: ARCI A=Addiction Research Center Inventory Amphetamine scale; ; ARCI BG=Addiction Research Center Inventory Benzedrine Group scale; CTN=centanafadine; *d*-AMP=*d*-amphetamine; E_{max}=maximum effect; ; E_{min}=minimum effect; LDX=lisdexamfetamine; VAS=visual analog scale.

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 relative to *d*-AMP and LDX, indicating prominent negative effects. (**Figure 4**)
- CTN had significantly lower ARCI A and ARCI BG E_{max} scores compared with *d*-AMP and LDX; E_{max} was also significantly lower for CTN 400 mg (A and BG) and 800 mg (BG) compared with placebo. (**Figure 5a,b**)
- On Drug Similarity VAS, *d*-AMP and LDX were reported to be most similar to cocaine, *d*-AMP and ecstasy. CTN was not identified strongly with any particular drug, although both doses were modestly identified as a stimulant (median scores <25). (**Figure 6**)

Figure 5a. Time Course of ARCI A Scale Scores

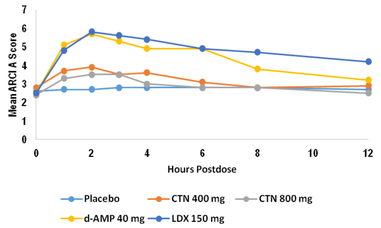


Figure 5b. Time Course of ARCI BG Scale Scores

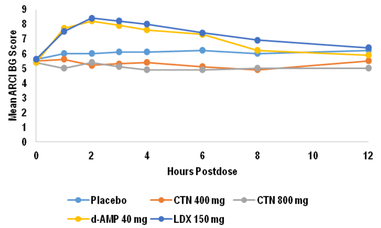
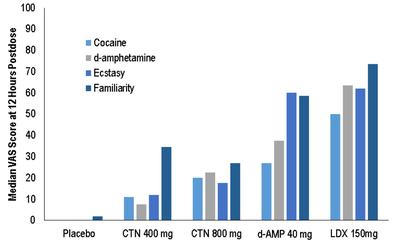


Figure 6. Median Drug Similarity VAS Scores



RESULTS (continued)

Safety

- The most common adverse events (those occurring in at least 3 subjects in any treatment group) in the treatment phase are shown in **Table 1**.

Preferred Term	Placebo N=32 N (%)	CTN 400 mg N=31 N (%)	CTN 800 mg N=32 N (%)	*d*-AMP 40 mg N=31 N (%)	LDX 150 mg N=33 N (%)
Number (%) of subjects with a TEAE	4 (12.5%)	21 (67.7%)	31 (96.9%)	24 (77.4%)	26 (78.8%)
Blood pressure increased	0 (0.0%)	1 (3.2%)	3 (9.4%)	4 (12.9%)	10 (30.3%)
Decreased appetite	0 (0.0%)	1 (3.2%)	2 (6.3%)	3 (9.7%)	5 (15.2%)
Dizziness	0 (0.0%)	0 (0.0%)	3 (9.4%)	0 (0.0%)	0 (0.0%)
Dyspepsia	0 (0.0%)	1 (3.2%)	3 (9.4%)	0 (0.0%)	0 (0.0%)
Elevated mood[a]	0 (0.0%)	5 (16.1%)	3 (9.4%)	2 (6.5%)	4 (12.1%)
Feeling of relaxation[a]	0 (0.0%)	3 (9.7%)	2 (6.3%)	0 (0.0%)	2 (6.1%)
Headache	1 (3.1%)	1 (3.2%)	7 (21.9%)	4 (12.9%)	2 (6.1%)
Hyperhidrosis	0 (0.0%)	2 (6.5%)	4 (12.5%)	1 (3.2%)	3 (9.1%)
Hypervigilance[a]	0 (0.0%)	2 (6.5%)	3 (9.4%)	7 (22.6%)	10 (30.3%)
Insomnia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	6 (18.2%)
Nausea	0 (0.0%)	5 (16.1%)	18 (56.3%)	1 (3.2%)	1 (3.0%)
Tachycardia	0 (0.0%)	3 (9.7%)	4 (12.5%)	4 (12.9%)	5 (15.2%)
Vomiting	0 (0.0%)	6 (19.4%)	19 (59.4%)	0 (0.0%)	1 (3.0%)

Percentage is calculated based on the number of subjects per treatment as the denominator. For each row category, a subject with two or more adverse events in that category is counted only once.

[a] Adverse event of special interest.

DISCUSSION

- *d*-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 *d*-AMP and LDX. While CTN was associated with liking and stimulant-like effects, it was also associated with significant disliking and negative effects. The prominent negative effects at 800 mg indicate that there would be little incentive to escalate the dose.
- CTN was only rather weakly characterized as a stimulant, which could in part be related to its prominent NE and 5-HT action modulating the expression of euphoria by its DA activity.
- The observed pattern of subjective effects has been observed with other drugs, such as atomoxetine, sibutramine, modafinil and phentermine, which are either unscheduled or Schedule IV, and show low or no abuse potential.[1,3-5]
- The results of the present exploratory study indicate that the subjective effects profile of CTN is distinct from that of *d*-AMP and LDX, and suggest a lower abuse potential compared with these typical stimulants.

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This study was sponsored by Neurovance