Limited Oral Abuse Potential of Cebranopadol, a Novel Potent Analgesic, Compared to Tramadol and Oxycodone in Recreational Opioid Users

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Background

Moderate to severe acute and chronic pain remain an important public health issue in the United States, and opioid pain medications continue to be the most effective analgesics, but they carry a risk of misuse, abuse, and overdose.[1] Studies estimate that between 3−19% of people who take prescription opioids for pain develop opioid use disorder.[2] Novel options that provide an opioid level of pain control with an improved safety profile are needed. Cebranopadol is a first-in-class, dual nociceptin/orphanin FQ peptide (NOP) receptor and μ−opioid peptide (MOP) receptor agonist analgesic (Dual-NMR analgesic) that derives its benefit partly from activation of the NOP receptor to provide effective pain relief and may be at reduced risk of negative effects typically associated with its MOP receptor agonism, including abuse potential, physical dependence, and respiratory depression.[3,4]

Purpose

Scientific advances in understanding pain and its manifestations have identified the NOP receptor as a valuable therapeutic target for pain management. Preclinical data demonstrate that NOP agonism attenuates the abuse potential and negative side effects associated with opioids while allowing for effective analgesia across pain types.[3,4]
A previous single-dose, double-blind, crossover human abuse potential study demonstrated that cebranopadol 200 μg and 400 μg have lower abuse potential than hydromorphone 8 mg and 16 mg immediate release (IR) and cebranopadol doses of 800 μg were liked similarly to hydromorphone 8 mg and less than hydromorphone 16 mg.[5] The purpose of this study was to assess the oral abuse potential of supratherapeutic doses of cebranopadol compared to placebo, tramadol (a Schedule IV opioid) and oxycodone (a Schedule II opioid) in recreational opioid users.

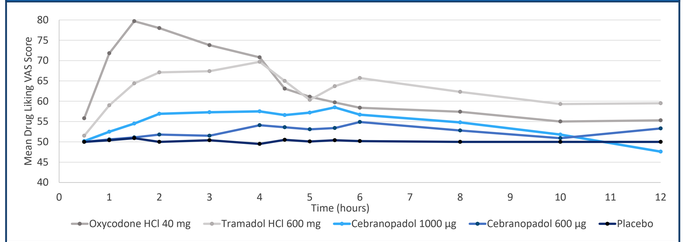
Methods

This study used a randomized, double-blind, five-way crossover design to evaluate the abuse potential of cebranopadol in adult nondependent recreational opioid users versus placebo, oxycodone, and tramadol. Eligible subjects underwent a naloxone challenge to confirm they were not physically dependent on opioids, and a qualification phase to assess that subjects could tolerate and discriminate the effects of oxycodone and tramadol from placebo. To qualify for the study, subjects had to have a maximum (E_{max}) drug liking score in response to oxycodone IR and tramadol IR ≥15 points vs. placebo, with a minimum score of 65 points, as per the Assessment of Abuse Potential of Drugs Guidance for Industry (January 2017). Drug Liking was measured using a bipolar 100-point Visual Analog Scale (VAS). Qualified subjects underwent a ≥72-hour washout before receiving study drug in the Treatment Phase. Subjects were randomized to receive single oral doses of cebranopadol 600 μg or 1000 μg, oxycodone IR 40 mg, tramadol IR 600 mg, or placebo in a crossover manner. Each treatment period was separated by a ≥14-day washout period to prevent carryover effects. The primary endpoint was Drug Liking "At This Moment" E_{max}. Key secondary measures included Overall Drug Liking and Take Drug Again measured by VAS.

Validation

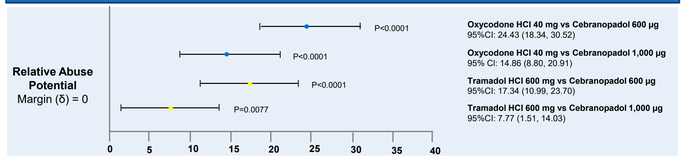
Study validity was confirmed as demonstrated by significantly greater Drug Liking E_{max} for oxycodone and tramadol compared to placebo using a prespecified margin of 15 **[Figure 3]**.

Figure 1. "Drug Liking" Over Time



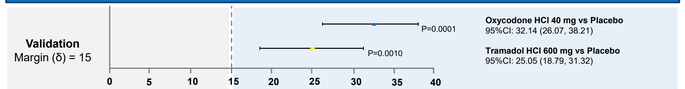
The **Drug Liking Visual Analog Scale (VAS)** is a 100-point bipolar scale where 0 = "Strong disliking"; 50 = "Neither like nor dislike"; 100 = "Strong liking"

Figure 2. Analysis Results for Drug Liking VAS E_{max} – Relative Abuse Potential



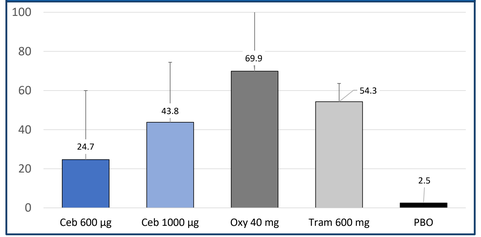
Relative Abuse Potential indicates the difference in drug liking VAS E_{max} of cebranopadol and comparator drug, tramadol 600 mg or oxycodone 40 mg. Values >0 indicate that cebranopadol was les liked than comparator drug.

Figure 3. Analysis Results for Drug Liking VAS E_{max} – Validation



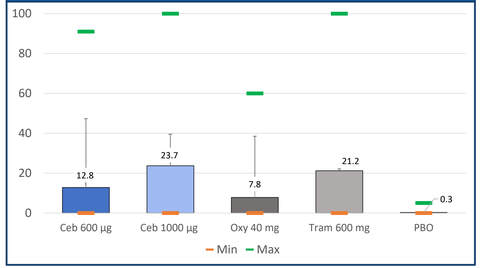
Relative Abuse Potential indicates the difference in drug liking VAS E_{max} of cebranopadol and comparator drug, tramadol 600 mg or oxycodone 40 mg. Values >0 indicate that cebranopadol was les liked than comparator drug.

Figure 4. "Good Drug Effects" VAS E_{max}



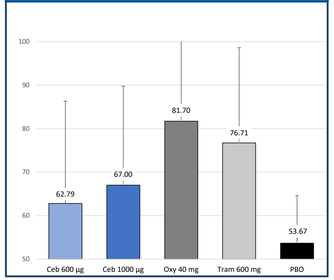
Good Drug Effects VAS is a unipolar 100 point scale of a subject's experience of good effects of the drug where 0= "No good effects"; 100="extremely good effects".
Standard Deviation is represented by error bars.
Ceb – Cebranopadol; Oxy – Oxycodone; Tram – Tramadol; PBO - Placebo

Figure 5. "Bad Drug Effects" VAS E_{max}



Bad Drug Effects VAS is a unipolar 100 point scale of a subject's experience of bad effects of the drug where 0=No bad drug effects and 100="extremely bad effects".
Standard Deviation is represented by error bars.
Ceb – Cebranopadol; Oxy – Oxycodone; Tram – Tramadol; PBO - Placebo

Figure 6. "Take Drug Again" VAS E_{max}



The Take Drug Again Visual Analog Scale (VAS) is a 100-point bipolar scale where 0 = "Definitely not"; 50 = "Do not care"; 100 = "Definitely would"
The Overall Drug Liking Visual Analog Scale (VAS) is a 100-point bipolar scale where 0 = "Strong disliking"; 50 = "Neither like nor dislike"; 100 = "Strong liking"
Standard Deviation is represented by error bars.
Ceb – Cebranopadol; Oxy – Oxycodone; Tram – Tramadol; PBO - Placebo

Figure 7. Overall Drug Liking VAS E_{max}

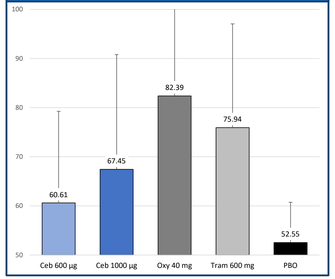


Table 1. TEAEs Occurring in ≥5% of Subjects in Treatment Phase (Safety Population)

Preferred Term	Placebo (N=45) n (%)	Cebranopadol 600 μg (N=45) n (%)	Cebranopadol 1000 μg (N=43) n (%)	Oxycodone HCl 40 mg (N=44) n (%)	Tramadol HCl 600 mg (N=39) n (%)
Nausea	2 (4.4%)	8 (17.8%)	15 (34.9%)	10 (22.7%)	13 (33.3%)
Vomiting	0 (0.0%)	7 (15.6%)	13 (30.2%)	7 (15.9%)	10 (25.6%)
Hiccups	0 (0.0%)	1 (2.2%)	1 (2.3%)	3 (6.8%)	1 (2.6%)
Somnolence	3 (6.7%)	2 (4.4%)	6 (14.0%)	4 (9.1%)	3 (7.7%)
Dizziness	1 (2.2%)	3 (6.7%)	4 (9.3%)	4 (9.1%)	1 (2.6%)
Headache	2 (4.4%)	3 (6.7%)	2 (4.7%)	2 (4.5%)	3 (7.7%)
Generalised tonic-clonic seizure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.1%)
Pruritus	0 (0.0%)	2 (4.4%)	3 (7.0%)	10 (22.7%)	6 (15.4%)
Nasal pruritus	0 (0.0%)	0 (0.0%)	1 (2.3%)	4 (9.1%)	1 (2.6%)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (11.4%)	5 (12.8%)
Hot flush	0 (0.0%)	1 (2.2%)	0 (0.0%)	4 (9.1%)	3 (7.7%)

Results

Of the forty-five subjects included in the treatment phase, 38 subjects completed the study, and 33 met criteria for inclusion in the Modified Completers population** (pharmacodynamic analysis). Time to peak effect for Drug Liking for oxycodone and tramadol was 1.5 and 4 hours, respectively, compared to cebranopadol at 5 to 6 hours **[Figure 1]**. For the primary endpoint, the Drug Liking "At This Moment" E_{max} for both cebranopadol 600 μg and 1000 μg were significantly lower than tramadol 600 mg and oxycodone 40 mg **[Figure 2]**. Analysis of Drug Liking in the Modified Completers showed that both cebranopadol doses were not equivalent to placebo determined by Drug Liking E_{max} score in response to cebranopadol 600 μg and 1000 μg ≥11 points vs. placebo (7.71; 90%CI[2.63,12.79] and 17.28;[12.16, 22.41], respectively). Evaluation of Drug Liking in the Completers* population demonstrated that cebranopadol 600 μg was similar to placebo (6.09; 90%CI[1.33, 10.85]). The secondary endpoints, Good Drug Effects **[Figure 4]** and Bad Drug Effects **[Figure 5]**, showed that both doses of cebranopadol were less desirable than tramadol or oxycodone. This was consistent with the key secondary endpoints Take Drug Again **[Figure 6]** and Overall Drug Liking **[Figure 7]** where subjects rated cebranopadol 600 μg and 1000 μg lower than both tramadol and oxycodone. During the study, three SAEs were reported: two subjects experienced seizures after receiving 600 mg of tramadol, and one subject experienced atrial fibrillation after receiving cebranopadol 1000 μg. None of the subjects required hospitalization. Due to safety concerns, 4 subjects received placebo instead of tramadol during the last treatment period. The most commonly reported adverse event was nausea.

*The Completer population was defined as all subjects who received cebranopadol with at least one response on the VAS for drug liking within 2 hours of peak plasma levels (T_{max}) for each treatment
**The Modified Completer population was defined as subjects in the Completer population, excluding subjects with similar reported peak effect (E_{max}) on all treatments, and excluding subjects with an E_{max} for placebo >60 and the difference between E_{max} for placebo and oxycodone ≤5.

Conclusion

When compared to both tramadol and oxycodone, supratherapeutic doses of cebranopadol are less liked, have a greater time to peak liking, have less reported good effects and generally greater bad effects, and have lower Take Drug Again values. In this study, cebranopadol has demonstrated significantly lower abuse potential compared to both Schedule II (oxycodone) and Schedule IV (tramadol) opioids. This study confirms what has been observed in prior studies while furthering the understanding of the abuse potential of cebranopadol. Cebranopadol may serve as a much-needed novel treatment option for patients with moderate to severe pain.

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