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Assessment of the Abuse Potential of Cebranopadol in Nondependent Recreational Opioid Users

A Phase 1 Randomized Controlled Study

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Abstract:

Background: Cebranopadol is a nociceptin/orphanin FQ peptide/opioid receptor agonist with central antinociceptive activity. We hypothesize that this novel mechanism of action may lead to a lower risk of abuse compared with pure μ -opioid peptide receptor agonists.

Methods: We conducted a single-dose, nested-randomized, double-blind crossover study in nondependent recreational opioid users to evaluate the abuse potential of single doses of cebranopadol relative to hydromorphone immediate release and placebo. The study consisted of a qualification phase and a 7-period treatment phase (cebranopadol 200, 400, and 800 μ g; hydromorphone 8 and 16 mg; and 2 placebos). The primary end point was the peak effect of drug liking at this moment, measured by visual analog scale (VAS). Various secondary end points (eg, VAS rating for good drug effects, high, bad drug effects, take drug again, drug similarity, and pupillometry) were also investigated.

Results: Forty-two subjects completed the study. Cebranopadol 200 and 400 μ g did not differentiate from placebo on the abuse potential assessments and generated smaller responses than hydromorphone. Responses observed with cebranopadol 800 μ g were similar to hydromorphone 8 mg and smaller than hydromorphone 16 mg. The maximum effect for VAS drug liking at this moment was delayed compared with hydromorphone (3 and 1.5 hours, respectively). Cebranopadol administration was safe; no serious adverse events or study discontinuation due to treatment-emergent adverse events occurred.

Conclusions: These results confirm our hypothesis that cebranopadol, a nociceptin/orphanin FQ peptide/opioid receptor agonist, has lower abuse potential than hydromorphone immediate release, a pure μ -opioid peptide agonist.

Key Words: abuse potential, cebranopadol, hydromorphone, NOP/opioid receptor agonist

(*J Clin Psychopharmacol* 2019;39: 46–56)

Moderate to severe chronic pain of nociceptive origin (eg, due to osteoarthritis or low back pain) or of neuropathic origin (eg, diabetic peripheral neuropathy or postherpetic neuralgia) remains a therapeutic challenge; many patients are nonresponders to the

treatments that are available. Strong analgesics acting via μ -opioid peptide (MOP) receptor agonism have been shown to be effective in several moderate to severe chronic pain conditions.^{1–3} However, in most regions of the world, these strong analgesics remain a last resort in the therapeutic armamentarium, if they are used at all. The reluctance to use such medications is linked to fear of accidental overdose leading to respiratory arrest and death, drug abuse, or addiction.^{4–6} There is a considerable need for new chemical entities that are highly effective against moderate to severe chronic pain and have intrinsically lower abuse potential than the strong analgesics that are available.

Cebranopadol is a highly potent, centrally acting analgesic with a unique mode of action that combines nociceptin/orphanin FQ peptide (NOP) and opioid peptide receptor agonism.^{7–12}

Cebranopadol is an investigational product undergoing clinical development. It is formulated as an immediate-release (IR) film-coated tablet for oral administration. Its plasma concentration increases gradually and slowly after oral administration. The peak plasma concentration and peak drug effects (including abuse-relevant and central nervous system–related effects such as changes in pupil diameter) are reached ~4 to 6 hours postdose. Cebranopadol has a long operational half-life of ~24 hours, lending itself to once daily administration.¹³ Its anticipated therapeutic dose range is 200 to 600 μ g/d, to be reached after a period of up-titration.

Cebranopadol has shown broad activity in various animal models of acute, nociceptive, inflammatory, cancer, and especially chronic neuropathic pain. In contrast to opioids such as morphine, cebranopadol displays higher analgesic potency in chronic pain (especially of neuropathic origin) than in acute nociceptive pain. Based on its nonclinical tolerability profile, a broader therapeutic window is anticipated for cebranopadol than for morphine.^{8–10} The therapeutic window between antinociception and respiratory depression in rats is larger for cebranopadol than for fentanyl. This may be explained by the NOP receptor agonist action of cebranopadol that may counteract certain side effects caused by its MOP receptor agonist action.¹⁴ A clinical trial in healthy volunteers also showed that the effect of cebranopadol on respiratory function is smaller than that of fentanyl.¹⁵

Nonclinical data in the literature indicate that NOP receptor activity may attenuate some of the MOP receptor–related effects, such as tolerance development, physical dependence, and addiction.^{16–23} These data are in line with nonclinical findings for cebranopadol, which show lower physical dependence potential,²⁴ slower tolerance development,⁸ and limited MOP receptor agonist–like properties compared with morphine. The reduced morphine-like discriminative stimulus properties of cebranopadol have been shown to be due to its intrinsic NOP receptor agonistic activity.²⁵

Safety, tolerability, and efficacy of cebranopadol have been investigated in single- and multiple-dose clinical phase 1 studies in healthy subjects and phase 2/3 trials in patients suffering from chronic pain due to osteoarthritis, low back pain, diabetic peripheral neuropathy, cancer-related pain, and after bunionectomy.^{26,27}

In clinical trials in which cebranopadol was administered daily for up to 15 weeks, the Clinical Opioid Withdrawal Scale

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The research was funded by Grünenthal GmbH and Forest Research Institute, Inc. Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

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ISSN: 0271-0749

DOI: 10.1097/JCP.0000000000000995

was used to assess withdrawal symptoms after the administration of investigational medicinal product (IMP) was stopped abruptly without tapering. No clinically relevant differences of cebranopadol versus placebo were observed,²⁷ in line with an anticipated low potential for drug dependence.

The abuse potential of novel analgesics combining NOP and MOP receptor agonism has not been profiled in humans to date. Based on nonclinical data, we hypothesized that this novel mechanism of action may lead to a lower risk of abuse compared with pure MOP receptor agonists such as morphine, hydrocodone, and hydromorphone. A human abuse liability study in healthy recreational drug users is considered to be the most predictive premarketing tool available to evaluate the abuse potential of IMP and was therefore used to assess the abuse potential of cebranopadol compared with placebo and hydromorphone, a well-known strong analgesic with MOP receptor agonistic activities.

MATERIALS AND METHODS

Subjects

Healthy men and women, 18 to 55 years of age, with a history of recreational opioid use, were enrolled in the study. Recreational opioid use was defined as nontherapeutic use for at least 10 times in the subject's lifetime and at least once in the 12 weeks prior to the enrollment visit, which is in line with the recommendations in the Food and Drug Administration guidance²⁸ and published data investigating the abuse potential of opioids.^{29–31}

Study-specific exclusion criteria included a current diagnosis of substance dependence (except nicotine and caffeine) as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 2000). Subjects who were unwilling or unable to abstain from recreational drug use for the duration of the study, who had been in a drug rehabilitation program in the 12 months prior to enrollment, or who had a positive or missing alcohol breath test or urine drug of abuse test result (except for cannabinoids [tetrahydrocannabinol]) were excluded from participation.

No concomitant medications were allowed in the 2 weeks prior to enrollment and during the study, except those used for the treatment of adverse events and the continuous use of hormonal contraceptives. All subjects gave written informed consent and were compensated for their participation in the study according to local guidelines.

This study was conducted at the clinical unit of INC Research Toronto Inc (Toronto, Ontario, Canada) in accordance with Good Clinical Practice regulations, the ethical principles that have their origin in the Declaration of Helsinki, and local laws. The study was approved by the local institutional review board (Ontario IRB/REB div. 1373737 Ont. Ltd, Aurora, Ontario, Canada) and Health Canada.

Study Design and Treatment

This was a nested-randomized, single-site, double-blind, double-dummy, placebo- and active-controlled, crossover, single-oral-dose, phase 1 study in 48 healthy nondependent recreational opioid users to evaluate the abuse potential of 3 single oral doses of cebranopadol compared with 2 single doses of hydromorphone IR tablets and placebo.

The study design and dose selected for this study reflected the guidance for abuse potential studies and the published data for abuse liability studies.^{28–34}

After subjects were enrolled in the study, they went through a qualification phase. During this phase, all subjects completed a naloxone challenge test to confirm opioid nondependence. Subjects

who did not develop any signs and symptoms of opioid withdrawal were administered IMP at least 12 hours later. In a double-blind crossover manner, hydromorphone IR 12 mg and placebo were administered to assess if the subjects could discriminate between the active drug and placebo, could tolerate the active drug, felt comfortable with the pharmacodynamic (PD) measures, could comply with instructions, and were cooperative.

Only subjects who could differentiate between placebo and hydromorphone (ie, with peak effect [E_{max}] on the drug liking [at this moment] visual analog scale [VAS] of at least 15 points higher for hydromorphone IR 12 mg than for placebo and with an appropriate pattern of response for other abuse potential measures) could continue in the study.

Following a washout period of at least 72 hours after the qualification phase, each subject was randomly allocated to receive a single oral dose of IMP in each of the 7 treatment periods according to a 6 × 6 Williams square design. A double-dummy procedure was implemented, owing to the formulation differences of IMP. All subjects received cebranopadol 200, 400, and 800 µg; hydromorphone IR 8 and 16 mg as positive control; and matching placebo (twice) as single oral doses in a fasted state. In order to avoid any possible carryover effects (given the long terminal phase half-life of cebranopadol of 62–96 hours), all treatment periods were separated by 14-day washout periods. After administration of the highest cebranopadol dose, a fixed placebo treatment period was included, resulting in an effective washout of at least 28 days after this dose.

The low and medium doses of cebranopadol that were used are within the expected therapeutic dose range. The high dose of 800 µg, currently assumed to be a supratherapeutic dose, is the highest dose known to be tolerated in healthy subjects after single-dose administration. Doses of hydromorphone 8 to 25 mg (placed in schedule II under the Controlled Substances Act in the United States) have been associated with increased liking.^{29,33} The high dose of hydromorphone IR (16 mg) was selected on the basis that, in previous abuse liability studies, it produced statistically significant differentiation from placebo treatment while being well tolerated by the subjects.^{29,33}

Subjects were confined to the clinical unit from 1 day before until 56 hours after administration of IMP. Pharmacodynamic assessments and blood samples for pharmacokinetics were collected from predose until 56 hours postdose in each treatment period. Safety assessments were performed from enrollment until the end of the study.

A final examination was conducted 5 to 10 days after discharge from the last treatment period or upon early discontinuation.

Investigational medicinal products (cebranopadol film-coated tablets 100 and 400 µg, hydromorphone hydrochloride IR tablets [overencapsulated Dilaudid 4-mg tablets], and matching placebos) were manufactured, packed, and labeled by Grünenthal GmbH.

Pharmacodynamic Evaluations

Subjective and objective measures were collected electronically using compliant (ie, according to the Food and Drug Administration Code of Federal Regulations Part 11) proprietary software (Scheduled Measurement System; INC Research Toronto Inc). Subjects participated in training at admission to the qualification phase and on the day before each treatment period.

The primary end point was defined as drug liking (at this moment) VAS E_{max} , because it is considered to be one of the most sensitive indices of abuse liability.^{28,32,35}

The secondary measures included VAS ratings for drug liking (at this moment) (the parameters time of peak effect [tE_{max}] and area under the effect curve to 1 and 8 hours [AUE_{0-1h} and AUE_{0-8h}] were assessed), any effect, high, bad effect, good effect, feeling sick, floating, detached, take drug again, drug similarity,

overall drug liking, and alertness/drowsiness. All VAS scales were 100-point scales. They were presented either as bipolar (drug liking [at this moment], overall drug liking, and alertness/drowsiness) or unipolar scales (the remaining scales). The following scales were also used: the Addiction Research Center Inventory (ARCI) scales for euphoria (morphine-benzedrine group [MBG]), stimulant-like effects (benzedrine group [BG]), and sedation (pentobarbital-chlorpromazine-alcohol group [PCAG]).

The measurements took place predose (for some measures) and between 0.5 to 56 hours postdose, with the exception of VAS ratings for overall drug liking, take drug again, and drug similarity, which were recorded only at 12, 24, and 56 hours after IMP administration.

Pupillometry measures included the apparent minimum postdose pupil diameter (PC_{min}), the time to reach this minimum diameter (PT_{min}), and the area under the curve to 1 and 8 hours relative to baseline ($PAOC_{0-1h}$, and $PAOC_{0-8h}$). Measurements were collected under mesopic lighting conditions. A NeuroOptics pupillometer (Irvine, CA) was used to measure pupil diameter. Data from a series of frames were used in the calculation. The final display showed the weighted average and SD of the pupil size.

Psychomotor and cognitive effects were evaluated using the Divided Attention Test.³⁶ This test required subjects to perform 2 tasks (a manual tracking test and a target detection task) simultaneously. The following outcome measures were used to assess performance of these tasks:

- percentage over road: percentage of time over the road (%)
- response latency of correct responses (ms)
- percentage of target hits (%)

Assessed parameters were E_{max} , tE_{max} , AUE_{0-1h} , and AUE_{0-8h} .

Safety Evaluation

Data from subjects who received at least 1 IMP administration during the treatment phase were used for assessments of safety and tolerability (safety set). Adverse events, 12-lead electrocardiograms (ECGs), vital signs, physical examination findings (including oral body temperature), safety laboratory parameters (including clinical chemistry, clotting, hematology, and urinalysis), and alcohol breath test, urine drug test, and urine pregnancy test (women only) results were obtained at defined time points during the study. Continuous telemetric safety monitoring (5-lead ECG, oxygen saturation, pulse rate, and respiratory rate) was performed up to 24 hours after administration of IMP in each treatment period. Abuse liability-related adverse events, based on a prespecified list of *Medical Dictionary for Regulatory Activities* terms of interest, were evaluated separately.

Pharmacokinetic Evaluation

Blood samples were taken predose and up to 56 hours after administration of IMP in each treatment period, using K3-EDTA as the anticoagulant. The plasma samples were analyzed at a bio-analytical laboratory (A&M, Labor für Analytik und Metabolismusforschung Service GmbH, Bergheim, Germany) using fully validated assays for either cebranopadol or hydromorphone. Cebranopadol was extracted by liquid-liquid extraction of the samples with methyl tert-butylether and quantified using reverse-phase liquid chromatography–tandem mass spectrometry methods. The following analytical conditions for determination of cebranopadol were used: HPLC column Ascentis Express C18, 2.7 μ m, 75 \times 2.1 mm; mobile phase A: water +1 mol/L ammonium carbamate (99:1; vol:vol) and mobile phase B: methanol +1 mol/L ammonium carbamate (99:1; vol:vol); heated electrospray ionization with selected reaction monitoring in positive mode at 400°C and a collision energy of 15 eV; internal standard [²H₅]-cebranopadol;

monitored ions for cebranopadol $m/z = 379.1$ to 334.1 and [²H₅]-cebranopadol $m/z = 384.1$ to 339.1. Hydromorphone was extracted by protein precipitation with acidified acetonitrile followed by dilution of the filtrate with acidified water; hydromorphone was quantified using liquid chromatography–tandem mass spectrometry methods. The analytical conditions for determination of hydromorphone were as follows: HPLC column XBridge BEH C18, 2.5 μ m, 50 \times 2.1 mm; mobile phase A: water +1 mol/L ammonium carbamate (99:1; vol:vol) and mobile phase B: methanol +1 mol/L ammonium carbamate (99:1; vol:vol); heated electrospray ionization with selected reaction monitoring in positive mode at 400°C and a collision energy of 32 eV; internal standard [²H₆]-hydromorphone; monitored ions for hydromorphone $m/z = 286.2$ to 185.2 and [²H₆]-hydromorphone $m/z = 292.2$ to 185.2. For details of the analytical methods used for hydromorphone and cebranopadol, see Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/JCP/A543>.

The noncompartmental parameters C_{max} (maximum observed concentration), t_{max} (time to attain maximum concentration), and AUC_{0-t} (area under the concentration-time curve up to the sampling time t) were derived from the plasma concentration-time profiles of all analytes and summarized descriptively. Pharmacokinetic analysis included all subjects who completed the 7 treatment periods and who had no major protocol deviations.

Statistical Analysis

The PD analysis included all subjects who completed the 7 treatment periods with or without protocol deviations (completer set). No explicit imputation was performed for missing data.

A linear mixed-effects model was fitted to each parameter. The model accounted for the effects of treatment, period, sequence, and sex as fixed effects; baseline (predose) measurements as a covariate (if appropriate); and subject nested in the sequence as a random effect. The potential influence of the first order carry-over effect was investigated and included as a fixed effect in the model if significant at the 25% level. If the normality assumption for the residuals or the homogeneity assumption for the variances was violated, Friedman test was used to test the overall treatment effect, whereas the Wilcoxon signed rank test was used to compare the pairwise treatment differences in the case of a symmetric distribution, and the sign test was used if the symmetry assumption was violated. The comparisons are reported without adjustment for multiple testing.

The treatment comparisons of interest were as follows:

- hydromorphone IR 8 mg and 16 mg versus placebo.
- cebranopadol 200, 400, and 800 μ g versus placebo.
- cebranopadol 200, 400, and 800 μ g versus hydromorphone IR 8 and 16 mg.

For overall drug liking VAS and take drug again VAS, the peak responses for all treatments were calculated. For drug similarity VAS, a descriptive analysis was conducted.

The drug liking (at this moment) VAS was used to validate the study by comparing E_{max} for hydromorphone IR and placebo. Data from the qualification phase were summarized for the completer set using descriptive statistics.

RESULTS

Subjects

Of the 226 enrolled subjects, 85 subjects met the qualification phase criteria, 48 subjects (36 males and 12 females) entered the treatment phase, and 42 subjects completed all 7 treatment periods.

TABLE 1. Descriptive Statistics of Derived Parameters for Drug Liking (at This Moment) VAS (Primary End Point, Completer Set)

End Point	Statistics	Cebranopadol				HMO	
		PBO (n = 42)	200 µg (n = 42)	400 µg (n = 42)	800 µg (n = 42)	8 mg (n = 42)	16 mg (n = 42)
E_{\max}	Mean	55.9	53.0	59.3	68.1	69.0	84.6
	(SD)	(13.22)	(5.42)	(16.46)	(18.60)	(19.68)	(16.75)
	Median	51.0	51.0	51.0	60.5	62.0	91.5
tE_{\max} (h)	Median	0.99	1.50	1.74	2.99	1.49	1.53
	Range	0–36	0–36	0–56	0–56	0–56	0–36
AUE _{0–1h}	Mean	25.52	25.18	25.60	25.98	28.19	31.44
	(SD)	(3.075)	(0.971)	(2.174)	(2.500)	(6.651)	(6.797)
	Median	25.00	25.00	25.00	25.00	25.38	30.11
AUE _{0–sh}	Mean	376.18	374.79	398.66	426.36	429.19	487.01
	(SD)	(35.512)	(21.420)	(67.221)	(93.889)	(117.558)	(119.246)
	Median	375.75	375.79	375.96	394.66	388.75	474.50

AUE_{0–xh} indicates area under the curve from time zero to x hours postdose; HMO, hydromorphone IR; PBO, placebo (fully randomized only).

A total of 37 subjects discontinued during the qualification phase or did not qualify to continue in the treatment phase. Of 6 subjects who discontinued prematurely during the treatment phase, 1 subject withdrew consent, and 5 subjects discontinued early for other reasons.

Most subjects who received IMP were white (85%). The mean age was 37.0 years (range, 18–52 years; n = 48). Subjects (safety set) reported a wide range of substances in their abuse history: alcohol was reported in 41 subjects (85.4%), and the most frequently reported opioids were oxycodone (46 subjects [95.8%]) and codeine (39 subjects [81.3%]). All subjects allocated to IMP were not dependent based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria and the naloxone challenge test results.

In the qualification phase, mean E_{\max} for the primary measure (drug liking [at this moment] VAS) for subjects in the completer set

was at the neutral point (50.9) for placebo, with a corresponding median of 50.0. For hydromorphone IR 12 mg, mean E_{\max} was 97.5, with a corresponding median of 100. These data confirm that subjects who were included in the treatment phase were qualified, given their appropriate responses to placebo and hydromorphone IR and ability to discriminate between the effects of the positive control (hydromorphone IR) and placebo.

Pharmacodynamics

Primary PD Measure: Drug Liking (at This Moment) VAS

Both doses of hydromorphone IR resulted in significantly higher values compared with placebo for the primary end point drug liking (at this moment) VAS E_{\max} ($P < 0.001$). See Table 1 and Table 2 for descriptive statistics of the derived parameters

TABLE 2. Analysis Results for the Primary End Point Drug Liking (at This Moment) VAS E_{\max} (Primary End Point; Completer Set, n = 42)

	Median Difference	Interquartile Range	P
Overall treatment effect			<0.001
HMO vs PBO (study validity)			
HMO 8 mg–PBO	3.5	0.0 to 30.0	<0.001
HMO 16 mg–PBO	33.0	13.0 to 49.0	<0.001
Cebranopadol vs PBO			
Cebranopadol 200 µg–PBO	0.0	0.0 to 1.0	>0.999
Cebranopadol 400 µg–PBO	0.0	0.0 to 1.0	0.524
Cebranopadol 800 µg–PBO	5.0	0.0 to 26.0	0.011
Cebranopadol vs HMO			
Cebranopadol 200 µg–HMO 8 mg	–7.5	–35.0 to 0.0	0.007
Cebranopadol 400 µg–HMO 8 mg	–0.5	–24.0 to 0.0	0.013
Cebranopadol 800 µg–HMO 8 mg	0.0	–12.0 to 13.0	>0.999
Cebranopadol 200 µg–HMO 16 mg	–36.5	–49.0 to –16.0	<0.001
Cebranopadol 400 µg–HMO 16 mg	–26.0	–44.0 to –11.0	<0.001
Cebranopadol 800 µg–HMO 16 mg	–11.5	–39.0 to 0.0	<0.001

Overall treatment effect was assessed using Friedman test. Pairwise treatment comparisons were assessed using the sign test for the within-subject differences. Bold P values indicate statistically significant differences.

HMO indicates hydromorphone IR; PBO, placebo (fully randomized only).

and the statistical results of overall treatment effects, respectively. While cebranopadol 200 and 400 μg were not different from placebo ($P > 0.999$ and $P = 0.524$, respectively), a significant difference was observed between cebranopadol 800 μg and placebo ($P = 0.011$). Cebranopadol 200 and 400 μg had significantly lower drug liking (at this moment) VAS E_{max} values compared with both hydromorphone IR doses. The effect of cebranopadol 800 μg on drug liking (at this moment) VAS E_{max} was comparable with that of hydromorphone IR 8 mg. The time course of the drug liking VAS is depicted in Figure 1. Mean placebo and cebranopadol 200 and 400 μg drug liking (at this moment) VAS scores remained relatively close to the neutral point (approximately 50) and within the placebo range (40–60) for up to 56 hours postdose. In contrast, mean drug liking (at this moment) VAS scores were higher for hydromorphone IR and peaked earlier (Fig. 1). While cebranopadol 200 and 400 μg showed minimal effects over time, cebranopadol 800 μg showed detectable effects that were consistently delayed (approximately 3 hours postdose) relative to hydromorphone IR (approximately 1.5 hours postdose).

Secondary PD Measures

The results of descriptive statistics for E_{max} for selected secondary PD parameters are displayed in Table 3. Supplementary Table 2, Supplemental Digital Content 2, <http://links.lww.com/JCP/A544>, summarizes the results of the nonparametric analysis of selected secondary PD parameters.

Overall and Positive Effects

Visual analog scale ratings for overall drug liking, take drug again, good effect, and high and the ARCI MBG score are described as overall and positive effects. Both hydromorphone IR doses showed significantly greater effects relative to placebo on measures of overall and positive effects. Cebranopadol 200 μg did not differentiate from placebo on any of the end points. Cebranopadol 400 μg showed statistically significant differences to placebo only for take drug again VAS E_{max} . The highest dose of cebranopadol was different to placebo for all overall and positive effect VAS E_{max} values. All cebranopadol doses displayed statistically significantly lower effects compared with hydromorphone IR 16 mg for almost all overall and positive effect measures. Cebranopadol 200 and 400 μg showed lower effects than hydromorphone IR 8 mg for most end points, whereas cebranopadol 800 μg showed effects similar to hydromorphone IR 8 mg.

Negative Effects

Negative effects, as measured by the bad effect VAS and feeling sick VAS, were generally more moderate than positive effects. Hydromorphone IR 8 mg did not differ significantly from placebo on these measures, whereas 16 mg hydromorphone IR had a statistically significantly greater effect than placebo on the bad effects and feeling sick VAS. Cebranopadol 200 and 400 μg were comparable with the effect of placebo on these measures, whereas the highest dose had a statistically significantly greater effect on the bad effect VAS E_{max} compared with placebo. Pairwise comparisons between cebranopadol and hydromorphone IR at all dose levels did not reveal statistically significant differences between both treatments for almost all measures.

Sedative Effects

Sedative effects, as measured by the alertness/drowsiness VAS and the ARCI PCAG and BG subscales, for both doses of hydromorphone IR were significantly greater compared with placebo. Cebranopadol 200 μg showed no significant differences from placebo, whereas cebranopadol 400 and 800 μg showed a difference for minimum effect (E_{min}) for the alertness/drowsiness VAS. For the ARCI PCAG score, only the highest dose of cebranopadol differentiated significantly from placebo. Cebranopadol 200 μg showed significantly lower sedative effects compared with both hydromorphone IR doses for the alertness/drowsiness VAS and ARCI PCAG measures. Cebranopadol 400 μg showed significantly lower sedative effects for all 3 end points compared with hydromorphone IR 16 mg. Cebranopadol 800 μg was not significantly different from hydromorphone IR 8 mg for any of the end points and was only different from hydromorphone IR 16 mg for E_{max} on the ARCI PCAG scale.

Other Effects

Both hydromorphone IR doses showed greater other effects (any effects VAS, floating VAS, and detached VAS) compared with placebo for most end points. Cebranopadol 200 and 400 μg were not different from placebo for any of the end points, whereas cebranopadol 800 μg differed significantly from placebo. All 3 doses of cebranopadol showed significantly lower effects compared with hydromorphone IR 16 mg. Cebranopadol 200 μg had lower other effects relative to hydromorphone IR 8 mg for most

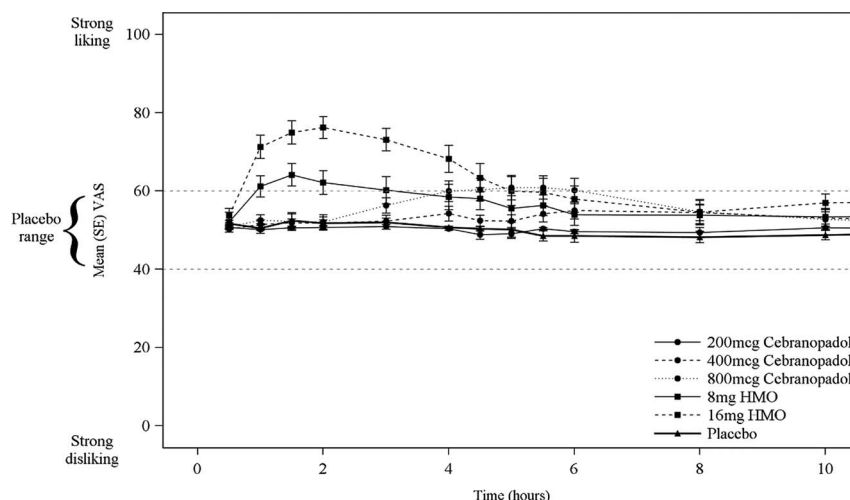


FIGURE 1. Mean curves for drug liking VAS up to 10 hours postdose (completer set). HMO indicates hydromorphone IR.

TABLE 3. Descriptive Statistics of E_{\max} for Selected Secondary PD Measures (Completer Set)

End Point	Statistics	Cebranopadol			Hydromorphone IR	
		Placebo (n = 42)	200 μ g (n = 42)	400 μ g (n = 42)	800 μ g (n = 42)	8 mg (n = 42)
Overall effects measures						
Overall drug liking VAS						
Mean (SD)	51.3 (12.41)	53.5 (10.93)	59.5 (19.04)	62.1 (27.60)	65.7 (24.00)	81.2 (22.40)
Median	50.0	50.0	50.0	57.0	66.5	88.0
Take drug again VAS						
Mean (SD)	13.0 (29.61)	22.2 (32.57)	35.5 (39.63)	44.6 (42.35)	50.8 (38.70)	77.0 (34.11)
Median	0.0	0.0	20.5	43.5	52.5	95.0
Positive effects measures						
Good effects VAS						
Mean (SD)	18.5 (33.07)	17.0 (25.70)	26.0 (36.38)	49.0 (39.91)	48.7 (40.47)	84.5 (28.51)
Median	0.0	1.5	0.5	55.0	50.5	100.0
High VAS						
Mean (SD)	21.0 (32.82)	22.3 (29.27)	27.6 (35.12)	48.7 (38.15)	54.1 (36.67)	82.9 (28.62)
Median	0.0	3.5	7.0	51.0	51.0	100.0
ARCI MBG						
Mean (SD)	3.0 (3.82)	2.7 (3.18)	4.1 (4.78)	5.1 (4.75)	5.0 (4.90)	7.9 (5.57)
Median	1.0	2.0	2.0	2.5	2.0	8.5
Negative effects measures						
Bad effects VAS						
Mean (SD)	8.9 (21.32)	10.9 (24.10)	10.6 (23.76)	24.5 (35.88)	13.2 (26.48)	20.1 (32.88)
Median	0.0	0.0	0.0	3.0	0.0	1.0
Feeling sick VAS						
Mean (SD)	10.1 (22.64)	11.5 (23.30)	7.2 (16.36)	21.8 (34.98)	7.7 (19.83)	24.5 (33.72)
Median	0.0	0.0	0.0	1.0	0.0	1.0
Sedative effects measures						
Alertness/drowsiness VAS (E_{\min})						
Mean (SD)	42.7 (21.44)	38.0 (21.34)	33.2 (21.31)	26.8 (21.14)	27.1 (21.14)	23.1 (19.29)
Median	50.0	48.0	45.5	30.0	27.0	22.5
ARCI PCAG						
Mean (SD)	5.1 (2.93)	5.5 (3.16)	6.2 (3.47)	8.2 (3.91)	7.3 (3.69)	9.3 (3.46)
Median	4.0	4.0	4.5	8.5	7.0	10.0
Any effects measures						
Any effects VAS						
Mean (SD)	20.5 (33.30)	19.7 (28.00)	32.7 (40.59)	56.8 (41.74)	57.0 (43.36)	85.6 (29.59)
Median	0.0	2.5	8.5	69.0	74.5	100.0

Placebo—fully randomized only.

end points, whereas cebranopadol 400 and 800 μ g did not differ from hydromorphone IR 8 mg for most of the measures.

Drug Similarity

Ratings of similarity to placebo were not markedly different between placebo and cebranopadol 200 μ g, whereas cebranopadol 800 μ g was identified as being modestly similar to codeine/morphine, although to a lower extent than hydromorphone IR 8 mg. In contrast, hydromorphone IR 16 mg was associated with high codeine/morphine similarity responses. There was little effect on ratings of similarity to other drugs/classes, other than a weak similarity to benzodiazepines, particularly for hydromorphone IR. Descriptive statistics of drug similarity VAS scores are summarized in Supplementary Table 3, Supplemental Digital Content 3, <http://links.lww.com/JCP/A545>.

Pupillometry

Mean pupil diameter values over time are illustrated in Figure 2. Placebo treatments were associated with minimal fluctuation in pupil diameter over time, whereas a dose-dependent decrease in pupil diameter was observed for cebranopadol 200, 400, and 800 μ g. Decrease in pupil diameter occurred earlier for hydromorphone IR (2 hours postdose) than for cebranopadol (6–8 hours postdose) and was most pronounced for hydromorphone IR 16 mg. The effect on pupil diameters lasted longer for cebranopadol 800 μ g than for hydromorphone IR 16 mg, in line with the pharmacokinetic profile of cebranopadol.

Divided Attention Test

Treatment-related effects on accuracy, reaction time, and attention variables were minimal; overall effects for these end points were

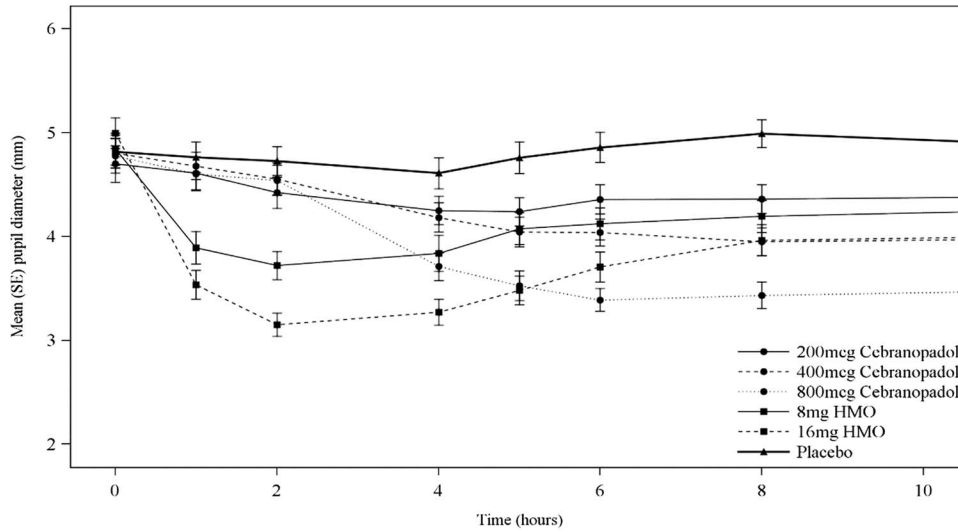


FIGURE 2. Mean pupillometry profiles up to 10 hours postdose (completer set). HMO indicates hydromorphone IR.

similar for active treatments and placebo. Hydromorphone IR 16 mg was associated with significant impairment in manual tracking compared with placebo. Cebranopadol 800 µg was also associated with significant effects relative to placebo for some of the test variables, whereas the lower doses of both active treatments drugs (hydromorphone IR 8 mg and cebranopadol 200 and 400 µg) showed no significant effects. Although cebranopadol 800 µg was associated with greater impairment for some parameters compared with hydromorphone IR 8 mg, these effects were not greater than for hydromorphone IR 16 mg. The analysis results for the Divided Attention Test are presented in Supplementary Table 4, Supplemental Digital Content 4, <http://links.lww.com/JCP/A546>.

Pharmacokinetics

Plasma concentration of cebranopadol increased with the dose administered and reached a maximum between 4 and 6 hours after administration (median t_{max} , 5.12 hours). Generally, the concentration-time profiles revealed a similar pattern for all 3 cebranopadol doses (Fig. 3 and Table 4), and C_{max} and AUC

increased in a dose-proportional manner. The plasma concentration-time profile of hydromorphone IR was as expected and described in the literature.³⁷ Exposure increased with dose and reached a maximum concentration between 0.5 and 2 hours (median t_{max} , 1.0 hours) after administration (Fig. 4 and Table 4).

Safety

Single doses of cebranopadol 200 and 400 µg were safe and well tolerated, whereas cebranopadol 800 µg as a single dose was less well tolerated than the lower doses. There were no deaths or other serious adverse events. Somnolence, euphoric mood, nausea, headache, dizziness, vomiting, and fatigue were the most frequently reported adverse events.

The incidence of the dose-limiting and potentially aversive effect of vomiting was more than 3 times higher for cebranopadol 800 µg than for hydromorphone IR 16 mg (15.2% vs 4.4%). The incidence of nausea for cebranopadol 800 µg was similar to that observed for hydromorphone IR 16 mg (19.6% vs 22.2%). Of note, the incidences of both nausea and vomiting were much

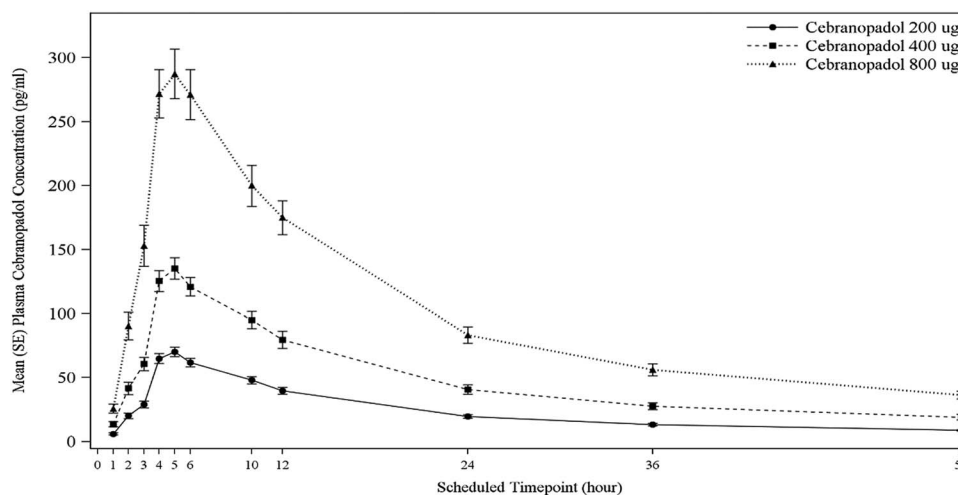


FIGURE 3. Mean cebranopadol plasma concentration over time (PK set, n = 42). Data points were plotted at a particular time point only if at least 75% of subjects had quantifiable concentrations at this time point. All concentrations below the lower limit of quantification (2.0 pg/mL) were set to zero. PK indicates pharmacokinetic.

TABLE 4. Descriptive Statistics of Pharmacokinetic Parameters by Treatment (Pharmacokinetic Set)

Parameter	Dose Level of Cebranopadol					
	200 µg	n	400 µg	n	800 µg	n
Cebranopadol						
C_{max} , pg/mL	74.5 (25.3)	41	149 (52.6)	42	310 (125)	41
t_{max} , h	5.12 [4.10–12.2]	41	5.12 [4.10–10.1]	42	5.12 [3.05–12.1]	41
AUC_{0-t} , h · pg/mL	1276 (459)	41	2605 (1248)	42	5484 (2411)	41
$t_{1/2,z}$, h	25.7 (7.97)	40	27.4 (14.9)	41	24.4 (9.00)	38
Parameter	Dose Level of Hydromorphone					
	8 mg	n	16 mg	n	n	n
Hydromorphone						
C_{max} , ng/mL	3.76 (1.60)	41	7.75 (3.80)	42		42
t_{max} , h	1.00 [0.50–2.00]	41	1.00 [0.50–2.00]	42		42
AUC_{0-t} , h · ng/mL	17.0 (5.50)	41	35.0 (11.0)	42		42
$t_{1/2,z}$, h	15.1 (6.96)	36	15.8 (4.74)	38		38

Arithmetic means and SDs for AUC_{0-t} and C_{max} ; median and range for t_{max} are shown.

AUC_{0-t} indicates the area under the concentration-time curve up to the last time point with a quantifiable concentration (maximum of 56 h); C_{max} , maximum plasma concentration; $t_{1/2,z}$, terminal half-life; t_{max} , time to attain maximum concentration.

higher for cebranopadol 800 µg than for hydromorphone IR 8 mg (19.6% vs 2.3% and 15.2% vs 4.5%, respectively). While the incidence of somnolence was also similar for cebranopadol 800 µg and hydromorphone IR 8 mg (37.0% vs 40.9%), the incidence of fatigue was higher for cebranopadol 800 µg than for hydromorphone 16 mg (10.9% vs 6.7%). The incidences of treatment-emergent adverse events (TEAEs) reported in at least 5% of subjects are given in Table 5. A summary of euphoria-related adverse events, as potentially abuse-related TEAEs, is shown in Supplementary Table 5, Supplemental Digital Content 5, <http://links.lww.com/JCP/A547>. Of these, euphoric mood was the most commonly reported in all cebranopadol treatment groups pooled together (21/47 subjects [44.7%]), followed by dizziness (17.0%) and elevated mood and feeling of relaxation (2.1% each). Overall, hydromorphone IR was associated with a higher incidence of euphoric mood (33/46 subjects [71.7%]), even though subjects were exposed to hydromorphone IR in only fewer periods (2) than to cebranopadol

(3). Incidence of euphoric mood was dose dependent for both cebranopadol and hydromorphone IR. Elevated mood was reported by 1 subject under treatment with cebranopadol 800 µg, and feeling abnormal by 1 subject after administration of hydromorphone IR 16 mg. No TEAEs were reported for the categories “drug abuse,” “dependence,” “withdrawal,” “substance-related disorders,” and “mood disorders and disturbances.”

No clinically relevant effects on vital signs, laboratory parameters, and ECG parameters were observed.

DISCUSSION

Significant effects of the positive control (hydromorphone IR 8 and 16 mg), relative to placebo, were found for the primary end point drug liking (at this moment) VAS E_{max} and for most secondary end points of overall, positive, sedative, and other subjective effects measures. Moreover, hydromorphone IR was associated

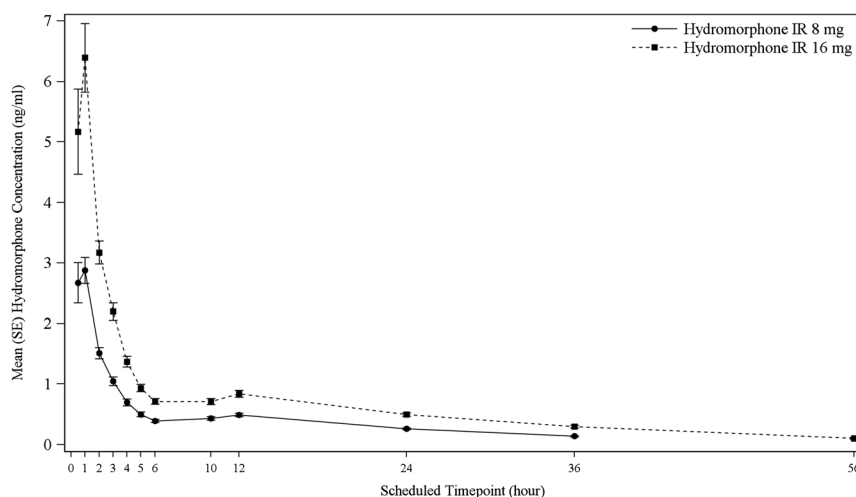


FIGURE 4. Mean hydromorphone plasma concentration over time (PK set, n = 42). Data points were plotted at a particular time point only if at least 75% of subjects had quantifiable concentrations at this time point. All concentrations below the lower limit of quantification (0.05ng/mL) were set to zero. PK indicates pharmacokinetic.

TABLE 5. TEAEs Reported in at Least 5% of the Subjects (Safety Set)

Preferred Term	Placebo		Cebranopadol			Hydromorphone IR	
	Treatment F (n = 45)	Treatment G (n = 45)	200 µg (n = 45)	400 µg (n = 46)	800 µg (n = 46)	8 mg (n = 44)	16 mg (n = 45)
No. (%) subjects with TEAE	15 (33.3%)	12 (26.7%)	26 (57.8%)	30 (65.2%)	35 (76.1%)	28 (63.6%)	39 (86.7%)
Asthenopia	1 (2.2%)	0	0	1 (2.2%)	2 (4.3%)	0	0
Nausea	0	1 (2.2%)	2 (4.4%)	2 (4.3%)	9 (19.6%)	1 (2.3%)	10 (22.2%)
Vomiting	0	0	1 (2.2%)	0	7 (15.2%)	2 (4.5%)	2 (4.4%)
Fatigue	2 (4.4%)	1 (2.2%)	2 (4.4%)	1 (2.2%)	5 (10.9%)	0	3 (6.7%)
Feeling hot	1 (2.2%)	0	2 (4.4%)	0	2 (4.3%)	2 (4.5%)	1 (2.2%)
Gait disturbance	0	0	0	1 (2.2%)	2 (4.3%)	0	0
Dizziness	0	1 (2.2%)	1 (2.2%)	4 (8.7%)	5 (10.9%)	4 (9.1%)	8 (17.8%)
Headache	3 (6.7%)	2 (4.4%)	6 (13.3%)	3 (6.5%)	6 (13.0%)	6 (13.6%)	8 (17.8%)
Somnolence	6 (13.3%)	4 (8.9%)	7 (15.6%)	16 (34.8%)	17 (37.0%)	18 (40.9%)	22 (48.9%)
Euphoric mood	2 (4.4%)	2 (4.4%)	1 (2.2%)	5 (10.9%)	17 (37.0%)	16 (36.4%)	28 (62.2%)
Pruritus	0	1 (2.2%)	0	0	3 (6.5%)	4 (9.1%)	10 (22.2%)

Placebo treatment F, fully randomized; placebo treatment G, fixed placebo (following the treatment with cebranopadol 800 µg).

with relatively weak negative effects, and the 16-mg dose, in particular, was identified as being similar to codeine/morphine on the drug similarity VAS. In addition, as expected for a full MOP receptor agonist, both doses of hydromorphone IR showed significant miosis with rapid onset after oral administration. Overall, the subjective and objective effects observed for hydromorphone IR in this study were consistent with those expected for an MOP receptor agonist and demonstrate the validity of the study and sensitivity of the population and measures used.^{18–20,22}

In general, cebranopadol 200 µg was not different from placebo for any of the subjective end points, including the primary end point drug liking (at this moment) VAS E_{max} . Also, the medium dose of cebranopadol (400 µg) was not significantly different from placebo for the primary and most of the secondary end points, although sporadic differences from placebo were observed. Although statistically significant for a few end points, the magnitude of effects was very small (median values often at or near the neutral point) and significantly smaller than the effects observed for hydromorphone IR 8 mg for most positive and overall effects end points. Cebranopadol 200 µg was thus not detected on the abuse potential scales (including any effect), whereas cebranopadol 400 µg was not consistently detected on these measures, although some subjects were able to detect effects of this dose.

Cebranopadol 800 µg showed significantly greater effects compared with placebo for most end points and was similar to hydromorphone IR 8 mg for the primary end point and most positive/overall effects measures. However, cebranopadol 800 µg showed significantly lower effects compared with hydromorphone IR 16 mg for most of these end points. The exceptions were the negative effects measures, where the effects of cebranopadol 800 µg were similar to hydromorphone IR 16 mg, and to a smaller extent, the sedative effects measures, where the effects of cebranopadol 800 µg were intermediate between the 2 hydromorphone IR doses. Although subjects were able to recognize positive effects of cebranopadol 800 µg similar to 8 mg of hydromorphone IR, the higher negative effects measures could lead to a lower likelihood for abuse. While nondependent recreational drug users in this study tolerated the 800-µg dose somewhat better than drug-naïve volunteers in other studies,³⁸ there was an increasing incidence of nausea and vomiting with increasing doses of cebranopadol. The incidence of nausea for cebranopadol 800 µg was similar to

that observed for hydromorphone IR 16 mg, whereas the incidence of vomiting was more than 3 times higher. Of note, the incidences of both nausea and vomiting were much higher for cebranopadol 800 µg than for hydromorphone IR 8 mg. Taken together with the higher reporting of negative effects, the occurrence of these side effects for the highest dose of cebranopadol might lower the potential for it to be abused.

The late onset of cebranopadol effects also suggests differences in abuse potential between cebranopadol and hydromorphone IR. Cebranopadol 800 µg was associated with a late onset of effects relative to both doses of hydromorphone IR. Consistent with the longer time to reach maximum plasma concentration (t_{max} ~5 hours), peak effects were reached ~1.5 hours later in comparison to hydromorphone IR. Cebranopadol 200 and 400 µg also showed this to some extent; however, the effects overall were generally small with these doses. Despite the late onset of effects and longer pharmacokinetic half-life of cebranopadol, evidence of a markedly longer duration of effect was observed only for some measures (eg, sedative and negative effects), but not for others (eg, drug liking [at this moment] VAS). The late onset and time course pattern of results for cebranopadol further highlight its intrinsic pharmacological differences to hydromorphone IR.

Significant effects on the pupillary diameter were observed for all doses of cebranopadol. The median maximum reduction in pupil diameter occurred considerably later (between ~5 and 8 hours postdose) after administration of cebranopadol than after administration of hydromorphone IR (~2 hours postdose). Although these effects clearly indicate MOP receptor agonistic effects of the cebranopadol doses (responsible for pain relief), this MOP receptor agonism did not lead to an increase in the positive subjective measures (eg, drug liking [at this moment] VAS E_{max}). The positive subjective effects were largely similar for cebranopadol 200 and 400 µg and placebo. These data suggest that MOP receptor activation resulting from cebranopadol does not translate 1:1 into positive abuse-relevant drug effects.

Based on pharmacometric simulations, a higher dose of cebranopadol than used in this study would be needed to reach the same maximum probability of having a drug liking (at this moment) VAS score higher than 60, as observed for hydromorphone IR 8 mg, and would be reached approximately 5 hours later for cebranopadol compared with hydromorphone IR.³⁹

The fact that cebranopadol also acts as an NOP receptor agonist could explain why the drug may produce less liking than classic MOP receptor agonists. In animal models, NOP receptor agonists have been shown to reduce a number of typical side effects of MOP receptor agonists. Nociceptin/orphanin FQ and nonpeptide NOP receptor agonists reduce the rewarding effects of classic opioids,^{22,40–43} whereas pharmacological blockade or genetic knockout of the NOP receptor potentiates the rewarding effect of morphine in rats.⁴⁴ In line with this, investigational drugs combining NOP and MOP receptor agonistic activity have been shown to produce a limited degree of reward.⁴⁵

Our hypothesis that a compound with combined NOP and MOP receptor agonism such as cebranopadol can display lower abuse potential compared with a pure MOP receptor agonist (eg, hydromorphone IR) cannot be rejected based on the results of the overall subjective, physiological, and cognitive assessments and adverse event evaluations.

ACKNOWLEDGMENTS

The authors thank E. Babich and D. Ankel-Fuchs (former and current employee of Grünenthal GmbH, Aachen, Germany) for their support in the design and conduct of the trial and medical writing assistance, respectively. The authors also thank M. Gautrois (Grünenthal GmbH, Aachen, Germany) for his valuable contribution to the pharmacokinetic section.

AUTHOR DISCLOSURE INFORMATION

K.G., R.N., E.K., and M.-H.E. are employees of Grünenthal GmbH. At the time the trial was conducted, M.S. was an employee of Medical Affairs and Center for Abuse Prevention and Evaluation, Grünenthal USA, Morristown, NJ; and K.A.S. was an employee of INC Research Early Phase (currently Altros Research Partners, Inc.). The other authors declare no conflicts of interest.

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