CEBRANOPADOL: A NOVEL FIRST-IN-CLASS ANALGESIC IN DEVELOPMENT FOR CHRONIC PAIN CONDITIONS - RESULTS FROM A HUMAN ABUSE POTENTIAL STUDY IN NON-DEPENDENT RECREATIONAL OPIOID USERS

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INTRODUCTION

A human abuse liability study is the most predictive pre-marketing tool to evaluate the abuse potential of investigational medicinal products. Cebranopadol is a novel first-in-class analgesic that acts as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist with central analgesic activity. Cebranopadol is currently in clinical development for the treatment of chronic pain conditions.

The abuse potential of novel analgesics combining NOP and OP receptor agonism has not been profiled to date. Based on preclinical data, we hypothesize that this novel mechanism of action will lead to lower risk for abuse compared to pure mu opioid peptide (MOP) receptor agonists such as morphine, hydrocodone, and hydromorphone (HMO).

A human abuse potential study was performed in accordance with the FDA Draft Guidance on Assessment of Abuse Potential of Drugs (Jan 2010)[1]. The study design reflected recommendations provided by the FDA.

PRIMARY OBJECTIVE

To evaluate the abuse potential of single doses of cebranopadol relative to HMO immediate release (IR) and placebo in non-dependent recreational opioid users.

METHODS

STUDY DESIGN

A nested-randomized, single site, double-blind, double-dummy, placebo- and active-controlled, crossover, single oral dose Phase 1 study in 48 healthy recreational opioid users. There was a Qualification Phase (ensuring that the subjects were not opioid-dependent, could discriminate between active drug and placebo and could tolerate HMO IR 12 mg) and a 7-period Treatment Phase (cebranopadol 200 and 400 µg [both within the therapeutic dose range] and 800 µg [supra-therapeutic dose]), HMO IR 8 and 16 mg, and 2 placebo treatments.

STUDY POPULATION

Healthy male and female subjects, 18 years to 55 years of age, with a history of recreational opioid use. For a subject disposition see Figure 1.

PHARMACODYNAMIC (PD) ASSESSMENTS (over 56 h post-dose)

Primary endpoint

Mean peak (E_{max}) Drug Liking (at this moment), measured by visual analog scale (VAS).

Secondary endpoints

VAS ratings for Any Drug Effects, Good Drug Effects, High, Bad Drug Effects, Take Drug Again, Feeling Sick, Alertness/Drowsiness, Floating, Detached, Overall Drug Liking, Drug Similarity; Addiction Research Center Inventory Morphine-Benzedrine Group, Benzedrine Group, and Pentobarbital-Chlorpromazine-Alcohol Group scales; Divided Attention Test, Pupillometry.

PHARMACOKINETIC (PK) AND SAFETY ASSESSMENTS (over 56 h post-dose)

Plasma concentrations of cebranopadol, its metabolites, and HMO, and adverse events (AEs) were determined/recorded.

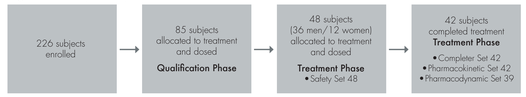
STATISTICS

A linear mixed effects model was fitted to each PD parameter with treatment, period, sequence, and sex as fixed effects, baseline as covariate and subject nested in the sequence as a random effect, where applicable. Least square means and 95% confidence intervals for treatments and treatment differences were computed, along with the statistical significances of the treatment differences. If the assumptions for a linear mixed effects model were not met, nonparametric methods were applied (like Friedman's test, Wilcoxon signed-rank test, or sign test). The VAS Drug Liking (at this moment) was used to validate the study by comparing the E_{max} of HMO IR and placebo.

RESULTS

SUBJECT DISPOSITION

Figure 1: Subject disposition



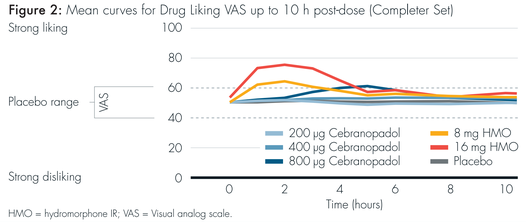
PHARMACODYNAMIC ASSESSMENTS

Table 1: Descriptive statistics of derived parameters for Drug Liking VAS (Completer Set)

		Placebo	Cebranopadol			Hydromorphone IR	
Endpoint	Statistic	(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
$AUE_{0\text{-}1h}$	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

$AUE_{0\text{-}1h}$ = Partial area under the curve 0 - 1 h; E_{max} = maximum effect; IR = immediate release; N = number of subjects; SD = standard deviation; tE_{max} = time to maximum effect.

Figure 2: Mean curves for Drug Liking VAS up to 10 h post-dose (Completer Set)



HMO = hydromorphone IR; VAS = Visual analog scale.

Drug Liking VAS (at this moment)

- The study can be considered valid as mean E_{max} values for both HMO IR doses were significantly higher than for placebo (Table 1, p <0.0001).
- Mean E_{max} values for cebranopadol 200 and 400 µg did not separate from placebo (Table 1, p >0.9999 and p = 0.5235) and were within the placebo response range (Figure 2).
- Mean E_{max} value for cebranopadol 800 µg was similar to HMO IR 8 mg and lower than HMO IR 16 mg (Table 1, p >0.9999 and p <0.0001, respectively), and was associated with a delayed onset of effects by approx. 1.5 h in comparison to both doses of HMO IR (Figure 2).
- No differences between placebo and all doses of cebranopadol on median $AUE_{0\text{-}1h}$ value were detected (p = 0.0872 or higher) whereas median $AUE_{0\text{-}1h}$ for HMO IR 16 mg separated from placebo (Table 1, p-value <0.0001).

Selected secondary PD measures

- Mean E_{max} for cebranopadol 200 and 400 µg generally did not separate from placebo on the abuse potential assessments (Table 2).
- Generally increasing values were noted on the overall and positive effects measures with increasing doses of cebranopadol and with cebranopadol 800 µg approaching those of HMO 8 mg, lower than for HMO IR 16 mg (Table 2).
- Cebranopadol 800 µg was associated with the highest level of negative effects (Table 2).

Table 2: Descriptive statistics of derived parameters for selected secondary PD measures (Completer Set)

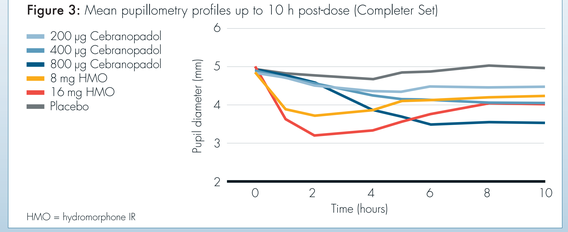
		Placebo	Cebranopadol			Hydromorphone IR	
Endpoint	Statistic	(N = 42)	200 µg (N = 42)	400 µg (N = 42)	800 µg (N = 42)	8 mg (N = 42)	16 mg (N = 42)
Overall Effects Measures							
Overall Drug Liking VAS (Bipolar; Neutral = 50)							
	Mean (SD)	51.3 (12.41)	53.5 (10.93)	59.5 (19.04)	62.1 (27.60)	65.7 (24.00)	81.2 (22.40)
	Median	50.0	50.0	50.0	57.0	66.5	88.0
Take Drug Again VAS (Unipolar; Neutral = 0)							
	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
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

ARCI = Addiction Research Center Inventory; MBG = Morphine Benzedrine Group; IR = immediate release; N = number of subjects; SD = standard deviation; VAS = visual analog scale.

Pupillometry

Placebo treatments were associated with minimal fluctuation in pupil diameter over time. A dose dependent decrease in pupil diameter was observed with cebranopadol 200, 400, and 800 µg. The magnitude of pupillary constriction was lower with all doses of cebranopadol than with HMO IR 16 mg. The decreases in pupil diameter occurred earlier with HMO IR (2 h post-dose) than with cebranopadol (6 h post-dose) and were most pronounced with HMO IR 16 mg. The effect on pupil diameters lasted longer with cebranopadol 800 µg than with HMO IR 16 mg (Figure 3).

Figure 3: Mean pupillometry profiles up to 10 h post-dose (Completer Set)



HMO = hydromorphone IR

PHARMACOKINETICS

Both C_{max} and AUC_{0t} increased in a dose dependent fashion for cebranopadol. Median times to C_{max} for cebranopadol were 5.12 h after dosing and were in line with the corresponding values in previous studies.

SAFETY

Single doses of cebranopadol 200, 400, and 800 µg were safe and well tolerated. Cebranopadol 800 µg as single dose was less well tolerated than cebranopadol 200 and 400 µg. There were no deaths or other serious AEs. The Treatment Emergent Adverse Events (TEAE) profile was as expected from other cebranopadol Phase 1 single-dose studies, except for euphoric mood (Table 3). Euphoric mood was reported by 37% of subjects after the intake of cebranopadol 800 µg and HMO IR 8 mg whereas 62% reported it after intake of HMO IR 16 mg. No clinically relevant effects on vital signs, laboratory parameters, and electrocardiograms were observed.

Table 3: TEAEs reported in at least 5% of the subjects in one of the active treatment groups overall (Safety Set)

	Placebo		Cebranopadol			Hydromorphone IR	
Preferred Term	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)
Number (%) of 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%)
Dry mouth	0	1 (2.2%)	0	1 (2.2%)	0	5 (11.4%)	5 (11.1%)

IR = immediate release; N = number of subjects; TEAE = treatment emergent adverse event.
Treatment G = Placebo fixed (following cebranopadol 800 µg); Treatment F = Placebo (fully randomized).

SUMMARY

- Cebranopadol 200 and 400 µg generally did not separate from placebo on the abuse potential assessments and generated responses lower than those with HMO IR.
- The response associated with cebranopadol 800 µg was similar to HMO IR 8 mg and lower than HMO IR 16 mg on the VAS Drug Liking, but its maximum effect was delayed in comparison to HMO IR (1.5 h and 3 h, respectively). Additionally, the negative effects measures associated with cebranopadol 800 µg were higher than those for HMO IR 8 mg and a lower score for take drug again was noted for this dose of cebranopadol compared to HMO IR 8 and 16 mg.
- Administration of cebranopadol was safe and well tolerated.

CONCLUSION

This study suggests that at the doses tested cebranopadol has lower abuse potential than HMO IR.

References

1. Food and Drug Administration Guidance for Industry. Assessment of Abuse Potential of Drugs. Draft guidance, January 2010.

Acknowledgments

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