Cebranopadol, a Novel Potent Analgesic: Pooled Analysis of Clinical Opiate Withdrawal Scales

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Introduction

Cebranopadol is a novel, highly potent, and centrally active opioid receptor agonist with high affinity for the μ-opioid (MOP) receptors and nociceptin/orphanin FQ peptide (NOP) receptors and lesser affinity for κ-opioid (KOP) receptors and δ-opioid (DOP) receptors. Agonism of the NOP receptor has been associated with a reduction in adverse events related to the agonism of the MOP receptor including respiratory depression, euphoria, sedation and physical dependence. Animal studies with cebranopadol have demonstrated a limited potential for the development of physical dependence.

During clinical trials, patients were monitored for the development of physical dependence and withdrawal. This descriptive analysis explores the development of physical dependence by evaluating the evidence of withdrawal in patients following discontinuation of cebranopadol.

Methods

Nine phase 2/3 clinical trials were conducted with cebranopadol across multiple pain types. Investigators administered the Clinical Opiate Withdrawal Scale (COWS), measuring the signs and symptoms of withdrawal in 6 of the 9 studies. The Clinical Opiate Withdrawal Scale (COWS) is a physician administered assessment of withdrawal symptoms across several domains including heart rate, pupil size, gastrointestinal upset, etc. which has been validated as a way of determining physical dependence. An analysis of the adverse events potentially related to drug withdrawal reported as well as an analysis of the COWS from the safety populations across the 5 studies in which the treatment period was at least 4 weeks was conducted.

Results

A total of 1,068 patients received treatment with cebranopadol with daily doses ranging from 25-800μg. Comparator agents included placebo (n=404), tapentadol prolonged release (PR) 200mg twice daily (BID) (n=126), pregabalin 300mg BID (N=65), or oxycodone controlled release (CR) 10-50mg BID (n=155), for a duration of 4 to 12 weeks. In contrast to standard clinical practice with opioids, all study drugs were discontinued abruptly at the end of each trial with the exception of pregabalin

References

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Table 1. COWS from Cebranopadol Phase 2 Studies

	GRT-MD-101 Osteoarthritis of the Knee (Phase 2)	KF6005-03 Osteoarthritis of the Knee (Phase 2)	KF6005-06 Chronic Low Back Pain (Phase 2)	KF6005-04 Diabetic Polyneuropathy (Phase 2)	KF6005-08 Diabetic Peripheral Neuropathy (Phase 2)
Safety population, n	618	95	637	122	314
ITT / FAS population, n [a]	618	95	635	122	312
Age, mean years	57.7	61.8	57.5	59.2	62.2
Cebranopadol dose	200-400, 400-800 μg [b]	75, 200, 400 μg	200, 400, 600 μg	25, 75, 200 μg	100, 300, 600 μg [b]
Comparator study drug	Placebo Oxycodone CR 10-50 mg BID	Placebo	Placebo Tapentadol PR 200 mg BID	Placebo	Placebo Pregabalin 225-300 mg BID
Treatment Period	15 weeks	4 weeks	14 weeks [c]	4 weeks	8 weeks
COWS					
Mild withdrawal (score 5-12)	200-400 μg: 2.6% 400-800 μg: 0% Placebo: 1.3% Oxycodone: 3.9%	75 μg: 0% 200 μg: 6.5% 400 μg: 5.0% Placebo: 0%	200 μg: 4.6% 400 μg: 6.5% 600 μg: 4.7% Placebo: 0% Tapentadol: 9.9%	25 μg: 3.3% 75 μg: 0% 200 μg: 0% Placebo: 0%	100 μg: 1.6% 300 μg: 7.5% 600 μg: 4.0% Placebo: 5.5% Pregabalin: 1.7%
Moderate withdrawal (score 13-24)	200-400 μg: 0% 400-800 μg: 0% Placebo: 0% Oxycodone: 0.6%	0% for all arms	200 μg: 0.9% 400 μg: 0% 600 μg: 0.9% Placebo: 0% Tapentadol: 3.6%	0% for all arms	100 μg: 1.6% 300 μg: 0% 600 μg: 0% Placebo: 0% Pregabalin: 0%
Moderately severe withdrawal (score 25-36)	0% for all arms	0% for all arms	Cebranopadol: 0% Placebo: 0.9% Tapentadol: 0%	0% for all arms	0% for all arms
Severe Withdrawal (score >36)	0% for all arms	0% for all arms	0% for all arms	0% for all arms	0% for all arms

a Number of patients in the primary endpoint analysis.
b The dose for each subject was titrated within the indicated range during a Titration Phase.
c Includes a 2-week titration phase.

Results (continued)

which was tapered over one week. The overall incidence of the treatment emergent adverse event (TEAE) drug withdrawal syndrome was similar between cebranopadol and placebo with higher rates observed in the oxycodone and tapentadol arms within the respective studies. Additionally, when evaluating COWS, incidences of mild withdrawal were similar for cebranopadol across studies and lower than oxycodone CR or tapentadol PR in the respective studies. The incidences of moderate withdrawal were lower in the cebranopadol group than in the oxycodone CR or tapentadol PR groups during the respective studies.

Discussion

Analysis across Phase 2 studies has demonstrated limited physical dependence with cebranopadol. Across studies with duration of treatment of 4 weeks or longer, AEs potentially indicative of drug withdrawal were no more frequent than for patients who received placebo. Moreover, as measured by the COWS, withdrawal rates were significantly lower than for opioid comparators in both of the relevant trials, and rates of withdrawal more severe than mild did not differ from placebo. Interpretation does however present some challenges with the wide dose range of cebranopadol used across the studies, the variation in treatment periods, and the lack of an active comparator in some studies.

Table 2. Pooled analysis of COWS from Phase 2 Studies

n (%)	Cebranopadol (25-800 μg QD)	Oxycodone CR (10-50 mg BID)	Tapentadol PR (200 mg BID)	Pregabalin (225-300 mg BID)	Placebo
Total number of subjects	1068	155	126	65	404
No Withdrawal	861 (80.6%)	127 (81.9%)	92 (73.0%)	58 (89.2%)	353 (87.4%)
Mild withdrawal	36 (3.4%)	6 (3.9%)	11 (8.7%)	2 (3.1%)	8 (2.0%)
Moderate withdrawal	3 (0.3%)	1 (0.6%)	4 (3.2%)	0	0
Moderately severe withdrawal	0	0	0	0	1 (0.2%)
Severe Withdrawal	0	0	0	0	0
Missing	168 (15.7%)	21 (13.5%)	19 (15.1%)	5 (7.7%)	42 (10.4%)

Analysis only includes trials in which patients received at least 4 weeks of treatment.
Subjects in the category 'missing' did not attend the Following-up Visit or did not assess the Clinical Opiate Withdrawal Scale.
BID = twice daily; CR = controlled release; PR = prolonged release; N = number of subjects; % = percentage of subjects based on total number of subjects in the treatment group; QD = once daily.

Table 3. Frequency of reports of Drug withdrawal from Pooled Phase 2 Studies

n(%)	Cebranopadol (25-800 μg QD)	Oxycodone CR (10-50 mg BID)	Tapentadol PR (50-200 mg BID)	Pregabalin (50-300 mg BID)	Placebo
Total number of subjects	1068	155	126	65	404
Subjects with at least 1 TEAE in the SMQ Drug Withdrawal	3 (0.3%)	8 (5.2%)	2 (1.6%)	0 (0.0%)	2 (0.5%)
Drug withdrawal syndrome	3 (0.3%)	8 (5.2%)	2 (1.6%)	0 (0.0%)	2 (0.5%)

Analysis only includes patients who received greater than 5 days of therapy in trials that had at least a 4 week of treatment period.
TEAE=Treatment Emergent Adverse Event; SMQ=Standardised MedDRA Query

Discussion (continued)

It should also be noted that all drugs were discontinued abruptly at the end of therapy except for pregabalin which was tapered down over 1 week – contrary to labeling for all approved opioids. The sensitivity of assessment may also vary between trials and investigators

Conclusion

Despite being abruptly discontinued at the end of therapy in each trial, cebranopadol demonstrated limited withdrawal across a wide range of doses, including the high dose of 800μg daily which is greater than double the highest therapeutic dose that is expected to be used for pain in phase 3 trials, with duration of treatment up to 15 weeks. This seems to indicate that cebranopadol produces limited physical dependence at doses relevant for analgesia. Considering its safety across a wide range of doses, cebranopadol may serve as a much-needed treatment option for patients with moderate to severe pain.