Cebranopadol, A Novel First-in-Class Analgesic: Results From a Study in Patients With Moderate to Severe Pain Following Bunionectomy

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INTRODUCTION

- Acute pain can arise in many clinical situations, including the postoperative period, trauma, medical illness, childbirth, and acute exacerbation of chronic and cancer pain. The most common acute pain syndrome is post-operative pain.[1] Unrelieved pain produces short- and long-term physiological and psychological adverse consequences, in addition to causing needless patient suffering.[2]
- Post-operative pain can be specifically studied in bunionectomy (hallux valgus repair) which is a commonly used pain model in clinical trials to study the efficacy of analgesic drugs in acute pain.[3]
- Cebranopadol is a novel, highly potent analgesic acting as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist with central analgesic activity.
- In this Phase 2 trial cebranopadol was evaluated in patients with moderate to severe pain following bunionectomy.

METHODS

Diagnosis and Main Criteria for Inclusion

- Patients who underwent unilateral first metatarsal bunionectomy; non-Asian, male and non-lactating female patients aged between 18 years and 75 years, inclusive; physical status rated as I to II on the American Society of Anesthesiologists rating scale.
- Other analgesics or concomitant treatments that could interfere with the efficacy assessment of the investigational medicinal product (IMP) and/or safety of the patients were forbidden.

Trial Design

- Randomized, multi-center, double-blind, placebo-controlled, active-controlled, parallel-group, and single dose double-dummy administration.
- Treatment groups were either 1 of the 3 cebranopadol doses (200 µg, 400 µg or 600 µg) plus morphine-placebo or cebranopadol-placebo plus morphine CR (60 mg) or cebranopadol-placebo plus morphine-placebo.
- Patients who met the criteria after the pre-operative visit were hospitalized for the surgical procedure and the subsequent treatment period. The regional anesthetic technique consisted of a combination of sciatic (popliteal) block, and a continuous local anesthetic infusion to the sciatic nerve to assure profound intra-operative (surgical) anesthesia as an effective control of immediate post-operative pain. The sciatic block was terminated early in the morning after the surgery.
- Patients received a single oral dose of cebranopadol or placebo, and a single dose of morphine CR or placebo 1 h after the end of the sciatic block. Cebranopadol was expected to reach C_{max} 4-6 h after dosing, whereas morphine CR (60 mg) reportedly reaches C_{max} 2-2.5 h after dosing.[4] Rescue medication (1st line: acetaminophen, 2nd line: diclofenac) was allowed as soon as 1 h after the stop of the sciatic infusion.

Efficacy Evaluations

- The primary endpoint for this trial was the sum of pain intensity (SPI) based on an 11-point numeric rating scale from 2 h after first intake of the IMP up to 10 h (SPI_{2-10}). The SPI_{2-10} was calculated as the weighted sum of the pain intensity values over an 8-hour interval. The weights were taken as the time elapsed (in hours) since the previous measurement.
- Secondary endpoints were the SPI from 2 h to 6 h, 2 h to 12 h, 2 h to 14 h, 2 h to 18 h, 2 h to 24 h, and 4 h to 10 h after IMP intake, time to first rescue medication, amount of rescue medication, responder rate and subject global impression.

Safety and Tolerability Evaluations

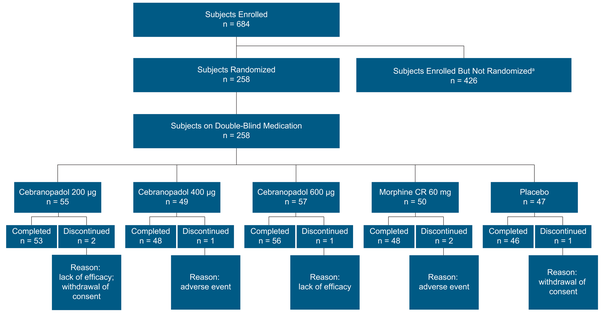
- Include adverse events, physical examination, vital signs, clinical laboratory, and electrocardiograms.

Statistical Analyses

- The primary evaluation was the estimation of the differences in SPI_{2-10} between the treatment groups and was done by means of analysis of variance (ANOVA) accounting for the effects of treatment and center. The main comparisons of interest were the ones between cebranopadol doses and placebo, but all treatments were compared with each other in an explorative manner.
- The Full Analysis Set (FAS) is defined as comprising all randomized patients with at least 1 pain intensity value after randomization and intake of all IMP (cebranopadol or morphine and the respective matching placebo).
- In general for the efficacy evaluation, the last observation carried forward imputation rule was applied for any subject who prematurely discontinued from the treatment or who took additional analgesics or rescue medication (for patients who took additional analgesics or rescue medication, imputation was only applied for 4 h after rescue medication intake).

RESULTS

Subject Disposition and Baseline Demographics



CR = controlled release; n = number of subjects.
[a]Reason: enrollment failure; other.

Figure 1. Disposition of Subjects

- In total, 4 sites in the USA enrolled 684 patients; 258 patients were randomly allocated to treatment, and took IMP (Safety Set).
  - Overall, the mean ± standard deviation (SD) baseline pain intensity was 4.9 ± 3.2 on the 11-point NRS. The treatment groups were well balanced with regard to baseline pain intensity.
  - The overall mean ± SD duration of the surgery (25.5 min ± 7.3 min) and of sciatic block (1012.4 min ± 153.3 min) was similar in all treatment groups.
- The FAS comprised a total of 223 women and 32 men. No further relevant differences in demographic parameters and baseline characteristics were noted between treatment arms.

Efficacy

- For the FAS, the mean SPI_{2-10} was similar for the cebranopadol 400 µg (36.62) and cebranopadol 600 µg (36.95) groups, and different from the cebranopadol 200 µg (47.84), morphine (43.82) and placebo (48.19) groups. Pairwise comparisons of SPI_{2-10} between both treatment groups and placebo based on an ANOVA and LOCF imputation resulted in mean (95% CI) differences of -11.4 (-19.30, -3.54), -11.1 (-18.66, -3.53), -4.6 (-12.42, 3.20), and -1.27 (-8.97, 6.44) for the cebranopadol 400 µg, cebranopadol 600 µg, morphine CR, and cebranopadol 200 µg groups, respectively (**Table 1**).

Table 1. Descriptive Statistics and Analysis of Variance for SPI_{2-10} (FAS)

	Cebranopadol 200 µg	Cebranopadol 400 µg	Cebranopadol 600 µg	Morphine CR 60 mg	Placebo
n	53	48	57	50	47
SPI_{2-10}, Mean (SD)	47.84 (19.59)	36.62 (19.27)	36.95 (22.90)	43.82 (22.54)	48.19 (15.25)
LS means vs placebo (95% CI)	-1.27 (-8.97, 6.44)	-11.42 (-19.30, -3.54)	-11.09 (-18.66, -3.53)	-4.61 (-12.42, 3.20)	-
P value	0.7459	0.0047	0.0042	0.2465	-

CI = confidence interval; CR = controlled release; LS = least squares means; n = number of subjects; SD = standard deviation; SPI_{2-10} = sum of pain intensity on an 11-point numerical rating scale.

- For reference periods longer than 2-10 h, the two highest cebranopadol dose groups and morphine showed similarly lower mean SPI results than the placebo group and the cebranopadol 200 µg group (**Table 2**). Based on this endpoint regarding SPI time windows, the separation from placebo starts for the cebranopadol 400 µg group and the cebranopadol 600 µg group at 2 h after IMP intake and seems to last until 24 h. This indicates a long duration of analgesic efficacy which is in accordance with the long half-life of cebranopadol.

Table 2. Descriptive Statistics for SPI_{2-6}, SPI_{2-12}, SPI_{2-14}, SPI_{2-18}, SPI_{2-24} (FAS)

	Cebranopadol 200 µg	Cebranopadol 400 µg	Cebranopadol 600 µg	Morphine CR 60 mg	Placebo
n	53	48	57	50	47
SPI_{2-6}, Mean (SD)	25.08 (11.28)	19.50 (10.56)	19.96 (12.79)	24.93 (11.71)	25.10 (9.26)
SPI_{2-12}, Mean (SD)	58.40 (23.14)	44.97 (23.06)	44.99 (27.21)	51.08 (25.91)	59.26 (18.50)
SPI_{2-14}, Mean (SD)	68.50 (26.93)	53.39 (26.85)	52.91 (31.50)	58.42 (29.50)	69.68 (22.23)
SPI_{2-18}, Mean (SD)	88.02 (34.18)	70.93 (35.13)	68.40 (40.20)	73.35 (36.90)	90.48 (29.29)
SPI_{2-24}, Mean (SD)	116.82 (45.75)	95.62 (48.09)	94.15 (54.46)	94.87 (48.84)	121.41 (41.00)

CR = controlled release; n= number of subjects; SD = standard deviation; SPI = sum of pain intensity on an 11-point numerical rating scale.

- On the Subject Global Impression scale, the cebranopadol 600 µg group performed better when compared with the placebo group (**Figure 2**). The other dose groups did not differ from placebo, both at 12 h and at 24 h. Similar results were seen for the comparison of cebranopadol and morphine CR. Both at 12 h and at 24 h, the cebranopadol 600 µg group performed better when compared with the morphine CR 60 mg group in terms of Subject Global Impression of the IMP.

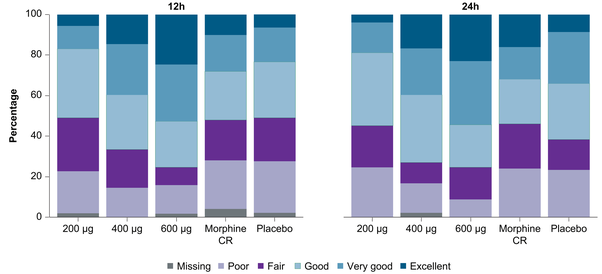


Figure 2. Subject Global Impression of the Investigational Medicinal Product

Safety

- Based on the Safety set in this study, the use of cebranopadol 200 µg, 400 µg, and 600 µg as a single dose for treatment in patients with post-operative pain was safe without clinically relevant, systematic effect on vital signs, laboratory parameters and ECG.
- The frequency of patients with at least 1 treatment emergent adverse event was highest in the morphine group (92.0%). The frequency was lowest in the cebranopadol 200 µg group (67.3%) and in the placebo group (68.1%). The cebranopadol 400 µg and 600 µg groups experienced frequencies of 77.6% and 84.2%, respectively (**Table 3**).
- The most frequently reported treatment emergent adverse events in the active treatment groups (>10%) were nausea, vomiting, dizziness, headache, and somnolence (**Table 3**).
- One subject in the cebranopadol 400 µg dose group was discontinued due to AEs bradycardia and hypotension. In the morphine CR 60 mg dose group two patients were discontinued due AEs; one subject was discontinued due to presyncope and the other subject due dizziness and upper abdominal pain.

Table 3. Treatment Emergent Adverse Events (≥5% of Subjects in Any Group) – Subject-Based Analysis – (Safety Set)

	Cebranopadol 200 µg	Cebranopadol 400 µg	Cebranopadol 600 µg	Morphine CR 60 mg	Placebo
n	55	49	57	50	47
Subjects with TEAEs, n (%)	37 (67.3)	38 (77.6)	48 (84.2)	46 (92.0)	32 (68.1)
Abdominal pain upper	0	2 (4.1)	2 (3.5)	3 (6.0)	1 (2.1)
Constipation	0	2 (4.1)	1 (1.8)	3 (6.0)	0
Nausea	16 (29.1)	24 (49.0)	37 (64.9)	33 (66.0)	8 (17.0)
Vomiting	5 (9.1)	10 (20.4)	28 (49.1)	20 (40.0)	1 (2.1)
ALT increased	1 (1.8)	3 (6.1)	1 (1.8)	1 (2.0)	3 (6.4)
AST increased	1 (1.8)	3 (6.1)	1 (1.8)	1 (2.0)	1 (2.1)
Blood alkaline phosphatase increased	0	3 (6.1)	1 (1.8)	0	2 (4.3)
Gamma-glutamyltransferase increase	1 (1.8)	3 (6.1)	2 (3.5)	2 (4.0)	3 (6.4)
Muscle spasm	2 (3.6)	0	3 (5.3)	0	2 (4.3)
Dizziness	11 (20.0)	11 (22.4)	15 (26.3)	12 (24.0)	3 (6.4)
Headache	5 (9.1)	6 (12.2)	8 (14.0)	3 (6.0)	10 (21.3)
Somnolence	1 (1.8)	5 (10.2)	8 (14.0)	8 (16.0)	1 (2.1)
Hyperhidrosis	0	0	3 (5.3)	3 (6.0)	0
Pruritus	0	3 (6.1)	2 (3.5)	1 (2.0)	0
Hot flush	1 (1.8)	2 (4.1)	4 (7.0)	2 (4.0)	0

CONCLUSIONS

- In this exploratory study in patients with moderate to severe acute post-operative pain, cebranopadol was effective in a dose dependent manner, safe and well tolerated.
- Cebranopadol in this study showed similar efficacy to morphine 60 mg CR but was better tolerated and received a better overall rating by the patients.

ClinicalTrials.gov Identifier: NCT00872885

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