Randomized Trial

Cebranopadol: A Novel, First-in-Class, Strong Analgesic: Results from a Randomized Phase IIa Clinical Trial in Postoperative Acute Pain

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Background: Cebranopadol is a potent, first-in-class analgesic with a novel mechanistic approach combining nociceptin/orphanin FQ peptide (NOP) and opioid peptide receptor agonism.

Objective: We aim to evaluate, for the first time, the analgesic efficacy, safety, and tolerability of cebranopadol in patients suffering from moderate to severe acute pain following bunionectomy.

Study Design: We conducted a phase IIa, randomized, multi-center, double-blind, double-dummy, placebo- and active-controlled, parallel group clinical trial.

Methods: A total of 258 patients who underwent a primary bunionectomy were randomly assigned to receive a single oral administration of cebranopadol 200 µg, 400 µg, or 600 µg, morphine controlled-release (CR) 60 mg, or placebo. The primary efficacy end-point was the sum of pain intensity (SPI) 2 to 10 hours ($SPI_{2–10}$) after the first investigational medicinal product (IMP) intake time-point.

Results: Cebranopadol doses of 400 µg and 600 µg were more effective in reducing postoperative acute pain compared to placebo, from 2 hours until approximately 22 hours after the first IMP intake time-point. No difference was observed between cebranopadol 200 µg and placebo. Per the subject global impression of the IMP assessment, patients who received cebranopadol 400 µg and 600 µg were more satisfied with the ability of the medication to treat their pain compared to those who received morphine CR 60 mg. On the primary end-point, the effect of morphine CR 60 mg was smaller than that of cebranopadol 400 µg and 600 µg. However, the analgesic effect of morphine CR 60 mg emerged later relative to IMP intake, as shown by the fact that similar SPI results as seen for cebranopadol 400 µg and 600 µg were obtained for later time windows. Cebranopadol treatment was safe, and single-dose administrations of 400 µg were better tolerated than morphine CR 60 mg. The relative frequency of patients with at least one treatment-emergent adverse event (TEAE) increased with increasing cebranopadol doses and was highest in the morphine CR 60 mg group.

Limitation: Although a double-dummy design was used to ensure blinding, a limitation of this trial was that cebranopadol and morphine CR were administered at 2 different time-points post-surgery, given the anticipated difference in the time to reach the maximum plasma concentration between the 2 treatments.

Conclusion: Administration of single cebranopadol doses of 400 µg and 600 µg induced more effective analgesia following bunionectomy surgery compared to the traditional opioid morphine on the primary end-point ($SPI_{2–10}$), while both cebranopadol doses and morphine ensured adequate 24-hour pain relief. Moreover, cebranopadol was better tolerated and received a better overall rating by the patients.

Key words: Opioids, morphine, µ-opioid receptor, nociceptin/orphanin FQ peptide receptor, analgesic, bunionectomy, surgery, post-operative pain, single hallux valgus repair

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Acute pain can arise in many clinical situations, including trauma, illness, and childbirth, but the most common acute pain syndrome is postoperative pain (1,2). Inadequate management of postoperative pain causes patient discomfort, delays recovery, prolongs hospital stays, and is associated with the complication of pain chronification (3,4). Opioids remain the mainstay of treatment for moderate to severe acute pain (5). Despite the high-analgesic efficacy, opioid therapy is often associated with serious side effects, mostly related to the central nervous system (e.g., dizziness, sedation, respiratory depression) or the gastrointestinal tract (e.g., constipation, nausea, vomiting) (6). A therapeutic agent with opioid-like analgesic potency, but without the typical opioid-related side effects remains a major unmet need in pain management.

Cebranopadol is a potent, first-in-class analgesic that combines nociceptin/orphanin FQ peptide (NOP) and opioid peptide receptor agonism. The NOP receptor is classified as a subcategory of the opioid receptor family, with very low affinity for classical opioid receptor ligands (7). It mediates central antinociceptive and anxiolytic effects through interaction with its endogenous agonist nociceptin/orphanin FQ (8,9). Cebranopadol binds with similarly high affinity to the NOP and μ-opioid (MOP) receptors, provides strong and efficacious analgesia in various animal pain models, affects neither motor coordination nor respiratory function in rodent models, has minimal effects on respiratory function in humans, and thus displays a better tolerability profile than opioids (6,10-13).

Postoperative pain after bunionectomy is a widely accepted model to study acute analgesic efficacy of novel agents in clinical trials (14-16). The surgery involves bony and soft tissue repair, consistently producing long-lasting moderate to severe post-operative pain requiring effective analgesic treatment. In addition, as no viscera are involved, the surgery is unlikely to cause gastrointestinal and respiratory dysfunction, which could overlap with opioid-related side effects. This allows a better distinction between surgery- and analgesic treatment-related side effects. The main objective of this proof-of-concept phase IIa trial was to assess, for the first time, the analgesic efficacy, safety, and tolerability of cebranopadol in patients suffering from moderate to severe acute pain following bunionectomy.

Methods

We conducted a phase IIa, randomized, multi-center, double-blind, double-dummy, placebo- and active-controlled, parallel group trial with cebranopadol in patients with moderate to severe postoperative acute pain, recruited from 4 investigational sites in the United States. The trial protocol and informed consent forms were approved by the relevant regulatory authority and ethical committee. All patients provided written informed consent before trial entry.

Trial Participants

Male or non-lactating female patients aged 18 to 75 years, inclusive, scheduled to undergo a primary unilateral standard first metatarsal bunionectomy (16) with distal osteotomy and internal fixation, with a physical status of I or II on the American Society of Anesthesiologists rating scale, were enrolled by the investigators. Patients undergoing concomitant surgical procedures, suffering from any clinically significant disorder or disease, or using other analgesics or concomitant treatments that could interfere with the efficacy and safety assessments of the investigational medicinal products (IMPs) and/or safety of the patient were not eligible.

Trial Design

A flow diagram is provided in Fig. 1. On Day -1, patients underwent a bunionectomy surgery. A popliteal sciatic block combined with a postoperative continuous local anesthetic infusion was used to ensure profound intraoperative anesthesia and to effectively control postoperative pain until IMP intake. One hour before terminating the sciatic block in the morning after the surgery, eligible patients were randomized to one of 5 treatment groups: cebranopadol 200 μg, 400 μg, or 600 μg plus morphine-placebo; morphine controlled-release (CR) 60 mg plus cebranopadol-placebo; or cebranopadol-placebo plus morphine-placebo.

Randomization was based on computer-generated randomization lists, provided by an external contract research organization. Investigators were given a unique series of numbers for assignment to each patient in ascending numerical order. Block randomization was applied, randomizing patients in a 1:1:1:1:1 ratio. Blinding of patients and investigators was achieved using a double-blind, double-dummy technique. The cebranopadol doses used in this trial were selected based on preclinical and clinical data. Morphine was chosen as the comparator as it is known to be efficacious in treating postoperative pain in general and specifically after bunionectomy. The CR formulation was chosen because its kinetic profile is closest to that of cebranopadol.

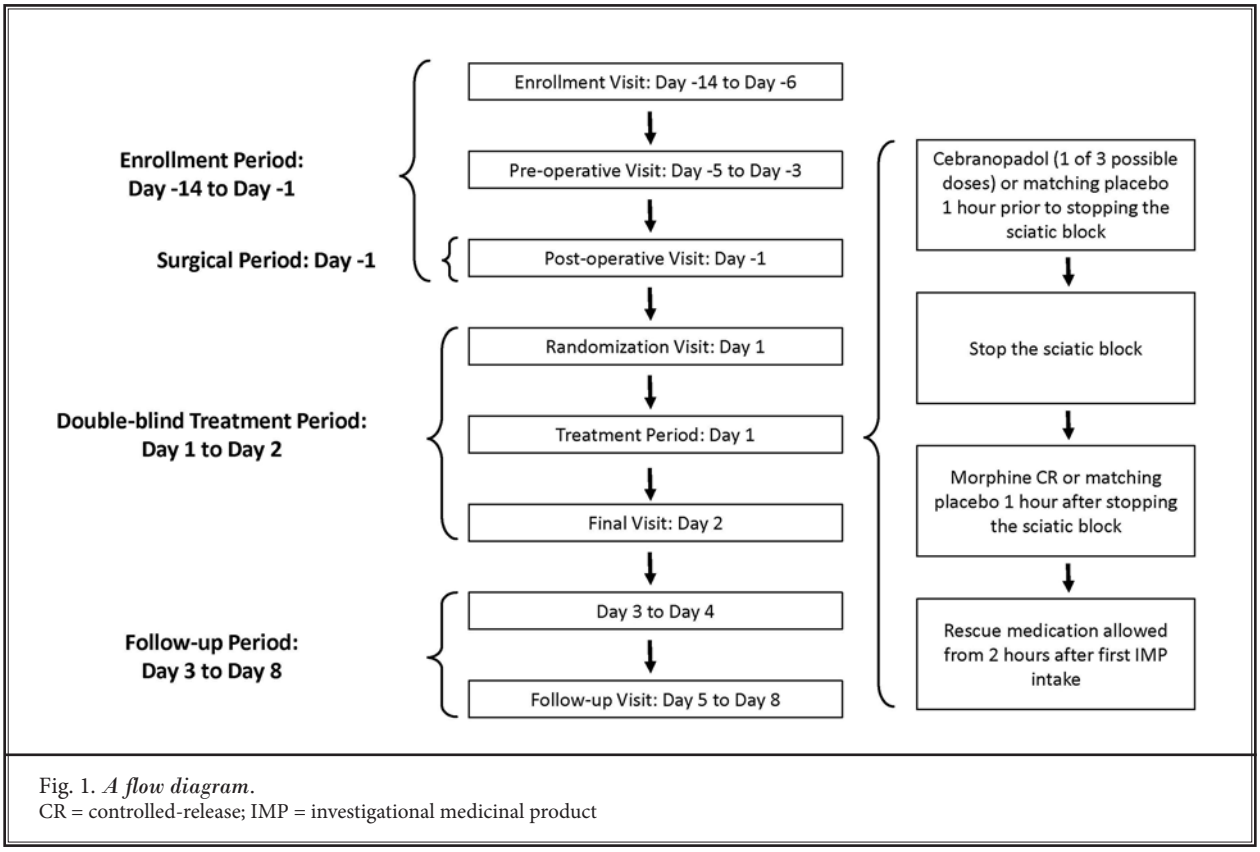

Fig. 1. *A flow diagram.*
CR = controlled-release; IMP = investigational medicinal product

Cebranopadol and morphine CR were administered at 2 different time-points, based on their expected time to reach the maximum plasma concentration (t_{max}): randomized patients received one oral dose of cebranopadol or matching placebo one hour before discontinuation of the sciatic block, followed by one oral dose of morphine CR or matching placebo one hour after discontinuation of the sciatic block. This was done to ensure that patients had sufficiently high plasma levels at the moment the pain intensity was expected to reach a moderate to severe level (17-22) and to allow comparison of efficacy and safety data between treatment groups. After completion of all assessments of the final visit (Day 2), patients were discharged from the research center on day 3. A follow-up visit was scheduled between day 5 and day 8.

Acetaminophen (maximum daily intake ≤ 3,000 mg) was allowed as first line rescue medication and diclofenac (maximum daily intake ≤ 150 mg) was allowed as second line rescue medication from 2 hours after the first IMP intake time-point.

Efficacy Outcome Measures and Assessments

The primary end-point for this trial was the sum of pain intensity (SPI) 2 to 10 hours (SPI2–10) after the first IMP intake time-point. Pain intensity was measured using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) and was recorded every 30 minutes up to 4 hours and thereafter every 2 hours up to 24 hours after the first IMP intake time-point (23,24).

Additional efficacy end-points included: 1) SPI 2 to 6 hours ($SPI_{2–6}$), 2 to 12 hours ($SPI_{2–12}$), 2 to 14 hours ($SPI_{2–14}$), 2 to 18 hours ($SPI_{2–18}$), 2 to 24 hours ($SPI_{2–24}$), and 4 to 10 hours ($SPI_{4–10}$); 2) time to first use of rescue medication within 24 hours; 3) amount of rescue medication used within 12 and 24 hours; 4) assessment of responders, i.e., patients with a pain intensity score ≤ 3 or with a baseline pain intensity score > 4 showing a reduction of ≥ 30%, at 10 and 12 hours and at the final visit (24 hours); 5) subject global impression of the IMP at 12 hours and at the final visit, evaluated by asking patients the following question: "How would you

rate the IMP you received for pain?." The patients were asked to rate the IMP as 'excellent,' 'very good,' 'good,' 'fair,' or 'poor.' All time-points were relative to the first IMP intake time-point.

Drug Concentration Measurements

Five 4 mL venous blood samples (one pre-dose and one in each of the time ranges 0.5 to 3 hours, 3 to 8 hours, 8 to 16 hours, and 16 to 36 hours after the first IMP intake time-point) were collected by venipuncture for the quantification of plasma cebranopadol, morphine, and morphine-6β-D-glucuronide (M6G) concentrations using validated liquid chromatography-tandem mass spectrometry bioanalytical assays. M6G was measured because it contributes to the analgesic effect of morphine. Currently, there is no evidence for a clinically relevant contribution of metabolites to the pharmacodynamic activity of cebranopadol after a single dose.

Safety Outcome Measures and Assessments

Safety-related end-points included: 1) frequency of treatment-emergent adverse events (TEAEs, defined as any adverse events that occurred after the first IMP intake time-point until the follow-up visit) and the percentage of patients discontinuing the trial due to TEAEs; 2) assessment of vital signs at all visits and during the double-blind treatment period; 3) physical examination at the enrollment, pre-operative, final, and follow-up visits; 4) 12-lead electrocardiogram (ECG) performed at all visits (except at the randomization visit) and on day 1 between 4 and 6 hours after the first IMP intake time-point; 5) clinical laboratory parameters evaluated at all visits, except at the randomization visit.

Statistical Analysis

A total number of 250 patients, with 50 patients per treatment group, were required to have a 2-sided 95% confidence interval for the difference of 2 means with a width of 16, assuming the common standard deviation (SD) is 20.

The safety set (SAF) included all patients who received IMP. The full analysis set (FAS) included all patients of the SAF who had at least one pain intensity value after IMP intake. All efficacy analyses were performed on the FAS using the last observation carried forward imputation approach for patients who prematurely discontinued or who took additional analgesics or rescue medication (imputation was only applied for 4 hours after rescue medication intake). SPI values were calculated as the weighted SPIs over the respective time. The weights were taken as the difference in time between 2 pain measurements. The primary and secondary SPI end-points were analyzed using an analysis of variance (ANOVA) model, accounting for the effects of treatment and center. As the treatment-by-center interaction was non-significant at the 0.1 level, the interaction was not included in the model. The primary end-point was additionally analyzed using an analysis of covariance (ANCOVA) with baseline pain intensity as covariate. The time to first use of rescue medication was descriptively summarized using Kaplan-Meier estimates. For the responder rates and the subject global impression of the IMP results, pairwise comparisons between treatment groups were performed using the Cochran-Mantel-Haenszel test stratified by center. The amount of rescue medication used was only analyzed descriptively. The analysis of safety parameters was descriptive on the SAF.

Results

Subject Disposition and Baseline Demographics

The trial started in March 2009 and was finished upon completion by the last patient in October 2009. In total, 684 patients were enrolled, of which 258 were randomly assigned to one of the 5 treatment groups. The overall rate of premature discontinuations was low (2.7%, n = 7). The reasons for premature discontinuation were adverse events (n = 3), lack of efficacy (n = 2), and withdrawal of consent (n = 2). Figure 2 presents the disposition of patients.

The SAF comprised all 258 randomized patients. The FAS comprised 255 patients; 3 patients were excluded because they did not take morphine-placebo. In total, 225 women and 33 men with a mean (± SD) age of 37.7 (± 11.1) years participated in this trial. The treatment groups were well-balanced for the demographic data, with an imbalance for ethnicity that was not considered relevant for the outcomes and with a large number of patients being overweight. The overall mean (± SD) baseline pain intensity was 4.9 (± 3.2), and all treatment groups were well-balanced relative to baseline pain intensity. All patients in the SAF received regional anesthesia according to the trial protocol. The overall mean (± SD) duration of the sciatic block and the overall mean time from the end of surgery until the first IMP intake time-point was similar in all treatment groups (Table 1).

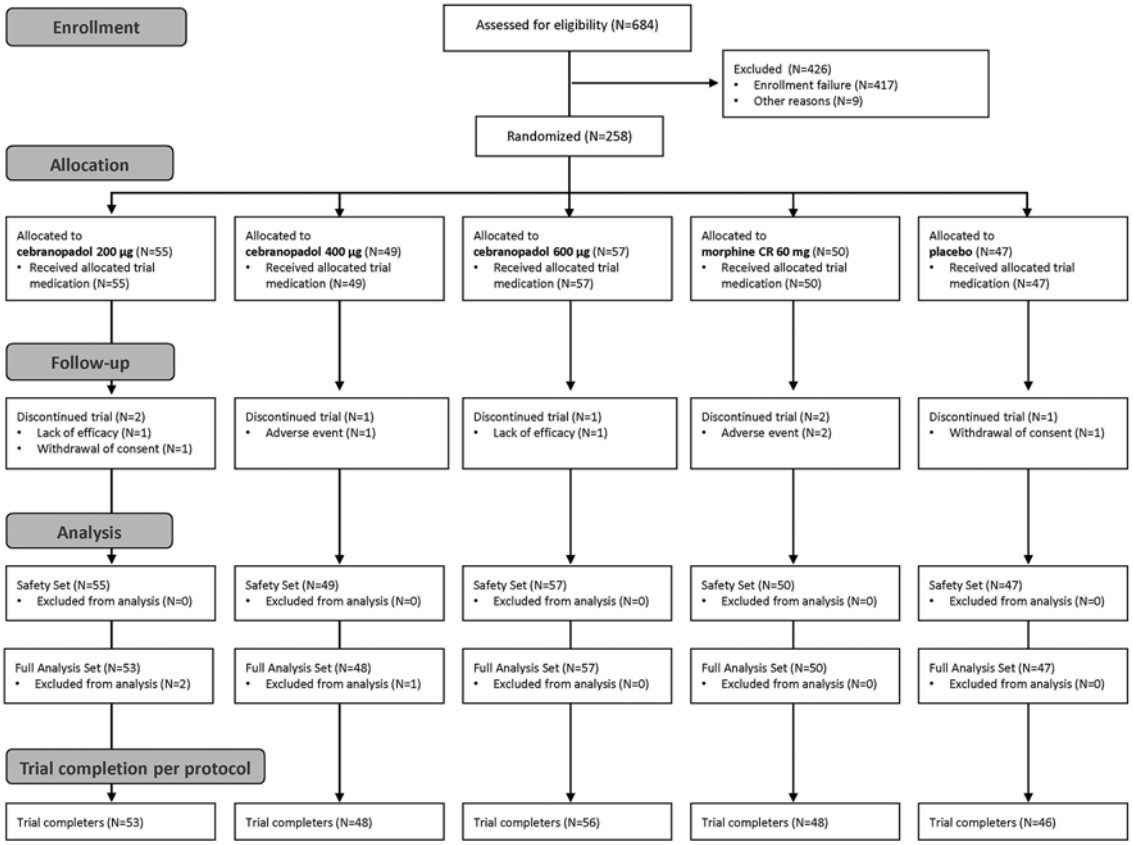

Fig. 2. *Disposition of patients. The SAF included all patients who received IMP. The FAS included all patients who received IMP and who had at least one pain intensity value after IMP intake. Three patients were excluded from the FAS: 2 patients in the cebranopadol 200 µg group and one patient in the cebranopadol 400 µg group because they did not take morphine-placebo.*
CR = controlled-release; n = number of patients

Efficacy

Primary Efficacy End-Point

The mean (± SD) $SPI_{2–10}$ was similar in the cebranopadol 400 µg (36.62 ± 19.3) and 600 µg (36.95 ± 22.9) groups, but clearly differed from the mean $SPI_{2–10}$ in the placebo group (48.19 ± 15.3, $P = 0.0047$ and $P = 0.0042$, respectively). No significant differences were observed between the cebranopadol 200 µg or morphine CR 60 mg group and the placebo group. These results were supported by the comparison of the mean pain course over time between the treatment groups (Fig. 3). The ANCOVA confirmed the results of the ANOVA and indicated that, in addition to cebranopadol 400 µg and 600 µg, morphine CR 60 mg showed a better efficacy than placebo ($P = 0.0454$; Table 2).

Secondary Efficacy End-points

The results of the primary end-point were confirmed by those of the secondary SPI end-points. For all reference periods, the cebranopadol 400 µg and 600 µg groups showed comparably lower mean SPI results compared to the placebo group. For the early reference periods (2–6 and 2–12 hours), the mean SPI in the morphine CR 60 mg group was comparably high as in the placebo group. However, for the longer reference periods (2–18 and 2–24 hours), the SPI results of the morphine CR 60 mg group were in line with those of the cebranopadol 400 µg and 600 µg groups and differed from those of the placebo group (Table 2).

The median time to first use of first line rescue medication was shortest in the placebo group (4.10 hours), followed by the morphine CR 60 mg (4.22 hours) and

Table 1. *Demographic and baseline characteristics – SAF.*

Parameter	Cebranopadol 200 µg n = 55	Cebranopadol 400 µg n = 49	Cebranopadol 600 µg n = 57	Morphine CR 60 mg n = 50	Placebo n = 47	Overall n = 258
Gender, F/M	46/9 (83.6/16.4)	45/4 (91.8/8.2)	51/6 (89.5/10.5)	41/9 (82.0/18.0)	42/5 (89.4/10.6)	225/33 (87.2/12.8)
Age, yr	35.0 ± 9.3	38.8 ± 11.4	37.2 ± 10.9	40.0 ± 12.1	38.0 ± 11.8	37.7 ± 11.1
Race/Ethnicity						
White	32 (58.2)	32 (65.3)	38 (66.7)	33 (66.0)	18 (38.3)	153 (59.3)
Black or of African descent	3 (5.5)	5 (10.2)	8 (14.0)	3 (6.0)	6 (12.8)	25 (9.7)
Hispanic or Latino	20 (36.4)	11 (22.4)	11 (19.3)	14 (28.0)	22 (46.8)	78 (30.2)
Other	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.1)	2 (0.8)
Body Mass Index, kg/m^2	27.67 ± 5.8	27.66 ± 5.8	27.03 ± 5.8	27.72 ± 5.7	27.34 ± 6.2	27.48 ± 5.8
Baseline pain intensity(a)	4.8 ± 3.2	5.0 ± 3.2	5.3 ± 3.4	5.0 ± 2.9	4.5 ± 3.5	4.9 ± 3.2
Regional anesthesia according to protocol	55 (100.0)	49 (100.0)	57 (100.0)	50 (100.0)	47 (100.0)	258 (100.0)
Duration of sciatic block, min	995.1 ± 119.5	1,010.6 ± 115.0	1,030.2 ± 230.0	1,009.5 ± 126.4	1,015.9 ± 136.4	1,012.4 ± 153.3
Time from the end of surgery to first IMP intake time-point, min	963.0 ± 114.0	982.0 ± 114.1	973.8 ± 108.3	979.1 ± 122.7	985.7 ± 132.4	976.2 ± 117.4

CR = controlled-release; F = female; IMP = investigational medicinal product; M = male; min = minutes; n = number of patients in the SAF
Data indicate mean values ± standard deviations or frequencies (%). Baseline was defined as the time-point of cebranopadol or matching placebo intake (day 1).
(a) Baseline pain intensity values were missing for one patient each in the cebranopadol 200 µg group, the cebranopadol 400 µg group, and the morphine CR 60 mg group and for 2 patients each in the cebranopadol 600 µg group and the placebo group.

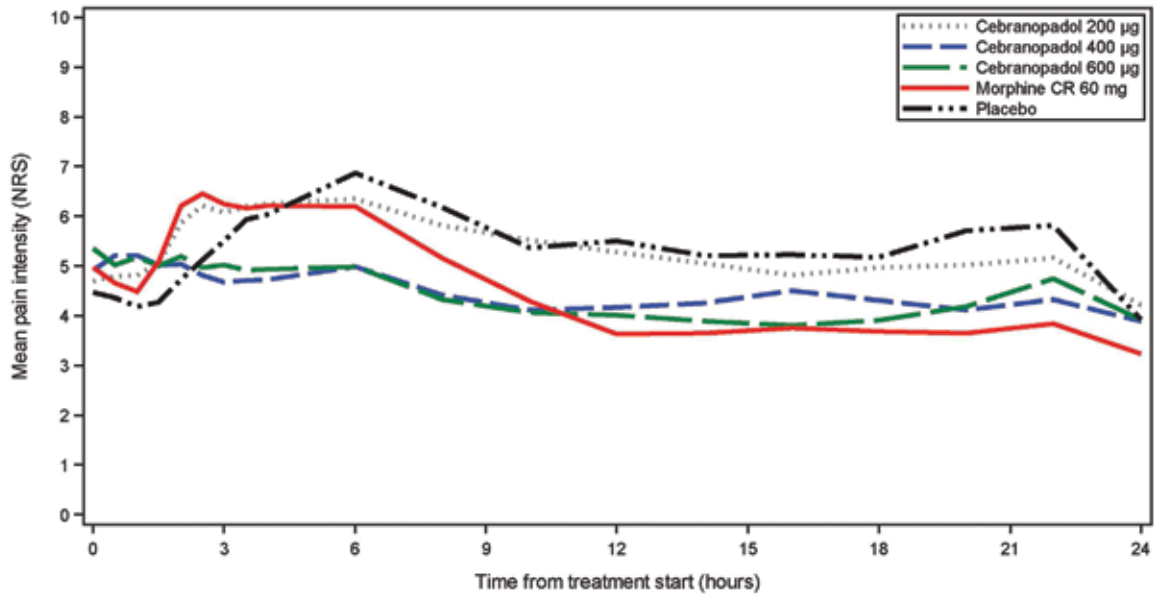

Fig. 3. *Mean pain intensity scores over time (LOCF) – FAS.*
CR = controlled-release; LOCF = last observation carried forward; NRS = numeric rating scale
For a description of the LOCF imputation method, refer to the 'Statistical Analysis' section.

Table 2. *ANCOVA for SPI2–10 and descriptive statistics for SPI2–10, SPI2–6, SPI2–12, SPI2–14, SPI2–18, SPI2–24, and SPI4–10 - FAS.*

	Cebranopadol 200 µg n = 53	Cebranopadol 400 µg n = 48	Cebranopadol 600 µg n = 57	Morphine CR 60 mg n = 50	Placebo n = 47
SPI_{2-10}	47.84 ± 19.6	36.62 ± 19.3	36.95 ± 22.9	43.82 ± 22.5	48.19 ± 15.3
Pairwise comparison vs. placebo – ANOVA					
LSmeans [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	
Pairwise comparison vs. placebo – ANCOVA					
LSmeans [95% CI]	-3.08 [-9.95,3.79]	-13.85 [-20.88,-6.82]	-13.98 [-20.78,-7.19]	-7.12 [-14.09,-0.15]	
P-value	0.3776	0.0001	<0.0001	0.0454	
Pairwise comparison vs. morphine CR 60 mg – ANOVA					
LSmeans [95% CI]	3.34 [-4.25,10.92]	-6.82 [-14.58,0.95]	-6.49 [-13.93,0.96]		4.61 [-3.20,12.42]
P-value	0.3869	0.0851	0.0875		0.2465
Pairwise comparison vs. morphine CR 60 mg – ANCOVA					
LSmeans [95% CI]	4.04 [-2.68,10.75]	-6.73 [-13.61,0.16]	-6.86 [-13.49,-0.24]		7.12 [0.15,14.09]
P-value	0.2375	0.0554	0.0424		0.0454
SPI_{2-6}	25.08 ± 11.3	19.50 ± 10.6	19.96 ± 12.8	24.93 ± 11.7	25.10 ± 9.3
SPI_{2-12}	58.40 ± 23.1	44.97 ± 23.1	44.99 ± 27.2	51.08 ± 25.9	59.26 ± 18.5
SPI_{2-4}	68.50 ± 26.9	53.39 ± 26.9	52.91 ± 31.5	58.42 ± 29.5	69.68 ± 22.2
SPI_{2-8}	88.02 ± 34.2	70.93 ± 35.1	68.40 ± 40.2	73.35 ± 36.9	90.48 ± 29.3
SPI_{2-24}	116.82 ± 45.8	95.62 ± 48.1	94.15 ± 54.5	94.87 ± 48.8	121.41 ± 41.0
SPI_{4-10}	35.42 ± 14.3	27.17 ± 14.8	27.01 ± 17.6	31.27 ± 18.1	36.86 ± 11.6

ANOVA = analysis of variance; ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled-release; LSmeans= treatment effect means obtained using the method of least squares; n = number of patients in the FAS; SPIx–y = sum of pain intensity from x up to y hours after the first IMP intake time-point; vs. = versus

SPI values are presented as mean values ± standard deviations. The lower the total scores, the better for the patient. The ANOVA model includes terms for treatment and center. The ANCOVA model includes terms for baseline pain intensity, treatment, and center. Only patients with non-missing baseline pain intensities were included in the ANCOVA

the cebranopadol 200 µg (4.33 hours) groups, and was longest in the cebranopadol 600 µg (8.22 hours) and 400 µg (8.93 hours) groups. Similar results were obtained for the time to first use of second line rescue medication. Kaplan-Meier plots of the time to first use of rescue medication are provided in Fig. 4. Within the first 24 hours after the first IMP intake time-point, the mean (± SD) amount of first line rescue medication administered was highest in the placebo group (1,797.9 mg ± 863.9), followed by the cebranopadol 200 µg group (1,490.6 mg ± 890.6), the morphine CR 60 mg group (1,320.0 mg ± 978.1), and the cebranopadol 400 µg (1,281.3 mg ± 972.5) and 600 µg (1,219.3 mg ± 881.4) groups. The mean (± SD) amount of second line rescue medication administered within the first 24 hours was 57.4 mg (± 47.8) in the placebo group, 40.0 mg (± 40.4) in the morphine CR 60 mg group, and 38.7 mg (± 41.2), 34.4 mg (± 45.1), and 30.7 mg (± 44.1) in the cebranopadol 200 µg, 400 µg, and 600 µg groups, respectively. Similar results were observed for use of rescue medication within the first 12 hours (Table 3).

The rate of responders at 10 hours after the first IMP intake time-point was similar in the cebranopadol 400 µg (61.7%), cebranopadol 600 µg (58.2%), and the morphine CR 60 mg (57.1%) groups and differed from the placebo group (33.3%; $P \leq 0.0267$). No difference was observed between the cebranopadol 200 µg (36.5%) and the placebo group. Similar results were observed at 12 hours. At the final visit, responder rates in none of the active treatment groups differed from the placebo group (Table 3).

The cebranopadol 600 µg group performed better in terms of subject global impression of the IMP at 12 hours after the first IMP intake time-point and at the

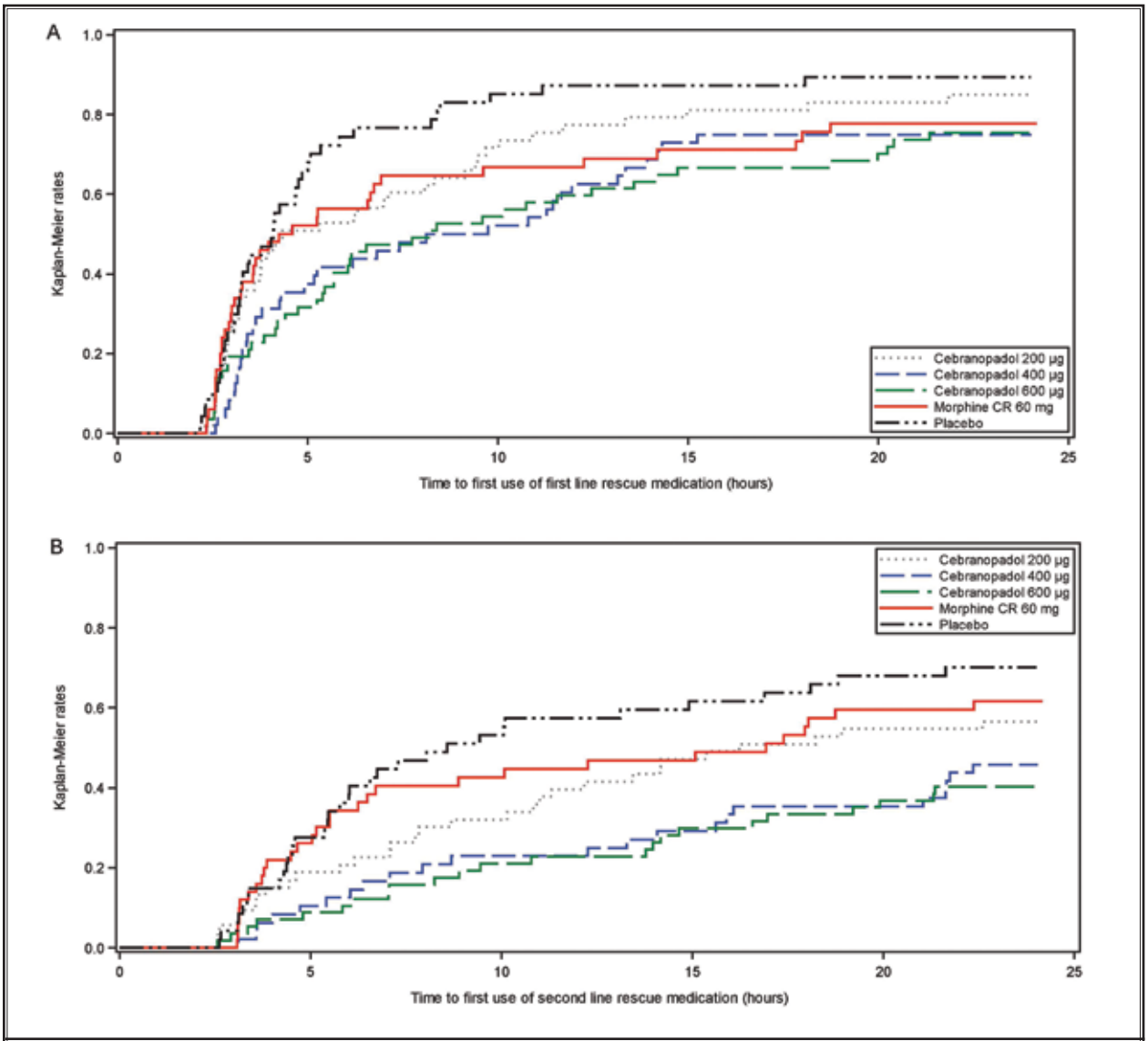

Fig. 4. *Kaplan-Meier plots of the time to first use of first (A) and second (B) line rescue medication – FAS.*
CR = controlled-release

final visit, compared with the placebo group ($P = 0.0037$ at 12 hours and $P = 0.0145$ at 24 hours) and morphine CR 60 mg group ($P = 0.0106$ and $P = 0.0216$, respectively). Only smaller differences were observed between the other cebranopadol groups and the placebo and morphine CR 60 mg groups (Table 3). When looking at the categories 'good,' 'very good,' and 'excellent' combined, patients evaluated cebranopadol 400 µg and 600 µg more favorably compared with morphine CR 60 mg, both at 12 hours and at the final visit (Fig. 5).

Drug Concentration

A total of 796 and 247 plasma samples were analyzed for cebranopadol and morphine (including M6G) concentrations, respectively. The concentration characteristics maximum plasma concentration (C_{max}) and t_{max} are summarized in Table 4. Similar t_{max} values were observed for all analytes.

Safety

Overall, 201 of 258 (77.9%) patients in the SAF

Table 3. *Rescue medication use, responder rates, and subject global impression of the IMP – FAS.*

	Cebranopadol 200 µg N = 53	Cebranopadol 400 µg N = 48	Cebranopadol 600 µg N = 57	Morphine CR 60 mg N = 50	Placebo N = 47
Rescue Medication Use					
Median time to first use, hrs					
First line (Acetaminophen)	4.33	8.93	8.22	4.22	4.10
Second line (Diclofenac)	16.22	24.00	24.00	13.67	8.57
Mean amount used within the first 12 hrs, mg(a)					
First line (Acetaminophen)	981.1 ± 664.8	750.0 ± 668.4	693.0 ± 653.0	800.0 ± 670.1	1,170.2 ± 636.5
Second line (Diclofenac)	21.7 ± 28.6	15.6 ± 31.2	13.2 ± 25.9	23.0 ± 27.1	30.9 ± 28.7
Mean amount used within the first 24 hrs, mg(a)					
First line (Acetaminophen)	1,490.6 ± 890.6	1,281.3 ± 972.5	1,219.3 ± 881.4	1,320.0 ± 978.1	1,797.9 ± 863.9
Second line (Diclofenac)	38.7 ± 41.2	34.4 ± 45.1	30.7 ± 44.1	40.0 ± 40.4	57.4 ± 47.8
Responder Rates(b)					
At 10 hrs, n (%)	19 (36.5)	29 (61.7)	32 (58.2)	28 (57.1)	15 (33.3)
P-value (vs. placebo)(c)	0.7600	0.0070	0.0133	0.0267	
P-value (vs. morphine)(c)	0.0487	0.7081	0.9462		0.0267
At 12 hrs, n (%)	22 (42.3)	29 (61.7)	34 (61.8)	29 (59.2)	16 (35.6)
P-value (vs. placebo)(c)	0.6075	0.0135	0.0105	0.0311	
P-value (vs. morphine)(c)	0.0893	0.8344	0.8284		0.0311
At the final visit (24 hrs), n (%)	31 (59.6)	27 (57.4)	33 (60.0)	35 (71.4)	25 (55.6)
P-value (vs. placebo)(c)	0.6409	0.8807	0.6540	0.1170	
P-value (vs. morphine)(c)	0.2495	0.1521	0.1826		0.1170
Subject Global Impression of the IMP					
At 12 hrs, n (%)					
Poor	11 (20.8)	7 (14.6)	8 (14.0)	12 (24.0)	12 (25.5)
Fair	14 (26.4)	9 (18.8)	5 (8.8)	10 (20.0)	10 (21.3)
Good	18 (34.0)	13 (27.1)	13 (22.8)	12 (24.0)	13 (27.7)
Very good	6 (11.3)	12 (25.0)	16 (28.1)	9 (18.0)	8 (17.0)
Excellent	3 (5.7)	7 (14.6)	14 (24.6)	5 (10.0)	3 (6.4)
Missing	1 (1.9)	0 (0.0)	1 (1.8)	2 (4.0)	1 (2.1)
P-value (vs. placebo)(d)	0.8659	0.1071	0.0037	0.6398	
P-value (vs. morphine)(d)	0.6786	0.2073	0.0106		0.6398
At the final visit (24 hrs), n (%)					
Poor	13 (24.5)	7 (14.6)	5 (8.8)	12 (24.0)	11 (23.4)
Fair	11 (20.8)	5 (10.4)	9 (15.8)	11 (22.0)	7 (14.9)
Good	19 (35.8)	16 (33.3)	12 (21.1)	11 (22.0)	13 (27.7)
Very good	8 (15.1)	11 (22.9)	18 (31.6)	8 (16.0)	12 (25.5)
Excellent	2 (3.8)	8 (16.7)	13 (22.8)	8 (16.0)	4 (8.5)
Missing	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
P-value (vs. placebo)(d)	0.3323	0.2461	0.0145	0.9260	
P-value (vs. morphine)(d)	0.4073	0.2153	0.0216		0.9260

CR = controlled-release; N = number of patients in the FAS; n = number of patients with this observation; vs. = versus
(a) Data are presented as mean values ± standard deviations.
(b) Responders are defined as patients with a pain intensity score ≤ 3 and patients with a baseline pain intensity score > 4 (i.e., moderate to severe pain) showing a reduction of ≥ 30%, only including patients with non-missing baseline pain intensity values.
(c) P-values obtained from a Cochran-Mantel-Haenszel test stratified by center comparing the proportions of responders and non-responders.
(d) P-values obtained from a Cochran-Mantel-Haenszel test stratified by center, ignoring the 'Missing' category.

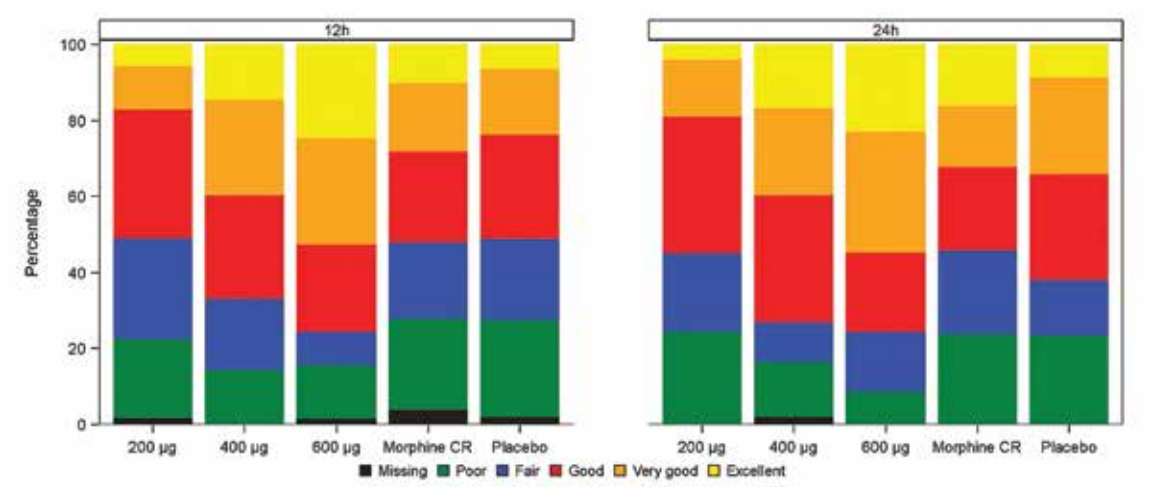

Fig. 5. *Subject global impression of the IMP – FAS.*
CR = controlled-release; h = hours
The labels '200 µg,' '400 µg,' and '600 µg' refer to the cebranopadol doses.

Table 4. *Concentration characteristics for cebranopadol, morphine, and M6G.*

	Cebranopadol 200 µg n = 55	Cebranopadol 400 µg n = 49	Cebranopadol 600 µg n = 57	Morphine CR 60 mg n = 50	
Analyte	**Cebranopadol**			**Morphine**	**M6G**
C_{max}, ng/mL	0.138 ± 0.062	0.286 ± 0.137	0.432 ± 0.218	16.8 ± 9.7	125 ± 43
t_{max}, h	5.28 (0.55–14.05)	5.25 (3.02–16.5)	5.33 (1.48–13.2)	5.38 (3.02–16.2)	6.08 (3.02–13.8)

C_{max} = maximum plasma concentration; CR = controlled-release; M6G = morphine-6β-D-glucuronide; n = number of patients of which plasma samples were analyzed for cebranopadol or morphine and M6G content; tmax = time to reach the maximum plasma concentration
C_{max} values are presented as means ± standard deviations and t_{max} values as medians (ranges). The t_{max} values for all analytes were derived using the time-point of cebranopadol or matching placebo intake (baseline) as the reference time-point.

reported TEAEs. The relative frequency of patients with at least one TEAE was highest in the morphine CR 60 mg group (92.0%), increased with the dose of cebranopadol (67.3%, 77.6%, and 84.2% in the cebranopadol 200 µg, 400 µg, and 600 µg groups, respectively), and was similar for the placebo (68.1%) and cebranopadol 200 µg (67.3%) groups (Table 5). The percentage of patients with TEAEs assessed as at least possibly related to the IMP was lower in the cebranopadol 400 µg (65.3%) and 600 µg (75.4%) groups compared to the morphine CR 60 mg (84.0%) group.

The TEAEs most frequently reported in the active treatment groups were nausea, vomiting, dizziness, headache, and somnolence. The percentage of patients with nausea, vomiting, dizziness, and somnolence was similar in the cebranopadol 600 µg and morphine CR 60 mg groups and was consistently lower in the cebranopadol 200 µg and 400 µg groups compared to the morphine CR 60 mg group (Table 5). One patient in the placebo group experienced a serious TEAE (idiopathic thrombocytopenic purpura), which was assessed as at least possibly related to the IMP. The patient received medication for this TEAE and the event resolved. Three patients were discontinued from the trial due to TEAEs: one patient in the cebranopadol 400 µg group due to bradycardia and hypotension and 2 patients in the morphine CR 60 mg group; one patient due to presyncope and one due to dizziness and upper abdominal pain. No deaths were reported.

No systemic or dose-dependent effects on vital signs and laboratory parameters were observed and no

Table 5. *TEAEs occurring in at least 5% of patients in any group (by preferred term) – patient-based analysis – SAF.*

	Cebranopadol 200 µg N = 55	Cebranopadol 400 µg N = 49	Cebranopadol 600 µg N = 57	Morphine CR 60 mg N = 50	Placebo N = 47
Patients with TEAEs, n (%)	37 (67.3)	38 (77.6)	48 (84.2)	46 (92.0)	32 (68.1)
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)
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)
Gamma-glutamyltransferase increased	1 (1.8)	3 (6.1)	2 (3.5)	2 (4.0)	3 (6.4)
Hot flush	1 (1.8)	2 (4.1)	4 (7.0)	2 (4.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.8)	3 (6.1)	1 (1.8)	1 (2.0)	3 (6.4)
Abdominal pain upper	0 (0.0)	2 (4.1)	2 (3.5)	3 (6.0)	1 (2.1)
Aspartate aminotransferase increased	1 (1.8)	3 (6.1)	1 (1.8)	1 (2.0)	1 (2.1)
Muscle spasms	2 (3.6)	0 (0.0)	3 (5.3)	0 (0.0)	2 (4.3)
Constipation	0 (0.0)	2 (4.1)	1 (1.8)	3 (6.0)	0 (0.0)
Blood alkaline phosphatase increased	0 (0.0)	3 (6.1)	1 (1.8)	0 (0.0)	2 (4.3)
Hyperhidrosis	0 (0.0)	0 (0.0)	3 (5.3)	3 (6.0)	0 (0.0)
Pruritus	0 (0.0)	3 (6.1)	2 (3.5)	1 (2.0)	0 (0.0)

CR = controlled-release; N = number of patients in the SAF; n = number of patients with this observation; TEAE = treatment-emergent adverse event

clinically relevant findings were reported for physical examinations. Individual cases of abnormally high or low ECG parameters were reported.

Discussion

This clinical trial demonstrated that the acute analgesic efficacy of cebranopadol, a novel, potent, first-in-class analgesic, was higher compared to placebo and even exceeded that of morphine CR in patients with moderate to severe acute pain following bunionectomy, while being well-tolerated. The majority of patients enrolled in this trial were women with a mean age of 37.7 years, consistent with the typical bunionectomy candidates in the general population. The primary end-point, $SPI_{2–10}$, showed that cebranopadol at doses of 400 µg and 600 µg was more effective in reducing postoperative pain, compared to placebo. The SPI levels for additional time windows confirmed these results and showed that the separation between the cebranopadol 400 µg and 600 µg groups and the placebo group started 2 hours after the first IMP intake time-point and lasted until approximately 22 hours thereafter for both dose groups. This long duration of analgesic efficacy is in accordance with the long half-life of cebranopadol and indicates that once-daily administrations would allow adequate 24-hour pain relief (17,18).

Morphine CR was chosen as the comparator in this trial since it was shown to be effective in acute pain treatment (e.g., after bunionectomy), and the kinetic profile of the CR formulation is closest to that of cebranopadol (16). Although 60 mg of morphine is considered a high dose for acute pain treatment, even at this high dose, it was shown to be less effective than cebranopadol 400 µg and 600 µg on the primary end-point. Even though t_{max} was similar for the 2 drugs, the analgesic effect of morphine CR 60 mg emerged later in time compared to that of cebranopadol 400 µg and 600 µg (similar SPI outcomes but at later time windows). This result may be related to a later onset of the analgesic effect of morphine than predicted from its pharmacokinetic profile.

The SPI results were confirmed by the other secondary end-points. The median time to first use of first and second line rescue medication was longest in the cebranopadol 400 µg and 600 µg groups and lower amounts (mg) of rescue medication were used by patients in these groups compared to the other treatment groups. In addition, patients were generally more satisfied with cebranopadol 400 µg and 600 µg than with the classical opioid morphine, as assessed by the subject global impression of the IMP. Responder rates at 10 and 12 hours were comparably high for the cebranopadol

400 µg and 600 µg groups and the morphine CR 60 mg group and were higher than in the placebo group.

Although a double-dummy design was used to ensure blinding, a limitation of this trial was that cebranopadol and morphine CR were administered at 2 different time-points post-surgery, given the anticipated difference in t_{max} between the 2 treatments. This design was applied to ensure adequate analgesia after surgery and to allow comparison of the efficacy and safety data between all treatment groups.

Single dose administrations of cebranopadol 400 µg were better tolerated than single morphine CR doses of 60 mg. The relative frequency of patients with at least one TEAE increased with increasing cebranopadol doses, but was highest in the morphine CR 60 mg group. Nausea, vomiting, and dizziness, typical opioid-related side effects, were less frequently reported in the cebranopadol 400 µg group compared to the morphine CR 60 mg group.

Conclusion

In this single-dose trial in patients with moderate to severe postoperative acute pain, cebranopadol, a novel NOP/MOP receptor agonist, was effective in a dose-dependent manner, safe, and well-tolerated. Single cebranopadol doses of 400 µg and 600 µg induced more effective analgesia following bunionectomy surgery, compared to the traditional opioid morphine on the primary end-point (SPI_{2-10}), while both cebranopadol doses and morphine ensured adequate 24-hour pain relief. Moreover, cebranopadol was better tolerated and received a better overall rating by the patients.

Conflict of Interest

Grünenthal GmbH funded and designed the trial and analyzed and interpreted the data. Drs. Scholz, Bothmer, Kok and Hoschen are employees of Grünenthal GmbH. Dr. Daniels was the international coordinating investigator and employee of Premier Research at the time the study was conducted.

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