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Cebranopadol, a novel first-in-class analgesic drug candidate: first experience in patients with chronic low back pain in a randomized clinical trial

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Abstract

Chronic low back pain (LBP) is a common condition, usually with the involvement of nociceptive and neuropathic pain components, high economic burden and impact on quality of life. Cebranopadol is a potent, first-in-class drug candidate with a novel mechanistic approach, combining nociceptin/orphanin FQ peptide and opioid peptide receptor agonism. We conducted the first phase II, randomized, double-blind, placebo- and active-controlled trial, evaluating the analgesic efficacy, safety, and tolerability of cebranopadol in patients with moderate-to-severe chronic LBP with and without neuropathic pain component. Patients were treated for 14 weeks with cebranopadol 200, 400, or 600 μg once daily, tapentadol 200 mg twice daily, or placebo. The primary efficacy endpoints were the change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks and during week 12 of the maintenance phase. Cebranopadol demonstrated analgesic efficacy, with statistically significant and clinically relevant improvements over placebo for all doses as did tapentadol. The responder analysis (≥30% or ≥50% pain reduction) confirmed these results. Cebranopadol and tapentadol displayed beneficial effects on sleep and functionality. Cebranopadol treatment was safe, with higher doses leading to higher treatment discontinuations because of treatment–emergent adverse events occurring mostly during titration. Those patients reaching the target doses had an acceptable tolerability profile. The incidence rate of most frequently reported treatment–emergent adverse events during maintenance phase was ≤10%. Although further optimizing the titration scheme to the optimal dose for individual patients is essential, cebranopadol is a new drug candidate with a novel mechanistic approach for potential chronic LBP treatment.

Keywords: Chronic low back pain, Cebranopadol, Nociceptin/orphanin FQ, Randomized controlled trial, Placebo control, First-in-class drug, First human phase II RCT

1. Introduction

For decades, researchers have been looking for an improved treatment that could effectively and safely alleviate moderate-to-severe chronic low back pain (LBP). Given the prevalence of this chronic pain condition, its economic burden, and its impact on work productivity and quality of life of those affected, improving this condition would have major societal impact.[11,14] Adequate pain management in chronic LBP remains challenging because of its complex pathophysiology, which is often characterized by a combination of nociceptive and neuropathic mechanisms (mixed pain concept).[12] A correct balance between analgesic efficacy and acceptable tolerability is not easy to achieve.[24] Strong opioids are frequently used for chronic severe pain management, although they are often associated with poor tolerability and development of addiction and tolerance.[1,23] Furthermore, neuropathic pain is often less responsive to opioid treatment than nociceptive pain. A therapeutic agent that addresses both pain components has the analgesic potential of strong opioids, but is associated with fewer opioid-type side effects would largely simplify the treatment of chronic LBP and would therefore represent a valuable new treatment strategy.[22]

Cebranopadol is a novel, centrally acting, potent, first-in-class analgesic drug candidate with a unique mode of action that combines nociceptin/orphanin FQ peptide (NOP) receptor and opioid peptide receptor agonism.[20,26,29] The endogenous agonist of the NOP receptor is nociceptin/orphanin FQ (N/OFQ), which does not bind to classical opioid peptide receptors. Although N/OFQ acts in a very similar way as opioids at the molecular and cellular level, it induces pharmacological effects that may differ from, and even oppose, those of opioids.[28,32] Preclinical studies demonstrated that, even after doses higher than those required to induce analgesia, cebranopadol affects neither motor coordination nor respiratory function and thus displays a better tolerability profile than opioids.[20]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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In rodents, functional interactions of the opioid and NOP receptor systems have been described, which result in either additive/synergistic analgesic activity or in antiopioid/pronociceptive activity, depending on the site of action (spinal or supraspinal, respectively).[28] In contrast, NOP receptor activation produced consistent antinociceptive effects in non-human primates, irrespective of the site of action.[16] Importantly, NOP receptor activation has been shown to counteract μ-opioid peptide receptor agonist-mediated development of tolerance, addiction, and physical dependence in rodent models.[2,18,21] Given that cebranopadol is effective in animal models of nociceptive and neuropathic pain, it yields the potential for the treatment of mixed pain conditions. In addition, as a nonselective drug acting at more than one opioid receptor, cebranopadol could have several advantages over selective agents or bivalent compounds, including multiple-level targeting of the pain pathway, a small molecular size and as such a higher permeability into the central nervous system, and more predictable pharmacokinetics.[29] As such, it merited the conduct of this phase II trial. Its main objective was to assess for the first time the analgesic efficacy, safety, and tolerability of cebranopadol in patients suffering from moderate-to-severe chronic LBP, with extensive characterization of the trial population for the presence of nociceptive and neuropathic pain symptoms.

2. Methods

We conducted the first human phase II, randomized, multicenter, double-blind, double-dummy, placebo- and active-controlled, parallel group trial with cebranopadol in patients with moderate-to-severe chronic LBP with and without a neuropathic pain component, recruited from 79 investigational sites in 11 European countries from November 2012 to July 2014. The clinical trial protocol, amendments, and informed consent forms were approved by the relevant regulatory authorities and ethical committees, and all patients provided written informed consent before entry in the trial. The Eudract trial number is 2012-001920-36 and the ClinicalTrials.gov identifier is NCT01725087.

2.1. Trial population

The trial included male and female patients aged 18 to 80 years with a clinical diagnosis of chronic LBP of nonmalignant origin, with moderate-to-severe pain being present for at least 3 months. Patients had to be on stable opioid or nonopioid analgesic medication with regular intake for at least 3 months and had to be dissatisfied with their current analgesic treatment. An average 24-hour, analgesic medication-free, baseline pain score of ≥5 on the 11-point numeric rating scale (NRS) was required during the 3 days preceding randomization. Patients were not eligible for the trial if they suffered from chronic LBP potentially associated with a specific spinal cause, or conditions other than LBP that could confound the (self-) evaluation of pain. Patients who underwent a recent or more than 1 previous low back surgery, any invasive procedure aimed to reduce LBP, or any kind of neuromodulation were also excluded from the trial. Other analgesics (eg, opioids, nonsteroidal antiinflammatory drugs, some antidepressants, etc.) or concomitant treatments that could interfere with the efficacy assessment of the trial medication or safety of the patients were either not acceptable or had to be given at a stable dose throughout the treatment period of the trial.

Patients were characterized at baseline with the painDETECT questionnaire,[10,13] the Quebec Task Force Classification (QTFC),[1,31] and the clinical presence of lumbar radiculopathy. The broadly validated painDETECT questionnaire was used to determine the likelihood of a neuropathic component of the LBP based on 7 questions addressing the frequency and quality of neuropathic symptoms. Based on the final score, patients were considered painDETECT positive (likelihood of a neuropathic pain component >90%, score 19-38), painDETECT unclear (ambiguous result, score 13-18), or painDETECT negative (a neuropathic pain component is unlikely/<15%, score −1 to 12). Patients in this trial were also classified into 4 groups according to the QTFC on spinal disorders: QTFC 1 (pain in the lumbar area without radiation and without neurologic signs), QTFC 2 (pain in the lumbar area with radiation proximally but without neurologic signs), QTFC 3 (pain in the lumbar area with radiation distally but without neurologic signs), and QTFC 4 (pain in the lumbar area with radiation to a limb and with neurologic signs). The presence of lumbar radiculopathy was assessed by the investigator based on a clinical examination and a series of questions on the symptoms and signs of lumbar radiculopathy. Patients were primarily recruited from pain specialists and primary care.

2.2. Trial design

A flow diagram of the trial is provided in **Figure 1**. The trial consisted of 3 periods: an enrollment period, a double-blind treatment period, and a follow-up period. During the enrollment period, patients' eligibility was assessed, previous analgesic medication was washed out, and the analgesic medication-free baseline pain intensity was determined.

The double-blind treatment period comprised a 14-day titration phase and a 12-week maintenance phase. Randomization of patients took place at the Baseline Visit (start of the treatment period), based on computer-generated randomization lists provided by an external supplier and was implemented using an interactive response technology system. A block randomization with stratification factors (country and painDETECT subgroup) was applied, randomizing patients in a 1:1:1:1:1 ratio to 1 of the 5 treatment arms: a placebo arm, a tapentadol prolonged release (PR) 200 mg twice daily arm, and 3 cebranopadol arms corresponding to 3 target doses (200, 400, and 600 μg) given once daily in the morning. These cebranopadol doses were chosen based on data from previous trials, albeit without in-depth knowledge of the appropriate target dose and length of the titration phase. Paracetamol/acetaminophen was allowed as a rescue medication for unacceptable chronic LBP (maximum total daily dose of 2 g and maximum 20 days of use during the maintenance phase). Tapentadol PR was included as an active

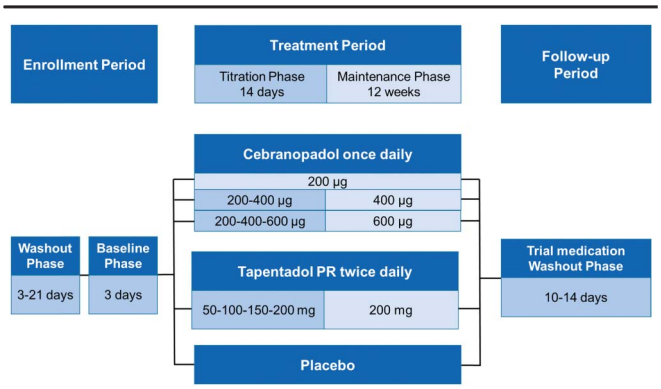

Figure 1. Flow diagram and trial medication. PR, prolonged release. Titration steps before up-titration to a next higher dose lasted for 3 days.

comparator as it is indicated for the treatment of severe chronic pain, including chronic back pain. Tapentadol PR was administered according to the labelling instructions, reaching the target dose of 200 mg twice daily on day 10. This dose was further taken during the remainder of the treatment period. Patients assigned to the cebranopadol 200 μg arm received fixed doses of cebranopadol 200 μg during the entire treatment period. Patients assigned to cebranopadol 400 or 600 μg were titrated in increments of 200 μg, starting with 200 μg and increasing to the target dose of 400 μg on day 4 (400 μg arm), and further to 600 μg on day 7 (600 μg arm). After reaching the target dose, patients stayed on this dose for the remainder of the treatment period. No dose adjustment of the trial medication in case of adverse events was allowed. Double-dummy methods were used to guarantee the blinding of patients and all personnel involved in the trial. Patients were instructed to take their trial medication twice daily (once in the morning and once in the evening) with a glass of water. After the Baseline Visit, routine visits were scheduled during the treatment period, after week 1 and week 2, and then every 2 weeks until the End-of-treatment (EoT) Visit, which was scheduled 14 weeks after the Baseline Visit.

The follow-up period ran from the day after the EoT Visit until the Follow-up Phone Call, which was scheduled 10 to 14 days after the last intake of trial medication. The Follow-up Visit was scheduled within 3 to 5 days after the last intake of trial medication.

2.3. Efficacy outcome measures and assessments

In support of a future marketing authorization in the European Union/other non–United States (US) countries, and in the United States, 2 different primary efficacy endpoints were applied. These endpoints were, respectively, defined as the change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks of the maintenance phase, and the change from baseline pain to the average 24-hour pain during week 12 of the maintenance phase. The primary endpoint for one region was considered as an additional endpoint for the other region. During the enrollment and treatment periods, patients once daily recorded their pain with a recall period of 24 hours (24-hour pain), using an 11-point NRS where 0 indicated "no pain" and 10 indicated "pain as bad as you can imagine."[8] Baseline pain was calculated as the average over the three 24-hour pain assessments recorded during the last 3 days before the Baseline Visit.

Additional efficacy endpoints included (1) the primary endpoints by painDETECT subgroup; (2) change from baseline in the Oswestry Disability Index (ODI) score; (3) change from baseline in the overall quality of sleep, based on the Chronic Pain Sleep Inventory (CPSI) scores; (4) responder rates, defined as achieving a predefined percentage improvement in 24-hour pain at week 12 of the maintenance phase compared with baseline; (5) the use of rescue medication during the treatment period; (6) change from baseline in the anxiety and depression subscale scores of the Hospital Anxiety and Depression Scale (HADS); and (7) Patient's Global Impression of Change (PGIC).

The ODI questionnaire assessed pain-related disability and covered 10 items on pain and activities of daily living.[7] The CPSI questionnaire measured the direct impact of pain on the quality of sleep and included 5 items which measured trouble falling asleep (CPSI 1), needing sleep medication (CPSI 2), awakening by pain during the night (CPSI 3) and in the morning (CPSI 4), and overall quality of sleep (CPSI 5).[17] The HADS and PGIC questionnaires were used to assess the presence of depression and anxiety,[34] and the global improvement of the patient's condition and satisfaction with treatment,[4,8] respectively.

2.4. Safety outcome measures and assessments

Safety-related endpoints and assessments included (1) the frequency of treatment–emergent adverse events (TEAEs, defined as any adverse events that occurred after the first intake of trial medication) and percentage of patients discontinuing the trial because of TEAEs; (2) frequency of potential withdrawal symptoms using the Clinical Opiate Withdrawal Scale (COWS)[33]; (3) changes from baseline on the Columbia-Suicide Severity Rating Scale (C-SSRS)[25]; and (4) changes from baseline in vital signs, safety laboratory parameters, and 12-lead electrocardiogram (ECG).

2.5. Statistical analyses

A total patient number of 600 patients with 120 patients per treatment arm were determined before trial initiation to provide 80% power at a 0.05 significance level (2-sided test) to detect a treatment difference in the primary endpoint of 0.9 points on the 11-point NRS with an SD of 2.5 points.

The Safety Set included all enrolled patients who took trial medication. The Full Analysis Set (FAS) included all patients of the Safety Set who took trial medication and had at least 1 pain assessment after the first intake of trial medication. The FAS was the population of primary interest for the efficacy parameters.

The primary endpoints were analyzed by means of a mixed-effects model for repeated measures on the FAS (the primary analysis). The model included fixed effects of pooled sites (country), treatment, time, treatment-by-time interaction, baseline, and a patient-specific random effect. The primary analysis consisted of the contrasts of the individual cebranopadol doses vs placebo during the entire 12 weeks of the maintenance phase or during week 12 of the maintenance phase. To control the family-wise error rate, first the 400 μg cebranopadol arm was tested vs placebo. In case of significance, a Hochberg procedure to the 200 and 600 μg cebranopadol arms vs placebo was applied. Several sensitivity analyses were performed for the analysis of the primary endpoints, ie, multiple imputations such as placebo mean imputation/pattern mixture model with increasing delta, and more traditional methods such as Last Observation Carried Forward (LOCF) and modified Baseline Observation Carried Forward (mBOCF). The additional efficacy endpoints were analyzed on the FAS in a descriptive manner only. The analysis of safety and tolerability parameters (eg, TEAEs, vital signs, safety laboratory, 12-lead ECG, COWS, and C-SSRS) was descriptive, and was performed on the Safety Set.

3. Results

3.1. Patient disposition and baseline demographics

The disposition of patients per treatment is presented in **Figure 2**. Of the 1090 patients that were enrolled in the trial, 641 were randomized to 1 of the 5 treatment arms. Overall, 360 of these 641 allocated patients (56.2%) completed the trial as planned, with 79.4% of trial completers in the placebo arm, 61.1% in the tapentadol PR arm, and 51.9%, 47.7%, and 41.5% in ,respectively, the cebranopadol 200, 400, and 600 μg arms. Main reasons for trial discontinuation were TEAEs (N = 193, most common in the active treatment arms), lack of efficacy (N = 35, most common in the placebo arm), and withdrawal of consent (N = 29).

The patient demographics and baseline characteristics are summarized in **Table 1**. The FAS comprised 635 patients,

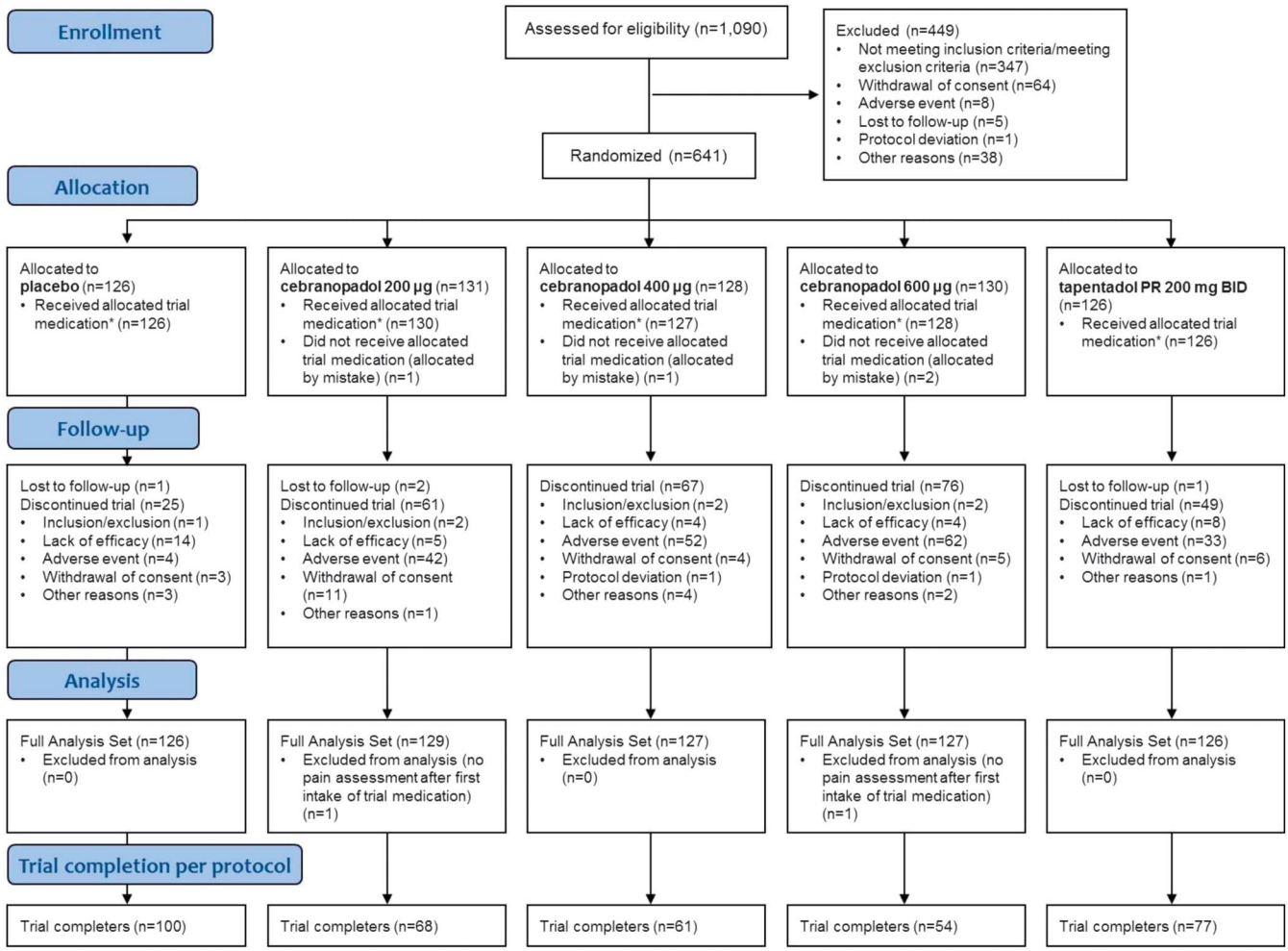

Figure 2. Disposition of patients. BID, twice daily; n, number of patients; PR, prolonged release. *Safety Set.

including 223 men and 412 women. The mean age of patients was 57.5 years, and most patients (99.7%) were white. No relevant differences in demographic parameters were noted between treatment arms.

In general, mean baseline pain assessments were similar across treatment arms. The mean of the average 24-hour baseline pain overall was 7.1 on the 11-point NRS. The mean duration of chronic LBP for all patients was 10.6 years, without relevant differences between treatment arms. On average, 36.5% of patients had been treated with opioids (including tramadol) and 91.0% with nonopioids for their LBP during the 3 months before enrollment. At the Baseline Visit, patients were evenly distributed across the painDETECT subgroups. The results of the QTFC on spinal disorders revealed that the percentage of patients classified to the QTFC 1, 2, 3, and 4 groups was 23.3%, 35.3%, 30.7%, and 10.6%, respectively. On average, 54.3% of patients presented with symptoms or signs of lumbar radiculopathy at the Baseline Visit as assessed by the investigator. The percentage of patients with lumbar radiculopathy was highest in the cebranopadol 600 µg arm (60.6%).

3.2. Efficacy

3.2.1. Primary endpoints

The results of the primary analysis of the primary efficacy endpoints are summarized in **Table 2**, whereas **Figure 3** graphically depicts the results. For the primary endpoints, all 3 cebranopadol arms as well as the tapentadol arm were statistically significantly different from placebo in terms of the change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks of the maintenance phase, and the change from baseline pain to the average 24-hour pain during week 12 of the maintenance phase (following the multiple comparison procedure for the cebranopadol arms while preserving the family-wise error rate at an alpha level of 0.05). The P values for these primary analyses were $P = 0.0346$, 0.0084, 0.0010, and 0.0040 for the estimated differences between, respectively, cebranopadol 200 (−0.55), 400 (−0.70), 600 µg (−0.92), or tapentadol (−0.74) and placebo, and $P = 0.0095$, 0.0122, 0.0021, and 0.0032 for the estimated differences between, respectively, cebranopadol 200 (−0.79), 400 (−0.79), 600 µg (−1.02), or tapentadol (−0.89) and placebo.

A numerical separation between the active treatment arms and the placebo arm on the weekly average 24-hour pain was already apparent during the titration phase (**Fig. 3**). In all treatment arms, a clinically relevant reduction of pain during the 12-week maintenance phase was observed. At week 12 of the maintenance phase, mean pain reductions from baseline were higher in the active treatment arms than in the placebo arm.

Sensitivity analyses using multiple imputations (placebo mean imputation/pattern mixture model with increasing delta) led to the same conclusions as the primary analysis of the primary endpoints with respect to the presence of a favorable treatment

Table 1

Demographic and baseline characteristics–Full Analysis Set.

Parameter	Placebo	Cebranopadol			Tapentadol	Overall
		200 μg	400 μg	600 μg	PR 200 mg BID	
Full Analysis Set, N (%)	126 (100.0)	129 (100.0)	127 (100.0)	127 (100.0)	126 (100.0)	635 (100.0)
Sex, N (%)						
Female	76 (60.3)	84 (65.1)	80 (63.0)	94 (74.0)	78 (61.9)	412 (64.9)
Male	50 (39.7)	45 (34.9)	47 (37.0)	33 (26.0)	48 (38.1)	223 (35.1)
Age, y						
Mean (SD)	56.9 (12.46)	58.0 (11.48)	57.5 (11.61)	56.9 (11.66)	58.2 (11.43)	57.5 (11.71)
Race, N (%)						
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.2)
White	126 (100.0)	128 (99.2)	127 (100.0)	127 (100.0)	125 (99.2)	633 (99.7)
Other	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
BMI, kg/m^2						
Mean (SD)	28.4 (4.08)	28.7 (4.34)	28.5 (4.28)	27.9 (4.08)	29.0 (3.86)	28.5 (4.14)
24-h pain*						
Mean (SD)	7.3 (1.26)	7.1 (1.17)	7.0 (1.15)	7.2 (1.12)	7.0 (1.15)	7.1 (1.17)
Duration since diagnosis of chronic LBP, y						
Mean (SD)	10.0 (10.30)	10.8 (10.93)	10.6 (9.95)	10.8 (10.82)	10.6 (9.82)	10.6 (10.35)
LBP treatment during 3 mo before enrollment, N (%)						
Opioids (incl tramadol)	45 (35.7)	45 (34.9)	45 (35.4)	56 (44.1)	41 (32.5)	232 (36.5)
Non-opioids	117 (92.9)	120 (93.0)	115 (90.6)	115 (90.6)	111 (88.1)	578 (91.0)
painDETECT subgroup, N (%)						
Positive	45 (35.7)	39 (30.2)	44 (34.6)	42 (33.1)	43 (34.1)	213 (33.5)
Unclear	36 (28.6)	40 (31.0)	38 (29.9)	36 (28.3)	35 (27.8)	185 (29.1)
Negative	42 (33.3)	48 (37.2)	45 (35.4)	47 (37.0)	43 (34.1)	225 (35.4)
Missing	3 (2.4)	2 (1.6)	0 (0.0)	2 (1.6)	5 (4.0)	12 (1.9)
QTFC classification, N (%)						
QTFC 1	24 (19.0)	32 (24.8)	32 (25.2)	20 (15.7)	40 (31.7)	148 (23.3)
QTFC 2	45 (35.7)	44 (34.1)	43 (33.9)	54 (42.5)	38 (30.2)	224 (35.3)
QTFC 3	42 (33.3)	40 (31.0)	43 (33.9)	35 (27.6)	35 (27.8)	195 (30.7)
QTFC 4	15 (11.9)	13 (10.1)	9 (7.1)	17 (13.4)	13 (10.3)	67 (10.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Lumbar radiculopathy, N (%)	70 (55.6)	69 (53.5)	70 (55.1)	77 (60.6)	59 (46.8)	345 (54.3)

* For 3 patients, no baseline pain was calculated as they did not have all 24-hour pain assessments in the 3 days before the Baseline Visit. Therefore, the overall N for the baseline 24-hour pain is 632 patients.
BID, twice daily; BMI, body mass index; LBP, low back pain; N, number of patients; PR, prolonged release; QTFC, quebec task force classification; SD, standard deviation.

effect of cebranopadol over placebo. More traditional single imputation methods (LOCF, mBOCF) were substantially affected by the number of cebranopadol-treated patients who discontinued the trial because of TEAEs, and did not show significant differences to placebo.

3.2.2. Additional efficacy endpoints

The mean 24-hour baseline pain scores and the results of the primary analysis of the primary endpoint for the European Union/non-US by painDETECT subgroup are summarized in **Table 3**. Patients in the painDETECT positive subgroup had higher mean baseline pain scores than those with an unclear or negative likelihood of a neuropathic pain component. Results for both primary endpoints were similar in all 3 painDETECT subgroups.

Furthermore, the results of the primary endpoints were supported by outcomes of additional efficacy endpoints, which are summarized in **Table 4**. For all patients, the mean changes from baseline in ODI score at the EoT Visit were higher in the active treatment arms than in the placebo arm, except for the cebranopadol 400 μg arm. For trial completers, mean changes from baseline in ODI score at the EoT Visit were higher in the active treatment arms (−14.9 to −17.7) compared to the placebo arm (−12.8) (**Table 4**). Reductions in the degree of disability were higher in trial completers than in all patients treated.

The mean changes from baseline in overall quality of sleep were higher for all active treatment arms than for placebo at the EoT Visit. Improvements were higher in trial completers than in all patients. The overall quality of sleep in the cebranopadol 200, 400, and 600 μg arms at baseline (39.5, 41.1, 40.6, respectively) improved by the EoT Visit with values of respectively 72.2, 70.9, and 66.2 for trial completers. The improvement in overall quality of sleep was higher in the cebranopadol arms than in the placebo arm (39.0 at baseline and 57.0 at EoT Visit) and similar to the changes seen in the tapentadol PR arm (40.5 at baseline and 70.1 at EoT Visit) (**Table 4**).

Responder analyses using an mBOCF approach (patients prematurely discontinuing because of TEAEs or lack of efficacy were regarded as nonresponders) showed that responder rates were lowest in the cebranopadol 600 μg arm, which was also the arm with the highest premature discontinuation rate. For observed cases at week 12 of the maintenance phase compared to baseline, ≥50% pain reduction was reported by 36.5%, 40.6%, and 38.9% of patients in, respectively, the cebranopadol 200, 400, and 600 μg arms, by 43.8% of patients in the tapentadol PR arm, and by 27.5% of patients in the placebo arm. Corresponding percentages for ≥30% pain reduction were 58.1%, 62.5%, 63.0%, 71.3%, and

Table 2

Primary analysis (MMRM) of the primary efficacy endpoints—Full Analysis Set.

	24-hour pain at baseline		Change from baseline (SE)			
	N	Mean (SD)	N	Estimate (SE)	95% CI	P
EU/non-US primary endpoint*						
Placebo	126	7.3 (1.26)	125	−1.97 (0.19)	−2.34 to −1.60	
Cebranopadol 200 μg	127	7.1 (1.17)	122	−2.52 (0.20)	−2.90 to −2.13	
Cebranopadol 400 μg	127	7.0 (1.15)	120	−2.67 (0.21)	−3.08 to −2.27	
Cebranopadol 600 μg	126	7.2 (1.12)	117	−2.89 (0.22)	−3.32 to −2.46	
Tapentadol PR 200 mg BID	126	7.0 (1.15)	123	−2.71 (0.19)	−3.09 to −2.33	
Cebranopadol 200 μg—Placebo				−0.55 (0.26)	−1.05 to −0.04	0.0346
Cebranopadol 400 μg—Placebo				−0.70 (0.27)	−1.23 to −0.18	0.0084
Cebranopadol 600 μg—Placebo				−0.92 (0.28)	−1.46 to −0.37	0.0010
Tapentadol PR 200 mg BID—Placebo				−0.74 (0.26)	−1.25 to −0.24	0.0040
US primary endpoint†						
Placebo	126	7.3 (1.26)	125	−2.16 (0.21)	−2.58 to −1.74	
Cebranopadol 200 μg	127	7.1 (1.17)	122	−2.95 (0.23)	−3.41 to −2.50	
Cebranopadol 400 μg	127	7.0 (1.15)	120	−2.95 (0.25)	−3.44 to −2.47	
Cebranopadol 600 μg	126	7.2 (1.12)	117	−3.18 (0.26)	−3.70 to −2.66	
Tapentadol PR 200 mg BID	126	7.0 (1.15)	123	−3.05 (0.23)	−3.50 to −2.60	
Cebranopadol 200 μg—Placebo				−0.79 (0.30)	−1.39 to −0.19	0.0095
Cebranopadol 400 μg—Placebo				−0.79 (0.32)	−1.41 to −0.17	0.0122
Cebranopadol 600 μg—Placebo				−1.02 (0.33)	−1.67 to −0.37	0.0021
Tapentadol PR 200 mg BID—Placebo				−0.89 (0.30)	−1.48 to −0.30	0.0032

For 3 patients, no baseline pain was calculated as they did not have all 24-hour pain assessments in the 3 days before the Baseline Visit. The MMRM includes terms for baseline, treatment, pooled sites, week, and treatment-by-week interaction and is based on the weekly average 24-hour pain intensity. Trial week defined as sequential 7-day interval subsequent to the Baseline Visit.

* Change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks of the maintenance phase.

† Change from baseline pain to the average 24-hour pain during Week 12 of the maintenance phase.

BID, twice daily; CI, confidence interval; EU, European Union; MMRM, mixed-effects model for repeated measures; N, number of patients with at least 1 week nonmissing change from baseline pain assessment; PR, prolonged release; SE, standard error.

46.1%, respectively (**Table 4**). Responder rates for trial completers were higher than for all patients. For patients in the cebranopadol arms, ≥50% pain reduction at week 12 of the maintenance phase was reported by 39.7% to 42.6% of trial completers, and by 18.1% to 27.1% of patients in the FAS.

The use of rescue medication was highest in the placebo arm (88.9%). In the tapentadol PR arm, 77.8% of patients used rescue medication. In the cebranopadol arms, the percentage of patients who used rescue medication decreased with increasing dose (77.5%, 70.9%, and 67.7% in the cebranopadol 200, 400, and 600 μg arms, respectively), as did the total number of days with rescue medication intake (2285, 1924, and 1453 days, respectively) and the number of days with rescue medication per patient and per week (1.8, 1.8, and 1.6 days, respectively). An additional analysis revealed that the average amount of daily rescue medication intake during the 12 weeks of the maintenance phase was significantly lower in all cebranopadol arms than in the placebo arm.

For all patients and for trial completers, changes from baseline at the EoT Visit of the anxiety and depression subscale scores of the HADS indicated that across treatment arms, anxiety, and depression improved for some patients, whereas it worsened for others. No clear effect of any treatment on anxiety or depression could be observed.

The analysis of PGIC at the EoT Visit showed that the percentage of trial completers who reported their overall condition to be "very much improved" or "much improved" was highest for patients in the active treatment arms (respectively, 44.1%, 54.1%, and 53.7% in the cebranopadol 200, 400, and 600 μg arms, and 54.5% in the tapentadol PR arm) compared with patients in the placebo arm (36.0%). A few patients only scored "much worse and very much worse" amongst the trial completers.

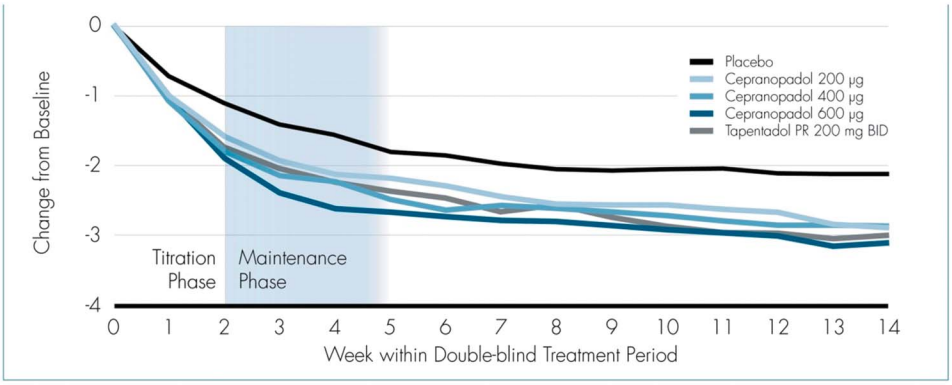

Figure 3. Change from baseline to the weekly average 24-hour pain (NRS)—Primary analysis (MMRM estimates)—Full Analysis Set. BID, twice daily; MMRM, mixed-effects model for repeated measures; NRS, numeric rating scale; PR, prolonged release.

Table 3

Primary analysis (MMRM) of the primary efficacy endpoint for the EU/non-US by painDETECT subgroup—Full Analysis Set.

	24-hour pain at baseline		Change from baseline (SE)			
	N	Mean (SD)	N	Estimate (SE)	95% CI	*P*
painDETECT positive						
Placebo	45	7.6 (1.2)	45	−2.03 (0.34)	−2.70 to −1.36	
Cebranopadol 200 μg	39	7.4 (1.2)	39	−2.05 (0.36)	−2.76 to −1.33	
Cebranopadol 400 μg	44	7.4 (0.9)	41	−2.14 (0.37)	−2.87 to −1.41	
Cebranopadol 600 μg	42	7.4 (1.0)	41	−2.82 (0.37)	−3.55 to −2.09	
Tapentadol PR 200 mg BID	43	7.5 (1.1)	42	−2.75 (0.35)	−3.45 to −2.05	
Cebranopadol 200 μg—Placebo		−0.2		−0.02 (0.45)	−0.90 to 0.87	0.9711
Cebranopadol 400 μg—Placebo		−0.2		−0.11 (0.46)	−1.01 to 0.79	0.8103
Cebranopadol 600 μg—Placebo		−0.2		−0.79 (0.46)	−1.70 to 0.12	0.0886
painDETECT unclear						
Placebo	36	7.2 (1.3)	36	−1.79 (0.33)	−2.45 to −1.14	
Cebranopadol 200 μg	40	7.1 (1.1)	39	−2.66 (0.35)	−3.35 to −1.97	
Cebranopadol 400 μg	38	6.7 (1.2)	37	−3.23 (0.36)	−3.95 to −2.52	
Cebranopadol 600 μg	36	7.1 (1.3)	35	−2.85 (0.38)	−3.61 to −2.10	
Tapentadol PR 200 mg BID	35	6.8 (0.8)	35	−2.85 (0.35)	−3.55 to −2.15	
Cebranopadol 200 μg—Placebo		−0.1		−0.87 (0.47)	−1.79 to 0.06	0.0652
Cebranopadol 400 μg—Placebo		−0.5		−1.44 (0.48)	−2.38 to −0.50	0.0030
Cebranopadol 600 μg—Placebo		−0.1		−1.06 (0.49)	−2.03 to −0.09	0.0325
painDETECT negative						
Placebo	42	7.1 (1.3)	41	−2.11 (0.32)	−2.75 to −1.47	
Cebranopadol 200 μg	47	6.9 (1.2)	43	−2.70 (0.33)	−3.35 to −2.06	
Cebranopadol 400 μg	45	7.0 (1.2)	42	−2.67 (0.36)	−3.37 to −1.96	
Cebranopadol 600 μg	46	7.1 (1.0)	40	−2.79 (0.41)	−3.59 to −1.99	
Tapentadol PR 200 mg BID	43	6.8 (1.2)	41	−2.50 (0.34)	−3.17 to −1.82	
Cebranopadol 200 μg—Placebo		−0.2		−0.59 (0.43)	−1.45 to 0.27	0.1746
Cebranopadol 400 μg—Placebo		−0.1		−0.56 (0.45)	−1.45 to 0.34	0.2223
Cebranopadol 600 μg—Placebo		0.0		−0.67 (0.50)	−1.65 to 0.31	0.1784

The MMRM includes terms for baseline, treatment, pooled sites, week, and treatment-by-week interaction and is based on the weekly average 24-hour pain intensity. An unstructured covariance matrix was used for the model. Trial week defined as sequential 7-day interval subsequent to the Baseline Visit. Results for patients with missing painDETECT scores are not presented in table.

BID, twice daily; CI, confidence interval; MMRM, mixed-effects model for repeated measures; N, number of patients with at least 1 week with nonmissing change from baseline pain assessment; PR, prolonged release; SD, standard deviation; SE, standard error.

Results of further additional outcomes including the EuroQol-5 Dimension quality of life questionnaire, the Short-Form 12 Health Survey, the Brief Pain Inventory (Short Form), the Pain assessment for LBP (Impact) and Pain assessment for LBP (Symptoms), and the change from baseline in current and worst pain are summarized in Table S1 (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A437) and Table S2 (available online at http://links.lww.com/PAIN/A438).

3.3. Safety

The incidence of TEAEs overall during the trial and by treatment phase is presented in **Table 5**. Overall, 512 of 637 patients in the Safety Set (80.4%) reported TEAEs: 83.1% in the cebranopadol 200 μg arm, 84.3% in the cebranopadol 400 μg arm, 89.8% in the cebranopadol 600 μg arm, 79.4% in the tapentadol PR arm, and 65.1% of patients in the placebo arm. Across all cebranopadol arms, 85.7% of patients reported at least 1 TEAE. During the entire titration phase, at least 1 TEAE was reported by 68.3% of patients across the cebranopadol arms, 57.9% of patients in the tapentadol PR arm, and 33.3% of patients in the placebo arm. During the maintenance phase, at least 1 TEAE was reported by 66.4%, 68.8%, and 54.2% of patients, respectively. Most of the TEAEs in all treatment arms were recovered/resolved at the end of the trial. Overall, there was no consistent trend pointing to a cebranopadol-related age or sex difference in the incidence of the identified adverse drug reactions.

The most frequently reported TEAEs (occurring in at least 5% of patients who took cebranopadol overall) were dizziness, nausea, somnolence, vomiting, constipation, fatigue, headache, and hyperhidrosis. The overall incidence of these TEAEs in the 3 cebranopadol arms, the tapentadol PR arm and the placebo arm was, respectively, 35.8%, 28.6%, and 8.7% for dizziness, 29.4%, 26.2%, and 6.3% for nausea, 18.2%, 14.3%, and 4.8% for somnolence, 17.9%, 11.9%, and 4.0% for vomiting, 16.1%, 17.5%, and 4.0% for constipation, 14.3%, 14.3%, and 2.4% for fatigue, 10.4%, 7.9%, and 8.7% for headache, and 9.9%, 9.5%, and 1.6% for hyperhidrosis. During the titration phase, the same TEAEs were most frequently reported, with very similar incidences compared to the overall trial period. During the maintenance phase, a similar percentage of patients reported TEAEs compared to the titration phase, but the incidence of the individual TEAEs was much lower in all treatment groups (**Fig. 4**).

Eighteen serious TEAEs were reported in 14 patients (2.2%) during the course of the trial: 3 patients in the cebranopadol 200 μg arm, 4 patients in the cebranopadol 400 μg arm, 2 patients in the cebranopadol 600 μg arm, 3 patients in the tapentadol PR arm, and 2 patients in the placebo arm. No serious TEAE was reported in more than 1 patient and 5 of them were considered at least possibly related to the trial medication by the investigator (**Table 6**). No deaths occurred during the trial.

Overall, the proportion of patients discontinuing the trial during the 14-week treatment period because of TEAEs was higher in the active treatment arms than in the placebo arm. The discontinuation rates were 32.1% in the cebranopadol 200 μg arm, 40.6% in the cebranopadol 400 μg arm, 47.7% in the cebranopadol 600 μg arm, and 26.2% in the tapentadol PR arm compared to 3.2% in the placebo arm. A Kaplan–Meier plot of

Table 4

Efficacy and physical function assessments—Full Analysis Set.

Parameter	Placebo	Cebranopadol			Tapentadol
		200 μg	400 μg	600 μg	PR 200 mg BID
Oswestry Disability Index score					
Baseline					
N	125	128	127	127	126
Mean (SD)	42.0 (17.5)	41.4 (16.4)	40.4 (15.2)	41.1 (14.8)	39.9 (13.8)
Change from baseline at EoT Visit—trial completers					
N	98	66	61	54	77
Mean (SD)	−12.8 (16.2)	−17.7 (19.3)	−14.9 (17.4)	−17.6 (14.5)	−16.2 (15.6)
Chronic Pain Sleep Inventory score—Overall quality of sleep					
Baseline					
N	126	128	127	126	125
Mean (SD)	39.0 (26.9)	39.5 (26.0)	41.1 (27.8)	40.6 (27.7)	40.5 (27.9)
EoT Visit—trial completers					
N	100	68	61	53	75
Mean (SD)	57.0 (28.7)	72.2 (25.3)	70.9 (26.7)	66.2 (28.4)	70.1 (25.6)
Responder rates at week 12 of the maintenance phase—observed cases					
Total, N (%)	102 (100.0)	74 (100.0)	64 (100.0)	54 (100.0)	80 (100.0)
≥30% pain reduction, N (%)	47 (46.1)	43 (58.1)	40 (62.5)	34 (63.0)	57 (71.3)
≥50% pain reduction, N (%)	28 (27.5)	27 (36.5)	26 (40.6)	21 (38.9)	35 (43.8)

Change from baseline: Baseline is the last value before first intake of trial medication, in general the value assessed at Baseline Visit (visit 3).
Oswestry Disability Index score: Higher scores indicate greater levels of disability.
Responder rates: Responder rates are based on pain reduction compared to baseline. Worsening in 24-hour pain is regarded as non-response. If a weekly pain score was missing or not under trial medication (after premature discontinuation), the patient was evaluated as assessment missing. The denominator for the % of responders was the number of patients with values in the respective week.
BID, twice daily; EoT visit, end-of-treatment visit; N, number of patients; PR, prolonged release; SD, standard deviation.

time to treatment discontinuation for the Safety Set is provided in **Figure 5**. In the active treatment arms, a considerable number of discontinuations because of TEAEs were observed during the titration phase; of the 189 patients in the active treatment arms who discontinued because of TEAEs during the whole treatment period, 104 (55.0%) did so during the titration phase (by treatment arm: respectively, 40.5%, 53.8%, and 72.6% in the cebranopadol 200, 400, and 600 μg arms, and 42.4% in the tapentadol PR arm). The most frequently reported TEAEs leading to early discontinuation were dizziness, nausea, and vomiting.

Data from the COWS showed that cases of mild withdrawal symptoms were reported at similar low frequencies in the 3 cebranopadol arms (4.6%-6.5%), and reported more often in the tapentadol PR arm (9.9%) compared to the cebranopadol arms. Moderate withdrawal symptoms were reported by 1 patient (0.9%) each in the cebranopadol 200 and 600 μg arms, and 4 patients (3.6%) in the tapentadol PR arm. In the placebo arm, a single case of moderately severe withdrawal symptoms was reported (0.9%), but no cases of mild or moderate withdrawal symptoms were reported. Data from the C-SSRS did not indicate a risk of suicidal ideation or behavior with the use of cebranopadol. The use of cebranopadol 200, 400, and 600 μg for treatment of chronic LBP was not associated with clinically relevant, systematic effects on vital signs, safety laboratory parameters and 12-lead ECG.

4. Discussion

This is the first human trial to demonstrate analgesic efficacy of cebranopadol in patients suffering from moderate-to-severe chronic LBP. The population of patients enrolled in this trial provides a realistic representation of the clinical population of

Table 5

Number of subjects with TEAEs overall during the trial and by treatment phase—Safety Set.

N (%)	Placebo	Cebranopadol			Tapentadol PR	Cebranopadol overall
		200 μg	400 μg	600 μg	200 mg BID	
Overall during the trial						
Total no. of patients	126 (100.0)	130 (100.0)	127 (100.0)	128 (100.0)	126 (100.0)	385 (100.0)
No. of patients with TEAEs	82 (65.1)	108 (83.1)	107 (84.3)	115 (89.8)	100 (79.4)	330 (85.7)
Titration phase						
Total no. of patients	126 (100.0)	130 (100.0)	127 (100.0)	128 (100.0)	126 (100.0)	385 (100)
No. of patients with TEAEs	42 (33.3)	77 (59.2)	87 (68.5)	99 (77.3)	73 (57.9)	263 (68.3)
Maintenance phase						
Total no. of patients	120 (100)	110 (100)	93 (100)	77 (100)	109 (100)	280 (100)
No. of patients with TEAEs	65 (54.2)	75 (68.2)	56 (60.2)	55 (71.4)	75 (68.8)	186 (66.4)

TEAEs coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.
The assignment of TEAEs toward treatment phases is based on the start date of the adverse event. The percentage is based on the number of patients in the respective treatment phase.
BID, twice daily; N, number of patients; PR, prolonged release; TEAE, treatment–emergent adverse event.

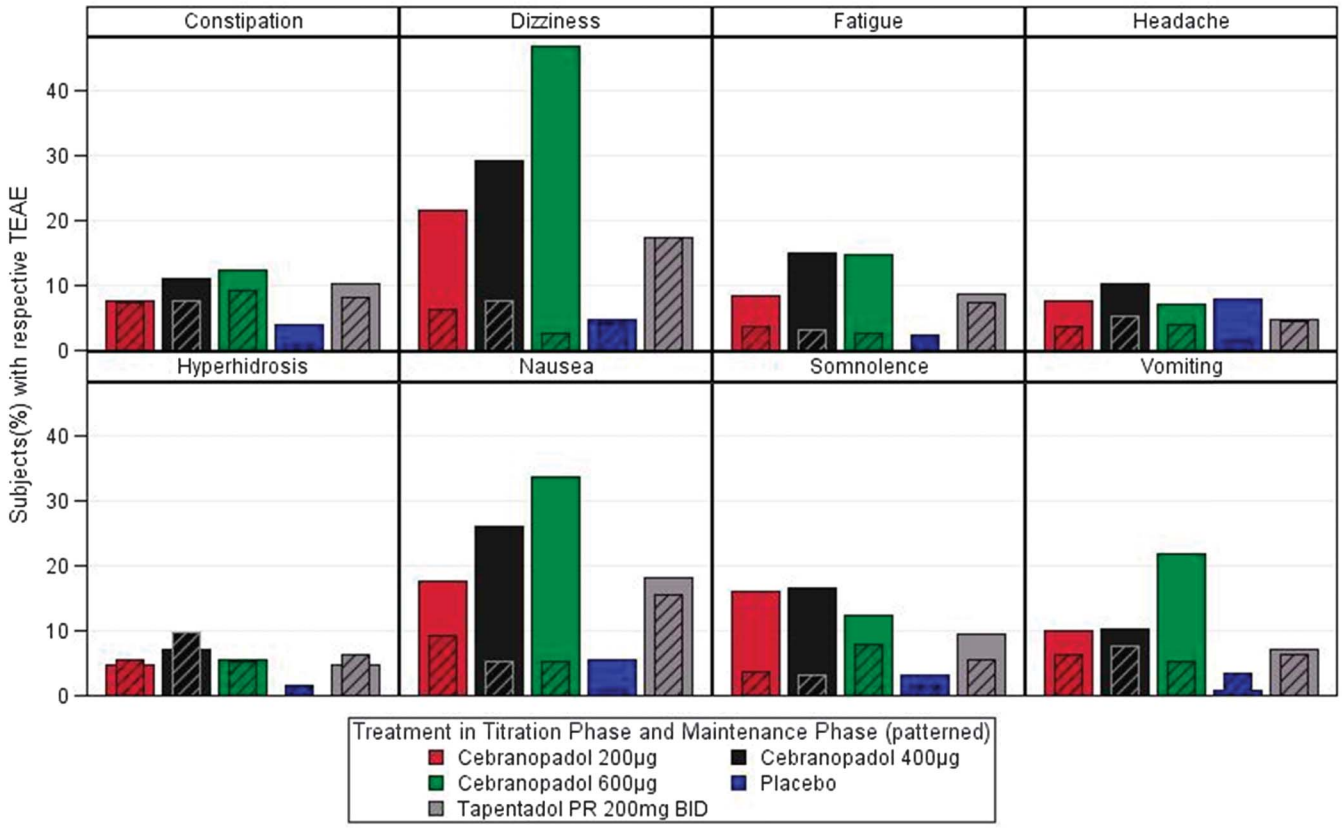

Figure 4. Most frequent TEAEs by treatment phase—Subject-based analysis—Safety Set. BID, twice daily; TEAE, treatment–emergent adverse event. TEAEs coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. The assignment of TEAEs toward treatment phases is based on the start date of the adverse event. The percentage is based on the number of patients in the respective treatment phase.

patients with moderate-to-severe chronic LBP, as shown by the demographic characteristics of the trial population, the proportion of patients in the subgroups (painDETECT and QTFC classification on spinal disorders), and the recorded baseline pain intensity levels. In addition, a substantial number of patients in this trial suffered from lumbar radiculopathy, which is the most common neuropathic pain syndrome experienced by patients with chronic LBP.[12] The baseline pain intensity levels were well balanced between all treatment arms. As reported before, the presence of a neuropathic pain component is associated with a higher pain intensity, greater numbers and severity of comorbidities, and reduced quality of life compared with nociceptive pain.[12] This became also apparent in this trial, with higher baseline pain intensity levels for patients scoring painDETECT positive.

Two primary efficacy endpoints were evaluated in this trial. Both primary endpoints were achieved, demonstrating analgesic efficacy of cebranopadol in chronic LBP. A statistically significant and clinically relevant improvement over placebo was demonstrated for all cebranopadol doses. Moreover, the analgesic effect was established quickly, with a numerical separation in pain intensity between cebranopadol and placebo during week 2 of the titration phase. These results are confirmed by the responder analysis, which showed that a higher percentage of patients in the 3 cebranopadol arms than in the placebo arm reported ≥30% or ≥50% of pain reduction at week 12 of the maintenance phase compared to baseline, both benchmarks being recommended to determine clinically important differences in pain intensity.[5] Tapentadol PR was included as an active comparator as it is indicated for the treatment of severe chronic pain, including chronic back pain. The estimated mean on the primary endpoints for tapentadol PR was within that of the 2 higher doses of cebranopadol thus confirming assay sensitivity of the trial and clinical relevance of the results.

When the presence or absence of a neuropathic pain component was taken into account by the use of the painDETECT questionnaire, clinically relevant differences to placebo were observed in painDETECT positive patients treated with cebranopadol 600 µg as well as for all patients scoring painDETECT negative and painDETECT unclear. Of note, the painDETECT questionnaire identifies patients with a likelihood of a neuropathic pain component in general, whereas this subgroup can be quite heterogeneous given that a variety of nerve-damaging stimuli affecting spinal nerve roots as well as peripheral nerves in tissues adjacent to the spine are likely to generate a neuropathic pain component. Also, subgroups were generally small and hence conclusions should be drawn with caution.

In addition to its analgesic activity, cebranopadol did show positive results for some of the additional efficacy endpoints of exploratory nature, including recommended key domains in chronic LBP such as physical functioning and sleep disturbance.[3] Cebranopadol treatment induced a reduction in the degree of disability in all active treatment arms compared to placebo, as measured by the ODI questionnaire. In addition to the unfavorable effects on physical functioning, chronic LBP is associated with disturbed sleep. Sleep disorders in people with chronic pain often do negatively affect mood, willingness to perform daytime activities, and even severity of perceived pain. Indeed, the association between poor sleep quality and pain might be bidirectional: pain disturbs sleep and sleep disturbance can

Table 6

Serious TEAEs reported during the entire trial.

Treatment arm	Serious TEAE	Reported causality
Placebo	Peripheral arterial occlusive disease	Not related
Placebo	Abdominal pain	Not related
Cebranopadol 200 μg	Cardiac failure	Unlikely
Cebranopadol 200 μg	Appendicitis	Unlikely
Cebranopadol 200 μg	Hepatic steatosis	Possible
Cebranopadol 200 μg	Weight decreased	Possible
Cebranopadol 200 μg	Chest discomfort	Probable/Likely
Cebranopadol 200 μg	Dyspepsia	Probable/Likely
Cebranopadol 200 μg	Hypertension	Unclassifiable
Cebranopadol 400 μg	Pelvic fracture	Not related
Cebranopadol 400 μg	Salivary gland calculus	Not related
Cebranopadol 400 μg	Oedema peripheral	Unlikely
Cebranopadol 400 μg	Faeces discolored	Possible
Cebranopadol 600 μg	Transient ischemic attack	Unlikely
Cebranopadol 600 μg	Atrial flutter	Unlikely
Tapentadol PR 200 mg BID	Lentigo maligna	Not related
Tapentadol PR 200 mg BID	Depression	Unlikely
Tapentadol PR 200 mg BID	Pancreatitis acute	Unlikely

BID, twice daily; PR, prolonged release; TEAE, treatment-emergent adverse event.

enhance pain perception.[30] Persistent pain may lead to functional changes to the neural systems that regulate both sleep and pain, but the exact neurobiological mechanisms remain poorly understood. Results of this trial show that cebranopadol treatment improved the overall quality of sleep compared to placebo. In addition, a higher percentage of patients in the cebranopadol arms completing the trial rated their overall condition as very much or much improved compared to the placebo arm. These results clearly indicate that chronic pain has a huge impact on the general well-being and daily quality of life of patients. Not surprisingly, pain may affect the patient's psychological well-being, resulting in an increased risk of suicidal behavior[9,15] and a high risk to experience anxiety and depression.[27] Consistent with its beneficial effect on chronic LBP, there is no evidence from results of the C-SSRS or HADS questionnaire that cebranopadol would increase the risk of suicidal ideation or behavior, or would have a detrimental effect on anxiety and depression.

In this trial, strong efficacy has been shown with cebranopadol over the 14-week treatment period. Moreover, higher efficacy was noted with increasing doses of cebranopadol. Overall, treatment with cebranopadol was safe at the tested daily doses of 200, 400, and 600 μg. However, higher doses led to higher treatment discontinuation rates with more than half of the discontinued patients in the 600 μg cebranopadol treatment arm. These were primarily because of TEAEs occurring during the 14-day titration phase, and may have been the result of the forced titration regimen imposed in this trial, resulting in doses being increased too quickly during the titration phase. As this was the first trial with cebranopadol in this patient population, the titration scheme was not yet optimized. This issue was not observed for the tapentadol treatment arm for which the established and well-tolerated titration scheme of the intake instructions of the marketed product was followed. The completion rate for the tapentadol treatment arm in this study was comparable to the results of the pooled analysis including data from three phase 3 studies in moderate-to-severe chronic osteoarthritis pain or LBP[19] with 56.5% tapentadol-treated subjects completing the trial. Data from more recent trials with cebranopadol in different indications provide new insights, suggesting that an optimized titration regimen of cebranopadol could decrease the discontinuation rates because of TEAEs, as well as the overall occurrence of TEAEs.[6]

A limitation of this trial was the use of a fixed-dose approach with predefined steps of dose increase and duration which impeded administration of optimal individual doses and length of titration. Given that the data from this trial with cebranopadol suggest its overall efficacy as well as higher efficacy with increasing doses, subsequent trials should focus on studying a more flexible dose regimen to potentially maximize the benefit for the individual patient throughout the trial.

In contrast to typical strong opioids, abrupt discontinuation of cebranopadol intake after up to 14 weeks of treatment did generally not result in withdrawal symptoms, as assessed using the COWS. Only few mild and single cases of moderate

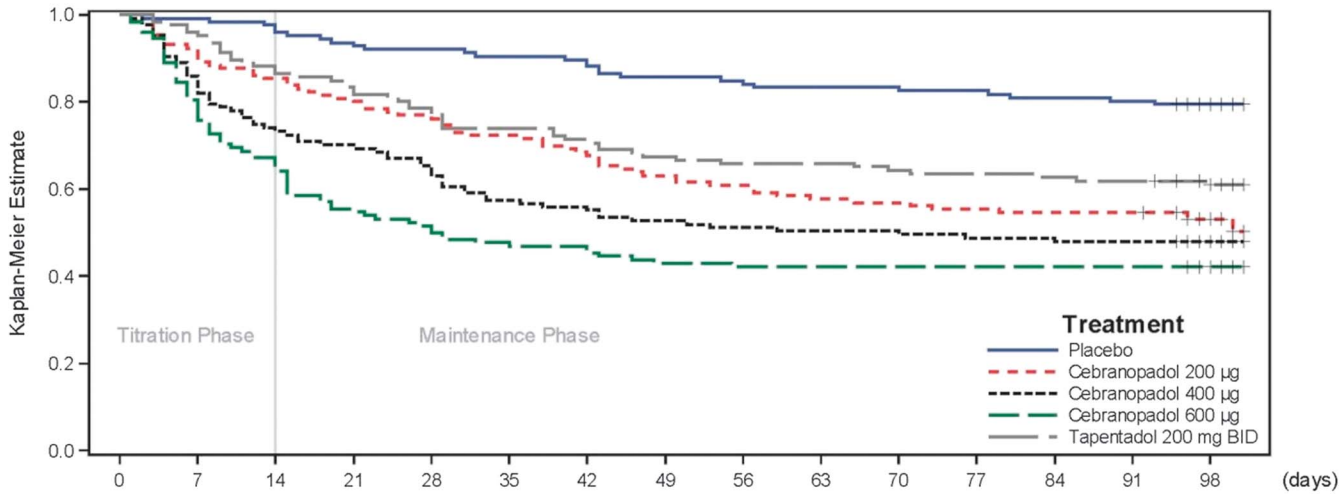

Figure 5. Kaplan–Meier plot of time to treatment discontinuation—Safety Set. BID, twice daily. + = censored.

withdrawal symptoms were reported, and mild withdrawal symptoms were reported at similar frequencies in the 3 cebranopadol arms. Therefore, slow tapering off of the cebranopadol treatment seems not required.

5. Conclusions

This was the first clinical trial to evaluate the analgesic efficacy, safety, and tolerability of cebranopadol taken once daily in patients suffering from moderate-to-severe chronic LBP, with and without a neuropathic pain component. Cebranopadol was effective at all tested doses, showing statistically significant differences from placebo for the primary endpoints. In addition, cebranopadol displayed other beneficial effects including improved sleep and functionality. In general, positive responses to treatment with cebranopadol and tapentadol were observed, irrespective of the presence or absence of neuropathic pain components in their chronic LBP. Cebranopadol in the tested dose range was safe. Higher cebranopadol doses led to higher treatment discontinuation rates which were primarily because of TEAEs occurring during the titration phase. Patients reaching the cebranopadol target doses presented with an acceptable tolerability profile. The incidence rate of most frequently reported TEAEs during the maintenance phase was ≤10%. Although further optimization of the titration scheme to the optimal dose for each individual patient is essential, cebranopadol appears to be a new drug candidate with a novel mechanistic approach for the potential treatment of chronic LBP.

Conflict of interest statement

Grünenthal GmbH funded and designed the trial, and analyzed and interpreted the data. A. Christoph, M. -H. Eerdekens, M. Kok, and G. Volkers are employees of Grünenthal GmbH. R. Freynhagen was international coordinating investigator of the trial. He reported research support, personal consulting, or lecture fees in the past 2 years from Astellas, Develco Pharma, Galapagos, Grünenthal, Lilly, Merck, Mitsubishi Tanabe Pharma, and Pfizer.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A437 and http://links.lww.com/PAIN/A438.

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