Original Article

Cebranopadol, a Novel First-in-Class Analgesic Drug Candidate: First Experience With Cancer-Related Pain for up to 26 Weeks

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Abstract

Context. Pain is one of the most prevalent symptoms associated with cancer. Strong opioids are commonly used in the analgesic management of the disease, but carry the risk of severe side effects. Cebranopadol is a first-in-class drug candidate, combining nociceptin/orphanin FQ peptide and opioid peptide receptor agonism. For cancer patients, frequently experiencing multimorbidities and often exposed to polypharmacy, cebranopadol is easy to handle given its once-daily dosing, the small tablet size that enables swallowing, and the option to flexibly titrate to an effective dose.

Objectives. We assessed the safety and tolerability of prolonged treatment with oral cebranopadol for up to 26 weeks in patients suffering from chronic moderate-to-severe cancer-related pain.

Methods. This was a non-randomized, multi-site, open-label, single-arm clinical trial with patients who had completed a double-blind trial comparing morphine prolonged release with cebranopadol. In this extension trial, patients were treated with oral cebranopadol for up to 26 weeks.

Results. Cebranopadol was safe and well tolerated in patients with chronic moderate-to-severe pain related to cancer in the dose range tested (200−1000 μg once daily). The median and mean pain levels remained in the range of mild pain during the treatment period.

Conclusion. Our data suggest that cebranopadol was safe and well tolerated when administered for up to 26 weeks in patients with chronic cancer-related pain who were previously treated with cebranopadol or morphine prolonged release. J Pain Symptom Manage 2019;58:390−399.

Key Words

Cebranopadol, cancer pain, open-label, prolonged treatment, nociceptin/orphanin FQ peptide

Introduction

Cancer has become a major cause of morbidity and mortality worldwide. Based on current trends, an increase in incidence can be expected from 12.7 million new cases in 2008 to 22.2 million by 2030.[1] Although cancer still constitutes a major public health threat, significant progress has recently been made in its treatment. This has led to a longer survival and increased the number of patients living with progressive cancer[2] and the symptoms thereof, which include pain arising from the primary cancer and/or resulting from anticancer treatments.

Pain is one of the most common symptoms associated with malignant tumors, occurring in 59% of patients undergoing anticancer treatment and approximately 75% of patients with advanced disease.[3,4] In addition, unrelieved pain denies patients

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comfort and greatly impacts their activities, emotions, motivation, and overall quality of life in addition to the burden of having a life-threatening disease.[3,5] Furthermore, 5% to 56% of long-term cancer survivors experience persistent pain from diverse etiologies (e.g., postsurgical and radiotherapy-, or chemotherapy-induced pain), despite the availability of various analgesics.[6,7] This indicates the need for further improvements in pain therapy, both in patients living with cancer and in cancer survivors.

Chronic cancer-related pain, that is, pain caused by the tumor itself as well as resulting from anticancer treatments, may have different underlying pathophysiologies with nociceptive and neuropathic components,[3] and can be considered as mixed pain. The established approach to this complex form of pain has relied heavily on the use of so-called "strong opioids," of which morphine, oxycodone, hydromorphone, and fentanyl are representatives.[8] However, the archetypal opioid morphine has a weak evidence base for its use in cancer-related pain and is associated with a significant side-effect profile.[9,10]

Cebranopadol is a novel, first-in-class, small-molecule analgesic, characterized by its high nociceptin/orphanin FQ peptide (NOP) and opioid receptor agonistic activity[11–13]. As NOP and opioid receptor agonists modulate pain via distinct yet related targets, a combined agonistic activity may be particularly suited to provide potent analgesia with a better tolerability profile than classical opioids.[11] Although strong opioids induce potent analgesia, the fact that their use may lead to the development of tolerance and physical dependence can limit their clinical utility. Importantly, NOP receptor activation has been associated with reduced development of tolerance,[14] addiction,[15] and physical dependence.[16]

Cebranopadol is in clinical development. It has shown an improved profile regarding respiratory safety[17] and a lower abuse potential[18] compared with classical opioids, which may be of relevance in chronic pain management. Its analgesic efficacy has been shown in acute and chronic pain conditions.[19–21]

The pharmacokinetic properties of cebranopadol allow for once-daily administration[22] and its small tablet size facilitates easy swallowing. This decreases the medication burden for patients receiving anticancer treatments, with progressive illness, or with comorbidities often requiring several concomitant medications, and thus may contribute to improving quality of life and treatment adherence.

So far, most data on long-term use of strong analgesics have been collected in non-cancer populations, with only limited data available for cancer populations. The current trial investigated prolonged treatment with oral cebranopadol for up to 26 weeks in patients suffering from cancer-related pain.

Methods

Trial Setting, Ethics, and Consent

We conducted a non-randomized, multi-site, open-label, single-arm extension trial to describe the safety and tolerability of prolonged treatment with oral cebranopadol for up to 26 weeks in patients suffering from moderate-to-severe cancer-related pain, who had previously just completed a double-blind trial comparing morphine prolonged release (PR) twice daily with cebranopadol once daily for six weeks (NCT01964378).[20] The current trial started on December 18, 2013 with the enrollment of the first patient and was completed on May 3, 2016 when the last patient completed the last follow-up examination. A total of 22 sites in 10 countries enrolled patients. 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 2013-001877-26 and the ClinicalTrials.gov identifier is NCT02031432.

Trial Design

A flow diagram of the trial is provided in Fig. 1. The first visit took place on the day of treatment completion of the preceding double-blind trial. Open-label oral cebranopadol was initially titrated to an optimal individual beneficial dose (defined as a balance between self-reported analgesia and side effects) in an approximately two-week titration phase. Patients were started on cebranopadol 200 µg daily (i.e., the lowest-allowed dose level). However, if patients were treated with either of the two highest dose levels in the maintenance phase of the preceding trial (i.e., cebranopadol 800 or 1000 µg daily, or morphine PR 120 or 150 mg daily), titration in the current trial could be started at cebranopadol 400 µg daily, if considered suitable by the investigator. These options allowed a smooth transition from one trial to the other while maintaining the blind of the preceding trial.

The dose selected by the end of the titration phase was continued during a 24-week maintenance phase with possibility for further dose adjustments. Available dose levels were cebranopadol 200, 400, 600, 800, or 1000 µg daily.

Cebranopadol could be taken with or without food, once daily in the morning. In addition, at any time during the trial, the dose could be discontinued for a certain period (e.g., because of adverse events [AEs]) depending on the patients' needs. During both the titration phase and the maintenance phase, all patients were allowed to receive on-demand analgesic treatment (e.g., immediate release opioids), for unbearable breakthrough pain, as prescribed by

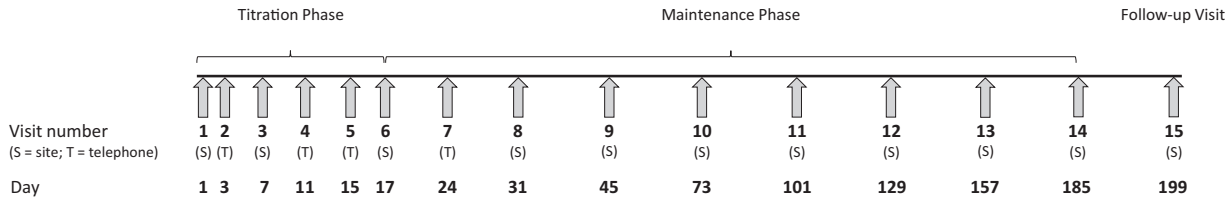

Fig. 1. Flow diagram of the extension trial.

the investigator. The average use of such on-demand medication during the previous day (for the first treatment visit) and during the last three days (for all other visits) was collected. The recommended maximum daily dose of on-demand opioid medication was not to exceed 90 mg of an oral morphine equivalent.

The planned total duration of the trial for an individual patient was approximately 28 weeks, including the 26-week treatment period (consisting of titration and maintenance phase) and follow-up. Patients attended the site for 11 scheduled visits and there were four telephone contacts (Fig. 1).

Trial Population

Male or non-pregnant and non-lactating female patients aged at least 18 years at the enrollment visit (Visit 1, Fig. 1), who had completed treatment in the preceding trial, and were in need of around-the-clock analgesia with strong opioids, were eligible for the trial.

Patients were excluded if they suffered from any clinically significant disorder other than the underlying cancer, or used any forbidden concomitant treatments that could possibly interfere with their safety in the trial. Chemotherapy and hormonal cancer therapy were allowed if not known to prolong QT. Furthermore, patients with a known history of torsade de pointes and/or presence of risk factors for torsade de pointes (e.g., heart failure, hypokalemia, bradycardia) were excluded.

End points

The **primary end point** was the incidence of treatment-emergent AEs (TEAEs).

The **secondary safety end point** was the intensity of the TEAEs.

The **secondary efficacy end point** was the average pain intensity on an 11-point numerical rating scale (NRS), ranging from 0 (no pain) to 10 (pain as bad as you can imagine), in the last week of the treatment period, and changes from baseline (i.e., the enrollment visit).

The following were the **exploratory safety-related end points**: outcomes, time to onset, duration, relationship to cebranopadol, and countermeasures (e.g., new medication) of TEAEs; time to discontinuation from treatment due to TEAEs; time to discontinuation from treatment due to TEAEs judged as at least possibly related to cebranopadol by the investigator; clinically relevant changes from baseline in vital signs assessments, weight, laboratory values, and evaluations of the 12-lead electrocardiogram during the trial; and Columbia-Suicide Severity Rating Scale scores (suicidal behavior and suicidal ideation) at every site visit and changes from baseline.

Exploratory efficacy-related end points included the following: the worst pain intensity (on the 11-point NRS) in the last week of the treatment period and changes from baseline; the mean scores of the Chronic Pain Sleep Inventory (CPSI) during the treatment period and changes from baseline; the Patient's Global Impression of Change (PGIC) at Visit 9 (i.e., during the maintenance phase, Fig. 1) and at the end of treatment (EoT) visit (Visit 14, Fig. 1); the Clinical Global Impression of Change (CGIC) at Visit 9 and at the EoT visit; time to discontinuation from treatment because of lack of efficacy; and use of on-demand medication during the treatment period.

Other end points: Eastern Cooperation Oncology Group performance status during the treatment period.

Statistical Methods

The enrolled set included all patients who signed the informed consent form. The safety set (SAF) included all allocated patients who took at least one dose of cebranopadol in the extension trial. All analyses were based on the SAF, using descriptive statistics. No formal statistical tests were planned on trial end points. As this was an extension trial including patients who completed treatment in the preceding trial, no sample size calculation was performed.

Baseline values were assessed at the enrollment visit of this extension trial, whereas patients were still treated with the investigational medicinal product of the preceding trial (i.e., cebranopadol or morphine PR). That investigational medicinal product was taken for the last time in the evening of the day of the enrollment visit of the extension trial.

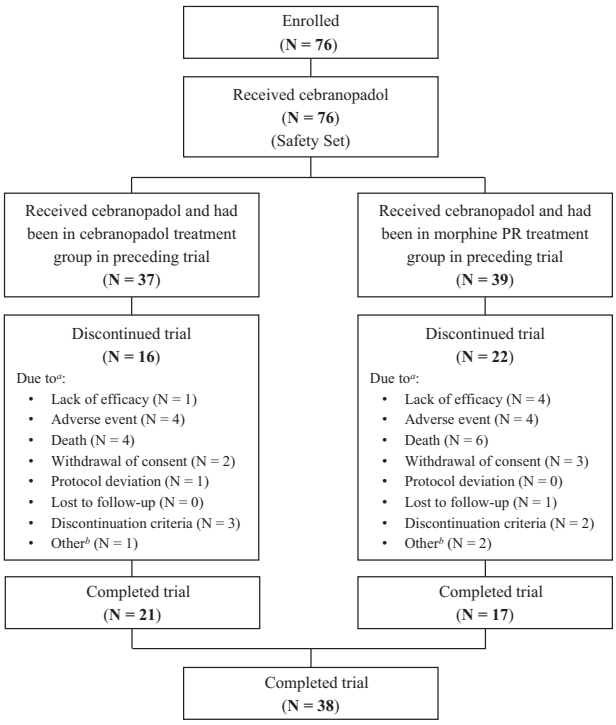

Fig. 2. Patient disposition. *N* = number of patients; PR = prolonged release. [a]The reasons for patient discontinuation were the main reasons reported for end of trial. Only one main reason is reported per patient. [b]Other reasons were forbidden medication required for one patient (cebranopadol treatment group in preceding trial) and cancer progression for two patients (morphine PR treatment group in preceding trial).

Results

Patient Disposition

The disposition of patients is presented in Fig. 2. A total of 76 patients who had completed the preceding trial were enrolled and received cebranopadol in this extension trial. In total, 38 patients (50.0%) completed this trial. The main reasons for discontinuation were deaths (10 patients) and AEs (eight patients).

Demographics and Baseline Characteristics

The patient demographics and baseline characteristics are summarized in Table 1. The SAF comprised 76 patients, including 32 women (42.1%) and 44 men (57.9%). The mean age was 61.7 years and all patients were white. Demographics and baseline characteristics of patients who had received cebranopadol and patients who had received morphine PR in the preceding trial were generally similar, with only slight differences in weight and age.

The trial population included patients with advanced cancer. At enrollment, most patients (76.3%) had cancer stage IV (Table 1), indicating the presence of metastases. The most common types and locations of cancer among the patients were prostate (23.7%), breast (15.8%), and lung and bronchus (14.5%) cancer. More than 30% of the patients had distant metastases in the bones.

Main antineoplastic and analgesic concomitant medications (i.e., medications used during and after cebranopadol intake) are presented in Table 2. Antineoplastic agents were still being used in 24 patients (31.6%) and endocrine therapies in 21 patients (27.6%). Opioids were used by 70 patients (92.1%). This included patients who used opioids during treatment with cebranopadol (as on-demand medication) and patients with opioids started after last cebranopadol intake (i.e., during the follow-up period; as around-the-clock analgesics).

Exposure

In total, 43 patients (56.6%) were treated with cebranopadol for more than 20 weeks (Fig. 3) and 38 patients (50.0%) completed the trial (Fig. 2). Considering all 67 patients (88.2%) who started the maintenance phase, the mean (SD) and median daily dose of cebranopadol received in the maintenance phase were 539.3 (277.5) and 438.6 µg, respectively. Median cebranopadol doses remained stable throughout this entire phase (data not shown).

Primary End Point

In total, 64 patients (84.2%) experienced at least one TEAE. Table 3 summarizes the TEAEs that occurred in at least 5% of the patients by System Organ Class and Preferred Term. The most frequently reported TEAEs were asthenia (21 patients [27.6%]), malignant neoplasm progression (20 [26.3%]), and decreased appetite (17 [22.4%]). The observed TEAEs were generally in line with the existing knowledge on cebranopadol or the underlying disease, except for peripheral edema, reported in nine patients (11.8%). However, all patients with reported peripheral edema had at least one relevant confounding factor, such as hypoalbuminemia, ascites, Cushing syndrome, chronic kidney disease, or a known cardiovascular history. No patients discontinued from the trial because of peripheral edema.

Secondary Safety End Point

Most TEAEs were mild (36.6%) or moderate (45.4%) in intensity. The most frequently reported severe TEAEs were malignant neoplasm progression (17 events), asthenia (eight events), decreased appetite (four events), and constipation, nausea, dyspnea, and hemoptysis (three events each).

Secondary Efficacy End Point

The level of median and mean of average baseline pain intensities was mild (approximately three points

Table 1
Descriptive Statistics for Demographic Parameters and Baseline Characteristics—Safety Set

	Cebranopadol in Preceding trial[a]	Morphine PR in Preceding trial[a]	Overall Cebranopadol in Extension trial[a]
Safety Set, *N* (%)	37 (100)	39 (100)	76 (100)
Age, yrs			
Mean (SD)	63.9 (9.0)	59.6 (10.2)	61.7 (9.8)
Min, Max	45, 78	35, 76	35, 78
Gender,[b] *n* (%)			
Female	17 (45.9)	15 (38.5)	32 (42.1)
Male	20 (54.1)	24 (61.5)	44 (57.9)
Race,[b] *n* (%)			
White	37 (100)	39 (100)	76 (100)
Height,[b] cm			
Mean (SD)	168 (9.2)	169 (7.8)	168 (8.4)
Min, Max	151, 186	148, 184	148, 186
Weight,[c] kg			
Mean (SD)	74.5 (13.7)	69.6 (14.1)	72.0 (14.0)
Min, Max	37, 97	41, 97	37, 97
Body mass index, kg/m^2			
Mean (SD)	26.3 (4.3)	24.5 (4.5)	25.4 (4.5)
Min, Max	14.5, 34.2	17.2, 34.1	14.5, 34.2
Cancer pain history—type of pain,[d] *n* (%)			
Neuropathic	17 (45.9)	10 (25.6)	27 (35.5)
Visceral	16 (43.2)	20 (51.3)	36 (47.4)
Somatic	22 (59.5)	26 (66.7)	48 (63.2)
Cancer history—stage at enrolment,[d] *n* (%)			
I	1 (2.7)	0	1 (1.3)
II	2 (5.4)	2 (5.1)	4 (5.3)
III	1 (2.7)	7 (17.9)	8 (10.5)
IV	32 (86.5)	26 (66.7)	58 (76.3)
Unknown	1 (2.7)	6 (15.4)	7 (9.2)

PR = prolonged release; *N* = number of patients in the population; Min = minimum; Max = maximum; *n* = number of patients with this observation.
[a]Treatments refer to the allocation of patients in the preceding double-blind trial. The column "Overall cebranopadol in extension trial" refers to the treatment in the current open-label extension trial.
[b]Data collected in the preceding double-blind trial.
[c]Weight at enrollment visit (Visit 1) of this extension trial.
[d]Multiple entries were possible.

on the 11-point NRS). On average, the pain levels increased only slightly over the treatment period, and medians remained stable throughout the entire maintenance phase. During the trial, there were no changes from baseline in median and only slight changes from baseline in mean of average pain intensity (at EoT visit: 0.8 points). Overall, over the entire duration of the trial, irrespective of treatment in the preceding trial, the median and mean pain levels remained in the range of mild pain (at EoT visit: median 3.0 points and mean [SD] 3.5 [2.35] points).

Exploratory Safety-Related End Points

More than half of the TEAEs (52.8%) was recovered/resolved, whereas more than one-third (39.3%) was not recovered/not resolved (e.g., asthenia, decreased appetite, and malignant neoplasm progression) at the last visit for individual patients (note that the assessments reflect the latest status collected during the trial, not the final outcome). Overall, time to onset and duration did not show an unexpected pattern, and no trends were detected between the titration and maintenance phase given the population studied and considering the trial limitations (see Discussion). Most TEAEs (92.4%) were assessed as not related (i.e., not related or unlikely related) to cebranopadol by the investigator. For more than half of the TEAEs (54.6%), no countermeasures were taken, whereas 42.5% of the TEAEs were treated with newly started medication.

Seventeen patients (22.4%) had 23 TEAEs leading to discontinuation from treatment, including nine

Table 2
Antineoplastic and Analgesic Concomitant Medication—Safety Set

	n (%)
Antineoplastic agents[a]	24 (31.6)
Endocrine therapy[a]	21 (27.6)
Immunostimulants[a]	4 (5.3)
Analgesics[b]	72 (94.7)
Opioids	70 (92.1)
Other analgesics and antipyretics	40 (52.6)

n = number of patients using this antineoplastic or analgesic concomitant medication.
[a]Anatomical Therapeutic Chemical Level 2.
[b]Anatomical Therapeutic Chemical Levels 2 and 3.

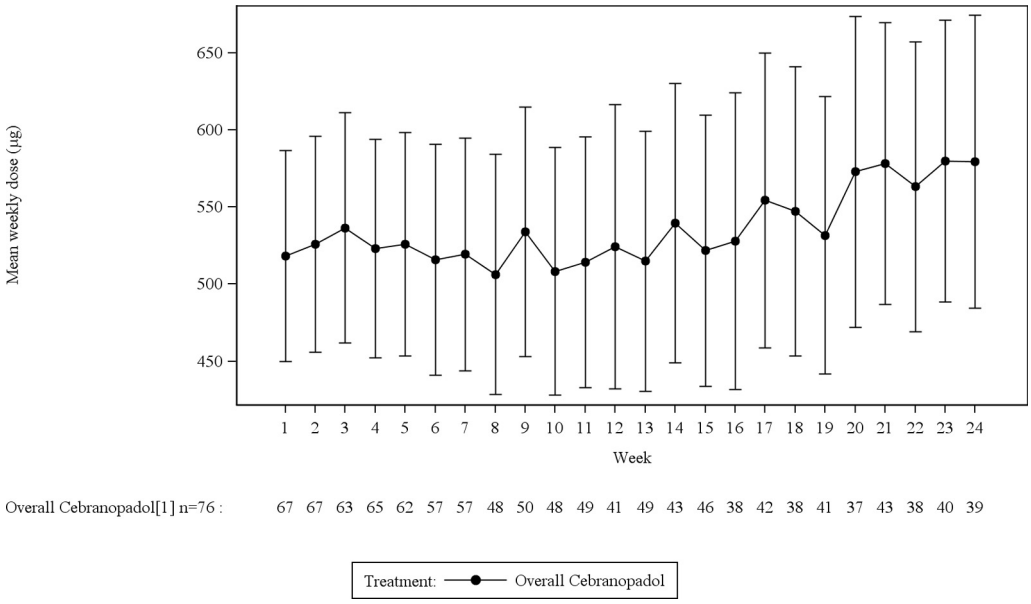

Fig. 3. Extent of exposure (mean weekly dose received)—maintenance phase—safety set.

patients who died, six who discontinued because of non-fatal serious AEs (SAEs), and two who discontinued because of non-serious TEAEs. The median time to discontinuation from cebranopadol for these 17 patients was 116.0 days. Of note, the TEAEs leading to discontinuation were generally unique events of varying medical concepts, except for malignant neoplasm progression (reported in 19 patients [25.0%], of which 12 [15.8%] discontinued). Only two patients (one patient from each treatment group in the preceding trial) discontinued because of TEAEs in the titration phase. No patient discontinued because of a TEAE at least possibly related to cebranopadol. Overall, the frequency and type of TEAEs leading to discontinuation reflect the underlying condition of the population studied and/or treatment thereof.

In total, 10 patients (13.2%) died during the trial. Seven died because of malignant neoplasm progression, one because of myocardial infarction, one because of subarachnoid hemorrhage, and one because of superior vena cava syndrome. None of these fatal events were assessed as related to cebranopadol. Overall, the frequency and type of SAEs (71 SAEs in 32 subjects) reflect the underlying condition of the population studied and/or treatment thereof.

No relevant overall trends or observations in single patients were observed for vital signs, weight, laboratory values, or electrocardiogram parameters that cannot be explained by the underlying disease or treatment thereof (e.g., mean weight, Table 4).

One patient developed suicidal ideation during the treatment period. This patient had cancer progression and discontinued the trial. One additional patient had suicidal ideation already before enrollment. There were no patients with suicidal behavior.

Exploratory Efficacy-Related End Points

The mean of the worst pain intensity (on the 11-point NRS) in the last week of the treatment period showed a slight worsening compared with baseline (mean change [SD]: 0.9 [2.99]; Table 4), which should be interpreted with caution, given the natural progression of the underlying disease, as reflected by more patients having Eastern Cooperation Oncology Group status 3 or 4 at EoT visit than at baseline (Table 4).

The changes from baseline in the mean and median sleep problem index and in the mean and median overall quality of sleep (assessed by CPSI) during the treatment period were small and indicated that sleep quality was maintained during the trial (Table 4).

At Visit 9 (i.e., during the maintenance phase, Fig. 1), almost 80% of the patients with data available rated their condition as improved (very much, much, or minimally improved) on the PGIC and more than 50% as very much or much improved. At the EoT visit, almost 60% rated their condition as improved and more than 30% as very much or much improved. At Visit 9 and the EoT visit, the investigator rated the condition of more than 70% of the patients as improved (very much, much, or minimally improved), and of more than 50% as very much or much improved on the CGIC (Fig. 4).

Only five patients (four patients from the morphine PR group and one patient from the cebranopadol group in the preceding trial) discontinued from treatment because of lack of efficacy, with time to

Table 3
TEAEs Occurring in At Least 5% of the Patients by Primary System Organ Class and Preferred Term—Safety Set

Primary System Organ Class[a] Preferred Term	*n* (%), [*e*] (%)
Patients with TEAEs	64 (84.2), [661] (100)
Blood and lymphatic system disorders	28 (36.8), [53] (8.0)
Anemia	9 (11.8), [10] (1.5)
Leukocytosis	5 (6.6), [5] (0.8)
Leukopenia	6 (7.9), [7] (1.1)
Thrombocytopenia	6 (7.9), [6] (0.9)
Thrombocytosis	7 (9.2), [10] (1.5)
Gastrointestinal disorders	32 (42.1), [87] (13.2)
Abdominal pain	4 (5.3), [5] (0.8)
Abdominal pain upper	5 (6.6), [6] (0.9)
Constipation	11 (14.5), [13] (2.0)
Diarrhea	4 (5.3), [4] (0.6)
Nausea	15 (19.7), [18] (2.7)
Vomiting	8 (10.5), [11] (1.7)
General disorders and administration site conditions	38 (50.0), [70] (10.6)
Asthenia	21 (27.6), [23] (3.5)
Fatigue	9 (11.8), [10] (1.5)
Feeling drunk	4 (5.3), [4] (0.6)
Edema peripheral	9 (11.8), [9] (1.4)
Pyrexia	9 (11.8), [10] (1.5)
Infections and infestations	26 (34.2), [44] (6.7)
Bacteriuria	5 (6.6), [5] (0.8)
Upper respiratory tract infection	4 (5.3), [4] (0.6)
Urinary tract infection	6 (7.9), [7] (1.1)
Investigations	24 (31.6), [47] (7.1)
Gamma-glutamyltransferase increased	4 (5.3), [4] (0.6)
Metabolism and nutrition disorders	24 (31.6), [41] (6.2)
Decreased appetite	17 (22.4), [21] (3.2)
Musculoskeletal and connective tissue disorders	24 (31.6), [55] (8.3)
Arthralgia	8 (10.5), [8] (1.2)
Back pain	8 (10.5), [11] (1.7)
Musculoskeletal pain	7 (9.2), [10] (1.5)
Pain in extremity	4 (5.3), [5] (0.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	23 (30.3), [40] (6.1)
Malignant neoplasm progression	20 (26.3), [28] (4.2)
Nervous system disorders	24 (31.6), [49] (7.4)
Dizziness	5 (6.6), [6] (0.9)
Headache	8 (10.5), [8] (1.2)
Somnolence	8 (10.5), [9] (1.4)
Psychiatric disorders	21 (27.6), [41] (6.2)
Anxiety	4 (5.3), [7] (1.1)
Depressed mood	4 (5.3), [4] (0.6)
Insomnia	5 (6.6), [5] (0.8)
Nervousness	4 (5.3), [4] (0.6)
Respiratory, thoracic, and mediastinal disorders	18 (23.7), [35] (5.3)
Dyspnea	7 (9.2), [8] (1.2)

TEAE = treatment-emergent adverse event; *e* = number of events, *n* = number of patients who had the specified TEAE.
[a]Adverse events were coded according to the Medical Dictionary for Regulatory Activities version 18.1.

discontinuation from treatment of six, 16, 38, 60, and 77 days.

At Visit 2 (i.e., at the beginning of the titration phase, Fig. 1), the mean (SD) number of on-demand medication units administered during the previous day was 1.1 (1.77). At the other visits, the mean number of daily units administered during the last three days ranged from 0.47 to 1.45. As the median at each of the visits was 0.0, most of the patients did not report use of on-demand medication in the evaluated period per visit (three days before each visit for Visit 3 to EoT visit).

Discussion

This was the first trial investigating the prolonged treatment (up to 26 weeks) with cebranopadol, a novel first-in-class NOP and opioid receptor agonist, in 76 patients with chronic moderate-to-severe cancer-related pain. The current trial contributes to the knowledge on long-term use of strong analgesics, as only limited data are available for cancer patients until now. Overall, as in the preceding double-blind trial, the population included in this open-label extension trial was representative for the general population of patients with advanced-stage cancer and persistent cancer-related pain, who require around-the-clock analgesic management with strong opioids. In total, half of the patients completed the trial.

With regard to the safety of cebranopadol, most patients experienced at least one TEAE during the trial, most of which were mild or moderate in intensity. Most of these TEAEs (92.4%) were considered unrelated to cebranopadol and in more than half of the cases (54.6%), no countermeasures were needed. The TEAEs were in line with the existing knowledge on cebranopadol or the underlying disease. The only unexpected TEAE was peripheral edema, observed in nine patients (11.8%). None of these patients withdrew as a result of this TEAE. Ten patients (13.2%) died during the trial. None of the deaths were assessed as being related to cebranopadol by the investigator. No safety signal was identified based on the TEAEs leading to discontinuation and SAEs.

Although the efficacy data need to be interpreted with caution given the presence of confounding factors, such as allowed use of concomitant analgesics, the open-label design and the progressive underlying condition, continuous mild pain intensity levels, as well as limited use of on-demand opioids (median dose being 0.0 in the evaluated period, as reported by most patients at each visit), and positive assessments of treatment effects via PGIC and CGIC suggest that a relevant proportion of the patients benefited from the treatment with cebranopadol over up to 26 weeks.

Strong opioids (e.g., morphine) have been widely accepted as the gold standard in the analgesic management of moderate-to-severe cancer-related pain.[23] Unfortunately, although providing potent analgesia, the use of conventional opioids may lead

Table 4
Exploratory and Other End Points—Safety Set

End Point		Baseline	EoT Visit
Weight, kg			
N		76	61
Mean (SD)		71.99 (14.038)	69.70 (13.932)
Worst pain intensity (11-point NRS)			
N		76	59
Mean (SD)		4.3 (2.52)	5.1 (2.89)
CPSI[a]			
Sleep problem index (0–300 scale)			
N		76	58
Mean (SD)		35.0 (54.03)	44.5 (71.10)
Median (Q1, Q3)		9.5 (0.0, 49.5)	20.0 (1.0, 55.0)
Overall sleep quality (0–100 scale)			
N		76	58
Mean (SD)		74.0 (27.91)	71.3 (30.97)
Median (Q1, Q3)		82.5 (53.5, 97.0)	80.0 (53.0, 98.0)
ECOG performance status	*N* (total)	76	63
0	*n*	16	10
1	*n*	35	20
2	*n*	24	21
3	*n*	1	8
4	*n*	0	4
5	*n*	0	0

EoT = end of treatment; *N* = number of patients in the population; NRS = numerical rating scale; CPSI = Chronic Pain Sleep Inventory; Q1 = first quartile; Q3 = third quartile; ECOG = Eastern Cooperation Oncology Group; *n* = number of patients with this observation.
[a]Increases of scores correspond to worsening, and decreases of scores to improvement of sleep.

to the development of tolerance and physical dependence. Throughout the treatment period of this trial, and irrespective of the treatment in the preceding trial (i.e., cebranopadol or morphine PR), the median and mean of average pain intensity values (in the last week) remained within the range of mild pain. In light of the trial design limitations, these results suggest that the cancer pain was adequately controlled in this difficult-to-manage population.

Sleep disturbances were evaluated because these are often experienced by patients with advanced cancer.[24] The CPSI data indicated that sleep quality was maintained. Furthermore, only two patients (one patient from each treatment group in the preceding trial), discontinued because of TEAEs in the titration phase, indicating that patients could easily switch from morphine PR to cebranopadol while maintaining pain control or stay on cebranopadol for prolonged treatment.

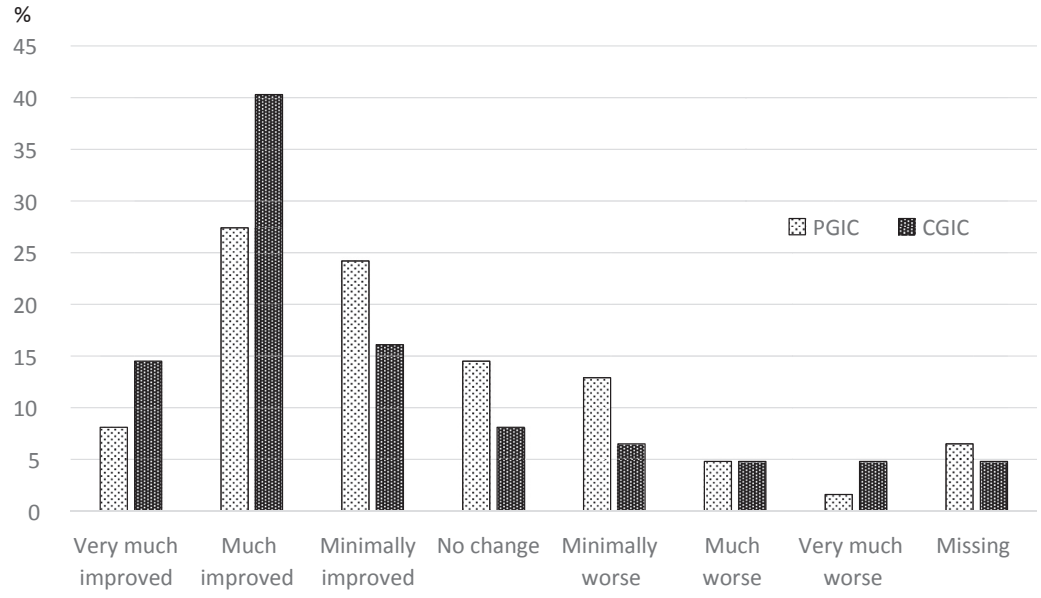

Fig. 4. PGIC and CGIC at end of treatment visit—seven-point scale—bar chart—safety set. PGIC = Patient's Global Impression of Change; CGIC = Clinical Global Impression of Change.

A limitation of the current trial was the presence of confounding factors, such as allowed use of concomitant analgesics, including on-demand opioid medication. However this probably represents a "real world" situation where several options are available for breakthrough pain medication.[25] Furthermore, this was an open-label trial without comparator. Other limitations included progression of the underlying disease and concomitant cancer treatment, but these also reflect the context of modern cancer-related pain management.

Conclusion

Considering the trial design limitations, cebranopadol was safe and well tolerated during a prolonged treatment duration of up to 26 weeks in the dose range tested (200−1000 μg once daily) when given to patients with chronic moderate-to-severe cancer-related pain and receiving multiple concomitant treatments. The intake, dosing, and titration were easy to manage and the chronic cancer-related pain was adequately controlled in this difficult-to-manage population. Switching from morphine PR to cebranopadol was safe, well tolerated, and successful in terms of analgesia.

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