Clinical trial results:
Efficacy, safety, and tolerability of oral Cebranopadol versus morphine sulphate PR in subjects with chronic moderate to severe pain related to cancer.

Summary

EudraCT number	2012-001316-35
Trial protocol	BE GB DE HU SE ES SK PL NL AT DK BG HR
Global end of trial date	16 October 2015

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	KF6005/07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01964378
WHO universal trial number (UTN)	U1111-1143-1808

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
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Scientific contact	GRT Trial Information Desk, Grünenthal GmbH, +49 2415693223, clinical-trials@grunenthal.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2015
Global end of trial reached?	Yes
Global end of trial date	16 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of orally administered Cebranopadol in comparison with morphine sulfate PR in subjects suffering from chronic moderate to severe pain related to cancer.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory and competent authorities were notified of the trial as required by national regulations, and, where necessary, relevant authorization was obtained.
Subjects were informed and monitored by the investigator not to take prohibited medications.
The last intake of Investigational Medicinal Product (IMP) took place in the evening of the day of the End of Treatment Visit. The use of rescue medication was allowed until the next day. From that day onwards (Follow-up Period), subjects were allowed to use any analgesic concomitant medication (unless specified otherwise under concomitant medications/therapies) or could start their participation in the extension trial (KF6005/09). For subjects not participating in the extension trial, a Follow-up Visit was planned 4 – 7 days after last IMP intake. At least 14 days (up to 18 days) after the End of Treatment Visit, investigators were to call the subjects for a final update on adverse events.

Background therapy:

Allowed concomitant treatments with certain limitations were:
- Hypnotics.
- Anti-emetics for treatment of adverse events or as part of a chemotherapy and/or radiotherapy regimen.
- Non-steroidal anti-inflammatory & antirheumatic drugs & non-opioid analgesics.
- Chemotherapy & hormonal anti-cancer therapy.
- Radiotherapy (pain-relieving radiotherapy was not allowed).
- Laxatives.
- Serotonin & noradrenaline reuptake inhibitors, anticonvulsants, neuroleptics and antiparkinsonian drugs
- Physiotherapy and other non-pharmacological pain therapy.
- Corticosteroids and bisphosphonates.
- Strong inducers or inhibitors of cytochrome P450 3A4, if stable for at least 2 weeks before enrollment.

Evidence for comparator:

Morphine sulfate PR was selected as comparator because its mechanism of action is primarily based on MOP agonism, whereas cebranopadol combines MOP agonism with NOP agonism, and represents the most commonly used gold standard opioid with the longest history of use in patients suffering from cancer-related pain. It is broadly acknowledged that morphine is highly effective in the treatment of cancer-related pain.

Actual start date of recruitment	29 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Slovakia: 40
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	200
EEA total number of subjects	190

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	103
From 65 to 84 years	94
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The trial started on 29 Oct 2013 with the enrollment of the first subject and was completed on 16 Oct 2015 when the last subject completed the last follow-up examination.

Pre-assignment

Screening details:

A total of 200 subjects were enrolled.

Pre-assignment period milestones

Number of subjects started	200
Intermediate milestone: Number of subjects	Allocated to treatment: 132
Intermediate milestone: Number of subjects	Treated with IMP: 126
Number of subjects completed	126

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 4
Reason: Number of subjects	inclusion/exclusion criteria not met: 65
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Adverse event, serious fatal: 2
Reason: Number of subjects	not specified: 2

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Blinding implementation details:

A double-dummy technique was used to ensure blinding of the IMP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cebranopadol

Arm description:

Subjects took one or two tablet(s) of cebranopadol in the morning and one or two placebo double-dummy morphine-like capsule(s) in the morning and the evening.

Arm type	Experimental
Investigational medicinal product name	Cebranopadol
Investigational medicinal product code	GRT6005
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The minimum daily dose of cebranopadol was 200 µg. The incremental/decremental dose of cebranopadol was 200 µg per day. The maximum daily dose was 1000 µg/day. The aim of the titration was to reach the subject’s individual optimal dose defined as a balance between self-reported analgesia

and side effects. The first decision on uptitration was taken on Day 3 (after 1 day of IMP intake). From Day 4 on, decisions for uptitration to the next higher dose step were taken after at least 4 days on a dose level. During the Titration Phase, downward titration by 1 step was allowed. In the Maintenance Phase, subjects continued at the same dose that provided optimal therapeutic benefit during the Titration Phase. No dose adjustments were allowed during the Maintenance Phase.

Arm title	Morphine Prolonged Release

Arm description:

Subjects took morphine capsule(s) in the morning and in the evening and placebo double-dummy cebranopadol-like tablet(s) in the morning.

Arm type	Active comparator
Investigational medicinal product name	Morphine Prolonged Release
Investigational medicinal product code	
Other name	Morphine sulfate pentahydrate
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The minimum daily dose of morphine prolonged release was 30 mg. The incremental/decremental dose of morphine was 30 mg per day. The maximum daily dose was 150 mg. The aim of the titration was to reach the subject’s individual optimal dose defined as a balance between self-reported analgesia and side effects. The first decision on uptitration was taken on Day 3 (after 1 day of IMP intake). From Day 4 on, decisions for uptitration to the next higher dose step were taken after at least 4 days on a dose level. During the Titration Phase, downward titration by 1 step was allowed. In the Maintenance Phase, subjects continued at the same dose that provided optimal therapeutic benefit during the Titration Phase. No dose adjustments were allowed during the Maintenance Phase.

Number of subjects in period 1[1]	Cebranopadol	Morphine Prolonged Release
Started	65	61
Completed	41	45
Not completed	24	16
Adverse event, serious fatal	3	2
Consent withdrawn by subject	7	5
Adverse event, non-fatal	12	5
inclusion/exclusion criteria not met	1	-
Lost to follow-up	-	1
not specified	1	1
Lack of efficacy	-	1
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 200 subjects were enrolled. The baseline period reports the number of subjects that were exposed to at least one dose of Investigational Medicinal Product (IMP), i.e. Safety Analysis Set.

Baseline characteristics

Reporting groups	
Reporting group title	Cebranopadol
Reporting group description:	
Subjects took one or two tablet(s) of cebranopadol in the morning and one or two placebo double-dummy morphine-like capsule(s) in the morning and the evening.	
Reporting group title	Morphine Prolonged Release
Reporting group description:	
Subjects took morphine capsule(s) in the morning and in the evening and placebo double-dummy cebranopadol-like tablet(s) in the morning.	

Reporting group values	Cebranopadol	Morphine Prolonged Release	Total
Number of subjects	65	61	126
Age categorical Units: Subjects			
Adults (18-64 years)	36	35	71
From 65-84 years	29	26	55
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.8	61	
standard deviation	± 9.18	± 10.64	-
Gender categorical Units: Subjects			
Female	27	22	49
Male	38	39	77
Race Units: Subjects			
White	65	61	126
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	58	60	118
Not Reported	5	1	6
Prior opioid treatment Units: Subjects			
WHO Step II analgesic	27	28	55
WHO Step III analgesic excluding morphine	22	21	43
Morphine	16	12	28
ECOG Status			
Eastern Cooperative Oncology Group (ECOG) performance status: 0 = Fully active. 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. 3 = Capable of only limited self-care. 4 = Completely disabled. 5 = Dead.			
Units: Subjects			
Status 0	17	13	30
Status 1	30	30	60
Status 2	18	18	36

Status 3	0	0	0
Status 4	0	0	0
Status 5	0	0	0
Cancer history - Stage IV			
There were 10 subjects (N=3 cebranopadol and N=7 morphine with an unknown stage at enrolmment) Multiple entries were possible for cancer history stage thus only the details for Stage IV, the most frequent staging, is reflected.			
Units: Subjects			
Stage IV	52	45	97
Other	12	16	28
Missing	1	0	1
Subjects with neuropathic pain component			
Based on medical history.			
Units: Subjects			
Neuropathic component present	28	24	52
No neuropathic component present	37	37	74
Subjects with a visceral pain component			
Units: Subjects			
Visceral pain present	31	28	59
No viseral pain present	34	33	67
Subjects with a somatic pain component			
Units: Subjects			
Somatic pain component present	39	34	73
No somatic pain component present	26	27	53
Height			
Units: meter			
arithmetic mean	1.6889	1.692	
standard deviation	± 0.09097	± 0.07952	-
Weight			
Units: kilogram(s)			
arithmetic mean	73.52	71.23	
standard deviation	± 14.126	± 12.807	-
Body Mass Index (BMI)			
Units: kilogram(s)/square meter			
arithmetic mean	25.74	24.84	
standard deviation	± 4.39	± 4.022	-
Baseline pain intensity			
For this assessment, each subject was asked "Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours" on an 11-point Numerical Rating Scale, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The value was calculated from the mean of the 3 assessments of average pain intensity in the last 24 hours recorded during the last 3 days prior to the dosing visit, calculated when at least one assessment in this three-day window was available.			
Units: units on a scale			
arithmetic mean	6.23	6.3	
standard deviation	± 1	± 1.23	-
Worst daily pain intensity			
For this assessment, each subject was asked "Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours" on an 11-point Numerical Rating Scale, where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The value reported is the mean of the 3 assessments of worst pain intensity in the last 24 hours recorded during the last 3 days prior to the first dosing visit, calculated when at least one assessment in this three-day window was available.			

Units: units on a scale			
arithmetic mean	7.27	7.29	
standard deviation	± 1.222	± 1.117	-
Time since cancer pain onset			
Time since cancer pain onset (in weeks) before informed consent signature.			
Units: weeks			
arithmetic mean	62.25	60.22	
standard deviation	± 111.915	± 79.792	-

End points

End points reporting groups

Reporting group title	Cebranopadol
Reporting group description:	
Subjects took one or two tablet(s) of cebranopadol in the morning and one or two placebo double-dummy morphine-like capsule(s) in the morning and the evening.	
Reporting group title	Morphine Prolonged Release
Reporting group description:	
Subjects took morphine capsule(s) in the morning and in the evening and placebo double-dummy cebranopadol-like tablet(s) in the morning.	
Subject analysis set title	Cebranopadol Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS describes a subset of subjects in the FAS. The PPS included all allocated subjects who completed at least 2 weeks of treatment in the maintenance phase and had no major protocol deviations relevant for efficacy evaluations.	
Subject analysis set title	Morphine Prolonged Release Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PPS describes a subset of subjects in the FAS. The PPS included all allocated subjects who completed at least 2 weeks of treatment in the maintenance phase and had no major protocol deviations relevant for efficacy evaluations.	
Subject analysis set title	Cebranopadol Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all allocated subjects who took at least 1 dose of the IMP and had at least 1 day with information for the amount of rescue medication intake after the first intake of double-blind IMP.	
Subject analysis set title	Morphine Prolonged Release Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set includes all allocated subjects who took at least 1 dose of the IMP and had at least 1 day with information for the amount of rescue medication intake after the first intake of double-blind IMP.	

Primary: Average amount of daily rescue medication (morphine IR) intake over the last 2 weeks of the Maintenance Phase

End point title	Average amount of daily rescue medication (morphine IR) intake over the last 2 weeks of the Maintenance Phase
End point description:	
Morphine sulfate immediate release (IR) 10 mg tablets were supplied as rescue medication to trial participants. The daily use of morphine sulfate 10 mg immediate release tablets was documented by each participant in the trial. The total daily amount of morphine IR was subject to an upper limit recommendation. The primary endpoint was the average amount of daily rescue medication intake over the last 2 weeks of the maintenance period. No dose adjustments of the morphine prolonged release or cebranopadol was allowed during the maintenance period.	
End point type	Primary
End point timeframe:	
Maintenance Period (Week 3 and Week 4)	

End point values	Cebranopadol Per Protocol Population	Morphine Prolonged Release Per Protocol Population	Cebranopadol Full Analysis Population	Morphine Prolonged Release Full Analysis Population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	45	64	61
Units: milligram(s)/24 hours				
least squares mean (standard error)	4.25 (± 1.7)	8.92 (± 1.72)	3.46 (± 1.71)	10.94 (± 1.75)

Statistical analyses

Statistical analysis title	Rescue Intake Cebranopadol vs Morphine PR - FAS

Statistical analysis description:

The MMRM (mixed model repeated measurement) model includes fixed effects of pooled country, treatment, week, treatment-by-week interaction, history of opioid intake, baseline pain intensity as covariate & subject-specific random effects. Dependent variable being the weekly average rescue medication intake. For subjects in the FAS having no data in the Maintenance Phase the average amount of rescue medication over the last 3 days of titration was imputed to the 1st week of the Maintenance Phase.

Comparison groups	Cebranopadol Full Analysis Population v Morphine Prolonged Release Full Analysis Population
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	MMRM
Parameter estimate	MMRM
Point estimate	-7.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.05
upper limit	-2.918
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

[1] - A non-inferiority margin of 8 mg.

Statistical analysis title	Rescue Intake Cebranopadol vs Morphine PR – PPS

Statistical analysis description:

The MMRM (mixed model repeated measurement) model includes fixed effects of pooled country, treatment, week, treatment-by-week interaction, history of opioid intake, baseline pain intensity as covariate & subject-specific random effects. Dependent variable being the weekly average rescue medication intake. For subjects in the FAS having no data in the Maintenance Phase the average amount of rescue medication over the last 3 days of titration was imputed to the 1st week of the Maintenance Phase.

Comparison groups	Cebranopadol Per Protocol Population v Morphine Prolonged Release Per Protocol Population

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.0001
Method	MMRM
Parameter estimate	MMRM
Point estimate	-4.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.245
upper limit	-0.099
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

[2] - A non-inferiority margin of 8 mg.

Secondary: Proportion of subjects with clinically relevant pain reductions

End point title	Proportion of subjects with clinically relevant pain reductions

End point description:

The secondary efficacy endpoint was the proportion of subjects with clinically relevant pain reduction (Responder / Non-responder) over the last 2 weeks of the Maintenance Phase.
Definition of clinically relevant pain reduction:
• Average pain intensity of less than 4 points on the 11-point NRS.
Or
• Reduction in average pain intensity by at least 30% (compared to the baseline assessment).
Or
• Reduction in average pain intensity by greater than or equal to 2 points (compared to the baseline assessment).
(The average pain intensity is the average of the 24-hour pain intensities over the last 2 weeks of the Maintenance Phase.)

End point type	Secondary

End point timeframe:

Maintenance week 3 and 4.

End point values	Cebranopadol Per Protocol Population	Morphine Prolonged Release Per Protocol Population	Cebranopadol Full Analysis Population	Morphine Prolonged Release Full Analysis Population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	45	64	61
Units: Subjects				
Responder	35	40	48	51
Non-responder	8	5	16	10

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first IMP intake up to day of last IMP (6 weeks)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Cebranopadol
Reporting group description: -	
Reporting group title	Morphine Prolonged Release
Reporting group description: -	

Serious adverse events	Cebranopadol	Morphine Prolonged Release	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 65 (21.54%)	11 / 61 (18.03%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	5 / 65 (7.69%)	7 / 61 (11.48%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Metastases to central nervous system			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 65 (1.54%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 65 (1.54%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 65 (1.54%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cebranopadol	Morphine Prolonged Release	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 65 (80.00%)	48 / 61 (78.69%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 65 (9.23%)	5 / 61 (8.20%)	
occurrences (all)	7	5	
Paraesthesia			
subjects affected / exposed	4 / 65 (6.15%)	1 / 61 (1.64%)	
occurrences (all)	4	1	
Dizziness			
subjects affected / exposed	2 / 65 (3.08%)	6 / 61 (9.84%)	
occurrences (all)	2	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 65 (10.77%)	10 / 61 (16.39%)	
occurrences (all)	7	10	
Oedema peripheral			
subjects affected / exposed	7 / 65 (10.77%)	0 / 61 (0.00%)	
occurrences (all)	8	0	

Asthenia			
subjects affected / exposed	6 / 65 (9.23%)	8 / 61 (13.11%)	
occurrences (all)	6	9	
Pyrexia			
subjects affected / exposed	4 / 65 (6.15%)	4 / 61 (6.56%)	
occurrences (all)	6	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 65 (4.62%)	5 / 61 (8.20%)	
occurrences (all)	3	5	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 65 (3.08%)	4 / 61 (6.56%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 65 (12.31%)	15 / 61 (24.59%)	
occurrences (all)	11	15	
Nausea			
subjects affected / exposed	8 / 65 (12.31%)	10 / 61 (16.39%)	
occurrences (all)	11	12	
Vomiting			
subjects affected / exposed	8 / 65 (12.31%)	5 / 61 (8.20%)	
occurrences (all)	13	6	
Diarrhoea			
subjects affected / exposed	4 / 65 (6.15%)	5 / 61 (8.20%)	
occurrences (all)	4	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 65 (6.15%)	1 / 61 (1.64%)	
occurrences (all)	4	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 65 (3.08%)	6 / 61 (9.84%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5	9 / 61 (14.75%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2013	This amendment was in place before First Subject Enrolled. The selection criteria were adapted to exclude opioid-naive subjects. The primary endpoint was changed to assess the amount of rescue medication taken. The primary endpoint was analyzed on the Full Analysis Set and on the Per Protocol Set. The number of planned interim analyses was reduced to 1. The sample size was adapted to include 524 allocated subjects due to the change of the primary endpoint. Morphine sulfate PR as a once daily formulation was replaced by a twice daily formulation. Administration strategy (double-dummy), selection criteria, rules for concomitant medication and times for pain assessments were adapted accordingly to cover the change of comparator formulation and improved scientific knowledge on cebranopadol. It was planned to offer an extension trial to subjects who completed the treatment of this trial (separate trial protocol).
16 December 2014	Protocol exclusion and discontinuation criteria on creatinine clearance were adapted based on new scientific data. Exclusion criteria were adapted to allow re-enrollment of subjects who would be eligible for the trial due to the changes made as part of this amendment or if a subject was an enrollment failure due to technical failure of equipment. The enrollment period was extended. For allowed concomitant medication and therapies, clarifications were made for chemotherapy, medications effecting the QT interval, corticosteroids and anti-emetic treatment. Further clarifications concerned history/presence of cerebral tumor, check of previous opioid medication and assessment of Child-Pugh score and DN4 questionnaire. The tests to be performed when a subject prematurely discontinues the trial were extended. The statistical sections of the protocol were aligned with the descriptions given in the statistical analysis plan. Sensitivity analyses were changed to allow for a direct comparison of the primary and sensitivity results of the primary endpoint assuming missing mechanisms. Reference to Forest Research Institute was removed as they were no longer involved in the development of cebranopadol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported