Clinical trial results:
An open-label, multi-site trial to describe the safety and tolerability of oral cebranopadol administered for 26 weeks in subjects with cancer-related pain who have completed treatment in the KF6005/07 trial

Summary

EudraCT number	2013-001877-26
Trial protocol	SE GB BE HU SK AT DE DK PL ES BG NL HR
Global end of trial date	03 May 2016

Results information

Result version number	v1 (current)
This version publication date	29 January 2017
First version publication date	29 January 2017

Trial information

Trial identification

Sponsor protocol code	KF6005/09

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1144-0778
Other trial identifiers	Grünenthal GmbH: 168935

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	GRT Trial Information Desk, Grünenthal GmbH, 0049 2415693223, clinical-trials@grunenthal.com
Scientific contact	GRT Trial Information Desk, Grünenthal GmbH, 0049 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	12 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2016
Global end of trial reached?	Yes
Global end of trial date	03 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to describe the safety and tolerability of prolonged exposure to cebranopadol in subjects suffering from cancer related pain

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. Subjects were followed-up at a regular basis with a total of 15 planned visits over 28 weeks. A final follow-up visit was planned 2 weeks after the last intake of cebranopadol Investigational Medicinal Product (IMP).

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 during treatment and until the follow-up visit (starting from the 2 weeks before enrollment into the KF6005/07 trial).
- Investigators were free to prescribe on demand medication (within limits - if not listed as forbidden medication). This medication could be used in case of unbearable or breakthrough pain according to the respective summary of product characteristics.

Evidence for comparator:

There was no comparator in this trial.

Actual start date of recruitment	18 December 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: 17
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Bulgaria: 4

Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Slovakia: 21
Worldwide total number of subjects	76
EEA total number of subjects	72

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)	43
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject was enrolled on the 18 Dec 2013 (first dose taken on the 19 Dec 2013) and the last subject completed the trial on the 03 May 2016. All subjects in this trial completed the maintenance period in the KF6005/07 trial.

Pre-assignment

Screening details:

Subjects who completed treatment in KF6005/07 and who were still in need of around-the-clock pain analgesia with strong opioids directly entered the KF6005/09 trial from the KF6005/07 trial. Seventy-six subjects (37 previously on cebranopadol and 39 subjects previously morphine treatment) were enrolled in this trial.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Subjects who completed the treatment in KF6005/07 were to start on a daily dose of 200 or 400 µg cebranopadol in the KF6005/09 trial. The treatment code from the KF6005/07 was not unblinded at the time when the subject started the cebranopadol treatment. All subjects were titrated to their optimal dose.

Arms

Arm title	Cebranopadol

Arm description:

Subjects who completed the treatment in KF6005/07 and were suitable and willing to participate in this trial went into a Titration Phase (approximately 2 weeks). During the Titration Phase, the subjects were titrated to their individual optimal daily dose of cebranopadol, defined as a balance between self-reported analgesia and side effects.

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

Dosage and administration details:

Subjects started on a cebranopadol treatment based on a predefined set of criteria. The decision on up-titration took place after 4 days of IMP use on certain dose level (exception: first dose level). Subjects were allowed to titrate up to a maximum daily dose of 1000 µg/day. Subjects were instructed to take cebranopadol orally once daily in the morning. The recommendation was to take cebranopadol between 06:00 h and 10:00 h, with a glass of water. The dose selected at the end of the Titration Phase was used during the Maintenance Phase. However, the dose could have been adjusted during the Maintenance Phase. Additionally, at any time during the trial, the dose may be discontinued for a certain period of time (e.g., because of adverse events). During the Titration Phase and the Maintenance Phase, all subjects were permitted to receive treatment for unbearable (breakthrough) pain.

Number of subjects in period 1	Cebranopadol
Started	76
Subjects completed the titration phase	67
Subjects that completed treatment	39
Completed	38
Not completed	38
Adverse event, serious fatal	10
Consent withdrawn by subject	5
withdrawn as forbidden meds required	1
Adverse event, non-fatal	8
cancer progression	2
Lost to follow-up	1
pre-specified protocol discontinuation criterion	5
Lack of efficacy	5
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	43	43	
From 65-84 years	33	33	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	61.7		
standard deviation	± 9.81	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	44	44	
Race Units: Subjects			
Asian	0	0	
Black	0	0	
White	76	76	
Height Units: meter			
arithmetic mean	1.684		
standard deviation	± 0.0844	-	
Weight Units: kilogram(s)			
arithmetic mean	72		
standard deviation	± 14.04	-	
Body Mass Index (BMI) Units: kilogram(s)/square meter			
arithmetic mean	25.36		
standard deviation	± 4.5	-	
Average pain during the last week			
The electronic case report form (eCRF) pain intensity assessment, baseline average pain intensity is the value of average pain during the last week recorded at baseline. The subject scored their average pain intensity during the last week on an 11-point Numerical Rating Scale (NRS) where a score of 0 indicated			

"no pain" and a score of 10 indicated "pain as bad as you can imagine".			
Units: units on a scale			
arithmetic mean	2.9		
standard deviation	± 1.97	-	

End points

End points reporting groups

Reporting group title	Cebranopadol

Reporting group description:

Subjects who completed the treatment in KF6005/07 and were suitable and willing to participate in this trial went into a Titration Phase (approximately 2 weeks). During the Titration Phase, the subjects were titrated to their individual optimal daily dose of cebranopadol, defined as a balance between self-reported analgesia and side effects.

Primary: Incidence of treatment emergent adverse events

End point title	Incidence of treatment emergent adverse events[1]

End point description:

The safety of cebranopadol was assessed by the number of subjects with treatment emergent adverse events (TEAEs). A TEAE was any adverse event that occurred after the first administration of IMP, i.e. cebranopadol in this trial. In addition, pretreatment adverse events which worsened during the treatment period were also considered TEAEs.

End point type	Primary

End point timeframe:

up to 28 weeks (26 weeks of cebranopadol treatment and 2 weeks follow-up after the last dose was planned per subject).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary end point for this open-label, single-arm trial was the incidence of Treatment Emergent Adverse Events during the 26 week open-label treatment period and the 2 week follow-up period. This was collected to assess long term safety on cebranopadol. No statistical testing or inference was planned on this primary objective.

End point values	Cebranopadol			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: subjects	64			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of Treatment Emergent Adverse Events

End point title	Intensity of Treatment Emergent Adverse Events

End point description:

A treatment emergent adverse event (TEAE) was any adverse event that occurred after the first administration of IMP, i.e. cebranopadol in this trial. In addition, pretreatment adverse events which worsened during the treatment period were also considered TEAEs. The "intensity" of adverse event were classified as: Mild: signs and symptoms which can be easily tolerated. Symptoms could be ignored and disappeared when the participant is distracted. Moderate: symptoms caused discomfort but were tolerable, they could not be ignored and affect concentration. Severe: symptoms affected the usual daily activity.

End point type	Secondary

End point timeframe:

up to 28 weeks (26 weeks of cebranopadol treatment)

End point values	Cebranopadol			
Subject group type	Reporting group			
Number of subjects analysed	76[2]			
Units: Events				
Mild intensity	242			
Moderate intensity	300			
Severe intensity	119			

Notes:

[2] - There were a total of 661 reported Treatment Emergent Adverse Events reported in 76 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in the average pain intensity

End point title	Changes from baseline in the average pain intensity

End point description:

The subject scored their average pain intensity during the last week on an 11-point Numerical Rating Scale (NRS) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". Absolute change from baseline for average pain intensity during the last week were summarized descriptively for all subjects that scored their pain intensities.

End point type	Secondary

End point timeframe:

Baseline Visit to Visit 14 (End of Treatment Visit) , i.e. up to 26 weeks.

End point values	Cebranopadol			
Subject group type	Reporting group			
Number of subjects analysed	59[3]			
Units: units of a scale				
arithmetic mean (standard deviation)	0.8 (± 2.14)			

Notes:

[3] - Subjects with data available.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A treatment emergent adverse event was any adverse event that occurred after the first administration of IMP, i.e. cebranopadol in this trial. In addition, pretreatment adverse events which worsened during the treatment period were also considered TEAEs.

Adverse event reporting additional description:

One subject experienced a serious non-treatment emergent adverse event preferred term "malignant neoplasm progression" before starting cebranopadol in this trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cebranopadol

Reporting group description:

Subjects who completed the treatment in KF6005/07 and were willing to participate in this trial went into a Titration Phase (approximately 2 weeks). During the Titration Phase, the subjects were titrated to their individual optimal daily dose of cebranopadol, defined as a balance between self-reported analgesia and side effects. The dose selected at the end of the Titration Phase was
used during the Maintenance Phase. However, the dose could have been adjusted during the Maintenance Phase. During the Titration Phase and the Maintenance Phase, all subjects were permitted to receive treatment for unbearable (breakthrough) pain.

Serious adverse events	Cebranopadol		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 76 (42.11%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	19 / 76 (25.00%)		
occurrences causally related to treatment / all	0 / 26		
deaths causally related to treatment / all	0 / 7		
Metastases to liver	Additional description: One of the subject's with the serious adverse event "metastases to liver" also had "malignant neoplasm progression" reported as a serious adverse event with outcome death. Thus the number of fatalities is 10.		
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Malignant melanoma			

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic thrombosis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 76 (2.63%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Adjustment disorder with depressed mood			

subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Alcohol abuse				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Concussion				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Cardiac failure				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebral infarction				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 76 (3.95%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Anaemia of malignant disease				
subjects affected / exposed	2 / 76 (2.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				

subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin lesion				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis of jaw				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Epididymitis				
subjects affected / exposed	1 / 76 (1.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 76 (1.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cebranopadol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 76 (82.89%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 76 (10.53%)		
occurrences (all)	8		
Somnolence			

subjects affected / exposed	8 / 76 (10.53%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Leukocytosis			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Leukopenia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Thrombocytopenia			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	6		
Thrombocytosis			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	10		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 76 (25.00%)		
occurrences (all)	21		
Fatigue			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	10		
Feeling drunk			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	9		
Pyrexia			

subjects affected / exposed	9 / 76 (11.84%)		
occurrences (all)	10		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 76 (14.47%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	15 / 76 (19.74%)		
occurrences (all)	18		
Vomiting			
subjects affected / exposed	8 / 76 (10.53%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	8		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Anxiety			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	7		
Nervousness			

subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 76 (10.53%)		
occurrences (all)	11		
Arthralgia			
subjects affected / exposed	8 / 76 (10.53%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	7 / 76 (9.21%)		
occurrences (all)	10		
Pain in extremity			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	5		
Infections and infestations			
Bacteriuria			
subjects affected / exposed	5 / 76 (6.58%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	4 / 76 (5.26%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	6 / 76 (7.89%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 76 (22.37%)		
occurrences (all)	21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2015	Protocol Amendment dated 06 Jan 2015. Protocol exclusion and discontinuation criteria on creatinine clearance were adapted based on new scientific data. Clarifications were made for allowed concomitant medication and therapies medications affecting the QT interval. Clarifications were made for when the Child-Pugh score has to be assessed. The time window for the Follow-up Visit was specified. Reference to Forest Research Institute was removed as they are 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