Clinical trial results:
Efficacy, safety and tolerability of multiple doses of oral cebranopadol in subjects with moderate to severe chronic pain due to diabetic peripheral neuropathy

Summary

EudraCT number	2013-000473-68
Trial protocol	AT IT NL BE ES DE DK
Global end of trial date	28 January 2015

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	KF6005/08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01939366
WHO universal trial number (UTN)	U1111-1151-4331

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	GRT Trial Information Desk, Grünenthal GmbH, +49 2415693223, Clinical-Trials@grunenthal.com
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	28 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 January 2015
Global end of trial reached?	Yes
Global end of trial date	28 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the analgesic efficacy, safety, and tolerability of once daily orally administered cebranopadol in a total of 3 fixed doses (100 µg, 300 µg, and 600 µg cebranopadol) compared to placebo in subjects with moderate to severe chronic pain due to DPN.

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 authorities were notified of the trial and amendments as required by national regulations, and where necessary relevant authorization was obtained. Furthermore, the competent authorities were notified of this trial in accordance with national requirements.

Background therapy:

Allowed concomitant treatments were:
• Anti-diabetic medication (kept stable for the duration of the trial, unless changes were medically warranted).
• Acetylsalicylic acid at oral doses equal or lower than 325 mg per day for cardiovascular prophylaxis.
• Anti-emetics and laxatives for the treatment but not for prophylaxis.
• Selective serotonin reuptake inhibitors and hypnotics including benzodiazepines and non-benzodiazepines if previously used regularly, on a stable dose, according to the Summary of Product Characteristics for at least 4 weeks prior to Enrollment Visit and planned to continue on the same dose regimen throughout the trial.
• Triptans for the treatment of migraine.
• Vitamin B12 injections.
• Inhaled steroids and topical (skin) steroids.
• Non-pharmacological pain therapies, provided that the subjects have been on that therapy for at least 4 weeks prior to the Enrollment Visit and continue to undergo therapy for the duration of the trial at the same frequency and intensity as before.
– Transcutaneous electrical nerve simulation (TENS).
– Acupuncture.
– Biofeedback.
– Chiropractic manipulation.

Paracetamol (500 mg tablets) was provided as rescue medication for unacceptable pain due to DPN, with the following exception: no rescue medication was allowed during the last 3 days before Baseline Visit. The maximum total daily dose of paracetamol was 2 g. Paracetamol should not have been taken for more than 3 consecutive days at the maximum allowed total daily dose. In addition, the use of rescue medication at the maximum allowed total daily dose was not to be exceeded for 20 days in total during the Maintenance Phase and the Follow-up Period.

Evidence for comparator:

Neuropathic pain

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.
Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.
In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.
In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score.

Actual start date of recruitment	27 September 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	Netherlands: 16
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 154
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	314
EEA total number of subjects	259

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)	181
From 65 to 84 years	133
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject signed informed consent on the 27 September 2013 and the last subject completed the trial on the 28 January 2015.

Pre-assignment

Screening details:

699 subjects signed informed consent in 82 active sites.
The main reason for a subject not being allocated to treatment was a failure to meet the inclusion/exclusion criteria (322 subjects).
13 allocated subjects from 2 sites were excluded from the SAF and FAS analyses due to CGP non-compliance; 2 more subjects were allocated but not treated.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Matching placebo and double dummy technique.

Arms

Are arms mutually exclusive?	Yes
Arm title	Matching Placebo

Arm description:

Placebo was matched to pregabalin and cebranopadol.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching cebranopadol film-coated tablets were taken once daily in the morning, placebo capsules matching over-encapsulated pregabalin were taken BID (morning and evening).

Arm title	Cebranopadol 100 µg

Arm description:

Participants randomized to 100 µg cebranopadol started with 100 µg per day and remained on 100 µg per day.

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:

Cebranopadol film-coated tablets were taken once daily in the morning.

Arm title	Cebranopadol 300 µg

Arm description:

Participants randomized to 300 µg cebranopadol started with 100 µg per day. On day 4 participants increased their dose to 300 µg per day and then remained on 300 µg per day.

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:

Cebranopadol film-coated tablets were taken once daily in the morning.

Arm title	Cebranopadol 600 µg

Arm description:

Participants randomized to 600 µg cebranopadol started with 200 µg per day and increased to 400 µg per day on day 4 and to 600 µg on day 7, thereafter they remained on 600 µg per day.

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

Dosage and administration details:

Cebranopadol film-coated tablets were taken once daily in the morning.

Arm title	Pregabalin 600 mg

Arm description:

Stepwise titration from 75 mg twice a day to 300 mg twice a day over 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pregabalin over-encapsulated capsules were taken in the morning and in the evening. In the 2-week Titration Phase, the pregabalin starting dose was 75 mg twice daily (BID) on Day 1 with an increase to 150 mg BID on Day 4, to 225 mg BID on Day 8, and to 300 mg BID on Day 12. In the Maintenance Phase, pregabalin was to be taken at the target dose of 300 mg BID but with the option to permanently reduce to 225 mg BID if not tolerated. At the end of the Maintenance Phase, the pregabalin dose was to be gradually tapered off over 1 week (150 mg BID for 4 days and 75 mg BID for 3 days).

Number of subjects in period 1	Matching Placebo	Cebranopadol 100 µg	Cebranopadol 300 µg
Started	62	64	61
Completed	48	52	41
Not completed	14	12	20
Consent withdrawn by subject	3	1	-
Adverse event, non-fatal	5	8	17
Not specified	1	-	-
Sponsor decision	2	-	-
Lost to follow-up	-	1	1
Inclusion criteria not met	-	-	1

Lack of efficacy	3	2

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Baseline characteristics

Reporting groups	
Reporting group title	Matching Placebo
Reporting group description: Placebo was matched to pregabalin and cebranopadol.	
Reporting group title	Cebranopadol 100 µg
Reporting group description: Participants randomized to 100 µg cebranopadol started with 100 µg per day and remained on 100 µg per day.	
Reporting group title	Cebranopadol 300 µg
Reporting group description: Participants randomized to 300 µg cebranopadol started with 100 µg per day. On day 4 participants increased their dose to 300 µg per day and then remained on 300 µg per day.	
Reporting group title	Cebranopadol 600 µg
Reporting group description: Participants randomized to 600 µg cebranopadol started with 200 µg per day and increased to 400 µg per day on day 4 and to 600 µg on day 7, thereafter they remained on 600 µg per day.	
Reporting group title	Pregabalin 600 mg
Reporting group description: Stepwise titration from 75 mg twice a day to 300 mg twice a day over 2 weeks.	

Reporting group values	Matching Placebo	Cebranopadol 100 µg	Cebranopadol 300 µg
Number of subjects	62	64	61
Age categorical			
Safety Set			
Units: Subjects			
Adults (18-64 years)	32	37	38
From 65-84 years	30	27	23
85 years and over	0	0	0
Age continuous			
Safety Set			
Units: years			
arithmetic mean	63.3	62.2	61.6
standard deviation	± 10.3	± 8.6	± 8.7
Gender categorical			
Safety Set			
Units: Subjects			
Female	13	20	23
Male	49	44	38
Height			
Safety Set			
Units: meter			
arithmetic mean	1.736	1.721	1.736
standard deviation	± 0.076	± 0.098	± 0.092
Weight			
Safety Set			
Units: kilogram(s)			
arithmetic mean	99	95.77	96.51

standard deviation	± 15.99	± 15.62	± 18.12
Body Mass Index (BMI)			
Safety Set			
Units: kilogram(s)/square meter			
arithmetic mean	32.8	32.3	31.87
standard deviation	± 4.53	± 4.41	± 4.39
Pain Assessment - Average 24-hour pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours." Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: average pain during the last 24 hours. Safety Set.			
Units: unit(s)			
arithmetic mean	6.84	6.92	6.8
standard deviation	± 1.15	± 1.34	± 1.37
Pain Assessment - Worst 24-hour pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: worst pain during the last 24 hours. Safety Set.			
Units: unit(s)			
arithmetic mean	7.33	7.41	7.32
standard deviation	± 1.14	± 1.36	± 1.28
Pain Assessment - Current Morning Pain			
The pain was assessed in the morning before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes how much pain you have right now". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: current pain in the morning. Safety Set.			
Units: unit(s)			
arithmetic mean	6.58	6.6	6.58
standard deviation	± 1.48	± 1.58	± 1.53
Pain Assessment - Current Evening Pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes how much pain you have right now". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: current pain in the evening. Safety Set.			
Units: unit(s)			
arithmetic mean	6.55	6.98	6.87
standard deviation	± 1.34	± 1.5	± 1.46
Diabetic Peripheral Neuropathic Pain Impact Measure (DPNPI)			
The DPNPI measure was developed at Forest Research Institute to assess the key impacts of living with painful DPN on daily and physical functioning. Three domains in the DPNPI: Physical/Mobility (8 items), Sleep (5 items), and Daily Activity (5 items) are reported as a total score (0 to 100). A lower score indicates a better health state. Full Analysis Set.			
Units: units on a scale			
arithmetic mean	57.4	59.7	56.8
standard deviation	± 18.1	± 18	± 22.1
Neuropathic Pain Symptom Inventory (NPSI)			
The NPSI is a self-administered questionnaire specifically designed for the evaluation of different neuropathic pain qualities/intensity of neuropathic pain components. The questionnaire includes a list of 10 descriptors resulting in a total score from 0 to 1. A score of 0 indicates that there are no neuropathic symptoms. A score of 1 indicates that all neuropathic symptoms are present and at their worst possible intensity.			

Full Analysis Set.			
Units: units on a scale			
arithmetic mean	0.48	0.505	0.523
standard deviation	± 0.208	± 0.203	± 0.202
Sleep Problems Index			
The Sleep Problems Index measures 3 items of the Chronic Pain Sleep Inventory (CPSI), i.e. trouble falling asleep (CPSI1), awakened by pain during the night (CPSI3) and awakened by pain in the morning (CPSI4). Each item of the CPSI is scaled separately using 100 mm visual analog scales. Higher scores indicate greater Sleep Problems. Full Analysis Set.			
Units: Units on a scale			
arithmetic mean	153.9	173.5	158.1
standard deviation	± 85.9	± 78.1	± 94.9
EuroQol-5 Dimension quality of life questionnaire			
The EQ-5D Health Questionnaire will be completed by the subjects and has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions has 5 possible levels: no, slight, moderate, severe and extreme. The index uses general population weighted estimates for various health states. In general, the range of the single weighted average index and tends to vary between 0 = death and 1 = perfect health. Full Analysis Set.			
Units: Units on a scale			
arithmetic mean	0.51	0.515	0.506
standard deviation	± 0.21	± 0.207	± 0.248

Reporting group values	Cebranopadol 600 µg	Pregabalin 600 mg	Total
Number of subjects	62	65	314
Age categorical			
Safety Set			
Units: Subjects			
Adults (18-64 years)	39	35	181
From 65-84 years	23	30	133
85 years and over	0	0	0
Age continuous			
Safety Set			
Units: years			
arithmetic mean	62.2	61.7	
standard deviation	± 8.1	± 9.9	-
Gender categorical			
Safety Set			
Units: Subjects			
Female	22	16	94
Male	40	49	220
Height			
Safety Set			
Units: meter			
arithmetic mean	1.717	1.736	
standard deviation	± 0.104	± 0.11	-
Weight			
Safety Set			
Units: kilogram(s)			
arithmetic mean	93.72	92.25	
standard deviation	± 16.05	± 17.28	-
Body Mass Index (BMI)			

Safety Set			
Units: kilogram(s)/square meter			
arithmetic mean	31.7	30.66	
standard deviation	± 4.29	± 5.26	-
Pain Assessment - Average 24-hour pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes your pain on average during the last 24 hours." Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: average pain during the last 24 hours. Safety Set.			
Units: unit(s)			
arithmetic mean	6.8	6.78	
standard deviation	± 1.25	± 1.22	-
Pain Assessment - Worst 24-hour pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes your pain at its worst during the last 24 hours". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: worst pain during the last 24 hours. Safety Set.			
Units: unit(s)			
arithmetic mean	7.38	7.32	
standard deviation	± 1.21	± 1.16	-
Pain Assessment - Current Morning Pain			
The pain was assessed in the morning before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes how much pain you have right now". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: current pain in the morning. Safety Set.			
Units: unit(s)			
arithmetic mean	6.44	6.61	
standard deviation	± 1.46	± 1.44	-
Pain Assessment - Current Evening Pain			
The pain was assessed in the evening before IMP intake. The subject was asked to answer the following question: "Please rate your pain by selecting the one number that best describes how much pain you have right now". Subject's pain assessments on an 11-point NRS (0 = no pain, 10 = pain as bad as you can imagine) using an e-diary: current pain in the evening. Safety Set.			
Units: unit(s)			
arithmetic mean	6.68	6.75	
standard deviation	± 1.33	± 1.36	-
Diabetic Peripheral Neuropathic Pain Impact Measure (DPNPI)			
The DPNPI measure was developed at Forest Research Institute to assess the key impacts of living with painful DPN on daily and physical functioning. Three domains in the DPNPI: Physical/Mobility (8 items), Sleep (5 items), and Daily Activity (5 items) are reported as a total score (0 to 100). A lower score indicates a better health state. Full Analysis Set.			
Units: units on a scale			
arithmetic mean	57.7	56.6	
standard deviation	± 21	± 18.9	-
Neuropathic Pain Symptom Inventory (NPSI)			
The NPSI is a self-administered questionnaire specifically designed for the evaluation of different neuropathic pain qualities/intensity of neuropathic pain components. The questionnaire includes a list of 10 descriptors resulting in a total score from 0 to 1. A score of 0 indicates that there are no neuropathic symptoms. A score of 1 indicates that all neuropathic symptoms are present and at their worst possible intensity. Full Analysis Set.			
Units: units on a scale			

arithmetic mean	0.49	0.491	
standard deviation	± 0.206	± 0.178	-
Sleep Problems Index			
The Sleep Problems Index measures 3 items of the Chronic Pain Sleep Inventory (CPSI), i.e. trouble falling asleep (CPSI1), awakened by pain during the night (CPSI3) and awakened by pain in the morning (CPSI4). Each item of the CPSI is scaled separately using 100 mm visual analog scales. Higher scores indicate greater Sleep Problems. Full Analysis Set.			
Units: Units on a scale			
arithmetic mean	155.9	171.6	
standard deviation	± 88.9	± 83.1	-
EuroQol-5 Dimension quality of life questionnaire			
The EQ-5D Health Questionnaire will be completed by the subjects and has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the 5 dimensions has 5 possible levels: no, slight, moderate, severe and extreme. The index uses general population weighted estimates for various health states. In general, the range of the single weighted average index and tends to vary between 0 = death and 1 = perfect health. Full Analysis Set.			
Units: Units on a scale			
arithmetic mean	0.504	0.5	
standard deviation	± 0.21	± 0.217	-

End points

End points reporting groups

Reporting group title	Matching Placebo
Reporting group description:	
Placebo was matched to pregabalin and cebranopadol.	
Reporting group title	Cebranopadol 100 µg
Reporting group description:	
Participants randomized to 100 µg cebranopadol started with 100 µg per day and remained on 100 µg per day.	
Reporting group title	Cebranopadol 300 µg
Reporting group description:	
Participants randomized to 300 µg cebranopadol started with 100 µg per day. On day 4 participants increased their dose to 300 µg per day and then remained on 300 µg per day.	
Reporting group title	Cebranopadol 600 µg
Reporting group description:	
Participants randomized to 600 µg cebranopadol started with 200 µg per day and increased to 400 µg per day on day 4 and to 600 µg on day 7, thereafter they remained on 600 µg per day.	
Reporting group title	Pregabalin 600 mg
Reporting group description:	
Stepwise titration from 75 mg twice a day to 300 mg twice a day over 2 weeks.	

Primary: Change in Average Pain Intensity

End point title	Change in Average Pain Intensity
End point description:	
Subjects will be asked to record their pain intensity in the evening. Subjects were asked to rate how much pain they had on average in the past 24 hours. The subject scored their pain intensity 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". Baseline average pain scores were calculated from the averages of all scores recorded during the 3 days prior to randomization. The average pain at week 6 will be the average pain scores calculated from all pain scores measured during week 6.	
End point type	Primary
End point timeframe:	
Baseline to End of Week 6 of the Maintenance Phase	

End point values	Matching Placebo	Cebranopadol 100 µg	Cebranopadol 300 µg	Cebranopadol 600 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	64	60	58
Units: unit(s)				
number (confidence interval 95%)				
Change in Average Pain Intensity	-1.55 (-2.1 to -1)	-2.24 (-2.78 to -1.7)	-2.28 (-2.86 to -1.71)	-2.56 (-3.2 to -1.91)

End point values	Pregabalin 600 mg			

Subject group type	Reporting group			
Number of subjects analysed	64			
Units: unit(s)				
number (confidence interval 95%)				
Change in Average Pain Intensity	-2.79 (-3.33 to -2.26)			

Statistical analyses

Statistical analysis title	Cebranopadol 100 µg versus Matching Placebo

Statistical analysis description:

The mixed model repeated measurement (MMRM) model included fixed effects of pooled sites, treatment, week, treatment-by-week interaction, baseline pain, and a subject-specific random effect. The model was based on the weekly average 24-hour pain intensity of the 2 weeks in the Titration Phase and 6 weeks in the Maintenance Phase. An unstructured covariance matrix was used to model the covariance structure, denominator degrees of freedom were estimated using the Kenward-Roger approximation.

Comparison groups	Matching Placebo v Cebranopadol 100 µg
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0621 [2]
Method	Mixed models analysis
Parameter estimate	Mixed Model Analysis
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.37

Notes:

[1] - The analysis consisted of the contrasts (mixed model Wald tests) of individual cebranopadol doses versus placebo during Week 6 of Maintenance Phase.

[2] - Due to the exploratory character of this trial, no multiple testing adjustment for control of the false positive rate was applied.

Statistical analysis title	Cebranopadol 300 µg versus Matching Placebo

Statistical analysis description:

The mixed model repeated measurement (MMRM) model included fixed effects of pooled sites, treatment, week, treatment-by-week interaction, baseline pain, and a subject-specific random effect. The model was based on the weekly average 24-hour pain intensity of the 2 weeks in the Titration Phase and 6 weeks in the Maintenance Phase. An unstructured covariance matrix was used to model the covariance structure, denominator degrees of freedom were estimated using the Kenward-Roger approximation.

Comparison groups	Matching Placebo v Cebranopadol 300 µg

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0564 [4]
Method	Mixed models analysis
Parameter estimate	Mixed Model Analysis
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[3] - The analysis consisted of the contrasts (mixed model Wald tests) of individual cebranopadol doses versus placebo during Week 6 of Maintenance Phase.
[4] - Due to the exploratory character of this trial, no multiple testing adjustment for control of the false positive rate was applied.

Statistical analysis title	Cebranopadol 600 µg versus Matching Placebo

Statistical analysis description:

The mixed model repeated measurement (MMRM) model included fixed effects of pooled sites, treatment, week, treatment-by-week interaction, baseline pain, and a subject-specific random effect. The model was based on the weekly average 24-hour pain intensity of the 2 weeks in the Titration Phase and 6 weeks in the Maintenance Phase. An unstructured covariance matrix was used to model the covariance structure, denominator degrees of freedom were estimated using the Kenward-Roger approximation.

Comparison groups	Matching Placebo v Cebranopadol 600 µg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0153 [6]
Method	Mixed Model Analysis
Parameter estimate	Mixed Model Analysis
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.41

Notes:

[5] - The analysis consisted of the contrasts (mixed model Wald tests) of individual cebranopadol doses versus placebo during Week 6 of Maintenance Phase.
[6] - Due to the exploratory character of this trial, no multiple testing adjustment for control of the false positive rate was applied.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline Visit first IMP dose (Day 1) to Visit 9 (Day 71).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Matching Placebo
Reporting group description: Placebo was matched to pregabalin and cebranopadol.	
Reporting group title	Cebranopadol 100 µg
Reporting group description: Participants randomized to 100 µg cebranopadol started with 100 µg per day and remained on 100 µg per day.	
Reporting group title	Cebranopadol 300 µg
Reporting group description: Participants randomized to 300 µg cebranopadol started with 100 µg per day. On day 4 participants increased their dose to 300 µg per day and then remained on 300 µg per day.	
Reporting group title	Cebranopadol 600 µg
Reporting group description: Participants randomized to 600 µg cebranopadol started with 200 µg per day and increased to 400 µg per day on day 4 and to 600 µg on day 7, thereafter they remained on 600 µg per day.	
Reporting group title	Pregabalin
Reporting group description: Stepwise titration from 75 mg twice a day to 300 mg twice a day over 2 weeks.	

Serious adverse events	Matching Placebo	Cebranopadol 100 µg	Cebranopadol 300 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 62 (3.23%)	1 / 64 (1.56%)	2 / 61 (3.28%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			

subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoglycaemic coma			
subjects affected / exposed	0 / 62 (0.00%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to			

subjects affected / exposed	2 / 62 (3.23%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Matching Placebo	Cebranopadol 100 µg	Cebranopadol 300 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 62 (69.35%)	47 / 64 (73.44%)	50 / 61 (81.97%)
Investigations			
Weight increase			
subjects affected / exposed	1 / 62 (1.61%)	0 / 64 (0.00%)	0 / 61 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 62 (9.68%)	8 / 64 (12.50%)	10 / 61 (16.39%)
occurrences (all)	7	9	11

Headache			
subjects affected / exposed	2 / 62 (3.23%)	3 / 64 (4.69%)	6 / 61 (9.84%)
occurrences (all)	2	3	6
Somnolence			
subjects affected / exposed	1 / 62 (1.61%)	3 / 64 (4.69%)	8 / 61 (13.11%)
occurrences (all)	1	4	8
Tremor			
subjects affected / exposed	0 / 62 (0.00%)	1 / 64 (1.56%)	1 / 61 (1.64%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 62 (3.23%)	8 / 64 (12.50%)	11 / 61 (18.03%)
occurrences (all)	2	8	11
Oedema peripheral			
subjects affected / exposed	1 / 62 (1.61%)	3 / 64 (4.69%)	3 / 61 (4.92%)
occurrences (all)	1	3	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 62 (3.23%)	0 / 64 (0.00%)	6 / 61 (9.84%)
occurrences (all)	2	0	6
Constipation			
subjects affected / exposed	2 / 62 (3.23%)	3 / 64 (4.69%)	6 / 61 (9.84%)
occurrences (all)	4	3	7
Diarrhoea			
subjects affected / exposed	5 / 62 (8.06%)	4 / 64 (6.25%)	2 / 61 (3.28%)
occurrences (all)	5	4	2
Dry mouth			
subjects affected / exposed	1 / 62 (1.61%)	1 / 64 (1.56%)	1 / 61 (1.64%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	6 / 62 (9.68%)	6 / 64 (9.38%)	22 / 61 (36.07%)
occurrences (all)	6	6	28
Vomiting			
subjects affected / exposed	2 / 62 (3.23%)	2 / 64 (3.13%)	10 / 61 (16.39%)
occurrences (all)	2	2	20
Skin and subcutaneous tissue disorders			

Hyperhidrosis			
subjects affected / exposed	2 / 62 (3.23%)	3 / 64 (4.69%)	8 / 61 (13.11%)
occurrences (all)	2	3	8
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	4 / 62 (6.45%)	1 / 64 (1.56%)	1 / 61 (1.64%)
occurrences (all)	5	1	1
Infections and infestations			
Bacteriuria			
subjects affected / exposed	6 / 62 (9.68%)	5 / 64 (7.81%)	3 / 61 (4.92%)
occurrences (all)	6	5	3
Nasopharyngitis			
subjects affected / exposed	6 / 62 (9.68%)	3 / 64 (4.69%)	1 / 61 (1.64%)
occurrences (all)	7	3	1

Non-serious adverse events	Cebranopadol 600 µg	Pregabalin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 62 (83.87%)	49 / 65 (75.38%)	
Investigations			
Weight increase			
subjects affected / exposed	0 / 62 (0.00%)	5 / 65 (7.69%)	
occurrences (all)	0	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 62 (33.87%)	12 / 65 (18.46%)	
occurrences (all)	21	18	
Headache			
subjects affected / exposed	3 / 62 (4.84%)	4 / 65 (6.15%)	
occurrences (all)	3	4	
Somnolence			
subjects affected / exposed	8 / 62 (12.90%)	3 / 65 (4.62%)	
occurrences (all)	9	4	
Tremor			
subjects affected / exposed	1 / 62 (1.61%)	4 / 65 (6.15%)	
occurrences (all)	1	5	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	10 / 62 (16.13%)	5 / 65 (7.69%)	
occurrences (all)	11	5	
Oedema peripheral			
subjects affected / exposed	1 / 62 (1.61%)	6 / 65 (9.23%)	
occurrences (all)	1	8	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 62 (0.00%)	0 / 65 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	7 / 62 (11.29%)	6 / 65 (9.23%)	
occurrences (all)	8	6	
Diarrhoea			
subjects affected / exposed	3 / 62 (4.84%)	2 / 65 (3.08%)	
occurrences (all)	3	2	
Dry mouth			
subjects affected / exposed	8 / 62 (12.90%)	1 / 65 (1.54%)	
occurrences (all)	9	1	
Nausea			
subjects affected / exposed	16 / 62 (25.81%)	6 / 65 (9.23%)	
occurrences (all)	16	6	
Vomiting			
subjects affected / exposed	17 / 62 (27.42%)	1 / 65 (1.54%)	
occurrences (all)	20	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	6 / 62 (9.68%)	1 / 65 (1.54%)	
occurrences (all)	7	1	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 62 (3.23%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bacteriuria			
subjects affected / exposed	3 / 62 (4.84%)	6 / 65 (9.23%)	
occurrences (all)	3	6	

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 62 (1.61%) 1	5 / 65 (7.69%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2013	- Introduction of an additional mandatory criterion for discontinuation in case of lack of efficacy. - Exchange of the English example of the COWS questionnaire in the appendix. - Minor corrections regarding the description of the handling of prematurely discontinued subjects, physical examination, medical history, concomitant medication, and the microscopic examination of the urine dipstick test. - Correction of the description regarding the process for generation of subject numbers.
12 December 2013	Additional mandatory criterion for the compulsory discontinuation of subjects in the UK in case of an increase in the QTcF interval of >60 ms compared to baseline.
16 January 2014	Modification of inclusion and exclusion criteria to better reflect daily clinical practice and broaden the target population.
28 July 2014	Prolongation of the subject recruitment period by 6 months which became necessary due to the slower than anticipated recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported