



## Clinical trial results:

### Efficacy, safety, and tolerability of GRT6005 in subjects with moderate to severe chronic low back pain

#### Summary

EudraCT number	2012-001920-36
Trial protocol	AT DE BE GB ES SE DK HU FI NL
Global end of trial date	10 July 2014

#### Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	26 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	KF6005/06
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01725087
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52078
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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	08 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2014
Global end of trial reached?	Yes
Global end of trial date	10 July 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this trial is to assess the analgesic efficacy, safety, and tolerability of once daily orally administered GRT6005 in a total of 3 fixed doses (i.e., 200 µg, 400 µg, and 600 µg GRT6005) compared to placebo in subjects with moderate to severe chronic LBP.

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:

Other analgesic medications (including non-steroidal anti-inflammatory drugs, cyclooxygenase II inhibitors and opioids, including long-acting formulations and combination products) except for rescue medication, paracetamol/acetaminophen were prohibited during the trial.

Paracetamol/acetaminophen (500 mg tablets) was provided as rescue medication for unacceptable pain due to chronic LBP. No rescue medication was allowed during the last 3 days before intake of first IMP. The maximum total daily dose of paracetamol/acetaminophen was 2 g during the washout phase and after allocation to treatment. Paracetamol/acetaminophen was not 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 exceed 20 days in total during the maintenance phase.

Neuroleptics, serotonin norepinephrine re-uptake inhibitors, antidepressants commonly used for the treatment of painful conditions such as tricyclic antidepressants, anticonvulsants (including  $\alpha 2\delta$ -subunit blockers including gabapentin and pregabalin), and monoamine oxidase (MAO) inhibitors were washed out for at least 3 days or 5 times their half-life and were prohibited for the remaining trial duration. Topically applied lidocaine and capsaicin were prohibited.

Evidence for comparator:

Opioid analgesics, including tapentadol have been shown to be efficacious in chronic non-malignant pain including chronic LBP and can be an important asset in the therapeutic armamentarium.

A placebo control was chosen following recommendations of the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain (CPMP/EWP/612/00) to establish the baseline frequency and magnitude of changes in clinical endpoints that may occur in the absence of treatment with an active drug substance.

Actual start date of recruitment	30 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Poland: 172
Country: Number of subjects enrolled	Spain: 93
Country: Number of subjects enrolled	Sweden: 48
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Austria: 45
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Finland: 22
Country: Number of subjects enrolled	Germany: 120
Country: Number of subjects enrolled	Hungary: 65
Worldwide total number of subjects	637
EEA total number of subjects	637

Notes:

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**Subjects enrolled per age group**

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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)	436
From 65 to 84 years	201
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First subject signed informed consent on the 30 November 2012 and the last subject completed the trial on the 10 July 2014.

### Pre-assignment

Screening details:

1090 subjects signed informed consent in 79 active sites in 11 European countries. The primary reason for subjects not being allocated to treatment were a failure to meet the inclusion criteria/exclusion criteria (347 subjects), withdrawal of informed consent (64 subjects), or the occurrence of non-treatment emergent adverse events (8 subjects)

### 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:

All IMPs were administered in a double-dummy design to maintain the blind.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Placebo tablets matching cebranopadol film coated tablets were taken once daily for 14 weeks; placebo tablets matching tapentadol PR film-coated tablets were taken twice a day for 14 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Three placebo tablets (2 matching cebranopadol [GRT6005] and 1 matching tapentadol prolonged release film-coated tablets) were taken in the morning, 1 placebo tablet matching tapentadol prolonged release film-coated tablets in the evening.

<b>Arm title</b>	Cebranopadol 200 µg
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Arm description:

Cebranopadol film-coated tablets were taken once daily at target doses of 200 µg in the maintenance phase.

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

Dosage and administration details:

Cebranopadol film-coated tablets were taken once daily at target doses of 200 µg and were maintained at this dose up to the end of the maintenance phase.

<b>Arm title</b>	Cebranopadol 400 µg
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**Arm description:**

Cebranopadol film-coated tablets were taken once daily at target doses of 400 µg in the maintenance phase.

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

**Dosage and administration details:**

Subjects assigned to 400 µg were titrated in increments of 200 µg starting with 200 µg and increasing to the target dose of 400 µg on Day 4. They were then kept on this target dose for the remainder of the 14-day titration phase and the 12-week maintenance phase.

<b>Arm title</b>	Cebranopadol 600 µg
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**Arm description:**

Cebranopadol film-coated tablets were taken once daily at target doses of 600 µg in the maintenance phase.

Arm type	Experimental
Investigational medicinal product name	Cebranopadol 600 µg
Investigational medicinal product code	GRT6005
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

Subjects assigned to 600 µg GRT6005 were titrated in increments of 200 µg starting with 200 µg and increasing stepwise to 400 µg on Day 4 and to the target dose of 600 µg on Day 7. They were then kept on this target dose during the remainder of the 14-day titration phase and the 12-week maintenance phase.

<b>Arm title</b>	Tapentadol prolonged release
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**Arm description:**

Tapentadol prolonged release (PR) film-coated tablets at doses of 50 mg, 100 mg, and 150 mg twice daily were used for titration only; the target dose was 200 mg BID.

Arm type	Active comparator
Investigational medicinal product name	Tapentadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

Tapentadol prolonged release was used with forced titration in increments of 50 mg tapentadol twice daily every 3 days in fixed steps starting with 50 mg tapentadol twice daily on Day 1. The dose was increased to 100 mg twice daily on Day 4, to 150 mg twice daily on Day 7, and to the target dose of 200 mg twice daily on Day 10. The titration phase lasted 14 days, the maintenance phase with tapentadol 200 mg daily lasted 12 weeks.

Each morning, all subjects additionally took 2 placebo tablets matching GRT6005 film-coated tablets.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg
Started	126	129	127
Completed	100	68	61
Not completed	26	61	66
Consent withdrawn by subject	3	10	4
Inclusion criteria not met/Exclusion criteria met	1	1	1
Adverse event, non-fatal	4	42	52
Not specified	3	1	4
Lost to follow-up	1	2	-
Lack of efficacy	14	5	4
Protocol deviation	-	-	1

<b>Number of subjects in period 1<sup>[1]</sup></b>	Cebranopadol 600 µg	Tapentadol prolonged release
Started	127	126
Completed	54	77
Not completed	73	49
Consent withdrawn by subject	5	6
Inclusion criteria not met/Exclusion criteria met	-	-
Adverse event, non-fatal	62	33
Not specified	2	1
Lost to follow-up	-	1
Lack of efficacy	4	8
Protocol deviation	-	-

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: 1090 subjects signed informed consent.

641 subjects were allocated to IMP.

637 subjects were dosed.

635 subjects were in the Full Analysis Set.

533 subjects were in the Per Protocol Set.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo tablets matching cebranopadol film coated tablets were taken once daily for 14 weeks; placebo tablets matching tapentadol PR film-coated tablets were taken twice a day for 14 weeks.	
Reporting group title	Cebranopadol 200 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 200 µg in the maintenance phase.	
Reporting group title	Cebranopadol 400 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 400 µg in the maintenance phase.	
Reporting group title	Cebranopadol 600 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 600 µg in the maintenance phase.	
Reporting group title	Tapentadol prolonged release
Reporting group description: Tapentadol prolonged release (PR) film-coated tablets at doses of 50 mg, 100 mg, and 150 mg twice daily were used for titration only; the target dose was 200 mg BID.	

Reporting group values	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg
Number of subjects	126	129	127
Age categorical Units: Subjects			
Adults (18-64 years)	86	85	88
From 65-84 years	40	44	39
Age continuous			
The age range was 18 to 80 years of age for this trial. The ages ranged from 22 to 79 years of age. There were no subjects older than 79 years.			
Units: years			
arithmetic mean	56.9	58	57.5
standard deviation	± 12.46	± 11.48	± 11.61
Gender categorical Units: Subjects			
Female	76	84	80
Male	50	45	47
Race Units: Subjects			
Black	0	0	0
White	126	128	127
Other	0	1	0
Treatment with opioids (including tramadol) for LBP during the 3 months prior to enrollment			
Subjects had to be on stable analgesic medications (non-opioid and/or opioid medications) for their chronic LBP with regular intake (i.e., at least 4 days per week) for at least 3 months prior to Visit 1. If subjects required opioid treatment, they must have been taking daily doses of opioid based analgesics equivalent to ≤160 mg of oral morphine.			

Units: Subjects			
No	81	84	82
Yes	45	45	45
Treatment with non-opioids for LBP during 3 months prior to enrollment			
Subjects had to be on stable analgesic medications (non-opioid and/or opioid medications) for their chronic LBP with regular intake (i.e., at least 4 days per week) for at least 3 months prior to Visit 1.			
Units: Subjects			
No	9	9	12
Yes	117	120	115
Dissatisfaction with current analgesic treatment			
Subjects must have been dissatisfied with current analgesic treatment to qualify for entry into this trial.			
Units: Subjects			
Due to inadequate analgesia	122	125	120
Due to poor tolerability	4	4	7
Quebec Task Force Classification on spinal disorders			
Subjects with pain in the lumbar area without radiation and with absence of neurologic signs were classified as QTFC 1. Subjects had pain with radiation proximally (i.e., to a lower limb, but not beyond the knee) and not accompanied by neurologic signs were classified as QTFC 2. Subjects had pain with radiation distally (i.e., beyond the knee) but without neurologic signs were classified as QTFC 3. Subjects with pain in the lumbar area with radiation to a limb and with the presence of neurologic signs were classified as QTFC 4.			
Units: Subjects			
QTF Classification 1	24	32	32
QTF Classification 2	45	44	43
QTF Classification 3	42	40	43
QTF Classification 4	15	13	9
Missing	0	0	0
Assessment of lumbar radiculopathy			
Subjects with lumbar radiculopathy were identified by an overall positive assessment of the question "The symptoms and signs are those of lumbar radiculopathy?" based on a set of questions to assess specific signs and symptoms.			
Units: Subjects			
No	51	57	54
Yes	70	69	70
Not Done	5	3	3
painDETECT assignment at baseline			
The painDETECT Pain Questionnaire was used to assess the likelihood of a neuropathic pain component.			
Units: Subjects			
positive	45	39	44
unclear	36	40	38
negative	42	48	45
missing	3	2	0
Height			
Units: meter			
arithmetic mean	1.681	1.672	1.679
standard deviation	± 0.1009	± 0.0951	± 0.1026
Weight			
Units: kilogram(s)			
arithmetic mean	80.3	80.6	80.9
standard deviation	± 14.49	± 14.83	± 16.49



Body Mass Index Units: kilogram(s)/square meter arithmetic mean standard deviation	28.37 ± 4.076	28.74 ± 4.341	28.53 ± 4.284
Baseline 24-hour pain assessment			
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. For allocation to treatment, subjects had to have an average 24-hour baseline pain of ≥5 on an 11-point numeric rating scale (NRS) during the 3 days prior to Visit 3 without the use of rescue medication.			
Units: units on a scale arithmetic mean standard deviation	7.3 ± 1.26	7.1 ± 1.17	7 ± 1.15
History of low back pain Units: Year(s) arithmetic mean standard deviation	10 ± 10.3	10.8 ± 10.93	10.6 ± 9.95

Reporting group values	Cebranopadol 600 µg	Tapentadol prolonged release	Total
Number of subjects	127	126	635
Age categorical Units: Subjects			
Adults (18-64 years)	91	85	435
From 65-84 years	36	41	200
Age continuous			
The age range was 18 to 80 years of age for this trial. The ages ranged from 22 to 79 years of age. There were no subjects older than 79 years.			
Units: years arithmetic mean standard deviation	56.9 ± 11.66	58.2 ± 11.43	-
Gender categorical Units: Subjects			
Female	94	78	412
Male	33	48	223
Race Units: Subjects			
Black	0	1	1
White	127	125	633
Other	0	0	1
Treatment with opioids (including tramadol) for LBP during the 3 months prior to enrollment			
Subjects had to be on stable analgesic medications (non-opioid and/or opioid medications) for their chronic LBP with regular intake (i.e., at least 4 days per week) for at least 3 months prior to Visit 1. If subjects required opioid treatment, they must have been taking daily doses of opioid based analgesics equivalent to ≤160 mg of oral morphine.			
Units: Subjects			
No	71	85	403
Yes	56	41	232
Treatment with non-opioids for LBP during 3 months prior to enrollment			
Subjects had to be on stable analgesic medications (non-opioid and/or opioid medications) for their chronic LBP with regular intake (i.e., at least 4 days per week) for at least 3 months prior to Visit 1.			
Units: Subjects			
No	12	15	57

Yes	115	111	578
Dissatisfaction with current analgesic treatment			
Subjects must have been dissatisfied with current analgesic treatment to qualify for entry into this trial.			
Units: Subjects			
Due to inadequate analgesia	122	118	607
Due to poor tolerability	5	8	28
Quebec Task Force Classification on spinal disorders			
<p>Subjects with pain in the lumbar area without radiation and with absence of neurologic signs were classified as QTFC 1.</p> <p>Subjects had pain with radiation proximally (i.e., to a lower limb, but not beyond the knee) and not accompanied by neurologic signs were classified as QTFC 2.</p> <p>Subjects had pain with radiation distally (i.e., beyond the knee) but without neurologic signs were classified as QTFC 3.</p> <p>Subjects with pain in the lumbar area with radiation to a limb and with the presence of neurologic signs were classified as QTFC 4.</p>			
Units: Subjects			
QTF Classification 1	20	40	148
QTF Classification 2	54	38	224
QTF Classification 3	35	35	195
QTF Classification 4	17	13	67
Missing	1	0	1
Assessment of lumbar radiculopathy			
Subjects with lumbar radiculopathy were identified by an overall positive assessment of the question "The symptoms and signs are those of lumbar radiculopathy?" based on a set of questions to assess specific signs and symptoms.			
Units: Subjects			
No	46	63	271
Yes	77	59	345
Not Done	4	4	19
painDETECT assignment at baseline			
The painDETECT Pain Questionnaire was used to assess the likelihood of a neuropathic pain component.			
Units: Subjects			
positive	42	43	213
unclear	36	35	185
negative	47	43	225
missing	2	5	12
Height			
Units: meter			
arithmetic mean	1.658	1.664	
standard deviation	± 0.0958	± 0.1015	-
Weight			
Units: kilogram(s)			
arithmetic mean	76.8	80.6	
standard deviation	± 14.15	± 15	-
Body Mass Index			
Units: kilogram(s)/square meter			
arithmetic mean	27.9	28.99	
standard deviation	± 4.078	± 3.862	-
Baseline 24-hour pain assessment			
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. For allocation to treatment, subjects had to have an average 24-hour baseline pain of ≥5 on an 11-point numeric rating scale (NRS) during the 3 days prior to Visit 3 without the use of rescue medication.			

Units: units on a scale arithmetic mean standard deviation	7.2 ± 1.12	7 ± 1.15	-
History of low back pain Units: Year(s) arithmetic mean standard deviation	10.8 ± 10.82	10.6 ± 9.82	-

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo tablets matching cebranopadol film coated tablets were taken once daily for 14 weeks; placebo tablets matching tapentadol PR film-coated tablets were taken twice a day for 14 weeks.	
Reporting group title	Cebranopadol 200 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 200 µg in the maintenance phase.	
Reporting group title	Cebranopadol 400 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 400 µg in the maintenance phase.	
Reporting group title	Cebranopadol 600 µg
Reporting group description: Cebranopadol film-coated tablets were taken once daily at target doses of 600 µg in the maintenance phase.	
Reporting group title	Tapentadol prolonged release
Reporting group description: Tapentadol prolonged release (PR) film-coated tablets at doses of 50 mg, 100 mg, and 150 mg twice daily were used for titration only; the target dose was 200 mg BID.	

### Primary: Change from baseline pain to the weekly average 24-hour pain (NRS) during the entire 12 weeks of maintenance phase

End point title	Change from baseline pain to the weekly average 24-hour pain (NRS) during the entire 12 weeks of maintenance phase
End point description: For the EU and other non-US marketing authorization region the change from baseline to the weekly average 24-hour pain (NRS) during the entire 12 weeks of the maintenance phase was defined as the primary endpoint. Pain was assessed between 19:00 and 22:00 before IMP intake. The subjects were asked via e-diary to answer the following question: "Please rate your pain by selecting the number that best describes your pain on average during the last 24 hours." The 11-point NRS (Numeric Rating Scale) was used where subjects rated their average pain intensity from 0 [no pain] to 10 [pain as bad as you can imagine].	
End point type	Primary
End point timeframe: Baseline up to end of Maintenance phase (14 weeks)	

End point values	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg	Cebranopadol 600 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	122	120	117
Units: units on the Numeric Rating Scale				
number (confidence interval 95%)	-1.97 (-2.34 to -1.6)	-2.52 (-2.9 to -2.13)	-2.67 (-3.08 to -2.27)	-2.89 (-3.32 to -2.46)

<b>End point values</b>	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: units on the Numeric Rating Scale				
number (confidence interval 95%)	-2.71 (-3.09 to -2.33)			

## Statistical analyses

<b>Statistical analysis title</b>	MMRM 200 µg cebranopadol compared to placebo
Statistical analysis description:	
The primary end point was analysed by means of a mixed-effects model for repeated measures (MMRM) with the fixed effects of pooled sites, treatment, time, treatment-by-time interaction, and baseline pain, and used a random intercept. The primary analysis consisted of the contrasts (i.e. mixed model Wald tests) of the individual cebranopadol doses with placebo. To control the family-wise error rate, a gatekeeping and Hochberg multiple comparison procedure was used.	
Comparison groups	Cebranopadol 200 µg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0346 <sup>[1]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[1] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 200 µg and Placebo was performed and considered statistically significant.

<b>Statistical analysis title</b>	MMRM 400 µg cebranopadol compared to placebo
Statistical analysis description:	
The primary end point was analysed by means of a mixed-effects model for repeated measures (MMRM) with the fixed effects of pooled sites, treatment, time, treatment-by-time interaction, and baseline pain, and used a random intercept. The primary analysis consisted of the contrasts (i.e. mixed model Wald tests) of the individual cebranopadol doses with placebo. To control the family-wise error rate, a gatekeeping and Hochberg multiple comparison procedure was used.	
Comparison groups	Cebranopadol 400 µg v Placebo

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0084 <sup>[2]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[2] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 400 µg and Placebo was performed and considered statistically significant.

<b>Statistical analysis title</b>	MMRM 600 µg cebranopadol compared to placebo
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Statistical analysis description:

The primary end point was analysed by means of a mixed-effects model for repeated measures (MMRM) with the fixed effects of pooled sites, treatment, time, treatment-by-time interaction, and baseline pain, and used a random intercept. The primary analysis consisted of the contrasts (i.e. mixed model Wald tests) of the individual cebranopadol doses with placebo. To control the family-wise error rate, a gatekeeping and Hochberg multiple comparison procedure was used

Comparison groups	Cebranopadol 600 µg v Placebo
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 <sup>[3]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.28

Notes:

[3] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 600 µg and Placebo was performed and considered statistically significant.

### **Primary: Change from baseline to the average 24-hour pain (NRS) during Week 12 of the maintenance phase**

End point title	Change from baseline to the average 24-hour pain (NRS) during Week 12 of the maintenance phase
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End point description:

For the US marketing authorization region the change from baseline to the weekly average 24-hour pain (NRS) during week 12 of the maintenance phase was defined as the primary endpoint. Pain was assessed between 19:00 and 22:00 before IMP intake. The subjects were asked via e-diary to answer the following question: "Please rate your pain by selecting the number that best describes your pain on average during the last 24 hours." The 11-point NRS (Numeric Rating Scale) was used where subjects rated their average pain intensity from 0 [no pain] to 10 [pain as bad as you can imagine].

End point type	Primary
End point timeframe:	
Baseline up to end of maintenance phase (14 weeks)	

End point values	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg	Cebranopadol 600 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	122	120	117
Units: units on the Numeric Rating Scale				
number (confidence interval 95%)	-2.16 (-2.58 to -1.74)	-2.95 (-3.41 to -2.5)	-2.95 (-3.44 to -2.47)	-3.18 (-3.7 to -2.66)

End point values	Tapentadol prolonged release			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: units on the Numeric Rating Scale				
number (confidence interval 95%)	-3.05 (-3.5 to -2.6)			

## Statistical analyses

Statistical analysis title	MMRM cebranopadol 200 µg compared to placebo
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Statistical analysis description:

The primary end point was analysed by means of a mixed-effects model for repeated measures (MMRM) with the fixed effects of pooled sites, treatment, time, treatment-by-time interaction, and baseline pain, and used a random intercept. The primary analysis consisted of the contrasts (i.e. mixed model Wald tests) of the individual cebranopadol doses with placebo. To control the family-wise error rate, a gatekeeping and Hochberg multiple comparison procedure was used.

Comparison groups	Cebranopadol 200 µg v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0095 <sup>[4]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[4] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 200 µg and Placebo was performed and considered statistically significant.

<b>Statistical analysis title</b>	MMRM cebranopadol 400 µg compared to placebo
Statistical analysis description:	
The primary end point was analysed by means of a mixed-effects model for repeated measures (MMRM) with the fixed effects of pooled sites, treatment, time, treatment-by-time interaction, and baseline pain, and used a random intercept. The primary analysis consisted of the contrasts (i.e. mixed model Wald tests) of the individual cebranopadol doses with placebo. To control the family-wise error rate, a gatekeeping and Hochberg multiple comparison procedure was used.	
Comparison groups	Cebranopadol 400 µg v Placebo
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122 <sup>[5]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.41
upper limit	-0.17
Variability estimate	Standard error of the mean
Dispersion value	0.32

Notes:

[5] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 400 µg and Placebo was performed and considered statistically significant.

<b>Statistical analysis title</b>	MMRM cebranopadol 600 µg compared to placebo
Comparison groups	Cebranopadol 600 µg v Placebo
Number of subjects included in analysis	242
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0021 <sup>[6]</sup>
Method	MMRM
Parameter estimate	MMRM
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.67
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[6] - Following the gatekeeping and Hochberg multiple comparison procedure the comparison between Cebranopadol 600 µg and Placebo was performed and considered statistically significant.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events (TEAEs) are defined as any Adverse Event that occurred after first intake of Investigational Medicinal Product (IMP) up to the last follow-up contact/visit (i.e. up to 14 days after last IMP intake).

Adverse event reporting additional description:

A TEAE is defined as any AE that occurred on or after the first intake of IMP. In addition, pre-treatment AEs which worsen during the treatment period are also considered TEAEs.

Investigator rated causalities reported: Certain, Probable/Likely, Possible reported as being causally related to treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

### Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Cebranopadol 200 µg
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Reporting group description: -

Reporting group title	Cebranopadol 400 µg
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Reporting group description: -

Reporting group title	Cebranopadol 600 µg
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Reporting group description: -

Reporting group title	Tapentadol prolonged release
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Reporting group description: -

Serious adverse events	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 126 (1.59%)	3 / 130 (2.31%)	4 / 127 (3.15%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lentigo maligna			

subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (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
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (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
Cardiac failure			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (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
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 126 (0.79%)	0 / 130 (0.00%)	0 / 127 (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
Chest discomfort			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland calculus			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	1 / 127 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 126 (0.79%)	0 / 130 (0.00%)	0 / 127 (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
Pancreatitis acute			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (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
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (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
Metabolism and nutrition disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 130 (0.77%)	0 / 127 (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

<b>Serious adverse events</b>	Cebranopadol 600 µg	Tapentadol prolonged release	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 128 (1.56%)	3 / 126 (2.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lentigo maligna			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 128 (0.78%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			

subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 128 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (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			
Hepatic steatosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Cebranopadol 200 µg	Cebranopadol 400 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 126 (63.49%)	107 / 130 (82.31%)	105 / 127 (82.68%)
Vascular disorders			
Chills			
subjects affected / exposed	0 / 126 (0.00%)	0 / 130 (0.00%)	0 / 127 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 126 (8.73%)	34 / 130 (26.15%)	42 / 127 (33.07%)
occurrences (all)	11	39	48
Somnolence			
subjects affected / exposed	6 / 126 (4.76%)	24 / 130 (18.46%)	25 / 127 (19.69%)
occurrences (all)	6	26	27
Disturbance in attention			
subjects affected / exposed	0 / 126 (0.00%)	4 / 130 (3.08%)	5 / 127 (3.94%)
occurrences (all)	0	4	5
Headache			
subjects affected / exposed	11 / 126 (8.73%)	14 / 130 (10.77%)	15 / 127 (11.81%)
occurrences (all)	17	14	21
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 126 (2.38%)	13 / 130 (10.00%)	21 / 127 (16.54%)
occurrences (all)	3	15	22
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 126 (6.35%)	29 / 130 (22.31%)	38 / 127 (29.92%)
occurrences (all)	8	36	47
Vomiting			
subjects affected / exposed	5 / 126 (3.97%)	19 / 130 (14.62%)	19 / 127 (14.96%)
occurrences (all)	5	23	24
Constipation			
subjects affected / exposed	5 / 126 (3.97%)	18 / 130 (13.85%)	21 / 127 (16.54%)
occurrences (all)	6	18	22
Abdominal pain upper			

subjects affected / exposed occurrences (all)	7 / 126 (5.56%) 7	8 / 130 (6.15%) 8	6 / 127 (4.72%) 7
Dry mouth subjects affected / exposed occurrences (all)	3 / 126 (2.38%) 3	3 / 130 (2.31%) 3	7 / 127 (5.51%) 7
Respiratory, thoracic and mediastinal disorders Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 126 (9.52%) 12	8 / 130 (6.15%) 8	3 / 127 (2.36%) 3
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	11 / 130 (8.46%) 13	17 / 127 (13.39%) 18
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	6 / 130 (4.62%) 6	4 / 127 (3.15%) 4

<b>Non-serious adverse events</b>	Cebranopadol 600 µg	Tapentadol prolonged release	
Total subjects affected by non-serious adverse events subjects affected / exposed	115 / 128 (89.84%)	98 / 126 (77.78%)	
Vascular disorders Chills subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 2	9 / 126 (7.14%) 9	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	62 / 128 (48.44%) 69	36 / 126 (28.57%) 45	
Somnolence subjects affected / exposed occurrences (all)	21 / 128 (16.41%) 23	18 / 126 (14.29%) 18	
Disturbance in attention subjects affected / exposed occurrences (all)	5 / 128 (3.91%) 6	7 / 126 (5.56%) 7	
Headache			



subjects affected / exposed occurrences (all)	11 / 128 (8.59%) 16	10 / 126 (7.94%) 12	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	21 / 128 (16.41%) 21	18 / 126 (14.29%) 22	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)  Constipation subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Dry mouth subjects affected / exposed occurrences (all)	46 / 128 (35.94%) 48  31 / 128 (24.22%) 35  23 / 128 (17.97%) 24  4 / 128 (3.13%) 4  3 / 128 (2.34%) 4	33 / 126 (26.19%) 44  15 / 126 (11.90%) 16  22 / 126 (17.46%) 23  7 / 126 (5.56%) 7  14 / 126 (11.11%) 14	
Respiratory, thoracic and mediastinal disorders Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 128 (4.69%) 6	12 / 126 (9.52%) 13	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	10 / 128 (7.81%) 11	12 / 126 (9.52%) 13	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 128 (4.69%) 6	8 / 126 (6.35%) 8	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2013	<ul style="list-style-type: none"><li>• Discontinuation criterion "Subject did not meet inclusion/exclusion criteria": Criterion was changed from compulsory to optional discontinuation, to allow case-by-case decisions and avoid compulsory withdrawal of subjects when there is no impact on safety and tolerability and on integrity and reliability of data.</li><li>• Specification of individual exclusion criteria and discontinuation criteria for: hepatic impairment, hepatitis, QT prolongation and ECG reading, previous invasive procedures aimed at reducing low back pain.</li><li>• painDETECT exclusion criterion wording was changed to better explain that this only applies when the maximum number of subjects in the stratification subgroup has been reached.</li><li>• Inconsistencies and errors were corrected and clarifications or references added that did not change the content of the original protocol.</li></ul>
15 November 2013	Based on the availability of new data on GRT6005 regarding subjects with impaired renal function, the exclusion criterion was adapted to lower the cut-off value for creatinine clearance. Additionally, it was allowed to re-enroll subjects who failed enrollment in this trial only because of the exclusion criteria that were changed in Amendment 01 and Amendment 02, but for no other reason, and who may be eligible after the implementation of these amendments. Further changes were implemented in order to correct or clarify statements in the protocol.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported