Supplementary material 01

Inclusion Criteria

Inclusion criteria	Exclusion Criteria
Subjects eligible for enrolment in the study had to meet all of the following criteria: 1. Subjects who were willing to provide voluntary written informed consent. 2. Male and female (post-menopausal or surgically-sterile) subjects aged ≥ 18 and ≤ 75 years (≥ 18 and ≤ 65 years in India only). 3. Subjects with diabetes mellitus (Type 1 or 2) with distal symmetric chronic sensorimotor painful peripheral neuropathy. 4. A history of pain for at least 6 months and no greater than 5 years attributed to DPN (this requirement refers to duration of pain, not the duration of DPN). 5. A Douleur Neuropathique en 4 questions (DN4) score of ≥ 4. 6. A baseline 24-hour API score ≥ 4 and < 9 measured on an 11-point pain intensity NRS. Note 1: The baseline score was calculated as the mean of the 24-hour daily average pain scores during the 7 days prior to randomization. Note 2: Because some early versions of the protocol specified baseline 24-hour API score ≥ 5, a limited number of subjects who had a baseline 24-hour API score ≥ 4 and < 5 were permitted to undergo rescreening using the baseline 24-hour API score criteria of ≥ 4 and < 9 in the final version of the protocol (see Figure 2 and Appendix 16.1.1). 7. Pain uncontrolled with up to a maximum of 2 medications for the treatment of pain associated with DPN. The subject's medical history could indicate that the pain was not controlled with: • 1 medication for painful DPN; or • 2 medications for painful DPN taken over different time-periods in the past; or • 2 medications for painful DPN taken over the same time periods in the past (ie., combination therapy using 2 drugs). 8. Subjects were willing to discontinue their neuropathy medications for the duration of study	1. Subjects with a 24-hour daily API of ≥ 9 on the 11-point NRS at Visit 1 or Visit 3. 2. Other chronic pain conditions not associated with DPN that could confound the assessment of neuropathic pain. The subject was not excluded if the pain condition was located at a different region of the body (other than lower limbs); the pain intensity of the condition was not greater than the pain intensity of DPN; and the subject could assess pain due to DPN independently of the other pain condition. 3. Subjects with other causes of neuropathy or lower extremity pain which may include, but was not limited to: • Lower extremity pain of any severity caused by osteoarthritis of the ankle or foot, gout, bursitis, or fasciitis. • Past medical history or known current medical condition of diffuse peripheral neuropathy caused by alcoholism, malignancy, human immunodeficiency virus (HIV), syphilis, drug abuse, peripheral ischaemia, Vitamin B12 deficiency, abnormal folate, hypothyroidism, liver disease, chemotherapy, or radiation therapy. Subjects with folate or vitamin B12 levels below the laboratory reference range or thyroid stimulating hormone (TSH) level above the laboratory reference range were excluded. • Focal neuropathy in the lower extremities including nerve entrapment or local trauma • Acute or chronic inflammatory polyradiculopathy. • Multiple sclerosis or other conditions associated with central neuropathic pain. • Pain associated with distal limb ischaemia including intermittent claudication.

beginning with the washout period and continuing through the end of study visit (Visit 8).
9. For subjects with a glycosylated haemoglobin (HbA1c) value < 8%, stable glycaemic control for 3 months before randomization defined by:

- Insulin: < 25% change in the mean current insulin dose to maintain glycaemic control.
- Oral antidiabetic agents: < 50% change in the current oral dose to maintain glycaemic control.
- Addition of up to 1 oral hypoglycaemic agent at its therapeutic dose to the existing treatment regimen.

For subjects with an HbA1c between 8% and 11%, diabetic regimens could be changed after randomization to maintain glycaemic control. Subjects received guideline-based diabetes control that was individually adapted to his/her comorbidity and risk profile.
10. Subjects determined to have mechanical hyperalgesia and/or cold allodynia on the basis of appropriate methodology. (A limited randomization of at least 38 subjects with either mechanical hyperalgesia and/or cold allodynia was planned.)
11. Women of non-child bearing potential who were post-menopausal or surgically sterile. Menopause was defined as 12 months of spontaneous amenorrhea with a serum follicular stimulating hormone (FSH) level >40 mIU/mL. Surgically sterile was defined by a documented hysterectomy and/or bilateral oophorectomy at least 6 weeks before screening. Documented tubal ligation did not meet the definition of surgically sterile.
12. Male subjects who agreed to use an acceptable form of contraception from the first dose of study medication until 90 days after the last dose of study medication. All sexually active males must agree to use a condom and meet at least 1 of the following conditions:

- Had a vasectomy for greater than 6 months;
- Had a female partner who met 1 of the following conditions: has had a bilateral tubal ligation, hysterectomy, or bilateral

4. Subjects with complex regional pain syndrome or trigeminal neuralgia.
5. Use of the following medications within 7 days of Visit 2 (the baseline pain intensity assessment):

- Antidepressants, anticonvulsants or mexiletine (exceptions: fluvoxamine, norfluoxetine, nefazodone, carbamazepine, barbiturates, phenytoin and oxcarbazepine as subjects on these medications at screening were excluded).
- Opioids or morphinomimetics
- Fatty acid supplements, primrose oil, myoinositol, chromium picolinate, alpha-lipoic acid, benfotiamine, and actovegin that are known to be used in neuropathic pain.
- Acetyl salicylic acid except up to 325 mg/day for myocardial infarction or transient ischaemic attack prophylaxis.
- Benzodiazepines other than indicated at low doses for sleep disorders.
- Lidocaine patch.
- Non-drug therapies or procedures (i.e. nerve blocks, trans-cutaneous electrical nerve stimulation [TENS]) for the relief of pain of DPN.

6. Use of herbal medication or supplements, St. John's wort, or grapefruit juice (more than 0.9 L/day) within 3 weeks prior to Visit 2.
7. Use of a capsaicin patch within 3 months before Screening.
8. Had a diabetic foot ulcer of ≤ 3 months duration. Subjects with a diabetic foot ulcer with > 3 months duration were included in the study only if the ulcer was stable for a period of at least 3 months prior to Screening.
9. Had a lower extremity amputation other than toes.
10. Had any of the following laboratory abnormalities, medical conditions, or disorders:

- Alanine aminotransferase (ALT) > 1.5x upper limit of normal (ULN) or direct bilirubin > 1.5x ULN.
- Chronic hepatitis B or C with a positive Hepatitis B surface antigen (HBsAg) or Hepatitis C core antigen antibody.
- Serum creatinine >150 µmol/L

oophorectomy; was post-menopausal; or used one of the following forms of contraception: • Consistent use of oral, injected, or implanted hormonal methods of contraception. • Placement of intra-uterine device (IUD) or intra-uterine system (IUS). • Barrier methods only when used with spermicidal foam/gel/film/cream or suppository. Barrier methods such as condom or occlusive cap (diaphragm or cervical/vault caps) were acceptable. 13. Male subjects (including those who had vasectomies) whose partners were pregnant agreed to use condoms from the first dose of study medication and until 90 days after last dose of study medication.	• Corrected QT (QTcP) interval of > 430 msec in males or > 450 msec in females. Note: A limited number of subjects who did not meet the QTc criteria (corrected by Bazett's method) in earlier version of the protocol were permitted to undergo rescreening in later versions of the protocol using Pfeufer's method of QT correction. • Uncontrolled hypertension at screening (sitting systolic BP > 160 mm Hg or sitting diastolic BP > 90 mm Hg). • Current diagnosis of active epilepsy or any active seizure disorder requiring chronic therapy with antiepileptic drugs. • Patients with clinically significant or uncontrolled hepatic, gastrointestinal, cardiovascular, respiratory, neurological (other than neuropathy), psychiatric, hematological, renal, or dermatological disease, or any other medical condition that could, in the Investigator's medical judgment, interfere with the accurate assessment of safety or efficacy or could potentially affect a subject's safety or study outcome. 11. Had participated in another study with an investigational compound within 90 days prior to study medication administration, or concurrent participation in another clinical study. 12. Had major depression. 13. Presence or history of cancer in the past 5 years with the exception of adequately treated, localised basal cell skin cancer or in situ uterine cervical cancer. 14. HbA1c value > 11%. 15. Subjects taking strong or moderate inhibitors of cytochrome P450 CYP3A4 including oral/systemic ketoconazole, itraconozole, miconazole, clotrimazole, fluconazole, posaconazole, voriconazole, clarithromycin, erythromycin, ciprofloxacin, telithromycin, norfloxacin, chloramphenicol, fluvoxamine, norfluoxetine, nefazodone, verapamil, diltiazem, indinavir, nelfinavir, saquinavir, ritonavir, amprenavir, lopinavir, atazanavir, darunavir, aprepitant, and cyclosporine.

	16. Subjects taking inducers of CYP3A4, including rifabutin, rifampin, pioglitazone, carbamazepine, dexamethasone, barbiturates, phenytoin, and oxcarbazepine. 17. Subjects taking statins who had abnormal creatine kinase (CK) levels and subjects receiving combination therapy of statin with fibrate or statin with niacin. Subjects taking statins who had normal CK levels could be enrolled but were advised to maintain a stable lifestyle throughout the study, with no intensive physical activity. 18. Had undergone gastrointestinal surgery that could affect absorption of the investigational product (eg, bariatric surgery). 19. Had contraindications to rescue medications. 20. Had a history of human immunodeficiency virus (HIV) exposure.

EU Clinical Trials Register

Clinical trial results:
A Phase 2, 4 Week Randomized, Double-Blind, Parallel Group, Placebo Controlled Proof of Concept Study to Evaluate Efficacy, Safety and Tolerability of GRC 17536 in Patients with Painful Diabetic Peripheral Neuropathy

These results have been removed from public view whilst they are reviewed and may need to be corrected before being returned to public view

Summary

EudraCT number	2012-002320-33
Trial protocol	DE GB CZ
Global end of trial date	23 July 2014

Results information

Result version number	v1
This version publication date	24 July 2015
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	GRC 17536-203

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Glenmark Pharmaceuticals S.A
Sponsor organisation address	Chemin de la Combeta, 5, Ch-2300 , La Chaux-de-fonds, Switzerland,
Public contact	Dr. Shailendra Sachan, Glenmark Pharmaceuticals S.A, +91 2267720000, Shailendra.Sachan@glenmarkpharma.com
Scientific contact	Dr. Monika Tandon, Glenmark Pharmaceuticals S.A, +91 2267720000, Monika.Tandon@glenmarkpharma.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	04 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2014
Global end of trial reached?	Yes
Global end of trial date	23 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of GRC 17536 in the treatment of pain associated with diabetic peripheral neuropathy

Protection of trial subjects:

In the interests of subject safety and acceptable standards of medical care the Investigator was permitted to prescribe treatment(s) at his/her discretion. All treatments taken by the subjects during the study were recorded in the subjects' CRF (medication, dose, treatment duration and indication).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2012
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	Czech Republic: 18
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	India: 114
Worldwide total number of subjects	138
EEA total number of subjects	24

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)	126
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first patient enrollment: 20 Dec 2012
Date of last patient completed: 23 Jul 2014
Countries: Czech Republic, Germany, India

Pre-assignment

Screening details:

Screening period:2-week screening and washout period, Patients with painful diabetic peripheral neuropathy

Period 1

Period 1 title	GRC 17536 Vs Placebo (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GRC 17536 250 mg

Arm description:

GRC 17536 250 mg administered BID orally for 28 days.

Arm type	Experimental
Investigational medicinal product name	GRC 17536 250 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

GRC 17536 250 mg administered orally, BID, for 28 days.

Arm title	Placebo

Arm description:

Placebo to match investigational product, administered BID orally for 28 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Placebo administered BID orally for 28 days.

Number of subjects in period 1	GRC 17536 250 mg	Placebo	
Started	72	66	
Completed	64	61	
Not completed	8	5	
Protocol deviation	1	-	
Physician decision	2	-	
Adverse event, non-fatal	1	-	
Subject withdrawal	4	5	

Baseline characteristics

Reporting groups	
Reporting group title	GRC 17536 250 mg
Reporting group description:	
GRC 17536 250 mg administered BID orally for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match investigational product, administered BID orally for 28 days.	

Reporting group values	GRC 17536 250 mg	Placebo	Total
Number of subjects	72	66	138
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18-75 years)	72	66	138
Age continuous Units: years			
arithmetic mean	56.07	56.11	
standard deviation	± 8.57	± 8.53	-
Gender categorical Units: Subjects			
Female	19	23	42
Male	53	43	96

Subject analysis sets	
Subject analysis set title	GRC 17536 250 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1. Intent-to-Treat (ITT) population was defined as all randomized subjects with non-missing API score at baseline, who received at least 1 dose of randomized study medication, and had an API score from at least 1 post-baseline visit (inclusive of 4 days of data). 2. Exploratory analysis was performed in the non-denervation group with moderate to severe pain [ITT population excluding subjects with a baseline mean 24-hour API score <5 based on NRS and excluding subjects with cold detection threshold (CDT) <18°C and/or warm detection threshold (WDT) >49°C]	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1. Intent-to-Treat (ITT) population was defined as all randomized subjects with non-missing API score at	

baseline, who received at least 1 dose of randomized study medication, and had an API score from at least 1 post-baseline visit (inclusive of 4 days of data).

2. Exploratory analysis was performed in the non-denervation group with moderate to severe pain [ITT population excluding subjects with a baseline mean 24-hour API score <5 based on NRS and excluding subjects with cold detection threshold (CDT) <18°C and/or warm detection threshold (WDT) >49°C]

Reporting group values	GRC 17536 250 mg	Placebo	
Number of subjects	70	66	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (18-75 years)	70	66	
Age continuous Units: years			
arithmetic mean	55.03	57.29	
standard deviation	± 9.46	± 7.5	
Gender categorical Units: Subjects			
Female	19	23	
Male	51	43	

End points

End points reporting groups

Reporting group title	GRC 17536 250 mg
Reporting group description:	
GRC 17536 250 mg administered BID orally for 28 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo to match investigational product, administered BID orally for 28 days.	
Subject analysis set title	GRC 17536 250 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1. Intent-to-Treat (ITT) population was defined as all randomized subjects with non-missing API score at baseline, who received at least 1 dose of randomized study medication, and had an API score from at least 1 post-baseline visit (inclusive of 4 days of data). 2. Exploratory analysis was performed in the non-denervation group with moderate to severe pain [ITT population excluding subjects with a baseline mean 24-hour API score <5 based on NRS and excluding subjects with cold detection threshold (CDT) <18°C and/or warm detection threshold (WDT) >49°C]	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1. Intent-to-Treat (ITT) population was defined as all randomized subjects with non-missing API score at baseline, who received at least 1 dose of randomized study medication, and had an API score from at least 1 post-baseline visit (inclusive of 4 days of data). 2. Exploratory analysis was performed in the non-denervation group with moderate to severe pain [ITT population excluding subjects with a baseline mean 24-hour API score <5 based on NRS and excluding subjects with cold detection threshold (CDT) <18°C and/or warm detection threshold (WDT) >49°C]	

Primary: Change from baseline to end of treatment (week 4) in the mean 24-hour average pain intensity (API) score

End point title	Change from baseline to end of treatment (week 4) in the mean 24-hour average pain intensity (API) score
End point description:	
End point type	Primary
End point timeframe:	
4 weeks	

End point values	GRC 17536 250 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	66		
Units: number				
least squares mean (confidence interval 95%)	-1.94 (-2.32 to -1.56)	-1.68 (-2.07 to -1.29)		

Statistical analyses

Statistical analysis title	Statistical Analysis of Primary Efficacy Endpoint
Comparison groups	GRC 17536 250 mg v Placebo
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.28

Notes:

[1] - ANCOVA

Other pre-specified: Exploratory Analysis – Change from baseline to end of treatment (week 4) in the mean 24-hour average pain intensity (API) score (in non-denervation group with moderate to severe pain)

End point title	Exploratory Analysis – Change from baseline to end of treatment (week 4) in the mean 24-hour average pain intensity (API) score (in non-denervation group with moderate to severe pain)

End point description:

Change from baseline to end of treatment (week 4) in the mean 24-hour average pain intensity (API) score in the non-denervation group with moderate to severe pain (ITT population excluding subjects with a baseline mean 24-hour API score <5 based on NRS and excluding subjects with CDT <18°C and/or WDT >49°C)

End point type	Other pre-specified

End point timeframe:

Week 4

End point values	GRC 17536 250 mg	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	35		
Units: Number				
least squares mean (confidence interval 95%)	-2.48 (-3.01 to -1.95)	-1.52 (-2 to -1.04)		

Statistical analyses

Statistical analysis title	Exploratory Analysis
Comparison groups	GRC 17536 250 mg v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	Mixed models analysis

Parameter estimate	Mean difference (final values)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	-0.24

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 9 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	GRC 17536 250 mg
Reporting group description: GRC 17536 250 mg administered BID orally for 28 days.	
Reporting group title	Placebo
Reporting group description: Placebo administered BID orally for 28 days.	

Serious adverse events	GRC 17536 250 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (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	GRC 17536 250 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 72 (31.94%)	25 / 66 (37.88%)	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	

occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	2 / 72 (2.78%)	0 / 66 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 66 (3.03%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	
occurrences (all)	1	1	

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Blood creatine phosphokinase abnormal			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 72 (1.39%)	3 / 66 (4.55%)	
occurrences (all)	1	3	
Blood potassium increased			
subjects affected / exposed	2 / 72 (2.78%)	2 / 66 (3.03%)	
occurrences (all)	2	2	
Blood sodium decreased			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Urine analysis abnormal			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Leukocytosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Neutrophilia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	1 / 72 (1.39%)	3 / 66 (4.55%)	
occurrences (all)	1	3	
Nervous system disorders			

Ageusia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	2 / 72 (2.78%)	1 / 66 (1.52%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Hypogeusia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 72 (1.39%)	2 / 66 (3.03%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	2 / 72 (2.78%)	0 / 66 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	2 / 72 (2.78%)	3 / 66 (4.55%)	
occurrences (all)	2	3	
Dysphagia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Gastric ulcer			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	

occurrences (all)	1	0	
Hyperchlorhydria			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Diabetic nephropathy			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Glycosuria			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	0 / 72 (0.00%)	2 / 66 (3.03%)	
occurrences (all)	0	2	
Renal impairment			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Skin hypopigmentation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	

occurrences (all)	0	1	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Dyslipidaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 72 (2.78%)	2 / 66 (3.03%)	
occurrences (all)	2	2	
Hypoglycaemia			
subjects affected / exposed	0 / 72 (0.00%)	3 / 66 (4.55%)	
occurrences (all)	0	3	
Hyponatraemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Impaired fasting glucose			
subjects affected / exposed	1 / 72 (1.39%)	0 / 66 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 66 (1.52%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2012	Following change was made in the Protocol Version 3.0 (Germany only), 25 Oct 2012: -ALT/AST based treatment stopping rule.
22 February 2013	Following changes were made in the Protocol Version 5.0 (Germany only), 22 Feb 2013: - Corrected QT (QTc) interval of >430 msec in males or >450 msec in females according to the method described by Pfeufer et al. - Change in the baseline 24-hour average daily pain intensity score at study entry from ≥5 and < 9 to ≥4 and < 9.
26 February 2013	Following changes were made in the Protocol Version 4.0, 26 Feb 2013: - Corrected QT (QTc) interval of >430 msec in males or >450 msec in females according to the method described by Pfeufer et al. - Change in the baseline 24-hour average daily pain intensity score at study entry from ≥5 and < 9 to ≥4 and < 9.
01 March 2013	Following changes were made in the Protocol Version 4.0 (India only), 01 Mar 2013: - Corrected QT (QTc) interval of >430 msec in males or >450 msec in females according to the method described by Pfeufer et al. - Change in the baseline 24-hour average daily pain intensity score at study entry from ≥5 and < 9 to ≥4 and < 9.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported