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

Summary

EudraCT number	2012-002320-33
Trial protocol	GB DE CZ
Global end of trial date	23 July 2014
Results information	
Result version number	v2 (current)
This version publication date	12 March 2016
First version publication date	24 July 2015
Version creation reason	• New data added to full data set Public contact name changed to Amol Pendse (Amol.Pendse@glenmarkpharma.com)

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	Amol Pendse, Glenmark Pharmaceuticals S.A, +91 2267720000, Amol.Pendse@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
Physician decision	2	-
Adverse event, non-fatal	1	-
Protocol deviation	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	Placebo v GRC 17536 250 mg
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	Placebo
Reporting group description: Placebo administered BID orally for 28 days.	
Reporting group title	GRC 17536 250 mg
Reporting group description: GRC 17536 250 mg administered BID orally for 28 days.	

Serious adverse events	Placebo	GRC 17536 250 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
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	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	GRC 17536 250 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 66 (37.88%)	23 / 72 (31.94%)	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Hypertension			

subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Local swelling			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 66 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	2 / 66 (3.03%)	0 / 72 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	3 / 66 (4.55%)	1 / 72 (1.39%)	
occurrences (all)	3	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 66 (1.52%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Blood creatine phosphokinase abnormal			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 66 (4.55%)	1 / 72 (1.39%)	
occurrences (all)	3	1	
Blood potassium increased			
subjects affected / exposed	2 / 66 (3.03%)	2 / 72 (2.78%)	
occurrences (all)	2	2	
Blood sodium decreased			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Urine analysis abnormal			
subjects affected / exposed	1 / 66 (1.52%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 66 (1.52%)	2 / 72 (2.78%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	

Hypogeusia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Neutrophilia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 66 (3.03%)	1 / 72 (1.39%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	0 / 66 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	3 / 66 (4.55%)	2 / 72 (2.78%)	
occurrences (all)	3	2	
Dysphagia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Gastric ulcer			
subjects affected / exposed	1 / 66 (1.52%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			

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

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