Clinical trial results:
A STUDY OF PREGABALIN IN THE TREATMENT OF SUBJECTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY WITH BACKGROUND TREATMENT OF NSAID FOR OTHER PAIN CONDITIONS

Summary

EudraCT number	2011-002743-10
Trial protocol	SE CZ IT
Global end of trial date	06 November 2013

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	A0081268

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01455415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	13 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of pregabalin compared with placebo for the symptomatic relief of Diabetic Peripheral Neuropathy (DPN) pain in subjects with painful DPN who use one Non-Steroidal Anti-Inflammatory Drug (NSAID) (including Cyclooxygenase type 2 [COX-2] inhibitors) primarily for the treatment of conditions other than DPN pain.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
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: 35
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 265
Worldwide total number of subjects	301
EEA total number of subjects	36

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)	204

From 65 to 84 years	97
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

501 subjects were screened, of whom 197 were withdrawn before randomization. 304 were randomized, of whom 3 discontinued before being treated. Subjects were randomized at 47 centers in 3 countries: US (43), Czech Republic (3), and Italy (1). 4 centers received study drug but did not randomize subjects.

Pre-assignment

Screening details:

Subjects completed daily pain and sleep diary from Visit 1 (Screening) to Visit 9. Subjects with a mean pain score greater than or equal to (>=) 4 (moderate to severe pain) and those having completed >=4 daily pain diaries over past 7 days and having a mean score of >=4 at Visit 2 (Baseline) were randomized.

Period 1

Period 1 title	Intervention Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin/Placebo: Intervention Period 1

Arm description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pregabalin 300 milligram per day (mg/day) or 150 mg/day in 3 divided doses 3 times a day orally for 6 weeks.

Arm title	Placebo/Pregabalin: Intervention Period 1

Arm description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

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

Dosage and administration details:

Placebo matched to pregabalin in 3 divided doses 3 times a day for 6 weeks.

Number of subjects in period 1	Pregabalin/Placebo: Intervention Period 1	Placebo/Pregabalin: Intervention Period 1
Started	154	147
Completed	137	124
Not completed	17	23
Consent withdrawn by subject	3	5
Lost to follow-up	3	2
Protocol violation	-	2
Medication error without associated adverse event	-	1
Adverse event	10	12
Unspecified	1	1

Period 2

Period 2 title	Washout
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin/Placebo: Washout Period

Arm description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

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

Dosage and administration details:

Placebo matched to pregabalin in 3 divided doses 3 times a day for 2 weeks.

Arm title	Placebo/Pregabalin: Washout Period

Arm description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to pregabalin in 3 divided doses 3 times a day for 2 weeks.

Number of subjects in period 2	Pregabalin/Placebo: Washout Period	Placebo/Pregabalin: Washout Period
Started	137	124
Completed	131	118
Not completed	6	6
Lost to follow-up	1	-
Protocol violation	-	1
Medication error without associated adverse event	1	1
Adverse event	3	3
Unspecified	1	1

Period 3

Period 3 title	Intervention Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin/Placebo: Intervention Period 2

Arm description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

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

Dosage and administration details:

Placebo matched to pregabalin in 3 divided doses 3 times a day for 6 weeks.

Arm title	Placebo/Pregabalin: Intervention Period 2

Arm description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Pregabalin 300 mg/day or 150 mg/day in 3 divided doses 3 times a day orally for 6 weeks.

Number of subjects in period 3	Pregabalin/Placebo: Intervention Period 2	Placebo/Pregabalin: Intervention Period 2
Started	131	118
Treated	129	118
Completed	117	103
Not completed	14	15
Consent withdrawn by subject	3	3
Lost to follow-up	3	1
Protocol violation	-	2
Medication error without associated adverse event	-	1
Adverse event	4	4
Unspecified	4	2
Lack of efficacy	-	2

Period 4

Period 4 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes

Arm title	Pregabalin/Placebo: Follow-up

Arm description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

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

Dosage and administration details:

Subjects received placebo matched to pregabalin in 3 divided doses 3 times a day for Day 1-7.

Arm title	Placebo/Pregabalin: Follow-up

Arm description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects who received pregabalin 300 mg/day as final dose, were given pregabalin 150 mg/day in 3 divided doses 3 times a day orally for Day 1-3.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects who received pregabalin 300 mg/day as final dose, were given placebo matched to pregabalin in 3 divided doses 3 times a day orally for Day 4-7.

Number of subjects in period 4	Pregabalin/Placebo: Follow-up	Placebo/Pregabalin: Follow-up
Started	117	103
Completed	114	101
Not completed	3	2
Consent withdrawn by subject	2	-
Adverse event	-	1
Unspecified	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pregabalin/Placebo: Intervention Period 1
Reporting group description:	
Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.	
Reporting group title	Placebo/Pregabalin: Intervention Period 1
Reporting group description:	
Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.	

Reporting group values	Pregabalin/Placebo: Intervention Period 1	Placebo/Pregabalin: Intervention Period 1	Total
Number of subjects	154	147	301
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.4	58.4	
standard deviation	± 9.83	± 9.52	-
Gender categorical			
Units: Subjects			
Female	65	72	137
Male	89	75	164

End points

End points reporting groups

Reporting group title	Pregabalin/Placebo: Intervention Period 1

Reporting group description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Placebo/Pregabalin: Intervention Period 1

Reporting group description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Pregabalin/Placebo: Washout Period

Reporting group description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Placebo/Pregabalin: Washout Period

Reporting group description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Pregabalin/Placebo: Intervention Period 2

Reporting group description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Placebo/Pregabalin: Intervention Period 2

Reporting group description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Pregabalin/Placebo: Follow-up

Reporting group description:

Subjects were randomized to double-blind treatment with pregabalin for 6 weeks in intervention period 1 followed by placebo in intervention period 2. There was a 2-week single-blind washout (blinded to subjects) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Placebo/Pregabalin: Follow-up

Reporting group description:

Subjects were randomized to double-blind treatment with placebo for 6 weeks in intervention period 1 followed by pregabalin in intervention period 2. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Subject analysis set title	Pregabalin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received pregabalin in either period of the 2-period crossover study design.This crossover study consisted of two double blind 6- week
intervention periods where subjects were randomized to pregabalin or placebo for the first intervention period, and were then switched to the other intervention for the second intervention period. There was a

2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received placebo in either period of the 2-period crossover study design. This crossover study consisted of two double blind 6-week intervention periods where subjects were randomized to pregabalin or placebo for the first intervention period, and were then switched to the other intervention for the second intervention period. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Primary: Average Diabetic Peripheral Neuropathy (DPN) Pain Based on a Numeric Rating Scale (NRS) Over the Last 7 Days of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Average Diabetic Peripheral Neuropathy (DPN) Pain Based on a Numeric Rating Scale (NRS) Over the Last 7 Days of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

The daily pain diary consisted of an 11-point numeric scale ranging from 0 (“no pain”) to 10 (“worst possible pain”). Subjects described their pain during the past 24 hours by having chosen the appropriate number between 0 and 10. Self assessment was performed daily in the evening before bedtime on a telephone via interactive voice recognition system (IVRS) (time window for completion between 6.00 pm to midnight). The endpoint mean pain score was defined as the mean of the last 7 daily diary pain ratings while taking study drug in each treatment period - intervention period 1 and intervention period 2, respectively. A rating of 1 - 3 was considered as mild pain; 4 - 6 as moderate pain; and 7 - 10 as severe pain. The intent-to-treat (ITT) population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Primary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	4.98 (± 0.127)	5.018 (± 0.126)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Longitudinal analysis was done using repeated measure linear mixed effects model including visit,treatment,indicator variable for Week 6,and treatment by visit and by indicator variable interaction as fixed effect factors and subject within sequence and within-subject error (estimated using unstructured covariance structure)as random factors. Treatment differences were tested using within-subject variability as the error term. Kenward-Roger method used to estimate denominator degrees of

Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7174 [1]
Method	Repeated measure mixed effects model
Parameter estimate	Mean difference (final values)
Point estimate	-0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.248
upper limit	0.171
Variability estimate	Standard error of the mean
Dispersion value	0.106

Notes:

[1] - Primary analysis was two-sided and performed at the 0.05 significance level. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Secondary: Percentage of Subjects Achieving 30% Reduction in Mean DPN Pain Score from Baseline at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Percentage of Subjects Achieving 30% Reduction in Mean DPN Pain Score from Baseline at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Daily pain diary consisted of an 11-point numeric scale ranging from 0 ("no pain") to 10 ("worst possible pain"). Subjects described their pain during the past 24 hours by having chosen the appropriate number between 0 and 10. Self assessment was performed daily in the evening before bedtime on a telephone via IVRS (time window for completion between 6.00 pm to midnight). The endpoint mean pain score was defined as the mean of the last 7 daily diary pain ratings while taking study drug in each treatment period - intervention period 1 and intervention period 2, respectively. A rating of 1 - 3 was considered as mild pain; 4 - 6 as moderate pain; and 7 - 10 as severe pain. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: Percentage (%) of Subjects				
number (not applicable)	34.56	31.16		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a logistic regression model which included baseline pain, sequence, period and

treatment as covariate. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3287 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.73

Notes:

[2] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Percentage of Subjects Achieving 50% Reduction in Mean DPN Pain Score from Baseline at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Percentage of Subjects Achieving 50% Reduction in Mean DPN Pain Score from Baseline at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Daily pain diary consisted of an 11-point numeric scale ranging from 0 ("no pain") to 10 ("worst possible pain"). Subjects described their pain during the past 24 hours by having chosen the appropriate number between 0 and 10. Self assessment was performed daily in the evening before bedtime on a telephone via IVRS (time window for completion between 6.00 pm to midnight). The endpoint mean pain score was defined as the mean of the last 7 daily diary pain ratings while taking study drug in each treatment period - intervention period 1 and intervention period 2, respectively. A rating of 1 - 3 was considered as mild pain; 4 - 6 as moderate pain; and 7 - 10 as severe pain. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: percentage of subjects				
number (not applicable)	20.22	15.58		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a logistic regression model which included baseline pain, sequence, period and

treatment as covariate. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0625 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.51

Notes:

[3] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Brief Pain Inventory-Short Form (BPI-sf) Score for Pain-Severity Domain at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Brief Pain Inventory-Short Form (BPI-sf) Score for Pain-Severity Domain at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

The BPI-sf is a self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions during a 24 hour period prior to evaluation. Four items measure pain (0: no pain; 10: worst pain possible) at its "worst, "least", "average", and "now" (current pain) on an 11-point scale. Scores range from 0 - 10 with higher scores indicating greater pain severity. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	4.49 (± 0.11)	4.48 (± 0.11)		

Statistical analyses

Statistical analysis title	Pregabalin, Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline pain severity, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9448 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[4] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Mean Sleep Interference Rating Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Mean Sleep Interference Rating Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

The daily sleep diary consists of an 11-point numeric rating scale with which the subject rates how painful DPN pain has interfered with their sleep during the past 24 hours. Zero indicates "does not interfere with sleep" and 10 indicates "completely interferes (unable to sleep due to pain)". Self assessment was performed daily in the evening before bedtime on a telephone via IVRS (time window for completion between 6.00 pm to midnight) after completion of the daily pain diary. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	4.11 (± 0.12)	4.35 (± 0.12)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model including baseline score, sequence, period, and treatment as fixed effect factors and subject within sequence and within subject error as random factors. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0272 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[5] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Hospital Anxiety and Depression Scale - Anxiety (HADS-A) Total Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Hospital Anxiety and Depression Scale - Anxiety (HADS-A) Total Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a 14- item self-administered questionnaire that consists of 2 scales, one measuring anxiety (HADS-A), and the other measuring depression (HADS-D). Each subscale consists of 7 statements and the subject responds as to how each item applies to him/her over the past week on 4- point response scale. Separate scores are calculated for anxiety and depression and a score (ranging from 0 to 21) is obtained for each subscale. The higher the score, the more severe the anxiety or depression. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	4.9 (± 0.18)	4.96 (± 0.18)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline HADS-A score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject

variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7344 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[6] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: HADS-D Total Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	HADS-D Total Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

HADS is a 14- item self-administered questionnaire that consists of 2 scales, one measuring anxiety (HADS-A), and the other measuring depression (HADS-D). Each subscale consists of 7 statements and the subject responds as to how each item applies to him/her over the past week on 4- point response scale. Separate scores are calculated for anxiety and depression and a score (ranging from 0 to 21) is obtained for each subscale. The higher the score, the more severe the anxiety or depression. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	4.42 (± 0.17)	4.5 (± 0.17)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline HADS-D score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as

random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6007 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[7] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) Total Quality of Life (TQOL) Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) Total Quality of Life (TQOL) Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN: 35-item subject-rated questionnaire used to assess impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. All symptoms(1 - 7) are scored as either 1 or 0, indicating presence or absence of the symptom. With exception of questions 31 and 32,the other items are scored according to the 5-point Likert Scale (0 - 4,"no problem" to "severe problem").In question 31, "good", the middle item, is scored as 0, "very good"as -1,"excellent" as -2,"fair" as 1, and "poor"as 2. In question 32, "about the same", the middle item, is scored as 0,"somewhat better" as -1, "much better" as -2,"somewhat worse" as 1, and "much worse"as 2. TQOL score summed as follow: sum (Σ) (1 - 7, 8 - 35).The (sub)scales are calculated without weighting of any kind, and reported as the integer sum of listed questionnaire items (range: -4 - 136). The QOL-DN version that was administered in this study was modified with a 2-week recall period. The ITT population was analyzed.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	37.22 (± 1.03)	38.3 (± 1.02)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline total score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2987 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.13
upper limit	0.96
Variability estimate	Standard error of the mean
Dispersion value	1.04

Notes:

[8] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk QOL-DN Symptoms Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk QOL-DN Symptoms Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN is a 35-item subject-rated questionnaire used to assess the impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. All symptoms (1 - 7) are scored as either 1 or 0, indicating presence or absence of the symptom. Item 9 is scored according to the 5-point Likert Scale (0 - 4, "no problem" to "severe problem"). The symptoms domain score should be summed as follow: Σ (1 - 7, 9). The scales and subscales are calculated without weighting of any kind, and reported as the integer sum of the listed questionnaire items (range: 0 - 32). The QOL-DN version that was administered in this study was modified with a 2-week recall period. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	7.51 (± 0.25)	7.86 (± 0.25)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline symptoms domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors.The treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1769 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.26

Notes:

[9] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk QOL-DN Activities of Daily Living Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk QOL-DN Activities of Daily Living Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN is a 35-item subject-rated questionnaire used to assess the impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. The items are scored according to the 5-point Likert Scale (0 - 4, "no problem" to "severe problem"). Activities of the daily living domain score should be summed as follow: Σ (12, 22, 23, 25, 26). Scales and subscales are calculated without weighting of any kind, and reported as integer sum of listed questionnaire items (range: 0 - 20). The QOL-DN version that was administered in the study was modified with a 2-week recall period. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	2.82 (± 0.16)	2.94 (± 0.16)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis done using linear mixed effects model which included baseline activities of daily living domain score,sequence,period,and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo)has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field:In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5119 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[10] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk QOL-DN Physical Functioning / Large Fiber Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk QOL-DN Physical Functioning / Large Fiber Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN is 35-item subject-rated questionnaire used to assess impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. With exception of questions 31 and 32, items are scored according to 5-point Likert Scale(0 - 4,"no problem"to"severe problem").In question 31,"good",middle item,is scored as 0,"very good"as -1 ,"excellent"as -2,"fair" as 1, and "poor" as 2.In question 32,"about same",middle item, is scored as 0,"somewhat better"as -1, "much better" as -2,"somewhat worse" as 1, and"much worse" as 2. Physical functioning / large fiber domain score should be summed as: Σ(8, 11, 13 - 15, 24, 27 - 35).Scales and subscales are calculated without weighting of any kind,and reported as integer sum of listed questionnaire items (range: -4 - 56). QOL-DN version that was administered in the study was modified with 2-week recall period.The ITT population was analyzed according to what the randomization schedule intended for subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	23.17 (± 0.61)	23.66 (± 0.6)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis done using linear mixed effects model which included baseline physical functioning/large fiber domain score,sequence, period,and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4335 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.62

Notes:

[11] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk QOL-DN Small Fiber Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk QOL-DN Small Fiber Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN is a 35-item subject-rated questionnaire used to assess impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. The items are scored according to the 5-point Likert Scale (0 - 4, "no problem" to "severe problem"). The small fiber domain score should be summed as follow: Σ (10, 16, 17, 18). Scales and subscales are calculated without weighting of any kind, and reported as integer sum of the listed questionnaire items (range: 0 - 16). The QOL-DN version that was administered in this study was modified with a 2-week recall period. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	2.57 (± 0.16)	2.58 (± 0.16)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline small fiber domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9653 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[12] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Norfolk QOL-DN Autonomic Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Norfolk QOL-DN Autonomic Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

Norfolk QOL-DN is a 35-item subject-rated questionnaire used to assess the impact of diabetic neuropathy on quality of life of subjects with diabetic neuropathy. The items are scored according to the 5-point Likert Scale (0 - 4, "no problem" to "severe problem"). The autonomic domain score should be summed as follow: Σ (19, 20, 21). The scales and subscales are calculated without weighting of any kind, and reported as the integer sum of the listed questionnaire items (range: 0 - 12). The QOL-DN version that was administered in this study was modified with a 2-week recall period.The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	1.12 (± 0.1)	1.26 (± 0.1)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline autonomic domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.269 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[13] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Euro QoL-5 Dimensions (EQ-5D) Mobility Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	Euro QoL-5 Dimensions (EQ-5D) Mobility Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale (no problems, some/moderate problems, extreme problems) and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population

was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	1.65 (± 0.03)	1.65 (± 0.03)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline mobility domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9951 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[14] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: EQ-5D Self-Care Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Self-Care Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale [1 = no problems, 2 = some/moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better

health. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	1.18 (± 0.02)	1.18 (± 0.02)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline self-care domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin - placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9726 [15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.02

Notes:

[15] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: EQ-5D Usual Activities Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Usual Activities Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response

scale [1 = no problems, 2 =some / moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	1.53 (± 0.03)	1.51 (± 0.03)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline usual activities domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5497 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[16] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment

Secondary: EQ-5D Pain / Discomfort Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Pain / Discomfort Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale [1 = no problems, 2 = some/moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	2.03 (± 0.03)	1.98 (± 0.02)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a linear mixed effects model which included baseline pain/discomfort domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1495 [17]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[17] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: EQ-5D Anxiety / Depression Domain Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Anxiety / Depression Domain Score at the End of Each

	Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale [1 = no problems, 2 = some/moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	1.3 (± 0.03)	1.35 (± 0.03)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline anxiety/depression domain score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field:In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1297 [18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[18] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: EQ-5D Dolan 1997 Index Summary Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Dolan 1997 Index Summary Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale [1 = no problems, 2 = some / moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The utility score is calculated using the Dolan 1997 algorithm and the revised version which was provided to the EuroQol Group by Dolan in 2001 – but later published in medical care in 2002. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	0.63 (± 0.01)	0.65 (± 0.01)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline Dolan 1997 index summary score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4279 [19]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.01

Notes:

[19] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: EQ-5D Dolan 2002 Index Summary Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	EQ-5D Dolan 2002 Index Summary Score at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

EQ-5D is a subject-completed 5-item questionnaire designed to assess health related quality of life in terms of a single index value or utility score. There are 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension is rated on a 3-point response scale [1 = no problems, 2 = some / moderate problems, 3 = extreme problems] and the scores are combined to form a single index utility value between 0 and 1 with higher scores indicating better health. The utility score is calculated using the Dolan 1997 algorithm and the revised version which was provided to the EuroQol Group by Dolan in 2001 – but later published in medical care in 2002. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	0.63 (± 0.01)	0.64 (± 0.01)		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline Dolan 2001 index summary score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. Treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In cross over study, each subject receives both treatments. Total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5505 [20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.01

Notes:

[20] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: Patient Global Impression of Change (PGIC) Score at the End of Period 1 (Week 6) - Original Scores

End point title	Patient Global Impression of Change (PGIC) Score at the End of Period 1 (Week 6) - Original Scores

End point description:

The PGIC is a subject-rated instrument that measures the subject's assessment of change in his/her overall status on a scale ranging from 1 (very much improved) to 7 (very much worse). Due to the crossover design, PGIC was analyzed at the end of period 1 (V5). The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period. All subjects who were randomized and had a period 1 PGIC value were used for this analysis.

End point type	Secondary

End point timeframe:

End of Period 1 (V5)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	143		
Units: percentage of subjects				
number (not applicable)				
Very much improved	8.1	4.9		
Much improved	27.7	19.6		
Minimally improved	39.2	39.2		
No change	14.9	23.1		
Minimally worse	6.1	7		
Much worse	2	1.4		
Very much worse	1.4	2.1		
Missing	0.7	2.8		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a Cochran-Mantel-Haenszel (CMH) test with modified ridit transformation, under alternative hypothesis of raw mean scores differ.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0604 [21]
Method	Cochran-Mantel-Haenszel

Notes:

[21] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: PGIC Score at the End of Period 1 (Week 6) - Categorized Scores

End point title	PGIC Score at the End of Period 1 (Week 6) - Categorized Scores

End point description:

The PGIC is a subject-rated instrument that measures the subject's assessment of change in his/her overall status on a scale ranging from 1 (very much improved) to 7 (very much worse). Original scores (7 different scores) and categorized scores (4 different scores) were provided. Categorized scores were very much improved (consisting of very much improved and much improved); any improvement (consisting of very much improved, much improved, and minimally improved); no change (consisting of no change); and any worsening (consisting of minimally worse, much worse, and very much worse). Due to the crossover design, PGIC was analyzed at the end of period 1 (V5). The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period. All subjects who were randomized and had a period 1 PGIC value were used for this analysis.

End point type	Secondary

End point timeframe:

End of Period 1 (V5)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	148	143		
Units: percentage of subjects				
number (not applicable)				
Very much/much improved	35.8	24.5		
Any improvement	75	63.6		
No change	14.9	23.1		
Any worsening	9.5	10.5		

Statistical analyses

Statistical analysis title	Pregabalin vs Placebo

Statistical analysis description:

Analysis was done using a CMH test with modified ridit transformation, under alternative hypothesis of raw mean scores differ.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1511 [22]
Method	Cochran-Mantel-Haenszel

Notes:

[22] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Secondary: BPI-sf Score for Pain-Interference Domain at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point title	BPI-sf Score for Pain-Interference Domain at the End of Each Treatment Period (Week 6 of Each Treatment Period)

End point description:

The BPI-sf is a self-administered questionnaire developed to assess the severity of pain and the impact

of pain on daily functions during a 24 hour period prior to evaluation. Seven sub-questions evaluates the level of interference of pain on daily functioning (general activity, walking, work ability, mood, enjoyment of life, relations with other people, and sleep) on an 11-point scale (0: does not interfere; 10: completely interferes). Scores range from 0 - 10 with higher scores indicating greater interference. The ITT population included all randomized subjects with at least one dose of study drug. The ITT population was analyzed according to what the randomization schedule intended for the subjects to take in each period.

End point type	Secondary

End point timeframe:

End of Period (includes both Visits 5 and 9)

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	272	276		
Units: units on a scale				
least squares mean (standard error)	3.5 (± 0.12)	3.59 (± 0.11)		

Statistical analyses

Statistical analysis title	Pregabalin, Placebo

Statistical analysis description:

Analysis was done using linear mixed effects model which included baseline interference score, sequence, period, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin-placebo) has been tested using within-subject variability as error term. For 'number of subjects included in the analysis' field: In a cross over study, each subject receives both treatments. The total number of subjects was 301, not 548.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4548 [23]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[23] - Secondary analysis was two-sided and performed at the 0.05 significance level, without multiple comparisons' adjustment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the subjects were randomized through and including 28 calendar days after the last administration of the study drug.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Pregabalin

Reporting group description:

Subjects received pregabalin in either period of the 2- period crossover study design. This crossover study consisted of two double blind 6- week intervention periods where subjects were randomized to pregabalin or placebo for the first intervention period, and were then switched to the other intervention for the second intervention period. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo in either period of the 2- period crossover study design. This crossover study consisted of two double blind 6-week intervention periods where subjects were randomized to pregabalin or placebo for the first intervention period, and were then switched to the other intervention for the second intervention period. There was a 2-week single-blind washout (blinded to subject) between the intervention periods. A 1-week taper was administered at the end of the second intervention period, followed by a final follow-up visit.

Serious adverse events	Pregabalin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 272 (1.84%)	7 / 276 (2.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis acute			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 272 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 272 (0.37%)	0 / 276 (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: 2 %

Non-serious adverse events	Pregabalin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 272 (30.88%)	45 / 276 (16.30%)	
Nervous system disorders			
Dizziness			

subjects affected / exposed	28 / 272 (10.29%)	4 / 276 (1.45%)	
occurrences (all)	28	4	
Headache			
subjects affected / exposed	9 / 272 (3.31%)	8 / 276 (2.90%)	
occurrences (all)	9	10	
Somnolence			
subjects affected / exposed	14 / 272 (5.15%)	7 / 276 (2.54%)	
occurrences (all)	14	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	14 / 272 (5.15%)	4 / 276 (1.45%)	
occurrences (all)	15	4	
Oedema peripheral			
subjects affected / exposed	10 / 272 (3.68%)	8 / 276 (2.90%)	
occurrences (all)	11	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 272 (3.31%)	11 / 276 (3.99%)	
occurrences (all)	9	13	
Nausea			
subjects affected / exposed	9 / 272 (3.31%)	8 / 276 (2.90%)	
occurrences (all)	9	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 272 (2.94%)	4 / 276 (1.45%)	
occurrences (all)	8	6	
Pain in extremity			
subjects affected / exposed	7 / 272 (2.57%)	5 / 276 (1.81%)	
occurrences (all)	10	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2012	The laboratory parameter glycosylated hemoglobin (HbA1c) was additionally assessed at Visit 6 and 11 and this instruction was included in the protocol for clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported