



Clinical trial results:

A Phase 3b Multicenter, Double-Blind, Randomized, Placebo-Controlled, 2-Way Crossover Study of Pregabalin in the Treatment of Fibromyalgia With Concurrent Antidepressant Therapy for Comorbid Depression

Summary

EudraCT number	2011-002480-19
Trial protocol	ES IT
Global end of trial date	22 July 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	A0081275
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01432236
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, NY 10017
Public contact	Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, clinicaltrials.govcallcenter@pfizer.com
Scientific contact	Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, clinicaltrials.govcallcenter@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	07 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 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 in subjects with fibromyalgia and comorbid depression currently on a stable selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenalin reuptake inhibitor (SNRI) primarily being used to treat the depression.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 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	Spain: 39
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 120
Country: Number of subjects enrolled	Canada: 22
Worldwide total number of subjects	193
EEA total number of subjects	51

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)	180

From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this double blind, crossover study, a total of 197 subjects were randomized to either pregabalin/placebo or placebo/pregabalin treatment sequence. Of these, 193 took at least one dose of study medication. Four randomized subjects never took study medication. Randomized subjects were recruited from 4 countries at 38 study centers.

Pre-assignment

Screening details:

Subjects with mean Numeric Rating Scale (NRS) pain score of greater than or equal to (\geq) 4 at baseline, meeting all other inclusion/exclusion criteria were randomly assigned to receive double blind treatment with either pregabalin followed by placebo with background antidepressant or placebo followed by pregabalin with background antidepressant.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Pregabalin/Placebo

Arm description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods.

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

Dosage and administration details:

Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 milligram per day (mg/day) and increased up to 300 - 450 mg/day during the dose optimization process.

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

Dosage and administration details:

Placebo matched to pregabalin.

Arm title	Placebo/Pregabalin
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Arm description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods.

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

Dosage and administration details:

Placebo matched to pregabalin.

Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pregabalin was administered as IR capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process.

Number of subjects in period 1	Pregabalin/Placebo	Placebo/Pregabalin
Started	96	97
Completed	70	79
Not completed	26	18
Consent withdrawn by subject	4	5
Protocol violation	1	1
Adverse event	11	5
Unspecified	3	4
Lost to follow-up	2	2
Lack of efficacy	5	1

Baseline characteristics

Reporting groups

Reporting group title	Pregabalin/Placebo
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Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods.

Reporting group title	Placebo/Pregabalin
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Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods.

Reporting group values	Pregabalin/Placebo	Placebo/Pregabalin	Total
Number of subjects	96	97	193
Age categorical Units: Subjects			
Below 18 Years	0	0	0
18-44 years	22	29	51
45-64 years	69	60	129
65 years or above	5	8	13
Gender categorical Units: Subjects			
Female	87	93	180
Male	9	4	13

End points

End points reporting groups

Reporting group title	Pregabalin/Placebo
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Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods.

Reporting group title	Placebo/Pregabalin
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Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods.

Subject analysis set title	All Subjects
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All randomized subjects were included in this analysis.

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

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process. There was a 2-week single-blind taper/washout period between treatment periods.

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

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process in period 2. There was a 2-week single-blind taper/washout period between treatment periods

Primary: Mean Numeric Rating Scale (NRS) Pain Score at End of Period

End point title	Mean Numeric Rating Scale (NRS) Pain Score at End of Period
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End point description:

The daily pain diary consists of an 11-point numeric scale (NRS) ranging from 0 ("no pain") to 10 ("worst possible pain"). Subjects describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10. The endpoint mean pain scores for Period 1 and Period 2 are defined as the mean of the last 7 non-missing daily diary pain ratings while taking study medication in the double-blind phase during Period 1 and Period 2, respectively. ITT population, defined as all subjects who were randomized, treated (i.e., received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Primary
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End point timeframe:

End of each period, at Weeks 6, Week 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Units on a scale				
least squares mean (standard error)	4.84 (\pm 0.15)	5.45 (\pm 0.16)		

Statistical analyses

Statistical analysis title	Mean NRS Pain Score at End of Period
Statistical analysis description:	
Analysis was done using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0001 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	-0.31

Notes:

[1] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 352.

[2] - Primary analysis was two-sided and performed at the 0.05 significance level. Satterthwaite's approximation was used to estimate denominator degrees of freedom.

Secondary: Fibromyalgia Impact Questionnaire (FIQ) Score at Baseline

End point title	Fibromyalgia Impact Questionnaire (FIQ) Score at Baseline
End point description:	
This was a 20-item subjects reported outcome instrument. It contained 10 subscales, which were combined to yield a total score. The first 11 questions were related specifically to physical functioning subscale, ranging from 0 to 10. The remaining 9 questions assessed pain, fatigue, stiffness, difficulty working, and symptoms of anxiety and depression ranging from 0 to 10. The higher values indicated greater impairment. All 20 were combined to form a total score ranging from 0 to 100, provides an estimation of fibromyalgia impact with higher scores indicating more impairment. The severity categorizations for the FIQ are: less than 40 (mild), 40-60 (moderate), and above 60 (severe). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Pregabalin/Placebo	Placebo/Pregabalin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	97		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total (N=96, 96)	63.83 (± 11.58)	62.75 (± 12.51)		
Physical Impairment (N=96, 97)	4.58 (± 2.1)	4.44 (± 2.14)		
Feel Good (N=96, 97)	7.78 (± 2.47)	7.43 (± 2.32)		
Work Missed (N=96, 97)	3.38 (± 2.88)	3.49 (± 3.21)		
Do Work (N=96, 97)	6.61 (± 2.03)	6.38 (± 2.21)		
Pain (N=96, 96)	6.98 (± 1.25)	7.09 (± 1.32)		
Fatigue (N=96, 97)	8.17 (± 1.37)	8.08 (± 1.58)		
Rested (N=96, 97)	7.9 (± 1.51)	7.82 (± 1.96)		
Stiffness (N=96, 97)	7.56 (± 1.56)	7.64 (± 1.58)		
Anxiety (N=96, 97)	5.65 (± 2.73)	5.6 (± 2.59)		
Depression (N=96, 97)	5.23 (± 2.64)	4.84 (± 2.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: FIQ Score at End of Period

End point title	FIQ Score at End of Period
End point description:	
<p>This was a 20-item subject reported outcome instrument. It contained 10 subscales, which were combined to yield a total score. The first 11 questions were related specifically to physical functioning subscale, ranging from 0 to 10. The remaining 9 questions assessed pain, fatigue, stiffness, difficulty working, and symptoms of anxiety and depression ranging from 0 to 10. The higher values indicated greater impairment. All 20 were combined to form a total score ranging from 0 to 100, provides an estimation of fibromyalgia impact with higher scores indicating more impairment. The severity categorizations for the FIQ are: less than 40 (mild), 40-60 (moderate), and above 60 (severe). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation. 'N' for each category represents subjects that were actually treated with pregabalin and placebo during the study.</p>	
End point type	Secondary
End point timeframe:	
End of each period, at Weeks 6, Week 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	177		
Units: Units on a scale				
least squares mean (standard error)				
Total (N=176, 172)	43.78 (± 1.42)	50.38 (± 1.43)		
Physical impairment (N=176, 173)	3.35 (± 0.17)	3.77 (± 0.17)		
Feel good (N=176, 173)	4.69 (± 0.23)	5.53 (± 0.23)		
Work missed (N=176, 173)	2.02 (± 0.21)	2.62 (± 0.21)		

Do work (N=176, 172)	4.56 (\pm 0.2)	5.31 (\pm 0.2)		
Pain (N=176, 173)	4.91 (\pm 0.17)	5.54 (\pm 0.17)		
Fatigue (N=176, 173)	6.32 (\pm 0.19)	6.76 (\pm 0.19)		
Rested (N=176, 173)	5.64 (\pm 0.19)	6.41 (\pm 0.19)		
Stiffness (N=176, 173)	5.24 (\pm 0.19)	5.95 (\pm 0.19)		
Anxiety (N=176, 173)	3.8 (\pm 0.2)	4.35 (\pm 0.21)		
Depression (N=176, 173)	3.2 (\pm 0.2)	4.13 (\pm 0.2)		

Statistical analyses

Statistical analysis title	FIQ Total Score
Statistical analysis description:	
Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.0001 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.33
upper limit	-3.87

Notes:

[3] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[4] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Physical Impairment
Statistical analysis description:	
Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0078 ^[6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	-0.11

Notes:

[5] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[6] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Feel Good
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.0014 ^[8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	-0.33

Notes:

[7] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[8] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Work Missed
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.005 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	-0.18

Notes:

[9] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[10] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Do Work
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0002 ^[12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	-0.36

Notes:

[11] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[12] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Pain
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.0006 ^[14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.28

Notes:

[13] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[14] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Fatigue
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.0315 ^[16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.04

Notes:

[15] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[16] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Rested
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.0003 ^[18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	-0.35

Notes:

[17] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[18] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Stiffness
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Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.0007 ^[20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	-0.31

Notes:

[19] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[20] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Anxiety
Statistical analysis description:	
Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.0048 ^[22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	-0.17

Notes:

[21] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[22] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	Depression
Statistical analysis description:	
Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	< 0.0001 ^[24]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	-0.53

Notes:

[23] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[24] - Analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Patient Global Impression of Change (PGIC) at the End of Period 1

End point title	Patient Global Impression of Change (PGIC) at the End of Period 1
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End point description:

PGIC: Subject rated instrument to measure subject's change in overall status from baseline to the end

of period 1 (Week 6) on a 7-point scale; range from 1 (very much improved) to 7 (very much worse). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
End point timeframe:	
End of Period 1 at Week 6	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	93		
Units: Percentage of subjects				
number (not applicable)				
Very much improved	10.8	4.3		
Much improved	35.5	25.8		
Minimally improved	28	40.9		
No change	17.2	21.5		
Minimally worse	4.3	6.5		
Much worse	3.2	1.1		
Very much worse	1.1	0		

Statistical analyses

Statistical analysis title	PGIC at the End of Period 1
Statistical analysis description:	
The PGIC variable was analyzed using Cochran Mantel-Haenszel (CMH) test with modified ridit transformation.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0637 ^[25]
Method	Cochran-Mantel-Haenszel

Notes:

[25] - This analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Percentage of Subjects with Greater than or Equal to (\geq)30 Percent (%) and \geq 50% Pain Reduction Based on Daily Pain

End point title	Percentage of Subjects with Greater than or Equal to (\geq)30 Percent (%) and \geq 50% Pain Reduction Based on Daily Pain
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End point description:

Subject with at least a 30% reduction in mean pain score from baseline (at randomization) to the endpoint at the end of each period (Visit 6 and 12) was considered a 30% responder, for the respective period. Similarly, a subject with at least a 50% reduction in mean pain score from baseline (at randomization) to the endpoint at the end of each period (Visit 6 and 12) was considered a 50% responder, for the respective period. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
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End point timeframe:

Visits 2, 6, 12

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Percentage of subjects				
number (not applicable)				
30% Responders	45.3	27.7		
50% Responders	26	15.8		

Statistical analyses

Statistical analysis title	For 30 Percent Responders
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Statistical analysis description:

Analysis was conducted using a logistic regression model using sequence, period, and treatment as fixed factors and subject within sequence and within subject error as random factors. Log link transformation was used for the model.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.0007 ^[27]
Method	Regression, Logistic

Notes:

[26] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[27] - This secondary analyses was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	For 50 Percent Responders
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Statistical analysis description:

Analysis was conducted using a logistic regression model using sequence, period, and treatment as fixed factors and subject within sequence and within subject error as random factors. Log link transformation was used for the model.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[28]
P-value	= 0.0205 ^[29]
Method	Regression, Logistic

Notes:

[28] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[29] - This secondary analyses was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Subjective Sleep Questionnaire - Mean Sleep Quality at End of Period

End point title	Subjective Sleep Questionnaire - Mean Sleep Quality at End of Period
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End point description:

Subjective sleep questionnaire-mean sleep quality at end of each period (Week 6 and Week 14) included 5 items: subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (NRS) for the previous night. Subjective rating of quality of sleep during the past night was done by selecting a number between 0 (very poor) and 10 (excellent). Mean sleep quality was calculated as the mean of the last seven days, the potential range of responses was therefore 0-10. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
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End point timeframe:

End of each period, at Weeks 6 and 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Units on a scale				
least squares mean (standard error)	6.15 (± 0.14)	5.57 (± 0.14)		

Statistical analyses

Statistical analysis title	Subjective Sleep Questionnaire
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Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	< 0.0001 ^[31]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.84

Notes:

[30] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[31] - This was done using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Subjective Sleep Questionnaire - Mean Subjective Wake After Sleep Onset at End of Period

End point title	Subjective Sleep Questionnaire - Mean Subjective Wake After Sleep Onset at End of Period
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End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep),

how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective wake after sleep onset was the subjective estimate of the total amount of time the subject was awake after initial sleep onset until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
End point timeframe:	
End of each period, at Weeks 6 and 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Minutes				
least squares mean (standard error)	33.38 (± 2.73)	41.18 (± 2.76)		

Statistical analyses

Statistical analysis title	Subjective Sleep Questionnaire
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Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.0018 ^[33]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-7.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.66
upper limit	-2.96

Notes:

[32] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[33] - This was done using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Subjective Sleep Questionnaire - Mean Latency to Sleep Onset at End of Period

End point title	Subjective Sleep Questionnaire - Mean Latency to Sleep Onset at End of Period
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End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective latency to sleep onset was the subjective estimate of the amount of time to fall asleep after lights out. ITT

population defined, as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
End point timeframe:	
End of each period, at Weeks 6 and 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Minutes				
least squares mean (standard error)	33.54 (± 2.68)	39.33 (± 2.71)		

Statistical analyses

Statistical analysis title	Subjective Sleep Questionnaire
Statistical analysis description:	
Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.0117 ^[35]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.29
upper limit	-1.31

Notes:

[34] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[35] - This was done using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Subjective Sleep Questionnaire - Mean Subjective Total Sleep Time at End of Period

End point title	Subjective Sleep Questionnaire - Mean Subjective Total Sleep Time at End of Period
End point description:	
Subjective Sleep Questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective total sleep time was the subjective estimate of the total amount of time the subject was asleep after lights out until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Secondary

End point timeframe:

End of each period, at Weeks 6 and 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Minutes				
least squares mean (standard error)	422.98 (\pm 5.42)	414.63 (\pm 5.48)		

Statistical analyses

Statistical analysis title	Subjective Sleep Questionnaire
Statistical analysis description:	
Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.0511 ^[37]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	8.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	16.74

Notes:

[36] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[37] - This was done using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Subjective Sleep Questionnaire - Parameter Estimates for Subjective Number of Awakenings Per Night After Sleep Onset at End of Period

End point title	Subjective Sleep Questionnaire - Parameter Estimates for Subjective Number of Awakenings Per Night After Sleep Onset at End of Period
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End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective number of awakenings after sleep onset was the subjective estimate of the total number of times the subject awakened during the night until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
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End point timeframe:
End of each period, at Weeks 6 and 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	179	173		
Units: Number of times awakened				
least squares mean (standard error)	0.48 (\pm 0.07)	0.61 (\pm 0.07)		

Statistical analyses

Statistical analysis title	Subjective Sleep Questionnaire
Statistical analysis description: Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors. Analyzed as a count variable using a generalized linear model assuming a Poisson distribution and utilizing a log link transformation.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[38]
P-value	= 0.1139 ^[39]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.03

Notes:

[38] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[39] - This was done using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Hospital Anxiety and Depression Scale (HADS) at Baseline

End point title	Hospital Anxiety and Depression Scale (HADS) at Baseline
End point description: HADS: Subject rated questionnaire with 2 subscales. HADS-A (anxiety) assesses state of generalized anxiety (anxious mood, restlessness, anxious thoughts, panic attacks); HADS-D (depression) assesses state of lost interest and diminished pleasure response (lowering of hedonic tone). Each subscale comprised of 7 items with range 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of anxiety and depression symptoms. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Secondary
End point timeframe: Baseline	

End point values	Pregabalin/Placebo	Placebo/Pregabalin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	97		
Units: Units on a scale				
arithmetic mean (standard deviation)				
HADS-A (anxiety)	8.67 (± 3.95)	7.97 (± 3.77)		
HADS-D (depression)	8.34 (± 3.59)	7.73 (± 3.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS at End of Period

End point title	HADS at End of Period
End point description:	
HADS: Subject rated questionnaire with 2 subscales. HADS-A (anxiety) assesses state of generalized anxiety (anxious mood, restlessness, anxious thoughts, panic attacks); HADS-D (depression) assesses state of lost interest and diminished pleasure response (lowering of hedonic tone). Each subscale comprised of 7 items with range 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of anxiety and depression symptoms. ITT population, defined as all subjects who were randomized, treated (i.e., received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Secondary
End point timeframe:	
Week 6, Week 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	173		
Units: Units on a scale				
least squares mean (standard error)				
HADS-A (anxiety)	6.01 (± 0.28)	6.96 (± 0.28)		
HADS-D (depression)	6.17 (± 0.31)	7.05 (± 0.31)		

Statistical analyses

Statistical analysis title	For HADS-A (anxiety)
Statistical analysis description:	
Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[40]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.5

Notes:

[40] - Two-sided test with $\alpha=0.05$ was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Statistical analysis title	For HADS-D (depression)
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Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 ^[41]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	-0.39

Notes:

[41] - Two-sided test with $\alpha=0.05$ was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Secondary: Mean EuroQoL 5-Dimensions (EQ-5D) Score at Baseline

End point title	Mean EuroQoL 5-Dimensions (EQ-5D) Score at Baseline
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End point description:

EQ-5D is a standardized, subject-administered measure of health outcome. It provides a descriptive profile for 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), using 3 levels (no, moderate, or extreme problems) and a single index value characterizing current health status using a 100-point visual analog scale (0=worst, 100=best). EQ-5D summary index is obtained with a formula that weights each level of the dimensions. The index-based score is interpreted along a continuum of 0 (death) to 1 (perfect health). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Secondary
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End point timeframe:

Baseline

End point values	Pregabalin/Placebo	Pregabalin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	97		
Units: Units on a scale				
arithmetic mean (standard deviation)	0.4 (± 0.31)	0.37 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D score at End of Period

End point title	EQ-5D score at End of Period
End point description:	
EQ-5D is a standardized, subject-administered measure of health outcome. It provides a descriptive profile for 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), using 3 levels (no, moderate, or extreme problems) and a single index value characterizing current health status using a 100-point visual analog scale (0=worst, 100=best). EQ-5D summary index is obtained with a formula that weights each level of the dimensions. The index-based score is interpreted along a continuum of 0 (death) to 1 (perfect health). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Secondary
End point timeframe:	
End of each period, at Weeks 6 and 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	172		
Units: Units on a scale				
least squares mean (standard error)	0.58 (± 0.02)	0.56 (± 0.02)		

Statistical analyses

Statistical analysis title	For EQ-5D Score at End of Period
Statistical analysis description:	
Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subjectt within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3854 ^[42]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.06

Notes:

[42] - Two-sided test with $\alpha=0.05$ was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Other pre-specified: PGIC at the End of Period 2

End point title	PGIC at the End of Period 2
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End point description:

PGIC: subject rated instrument to measure subjects's change in overall status from baseline to the end of period 2 (Week 14) on a 7-point scale; range from 1 (very much improved) to 7 (very much worse). Because of the crossover design and PGIC recall period (since starting study medication), the Period 1 PGIC data were felt to provide the clearest comparison across treatments, whereas Period 2 PGIC data were felt to have a more complex interpretation. Thus PGIC at End of Period 2 was separately analyzed from PGIC at End of Period 1. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Other pre-specified
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End point timeframe:

End of Period 2 at Week 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	82	81		
Units: Percentage of subjects				
number (not applicable)				
Very much improved	18.3	8.6		
Much improved	34.1	25.9		
Minimally improved	28	38.3		
No change	11	14.8		
Minimally worse	6.1	8.6		
Much worse	1.2	2.5		
Very much worse	1.2	1.2		

Statistical analyses

Statistical analysis title	For PGIC at the End of Period 2
Statistical analysis description: The PGIC variable was analyzed using CMH test with modified ridit transformation.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.116 ^[43]
Method	Cochran-Mantel-Haenszel

Notes:

[43] - This analysis was conducted using a two-sided test with $\alpha=0.05$. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Other pre-specified: Mean Patient Static Global Assessment (PSGA) Score at Baseline

End point title	Mean Patient Static Global Assessment (PSGA) Score at Baseline
End point description: PSGA was a single-item self-rated instrument that measured the subject's overall status on an 11-point NRS ranging from 0 (very poor) to 10 (very good). ITT population defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Other pre-specified
End point timeframe: Baseline	

End point values	Pregabalin/Placebo	Placebo/Pregabalin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	97		
Units: Units on a scale				
arithmetic mean (standard deviation)	4.35 (\pm 2.04)	4.46 (\pm 1.92)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean PSGA score at End of Period

End point title	Mean PSGA score at End of Period
End point description: PSGA was a single-item self-rated instrument that measured the subject's overall status on an 11-point numeric rating scale (NRS) ranging from 0 (very poor) to 10 (very good). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Other pre-specified
End point timeframe: End of each period, at Weeks 6 and 14	

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	172		
Units: Units on a scale				
least squares mean (standard error)	5.83 (\pm 0.17)	5.27 (\pm 0.17)		

Statistical analyses

Statistical analysis title	Mean PSGA Score at End of Period
Statistical analysis description:	
Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.	
Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085 ^[44]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.97

Notes:

[44] - Two-sided test with $\alpha=0.05$ was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

Other pre-specified: Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline

End point title	Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline
End point description:	
C-SSRS assessed whether subjects experienced following: completed suicide (1), suicide attempt (2) (response of "Yes" on "actual attempt"), preparatory acts toward imminent suicidal behavior (3) ("Yes" on "preparatory acts or behavior"), suicidal ideation (4) ("Yes" on "wish to be dead", "non-specific active suicidal thoughts", "active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent), any suicidal behavior or ideation, self-injurious behavior (7) ("Yes" on "Has subject engaged in non-suicidal self-injurious behavior"). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.	
End point type	Other pre-specified
End point timeframe:	
Baseline	

End point values	Pregabalin/Placebo	Placebo/Pregabalin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	97		
Units: Subjects				
number (not applicable)				
Wish to be Dead	3	1		
Non-Specific Thoughts	0	1		
Without Intent to Act	0	0		
Some Intent to Act	0	0		
Specific Plan and Intent	0	0		
Actual Attempt	0	0		
Non-Suicidal Self-Injurious Behavior	0	0		
Interrupted Attempt	0	0		
Aborted Attempt	0	0		
Preparatory Acts or Behavior	0	0		
Suicidal Behavior Present	0	0		
Completed Suicide	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Categorical Scores on the Columbia Suicidality Severity Rating Scale (C-SSRS) at Post-Baseline

End point title	Number of Subjects With Categorical Scores on the Columbia Suicidality Severity Rating Scale (C-SSRS) at Post-Baseline
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End point description:

C-SSRS assessed whether subjects experienced following: completed suicide (1), suicide attempt (2) (response of Yes on "actual attempt"), preparatory acts toward imminent suicidal behavior (3) (Yes on "preparatory acts or behavior"), suicidal ideation (4) (Yes on "wish to be dead", "non-specific active suicidal thoughts", "active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent), any suicidal behavior or ideation, self-injurious behavior (7) (Yes on "Has subject engaged in non-suicidal self-injurious behavior"). Below table indicated 1 subject treated with Pregabalin reported preparatory act. On study unblinding it was clarified that preparatory act occurred while subject was taking placebo. ITT population, defined as all subject who were randomized, treated (ie, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Other pre-specified
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End point timeframe:

From Visit 3 to Visit 14

End point values	Pregabalin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	181	177		
Units: Subjects				
number (not applicable)				
Wish to be Dead	10	8		
Non-Specific Thoughts	3	1		
Without Intent to Act	2	0		
Some Intent to Act	0	0		
Specific Plan and Intent	0	0		
Actual Attempt	0	0		
Non-Suicidal Self-Injurious Behavior	0	0		
Interrupted Attempt	0	0		
Aborted Attempt	0	0		
Preparatory Acts or Behavior	1	0		
Suicidal Behavior Present	1	0		
Completed Suicide	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Work Productivity and Activity Index-Specific Health Problem (WPAI-SHP) Questionnaire at Baseline

End point title	Work Productivity and Activity Index-Specific Health Problem (WPAI-SHP) Questionnaire at Baseline
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End point description:

WPAI-SHP assessed work productivity and impairment. It was a subject-rated, six-item questionnaire regarding current employment, hours missed and actually worked, and degree to which a specified health problem affected work productivity and regular activities over the past 7 days. Subscale scores included percent work time missed due to the health problem; percent impairment while working due to problem; percent overall work impairment due to problem; and percent activity impairment due to problem. Each subscale score was expressed as an impairment percentage (0-100) where higher numbers indicated greater impairment and less productivity. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Other pre-specified
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End point timeframe:

Baseline

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	193			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Percent Absenteeism (N= 86)	15.22 (± 25.36)			
Percent Presenteeism (N= 83)	53.98 (± 21.52)			

Percent Overall Work Impairment (N= 82)	57.96 (± 23.42)			
Percent Activity Impairment (N=193)	64.97 (± 18.77)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Utilization Assessment (Total Office Visits, Number of Hospitalizations and Number of Emergency Room Visits) at Baseline

End point title	Health Utilization Assessment (Total Office Visits, Number of Hospitalizations and Number of Emergency Room Visits) at Baseline
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End point description:

The healthcare utilization assessment was used to capture healthcare utilization data at Baseline. This assessment contained 10 questions related to aspects of healthcare services. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation. Here "99999" in the mean and standard deviation of number of hospitalizations, signifies not available (NA). Mean and standard deviation were not calculated as no subject was evaluated for this time point.

End point type	Other pre-specified
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End point timeframe:

Baseline

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	193			
Units: Visits				
arithmetic mean (standard deviation)				
Total office visits (N= 193)	5.01 (± 6.6)			
Number of hospitalizations (N= 0)	99999 (± 99999)			
Number of emergency room visits (N= 12)	1.83 (± 1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Health Utilization Assessment (Time for Help No Payment) at Baseline

End point title	Health Utilization Assessment (Time for Help No Payment) at Baseline
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End point description:

The healthcare utilization assessment was used to capture healthcare utilization data at Baseline. This assessment contained 10 questions related to aspects of healthcare services. 'Time for help no payment' refers to time other people spent without receiving payment to help with activities the patient cannot

perform due to fibromyalgia. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

End point type	Other pre-specified
End point timeframe:	
Baseline	

End point values	All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	193			
Units: Hours				
arithmetic mean (standard deviation)	50.37 (± 98.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 16

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious adverse event (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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Pregabalin
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Reporting group description:

The below table included subjects who received pregabalin in either treatment period pooled together due to the crossover study design. This crossover study consisted of two double blind 6-week treatment periods where subjects were randomized to pregabalin or placebo for the first period, and were then switched to the other treatment for the second period (3 weeks dose optimization and 3 weeks fixed dose for each treatment period). Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process. There was a 2-week single-blind taper or washout period between treatment periods.

Reporting group title	Placebo
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Reporting group description:

The below table included subjects who received placebo in either treatment period pooled together due to the crossover study design. This crossover study consisted of two double blind 6-week treatment periods where subjects were randomized to pregabalin or placebo for the first period, and were then switched to the other treatment for the second period (3 weeks dose optimization and 3 weeks fixed dose for each treatment period). There was a 2-week single-blind taper or washout period between treatment periods.

Serious adverse events	Pregabalin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 181 (1.66%)	1 / 177 (0.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm malignant			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Detoxification			

subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (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: 0 %

Non-serious adverse events	Pregabalin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 181 (76.80%)	106 / 177 (59.89%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	2 / 181 (1.10%)	2 / 177 (1.13%)	
occurrences (all)	2	2	
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Asthenia		
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)
occurrences (all)	1	2
Chest discomfort		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Chest pain		
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)
occurrences (all)	1	2
Crying		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Cyst		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Energy increased		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Fatigue		
subjects affected / exposed	12 / 181 (6.63%)	8 / 177 (4.52%)
occurrences (all)	13	9
Feeling abnormal		
subjects affected / exposed	5 / 181 (2.76%)	0 / 177 (0.00%)
occurrences (all)	5	0
Feeling drunk		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Feeling hot		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Feeling jittery		
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Gait disturbance		
subjects affected / exposed	3 / 181 (1.66%)	0 / 177 (0.00%)
occurrences (all)	3	0

Hunger			
subjects affected / exposed	3 / 181 (1.66%)	1 / 177 (0.56%)	
occurrences (all)	3	1	
Inflammation			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	3 / 181 (1.66%)	1 / 177 (0.56%)	
occurrences (all)	3	1	
Malaise			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	7 / 181 (3.87%)	3 / 177 (1.69%)	
occurrences (all)	8	3	
Pain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 181 (0.00%)	4 / 177 (2.26%)	
occurrences (all)	0	4	
Swelling			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal dryness			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 181 (1.10%)	1 / 177 (0.56%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Nasal dryness			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	3 / 181 (1.66%)	5 / 177 (2.82%)	
occurrences (all)	3	5	
Rhinorrhoea			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Psychiatric disorders			

Abnormal dreams		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Anxiety		
subjects affected / exposed	8 / 181 (4.42%)	7 / 177 (3.95%)
occurrences (all)	8	10
Apathy		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Bradyphrenia		
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Confusional state		
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Depressed mood		
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)
occurrences (all)	1	2
Depression		
subjects affected / exposed	5 / 181 (2.76%)	4 / 177 (2.26%)
occurrences (all)	5	4
Disorientation		
subjects affected / exposed	5 / 181 (2.76%)	0 / 177 (0.00%)
occurrences (all)	5	0
Euphoric mood		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Initial insomnia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Insomnia		
subjects affected / exposed	13 / 181 (7.18%)	1 / 177 (0.56%)
occurrences (all)	14	1
Nervousness		
subjects affected / exposed	3 / 181 (1.66%)	2 / 177 (1.13%)
occurrences (all)	3	2

Nightmare			
subjects affected / exposed	1 / 181 (0.55%)	4 / 177 (2.26%)	
occurrences (all)	1	4	
Panic attack			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Suicidal ideation			
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)	
occurrences (all)	2	0	
Thinking abnormal			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	0 / 181 (0.00%)	3 / 177 (1.69%)	
occurrences (all)	0	3	
Eosinophil count increased			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Weight increased			

subjects affected / exposed occurrences (all)	16 / 181 (8.84%) 16	3 / 177 (1.69%) 3	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)	
occurrences (all)	2	0	
Fall			
subjects affected / exposed	4 / 181 (2.21%)	1 / 177 (0.56%)	
occurrences (all)	4	1	
Hand fracture			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	0 / 181 (0.00%)	2 / 177 (1.13%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	3 / 181 (1.66%)	0 / 177 (0.00%)	
occurrences (all)	3	0	
Post concussion syndrome			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Road traffic accident			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Skeletal injury			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Tendon rupture			

subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Areflexia			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	5 / 181 (2.76%)	0 / 177 (0.00%)	
occurrences (all)	5	0	
Burning sensation			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Clumsiness			
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)	
occurrences (all)	2	0	
Cognitive disorder			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Disturbance in attention			
subjects affected / exposed	5 / 181 (2.76%)	4 / 177 (2.26%)	
occurrences (all)	5	4	
Dizziness			

subjects affected / exposed	51 / 181 (28.18%)	12 / 177 (6.78%)
occurrences (all)	67	14
Dizziness postural		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Dysgeusia		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Headache		
subjects affected / exposed	14 / 181 (7.73%)	17 / 177 (9.60%)
occurrences (all)	4	20
Hypersomnia		
subjects affected / exposed	3 / 181 (1.66%)	0 / 177 (0.00%)
occurrences (all)	3	0
Hyporeflexia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Lethargy		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Memory impairment		
subjects affected / exposed	5 / 181 (2.76%)	1 / 177 (0.56%)
occurrences (all)	5	1
Mental impairment		
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Migraine		
subjects affected / exposed	1 / 181 (0.55%)	3 / 177 (1.69%)
occurrences (all)	1	3
Myoclonus		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Paraesthesia		
subjects affected / exposed	2 / 181 (1.10%)	1 / 177 (0.56%)
occurrences (all)	2	1
Presyncope		

subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Repetitive speech			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Sedation			
subjects affected / exposed	4 / 181 (2.21%)	2 / 177 (1.13%)	
occurrences (all)	4	2	
Somnolence			
subjects affected / exposed	36 / 181 (19.89%)	8 / 177 (4.52%)	
occurrences (all)	48	8	
Stupor			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Tension headache			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Neutrophilia			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)	
occurrences (all)	2	0	
Eye disorders			

Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 181 (0.00%) 0	1 / 177 (0.56%) 1	
Dry eye subjects affected / exposed occurrences (all)	3 / 181 (1.66%) 3	0 / 177 (0.00%) 0	
Eye disorder subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 181 (0.00%) 0	1 / 177 (0.56%) 1	
Vision blurred subjects affected / exposed occurrences (all)	7 / 181 (3.87%) 7	3 / 177 (1.69%) 3	
Visual impairment subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 181 (0.00%) 0	1 / 177 (0.56%) 1	
Abdominal distension subjects affected / exposed occurrences (all)	2 / 181 (1.10%) 2	1 / 177 (0.56%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 181 (1.66%) 3	3 / 177 (1.69%) 3	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	4 / 177 (2.26%) 4	
Constipation subjects affected / exposed occurrences (all)	19 / 181 (10.50%) 20	4 / 177 (2.26%) 4	
Dental caries			

subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Diarrhoea		
subjects affected / exposed	16 / 181 (8.84%)	7 / 177 (3.95%)
occurrences (all)	16	7
Dry mouth		
subjects affected / exposed	12 / 181 (6.63%)	1 / 177 (0.56%)
occurrences (all)	12	1
Dyspepsia		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Dysphagia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Flatulence		
subjects affected / exposed	4 / 181 (2.21%)	2 / 177 (1.13%)
occurrences (all)	4	2
Gastrooesophageal reflux disease		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Haemorrhoids		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Irritable bowel syndrome		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Lip swelling		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Nausea		
subjects affected / exposed	17 / 181 (9.39%)	12 / 177 (6.78%)
occurrences (all)	19	15
Odynophagia		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Paraesthesia oral		

subjects affected / exposed	3 / 181 (1.66%)	0 / 177 (0.00%)	
occurrences (all)	3	0	
Salivary gland pain			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 181 (0.55%)	5 / 177 (2.82%)	
occurrences (all)	1	5	
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	4 / 181 (2.21%)	4 / 177 (2.26%)	
occurrences (all)	4	4	
Pruritus generalised			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	3 / 177 (1.69%) 3	
Rash generalised subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Skin lesion subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 181 (0.00%) 0	1 / 177 (0.56%) 1	
Haematuria subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Incontinence subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Oliguria subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Pollakiuria subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	1 / 177 (0.56%) 1	
Urinary retention subjects affected / exposed occurrences (all)	1 / 181 (0.55%) 1	0 / 177 (0.00%) 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion subjects affected / exposed occurrences (all)	0 / 181 (0.00%) 0	1 / 177 (0.56%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 181 (1.66%) 3	2 / 177 (1.13%) 2	
Back pain			

subjects affected / exposed	3 / 181 (1.66%)	4 / 177 (2.26%)
occurrences (all)	3	4
Fibromyalgia		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Flank pain		
subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Joint swelling		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Medial tibial stress syndrome		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Muscle spasms		
subjects affected / exposed	4 / 181 (2.21%)	1 / 177 (0.56%)
occurrences (all)	4	1
Muscle twitching		
subjects affected / exposed	3 / 181 (1.66%)	0 / 177 (0.00%)
occurrences (all)	3	0
Muscular weakness		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Musculoskeletal pain		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Myalgia		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Neck pain		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Osteoarthritis		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Pain in extremity		

subjects affected / exposed	3 / 181 (1.66%)	3 / 177 (1.69%)	
occurrences (all)	3	3	
Pain in jaw			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)	
occurrences (all)	1	2	
Bronchitis viral			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)	
occurrences (all)	1	2	
Folliculitis			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 181 (0.00%)	3 / 177 (1.69%)	
occurrences (all)	0	3	
Gastroenteritis viral			
subjects affected / exposed	4 / 181 (2.21%)	2 / 177 (1.13%)	
occurrences (all)	4	2	
Influenza			
subjects affected / exposed	3 / 181 (1.66%)	2 / 177 (1.13%)	
occurrences (all)	3	2	
Laryngitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	5 / 181 (2.76%)	10 / 177 (5.65%)	
occurrences (all)	5	10	

Oral herpes			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Pharyngitis			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)	
occurrences (all)	1	2	
Tooth infection			
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 181 (2.21%)	2 / 177 (1.13%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	2 / 181 (1.10%)	1 / 177 (0.56%)	
occurrences (all)	2	1	
Vaginal infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 181 (0.55%)	2 / 177 (1.13%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Fluid retention			

subjects affected / exposed	2 / 181 (1.10%)	0 / 177 (0.00%)
occurrences (all)	2	0
Folate deficiency		
subjects affected / exposed	0 / 181 (0.00%)	1 / 177 (0.56%)
occurrences (all)	0	1
Food craving		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Hyperglycaemia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Hyperlipidaemia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0
Hypoglycaemia		
subjects affected / exposed	1 / 181 (0.55%)	1 / 177 (0.56%)
occurrences (all)	1	1
Increased appetite		
subjects affected / exposed	4 / 181 (2.21%)	0 / 177 (0.00%)
occurrences (all)	4	0
Polydipsia		
subjects affected / exposed	1 / 181 (0.55%)	0 / 177 (0.00%)
occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2012	Benefit and risk summary was added. Subject withdrawal and adverse event reporting were updated. Pregnancy testing requirements were expanded. Clarifications regarding prohibited and allowable medications were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported