



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 (\geq) 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 standard deviation | 59.4 ± 9.83 | 58.4 ± 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 (\pm 0.127) | 5.018 (\pm 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 (\pm 1.03) | 38.3 (\pm 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 (\pm 0.25) | 7.86 (\pm 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 (\pm 0.16) | 2.94 (\pm 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: $\Sigma(8, 11, 13 - 15, 24, 27 - 35)$. 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 (\pm 0.61) | 23.66 (\pm 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 (\pm 0.16) | 2.58 (\pm 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 (\pm 0.03) | 1.65 (\pm 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 (\pm 0.02) | 1.18 (\pm 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 (\pm 0.03) | 1.51 (\pm 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 |
|-----------------|--|

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 (\pm 0.03) | 1.35 (\pm 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 (\pm 0.12) | 3.59 (\pm 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 occurrences (all) | 28 / 272 (10.29%) 28 | 4 / 276 (1.45%) 4 | |
| Headache subjects affected / exposed occurrences (all) | 9 / 272 (3.31%) 9 | 8 / 276 (2.90%) 10 | |
| Somnolence subjects affected / exposed occurrences (all) | 14 / 272 (5.15%) 14 | 7 / 276 (2.54%) 7 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 14 / 272 (5.15%) 15 | 4 / 276 (1.45%) 4 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 10 / 272 (3.68%) 11 | 8 / 276 (2.90%) 8 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 9 / 272 (3.31%) 9 | 11 / 276 (3.99%) 13 | |
| Nausea subjects affected / exposed occurrences (all) | 9 / 272 (3.31%) 9 | 8 / 276 (2.90%) 9 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 8 / 272 (2.94%) 8 | 4 / 276 (1.45%) 6 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 7 / 272 (2.57%) 10 | 5 / 276 (1.81%) 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