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PROPRIETARY DRUG NAME/GENERIC DRUG NAME: Lyrica®

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NCT NO.: 00159666

PROTOCOL NO.: A0081004

PROTOCOL TITLE: A double-blind randomized placebo-controlled trial of the time to onset of meaningful pain relief in subjects with postherpetic neuralgia (PHN) treated with pregabalin (150-600 mg/day flexible optimized dose or 300 mg/day fixed dose) or placebo

Study Center(s): 42 study centers (10, Germany; 5, Italy; 7, Spain; 6, the United Kingdom; 14, the United States) recruited subjects.[1]

Study Initiation and Completion Dates: 28 October 2004 to 28 June 2006

Phase of Development: 3b

Study Objective(s): The *primary objective* was to evaluate the time to a 1-point or greater improvement (with accompanying ≥ 30% improvement in weekly pain score at last visit) in the Daily Pain Rating Scale score in subjects with pain associated with PHN, treated with pregabalin 150-600 mg/day flexible dose, pregabalin 300 mg/day fixed dose, or placebo.

The *secondary objectives* were to:

- Evaluate the safety and tolerability of pregabalin for the treatment of subjects with pain associated with PHN
- Evaluate the time to an initial decrease of at least 30% in the Daily Pain Rating Scale score in subjects with pain associated with PHN, treated with pregabalin 150 − 600 mg/day flexible dose, pregabalin 300 mg/day fixed dose or placebo, who experience meaningful pain relief (a decrease of at least 30% in mean weekly pain score) by the end of double-blind treatment

[1] Of the 33 centers, 1 center in Italy and 1 center in Spain did not randomize any subjects.

- Evaluate the proportion of subjects reporting a decrease of at least 30% in the Daily Pain Rating Scale score by day in each treatment group (pregabalin 150 − 600 mg/day flexible dose, pregabalin 300 mg/day fixed dose and placebo)

- Evaluate the proportion of subjects reporting a decrease of at least 30% in the mean weekly pain score by the end of double-blind treatment in each treatment group (pregabalin 150 − 600 mg/day flexible dose, pregabalin 300 mg/day fixed dose and placebo)

- Evaluate the proportion of subjects reporting a decrease of at least 50% in the mean weekly pain score by the end of double-blind treatment in each treatment group (pregabalin 150 − 600 mg/day flexible dose, pregabalin 300 mg/day fixed dose and placebo)

- Evaluate changes in pain intensity on the Visual Analogue Scale (VAS) of the Short Form McGill Pain Questionnaire (SF-MPQ)

- Evaluate the subject's global impression of change using the Patient Global Impression of Change (PGIC)

- Evaluate improvement in subject-reported daily sleep interference due to pain using the Daily Sleep Interference Scale

- Evaluate changes in subject Visual Analog Scale (VAS) Anxiety ratings

- Evaluate changes in subject Visual Analog Scale (VAS) ratings of dynamic (brush evoked) allodynia

METHODS

Study Design: This was randomized, double-blind, parallel group, multicenter study comparing pregabalin (150 − 600 mg/day flexible optimized dose and 300 mg/day fixed dose) with placebo to evaluate the time to onset of meaningful pain relief in subjects with pain associated with PHN. The study consisted of a 7-day screening phase, the randomization visit, a 28-day double-blind treatment phase with weekly clinic visits, and a 1-week taper.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 255 subjects were to be randomized to treatment (85 subjects per treatment group).

Analyzed: A total of 270 subjects (92, flexible-dose pregabalin; 88, fixed-dose pregabalin; 90, placebo) were randomized to treatment, and 269 subjects were analyzed for efficacy (91, flexible-dose pregabalin; 88, fixed-dose pregabalin; and 90, placebo).

Diagnosis and Main Criteria for Inclusion: To enter the study, subjects had to be male or female outpatients who were at least 18 years of age and generally in good health, based on

physical examination and medical history, except for the presence of PHN with pain present for at least 3 months after the healing of a herpes zoster skin lesion. Subjects were further required to have a pain score of at least 40 mm on the 100 mm VAS-pain at both the screening visit and the randomization visit (which was to occur 7 ±3 days after screening), as well as an average Daily Pain Rating Scale score of at least 4, where the average score was based on 4 self-assessments entered onto an electronic diary prior to the randomization visit. Subjects could have been receiving other medications or non-pharmacologic treatments for pain associated with PHN. However, the treatment(s) could not be among those prohibited by the protocol (eg, gabapentin, oxycodone or any opioid combination medication including oxycodone, or non-pharmacological treatments involving needles such as acupuncture, local and topical anesthetics, nerve blocks, potential retinotoxins or skeletal muscle relaxants), and the dose had to have been stable for at least 30 days prior to randomization. Key exclusion criteria included a history of neurolytic or neurosurgical therapy for PHN, the presence of a neurologic disorder unrelated to PHN that could confuse or confound the assessment of neuropathic pain, the presence of any severe pain associated with conditions other than PHN that could confound the assessment or self-evaluation of pain due to PHN, and the presence of a skin condition in the affected dermatome that in the judgment of the investigator could alter sensation. Female subjects had to be non-pregnant and non-lactating, and had to be practicing an acceptable method of contraception. All subjects were required to have provided written informed consent before any study-related procedures were performed.

Study Treatment: Subjects received pregabalin at a flexible optimized dose of 150-600 mg/day ("flexible-dose pregabalin"), pregabalin at a fixed dose of 300 mg/day ("fixed-dose pregabalin"), or placebo in double-blind fashion for 4 weeks, after which the study medication was tapered for 1 week. All study medication was taken as 2 capsules per day, 1 in the morning and 1 in the evening, with or without food. Subjects in the pregabalin 150 − 600 mg/day group started treatment with pregabalin 150 mg/day for 3 days and then had their dose of study medication assessed and adjusted as needed to achieve the optimal balance of pain relief and tolerability by Day 14 of study drug administration. Subjects in the pregabalin 300 mg/day group received a fixed dose of study medication throughout the double-blind treatment period.

Efficacy Evaluations: The primary efficacy measure was the Daily Pain Rating Scale. Secondary efficacy measures were the pain-related Daily Sleep Interference Scale, the VAS-pain, the VAS-anxiety, VAS ratings of dynamic (brush-evoked) allodynia, and PGIC. All measures were subject-rated. Electronic subject diaries were used daily to capture Daily Pain Rating Scale and pain-related Daily Sleep Interference Scale scores (except at 5 of the 6 sites in Spain, where paper versions of the electronic diaries were used). Other efficacy rating scales were completed at the weekly clinic visits.

Safety Evaluations: The safety evaluation was based on any adverse events (AEs) volunteered by the subject or observed by the investigator, clinical laboratory test data, vital sign measurements (blood pressure, pulse, body weight), and physical and neurological examination findings.

Statistical Methods:

Efficacy: The primary efficacy endpoint was defined as the time to onset of pain relief in subjects who at the Week 4 visit (or the final visit for subjects who withdrew early) achieved meaningful pain relief, defined as an improvement of at least 30% in the mean weekly score on the Daily Pain Rating Scale ("mean weekly pain score"). Onset of pain relief was defined as a 1-point decrease in the Daily Pain Rating Scale score. Subjects who completed the study but who were not responders were censored as not having experienced the event for the full length of time for which they had data in the efficacy evaluation period. Subjects who did not complete and were not responders were administratively censored to 28 days. The Kaplan-Meier procedure was applied to this assessment. Treatments were compared using a Cox model with effects for treatment, study center, and baseline pain score. It was to be concluded that the onset of pain relief was greater than 4 weeks if more than half of the subjects were censored. The results were generalized by applying the proportional hazards model to the data. The Hochberg procedure was used to adjust for comparing each of 2 pregabalin regimens with placebo. Secondary endpoints included the time to an initial decrease from baseline of at least 30% in the Daily Pain Rating Scale score, which was analyzed using the same methodology. For continuous outcomes not involving survival methods, an analysis of covariance was employed, with treatment, study center, and baseline pain score included as covariates; a mixed model repeated measures analysis of weekly pain scores and weekly pain-related sleep interference scores was also performed. For categorical outcomes, the Cochran-Mantel-Haenszel test (for PGIC scores) or a logistic regression model (proportion of responders) was employed, with center, treatment, and baseline pain score included as covariate. The last observation carried forward (LOCF) method was used to impute missing values except where survival analysis methods are applied. No adjustment for multiplicity was applied to the secondary endpoints.

Safety: Safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography: Subject disposition and data sets analyzed are summarized in Table S1. As can be seen in the table, far fewer subjects treated with flexible-dose pregabalin discontinued the study due to AEs (4 [4.4%]) than subjects treated with fixed-dose pregabalin (18.2% of subjects during the double-blind period, plus 1 [1.1%] additional subject who discontinued during the taper).

Table S1 Subject Disposition and Data Sets Analyzed

Number of subjects		Pregabalin flexible dose N (%)	Pregabalin fixed dose N (%)	Placebo N (%)
Screened (N)	479			
Randomized		92	88	90
Treated		91	88	90
Completed double-blind phase		86 (94.5)	70 (79.5)	75 (83.3)
Discontinued during double-blind		5 (5.5)	18 (20.5)	15 (16.7)
Adverse events		4 (4.4)	16 (18.2)	4 (4.4)
Lack of efficacy		1 (1.1)	0	4 (4.4)
Other		0	2 (2.3)	7 (7.7)
Discontinued during taper		2 (2.2)	6 (6.8)	6 (6.7)
Adverse events		0 (0.0)	1 (1.1)	1 (1.1)
Other		2 (2.2)	5 (5.7)	5 (5.6)
Analyzed for efficacy				
Full analysis set (ITT)		91 (98.9)	88 (100.0)	90 (100.0)
Excluded from ITT population				
Reason: Did not receive any treatment		1 (1.1)	0	0
Evaluated for safety				
Adverse events		91 (100.0)	88 (100.0)	90 (100.0)
Laboratory data		87 (95.6)	79 (89.8)	85 (94.4)

ITT = Intent-to-treat, N = Number of subjects

Men comprised 54.9%, 55.7%, and 56.7% of subjects in the flexible-dose pregabalin, fixed-dose pregabalin, and placebo treatment groups, respectively. The mean age was 68.6, 67.9, 65.6 years in the in the flexible-dose pregabalin, fixed-dose pregabalin, and placebo treatment groups, respectively. Within the overall study population, subjects' ages ranged from 40 to 86 years. A majority of subjects in each treatment group (92.3%, flexible-dose pregabalin; 97.7%, fixed-dose pregabalin; and 95.6%, placebo) were white.

All subjects (100.0%) had a primary diagnosis of PHN. The mean number of years since diagnosis was 2.4, 3.1, and 2.1 in the flexible-dose pregabalin, fixed-dose pregabalin, and placebo treatment groups, respectively.

At baseline, the average subject had moderate-to-severe pain, as indicated by the mean weekly pain and VAS-pain scores, and approximately two-thirds of the subjects experienced moderate-to-severe allodynia (Table S2).

Table S2 Baseline Mean (SD) Weekly Pain, Weekly Pain-Related Sleep Interference, VAS-Pain, VAS-Anxiety, and VAS-Allodynia (Affected Area) Scores – ITT Population

	Pregabalin flexible dose (N=91)	Pregabalin fixed dose (N=88)	Placebo (N=90)
Daily Pain Rating Scale			
Weekly mean (SD)	6.51 (1.43)	6.39 (1.51)	6.49 (1.52)
Pain-Related Daily Sleep Interference Scale			
Weekly mean (SD)	4.43 (2.20)	4.62 (2.32)	4.55 (2.46)
VAS-Pain			
Mean (SD)	67.19 (14.91)	66.01 (15.08)	66.70 (15.80)
VAS-Anxiety			
Mean (SD)	32.71 (30.39)	34.82 (30.68)	32.59 (30.07)
VAS-Allodynia (affected area)			
Mean (SD)	50.13 (29.32)	49.24 (29.23)	51.96 (30.79)
Number (%) of subjects with moderate-to-severe allodynia*	62 (68.1)	60 (68.2)	61 (67.8)

N = Number of ITT subjects in a treatment group, ITT = Intent-to-treat, SD = Standard deviation, VAS = Visual analog scale.
*Moderate-to-severe allodynia was defined as a VAS allodynia rating of 40 mm or greater when touched by a foam brush on an area of the skin affected by PHN.

Efficacy Results:

Primary: The primary efficacy endpoint was the time to onset of pain relief in subjects who achieved meaningful pain relief, where meaningful pain relief was defined as a 30% or greater decrease from baseline to endpoint in the mean weekly score and onset of pain relief was defined as a 1-point decrease in the Daily Pain Rating Scale score. The primary efficacy results showed that among the 69.2% and 58.0% of subjects treated with flexible-dose pregabalin and fixed-dose pregabalin who achieved meaningful pain relief, the median time to onset of pain relief[2] was 3.5 and 1.5 days, respectively. In comparison, 30.0% of subjects treated with placebo achieved meaningful pain relief; because less than 50% of the subjects achieved meaningful pain relief, the median time to onset of pain relief[2] was considered to be greater than 4 weeks. The 25th percentile time to onset of pain relief[2] was 1.0 days in both pregabalin treatment groups, compared with 8.0 days in the placebo treatment group. Statistical analysis of the time to onset of pain relief showed that subjects treated with flexible-dose pregabalin and subjects treated with fixed-dose pregabalin were statistically significantly more likely to experience relief from pain associated with PHN, with an earlier onset of pain relief, than subjects treated with placebo (flexible-dose pregabalin: hazard ratio [HR], 2.88, adjusted $p<0.0001$; fixed-dose pregabalin: HR, 3.21, adjusted $p<0.0001$).

[2] The median (or 25th percentile) times to onset of pain relief was the smallest observed number of days before at least 50% (or 25%) of responding subjects experienced a 1-point reduction from baseline in the Daily Pain Rating Scale score.

Secondary: Secondary efficacy results were as follows:

- Among the 83.5% and 79.5% of subjects treated with flexible-dose pregabalin and fixed-dose pregabalin, respectively, who achieved a 30% or greater improvement from baseline in the Daily Pain Rating Scale score at any time during the study (ie, with or without an accompanying 30% or greater improvement at endpoint), the median time to an initial improvement[3] of that magnitude was 5.0 and 2.0 days, respectively. In comparison, among the 57.8% of subjects treated with placebo who achieved a 30% or greater improvement from baseline in the Daily Pain Rating Scale score at any time during the study, the median time to an initial improvement[3] of that magnitude was 16.0 days. In the flexible-dose pregabalin, fixed-dose pregabalin, and placebo treatment groups, the 25th percentile time to an initial 30% or greater improvement in the Daily Pain Rating Scale score[3] was 2.0, 1.0, and 5.0 days, respectively, and the 75th percentile time[3] was 16.0, 16.5, and 37.0 days, respectively. Statistical analysis of the time to an initial 30% or greater improvement in the Daily Pain Rating Scale score showed that subjects treated with flexible-dose pregabalin were statistically significantly more likely to experience early improvement than subjects treated with placebo (HR, 1.59; 95% confidence interval [CI], 1.10, 2.30; adjusted p-value = 0.0274). Subjects treated with fixed-dose pregabalin were also more likely to experience a 30% improvement in the Daily Pain Rating Scale score than subjects treated with placebo, but the difference between the fixed-dose pregabalin and placebo treatment groups was not statistically significant (HR, 1.42; 95% CI, 0.99, 2.04; adjusted p-value, 0.0563). There was an overall treatment effect in favor of pregabalin (p = 0.0400).

- The least square (LS) mean change from baseline to endpoint (LOCF) in the mean weekly pain score was statistically significantly greater (improved) in the flexible-dose pregabalin (-2.96, p<0.0001) and fixed-dose pregabalin (-2.60, p = 0.0004) treatment groups than in the placebo treatment group (-1.60). Statistically significant differences in favor of each pregabalin treatment regimen relative to placebo were apparent starting at Week 1. Results of the repeated measures analysis of changes from baseline in the mean weekly pain score were consistent with the results of the LOCF analysis.

- A 30% or greater improvement in the mean weekly pain score at endpoint was achieved by statistically significantly greater proportions of subjects in the flexible-dose pregabalin (70.0%, p<0.0001) and fixed-dose pregabalin (58.0%, p = 0.0003) treatment groups than in the placebo treatment group (31.0%). A 50% or greater improvement in the mean weekly pain score was achieved by statistically significantly greater proportions of subjects in the flexible-dose pregabalin (46.7%, p = 0.0001) and fixed-dose pregabalin (39.8%, p = 0.0020) treatment groups than in the placebo treatment group (18.4%). For both measures, statistically significant

[3] The median (or 25th or 75th percentile) time to a 30% or greater reduction from baseline in the Daily Pain Rating Scale score was the smallest observed number of days before at least 50% (or 25% or 75%) of subjects experienced improvement of that magnitude.

differences in favor of each pregabalin treatment regimen relative to placebo were apparent starting at Week 1.

- The LS mean change from baseline to endpoint (LOCF) in the mean weekly pain-related Sleep Interference Scale score was statistically significantly greater (improved) in the flexible-dose pregabalin (-1.97; p<0.0001) and fixed-dose pregabalin (-1.79, p=0.0023) treatment groups than in the placebo treatment group (-1.04). Statistically significant differences in favor of each pregabalin treatment regimen relative to placebo were apparent starting at Week 1. Results of the repeated measures analysis of changes from baseline in the mean weekly pain-related Sleep Interference Scale scores were consistent with the results of the LOCF analysis.

- The LS mean change from baseline to endpoint (LOCF) in the VAS-pain score was statistically significantly greater (improved) in the flexible-dose pregabalin (-37.55, p<0.0001) and fixed-dose pregabalin (-33.19, p = 0.0008) treatment groups than in the placebo treatment group (-21.22). Statistically significant differences in favor of each pregabalin treatment regimen relative to placebo were apparent starting at Week 1.

- The LS mean change from baseline to endpoint (LOCF) in the VAS-anxiety score was statistically significantly greater (improved) in the flexible-dose pregabalin (-17.64, p = 0.0237) and fixed-dose pregabalin (-17.75, p = 0.0247) treatment groups than in the placebo treatment group (-10.29). Statistically significant differences in favor of each pregabalin treatment regimen relative to placebo were apparent starting at Week 1.

- The LS mean changes from baseline to endpoint in the VAS ratings of brush-evoked allodynia for the affected area was statistically significantly greater (improved) in the flexible-dose pregabalin (–26.23, p<0.0001) and fixed-dose pregabalin (-20.81, p = 0.0075) treatment groups than in the placebo treatment group (-11.83). Statistically significant differences in favor of each pregabalin treatment relative to placebo were apparent starting at Week 1.

- At baseline, mean VAS ratings of brush-evoked allodynia for unaffected areas in the flexible-dose pregabalin, fixed-dose pregabalin, and placebo treatment groups were, in general, consistent with most subjects having minimal pain in areas unaffected by PHN. As expected, the LS mean changes from baseline to endpoint in the VAS ratings of brush-evoked allodynia for unaffected areas were small, and the treatment differences were not statistically significant.

- The proportions of subjects in the flexible-dose pregabalin and fixed-dose pregabalin treatment groups who had a PGIC rating of minimally, much, and very much improved were 88.8% and 76.5%, respectively, compared with 59.3% in the placebo treatment group. No subjects treated with flexible-dose pregabalin and 3.7% of subjects treated with fixed-dose pregabalin had a PGIC rating of minimally, much, or very much worse, compared with 9.3% of subjects treated with placebo. The proportions of subjects in the flexible-dose pregabalin and fixed-dose pregabalin

treatment groups who had a PGIC rating of no change were 11.2% and 19.8%, respectively, compared with 31.4% in the placebo treatment group. The distribution of subjects across PGIC categories was statistically significantly different between flexible-dose pregabalin and placebo ($p<0.0001$) as well as between fixed-dose pregabalin and placebo ($p = 0.0387$).

- In all 3 treatment groups, PGIC ratings at endpoint were significantly correlated with changes from baseline to endpoint in mean weekly pain score and VAS ratings of brush-evoked allodynia in areas affected by PHN. In the fixed-dose pregabalin and placebo treatment groups, but not the flexible-dose pregabalin treatment group, PGIC ratings at endpoint were significantly correlated with changes from baseline to endpoint in VAS-anxiety scores. A correlation between PGIC ratings at endpoint and changes from baseline to endpoint in VAS ratings of brush-evoked allodynia in unaffected areas was not expected and was not observed.

Safety Results: The proportions of subjects treated with flexible-dose pregabalin, fixed-dose pregabalin, and placebo who experienced at least 1 treatment-emergent AE (all causalities) were 72.5%, 62.5%, and 43.3%, respectively. In each of the 3 treatment groups, the majority of treatment-emergent AEs (all causalities) that occurred were mild or moderate in intensity, with 6.6%, 9.1%, and 7.8% of subjects treated with flexible-dose pregabalin, fixed-dose pregabalin, and placebo, respectively, experiencing severe AEs.

The most commonly reported treatment-emergent AEs (all causalities) in both pregabalin treatment groups were dizziness, somnolence, fatigue, and weight increased. Each of these AEs occurred more than 3 times as frequently in subjects treated with either pregabalin treatment regimen as in subjects treated with placebo. In addition to these 4 AEs, pregabalin treatment was associated with increased incidences relative to placebo of visual abnormalities, vertigo, balance disorder, edema, and AEs related to cognition. With few exceptions, these types of AEs were, in the investigator's judgment, related to treatment. Treatment-emergent AEs (all causalities) that occurred in at least 2% of subjects treated with flexible-dose pregabalin or fixed-dose pregabalin and with an incidence of at least twice that in the placebo treatment group are shown in Table S3.

Table S3 Treatment-Emergent Adverse Events (All Causalities) that Occurred in ≥ 2% of Subjects in Either Pregabalin Treatment Group and With an Incidence ≥ 2 Times that of Placebo – Safety Population

Adverse Event (MedDRA SOC / Preferred Term)	Pregabalin Flexible Dose (N = 91) n (%)	Pregabalin Fixed Dose (N = 88) n (%)	Placebo (N = 90) n (%)
Ear and labyrinth disorders			
Vertigo	4 (4.4)	2 (2.3)	0
Eye disorders			
Visual disturbance	4 (4.4)	0	0
Diplopia	1 (1.1)	3 (3.4)	0
General disorders & admin. Site conditions			
Fatigue	8 (8.8)	5 (5.7)	1 (1.1)
Feeling abnormal	5 (5.5)	1 (1.1)	0
Edema peripheral	3 (3.3)	3 (3.4)	1 (1.1)
Pain [a]	2 (2.2)	0	0
Injury, poisoning, procedural complications			
Contusion	2 (2.2)	0	0
Fall	2 (2.2)	1 (1.1)	0
Investigations			
Weight increased	8 (8.8)	4 (4.5)	0
Metabolism and nutrition disorders			
Increased appetite	3 (3.3)	1 (1.1)	1 (1.1)
Musculoskeletal & connective tissue disorders			
Joint swelling	0 (0.0)	2 (2.3)	1 (1.1)
Nervous system disorders			
Dizziness	22 (24.2)	27 (30.7)	6 (6.7)
Somnolence	10 (11.0)	17 (19.3)	2 (2.2)
Balance disorder	3 (3.3)	4 (4.5)	0
Tremor	3 (3.3)	1 (1.1)	0
Memory impairment	3 (3.3)	0	0
Depressed level of consciousness	2 (2.2)	1 (1.1)	1 (1.1)
Coordination abnormal	0	2 (2.3)	0
Amnesia	0	2 (2.3)	0
Lethargy	0	2 (2.3)	0
Psychiatric disorders			
Confusional state	3 (3.3)	3 (3.4)	0
Disorientation	2 (2.2)	2 (2.3)	0
Euphoric mood	2 (2.2)	2 (2.3)	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0	2 (2.3)	1 (1.1)

N = Number of safety-evaluable subjects in a treatment group, n = Number of subjects with AE, MedDRA = Medical Dictionary for Regulatory Activities, version 9.0, SOC = System organ class.

[a]One subject experienced pain (investigator term, "total body ache") starting on Day 32, the 4th day of the taper; another subject experienced pain (investigator term, "increased pain") on Days 12-14; the investigator considered the AE to be due to the disease under study and increased the study medication dose in response to the AE.

One treatment-emergent AE (all causalities) occurred in at least 2% of placebo-treated subjects and with an incidence at least 2 times that in one or both pregabalin treatment groups. This AE, nausea, occurred in 4.4%, 0.0%, and 7.8% of subjects treated with flexible-dose pregabalin, fixed-dose pregabalin, and placebo, respectively.

The proportion of subjects who permanently discontinued treatment due to treatment-emergent AEs was greater in the fixed-dose pregabalin treatment group (17 [19.3%] subjects) than in the flexible-dose pregabalin (4, 4.4%) or placebo (5, 5.6%) treatment groups. (Note that, as indicated in Table S1, above, 16 [18.2%] subjects treated with fixed-dose pregabalin and 4 [4.4%] subjects treated with placebo discontinued due to AEs during the double-blind treatment phase. One [1.1%] additional subject treated with fixed-dose pregabalin and 1 [1.1%] additional subject treated with placebo discontinued due to AEs during the taper period.) In the flexible-dose pregabalin treatment group, no single type of AE led to the permanent discontinuation from treatment of more than 1 subject: 1 (1.1%) subject discontinued due to vertigo, nausea, and weight increased, and 1 (1.1%) subject each discontinued due to generalized edema, tremor, and myocardial infarction. In the fixed-dose pregabalin treatment group, dizziness was the most common adverse leading to treatment discontinuation (9 [10.2%] subjects), followed by vertigo, fatigue, and headache (2 [2.3%] subjects for each event). All other AEs led to the discontinuation of 1 (1.1%) subject each, and they included amnesia, confusional state, coordination abnormal, euphoric mood, nervousness, adverse drug reaction (investigator term, "adverse study drug reaction/tolerability issues"), cellulitis, pneumonia, dyspnea, pulmonary congestion, diplopia, bronchitis, and edema peripheral. In the placebo treatment group, the most common AE that led to discontinuation was dizziness (3 [3.3%] subjects); the other AEs (dyspnea exertional, nausea, disturbance in attention, headache, and hallucination) led to the discontinuation of 1 (1.1%) subject each. Most AEs leading to discontinuation in all 3 treatment groups were considered to be related to treatment. Adverse events leading to discontinuation were considered to be severe and treatment-related in 5 of the 17 subjects treated with fixed-dose pregabalin, in comparison with 1 subject treated with flexible-dose pregabalin and 1 subject treated with placebo.

No subjects died during the conduct of this study. From the first day the study medication was administered up through 30 days after the last dose of study medication, 1 subject in each treatment group experienced a serious adverse event (flexible-dose pregabalin group, myocardial infarction; fixed-dose pregabalin group, cellulitis, and placebo group, ovarian cyst torsion). A fourth subject, in the flexible-dose pregabalin treatment group, experienced an SAE (ejection fraction [30%]) that began before the first dose of study medication was administered. None of the SAEs were considered to be related to treatment.

There were no patterns in summaries of clinical laboratory test or vital sign data that suggested a relationship to treatment for either pregabalin treatment regimen.

CONCLUSION(S):

In subjects with pain associated with PHN, treatment with each of 2 different pregabalin regimens (a flexible optimized dose of 150 − 600 mg/day or pregabalin at a fixed dose of 300 mg/day) resulted in a faster onset of pain relief and a higher incidence of meaningful pain relief compared with placebo treatment. Treatment with each pregabalin regimen was also superior to placebo in PHN-associated sleep interference, anxiety, and allodynia. Both pregabalin treatment regimens were shown to be safe and generally well tolerated, with a safety profile consistent with that reported in the current Lyrica® product label. Flexibly adjusting the pregabalin dose based on the individual subject's response and tolerability provided an incremental benefit over administration of pregabalin at a fixed dose, in that this

treatment regimen permitted more subjects to remain on treatment for the duration of the study.