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**PROPRIETARY DRUG NAME® / GENERIC DRUG NAME:** Lyrica® / Pregabalin

**PROTOCOL NO.**: A0081047

**PROTOCOL TITLE**: A Double-Blind, Randomized, Multicenter Efficacy and Safety Study of Pregabalin (Lyrica®) as Monotherapy in Patients With Partial Seizures

**Study Centers***:* A total of 54 centers took part in the study and enrolled subjects; 3 in the Czech Republic, 1 in Hong Kong, 6 in the Ukraine, and 44 in the United States (US).

**Study Initiation, Primary Completion and Final Completion Dates:**
Study Initiation Date: 20 September 2007
Primary Completion Date: 14 April 2011
Final Completion Date: 21 June 2011. The study was terminated prematurely for efficacy.

**Phase of Development**: Phase 3

**Study Objectives:** To assess the efficacy of pregabalin as monotherapy in the treatment of subjects with partial seizures who were not well controlled on current antiepileptic drug (AED) treatment. Safety data were also collected and analyzed.

**METHODS**

**Study Design:** This was a double-blind, randomized, historically controlled, multicenter pregabalin study in subjects with partial seizures.

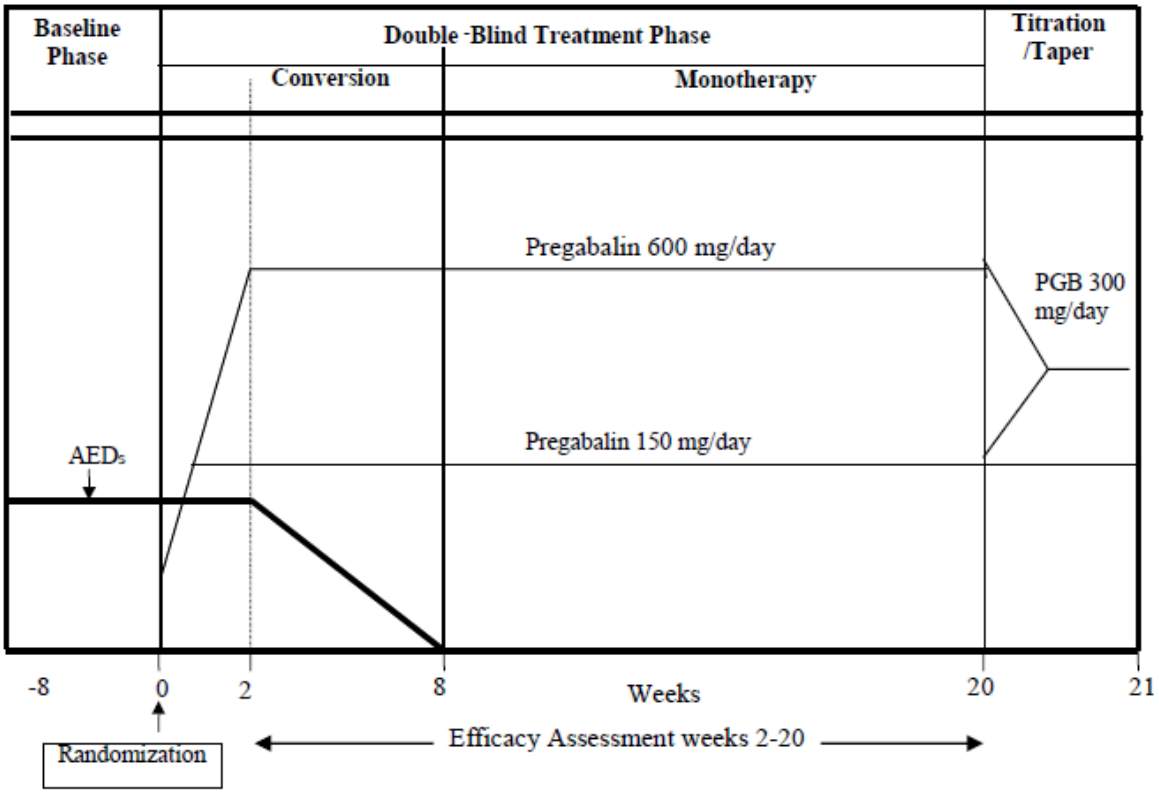
There were 3 phases to this study following the Screening Visit (Visit 1), as outlined below and summarized in Figure 1:

- An 8-Week Baseline Phase:
  Subjects who experienced ≥4 partial seizures during the 8-week Baseline phase with no 28-day seizure-free period and who met all other inclusion and none of the exclusion criteria were eligible for randomization.

- A 20-Week Double-Blind Treatment Phase:
  Eligible subjects were randomized to fixed doses of either pregabalin 150 mg/day or 600 mg/day (in a 1:4 ratio). Dose escalation to 600 mg/day occurred over 2 weeks, and previous AEDs treatment was gradually reduced within the following 6 weeks (Weeks 2-8) and were to be completely withdrawn by the end of Week 8. Double-blind pregabalin monotherapy continued for an additional 12 weeks, until Week 20.

- A 1-Week Titration/Taper Phase:
  Subjects who completed the double-blind monotherapy treatment phase had the option of continuing pregabalin monotherapy by entering an open-label extension study (an open-label multicenter extension study to determine long term safety and efficacy of pregabalin (Lyrica) as monotherapy in patients with partial seizures [NCT00596466]) for an additional 6 months or converting to alternative AEDs therapy and tapering pregabalin over the final week.

**Figure 1 Overview of Study Design**




Subjects were randomized to pregabalin 150 mg/day or 600 mg/day in a 1:4 ratio.
AED = antiepileptic drug; PGB = pregabalin.

One interim analysis (IA) was planned to be conducted when the first 50% subjects of the targeted sample size (ie, the first 125 subjects randomized of 250 planned) had completed the study. An independent, external Data Monitoring Committee (DMC) would conduct an unblinded analysis and would notify the Sponsor of their recommendation via the DMC liaison.

The schedule of activities is presented in Table 1.

## Table 1. Schedule of Activities

| | Screening | Double-Blind Treatment | | | | | | | Titration/Taper |
|---|---|---|---|---|---|---|---|---|---|
| | | Conversion | | | Monotherapy | | | | |
| **Visit** | **1** | **2[a]** | **3** | **4** | **5** | **6** | **7** | **8[b]/Early Termination[c]** | **9[d]** |
| **End of Week** | **- 8** | **---** | **2** | **5** | **8** | **12** | **16** | **20** | **21** |
| **Day** | **- 56** | **1** | **14** | **35** | **56** | **84** | **112** | **140** | **147** |
| Informed consent | X | | | | | | | | |
| Inclusion/exclusion | X | X | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical history[e] | X | | | | | | | | |
| Prior/concomitant medications | X | X | X | X | X | X | X | X | X |
| Physical exam including body weight | X | X | | | | | | X | |
| Neurological exam | X | X | | | | | | X | |
| 12-Lead electrocardiogram | X | | | | | | | | |
| Blood pressure and pulse | X | X | X | | X | | X | X | |
| Electroencephalogram[f] | X[f] | | | | | | | | |
| MRI or CT scan with contrast[f] | X[f] | | | | | | | | |
| Clinical labs | X | X | | | X | | X | X | |
| Serum pregnancy test | X | | | | | | | | |
| Urine pregnancy test | | X | | | X | | X | X | |
| Explain and dispense seizure diary | X | X | X | X | X | X | X | X | |
| Review seizure diary | | X | X | X | X | X | X | X | X |
| Randomize | | X | | | | | | | |
| Dispense drug | | X | X | X | X | X | X | X | |
| PK samples[g] | | X | | | X, X | | X | X | |
| Adverse events | | X | X | X | X | X | X | X | X |

CT = computed tomography; MRI = magnetic resonance imaging; PK = pharmacokinetic.

a. All measurements were performed prior to dosing with study medication except for the PK sample collection.
b. Subjects who completed this study and elected to enter the open-label extension study were screened at this visit for the extension study.
c. Early termination: these procedures were also to be performed for those subjects withdrawing early from the study.
d. Subjects who completed this study and elected to enter the open-label extension study had Visit 2 (Day 1) of the open-label extension study at this visit.
e. Included general medical and epilepsy history, as well as psychiatric, social, occupational, and educational history.
f. Not necessary if done within the 2 years prior to Screening.
g. PK samples were collected as follows: Visit 2 at 15-60 minutes postdose, Visit 5 predose and at least 1 hour postdose, Visit 7 predose and Visit 8 at any time during the visit.

**Number of Subjects (Planned and Analyzed):** It was planned to enroll 250 subjects in the study (ie, 200 subjects in the 600 mg/day treatment group and 50 subjects in the 150 mg/day treatment group). A total of 236 subjects were screened and 161 subjects were assigned to study treatment (6 in the Czech Republic, 2 in Hong Kong, 35 in the Ukraine, and 118 in the US).

**Diagnosis and Main Criteria for Inclusion:** Male or nonpregnant and nonlactating female subjects, aged ≥18 years, pregabalin-naive, with diagnosed epilepsy with partial seizures, documented history of at least 4 partial seizures in the 8 weeks prior to the Screening Visit, and receiving stable treatment with 1 to 2 AEDs during the 8 weeks prior to the Screening Visit, were included in the study.

Excluded were subjects with a current diagnosis of febrile seizures or seizures related to an ongoing acute medical illness; seizures occurring only in cluster patterns, or seizures of a metabolic, toxic, or infectious origin; primary generalized epilepsy (eg, absence epilepsy); progressive structural central nervous system lesion or a progressive encephalopathy; status epilepticus within the previous year, or any significant psychiatric disorders.

**Study Treatment:** Study medication was supplied by the Sponsor as blinded capsules of pregabalin (75 mg, 150 mg, 225 mg, and 300 mg). Subjects randomized to pregabalin 150 mg/day (administered as 75 mg twice daily [BID]) began and continued treatment at this dose until the end of the double-blind monotherapy treatment phase.

Subjects were randomized to pregabalin 600 mg/day, began treatment with 150 mg/day (75 mg BID) for Days 1-7. The dose was increased to 300 mg/day (150 mg BID) for Days 8-14, and then to 600 mg/day (300 mg BID) from Day 15 to the end of the double-blind monotherapy treatment phase.

At the end of the double-blind treatment phase, subjects entered a taper phase and could have elected to continue pregabalin in a 6-month open-label extension study. Alternatively, subjects could have elected to convert to alternative AEDs, which were introduced over 3 weeks, while pregabalin was withdrawn over a 1-week period.

If the subject was to continue taking marketed pregabalin after early withdrawal or study completion (and was not entering the open-label extension study), tapering of pregabalin could not have been warranted based on the Investigator's discretion.

In order to maintain the treatment blind, all subjects electing to enter the open-label extension study had their pregabalin doses adjusted to 300 mg/day under blinded conditions.

For those subjects electing to convert to alternative AEDs, tapering of pregabalin was as follows during Week 21 while alternative AEDs were introduced: for subjects randomized to 600 mg/day (300 mg BID), the dose was tapered for 6 days and completely withdrawn on the seventh day; for subjects randomized to 150 mg/day (75 mg BID), this dose was maintained for 6 days and then completely withdrawn on the seventh day. The blinded study medication was administrated orally, BID, with or without food.

**Efficacy and Pharmacokinetic Endpoints:**

Primary Efficacy Endpoint:

The primary efficacy endpoint of this study was the percent of subjects who meet at least 1 of the following predetermined exit criteria:

- An episode of status epilepticus;
- A secondarily generalized tonic-clonic seizure if none had been experienced within 2 years of study entry;
- A 28-day study seizure rate during the double-blind treatment phase that was >2 times the maximum 28-day study seizure rate during the Baseline phase (a 28-day period defined as 28 consecutive study days);
- A 2-day study seizure rate during the double-blind treatment phase that was >2 times the maximum 2-day study seizure rate during the Baseline phase (a 2-day period defined as 2 consecutive study days);
- An unacceptable increase in the frequency or intensity of seizure activity that, according to the Investigator, was clinically significant.

Secondary Efficacy Endpoints:

The secondary endpoints of this trial were:

- Exit rate for the 150 mg/day group;
- The completion rate defined as percent of subjects who completed the 20 weeks of double-blind treatment;
- Percent of subjects who met each of the 5 protocol-specified exit events;
- Mean time on pregabalin monotherapy;
- Percent of subjects seizure-free:
    - During the last 28 days on double-blind study medication (monotherapy phase);
    - During the entire monotherapy portion of the double-blind treatment phase;
    - During all of the double-blind treatment phase (excluding the titration/taper phase, ie, after Week 20).
- Pregabalin population pharmacokinetics;
- Pregabalin exposure-response analyses.

**Safety Evaluations:** Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), adverse events (AEs), physical and neurological examinations, and safety laboratory tests.

**Statistical Methods:**

Data Sets Analyzed: The data sets used in this study were as follows:

Intent-to-Treat (ITT): Randomized subjects who received at least 1 dose of pregabalin during the study.

- The ITT: Full Study set included all randomized subjects who met the ITT definition.
- The ITT: IA set included randomized subjects who met the ITT definition and were randomized within the same time frame as the first 125 subjects randomized.

Modified Intent-to-Treat (mITT): Randomized subjects who received at least 1 dose of pregabalin during the double-blind treatment phase, had a Baseline seizure assessment, and participated in the double-blind efficacy assessment after Week 2. Subjects in the mITT set were summarized and analyzed for efficacy according to the treatment to which they were randomized.

- The mITT: Full Study set included all randomized subjects who met the mITT definition.
- The mITT: Efficacy set included the first 125 randomized subjects who met the mITT definition.

Estimation of Seizure Exit Rates:

The seizure exit rates were estimated for each treatment group separately as:

Percent exit rate = $\left(1 - \hat{S}_{Day126}\right) \cdot 100\%$,

where $\hat{S}_{Day126}$ was the Kaplan-Meier survival estimate obtained directly from the LIFETEST procedure of the statistical analysis system output with corresponding row 'Day 126' and column 'Survival'.

Hypothesis testing of the primary efficacy endpoint involved a 2-step testing procedure in order to assess the efficacy of the pregabalin 600 mg/day group.

An IA was conducted during the course of this study which utilized a Pocock stopping boundary based upon a Lan-DeMets alpha spending function.

Subjects who did not exit during the study under the predetermined seizure exit criteria and completed the study were appropriately censored at Visit 8/Early Termination (ie, Week 20 [Day 140]). Subjects who dropped out of the study prior to completion of the

study but did not exit the study under the predetermined seizure exit criteria were reviewed by the DMC in a blinded manner prior to the IA, and the DMC decided whether to consider the observation as randomly censored or as a seizure-related exit at the subject's last recorded visit. The DMC performed a blinded review of the reasons for early discontinuation for those subjects included in the IA, and again for the additional subjects not included in the IA.

Analyses of Primary Endpoint: When a subject exited the study according to at least 1 of the exit criteria, the withdrawal was considered as occurrence of an 'event' and the 'time to event' was the number of days from Baseline (ie, 1 day before randomized study treatment was initially dispensed) to the date when the event/censoring occurred. Any events occurring during the 2-week titration phase were not included in the analysis. Subjects who did not exit during the study or who dropped out from the study for reasons other than the predefined exit criteria were censored at their last recorded visit during the double-blind efficacy phase.

The percentage of subjects in the pregabalin 600 mg/day group exiting by Day 126 (Week 18) of the study was compared with the historical control threshold of 74% using a 1-sample inference involving the Kaplan-Meier product limit estimates at Day 126 (ie, 112 days after the 2-week titration phase to reach 600 mg/day). Efficacy was to be declared if the upper bound of the 2-sided 95% confidence interval (CI) for the 600 mg/day group exit rate was below the 74% historical threshold. If efficacy was declared using the 74% threshold for the 600 mg/day group, then an evaluation of the same 2-sided 95% CI for the 600 mg/day group was to be made to see if the upper bound was below a more stringent historical control threshold of 68%. This 2-sided 95% CI at Day 126 was constructed using the Kaplan-Meier product limit estimate and Greenwood's formula for estimating the variance with a continuity correction.

The exit rate was derived by taking 1 minus the Kaplan-Meier product limit estimate for the survival function, and multiplying it by 100. The 2-sided 95% adjusted CI for the exit rate was derived in the same manner as explained previously based on a normal approximation, with the variance estimated by Greenwood's formula with a continuity correction.

The continuity correction method was considered the most conservative for estimating the exit rate. Additional methods involved constructing an uncorrected 2-sided 95% CI using a normal approximation and assuming a non-informative beta distribution which formed the relevant posterior beta distribution using the number of subjects who met an exit criterion.

Additional sensitivity analyses in which all subjects who discontinued early without meeting a seizure exit criterion were considered as meeting an exit criterion were conducted to assess the robustness of the primary efficacy analysis.

Supplemental Analyses: Supplemental analyses comparing the survival curves between the pregabalin 600 mg/day and the 150 mg/day groups were performed, as well as computing the relevant probabilities under the posterior distribution in assessing the exit rates at Day 126 between the 600 mg/day and 150 mg/day groups, using the mITT: Efficacy set.

Analyses of Secondary Endpoint: The secondary endpoints were presented using descriptive statistics by treatment group. The exit rate for the pregabalin 150 mg/day group was

calculated using a similar method as the primary efficacy endpoint involving the 600 mg/day group.

To be considered seizure-free for the secondary endpoint, subjects were required to complete 20 weeks of double-blind treatment.

Analyses of Pharmacokinetic (PK) Parameters: Plasma pregabalin concentrations were determined to support population PK and exposure-response analyses. The population PK analysis was used to derive the population mean and variance values for the PK parameters.

**RESULTS**

Based on the results of the IA, the study was terminated early for positive efficacy.

**Subject Disposition and Demography:** The ITT: IA set included 134 subjects who were assigned to study treatment and received at least 1 dose of pregabalin. Overall in the ITT: Full Study set, 161 subjects were assigned to study treatment and received at least 1 dose of pregabalin. The subject disposition and subjects analyzed is presented in Table 2.

## Table 2. Subject Disposition and Subjects Analyzed

| Number (%) of Subjects | ITT: IA Pregabalin N=134 | | ITT: Full Study Pregabalin N=161 | |
|---|---|---|---|---|
| | 150 mg/day | 600 mg/day | 150 mg/day | 600 mg/day |
| Screened: 236 | | | | |
| Assigned to study treatment: 161 | | | | |
| Treated | 27 | 107 | 32 | 129 |
| Completed treatment[a] | 11 (40.7) | 54 (50.5) | 15 (46.9) | 70 (54.3) |
| Completed study[b] | 11 (40.7) | 54 (50.5) | 15 (46.9) | 70 (54.3) |
| Discontinued[c] | 16 (59.3) | 53 (49.5) | 17 (53.1) | 59 (45.7) |
| Subject died | 0 | 1 (0.9) | 0 | 1 (0.8) |
| Related to study drug | 3 (11.1) | 13 (12.1) | 3 (9.4) | 16 (12.4) |
| Adverse event | 3 (11.1) | 13 (12.1) | 3 (9.4) | 16 (12.4) |
| Not related to study drug | 0 | 5 (4.7) | 0 | 5 (3.9) |
| Adverse event | 0 | 5 (4.7) | 0 | 5 (3.9) |
| Relationship to study drug not defined | 13 (48.1) | 34 (31.8) | 14 (43.8) | 37 (28.7) |
| Insufficient clinical response | 9 (33.3) | 24 (22.4) | 10 (31.3) | 24 (18.6) |
| Lost to follow-up | 0 | 1 (0.9) | 0 | 2 (1.6) |
| No longer willing to participate in study | 3 (11.1) | 7 (6.5) | 3 (9.4) | 8 (6.2) |
| Other | 0 | 1 (0.9) | 0 | 2 (1.6)[d] |
| Protocol violation | 0 | 1 (0.9) | 0 | 1 (0.8) |
| Withdrawn due to pregnancy | 1 (3.7) | 0 | 1 (3.1) | 0 |
| Analyzed for efficacy | | | | |
| Modified intent-to-treat (mITT)[e] | 23 (85.2) | 102 (95.3) | 28 (87.5) | 120 (93.0) |
| Analyzed for safety | | | | |
| Adverse events | 27 (100.0) | 107 (100.0) | 32 (100.0) | 129 (100.0) |
| Laboratory data | 26 (96.3) | 102 (95.3) | 31 (96.9) | 123 (95.3) |

IA = Interim Analysis; ITT = intent-to-treat; mITT = modified intent to treat; N = number of subjects.

a. Subjects completed the double-blind efficacy phase.
b. Subjects completed the taper/titration phase.
c. Discontinuations have been attributed to the last study treatment received.
d. One subject was withdrawn due to lack of compliance and another was withdrawn because the Investigator believed the subject was incorrectly reporting seizure activity.
e. mITT included all randomized subjects who received at least 1 dose of pregabalin and had a baseline seizure assessment. The mITT set for the IA (mITT: efficacy) was the set used for the definitive efficacy analyses; the mITT set for the full study (mITT: full study) was used for descriptive purposes only.

The demographic characteristics by treatment (ITT: Full Study) is presented in Table 3.

**Table 3. Demographic Characteristics by Treatment (ITT: Full Study)**

| Demographic Characteristic Parameter | Pregabalin | | | | | |
|---|---|---|---|---|---|---|
| | 150 mg/day | | | 600 mg/day | | |
| | Male N[a]=14 | Female N[a]=18 | Total N[a]=32 | Male N[a]=58 | Female N[a]=71 | Total N[a]=129 |
| Age (years), n (%): | | | | | | |
| 18-44 | 12 (85.7) | 14 (77.8) | 26 (81.3) | 42 (72.4) | 43 (60.6) | 85 (65.9) |
| 45-64 | 1 (7.1) | 4 (22.2) | 5 (15.6) | 15 (25.9) | 25 (35.2) | 40 (31.0) |
| ≥65 | 1 (7.1) | 0 | 1 (3.1) | 1 (1.7) | 3 (4.2) | 4 (3.1) |
| Mean (SD) | 35.1 (13.8) | 35.2 (11.6) | 35.2 (12.4) | 38.9 (11.7) | 40.8 (14.4) | 39.9 (13.2) |
| Range | 19-72 | 21-57 | 19-72 | 18-73 | 19-76 | 18-76 |
| Race, n (%): | | | | | | |
| White | 11 (78.6) | 17 (94.4) | 28 (87.5) | 50 (86.2) | 57 (80.3) | 107 (82.9) |
| Black | 1 (7.1) | 1 (5.6) | 2 (6.3) | 5 (8.6) | 13 (18.3) | 18 (14.0) |
| Asian | 1 (7.1) | 0 | 1 (3.1) | 2 (3.4) | 0 | 2 (1.6) |
| Other | 1 (7.1) | 0 | 1 (3.1) | 1 (1.7) | 1 (1.4) | 2 (1.6) |
| Weight (kg): | | | | | | |
| Mean (SD) | 90.9 (27.4) | 75.6 (19.4) | 82.3 (24.1) | 88.2 (19.0) | 76.7 (20.3) | 81.8 (20.5) |
| Range | 52.2-145.0 | 48.0-132.4 | 48.0-145.0 | 61.0-143.3 | 41.7-137.0 | 41.7-143.3 |
| N[b] (%) | 14 (100.0) | 18 (100.0) | 32 (100.0) | 57 (98.3) | 71 (100.0) | 128 (99.2) |
| Height (cm): | | | | | | |
| Mean (SD) | 179.1 (11.6) | 166.8 (6.9) | 172.4 (11.1) | 177.4 (6.7) | 163.3 (6.1) | 169.6 (9.5) |
| Range | 147.0-196.0 | 155.0-177.0 | 147.0-196.0 | 161.5-196.0 | 149.0-178.0 | 149.0-196.0 |
| N[b] (%) | 14 (100.0) | 17 (94.4) | 31 (96.9) | 56 (96.6) | 71 (100.0) | 127 (98.4) |

ITT = intent-to-treat; n = number of subjects in category; SD = standard deviation.
a. Number of subjects in treatment group.
b. Number of subjects providing data.

**Efficacy Results:**

In the primary analysis, the seizure-related exit rate for subjects in the pregabalin 600 mg/day group (mITT: Efficacy) was estimated as 31.9%, with a 95% CI (20.7%, 43.1%); this was statistically significantly less than the historical control rates of 68% and 74% (p-value <0.001; Table 4).

**Table 4. Summary Statistics for Primary Endpoint: Subjects Meeting at Least 1 Seizure Exit Criterion in the Pregabalin 600 mg/day Group (mITT: Efficacy)**

| | Pregabalin 600 mg/day N=102 |
|---|---|
| Total number of subjects[a] | 102 |
| Effective sample size[b] (n*) | 89.64 |
| Subjects who met at least 1 predefined exit criterion (%) | 29 (28.4) |
| Subjects censored[c] (%) | 73 (71.6) |
| Exit rate (SE)[d] | 31.9% (4.92%) |
| 95% adjusted CI for exit rate[e] | (20.7%, 43.1%) |
| p-Value ($H_0$: exit rate ≥68%)[f] | <0.001 |
| p-Value ($H_0$: exit rate ≥74%)[f] | <0.001 |

The events which occurred between the Week 2 Visit and Day 126 were included in the analysis.
CI = confidence interval; mITT = modified intent-totreat; N = number of subjects; SE = standard error.

a. Total number of subjects was derived from subjects in the mITT who provided discontinuation/completion data.
b. The effective sample size (n*) was found using Greenwood's formula for the variance.
c. Subjects who did not exit the study due to predefined exit criteria were censored at the last visit in the double-blind efficacy period.
d. The exit rate was defined as (1 minus Kaplan-Meier product limit estimate for survival function) × 100%. SE = square root (Variance of Kaplan-Meier Estimator at Day 126) × 100%.
e. The 2-sided 95% adjusted CI for exit rate at Day 126 (or Efficacy Day 112) was constructed using the Kaplan-Meier product limit estimation and Greenwood's formula for the variance with a continuity correction.
f. p-Values were obtained from Wald test.

A higher percentage of subjects in the pregabalin 150 mg/day group (mITT: Efficacy) met at least 1 seizure exit criterion compared with the 600 mg/day group (9/23 [39.1%] subjects in the 150 mg/day group versus 29/102 [28.4%] subjects in the 600 mg/day group; Table 4 and Table 5).

**Table 5. Summary of Subjects Who Met at Least 1 Exit Criterion or Were Adjudicated as an Exit by the DMC (mITT: Efficacy)**

| Treatment Phase<br>Number (%) of Subjects | Pregabalin | |
|---|---|---|
| | 150 mg/day<br>N=23 | 600 mg/day<br>N=102 |
| During the primary efficacy evaluation period[a] | | |
| Total[b] | 9 (39.1) | 29 (28.4) |
| Episode of status epilepticus | 0 | 1 (1.0) |
| SGTC seizure if not experienced within 2 years of entry | 0 | 3 (2.9) |
| 28-day SR during DB trt >2× the maximum 28-day SR during BL | 3 (13.0) | 11 (10.8) |
| 2-day SR during DB trt >2× the maximum 2-day SR during BL | 3 (13.0) | 8 (7.8) |
| Unacceptable increase in frequency/intensity of seizure activity | 4 (17.4) | 15 (14.7) |

BL = Baseline; DB = double-blind; DMC = Data Monitoring Committee; mITT = modified intent to treat; N = number of subjects; SGTC = secondarily generalized tonic-clonic; SR = seizure rate; trt = treatment.

a. The primary efficacy evaluation period was defined between the Week 2 Visit and Day 126. The exits which occurred between Week 2 Visit and Day 126 were included in the analysis.

b. Subjects may have met >1 exit criterion, so the total number of subjects meeting at least 1 criterion does not = the sum of subjects meeting the individual exit criteria.

Supplemental and sensitivity analyses in the mITT: Efficacy set as well as end of study analyses for the mITT: Full Study set confirmed the results of the primary analysis.

The seizure types experienced by subjects during the 8-week Screening and Baseline phases (mITT: Full Study) is summarized in Table 6.

**Table 6. Seizure Types at Screening and Baseline (mITT: Full Study)**

| Number. (%) of Subjects | Pregabalin | |
|---|---|---|
| | 150 mg/day<br>N=28 | 600 mg/day<br>N=120 |
| **8-Week Screening Phase** | | |
| Simple partial | 17 (60.7) | 60 (50.0) |
| Complex partial | 11 (39.3) | 68 (56.7) |
| Secondary generalized tonic-clonic | 10 (35.7) | 24 (20.0) |
| Generalized seizure(s) | 1 (3.6) | 6 (5.0) |
| Status epilepticus | 0 | 0 |
| Unclassified epileptic seizures | 0 | 2 (1.7) |
| **8-Week Baseline Phase** | | |
| Simple partial | 19 (67.9) | 74 (61.7) |
| Complex partial | 15 (53.6) | 81 (67.5) |
| Secondary generalized tonic-clonic | 12 (42.9) | 35 (29.2) |
| Generalized seizure(s) | 0 | 4 (3.3) |
| Status epilepticus | 0 | 0 |
| Unclassified epileptic seizures | 0 | 3 (2.5) |

Subjects may have had >1 type of seizure per phase.
mITT = modified intent-to-treat; N = number of subjects.

Sensitivity Analyses for the Primary Endpoint (mITT: Full Study):

The results of the analysis of the seizure exit rate for the pregabalin 600 mg/day group in the mITT: Full Study set (Table 7) were consistent with the results from the mITT: Efficacy set (Table 4).

**Table 7. Summary Statistics for Primary Endpoint: Subjects Meeting at Least 1 Seizure Exit Criterion in the Pregabalin 600 mg/day Group (mITT: Full Study)**

| | **Pregabalin 600 mg/day N=120** |
|---|---|
| Total number of subjects[a] | 120 |
| Effective sample size[b] (n*) | 108.14 |
| Subjects who met at least 1 predefined exit criterion (%) | 30 (25) |
| Subjects censored[c] (%) | 90 (75) |
| Exit rate (SE)[d] | 27.5% (4.29%) |
| 95% adjusted CI for exit rate[e] | (17.8%, 37.2%) |
| p-Value ($H_0$: exit rate ≥68%)[f] | <0.001 |
| p-Value ($H_0$: exit rate ≥74%)[f] | <0.001 |

The events which occurred between the Week 2 Visit and Day 126 were included in the analysis.
CI = confidence interval; mITT = modified intent to treat; N = number of subjects; SE = standard error.

a. Total number of subjects was derived from subjects in the mITT who provided discontinuation/completion data.
b. The effective sample size (n*) was found using Greenwood's formula for the variance.
c. Subjects who did not exit the study due to predefined exit criteria were censored at the last visit in the double-blind efficacy period.
d. The exit rate was defined as (1 minus Kaplan-Meier product limit estimate for survival function) × 100%. SE = square root (Variance of Kaplan-Meier Estimator at Day 126) × 100%.
e. The 2-sided 95% adjusted CI for exit rate at Day 126 (or Efficacy Day 112) was constructed using the Kaplan-Meier product limit estimation and Greenwood's formula for the variance with a continuity correction.
f. p-Values were obtained from Wald test.

The proportions of subjects in both treatment groups meeting the different exit criteria in the mITT: Full Study set (Table 8) were similar to the results in the mITT: Efficacy set (Table 5).

**Table 8. Summary of Subjects Who Met at Least 1 Exit Criterion or Were Adjudicated as an Exit by the DMC (mITT: Full Study)**

| Treatment Phase<br>Number (%) of Subjects | Pregabalin | |
|---|---|---|
| | 150 mg/day<br>N=28 | 600 mg/day<br>N=120 |
| During the primary efficacy evaluation period[a] | | |
| Total[b] | 10 (35.7) | 30 (25.0) |
| Episode of status epilepticus | 0 | 2 (1.7) |
| SGTC seizure if not experienced within 2 years of entry | 0 | 2 (1.7) |
| 28-day SR during DB treatment >2 × the maximum 28-day SR during BL | 3 (10.7) | 11 (9.2) |
| 2-day SR during DB treatment >2 × the maximum 2-day SR during BL | 4 (14.3) | 7 (5.8) |
| Unacceptable increase in frequency/intensity of seizure activity | 4 (14.3) | 17 (14.2) |

BL = Baseline; DB = double-blind; DMC = Data Monitoring Committee; mITT = modified intent-to-treat; N = number of subjects; SGTC = secondarily generalized tonic-clonic; SR = seizure rate.

a. The primary efficacy evaluation period was defined between the Week 2 Visit and Day 126. The exits which occurred between Week 2 Visit and Day 126 were included in the analysis.

b. Subjects may have met >1 exit criterion, so the total number of subjects meeting at least 1 criterion does not = the sum of subjects meeting the individual exit criteria.

In a sensitivity analysis using the mITT: Full Study set which considered all discontinuations as meeting exit criteria, the estimated seizure exit rates in the pregabalin 600 mg/day group were less than the historical control rates of 68% and 74% (Table 9).

**Table 9. Summary Statistics for Sensitivity Analyses of the Primary Endpoint: All Subject Discontinuations in the Pregabalin 600 mg/day Group Considered Meeting Exit Criteria (mITT: Full Study)**

| | Pregabalin 600 mg/day N=120 |
|---|---|
| Number of dropouts[a]: 20 (16.7%) | |
| Kaplan-Meier estimator with continuity correction | |
| Total number of subjects[b] | 120 |
| Effective sample size[c] (n*) | 120.0 |
| Subjects considered as exits | 48 (40%) |
| Subjects censored[d] (%) | 72 (60%) |
| Exit rate (SE)[e] | 40% (4.47%) |
| 95% adjusted CI for exit rate[f] | (29.9%, 50.1%) |
| Kaplan-Meier estimator without continuity correction | |
| Total number of subjects[b] | 120 |
| Effective sample size[c] (n*) | 120.0 |
| Subjects considered as exits | 48 (40%) |
| Subjects censored[d] (%) | 72 (60%) |
| Exit rate (SE)[e] | 40% (4.47%) |
| 95% adjusted CI for exit rate[f] | (30.4%, 49.6%) |
| Posterior beta distribution | |
| Total number of subjects[b] | 120 |
| Effective sample size[c] (n*) | 120.0 |
| Subjects considered as exits | 48 (40%) |
| Number of no exit events[g] | 72.00 |
| Subjects censored[d] (%) | 72 (60%) |
| Exit rate (SE)[e] | 40% (4.47%) |
| 95% adjusted CI for exit rate[f] | (30.9%, 49.9%) |

The events which occurred between the Week 2 Visit and Day 126 were included in the analysis.
CI = confidence interval; mITT = modified intent-to-treat; N = number of subjects; SE = standard error.

a. Dropouts = subjects marked as not applicable on the exit case report form page.
b. Total number of subjects was derived from subjects in the mITT who provided discontinuation/completion data.
c. The effective sample size (n*) was found using Greenwood's formula for the variance.
d. Subjects who did not exit the study due to predefined exit criteria were censored at the last visit in the double-blind efficacy period.
e. The exit rate was defined as (1 minus Kaplan-Meier product limit estimate for survival function) × 100%. SE = square root (Variance of Kaplan-Meier Estimator at Day 126) × 100%.
f. The 2-sided 95% adjusted CI for exit rate at Day 126 (or Efficacy Day 112) was constructed using the Kaplan-Meier product limit estimation and Greenwood's formula for the variance with a continuity correction.
g. Number of no exit events = n* – subjects considered as exits.

In a sensitivity analysis for the mITT: Full Study set using the Kaplan-Meier approach without continuity correction, as in the primary analysis, the rate of subjects who met at least 1 of the seizure exit criteria for subjects in the pregabalin 600 mg/day group was statistically significantly (p-value <0.001) less than the historical control rates of 68% and 74%.

The seizure-related exit rate for subjects in the 150 mg/day group (mITT: Full Study) was estimated as 37.7%, with a 95% CI of (15.4%, 60.0%); this was statistically significantly less than the historical control rates of 68% and 74% (p-value ≤0.001; Table 10).

**Table 10. Summary Statistics for Discontinuation Rate due to Seizure Exit Criteria in the Pregabalin 150 mg/day Group (mITT: Full Study)**

| | Pregabalin 150 mg/day N=28 |
|---|---|
| Total number of subjects[a] | 28 |
| Effective sample size[b] (n*) | 26.18 |
| Subjects who met at least 1 predefined exit criterion (%) | 10 (35.7) |
| Subjects censored[c] (%) | 18 (64.3) |
| Exit rate (SE)[d] | 37.7% (9.47%) |
| 95% adjusted CI for exit rate[e] | (15.4%, 60.0%) |
| p-Value ($H_0$: exit rate ≥68%)[f] | 0.001 |
| p-Value ($H_0$: exit rate ≥74%)[f] | <0.001 |

The events which occurred between the Week 2 Visit and Day 126 were included in the analysis.
CI = confidence interval; mITT = modified intent-to-treat; N=number of subjects; SE = standard error.

a. Total number of subjects was derived from subjects in the mITT who provided discontinuation/completion data.
b. The effective sample size (n*) was found using Greenwood's formula for the variance.
c. Subjects who did not exit the study due to predefined exit criteria were censored at the last visit in the double-blind efficacy period.
d. The exit rate was defined as (1 minus Kaplan-Meier product limit estimate for survival function) × 100%. SE = square root (Variance of Kaplan-Meier Estimator at Day 126) × 100%.
e. The 2-sided 95% adjusted CI for exit rate at Day 126 (or Efficacy Day 112) was constructed using the Kaplan-Meier product limit estimation and Greenwood's formula for the variance with a continuity correction.
f. p-Values were obtained from Wald test.

In subjects completing 20 weeks of the double-blind treatment period (mITT: Full Study), similar percentages of subjects in both treatment groups (15/28 [53.6%] subjects in the pregabalin 150 mg/day group and 70/120 [58.3%] subjects in the 600 mg/day group was observed.

Mean Time on Pregabalin Monotherapy (mITT: Full Study): A similar percentage of subjects in each group (22/28 [78.6%] subjects in the pregabalin 150 mg/day group and 97/120 [80.8%] subjects in the 600 mg/day group; mITT: Full Study) entered the monotherapy phase beginning at Week 8 (Table 11). The mean time that subjects were treated during the monotherapy phase was 73.8 days in the 150 mg/day group (range 5 days to 119 days) and 78.0 days in the 600 mg/day group (range 2 days to 128 days).

**Table 11. Mean Time (Days) on Pregabalin Monotherapy (mITT: Full Study)**

| Time (Days) | Pregabalin | |
|---|---|---|
| | 150 mg/day N=28 | 600 mg/day N=120 |
| Subjects entering the monotherapy phase[a] | | |
| n | 22 | 97 |
| Mean (SD) | 73.8 (30.15) | 78.0 (28.24) |
| Median | 84.0 | 84.0 |
| Min, Max | 5, 119 | 2, 128 |
| Subjects who met at least 1 predefined exit criterion or adjudicated as an exit by the DMC | | |
| n | 4 | 13 |
| Mean (SD) | 52.5 (42.37) | 41.1 (21.82) |
| Median | 53.0 | 38.0 |
| Min, Max | 6, 98 | 6, 71 |
| Seizure-free subjects[b] | | |
| n | 2 | 8 |
| Mean (SD) | 83.5 (0.71) | 91.6 (9.07) |
| Median | 83.5 | 89.5 |
| Min, Max | 83, 84 | 83, 107 |

DMC = Data Monitoring Committee; Max = maximum; Min = minimum; mITT = modified intent-to-treat; N = number of subjects in treatment group; n = number of subjects in category; SD = standard deviation.

a. The monotherapy phase = approximately Days 56-140 (based on the days of the subject's Visits 5 through 8). Some subjects converted as early as Week 2 (Visit 3), and their data were included in this table.

b. To be considered seizure-free, subjects must have completed the monotherapy phase and been seizure-free.

Percent of Subject Seizure-Free (mITT: Full Study): A slightly higher percentage of subjects in the pregabalin 600 mg/day group (70/120, 58.3%) compared with the 150 mg/day group (15/28, 53.6%) completed 20 weeks of treatment in the study (mITT: Full Study; Table 12).

**Table 12. Summary of Seizure-Free Subjects (mITT: Full Study)**

| Parameter<br>Number (%) of Subjects | Pregabalin | |
|---|---|---|
| | 150 mg/day N=28 | 600 mg/day N=120 |
| Number of completers | 15 (53.6) | 70 (58.3) |
| Seizure-free during the last 28 days on double-blind study medication (monotherapy phase)[a] | 5 (17.9) | 15 (12.5) |
| Seizure-free during the monotherapy portion of the double-blind treatment phase[b] | 2 (7.1) | 8 (6.7) |
| Seizure-free during all of the double-blind treatment phase[c] | 0 | 2 (1.7) |

mITT = modified intent-to-treat; N = number of subjects.

a. The last 28 days on double-blind study medication (monotherapy phase) = approximately Days 112-140 (based on the days of the subject's Visits 7 [Week 16] and 8 [Week 20]).

b. The monotherapy portion of the double-blind treatment phase = approximately Days 56-140 (based on the days of the subject's Visits 5 [Week 8] through 8 [Week 20]).

c. All of the double-blind treatment phase = Days 1– approximately 140 (based on the day of the subject's Visit 8 [Week 20]).

**Safety Results:** In all categories, percentages of subjects with AEs (all causalities and treatment-related) were higher in the pregabalin 600 mg/day group compared with the

150 mg/day group. One subject (3.1%) in the 150 mg/day group experienced an serious AE (SAE) (non-treatment related) (Table 13).

**Table 13. Overview of Treatment-Emergent Adverse Events (ITT: Full Study)**

| Number (%) of Subjects | Pregabalin | |
|---|---|---|
| | 150 mg/day | 600 mg/day |
| Subjects evaluable for adverse events | 32 | 129 |
| **All Causality** | | |
| Number of adverse events | 72 | 410 |
| Subjects with: | | |
| Adverse events | 23 (71.9) | 102 (79.1) |
| Serious adverse events | 1 (3.1) | 17 (13.2) |
| Severe adverse events | 1 (3.1) | 18 (14.0) |
| Discontinuations due to adverse events | 3 (9.4) | 22 (17.1) |
| Dose reductions/temporary discontinuations due to adverse events | 0 | 6 (4.7) |
| **Treatment-Related** | | |
| Number of adverse events | 39 | 249 |
| Subjects with: | | |
| Adverse events | 17 (53.1) | 81 (62.8) |
| Serious adverse events | 0 | 4 (3.1) |
| Severe adverse events | 1 (3.1) | 10 (7.8) |
| Discontinuations due to adverse events | 3 (9.4) | 16 (12.4) |
| Dose reductions/temporary discontinuations due to adverse events | 0 | 4 (3.1) |

Except for the number of adverse events, subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
ITT = intent-to-treat; N = number of subjects.

Treatment-emergent AEs (all causalities) reported for ≥5% of subjects in either group are summarized in Table 14.

**Table 14. Treatment-Emergent Adverse Events (All Causalities) Reported for ≥5% of Subjects in Either Group (ITT: Full Study)**

| System Organ Class<br>Preferred Term<br>Number (%) of Subjects | Pregabalin<br>150 mg/day<br>(N=32) | <br>600 mg/day<br>(N=129) |
|---|---|---|
| Eye disorders | 1 (3.1) | 13 (10.1) |
| Vision blurred | 1 (3.1) | 8 (6.2) |
| Gastrointestinal disorders | 4 (12.5) | 23 (17.8) |
| Dry mouth | 2 (6.3) | 2 (1.6) |
| Flatulence | 0 | 8 (6.2) |
| General disorders and administration site conditions | 5 (15.6) | 32 (24.8) |
| Fatigue | 2 (6.3) | 20 (15.5) |
| Oedema peripheral | 1 (3.1) | 8 (6.2) |
| Investigations | 5 (15.6) | 29 (22.5) |
| Alanine aminotransferase increased | 2 (6.3) | 1 (0.8) |
| Weight increased | 2 (6.3) | 21 (16.3) |
| Nervous system disorders | 15 (46.9) | 58 (45.0) |
| Balance disorder | 0 | 8 (6.2) |
| Disturbance in attention | 3 (9.4) | 4 (3.1) |
| Dizziness | 5 (15.6) | 25 (19.4) |
| Dysarthria | 2 (6.3) | 2 (1.6) |
| Headache | 0 | 13 (10.1) |
| Somnolence | 5 (15.6) | 22 (17.1) |
| Psychiatric disorders | 2 (6.3) | 27 (20.9) |
| Confusional state | 0 | 7 (5.4) |

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; v = version.

Treatment-related AEs reported for ≥5% of subjects in either group are summarized in Table 15. The most frequently reported treatment-related AEs in both groups were dizziness and somnolence.

**Table 15. Incidence of Treatment-Related Treatment- Emergent Adverse Events Reported for ≥5% of Subjects in Either Group (ITT: Full Study)**

| System Organ Class<br>Preferred Term<br>Number (%) of Subjects | Pregabalin<br>150 mg/day<br>(N=32) | <br>600 mg/day<br>(N=129) |
|---|---|---|
| Eye disorders | 1 (3.1) | 12 (9.3) |
| Vision blurred | 1 (3.1) | 8 (6.2) |
| Gastrointestinal disorders | 3 (9.4) | 17 (13.2) |
| Dry mouth | 2 (6.3) | 2 (1.6) |
| Flatulence | 0 | 8 (6.2) |
| General disorders and administration site conditions | 3 (9.4) | 22 (17.1) |
| Fatigue | 2 (6.3) | 14 (10.9) |
| Oedema peripheral | 0 | 7 (5.4) |
| Investigations | 3 (9.4) | 24 (18.6) |
| Weight increased | 2 (6.3) | 21 (16.3) |
| Nervous system disorders | 13 (40.6) | 55 (42.6) |
| Disturbance in attention | 3 (9.4) | 4 (3.1) |
| Dizziness | 5 (15.6) | 22 (17.1) |
| Dysarthria | 2 (6.3) | 1 (0.8) |
| Headache | 0 | 9 (7.0) |
| Somnolence | 5 (15.6) | 22 (17.1) |

AEs and SAEs are not separated out.
Subjects are counted only once per treatment in each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
AE = adverse event; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SAE = serious adverse event; v = version.

A total of 18 subjects experienced SAEs: 1 subject in the pregabalin 150 mg/day group 17 subjects in the 600 mg/day group. Five of the seizure SAEs in 600 mg/day group were the only SAEs considered treatment-related during the study (Table 16).

**Table 16. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)**

| System Organ Class<br>Preferred Term<br>Number (%) of Subjects | All Causalities | | Treatment-Related | |
|---|---|---|---|---|
| | Pregabalin | | Pregabalin | |
| | 150 mg/day (N=32) | 600 mg/day (N=129) | 150 mg/day (N=32) | 600 mg/day (N=129) |
| Cardiac disorders | 0 | 2 (1.6) | 0 | 0 |
| Angina pectoris | 0 | 1 (0.8) | 0 | 0 |
| Cardio-respiratory arrest | 0 | 1 (0.8) | 0 | 0 |
| Gastrointestinal disorders | 0 | 1 (0.8) | 0 | 0 |
| Abdominal pain | 0 | 1 (0.8) | 0 | 0 |
| General disorders and administration site conditions | 0 | 1 (0.8) | 0 | 0 |
| Chest pain | 0 | 1 (0.8) | 0 | 0 |
| Infections and infestations | 0 | 3 (2.3) | 0 | 0 |
| Meningitis bacterial | 0 | 1 (0.8) | 0 | 0 |
| Pneumonia | 0 | 2 (1.6) | 0 | 0 |
| Nervous system disorders | 0 | 10 (7.8) | | 5 (3.9) |
| Complex partial seizures | 0 | 1 (0.8) | | 0 |
| Convulsion | 0 | 5 (3.9) | | 1 (0.8) |
| Epilepsy | 0 | 1 (0.8) | | 1 (0.8) |
| Grand mal convulsion | 0 | 2 (1.6) | | 2 (1.6) |
| Lethargy | 0 | 1 (0.8) | | |
| Status epilepticus | 0 | 1 (0.8) | | 1 (0.8) |
| Pregnancy, puerperium and perinatal conditions | 1 (3.1) | 0 | | 0 |
| Abortion spontaneous | 1 (3.1) | 0 | | 0 |
| Psychiatric disorders | 0 | 1 (0.8) | | 0 |
| Homicidal ideation | 0 | 1 (0.8) | | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (0.8) | | 0 |
| Wheezing | 0 | 1 (0.8) | | 0 |

Subjects are counted only once per treatment in each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; v = version.

Overall, a total of 24 subjects were withdrawn from the study due to treatment-emergent AEs: 3/32 (9.4%) subjects in the pregabalin 150 mg/day group and 21/129 (16.3%) subjects in the 600 mg/day group (Table 17).

## Table 17. Discontinuations due to Treatment-Emergent Adverse Events (ITT: Full Study)

| Serial Number | System Organ Class/Preferred Term | Start Day/ Stop Day | Severity | Outcome | Causality |
|---|---|---|---|---|---|
| **Pregabalin 150 mg/day** | | | | | |
| 1 | Nervous system disorders/Somnolence | 1/1 | Severe | Resolved | Study drug |
| 2 | Nervous system disorders/Dizziness | 1/5 | Moderate | Resolved | Study drug |
| | Nervous system disorders/Dysarthria | 1/5 | Moderate | Resolved | Study drug |
| 3 | General disorders and administration site conditions/Fatigue | 90/113 | Mild | Resolved | Study drug |
| | Nervous system disorders/Disturbance in attention | 90/113 | Mild | Resolved | Study drug |
| **Pregabalin 600 mg/day** | | | | | |
| 4 | General disorders and administration site conditions/Asthenia | 64/92 | Mild | Resolved | Study drug |
| | General disorders and administration site conditions/Fatigue | 64/92 | Mild | Resolved | Study drug |
| 5 | Nervous system disorders/Dizziness | 1/[>43] | Mild | Still present | Study drug |
| 6 | Musculoskeletal and connective tissue disorders/Muscle spasms | 16/16 | Moderate | Resolved | Study drug |
| 7 | Skin and subcutaneous tissue disorders/Exfoliative rash | 74/[>90] | Mild | Still present | Study drug |
| 8[a] | Nervous system disorders/Convulsion[b] | 43/43 | Moderate | Resolved | Disease under study |
| 9 | Psychiatric disorders/Suicidal ideation | 6/[>65] | Mild | Still present | Study drug |
| 10[a] | Nervous system disorders/Convulsion[b] | 124/126 | Severe | Resolved | Disease under study |
| 11 | Ear and labyrinth disorders/Vertigo | 36/55 | Mild | Resolved | Study drug |
| 12 | Nervous system disorders/Sedation | 2/13 | Moderate | Resolved | Study drug |
| 13[a] | Nervous system disorders/Convulsion[b] | 78/78 | Severe | Resolved | Study drug |
| 14 | General disorders and administration site conditions/Fatigue | 1/2 | Moderate | Resolved | Study drug |
| 15 | Injury, poisoning and procedural complications/Toxicity to various agents | 18/28 | Severe | Resolved | Study drug |
| 16 | Investigations/Weight increased | 3/[>40] | Mild | Still present | Study drug |
| 17[a] | Nervous system disorders/Grand mal convulsion[b] | 41/43 | Severe | Resolved | Other |
| 18[a] | Nervous system disorders/Complex partial seizures[b] | 18/18 | Mild | Resolved | Other illness |
| 19 | Psychiatric disorders/Hallucination, visual | 1/1 | Moderate | Resolved | Study drug |
| 20 | Nervous system disorders/Dizziness | 1/22 | Moderate | Resolved | Study drug |
| 21 | Investigations/Neutrophil count decreased | 115/141 | Mild | Resolved | Disease under study |
| | Investigations/White blood cell count decreased | 115/141 | Mild | Resolved | Disease under study |
| 22[a] | Nervous system disorders/Status epilepticus[b] | 85/94 | Severe | Resolved | Study drug |
| 23[a] | Nervous system disorders/Epilepsy[b] | 43/53 | Severe | Resolved | Study drug |
| 24 | General disorders and administration site conditions/Edema | 36/[>66] | Severe | Still present | Study drug |

[ ] Values in brackets imputed from incomplete dates and times.
Does not include subject who died during the study.
ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. Subject met seizure exit criterion.
b. SAE (according to Investigator assessment).

In addition to the 21 subjects in the pregabalin 600 mg/day group, one subject had an AE of fatigue that was considered to be due to an SAE of bacterial meningitis and for which the action taken with study medication was given as "permanently discontinued."

No subjects in the pregabalin 150 mg/day group and 6/129 (4.7%) subjects in the 600 mg/day group had dose reductions or were temporarily discontinued from treatment due to treatment-emergent AEs (all causalities). No subjects in the pregabalin 150 mg/day group and 4/129 (3.1%) subjects in the 600 mg/day group had dose reductions or were temporarily discontinued from treatment due to treatment-related treatment-emergent AEs. (Table 18).

**Table 18. Temporary Discontinuations or Dose Reductions due to Adverse Events (ITT: Full Study)**

| Serial Number | System Organ Class/Preferred Term | Start Day/ Stop Day | Severity/ Outcome | Action | Causality |
|---|---|---|---|---|---|
| **Pregabalin 600 mg/day** | | | | | |
| 1 | Gastrointestinal disorders/Vomiting[a] | 64/67 | Mild/ Resolved | Stopped temporarily | Study drug |
| 2 | Nervous system disorders/Balance disorder[a] | 1/14 | Mild/ Resolved | Reduced | Other-drug administration error during titration phase |
| | Nervous system disorders/Dizziness[a] | 1/12 | Mild/ Resolved | Reduced | Study drug |
| 3 | Infections and infestations/Bacterial meningitis[a] | 109/117 | Severe/ Resolved | Stopped temporarily | Other illness-seizure exacerbation most likely due to bacterial meningitis |
| 4 | Injury, poisoning and procedural complications/Toxicity to various agents[a] | 2/3 | Moderate/ Resolved | Reduced | Study drug |
| 5 | Nervous system disorders/Dizziness[a] | 2/7 | Mild/ Resolved | Stopped temporarily | Study drug |
| | Nervous system disorders/Sedation[a] | 2/7 | Moderate/ Resolved | Stopped temporarily | Study drug |
| 6 | Nervous system disorders/Convulsion[a] | 4/4 | Severe/ Resolved | Stopped temporarily | Other subject quited medications with tapering, against protocol |

MedDRA (v14.0) coding dictionary applied.
ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities.
a. Treatment-emergent

Death: One subject, in the pregabalin 600 mg/day group, died during the study due to a cardiorespiratory arrest that was not treatment-related.

The rates of subjects with abnormal findings at physical examinations were unremarkable in both treatment groups at Baseline and Week 20 and similar for the 2 groups at all planned visits during the study.

A total of 23 subjects (2 in the pregabalin 150 mg/day group and 21 in the 600 mg/day group) experienced AEs of weight increased; all of the AEs were treatment-related. One subject, in the 600 mg/day group, withdrew from the study due to an AE of weight increased. Mean (standard deviation) changes from Baseline to Week 20 in weight were 0.5 (4.70) kg in the 150 mg/day group and 3.1 (4.87) kg in the 600 mg/day group.

Changes from Baseline in laboratory and vital signs parameters were generally minor and not clinically significant in both treatment groups.

On the neurological examination, the percentage of subjects who were postictal in the previous 24 hours decreased from Baseline (Week 0) to Week 20 in the pregabalin 150 mg/day group (from 12.9% to 6.7%, respectively) and increased from Baseline to Week 20 in the 600 mg/day group (from 14.0% to 18.8%, respectively). The percentages of subjects in both groups rated as "alert" were consistent in both groups at Baseline and Week 20 (range 93.6% to 100.0%). In general, the percentages of subjects with abnormalities on neurological examination subtests were higher in the 600 mg/day group compared with the 150 mg/day group. Overall the findings were consistent with the population with epilepsy under study and none of the findings was considered clinically significant.

**CONCLUSIONS:**

- Based on the primary efficacy analysis of seizure-related exit rates compared with a historical control, pregabalin 600 mg/day was effective as monotherapy in subjects who were not well controlled on 1-2 current AED treatments.

- In a supplemental analysis of the primary endpoint, the estimated seizure-related exit rate in the pregabalin 600 mg/day group was numerically lower than that in the pregabalin 150 mg/day group.

- Results of sensitivity analyses for the pregabalin 600 mg/day group supported the results of the primary analysis. In analyses which considered all discontinuations as meeting exit criteria, the upper confidence limits for the estimated exit rates were less than the historical control rates of 68% and 74%.

- The proportions of subjects who experienced AEs and who withdrew due to AEs were higher in the pregabalin 600 mg/day group compared with the pregabalin 150 mg/day group. The most frequently reported AEs in both groups were dizziness and somnolence, and the majority of AEs were considered mild or moderate in severity.

- The proportion of subjects who experienced SAEs was higher in the pregabalin 600 mg/day group compared with the pregabalin 150 mg/day group; more than half of the SAEs in the 600 mg/day group were seizure-related.

- Changes from Baseline in vital sign and laboratory parameters were generally minor and not considered to be clinically significant.

- The overall safety findings observed in this study were consistent with the safety profile seen in past pregabalin studies in subjects with epilepsy.

- This study, using a novel historical-control design, showed that pregabalin 600 mg/day was safe and efficacious as monotherapy treatment for partial seizures.