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

PROTOCOL NO.: A0081160

PROTOCOL TITLE: An Open-Label Multicenter Extension Study to Determine Long Term Safety and Efficacy of Pregabalin (Lyrica) as Monotherapy in Patients With Partial Seizures

Study Centers: A total of 39 centers took part in the study and enrolled subjects: 3 in the Czech Republic, 1 in Hong Kong, 6 in the Ukraine, and 29 in the United States.

Study Initiation Date and Final Completion Dates: 29 April 2008 to 26 December 2011

Phase of Development: Phase 3

Study Objective: To evaluate the long-term safety and efficacy of open-label pregabalin administered as monotherapy at dosages of 150 to 600 mg/day (administered twice daily [BID]) in subjects with partial seizures who responded to treatment and completed Study A0081047.

METHODS

Study Design: This study was an open-label extension study for subjects with partial seizures who completed approximately 20 weeks of double-blind administration of pregabalin at 1 of 2 dose levels (150 or 600 mg/day, based on treatment assignment) in Study A0081047. Eligible subjects for this study must have adequately responded to pregabalin treatment in Study A0081047. At the completion of Study A0081047, eligible subjects transitioned in a blinded fashion from blinded pregabalin over 7 days to a common starting dose of open-label pregabalin at 300 mg/day (administered BID). Once the transition was complete, open-label therapy with pregabalin was to begin and last for 24 weeks. At the end of 24 weeks, an alternative antiepileptic drug (AED) therapy was to be established and subjects tapered from pregabalin study treatment.

Dose adjustments of pregabalin over the range of 150-600 mg/day (administered BID) were permitted throughout this study and were to be based on investigator judgment with respect to seizure control and subject tolerability to pregabalin. If the subject was to continue taking pregabalin (marketed Lyrica®) after early withdrawal or study completion, then tapering of pregabalin may not have been warranted based on the investigator's discretion. Table 1 presents the schedule of activities.

Table 1. Schedule of Activities

	Screening	Open-Label Treatment						
Visit	1[a]	2[b]	3	4	5	6	7/ET[c]	8/FU
End of week	-	-	1	4	8	12	24	26-28
Study day	-7	1	7	28	56	84	168	182-196
Informed consent	X							
Inclusion/exclusion	X	X						
Concomitant medication		X	X	X	X	X	X	X
Physical examination including weight							X[d]	
Vital signs							X	
Neurological examination							X[e]	
Clinical laboratory tests							X	
Urine pregnancy test							X	X
Dispense seizure diary		X	X	X	X	X	X	
Review seizure diary		X	X	X	X	X	X	
Dispense study medication		X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X

ET = early termination; FU = follow-up.

a. Same as Visit 8, Week 20, Day 140 of Protocol A0081047.
b. Same as Visit 9, Week 21, Day 147 of Protocol A0081047.
c. ET = Early Termination from study or Week 24. These procedures were to be performed and subjects tapered off of pregabalin per guidelines.
d. Abbreviated physical examination.
e. Abbreviated neurological examination.

Number of Subjects (Planned and Analyzed): The number of subjects enrolled in this study was not determined on the basis of statistical considerations but rather was dependent upon the number of subjects who received study medication in the double-blind study (Protocol A0081047) and elected to continue open-label pregabalin treatment. No more than approximately 250 subjects (the maximum number of subjects enrolled in Protocol A0081047) could be enrolled in this extension trial. Eligibility was based on subjects meeting the inclusion/exclusion criteria as assessed at Screening (Visit 1). A total of 73 subjects received at least 1 dose of pregabalin in the study.

Diagnosis and Main Criteria for Inclusion: Subjects with a diagnosis of epilepsy with partial seizures who completed Study A0081047 and wished to continue to receive pregabalin. Exclusion criteria included early withdrawal from the previous protocol, an episode of status epliepticus, or primary generalized epilepsy.

Study Treatment: On Day 1 (Visit 2) of this study, transition from blinded oral pregabalin therapy in Study A0081047 was completed and all subjects were to receive open-label monotherapy treatment with pregabalin at 300 mg/day BID. Dose adjustments were permitted beginning on Day 1 and could have occurred over the dose range of 150 to 600 mg/day (150, 300, 450, or 600 mg/day, given BID) at the discretion of the Investigator. Subjects were to take pregabalin on every 12 hours ±1-hour schedule throughout this study.

Efficacy and Safety Endpoints: Long term safety and efficacy of pregabalin during open-label administration was assessed based on the nature, incidence, and severity of

adverse events (AEs) and clinical laboratory findings, and on the seizure diary data, respectively.

Safety Evaluations: Safety was evaluated by AE collection, laboratory and vital signs parameters, and physical and neurological examinations. Seizures (convulsions) in themselves were not to be considered AEs by definition; they were to be considered part of the disease under study. However, if seizures increased in frequency or intensity and/or were considered clinically meaningful by the investigator (eg, resulting in the subject's withdrawal from the study) they may have been reported as AEs. Additionally, if a seizure met the serious adverse event (SAE) criteria it was to be reported as an SAE.

Statistical Methods: The safety analysis set, which included all subjects who entered into the open label extension study and received at least 1 dose of pregabalin during the open-label extension period, was used for all data summaries and listings.

All summaries were for all pregabalin-treated subjects combined. For summaries by visit, nominal visits were used.

Descriptive statistics were provided for efficacy and safety parameters. Baseline value was defined as the last observed value prior to receiving the first dose of study medication in Study A0081047. Seizures from subjects' daily diaries were provided in a data listing for assessment of efficacy, but no summaries or statistical inferences were performed.

RESULTS

Subject Disposition and Demography: Seventy-three subjects received at least 1 dose of pregabalin in the study; 58/73 (79.5%) subjects completed the study after ≥6 months of treatment (Table 2). The most frequent reasons for discontinuation were insufficient clinical response (5/73, 6.8% subjects) and AEs (4/73, 5.5% subjects).

Table 2. Subject Disposition

Number (%) of Subjects	Pregabalin
Signed informed consent:	75[a]
Assigned to study treatment:	73
Treated	73
Completed	58 (79.5)
Discontinued	15 (20.5)
Related to study drug	3 (4.1)
Adverse event	3 (4.1)
Not related to study drug	1 (1.4)
Adverse event	1 (1.4)
Relationship to study drug not defined	11 (15.1)
Insufficient clinical response	5 (6.8)
No longer willing to participate in study	2 (2.7)
Other[b]	2 (2.7)
Protocol violation	2 (2.7)

a. This number includes 2 subjects who signed consent to participate in this study but did not receive study drug.
b. One subject moved out of the area, and the study center where another subject participated closed and relocated.

The mean pregabalin dose for all subjects during the study (excluding the taper phase) was 461.4 mg/day (the overall range of subjects' average daily doses was 275 mg/day to 600 mg/day). The most frequent daily dose (excluding the taper phase) was 300 mg/day (received by 55/73 [75.3%] subjects for at least 1 day).

Approximately half of the subjects who signed informed consent for the study were female (38/75 [50.7%] subjects), and the majority of subjects were white (66/75 [88.0%] subjects; (Table 3). The mean age of subjects signing informed consent was 40.0 years, and the mean weight was 83.1 kg; these characteristics were similar to those of the subjects in Study A0081047.

Table 3. Demographic Characteristics (All Subjects Who Signed Informed Consent)

Demographic Characteristic Parameter	Pregabalin		
	Male N=37	Female N=38	Total N=75
Age (years), n (%)			
18-44	26 (70.3)	22 (57.9)	48 (64.0)
45-64	10 (27.0)	13 (34.2)	23 (30.7)
≥65	1 (2.7)	3 (7.9)	4 (5.3)
Mean (SD)	39.4 (12.0)	40.7 (16.5)	40.0 (14.4)
Range	18-73	20-77	18-77
Race, n (%)			
White	31 (83.8)	35 (92.1)	66 (88.0)
Black	3 (8.1)	3 (7.9)	6 (8.0)
Asian	2 (5.4)	0	2 (2.7)
Other	1 (2.7)	0	1 (1.3)
Weight (kg)			
Mean (SD)	89.0 (21.9)	77.3 (15.4)	83.1 (19.7)
Range	47.6-139.2	51.2-126.5	47.6-139.2

This table includes 2 subjects who signed informed consent for this study but did not receive study drug.
n = number of subjects meeting prespecified criteria; N = number of subjects; SD = standard deviation.

Efficacy Results: A total of 63 subjects experienced at least 1 seizure during the study (beginning on or after Day 1 of the study) based on seizure diaries; the most frequent seizure types during the study were complex partial and simple partial seizures. Seven (9.6%) subjects were seizure-free for the duration of their time in the study; 6 of these subjects completed the study, receiving at least 169 days of study drug.

Safety Results: A total of 14 subjects (19.2%) experienced ≥3 treatment-emergent adverse events (TEAE) during the study. Nausea and headache were the most frequently reported TEAEs (Table 4).

Table 4. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term for Events Having a Frequency Rate ≥3

	Number (%) of Subjects:
Evaluable for adverse events	73
With adverse events	14 (19.2)
Gastrointestinal disorders	4 (5.5)
Nausea	4 (5.5)
Investigations	3 (4.1)
Weight increased	3 (4.1)
Musculoskeletal and connective tissue disorders	3 (4.1)
Arthralgia	3 (4.1)
Nervous system disorders	7 (9.6)
Convulsion	3 (4.1)
Headache	4 (5.5)

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

TEAEs treatment-related are summarized in Table 5.

Table 5. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

MedDRA Preferred Term Number (%) of Subjects	Pregabalin N=73
Gastrointestinal disorders	3 (4.1)
Constipation	1 (1.4)
Dry mouth	1 (1.4)
Nausea	1 (1.4)
General disorders and administration site conditions	1 (1.4)
Fatigue	1 (1.4)
Investigations	3 (4.1)
Weight increased	3 (4.1)
Nervous system disorders	7 (9.6)
Balance disorders	2 (2.7)
Convulsions	1 (1.4)
Dizziness	1 (1.4)
Headache	1 (1.4)
Lethargy	1 (1.4)
Migraine	1 (1.4)
Vascular disorder	1 (1.4)
Hypertension	1 (1.4)

Subjects were counted only once in each row.
SAE and AEs are not separated out in this table.
MedDRA (version 14.1) coding dictionary applied.
AE = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SAE = serious adverse events.

Three subjects experienced a total of 4 SAEs as summarized in Table 6. One SAE was considered treatment-related (convulsion).

Table 6. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

Number (%) of Subjects:	All Causality	Treatment-Related
Evaluable for adverse events	73	73
With adverse events	3 (4.1)	1 (1.4)
Injury, poisoning and procedural complications	1 (1.4)	0
Road traffic accident	1 (1.4)	0
Nervous system disorders	3 (4.1)	1 (1.4)
Convulsion	2 (2.7)	1 (1.4)
Transient ischaemic attack	1 (1.4)	0

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

No subjects died during this study.

Two subjects withdrew due to treatment-emergent AEs (convulsion) and 2 subjects withdrew due to non-treatment-emergent AEs (weight increased) that began during Study A0081047; the AE resulting in withdrawal was considered treatment-related for 3 of these subjects (Table 7).

Table 7. Discontinuations Due to Adverse Events

Serial Number	MedDRA System Organ Class/ Preferred Term	AE Start Day/ Stop Day		Severity	Outcome	Causality
		Since A0081047 Day 1	Since A0081160 Day 1			
Pregabalin						
1	Nervous system disorders/Convulsion[a]	221/222	76/77	Moderate	Resolved	Other illness-generalized seizure-cause undetermined
2	Investigations/weight increased	36/226	-111/79	Mild	Resolved	Study drug
3	Nervous system disorders/convulsion[a, b]	281/289	132/140	Severe	Resolved	Study drug
4	Investigations/weight increased	84/(>187)[c]	-62/(41)[c]	Mild	Still present[c]	Study drug

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA (version 14.1) coding dictionary applied.

a. Treatment-emergent.
b. Serious adverse event.
c. The outcome of this AE in the Study A0081160 database = 'still present', and no stop date was provided (data on file). However, this AE was also reported for this subject in Study A0081047, with outcome = 'resolved' and a stop date of 02 Jun 2011. Due to a programming algorithm combining the data for this AE across the 2 studies, the stop dates in Study A0081160 were imputed from the Study A0081047 stop date of 02 Jun 2011, and the outcome shown = 'resolved' (based on Study A0081047) instead of 'still present' (based on Study A0081160).

Overall, 17 of 72 (24%) subjects who were evaluable for laboratory abnormalities experienced a laboratory abnormality during the study. The laboratory abnormalities reported at the highest percentages were elevated urine epithelial cells (7/72, 9.7% subjects) and elevated eosinophils (4/68, 5.9% subjects). Median changes in laboratory parameters from Baseline to the last observation were not clinically significant.

CONCLUSIONS:

- Approximately 80% of subjects completed 6 months of treatment with open-label pregabalin monotherapy (150 mg to 600 mg/day BID).

- Seven (9.6%) subjects were seizure-free for the duration of their time during the study; 6 of these subjects completed the study.

- A total of 31 subjects (31/73, 42.5%) experienced 1 or more treatment-emergent AEs (all causalities). The majority of AEs were mild or moderate in severity. The most frequently reported treatment-emergent AE was convulsion (5/73, 6.8% subjects). Although no subject experienced treatment-emergent AEs of somnolence, 3 (4.1%) subjects experienced ongoing mild treatment-related AEs of somnolence that began during Study A0081047. Two (2.7%) subjects experienced treatment-emergent AEs of dizziness and 2 (2.7%) subjects experienced ongoing mild AEs of dizziness (1 treatment-related and 1 non treatment-related) that began during Study A0081047.

- Few subjects experienced SAEs (3/73, 4.1%) or withdrew from the study due to AEs (4/73, 5.5%).

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

- The overall safety findings observed in this study with long-term pregabalin monotherapy treatment in subjects with epilepsy (partial onset seizures) were consistent with the known safety profile of pregabalin in subjects with epilepsy.