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

PROTOCOL NO.: A0081101

PROTOCOL TITLE: A 12-Week, Open-Label, Safety Trial of Pregabalin in Patients With Fibromyalgia

Study Centers: A total of 51 centers took part in this study and enrolled subjects; 12 in Canada, 2 in Denmark, 5 in France, 4 each in Germany, India, Netherlands, and Sweden, 5 in Italy, 3 in Korea, 1 in Portugal, 2 in Switzerland, 5 in the United Kingdom (UK).

Study Initiation and Final Completion Dates: 20 November 2006 to 24 March 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To evaluate the safety of pregabalin at doses up to 600 mg/day in subjects who participated in the double-blind fibromyalgia Study A0081100 and who wished to receive open-label pregabalin therapy.

METHODS

Study Design:

This was a 12-week open-label extension of the preceding double-blind randomized fibromyalgia Study A0081100. Following the termination visit in Study A0081100, subjects had an option of starting pregabalin at a dose of 300 mg/day, or 150 mg twice daily (BID) under open-label conditions the day after the termination visit. This day was designated as Day 1 of the open-label study. Study medication could be adjusted for the remainder of the study to optimize pain control and to minimize adverse events (AEs). The minimum permissible daily dose was 150 mg/day (75 mg BID) pregabalin and the maximum daily dose was 600 mg/day (300 mg BID). During the study, there were 5 scheduled visits. A subject was considered to have completed the study after receiving 12 weeks of open-label treatment (Visit 5/termination visit). Visit schedule and study procedures are presented in Table 1.

Table 1. Timetable of Study Procedures

End of Study Week	Day 0[a] Baseline	Week 1	Week 4	Week 8	Week 12
Month			**1**	**2**	**3**
Clinic Visit	**1**[b]	**2**[b]	**3**	**4**	**5/ET**
Inclusion/exclusion	X				
Informed consent	X				
Physical exam	(X)	VS	VS	VS	X
Abbreviated neurological exam	(X)				X
12-Lead electrocardiogram	(X)				X
Clinical labs: serum pregnancy test	(X)		X		X
Clinical labs: hematology, chemistry	(X)		X		X
Clinical labs: urinalysis	(X)				X
Adverse events	(X)	X	X	X	X
Concomitant medication	(X)	X	X	X	X
Pain visual analogue scale	(X)		X		X
Pregabalin review/dosing/dispensing	X[a]	X[c]	X[c]	X[c]	X

ET = end of treatment/termination visit; VS = vital signs (heart rate and blood pressure); (X) = completed previously at the preceding double-blind study (Protocol A0081100) termination visit.

a. Subjects took the first dose of the open-label study medication the day following open-label Visit 1.

b. Subjects were contacted by telephone between Visits 1 and 2 and Visits 2 and 3 to assess tolerability before titrating to higher or lower doses.

c. Dosage adjustment where required.

Number of Subjects (Planned and Analyzed): There were 740 subjects planned for the study, but enrolled and included were 357 which included 96 in Canada, 29 in Denmark, 26 in France, 41 in Germany, 38 in Italy, 2 in Portugal, 28 in Sweden, 10 in Switzerland, 15 in the UK, 15 in India, 25 in Netherlands and 32 in Korea. All were analyzed for primary and secondary endpoints.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria: Subjects who met the inclusion criteria for the preceding fibromyalgia Study A0081100 and who had received pregabalin/placebo under double-blind conditions were included in the study.

Exclusion Criteria: Subjects who experienced a serious adverse event (SAE) during the previous fibromyalgia Study A0081100, which was determined to be related to the study medication by the Investigator or Sponsor, were excluded. Also excluded were subjects with a white blood cell count <2.5 × 109/L, a neutrophil count <1.5 × 109/L, and a platelet count <100 × 109/L on laboratory tests by Study A0081100, Visit 5.

Study Treatment: Pregabalin was administrated orally BID with or without food. The first bottle of the open-label study medication was dispensed at the termination visit of the preceding double-blind Study A0081100. Subjects began the open-label study medication the morning after this termination visit at a fixed dose of 300 mg/day. The pregabalin daily dose was adjusted thereafter by the Investigator to optimize pain control and to minimize AEs. Adjustments to total daily doses were permitted for the remainder of the study. The

minimum permissible daily dose was 150 mg/day (75 mg BID) and the maximum daily dose was 600 mg/day (300 mg BID) of pregabalin.

Efficacy Endpoints:

Primary Endpoint:

Pain Visual Analog Scale (VAS):

The Pain VAS is a horizontal line; 100 mm in length, self-administered by the subject in order to rate pain from 0 "no pain" to 100 "worst possible pain". Subjects completed this assessment at open-label Visit 1/Termination Visit in preceding double-blind protocol and at Visits 3 (Week 4) and 5/Termination Visit (Week 12).

The Baseline score were taken as follows:

- For subjects randomized to pregabalin in A0081100, the Baseline score was taken as the last score prior to treatment on A0081100.
- For subjects randomized to placebo in A0081100, the Baseline score was taken as the last score prior to treatment on A0081100.

Safety Evaluations: Observed or volunteered AEs were recorded throughout the study. Safety evaluations also included vital sign measurements (blood pressure [BP] and pulse rate), ECGs, physical examinations, and laboratory safety tests.

Statistical Methods:

Safety analysis set included all subjects who receive the study medication.

No inferential testing was planned for this study. The efficacy results were summarized with descriptive statistics only.

All subjects enrolled at sites participating in Study A0081100 and Study A0081101 were potentially eligible for enrollment. The sample size was not prespecified; total enrollment was dictated by the number of subjects from the preceding double-blind Study A0081100 who desired open-label pregabalin treatment in this study.

For pain VAS, Baseline was Visit 1 (Screening visit) in Study A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (termination visit) in Study A0081100 if the subject was randomized to placebo.

Baseline laboratory data, BP, physical examination, ECG and weight assessments were performed from Visit 1 (Screening visit) in Study A0081100 if the subject was randomized to pregabalin in Study A0081100 or Visit 7 (termination visit) in Study A0081100 if subject was randomized to placebo.

RESULTS

Subject Disposition and Demography: A total of 357 subjects were treated and 57 subjects withdrew from the study. Subject disposition for all subjects is summarized in Table 2.

Table 2. Summary of Subject Disposition

	Pregabalin N (%)
Screened	357
Assigned to treatment	357
Treated	357
Completed	300 (84.0)
Discontinued from study:	
Total	57 (16.0)
Related to study drug	40 (11.2)
Adverse event	32 (9.0)
Lack of efficacy	8 (2.2)
Not related to study drug	17 (4.8)
Adverse event	2 (0.6)
Other	3 (0.8)
Withdrew consent	12 (3.4)
Assessed for safety:	
Adverse events	357 (100)
Laboratory data[a]	352 (98.6)

N = total number of subjects in this study.
a. Five subjects had no Baseline or on-treatment laboratory test data.

The majority of all subjects were White (84.3%) and female (90.2%) and between 45 and 64 years of age. Demographic characteristics for all treated subjects are presented in Table 3.

Table 3 Demography and Baseline Characteristics

	All Pregabalin		
Sex	**Male N (%)**	**Female N (%)**	**All N (%)**
	35 (9.8%)	322 (90.2%)	357
Age (years)			
Mean (SD)	47.4 (10.5)	48.4 (11.2)	48.3 (11.1)
Range	20-72	21-77	20-77
Age categories (years)			
18-44	10 (28.6%)	119 (37.0%)	129 (36.1%)
45-64	24 (68.6%)	180 (55.9%)	204 (57.1%)
65 and over	1 (2.9%)	23 (7.1%)	24 (6.7%)
Race			
White	29 (82.9%)	272 (84.5%)	301 (84.3%)
Black	0	6 (1.9%)	6 (1.7%)
Other	6 (17.1%)	44 (13.7%)	50 (14.0%)
Weight (kg)			
Mean (SD)	83.6 (16.4)	71.5 (15.9)	72.6 (16.4)
Range	59.5-140.3	40.0-129.0	40.0-140.3
Duration of symptoms (months)			
Mean (SD)	121.9 (108)	103.4 (89.6)	105.2 (91.6)
Range	7.0-471.0	5.0-544.0	5.0-544.0
Pain VAS			
Mean (SD)	_	_	67.7 (17.7)
Range	_	_	5.0-99.0

Baseline data were recorded at the start of Study A0081100.
For pain VAS, Baseline was Visit 1 (Screening visit) in Study A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (termination visit) in Study A0081100 if the subject was randomized to placebo.
SD = standard deviation; VAS = visual analog scale.

Efficacy Results: Summaries of all subjects' mean Baseline and pain VAS scores at Week 4 and end of treatment are presented in Table 4 together with changes from Baseline at both timepoints.

Table 4. Summary of Pain VAS Scores

Timepoint	**Statistic**	**VAS Score[a]**
Baseline	N	335
	Mean (SD)	67.7 (17.7)
Week 4	N	327
	Mean (SD)	49.8 (25.6)
End of treatment	N	357
	Mean (SD)	47.5 (26.0)
Change from Baseline to Week 4	N	306
	Mean (SD)	-18.1 (24.1)
Change from Baseline to end of treatment	N	335
	Mean (SD)	-20.1 (26.8)

Baseline = Visit 1 (Screening visit) in A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (termination visit) in A0081100 if subject was randomized to placebo.
N = total number of subjects in this study; SD = standard deviation; VAS = visual analog scale.
a. Range 0-100 mm, where higher scores indicated more severe pain.

Safety Results:

An overall summary of treatment-emergent AEs (TEAEs), defined as any AE occurring after or during treatment with study drug, is presented in Table 5.

Table 5. Overall Summary of Treatment-Emergent Adverse Events

Number of Subjects (%)	Pregabalin N=357
All causality	
Number of adverse events[a]	724
Subjects with:	
Adverse events	271 (75.9)
Serious adverse events	7[b] (2.0)
Severe adverse events	27 (7.6)
Discontinuations due to adverse events	28 (7.8)
Temporary discontinuations or dose Reductions due to adverse events	76 (21.3)
Treatment-related	
Number of adverse events[a]	409
Subjects with:	
Adverse events	193 (54.1)
Serious adverse events	1 (0.3)
Severe adverse events	13 (3.6)
Discontinuations due to adverse events	26 (7.3)
Temporary discontinuations or dose reductions due to adverse events	72 (20.2)

N = number of subjects; SAE = serious adverse event.
a. Treatment-emergent to Protocol A0081101.
b. Included 1 SAE previously reported in A0081100.

In total 27 subjects reported all causality AEs that were severe in intensity, and of these 13 subjects reported severe AEs that were considered treatment related by the Investigator. The incidence of severe all-causality AEs reported are presented in Table 6.

Table 6. Incidence of Severe All-Causality Treatment-Emergent Adverse Events

Event	Number of Subjects (%) N=357
Dizziness	6 (1.7)
Headache	3 (0.8)
Back pain	2 (0.6)
Somnolence	2 (0.6)

N = number of subjects in the treatment group.

The number of subjects reporting severe treatment-related TEAEs was assessed; these AEs were events that were rated as severe by the Investigator and related to study drug in a causal manner. Table 7 summarizes the incidence of severe treatment-related TEAEs. The most commonly reported severe treatment-related TEAEs was dizziness, reported by 6 (1.7%) subjects.

Table 7. Incidence of Severe Treatment-Emergent, Treatment-Related Adverse Events

Event	Number of Subjects (%) N=357
Dizziness	6 (1.7)
Somnolence	2 (0.6)
Abdominal pain	1 (0.3)
Disturbance in attention	1 (0.3)
Fatigue	1 (0.3)
Feeling drunk	1 (0.3)
Headache	1 (0.3)
Migraine	1 (0.3)
Myoclonus	1 (0.3)

N = number of subjects in the treatment group.

The most frequently reported all causality and treatment related AEs were dizziness, headache, somnolence and fatigue. A summary of treatment emergent all causality and treatment related AEs occurring in at least 3% of subjects is presented in Table 8.

Table 8. Incidence of Adverse Events by Frequency (≥3% of Subjects)

Event	Number of Subjects (%) Pregabalin (N=357)	
	All Causality	Treatment Related
Dizziness	85 (23.8)	84 (23.5)
Headache	33 (9.2)	20 (5.6)
Somnolence	30 (8.4)	29 (8.1)
Fatigue	24 (6.7)	22 (6.2)
Nausea	21 (5.9)	18 (5.0)
Constipation	15 (4.2)	10 (2.8)
Dry mouth	14 (3.9)	14 (3.9)
Weight increased	14 (3.9)	14 (3.9)
Vomiting	13 (3.6)	8 (2.2)
Peripheral edema	12 (3.4)	12 (3.4)
Vertigo	12 (3.4)	11 (3.1)
Nasopharyngitis	11 (3.1)	0

N = number of subjects.

In total 152 subjects (42.6%) reported TEAEs of the nervous system of whom 136 (38.1%) reported events that were considered to be related to treatment by the Investigator. The incidence of each AE that were considered to be clinically relevant is presented in Table 9.

Table 9. Treatment-Emergent Adverse Events of Clinical Relevance

	Number of Subjects (%)				
Event	**Total**	**Mild**	**Moderate**	**Severe**	**Discontinuations**
All causality					
Dizziness	85 (23.8%)	47	32	6	8
Somnolence	30 (8.4%)	20	8	2	2
Weight increased	14 (3.9%)	12	2	0	1
Peripheral edema	12 (3.4%)	12	0	0	1
Blurred vision	6 (1.7%)	4	2	0	0
Elevated CK	2 (0.6%)	2	0	0	0
Visual disturbance	1 (0.3%)	1	0	0	0
Thrombocytopenia	0	0	0	0	0
Treatment related					
Dizziness	84 (23.5%)	46	32	6	8
Somnolence	29 (8.1%)	19	8	2	2
Weight increased	14 (3.9%)	12	2	0	1
Peripheral edema	12 (3.4%)	12	0	0	1
Blurred vision	5 (1.4%)	3	2	0	0
Visual disturbance	1 (0.3%)	1	0	0	0
Elevated CK	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0

CK = creatine kinase.

SAEs were reported in 6 subjects (10 events) during the study. In all cases the subjects recovered from the event(s). One SAE was considered related to treatment by both the Investigator and Sponsor. The SAEs are summarized in Table 10.

Table 10. Serious Adverse Events

Event	**Number of Subjects (%) N=357**
Diarrhea[a]	1
Vomiting[a]	1
Melena	1
Urinary tract infection	1
Spinal osteoarthritis	1
Vaginal cyst	1
Myoclonus[a]	1
Epistaxis	1
Cellulitis[b]	1
Fall	1
Left wrist fracture	1

N = number of subjects in the treatment group; SAE = serious adverse event.
a. Resulting in discontinuation.
b. This SAE was reported in the database for Study A0081100 and by convention was not reported again in A0081101. The event was recorded as an adverse event in the project database.

There were no deaths during this study. Table 11 and Table 12 summarize permanent and temporary reductions in the study.

Table 11. Discontinuations Due to Treatment-Emergent, Treatment-Related Adverse Events

Event	Mild	Moderate	Severe	Total
All causality[a]				
Dizziness	2	5	1	8
Vomiting	0	5	1	6
Nausea	0	3	0	3
Diplopia	2	1	0	3
Fatigue	1	1	1	3
Diarrhea	1	1	1	3
Somnolence	0	2	0	2
Treatment related[b]				
Dizziness	2	5	1	8
Vomiting	0	4	0	4
Nausea	0	3	0	3
Diplopia	2	1	0	3
Fatigue	1	1	1	3
Diarrhea	1	1	1	3
Somnolence	0	2	0	2

a. Table shows number of subjects discontinuing with each adverse event.
b. Investigator assessment of causality; subjects may have discontinued with more than 1 adverse event.

Table 12. Dose Reductions and Temporary Discontinuations Due to Severe Adverse Events

Serial Number	Adverse Event	Action	Severity	Relationship to Treatment (per Investigator)	Outcome
1	Somnolence	Dose reduced	Severe	Definitely	Recovered
2	Disturbance in attention	Dose reduced	Severe	Definitely	Recovered
	Dizziness	Dose reduced	Severe	Definitely	Recovered
3	Headache	Dose reduced	Severe	Possibly	Recovered

There were no significant median changes from Baseline to last observation for most laboratory test parameters. No evidence of a relationship between study treatment and these laboratory test parameters was seen from these median changes. Small changes in median creatine kinase (CK) and platelet count were noted but the changes were of uncertain clinical significance as assessed by the Investigator. Platelets showed a median decrease of 23 from a Baseline of level of 266 ($103/mm^3$). No subject demonstrated a reduction in platelets to less than 75 ($103/mm^3$), and no AEs related to reduced platelet counts were reported. One subject experienced an SAE of epistaxis, but the event was considered by the Investigator to be related to concomitant warfarin treatment. Levels of CK increased by a median of 16 from a Baseline of 140 U/L. Six subjects had clinically significant increases in CK values above Baseline, and mild treatment-emergent elevations of blood CK were reported as AEs in 2 subjects (0.6%). No cases of rhabdomyolysis or other AEs reflective of CK elevations were reported. There were a total of 15 treatment-emergent abnormal laboratory-related AEs, 3 of which were considered to be related to treatment by the Investigator (Table 13).

Table 13. Abnormal Laboratory-Related Treatment-Emergent Adverse Events

Event	N (%)	Mild	Moderate	Severe
All causality				
Neutropenia	1 (0.3%)	1	0	0
Lymphopenia	1 (0.3%)	1	0	0
Alanine aminotransferase increased	1 (0.3%)	0	1	0
Blood CK increased	2 (0.6%)	2	0	0
Blood glucose increased	1 (0.3%)	1	0	0
Hepatic enzyme increased	1 (0.3%)	0	1	0
White blood cells urine positive	4 (1.1%)	4	0	0
Protein urine present	2 (0.6%)	2	0	0
Hyperglycemia	1 (0.3%)	1	0	0
Hypocalcemia	1 (0.3%)	0	1	0
Treatment related				
Alanine aminotransferase increased	1 (0.3%)	0	1	0
Hepatic enzyme increased	1 (0.3%)	0	1	0
Hypocalcemia	1 (0.3%)	0	1	0

CK = creatine kinase; N = number of subjects in the treatment group.

The incidence of newly occurring and worsening laboratory test abnormalities is summarized in Table 14 and Table 15, respectively.

Table 14. Incidence of Laboratory Test Abnormalities (Normal Baseline)

Parameter	Criteria[a]	n	N
Newly occurring lab abnormalities			
Lymphocytes (%)	<0.8 x LLN	3	341
Lymphocytes (%)	>1.2 x ULN	1	341
Neutrophils (10^3/mm^3)	<0.8 x LLN	1	337
Neutrophils (10^3/mm^3)	>1.2 x ULN	3	337
Neutrophils (%)	<0.8 x LLN	1	317
Eosinophils (10^3/mm^3)	>1.2 x ULN	3	347
Eosinophils (%)	>1.2 x ULN	6	342
Monocytes (10^3/mm^3)	>1.2 x ULN	1	348
AST (IU/L)	>3.0 x ULN	1	340
Uric acid (mg/dL)	>1.2 x ULN	1	329
Random glucose (mg/dL)	>1.5 x ULN	4	324
Creatine kinase (U/L)	>2.0 x ULN	4	343
Urine specific gravity	<1.003	11	315
Urine specific gravity	>1.030	2	315

Baseline referred to Visit 1 (Screening visit) in A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (termination visit) in A0081100 if subject was randomized to placebo.
AST = aspartate aminotransferase; IU/L = International units per liter; LLN = lower limit of normal; n = number of subjects with laboratory abnormality meeting the specified criteria on treatment or during lag time; N = total number of subjects with at least 1 observation of the laboratory test on treatment or during lag time; ULN = upper limit of normal; U/L = units per liter.
a. Primary criteria for abnormality assessment shown for newly occurring abnormalities.

Table 15. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

Parameter	Criteria[a]	n	N
Worsening lab abnormalities			
Hematocrit (%)	<0.8 x baseline	1	23
Neutrophils ($10^3/mm^3$)	>1.2 x baseline	1	15
Eosinophils ($10^3/mm^3$)	>1.2 x baseline	1	5
Eosinophils (%)	>1.2 x baseline	1	10
ALT (IU/L)	>1.5 x baseline	1	33
BUN (mg/dL)	>1.3 x baseline	1	4
Random glucose (mg/dL)	>1.25 x baseline	1	27
Creatine kinase (mg/dL)	>1.5 x baseline	1	9
Urine specific gravity	<1.003	3	17

Baseline referred to Visit 1 (Screening visit) in A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (Termination visit) in A0081100 if subject was randomized to placebo.
ALT = alanine aminotransferase; BUN = blood urea nitrogen; n = number of subjects with laboratory abnormality meeting the specified criteria on treatment or during lag time; N = total number of subjects with at least 1 observation of the laboratory test on treatment or during lag time.
a. Secondary criteria for abnormality assessment shown for worsening abnormalities.

Vital signs (weight, sitting heart rate, sitting systolic and diastolic BP) were examined for clinically important changes from Baseline to end of treatment using predefined criteria. Possible clinically-important changes in weight and vital signs were noted for the following:

- Weight increase (if ratio to Baseline was ≥1.07): 50 subjects (15.9%);
- Weight decrease (if ratio to Baseline was ≤0.93): 9 subjects (2.9%);
- Decrease in diastolic BP (sitting; if <50 mm Hg and decreased from Baseline of ≥20 mm Hg): 1 subject (0.3%).

There were no clinically important changes in systolic BP or heart rate.

Fourteen subjects (3.9%) reported weight gain as an AE and in all cases the event was considered possibly, probably, or definitely related to treatment. No subjects had new clinically significant abnormal findings post Baseline. Few subjects had deterioration in neurological examination findings (Table 16). The most frequent change in neurological examination was reduction in ankle reflexes.

Table 16. Summary of Subjects with Deterioration in Neurological Examination Findings[a]

	All Pregabalin N = 357	
	N (%)	N at Risk[b]
Gait	1 (0.3)	339
Muscle Strength (ankle dorsiflexion)		
Left	3 (0.9)	339
Right	1 (0.3)	336
Reflexes (ankle)		
Left	10 (2.9)	339
Right	8 (2.4)	338

Baseline referred to Visit 1 (Screening visit) in A0081100 if the subject was randomized to pregabalin in A0081100, or Visit 7 (Termination visit) in A0081100 if subject was randomized to placebo.
N = number of the subject in the treatment group.
a. Findings with an increase in intensity relative to Baseline.
b. Subjects who had Baseline examination findings other than not evaluable or severe/absent.

Subjects with physical findings are given in Table 17.

Table 17. Brief Physical Examination Findings

Number of Subjects	Pregabalin (Any Dose) N=357 n (%)
Number of subjects with	
Physical exam done at Baseline	357 (100.0)
Physical exam done at final Visit	344 (96.4)

N = number of the subject in the treatment group; n = number of subjects with a physical examination finding.

Physical examination findings at Baseline and last observation are given in Table 18.

Table 18. Physical Examination Findings at Last Observation

Number of Subjects	Pregabalin (Any Dose) N=357		Pregabalin (Any Dose) N=357	
Site	Number Examined	Abnormal n (%)	Number Examined	Abnormal n (%)
Abdominal	356	6 (1.7)	339	9 (2.7)
Cardiovascular	357	8 (2.2)	340	5 (1.5)
Extremities	356	20 (5.6)	340	2 (0.6)
General appearance	357	9 (2.5)	338	18 (5.3)
Heent	357	13 (3.6)	340	7 (2.1)
Pulmonary	357	1 (0.3)	340	8 (2.4)
Skin	356	18 (5.1)	337	14 (4.2)

Baseline = Visit 1 (Screening visit) of A0081100 for subjects randomized to Pregabalin in A0081100.
Baseline = Visit 7 (Termination visit) of A0081100 for subjects randomized to placebo in A0081100.
N = number of subjects having an observation upon physical exam; n = number of the subjects in treatment group.

Conclusions:

In this 12-week open-label extension study in subjects with fibromyalgia, pregabalin at doses between 150 and 600 mg/day BID was safe and generally well tolerated. The safety profile was similar to that seen in other open-label and blinded studies. Efficacy, as measured by the pain VAS, supported maintenance of the treatment effect noted in the preceding double-blind Study A0081100.