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

PROTOCOL NO.: A0081251

PROTOCOL TITLE: An Open-Label, Extension Safety Trial of Pregabalin in Subjects With Neuropathic Pain Associated With HIV Neuropathy

Study Centers: Twenty six centers took part in the study and enrolled subjects; 9 each in South Africa and the United States of America (USA), 3 in India, 2 each in Columbia and Thailand, and 1 in Peru.

Study Initiation Date and Final Completion Date: 27 July 2010 and 14 May 2012. The study was terminated prematurely.

Phase of Development: Phase 3b

Study Objectives: The primary objective of this study was to evaluate the safety and tolerability of pregabalin in subjects with Human Immunodeficiency Virus (HIV) associated neuropathy. Secondary objectives were to assess the impact of pregabalin on work productivity and activity impairment; to assess the impact of pregabalin on function and quality of life; to assess pain intensity; and to evaluate global impression of change.

METHODS:

Study Design: Following completion of the previous pregabalin trial (A0081244: a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of pregabalin versus placebo in the treatment of neuropathic pain associated with HIV neuropathy [NCT01049217]), subjects who met all eligibility criteria and had completed at least Visit 9 of previous pregabalin study had the option of initiating treatment with pregabalin under open-label conditions for 6 months. Treatment in this trial was to start in the evening of the subject's termination visit in the preceding pregabalin study trial or up to 1 month following completion of previous pregabalin study.

Subjects initiated open-label treatment at 150 mg/day (75 mg twice daily [BID]). Further adjustments of total daily dose within the dose range 150 to 600 mg/day (BID) were permitted throughout the study based on subject's individual response and tolerability. Any dose adjustment was based on the Investigator's clinical judgment, however the dose of pregabalin was not to be titrated up or down concurrently with another pain medication. If dose adjustment of pregabalin or the concurrent pain medication was required, the dose of 1 pain medication was to be held constant while the other was being adjusted.

Subjects returned to the study site for efficacy and safety assessments at Months 1, 2, 3, 4, 5, 6 (Visits 3, 5, 6, 7, 8, and 9). A phone visit was also to be performed 2 weeks following Visit 1 and 2 weeks following Visit 3 to assess for adverse events (AEs) and potential dose adjustment. During Visit 9, a 1 week taper was initiated and subjects returned for a final visit 1 week later (Visit 10). Subjects who withdrew from treatment early were to return to the clinic and complete all early termination assessments and procedures described for Visit 9/10.

The schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

Protocol Activity	Screening/ Study Entry Clinic Visit 1	Phone Visit 2	Clinic Visit 3	Phone Visit 4[a]	Clinic Visit 5	Clinic Visit 6	Clinic Visit 7	Clinic Visit 8	Down Taper/ Early Termination Clinic Visit 9	End of Study/ Early Termination Clinic Visit 10
			Month 1		Month 2	Month 3	Month 4	Month 5	Month 6	
	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25
Window		±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days	±7 Days
Informed consent	X									
Medical history	X									
Physical examination	X[b]									X
Vital signs, weight	X[b]		X		X	X	X	X	X	X
Inclusion/exclusion criteria	X									
Assessments										
Safety assessment	X	X	X	X	X	X	X	X	X	X
Subject completion of pain VAS	X		X		X	X	X	X	X	
PGIC									X	
WPAI:SHP	X[c]								X	
SF-36	X[c]								X	
PHQ-8	X									
S-STS	X[c]		X		X	X	X	X	X	X
Laboratory collections										
Hematology	X[d]									X
Blood chemistry	X[d]									X
Urinalysis	X[d]									X
Pregnancy test (urine Visit 1/serum Visit 8)	X									X
Record concomitant medications	X		X		X	X	X	X	X	X
Study medication dispensing/dose change/instructions for dosing	X	X	X	X	X	X	X	X	X	
Study medication compliance		X	X	X	X	X	X	X	X	X

PGIC = Patient global impression of change; PHQ-8 = Patient Health Questionnaire-8; S-STS = Sheehan Suicidality Tracking Scale; SF-36 = Short Form 36; WPAI:SHP = Work Productivity and Activity Impairment: Specific Health Problem Questionnaire; VAS = Visual Analog Scale.

a. If dose adjustment was clinically indicated based on phone Visit 4 then an unplanned visit was scheduled or the dose adjustment occurred at Visit 5 as appropriate.
b. If study entry coincided within 3 days of termination from previous pregabalin study then physical examination and vital sign assessments from previous pregabalin study were sufficient.
c. If scale available from Visit 11 of previous pregabalin study then S-STS did not need to be repeated at Screening.
d. If study entry occurred within 30 days of final visit for previous pregabalin study then laboratory collections from previous pregabalin study were sufficient.

Number of Subjects (Planned and Analyzed): A total of 400 subjects were expected to be enrolled from the previous double-blind study (previous pregabalin study into the open-label phase, considering that subjects who withdrew early would not participate in the open-label phase.

In total, 221 subjects were screened, of which 217 subjects were assigned to open-label study treatment. Four subjects were not assigned to the study treatment due to entrance criteria not met (2 subjects) and pregnancy (2 subjects).

Of the 221 subjects screened, 158 were in South Africa, 22 in the USA, 17 in Thailand, 15 in India, 8 in Colombia, and 1 in Peru.

Diagnosis and Main Criteria for Inclusion: Both males and females (non-pregnant, non-lactating, postmenopausal or surgically sterilized) of age 18 years or older who participated in the preceding pregabalin study double-blind trial and completed at least through Visit 9 of that trial. Subjects with painful distal sensory polyneuropathy who were interested in treatment based on Investigator's clinical judgment and who had acceptable tolerability of study drug in previous pregabalin study were enrolled in the study. Subjects had to have a life expectancy of at least 12 months.

Study Treatment: Open-label pregabalin was taken orally BID. All subjects initiated dosing at 150 mg/day (75 mg BID). Adjustments of daily dose were permitted throughout the study to optimize pain control. The minimum allowable dose of pregabalin was 150 mg/day (75 mg BID) and the maximum allowable dose was 600 mg/day (300 mg BID). Capsules were to be taken in the morning and in the evening and could be taken with or without food.

Efficacy and Safety Endpoints:

Primary Endpoint: The primary endpoint was spontaneous AE monitoring.

Secondary Endpoints: Included assessment of results of Work Productivity and Activity Impairment Questionnaire (WPAI:SHP), Short Form 36 Health Survey (SF-36), pain Visual Analogue Scale (VAS) for the prior week, Patient Global Impression of Change (PGIC), Sheehan-Suicidality Tracking Scale (S-STS), and Patient Health Questionnaire-8 (PHQ-8).

Safety Evaluations: Included monitoring and reporting of AEs and serious AEs (SAEs); laboratory evaluations (hematology, chemistry, and urinalysis); vital signs, physical examination, and other safety measurements including tracking of treatment-emergent suicidal ideation and behaviors using the S-STS and evaluation of depression using PHQ-8.

If there were any positive responses on the S-STS (since last visit version; Items 1a, 1b, 3, 4, 5, 6, or 8) during the study, a risk assessment was performed by a qualified mental health professional to determine whether it was safe for the subject to continue to participate in the study.

Statistical Methods: For efficacy analyses, the intent-to-treat (ITT) population was defined as all enrolled subjects who took at least 1 dose of open label study drug. ITT subjects were

analyzed according to what the randomization schedule intended them to be taking during the double blind phase (previous pregabalin study). The per-protocol population (PP) was defined as all ITT subjects who completed the full double-blind phase treatment, had a total medication compliance within 80 to 120% during open label treatment, and had no other significant protocol violations. The efficacy analyses were to be repeated on the PP population. However, these analyses were not performed.

The safety population included every subject who signed the informed consent, had exposure to open label study drug and had at least 1 safety assessment.

Due to early termination of the study, only descriptive statistics were presented for the secondary efficacy variables: VAS, PGIC, SF-36, and WPAI.

The primary objective of the safety evaluation was to describe the long term safety of treatment with pregabalin in HIV subjects. Safety data was summarized; no inferential testing was done.

RESULTS:

Subject Disposition and Demography: Subject disposition is summarized in Table 2. In total, 221 subjects were screened, of which 217 subjects were assigned to open-label study treatment and received pregabalin. Subjects were categorized to pregabalin-pregabalin or placebo-pregabalin groups based on the treatment received during the previous double-blind pregabalin study.

Overall, 129 (59.4%) subjects completed the study and 88 (40.6%) subjects discontinued. Of the 88 subjects who discontinued, the majority (78 [88.6%] subjects) discontinued due to study being terminated by the Sponsor.

Table 2. Subject Disposition and Subjects Analyzed

	Pregabalin-Pregabalin N=108	Placebo-Pregabalin N=109	Total N=217
Number (%) of subjects	n (%)	n (%)	n (%)
Screened			221
Assigned to study treatment	108	109	217
Treated	108	109	217
Completed	67 (62.0)	62 (56.9)	129 (59.4)
Discontinued	41 (38.0)	47 (43.1)	88 (40.6)
Subject died	1 (0.9)	0	1 (0.5)
Relation to study drug not defined	40 (37.0)	46 (42.2)	86 (39.6)
Lost to follow-up	2 (1.9)	1 (0.9)	3 (1.4)
No longer willing to participate in study	1 (0.9)	2 (1.8)	3 (1.4)
Other	1 (0.9)	0	1 (0.5)
Study terminated by sponsor	35 (32.4)	43 (39.4)	78 (35.9)
Withdrawn due to pregnancy	1 (0.9)	0	1 (0.5)
Not related to study drug	0	1 (0.9)	1 (0.5)
Adverse event	0	1 (0.9)	1 (0.5)
Analyzed for efficacy (ITT)	108 (100.0)	109 (100.0)	217 (100.0)
Analyzed for safety			
Adverse events	108 (100.0)	109 (100.0)	217 (100.0)
Laboratory data	103 (95.4)	106 (97.2)	209 (96.3)
Safety population	108 (100.0)	109 (100.0)	217 (100.0)

All subjects received pregabalin during the study. The subjects were categorized to pregabalin-pregabalin or placebo-pregabalin groups based on the treatment received during the double-blind study (previous pregabalin study). Discontinuations have been attributed to the last study treatment received.
ITT = intent to treat population; N = total number of subjects in a given group; n = number of subjects in a given reporting criteria.

A summary of demographic characteristics is presented in Table 3.

Table 3. Demographic Characteristics

	Pregabalin-Pregabalin			Placebo-Pregabalin		
	Male n (%)	**Female n (%)**	**Total n (%)**	**Male n (%)**	**Female n (%)**	**Total n (%)**
N	37 (34.3)	71 (65.7)	108 (100)	41 (37.6)	68 (62.4)	109 (100)
Age (years):						
<18	0	0	0	0	0	0
18-44	14 (37.8)	56 (78.9)	70 (64.8)	17 (41.5)	48 (70.6)	65 (59.6)
45-64	22 (59.5)	15 (21.1)	37 (34.3)	24 (58.5)	20 (29.4)	44 (40.4)
≥65	1 (2.7)	0	1 (0.9)	0	0	0
Mean	48	39.5	42.4	46.3	41.8	43.5
SD	8.1	7.8	8.8	7.8	7.5	7.9
Range	33-65	25-59	25-65	33-62	26-61	26-62
Race:						
White	4 (10.8)	0	4 (3.7)	4 (9.8)	0	4 (3.7)
Black	18 (48.6)	61 (85.9)	79 (73.1)	23 (56.1)	62 (91.2)	85 (78.0)
Asian	9 (24.3)	7 (9.9)	16 (14.8)	10 (24.4)	5 (7.4)	15 (13.8)
Other	6 (16.2)	3 (4.2)	9 (8.3)	4 (9.8)	1 (1.5)	5 (4.6)
Weight (kg):						
Mean	75.6	72.7	73.7	66.9	76.2	72.6
SD	16.1	18.9	18	14.5	16.9	16.6
Range	54.5-121.5	44.0-144.7	44.0-144.7	38.3-105.2	38.0-121.4	38.0-121.4
BMI (kg/m^2):						
Mean	25.2	27.7	26.9	22.6	28.8	26.4
SD	5.3	7.1	6.6	3.7	6.6	6.4
Range	17.6-44.3	18.0-51.3	17.6-51.3	13.3-30.3	17.1-49.3	13.3-49.3
Height (cm):						
Mean	172.3	161.7	165.3	171.5	162.7	166
SD	8.5	7.6	9.4	8.6	7.4	8.9
Range	154.0-193.0	144.0-180.0	144.0-193.0	153.0-193.0	147.0-186.0	147.0-193.0

All subjects received pregabalin during the study. The subjects were categorized to pregabalin-pregabalin or placebo-pregabalin groups based on the treatment received during the double-blind study (previous pregabalin study).
BMI was calculated as $weight/(height \times 0.01)^2$.
BMI = body mass index; N = total number of subjects in a group; n = number of subjects in a given reporting criteria; SD = standard deviation.

Efficacy Results: There were no primary efficacy evaluations performed in this study. Secondary efficacy endpoints were summarized using descriptive statistics only due to early termination of the study.

Visual Analogue Scale for Pain: There was a decrease (less pain) in mean VAS pain score in both groups from Week 1 through Week 20. Mean VAS pain score remained low at Week 24 for both groups as summarized in Table 4.

Table 4. Pain Visual Analog Scale (Descriptive Statistics) - ITT Population

	Treatment Group	n	Minimum	Median	Maximum	Mean (SD)
Previous pregabalin study screening	Pregabalin-pregabalin	108	40	72	98	70.6 (14.13)
	Placebo-pregabalin	109	33	68	100	68.6 (14.00)
Week 1	Pregabalin-pregabalin	107	0	44	100	40.6 (26.55)
	Placebo-pregabalin	108	0	43.5	100	40.7 (26.57)
Week 4	Pregabalin-pregabalin	106	0	33.5	94	33.1 (25.14)
	Placebo-pregabalin	106	0	27.5	100	33.1 (27.11)
Week 8	Pregabalin-pregabalin	100	0	24.5	91	27.4 (21.01)
	Placebo-pregabalin	101	0	24	92	27.8 (24.25)
Week 12	Pregabalin-pregabalin	89	0	17	80	24.1 (22.41)
	Placebo-pregabalin	88	0	20	95	23.8 (23.45)
Week 16	Pregabalin-pregabalin	85	0	19	92	22.6 (20.82)
	Placebo-pregabalin	81	0	12	100	22.6 (25.32)
Week 20	Pregabalin-pregabalin	72	0	10.5	91	17.2 (19.18)
	Placebo-pregabalin	67	0	9	100	17.7 (22.78)
Week 24	Pregabalin-pregabalin	103	0	13	93	22.2 (22.54)
	Placebo-pregabalin	104	0	17	99	23.7 (23.94)

All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin groups based on the treatment they received during the double-blind study (previous pregabalin study).
Visual analog scale ranged from 0 to 100.
ITT = intent to treat; n = number of subjects being analyzed; SD = standard deviation.

Patient Global Impression Change: PGIC is summarized in Table 5. The majority of assessed subjects (84 subjects [81.5% and 80.8%] each in the pregabalin-pregabalin and placebo-pregabalin groups, respectively) reported that their overall status was 'very much improved' or 'much improved' at Week 24. Only 1 subject in each group reported a worsening.

Table 5. Summary of Patient Global Impression of Change (Frequency Table) - ITT Population

	Pregabalin-Pregabalin (N=108) n (%)	Placebo-Pregabalin (N=109) n (%)
Number of subjects assessed	103	104
Overall Status		
Very much improved	41 (39.8)	37 (35.6)
Much improved	43 (41.7)	47 (45.2)
Minimally improved	16 (15.5)	16 (15.4)
No change	2 (1.9)	3 (2.9)
Minimally worse	1 (<1.0)	0
Much worse	0	1 (<1.0)
Very much worse	0	0

All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin treatment groups based on the treatment they received during the double-blind study (previous pregabalin study).
Percentages are calculated using 'n' assessed in the denominator.
ITT = intent to treat; N = total number of subjects; n = number of subjects being analyzed.

Short Form-36: The SF-36 health survey subscales and component scores for ITT population are presented in Table 6. Overall, the individual scores for all 8 health aspects slightly improved at Week 24 (Visit 9) for both groups.

Table 6. The Short-Form 36 Version 2 Health Survey: Subscales and Component Scores (Descriptive Statistics) - ITT Population

Subscale	Visit	Treatment Group	n	Min	Median	Max	Mean (SD)
Physical functioning	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	0	55	100	54.86 (26.716)
		Placebo-pregabalin	109	5	55	100	56.24 (25.232)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	15	65	100	66.71 (25.340)
		Placebo-pregabalin	109	0	70	100	64.63 (27.434)
	Week 1	Pregabalin-pregabalin	51	20	75	100	73.14 (22.671)
		Placebo-pregabalin	53	25	80	100	75.47 (22.729)
	Week 24	Pregabalin-pregabalin	103	0	80	100	70.34 (27.594)
		Placebo-pregabalin	104	0	85	100	75.24 (25.086)
Role limitations due to physical problems	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	0	56.25	100	57.35 (26.390)
		Placebo-pregabalin	109	0	50	100	56.88 (25.614)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	12.5	71.88	100	68.75 (25.819)
		Placebo-pregabalin	109	6.3	62.5	100	67.32 (25.652)
	Week 1	Pregabalin-pregabalin	51	0	81.25	100	75.49 (22.873)
		Placebo-pregabalin	53	0	81.25	100	71.93 (27.616)
	Week 24	Pregabalin-pregabalin	103	6.3	75	100	71.18 (24.927)
		Placebo-pregabalin	104	0	75	100	72.96 (26.680)
Bodily pain	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	0	42	100	48.67 (22.483)
		Placebo-pregabalin	109	0	51	100	51.56 (21.114)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	10	62	100	63.55 (23.503)
		Placebo-pregabalin	109	0	62	100	65.28 (25.247)
	Week 1	Pregabalin-pregabalin	51	12	72	100	68.86 (20.430)
		Placebo-pregabalin	53	0	74	100	68.87 (26.010)
	Week 24	Pregabalin-pregabalin	102	12	74	100	69.57 (22.550)
		Placebo-pregabalin	104	21	74	100	72.19 (23.033)
General health perception	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	15	60	100	58.18 (19.975)
		Placebo-pregabalin	109	15	60	97	58.08 (18.506)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	15	67	100	69.36 (20.047)
		Placebo-pregabalin	109	0	67	100	66.63 (21.269)
	Week 1	Pregabalin-pregabalin	51	25	77	100	72.25 (20.369)
		Placebo-pregabalin	53	20	67	100	68.79 (20.411)
	Week 24	Pregabalin-pregabalin	103	10	75	100	73.14 (19.933)
		Placebo-pregabalin	104	5	72	100	71.31 (19.879)
Physical health component score	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	18.4	39.61	58.6	39.76 (9.314)
		Placebo-pregabalin	109	16.7	40.78	57.5	40.38 (7.920)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	19.5	45.59	60.3	45.38 (8.733)
		Placebo-pregabalin	109	11.8	45.42	60.7	44.85 (8.893)
	Week 1	Pregabalin-pregabalin	51	24.3	47.97	60.3	47.68 (7.268)
		Placebo-pregabalin	53	11.8	47.51	60.1	46.85 (9.578)
	Week 24	Pregabalin-pregabalin	102	29	47.08	61.5	47.28 (8.770)
		Placebo-pregabalin	104	23.6	49.67	61.2	48.48 (8.634)
Vitality	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	25	62.5	100	61.36 (16.151)
		Placebo-pregabalin	109	12.5	62.5	100	58.94 (18.209)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	12.5	68.75	100	66.61 (19.053)
		Placebo-pregabalin	109	12.5	68.75	100	67.26 (19.016)
	Week 1	Pregabalin-pregabalin	51	25	68.75	100	71.57 (19.418)
		Placebo-pregabalin	53	37.5	75	100	73.11 (17.660)
	Week 24	Pregabalin-pregabalin	103	18.8	68.75	100	68.51 (18.502)
		Placebo-pregabalin	104	0	68.75	100	66.29 (20.039)
Social functioning	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	12.5	62.5	100	67.25 (22.460)
		Placebo-pregabalin	109	25	62.5	100	66.97 (21.752)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	0	75	100	73.84 (21.788)
		Placebo-pregabalin	109	0	75	100	74.08 (22.676)
	Week 1	Pregabalin-pregabalin	51	37.5	87.5	100	78.92 (18.113)
		Placebo-pregabalin	53	37.5	87.5	100	82.08 (18.911)
	Week 24	Pregabalin-pregabalin	103	0	87.5	100	79.98 (20.883)
		Placebo-pregabalin	104	0	87.5	100	81.85 (20.304)

Table 6. The Short-Form 36 Version 2 Health Survey: Subscales and Component Scores (Descriptive Statistics) - ITT Population

Subscale	Visit	Treatment Group	n	Min	Median	Max	Mean (SD)
Role limitations due to emotional problems	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	0	66.67	100	65.43 (25.901)
		Placebo-pregabalin	109	0	66.67	100	66.13 (26.359)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	0	75	100	74.38 (24.849)
		Placebo-pregabalin	109	16.7	75	100	72.63 (25.334)
	Week 1	Pregabalin-pregabalin	51	25	83.33	100	81.05 (20.075)
		Placebo-pregabalin	53	0	91.67	100	79.87 (23.367)
	Week 24	Pregabalin-pregabalin	103	0	75	100	74.19 (27.029)
		Placebo-pregabalin	104	0	83.33	100	75.80 (25.640)
Mental health	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	20	70	100	68.75 (16.830)
		Placebo-pregabalin	109	20	70	100	67.43 (19.551)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	20	80	100	73.89 (18.862)
		Placebo-pregabalin	109	15	75	100	74.17 (19.620)
	Week 1	Pregabalin-pregabalin	51	30	80	100	76.27 (18.079)
		Placebo-pregabalin	53	45	85	100	80.00 (15.411)
	Week 24	Pregabalin-pregabalin	103	20	80	100	76.21 (18.196)
		Placebo-pregabalin	104	30	80	100	75.77 (18.588)
Mental health component score	Previous pregabalin study: baseline	Pregabalin-pregabalin	108	26.3	48.29	68.5	47.20 (9.640)
		Placebo-pregabalin	109	24.5	45.13	67.7	46.43 (10.664)
	Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	21.8	50.7	66.9	49.41 (9.855)
		Placebo-pregabalin	109	17.1	52.42	72.3	49.46 (10.557)
	Week 1	Pregabalin-pregabalin	51	32.4	52.33	67.8	51.41 (8.915)
		Placebo-pregabalin	53	31.8	54.04	72.3	52.71 (7.763)
	Week 24	Pregabalin-pregabalin	102	10.8	51.57	70.2	50.15 (10.394)
		Placebo-pregabalin	104	16.9	49.67	65.3	49.72 (9.884)

All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin groups based on the treatment they received during the double-blind study (previous pregabalin study).
Short-form 36 version 2 health survey subscales and component scores range from 0 to 100.
ITT = intent to treat; Max = maximum; Min = minimum; n = number of subjects that are being analyzed; SD = standard deviation.

Work Productivity and Activity Impairment: The majority of subjects (74 [68.5%] and 80 [73.4%] subjects in the pregabalin-pregabalin and placebo-pregabalin groups, respectively) were unemployed at the start of the study; and there were no changes observed during the study (68 [66.0%] and 77 [74.0%] subjects in the pregabalin-pregabalin and placebo-pregabalin groups, respectively remained unemployed at Week 24). Summaries of WPAI questionnaire results at scheduled visits (ITT population) for Question 1 and excluding Question 1 are presented in Table 7 and excluding Question 1 is presented in Table 8, respectively.

Table 7. Work Productivity and Activity Impairment Questionnaire at Scheduled Visits (Frequency Table for Question 1) - ITT Population

		Pregabalin-Pregabalin (N=108) n (%)	Placebo-Pregabalin (N=109) n (%)
Visit	**Currently Employed**		
Previous pregabalin study: baseline	n assessed	108	109
	Yes	34 (31.5%)	29 (26.6%)
	No	74 (68.5%)	80 (73.4%)
Previous pregabalin study: Week 16	n assessed	108	109
	Yes	38 (35.2%)	31 (28.4%)
	No	70 (64.8%)	78 (71.6%)
Previous pregabalin study: Week 17	n assessed	108	109
	Yes	41 (38.0%)	27 (24.8%)
	No	67 (62.0%)	82 (75.2%)
Week 1	n assessed	52	51
	Yes	12 (23.1%)	11 (21.6%)
	No	40 (76.9%)	40 (78.4%)
Week 24	n assessed	103	104
	Yes	35 (34.0%)	27 (26.0%)
	No	68 (66.0%)	77 (74.0%)

All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin groups based on the treatment they received during the double-blind study (previous pregabalin study).
Percentages are calculated using n assessed in the denominator.
n assessed is the number of subjects that were analyzed.
ITT = intent to treat; N = number of subjects in ITT population for the given treatment group; n = number of subjects.

Table 8. Work Productivity and Activity Impairment Questionnaire (Excluding Question 1) at Scheduled Visits (Descriptive Statistics) - ITT Population

Visit	Treatment Group	n	Min	Median	Max	Mean (SD)
How Many Hours did you Miss From Work due to leg/Foot Pain in the Last 7 Days?						
Previous pregabalin study: baseline	Pregabalin-pregabalin	34	0	0	40	6.53 (12.295)
	Placebo-pregabalin	30	0	0	20	2.30 (5.080)
Previous pregabalin study: Week 16	Pregabalin-pregabalin	38	0	0	30	2.05 (5.367)
	Placebo-pregabalin	33	0	0	40	2.42 (7.306)
Previous pregabalin study: Week 17	Pregabalin-pregabalin	41	0	0	28	3.07 (5.659)
	Placebo-pregabalin	28	0	0	11	1.07 (2.707)
Week 1	Pregabalin-pregabalin	12	0	0	24	2.25 (6.877)
	Placebo-pregabalin	11	0	0	8	0.82 (2.401)
Week 24	Pregabalin-pregabalin	35	0	0	22	2.17 (4.956)
	Placebo-pregabalin	28	0	0	45	2.32 (8.533)
How Many Hours did you Miss From Work due to Other Reason in the Last 7 Days?						
Previous pregabalin study: baseline	Pregabalin-pregabalin	34	0	4	96	16.97 (26.099)
	Placebo-pregabalin	30	0	0	72	5.97 (15.860)
Previous pregabalin study: Week 16	Pregabalin-pregabalin	38	0	0	72	10.16 (17.809)
	Placebo-pregabalin	33	0	0	72	7.76 (17.006)
Previous pregabalin study: Week 17	Pregabalin-pregabalin	41	0	0	120	9.05 (20.807)
	Placebo-pregabalin	28	0	0	24	1.86 (5.345)
Week 1	Pregabalin-pregabalin	12	0	0	18	3.42 (6.501)
	Placebo-pregabalin	11	0	0	5	0.91 (1.700)
Week 24	Pregabalin-pregabalin	35	0	0	108	9.20 (21.604)
	Placebo-pregabalin	28	0	1.5	72	7.71 (14.976)
How Many Hours did you Actually Work in the Last 7 Days?						
Previous pregabalin study: baseline	Pregabalin-pregabalin	34	0	37	78	32.44 (19.149)
	Placebo-pregabalin	30	0	30	84	27.50 (18.805)
Previous pregabalin study: Week 16	Pregabalin-pregabalin	38	0	40	80	37.16 (19.597)
	Placebo-pregabalin	33	0	40	60	33.00 (18.130)
Previous pregabalin study: Week 17	Pregabalin-pregabalin	41	0	36	98	32.93 (21.897)
	Placebo-pregabalin	28	0	40	84	35.93 (19.268)
Week 1	Pregabalin-pregabalin	12	12	35	60	35.58 (15.163)
	Placebo-pregabalin	11	0	34	56	30.36 (18.112)
Week 24	Pregabalin-pregabalin	35	4	40	84	41.51 (20.034)
	Placebo-pregabalin	28	3	40	96	34.86 (21.329)
How Much did Your leg/Foot Pain Affect Your Productivity in the Last 7 Days?						
Previous pregabalin study: baseline	Pregabalin-pregabalin	32	0	5.5	9	4.78 (2.624)
	Placebo-pregabalin	30	0	6	10	5.67 (2.440)
Previous pregabalin study: Week 16	Pregabalin-pregabalin	39	0	3	9	3.38 (2.711)
	Placebo-pregabalin	33	0	3	9	3.06 (2.692)
Previous pregabalin study: Week 17	Pregabalin-pregabalin	40	0	3.5	8	3.35 (2.547)
	Placebo-pregabalin	27	0	2	7	2.63 (2.436)
Week 1	Pregabalin-pregabalin	12	0	5	8	4.42 (2.843)
	Placebo-pregabalin	10	0	1.5	7	2.40 (2.716)
Week 24	Pregabalin-pregabalin	35	0	2	8	2.17 (1.917)
	Placebo-pregabalin	29	0	2	9	2.24 (2.415)
How Much did Your leg/Foot Pain Affect Your Daily Activities in the Last 7 Days?						
Previous pregabalin study: baseline	Pregabalin-pregabalin	108	0	6	9	5.97 (2.030)
	Placebo-pregabalin	109	0	6	10	6.00 (2.121)
Previous pregabalin study: Week 16	Pregabalin-pregabalin	108	0	3.5	9	3.44 (2.635)
	Placebo-pregabalin	109	0	3	10	3.52 (2.764)
Previous pregabalin study: Week 17	Pregabalin-pregabalin	108	0	3	9	3.59 (2.583)
	Placebo-pregabalin	109	0	3	10	3.39 (2.674)
Week 1	Pregabalin-pregabalin	52	0	3	9	3.48 (2.846)
	Placebo-pregabalin	51	0	3	9	3.47 (2.935)
Week 24	Pregabalin-pregabalin	103	0	2	9	2.51 (2.330)
	Placebo-pregabalin	104	0	2	10	2.72 (2.653)

Table 8. Work Productivity and Activity Impairment Questionnaire (Excluding Question 1) at Scheduled Visits (Descriptive Statistics) - ITT Population

All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin groups based on the treatment they received during the double-blind study (previous pregabalin study).
ITT = intent to treat; Max = maximum; Min = minimum; n = number of subjects analyzed; SD = standard deviation.

The study (which was an extension study of the previous pregabalin study) was terminated prematurely due to the termination of the previous pregabalin study (which was terminated early on the basis of futility).

Safety Results: Table 9 summarizes treatment-emergent AEs (TEAEs) reported in ≥5% of subjects during the study.

Table 9. Treatment-Emergent Non Serious Adverse Events (All-Causalities) For Events Having a Frequency Rate ≥5% in Any Treatment Group

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v15.0) Preferred Term	Pregabalin-Pregabalin n (%)	Placebo-Pregabalin n (%)
Number of subjects evaluable for adverse events	108	109
Number of subjects with adverse events	35 (32.4)	50 (45.9)
General disorders and administration site conditions	2 (1.9)	6 (5.5)
Oedema peripheral	2 (1.9)	6 (5.5)
Infections and infestations	7 (6.5)	13 (11.9)
Influenza	5 (4.6)	7 (6.4)
Pharyngitis	2 (1.9)	6 (5.5)
Musculoskeletal and connective tissue disorders	6 (5.6)	2 (1.8)
Back pain	6 (5.6)	2 (1.8)
Nervous system disorders	21 (19.4)	33 (30.3)
Dizziness	10 (9.3)	19 (17.4)
Headache	5 (4.6)	8 (7.3)
Somnolence	9 (8.3)	14 (12.8)

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v15.0) coding dictionary applied.
MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (MedDRA version 15.0); n = number of subjects in each treatment group.

Table 10 presents treatment-related TEAEs reported in ≥2% of subjects in either treatment group.

Table 10. Treatment-Emergent Treatment-Related Adverse Events Reported in ≥2% Subjects in Any Treatment Group

System Organ Class MedDRA (v15.0) Preferred Term	Pregabalin-Pregabalin (N=108) n (%)	Placebo-Pregabalin (N=109) n (%)
Total preferred term events	72	83
Gastrointestinal disorders	12 (11.1)	8 (7.3)
Constipation	2 (1.9)	3 (2.8)
Diarrhoea	3 (2.8)	1 (0.9)
General disorders and administration site conditions	3 (2.8)	5 (4.6)
Oedema peripheral	0	4 (3.7)
Pyrexia	3 (2.8)	0
Investigations	1 (0.9)	4 (3.7)
Weight increased	0	4 (3.7)
Nervous system disorders	21 (19.4)	28 (25.7)
Dizziness	10 (9.3)	18 (16.5)
Headache	3 (2.8)	3 (2.8)
Somnolence	9 (8.3)	13 (11.9)

AEs and SAEs are not separated out.
All subjects received pregabalin during the study. Subjects were assigned the pregabalin-pregabalin or placebo-pregabalin groups based on the treatment they received during the double-blind study (previous pregabalin study).
Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
AE = adverse event; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); N = number of subjects in each treatment group; n = number of subjects in a given reporting criteria; SAE = serious adverse event.

Serious Adverse Events: In total, 7 subjects (3.2%) reported 8 SAEs during the study. Four subjects in the pregabalin-pregabalin group reported 4 SAEs, and 3 subjects in the placebo-pregabalin group reported 4 SAEs. None of the SAEs were considered related to study treatment by the Investigator. SAEs are summarized in Table 11.

Table 11. Number (%) of Subjects in Treatment Groups Reporting Treatment-Emergent Serious Adverse Events During the Study

System Organ Class MedDRA (v15.0) Preferred Term	Pregabalin-Pregabalin	Placebo-Pregabalin
Number (%) of Subjects:	n (%)	n (%)
Evaluable for adverse events	108	109
With adverse events	4 (3.7)	3 (2.8)
Blood and lymphatic system disorders	0	1 (0.9)
Idiopathic thrombocytopenic purpura	0	1 (0.9)
Infections and infestations	2 (1.9)	1 (0.9)
Cellulitis	1 (0.9)	0
Gastroenteritis	0	1 (0.9)
HIV infection	1 (0.9)	0
Injury, poisoning and procedural complications	1 (0.9)	1 (0.9)
Facial bones fracture	0	1 (0.9)
Muscle strain	1 (0.9)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.9)
Kaposi's sarcoma	0	1 (0.9)
Nervous system disorders	1 (0.9)	0
Transient ischaemic attack	1 (0.9)	0

HIV = Human Immunodeficiency Virus; MedDRA (v15.0) = Medical Dictionary for Regulatory Activities (version 15.0); n = number of subjects in each treatment group.

Discontinuation From the Study due to Adverse Event: Two subjects permanently discontinued the study due to AEs as summarized in Table 12.

Table 12. Discontinuations Due to Adverse Events

Serial Number	System Organ Class[a]	Preferred Term[a]	Treatment Group	Adverse Event		Severity/ Outcome	Action
				Start Day	Stop Day		
1	Pregnancy, puerperium and perinatal conditions	Pregnancy	Pregabalin-pregabalin	Day 18	Day 57	NA/ pregnancy was terminated on Day 57	Permanently discontinued the study drug
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Kaposi's sarcoma	Placebo-pregabalin	Day 29	NA[b]	Severe/ unknown[c]	Permanently discontinued the study drug

Pregnancy was not reported as a withdrawal due to AE on subject summary page of case report form.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable.
a. MedDRA (version 15.0) dictionary is applied.
b. The subject was lost to follow-up.
c. The outcome of the event could not be obtained, as the subject was lost to follow-up.

A total of 22 subjects (8 and 14 subjects in the pregabalin-pregabalin and placebo-pregabalin groups, respectively) had either a dose reduction or temporary discontinuation due to an AE during the study. The AEs which resulted in most frequent discontinuations or dose reductions were somnolence (9 subjects) and dizziness (7 subjects).

Death: One subject died during post-therapy period due to progression of HIV infection. The subject received last dose of pregabalin 75 mg on Study Day 78 when the study treatment was stopped. The subject died on Study Day 116. The event was considered as not related to the study treatment by the Investigator.

Laboratory Tests: There were no discontinuations due to laboratory test abnormalities. Similar numbers of subjects experienced laboratory test abnormalities in each group.

Vital Signs, Body Weight, and Physical Examination: There were no significant changes from baseline in vital signs and body weight during the study.

Four (3.7%) subjects each in the pregabalin-pregabalin and placebo-pregabalin groups had significant changes since previous examination at screening visit. Four (3.7%) and 6 (5.5%) subjects in the pregabalin-pregabalin and placebo-pregabalin groups, respectively had significant changes since previous examination at final visit.

Suicidal Ideation: Four subjects (3.7%) in the pregabalin-pregabalin group and 9 subjects (8.3%) in the placebo-pregabalin group had suicidal ideation. In the pregabalin-pregabalin group, the suicidal ideation was observed only once in all 4 subjects. There was no fixed pattern of ideation behaviors with respect to the start of study. In the placebo-pregabalin group, 7/9 subjects reported suicidal ideation only once during the study. One subject reported ideation twice at Weeks 24 and 25. Another subject in the placebo-pregabalin group

self-administered the S-STS and recorded attempt of suicide and preparatory acts toward imminent suicidal behavior. However, upon clarification by the Principal Investigator, it was noted that the subject was unlikely to attempt suicide and had only depressed mood and occasional suicidal ideation (subject also reported suicidal ideation at Weeks 4, 24 and 25). A summary of results is presented in Table 13.

Table 13. Summary of Sheehan - Suicidality Tracking Scale (C-CASA)

Number (%) of Subjects	Pregabalin-Pregabalin (N=108)	Plcebo-Pregabalin (N=109)
C-CASA category <category>		
n assessed	108	109
Completed suicide <1>	0	0
Suicide attempt <2>	0	1 (0.9)
Preparatory acts toward imminent suicidal behavior <3>	0	1 (0.9)
Suicidal ideation <4>	4 (3.7)	9 (8.3)
Self injurious behavior, no suicidal intent <7>	0	0

Percentages are calculated using n assessed in the denominator.
n assessed is the number of subjects that are being analyzed.
C-CASA = Columbia Classification Algorithm of Suicide Assessment; N = number of subjects in safety population for the given treatment group; n = number of subjects assessed.

Patient Health Questionnaire: Summary of assessment of PHQ is presented in Table 14.

Table 14. Patient Health Questionnaire at Screening - ITT Population

Question			Pregabalin-Pregabalin (N=108) n (%)	Placebo-Pregabalin (N=109) n (%)
Have you had little interest or pleasure in doing things in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	59 (55.1%)	67 (62.0%)
		Several days	31 (29.0%)	25 (23.1%)
		More than half the days	14 (13.1%)	9 (8.3%)
		Nearly every day	3 (2.8%)	7 (6.5%)
Have you felt down, depressed or hopeless in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	84 (78.5%)	79 (73.1%)
		Several days	18 (16.8%)	21 (19.4%)
		More than half the days	5 (4.7%)	6 (5.6%)
		Nearly every day	0	2 (1.9%)
Have you had trouble falling/staying asleep in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	57 (53.3%)	59 (54.6%)
		Several days	33 (30.8%)	40 (37.0%)
		More than half the days	14 (13.1%)	4 (3.7%)
		Nearly every day	3 (2.8%)	5 (4.6%)
Have you felt tired or had little energy in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	52 (48.6%)	53 (49.1%)
		Several days	43 (40.2%)	40 (37.0%)
		More than half the days	12 (11.2%)	14 (13.0%)
		Nearly every day	0	1 (<1.0%)
Have you had poor appetite or overeating problems in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	75 (70.1%)	71 (65.7%)
		Several days	24 (22.4%)	26 (24.1%)
		More than half the days	5 (4.7%)	5 (4.6%)
		Nearly every day	3 (2.8%)	6 (5.6%)
Have you felt bad about yourself in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	92 (86.0%)	88 (81.5%)
		Several days	12 (11.2%)	13 (12.0%)
		More than half the days	2 (1.9%)	3 (2.8%)
		Nearly every day	1 (<1.0%)	4 (3.7%)
Have you had trouble concentrating on things in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	79 (73.8%)	84 (77.8%)
		Several days	23 (21.5%)	20 (18.5%)
		More than half the days	2 (1.9%)	3 (2.8%)
		Nearly every day	3 (2.8%)	1 (<1.0%)
Have you moved/spoken more slowly or been fidgetier than usual in the last 2 weeks?	Week 1	n assessed	107	108
		Not at all	87 (81.3%)	86 (79.6%)
		Several days	18 (16.8%)	16 (14.8%)
		More than half the days	0	3 (2.8%)
		Nearly every day	2 (1.9%)	3 (2.8%)
How difficult have these problems made it	Week 1	n assessed	107	108

Table 14. Patient Health Questionnaire at Screening - ITT Population

Question		Pregabalin-Pregabalin (N=108) n (%)	Placebo-Pregabalin (N=109) n (%)
	Not difficult at all	69 (64.5%)	68 (63.0%)
	Somewhat difficult	33 (30.8%)	36 (33.3%)
	Very difficult	5 (4.7%)	4 (3.7%)
	Extremely difficult	0	0

Percentages are calculated using n assessed in the denominator.
n assessed is the number of subjects that are being analyzed.
ITT = intent to treat; N = number of subjects in ITT population for the given treatment group; n = number of subjects analyzed.

CONCLUSION: Pregabalin 150-600 mg/day administered BID for up to 6-months was safe and well tolerated in this long-term, open-label safety study of subjects with painful HIV neuropathy as follow-on from the previous double-blind pregabalin study. There were no notable differences for subjects who initiated pregabalin in this study and those who continued pregabalin from previous pregabalin study. The safety profile of pregabalin in subjects in this study is consistent with that known with pregabalin as represented in product labeling. Efficacy as assessed from VAS scores showed lower levels of pain in this open-label, uncontrolled study relative to screening in the double-blind study, however, a very high placebo response was noted in the double-blind study.

According to PGIC, the majority of subjects (>80%) reported that their overall status was ‘very much improved’ or ‘much improved’. Overall, the individual scores for all 8 health aspects in the SF-36 slightly improved at the end of Week 24 (Visit 9) for both groups. According to the WPAI questionnaire, the majority of subjects were unemployed at Baseline (74 [68.5%] and 80 [73.4%] subjects in the pregabalin-pregabalin and placebo-pregabalin groups, respectively) and no significant changes were observed during the entire study.