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

PROTOCOL NO.: A0081147

PROTOCOL TITLE: Long Term Safety and Efficacy Study of Pregabalin in Subjects With Generalized Anxiety Disorder

Study Centers: A total of 60 centers in 16 countries took part in the study and enrolled subjects; 8 in the Czech Republic, 7 in the Russian Federation, 6 in Finland, 5 each in Argentina and India, 4 each in Indonesia, Lithuania and Croatia, 3 each in Austria, Costa Rica and Serbia, 2 each in Spain, Turkey and Mexico and 1 each in Slovenia and Greece.

Study Initiation Date and Final Completion Date: 13 May 2009 and 02 April 2012

Phase of Development: Phase 4

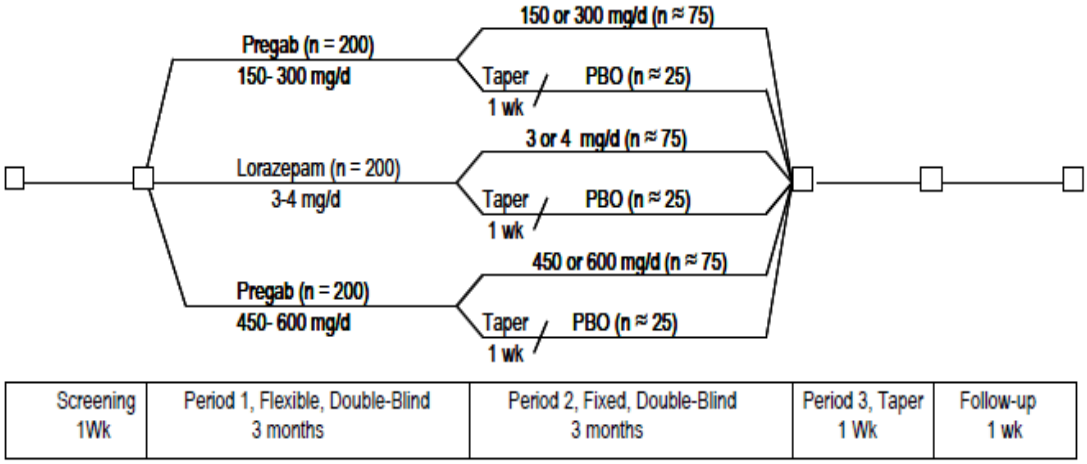
Study Objectives: To characterize the safety and efficacy of pregabalin in subjects with generalized anxiety disorder (GAD) at low and high doses relative to placebo and lorazepam following 3 and 6 months of treatment.

METHODS

Study Design: This was a double-blind, randomized, placebo- and active-control study in outpatient subjects with GAD to characterize the long-term efficacy and safety of pregabalin including drug discontinuation symptoms following treatment at low and high doses for up to 6 months. There were 3 consecutive study periods following Screening and Baseline assessments (Figure 1). The study employed a 6-arm randomization that allowed for 3 treatment groups in Period 1 and 6 treatment groups in Period 2. Randomization occurred once, at the onset of Period 1. Randomization assigned subjects to receive one of 3 treatments for Period 1: pregabalin high dose (450-600 mg/day), pregabalin low dose (150-300 mg/day), or lorazepam (3-4 mg/day). At the time of randomization, 25% of the subjects in each of these treatment groups were pre-assigned to receive placebo in a blinded fashion beginning in Period 2. The remaining subjects continued on the original treatment provided in Period 1 for the remainder of the study, an additional 3 months. Introduction of a placebo to a proportion of subjects in Period 2 was necessary to provide relevant drug discontinuation data at the lower and higher dose range of pregabalin, and lorazepam following 3 months of treatment. Discontinuation symptoms and rebound anxiety were assessed at 1 week and 2 weeks following the taper. All study treatments were administered twice per day (BID) and treatment was blinded using a double-dummy method. In Period 3, following 6 months of treatment, the remaining subjects who continued on the original treatment provided in Period 1 underwent a blinded taper over 1 week. A second assessment

of discontinuation symptoms and rebound anxiety was completed 1 week thereafter at Follow-up (Visit 18). Subjects who received placebo for 3 months during Period 2 were also evaluated.

Figure 1. Study Design



n = number of subjects; PBO = placebo; Pregab = pregabalin; Wk = week.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Period		**Period 1**									**Period 2**						**Period 3**	**Follow-Up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
End of Week[a]	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12[a]**	**13**	**14**	**15**	**18**	**21**	**24[a]**	**25**	**26**
Study Day[b]	**-7**	**1**	**7[c]**	**14[d]**	**21[d]**	**28[d]**	**35[d]**	**42[d]**	**63**	**84**	**91**	**98**	**105**	**126**	**147**	**168**	**175**	**182**
Protocol Activity	**Screening**	**BL**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**D/C1[e]**	**D/C2[e]**	**P2**	**P2**	**P2**	**P2**	**D/C1[f]**	**D/C2[f]**
Informed consent	X																	
Medical history	X																	
Psychiatric diagnosis	X																	
Physical examination	X																	
Vital signs	X	X	X		X			X	X	X	X	X				X	X	X
Body weight	X	X								X						X		
Laboratory assessments																		
Hematology	X																	X
Chemistry	X																	X
Urinalysis	X																	X
Serum/urine pregnancy test[c]	X	X																X
Urine drug screen	X									X[g]								
Breathalyzer	X																	
12-Lead ECG	X																	
Eligibility	X	X																
Randomization		X																
HAM-D	X	X																
HAM-A, CGI-S	X	X			X			X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PWC		X								X	X	X				X	X	X
S-STS	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Study treatment		Start	→	→	→	→	→	→	→	→	Taper[j]	→	→	→	→	→	Taper[k]	Stop
Dosing record			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Table 1. Schedule of Activities

Period		**Period 1**									**Period 2**						**Period 3**	**Follow-Up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
End of Week[a]	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**[a]	**13**	**14**	**15**	**18**	**21**	**24**[a]	**25**	**26**
Study Day[b]	**-7**	**1**	**7**[c]	**14**[d]	**21**[d]	**28**[d]	**35**[d]	**42**[d]	**63**	**84**	**91**	**98**	**105**	**126**	**147**	**168**	**175**	**182**
Protocol Activity	**Screening**	**BL**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**P1**	**D/C1**[e]	**D/C2**[e]	**P2**	**P2**	**P2**	**P2**	**D/C1**[f]	**D/C2**[f]
Adverse events (including DESS)	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

BL = Baseline; CGI-I = Clinical Global Impression - Improvement; CGI-S = Clinical Global Impression – Severity; D/C1 = Discontinuation Week 1; D/C2 = Discontinuation Week 2; DESS = Discontinuation-emergent signs and symptoms; ECG = electrocardiogram; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; P1 = Period 1; P2 = Period 2; PWC = Physicians Withdrawal Checklist; S-STS = Sheehan-suicidality tracking scale.

a. Week 12 and 24 visits were scheduled with consideration of timing to accommodate the needs of subjects who could experience severe discontinuation symptoms and need to return for evaluation.
b. Visit window for Visits 2-8, 12-13, 17 and 18 was ±3 days; Visit window for Visits 9, 10, 14-16 was ±5 days. Visit window for Visit 11, was 6-10 days to allow for minimum period for taper medication.
c. Pregnancy tests were also repeated as per request of Institutional Review Board / Independent Ethics Committees or if required by local regulations.
d. Weekly visit for evaluation and dose titration upon investigator's discretion.
e. Denote assessment time point for Discontinuation Week 1 & Week 2 (DC1 or DC2 of P1) after 3-month treatment (Period 1) and switch to placebo.
f. Denote assessment time point for Discontinuation Week 1 & Week 2 (DC1 or DC2 of P2) after 6-month treatment or early termination.
g. Benzodiazopine was not included in the panel at this time point. Urine drug screen was not required for early termination during Period 1.
h. Life time version of S-STS was used.
i. Since last study visit of S-STS was used.
j. For those who switched to placebo arm only during Period 2.
k. For all non-placebo arms during Period 2.

Number of Subjects (Planned and Analyzed): Approximately 600 subjects were planned to be randomized into this study from approximately 80 centers in 22 countries. To account for an expected drop-out rate of 50% at the end of Period 1, approximately 200 subjects per treatment group for Period 1 were to be randomized with equal chance to either a low dose of pregabalin, a high dose of pregabalin, or lorazepam in order to provide a sample size of 75 subjects per group for discontinuation and efficacy evaluation following 3 months of treatment. A total of 816 subjects (114 in the Czech Republic, 49 in the Russian Federation, 120 in Finland, 53 in Argentina, 56 in India, 16 in Indonesia, 126 in Lithuania, 29 in Croatia, 58 in Austria, 63 in Costa Rica, 15 in Serbia, 29 in Spain, 17 in Turkey, 39 in Mexico, 22 in Slovenia and 10 in Greece) were enrolled and 615 subjects were randomized and treated in the study.

Diagnosis and Main Criteria for Inclusion: The study included male and female subjects aged between 18 and 65 years with diagnosis of GAD, a Hamilton Anxiety Rating Scale (HAM-A) score ≥18 and Hamilton Depression Rating Scale (HAM-D) (item 1) score ≥2 at Screening and Baseline who needed pharmacological treatment.

Study Treatment: There were 2 treatment periods; during Period 1 subjects received pregabalin high dose, pregabalin low dose, or lorazepam and followed a flexible dose regimen during the first half of Period 1 and then a fixed dose regimen during the second half of Period 1. During Period 2, subjects received pregabalin high dose, pregabalin low dose, lorazepam, or placebo. Subjects who remained on pregabalin or lorazepam continued on the same fixed dose they achieved at the end of Week 6 in Period 1.

Double-Blind Flexible Dose in Period 1: Subjects were advised to take their first dose of study medication in the evening of Visit 2 (Baseline). For the low and high dose pregabalin, treatment was initiated with a 150 mg/day starting dose. For lorazepam, the starting dose was 2 mg/day. All doses were taken orally. The upward escalation occurred during the first 3 weeks and was predetermined based on treatment assignment. During this time no other dose adjustments were allowed. At the end of Week 3 (Visit 5), depending on efficacy and tolerability, the dose could be adjusted upward or remain at the lower dose level of the assigned treatment dose range. Further adjustments to the dose within the assigned range were allowed until the end of Week 6 (Visit 8).

Only subjects who had been adequately managed, ie, had a CGI-I score of 1 or 2 at Visit 8 (Week 6), the midpoint of Period 1 were permitted to remain in Period 1 and to continue long term treatment in Period 2. Subjects randomized to receive placebo after completion of Period 1 (Week 12), discontinued pregabalin or lorazepam treatment in a blinded fashion using a 1-week taper prior to entering Period 2, and received placebo treatment for the duration of the study.

Double-Blind Fixed Dose in Period 2: At the end of 3 Months (end of Period 1), subjects entering Period 2 continued on fixed-dose treatment with pregabalin or lorazepam, or were switched to placebo for 3 months according to the randomization scheme. The allowable fixed doses in Period 2 were:

- Low dose pregabalin: 150 mg/day (75 mg BID) or 300 mg/day (150 mg BID)

- High dose pregabalin: 450 mg/day (225 mg BID) or 600 mg/day (300 mg BID)

- Lorazepam: 3 mg/day (1 mg every day before noon and 2 mg every night at bedtime), or 4 mg/day (2 mg BID)

Taper in Period 3: At the end of 6 Months (end of Period 2), subjects who remained on treatment discontinued in a blinded fashion using a 1-week taper. Period 3 lasted for 1 week; treatment was completely discontinued at the end of the 1-week taper. Subjects who experienced severe signs and symptoms any time either during the scheduled 1-week taper or during the following week, could resort to a more gradual rescue taper at the Investigator's judgment. The rescue taper provided a decrease in medication in a blinded fashion over a period of up to 4 weeks.

Efficacy and Safety Endpoints:

Efficacy Endpoints

- HAM-A total: A 14 question rating scale that assesses anxiety symptoms which was measured at Baseline (prior to treatment) and at 3 and 6 months post-treatment.

- Clinical Global Impressions - Severity and Improvement (CGI-S and CGI-I) were collected at the same time points as the HAM-A.

Safety Endpoints

- Adverse events (AEs) from spontaneous reports were monitored throughout the trial. AEs were summarized by treatment group following 3 and 6 months of GAD treatment.

- Drug Discontinuation and Rebound Anxiety:

    - Physicians Withdrawal Checklist (PWC): A questionnaire to collect information to determine whether subjects experience discontinuation symptoms after cessation of study medication.

    - Rebound Anxiety: The HAM-A was used to characterize rebound anxiety, defined as a rapid return of the subject's original symptoms following drug discontinuation, that are worse compared to Baseline.

    - Discontinuation-Emergent Signs and Symptoms (DESS) associated with drug discontinuation were characterized at 3 and 6 months: DESS was determined from spontaneously-reported treatment-emergent AEs that either newly developed during the taper, or existed prior to but worsened during the tapering period.

Safety Evaluations: Safety evaluations included AEs, clinical laboratory assessments, vital signs (heart rate, blood pressure), 12-lead electrocardiograms, and full physical examination including body weight.

Sheehan-Suicidality Tracking Scale (S-STS) scores were also assessed as part of safety evaluations. The S-STS is an 8-item prospective rating scale that tracked treatment-emergent suicidal ideation and behaviors. This scale was adapted from the suicidality module of the Mini-International Neuropsychiatric Interview Structured Diagnostic Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Statistical Methods:

Per Protocol (PP) Analysis Set: The primary analysis set for efficacy and discontinuation effects analyses was the PP analysis set which included all subjects who were randomized, had a Baseline with at least 1 discontinuation or efficacy visit, and were not major protocol violators.

Full Analysis Set (FAS): The Full analysis set included all subjects who were randomized, had a Baseline with at least 1 discontinuation or efficacy visit. This analysis set was used in the analyses of efficacy and discontinuation effects.

Safety Sample: The primary analysis set for safety analyses was the Safety Sample, which constituted subjects who were randomized and received at least 1 dose of study medication.

The following efficacy endpoints were evaluated using a 1-sample 95% confidence interval (CI) and summary statistics (N, mean, median, standard deviation [SD], minimum, maximum) for 3 months (Week 12) and 6 months (Week 24) (imputed using last-observation-carried-forward method):

- Change from Baseline to 3 and 6 months in HAM-A score
- Change from Baseline to 3 and 6 months in CGI-S total score
- Total HAM-A score at Baseline and 3 and 6 months
- Total CGI-S score at Baseline and 3 and 6 months
- Total CGI-I score at 3 and 6 months

Change from Baseline to Discontinuation Weeks 1 and 2 in HAM-A total score and change from last visit on treatment prior to taper to discontinuation Weeks 1 and 2 in PWC were presented using the 1-sample 95% CI along with summary statistics (n, mean, median, SD, minimum, maximum) separately for each treatment cohort. For the following 2 endpoints, numbers and percentages of subjects were presented separately for each treatment cohort: 1) Incidence of the rebound anxiety; and 2) Incidence of DESS. To be included in the analyses, subjects should have had at least 1 discontinuation assessment at discontinuation Week 1 or Discontinuation Week 2.

RESULTS

Subject Disposition and Demography: A total of 816 subjects were screened and 615 subjects were randomized and treated. A total of 463 subjects completed Period 1 and

366 subjects completed the study. A total of 249 subjects discontinued. Overall, 55 subjects discontinued from the study due to reasons classified as 'other' by the investigator. These were not considered related to study drug. Of these, 39 subjects terminated early due to drug supply issues (termination was requested by the Sponsor). Nineteen of these 39 subjects had received at least 3 months of treatment. A total of 615 subjects were included in the FAS. Of these, 53 subjects were excluded from the PP (primary) analysis. Subject disposition is summarized in Table 2.

Table 2. Subject Disposition

Number (%) of Subjects		PGB_H → PGB_H	PGB_H → PBO	PGB_L → PGB_L	PGB_L → PBO	LOR → LOR	LOR → PBO
Screened	816						
Assigned to study treatment	615						
Treated		154	52	154	52	153	50
Completed Period 1		121 (78.6)	39 (75.0)	112 (72.7)	38 (73.1)	114 (74.5)	39 (78.0)
Early termination Period 1		33 (21.4)	13 (25.0)	42 (27.3)	14 (26.9)	39 (25.5)	11 (22.0)
Early termination Period 2		15 (9.7)	11 (21.2)	18 (11.7)	11 (21.2)	19 (12.4)	9 (18.0)
Early termination Period 3		2 (1.3)	0	3 (1.9)	1 (1.9)	0	1 (2.0)
Early termination follow-up		2 (1.3)	1 (1.9)	2 (1.3)	0	2 (1.3)	0
Completed study		102 (66.2)	27 (51.9)	89 (57.8)	26 (50.0)	93 (60.8)	29 (58.0)
Discontinued		52 (33.8)	25 (48.1)	65 (42.2)	26 (50.0)	60 (39.2)	21 (42.0)
Subject died		0	0	1 (0.6)	0	0	0
Related to study drug		19 (12.3)	12 (23.1)	27 (17.5)	14 (26.9)	22 (14.4)	8 (16.0)
Adverse event		11 (7.1)	9 (17.3)	15 (9.7)	4 (7.7)	8 (5.2)	5 (10.0)
Lack of efficacy		8 (5.2)	3 (5.8)	12 (7.8)	10 (19.2)	14 (9.2)	3 (6.0)
Not related to study drug		33 (21.4)	13 (25.0)	37 (24.0)	12 (23.1)	38 (24.8)	13 (26.0)
Adverse event		2 (1.3)	0	7 (4.5)	2 (3.8)	5 (3.3)	2 (4.0)
Lost to follow-up		2 (1.3)	0	5 (3.2)	0	4 (2.6)	2 (4.0)
Other		16 (10.4)	8 (15.4)	12 (7.8)	3 (5.8)	13 (8.5)	3 (6.0)
Subject no longer willing to participate in study		13 (8.4)	5 (9.6)	13 (8.4)	7 (13.5)	16 (10.5)	6 (12.0)
Analyzed For Safety							
Adverse events		154 (100.0)	52 (100.0)	154 (100.0)	52 (100.0)	153 (100.0)	50 (100.0)
Laboratory data		140 (90.9)	46 (88.5)	131 (85.1)	46 (88.5)	130 (85.0)	43 (86.0)

Discontinuations occurring outside the lag period had been attributed to the last study treatment received.
Period 3 lasted 1 week (Week 25, Visit 17).
Follow-up period lasted 1 week (Week 26, Visit 18)
Early Termination (study) included early termination at any period through follow-up.
LOR = lorazepam; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low.

The subject demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics

Number (%) of Subjects	PGB_H → PGB_H N=154	PGB_H → PBO N=52	PGB_L → PGB_L N=154	PGB_L → PBO N=52	LOR → LOR N=153	LOR → PBO N=50
Age (years)						
18-44	75 (48.7)	30 (57.7)	100 (64.9)	28 (53.8)	86 (56.2)	27 (54.0)
45-64	79 (51.3)	22 (42.3)	51 (33.1)	24 (46.2)	66 (43.1)	23 (46.0)
≥65	0	0	3 (1.9)	0	1 (0.7)	0
Mean (SD)	42.9 (11.4)	40.9 (11.9)	40.1 (12.4)	41.9 (12.3)	42.8 (11.4)	42.1 (10.8)
Range	18-64	21-61	18-65	21-64	21-65	19-62
Race						
White	132 (85.7)	44 (84.6)	122 (79.2)	43 (82.7)	124 (81.0)	42 (84.0)
Black	0	0	0	0	1 (0.7)	0
Asian	9 (5.8)	5 (9.6)	17 (11.0)	5 (9.6)	18 (11.8)	4 (8.0)
Other	13 (8.4)	3 (5.8)	15 (9.7)	4 (7.7)	10 (6.5)	4 (8.0)
Body mass index (kg/m^2):						
Mean (SD)	25.8 (4.8)	26.1 (4.6)	26.1 (6.4)	25.5 (4.3)	26.4 (5.1)	27.8 (5.4)
Range	18.7-47.9	18.2-40.7	12.9-66.8	17.3-35.7	15.8-46.1	20.0-45.4

LOR = lorazepam; N = total number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Efficacy Results:

HAM-A Total Score – Month 3 (End of Period 1):

HAM-A total score and changes from Baseline during Period 1 (PP analysis set) are presented in Table 4.

Table 4. Hamilton Anxiety Rating Scale (HAM-A) Total Score - Assessment of Efficacy - Period 1, Per Protocol Analysis Set

	PGB_H N=197	PGB_L N=183	LOR N=188
Week 0 (Baseline)			
Observed			
n	197	183	188
Mean (SD)	25.3 (4.4)	24.9 (3.9)	24.5 (4.4)
Median	25.0	24.0	24.0
Minimum, Maximum	18, 49	18, 35	18, 40
95% CI	24.7, 26.0	24.3, 25.4	23.9, 25.1
Week 12 (LOCF)			
Observed			
N	194	180	185
Mean (SD)	8.0 (6.2)	8.9 (7.2)	7.9 (6.7)
Median	7.0	7.0	6.0
Minimum, Maximum	0, 32	0, 34	0, 43
95% CI	7.1, 8.8	7.8, 10.0	6.9, 8.8
Change from Baseline			
N	194	180	185
Mean (SD)	-17.4 (7.4)	-16.0 (7.5)	-16.7 (7.9)
Median	-18.0	-17.0	-17.0
Minimum, Maximum	-45, 7	-31, 9	-39, 13
95% CI	-18.5, -16.4	-17.1, -14.9	-17.8, -15.5

Period 1 included data up to Week 12.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

HAM-A Total Score – Month 6 (End of Period 2):

HAM-A total score and changes from Baseline during Period 2 (PP analysis set) are presented in Table 5.

Table 5. Hamilton Anxiety Rating Scale (HAM-A) Total Score - Assessment of Efficacy – Period 2, Per Protocol Analysis Set

Number of Subjects	PGB_H → PGB_H N=117	PGB_H → PBO N=37	PGB_L → PGB_L N=103	PGB_L → PBO N=37	LOR → LOR N=106	LOR → PBO N=37
Week 0 (Baseline)						
Observed						
n	117	37	103	37	106	37
Mean (SD)	25.6 (3.8)	24.6 (4.7)	24.8 (3.8)	25.1 (3.9)	24.7 (4.4)	24.1 (4.0)
Median	26.0	23.0	24.0	25.0	24.0	24.0
Minimum, Maximum	18, 37	18, 36	18, 34	19, 35	18, 40	18, 34
95% CI	25.0, 26.3	23.0, 26.1	24.0, 25.5	23.8, 26.4	23.8, 25.5	22.8, 25.5
Week 24 (LOCF)						
Observed						
n	117	37	103	37	106	37
Mean (SD)	7.0 (6.5)	7.1 (7.1)	6.5 (6.0)	10.2 (7.5)	5.7 (6.1)	6.6 (6.3)
Median	6.0	5.0	5.0	10.0	4.0	6.0
Minimum, Maximum	0, 37	0, 30	0, 23	0, 28	0, 36	0, 27
95% CI	5.8, 8.2	4.7, 9.5	5.4, 7.7	7.7, 12.7	4.5, 6.9	4.5, 8.8
Change from Baseline						
n	117	37	103	37	106	37
Mean (SD)	-18.7 (7.3)	-17.5 (6.9)	-18.2 (6.6)	-14.9 (7.9)	-19.0 (7.2)	-17.5 (8.3)
Median	-19.0	-18.0	-19.0	-15.0	-20.0	-18.0
Minimum, Maximum	-32, 9	-36, 4	-32, -1	-31, 5	-37, 10	-33, 7
95% CI	-20.0, -17.3	-19.8, -15.2	-19.5, -17.0	-17.6, -12.3	-20.4, -17.6	-20.2, -14.7

Period 2 included data from Week 13-Week 24.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

CGI-S Score at Month 3 (End of Period 1):

CGI-S scores and change from Baseline during Period 1 (PP analysis set) are summarized in Table 6.

Table 6. Clinical Global Impressions - Severity (CGI-S) - Assessment of Efficacy - Period 1, Per Protocol Analysis Set

	PGB_H N=197	PGB_L N=183	LOR N=188
Week 0 (Baseline)			
Observed			
n	197	183	188
Mean (SD)	4.6 (0.7)	4.5 (0.7)	4.4 (0.7)
Median	5.0	4.0	4.0
Minimum, Maximum	3, 6	2, 6	3, 6
95% CI	4.5, 4.7	4.4, 4.6	4.3, 4.5
Week 12 (LOCF)			
Observed			
n	195	181	186
Mean (SD)	2.3 (1.1)	2.5 (1.2)	2.3 (1.0)
Median	2.0	2.0	2.0
Minimum, Maximum	0, 6	0, 6	1, 6
95% CI	2.1, 2.4	2.3, 2.6	2.2, 2.5
Change from Baseline			
n	195	181	186
Mean (SD)	-2.3 (1.1)	-2.1 (1.1)	-2.1 (1.2)
Median	-2.0	-2.0	-2.0
Minimum, Maximum	-5, 1	-5, 2	-5, 1
95% CI	-2.5, -2.1	-2.2, -1.9	-2.2, -1.9

Period 1 included data up to Week 12.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

CGI-S Score at Month 6 (End of Period 2):

CGI-S scores and change from Baseline during Period 2 (PP analysis set) are presented in Table 7.

Table 7. Clinical Global Impressions - Severity (CGI-S) - Assessment of Efficacy - Period 2, Per Protocol Analysis Set

Number of Subjects	PGB_H → PGB_H N=117	PGB_H → PBO N=37	PGB_L → PGB_L N=103	PGB_L → PBO N=37	LOR → LOR N=106	LOR → PBO N=37
Week 0 (Baseline)						
Observed						
n	117	37	103	37	106	37
Mean (SD)	4.7 (0.7)	4.5 (0.7)	4.5 (0.7)	4.5 (0.7)	4.4 (0.7)	4.5 (0.6)
Median	5.0	4.0	5.0	4.0	4.0	4.0
Minimum, Maximum	4, 6	3, 6	2, 6	3, 6	3, 6	4, 6
95% CI	4.6, 4.8	4.3, 4.7	4.4, 4.7	4.3, 4.8	4.3, 4.6	4.3, 4.7
Week 24 (LOCF)						
Observed						
n	117	37	103	37	106	37
Mean (SD)	2.3 (1.1)	2.2 (1.2)	2.1 (1.0)	2.5 (1.2)	1.9 (0.9)	2.4 (1.0)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Minimum, Maximum	1, 6	1, 5	1, 5	1, 5	1, 5	1, 5
95% CI	2.1, 2.5	1.8, 2.6	2.0, 2.3	2.1, 3.0	1.8, 2.1	2.0, 2.7
Change from Baseline						
n	117	37	103	37	106	37
Mean (SD)	-2.4 (1.1)	-2.3 (1.2)	-2.4 (1.0)	-2.0 (1.3)	-2.5 (1.1)	-2.2 (1.2)
Median	-3.0	-3.0	-2.0	-2.0	-2.5	-2.0
Minimum, Maximum	-5, 0	-4, 1	-5, 0	-4, 1	-5, 1	-4, 1
95% CI	-2.6, -2.2	-2.7, -1.9	-2.6, -2.2	-2.4, -1.6	-2.7, -2.3	-2.6, -1.8

Period 2 included data from Week 13-Week 24.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

CGI-I at Month 3 (End of Period 1):

CGI-I scores at Week 1 to Week 12 during Period 1 (PP analysis set) are summarized in Table 8.

Table 8. Clinical Global Impressions - Improvement (CGI-I) - Assessment of Efficacy-Period 1, Per Protocol Analysis Set

	PGB_H N=197	PGB_L N=183	LOR N=188
Week 12 (LOCF)			
Observed			
n	197	183	188
Mean (SD)	1.9 (1.1)	1.9 (1.0)	1.9 (1.2)
Median	2.0	2.0	2.0
Minimum, Maximum	1, 7	1, 6	1, 7
95% CI	1.7, 2.0	1.7, 2.0	1.8, 2.1

Period 1 included data up to Week 12.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

CGI-I at Month 6 (End of Period 2):

CGI-I scores at Week 13 to Week 24 during Period 2 (PP analysis set) are presented in Table 9.

Table 9. Clinical Global Impressions - Improvement (CGI-I) - Assessment of Efficacy-Period 2, Per Protocol Analysis Set

	PGB_H → PGB_H N=117	PGB_H → PBO N=37	PGB_L → PGB_L N=103	PGB_L → PBO N=37	LOR → LOR N=106	LOR → PBO N=37
Week 24 (LOCF)						
n	117	37	103	37	106	37
Mean	1.7	1.9	1.6	2.3	1.5	2.0
SD	0.99	1.15	0.75	1.53	0.91	1.07
Median	2.0	2.0	1.0	2.0	1.0	2.0
Minimum	1	1	1	1	1	1
Maximum	7	5	4	6	6	5
95% CI	1.6, 1.9	1.6, 2.3	1.4, 1.7	1.8, 2.8	1.3, 1.7	1.6, 2.3

Period 2 included data from Week 13-Week 24.
CI = confidence interval; LOCF = last-observation-carried-forward; LOR = lorazepam; N = total number of subjects; n = number of subjects with observation; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Discontinuation Effects Results:

PWC: PWC total score, change from Baseline and change from last day of treatment for Cohort 1 (<3-month last visit), Cohort 2 (3-month last visit) and Cohort 3 (6-month last visit); PP analysis set are summarized in Table 10, Table 11, and Table 12 respectively.

Table 10. Physicians Withdrawal Checklist (PWC) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 1 (<3-Month Last Visit), Per Protocol Analysis Set

	PGB_H (N=15)	PGB_L (N=19)	LOR (N=21)
Baseline			
Observed			
n	14	19	21
Mean (SD)	13.6 (8.2)	17.6 (10.7)	16.4 (8.6)
Median	15.5	22	17
Minimum, Maximum	0, 24	0, 37	0, 34
95% CI	8.9, 18.4	12.5, 22.8	12.5, 20.4
DC Week 1			
Change from Baseline			
n	14	19	18
Mean (SD)	-3.4 (11.9)	-3.3 (9.1)	-5.9 (7.4)
Median	-5.5	-1	-5.5
Minimum, maximum	-20, 24	-26, 16	-19, 11
95% CI	-10.2, 3.5	-7.7, 1.1	-9.6, -2.2
DC Week 2			
Change from Baseline			
n	13	15	16
Mean (SD)	-4.7 (10.6)	-2.7 (8.2)	-5.4 (8.3)
Median	-9	-2	-6
Minimum, maximum	-15, 25	-21, 16	-18, 11
95% CI	-11.1, 1.7	-7.2, 1.9	-9.8, -0.9
Last visit on treatment			
Observed			
n	15	18	20
Mean (SD)	10.1 (8.7)	16.8 (13.2)	13.1 (10.8)
Median	8	15	12
Minimum, maximum	0, 29	0, 47	0, 36
95% CI	5.3, 15.0	10.3, 23.4	8.1, 18.1
DC Week 1			
Change from last visit on treatment			
n	15	18	18
Mean (SD)	0.1 (9.9)	-2.8 (8.0)	-4.2 (6.1)
Median	-2	-1	-2.5
Minimum, maximum	-13, 30	-23, 16	-19, 3
95% CI	-5.4, 5.5	-6.8, 1.1	-7.2, -1.1
DC Week 2			
Change from last visit on treatment			
n	14	15	16
Mean (SD)	-2.0 (6.4)	-2.7 (9.0)	-3.2 (6.1)
Median	-4	-1	-0.5
Minimum, maximum	-11, 14	-26, 16	-21, 3
95% CI	-5.7, 1.7	-7.7, 2.3	-6.4, 0.0

Cohort 1: All subjects who discontinued prior to Week 9, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; n = number of subjects; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Table 11. Physicians Withdrawal Checklist (PWC) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 2 (3-Month Last Visit), Per Protocol Analysis Set

	PGB_H (N=58)	PGB_L (N=52)	LOR (N=52)
Baseline			
Observed			
n	57	51	52
Mean (SD)	17.4 (7.8)	17.1 (9.8)	14.8 (7.9)
Median	18	18	14
Minimum, Maximum	0, 38	0, 45	0, 34
95% CI	15.3, 19.5	14.3, 19.8	12.6, 17.0
DC Week 1			
Change from Baseline			
n	57	51	49
Mean (SD)	-8.5 (9.4)	-9.3 (9.5)	-7.6 (9.5)
Median	-10	-9	-7
Minimum, maximum	-32, 24	-32, 12	-34, 16
95% CI	-11.0, -6.0	-12.0, -6.6	-10.4, -4.9
DC Week 2			
Change from Baseline			
n	53	48	44
Mean (SD)	-8.3 (9.5)	-8.7 (9.7)	-8.0 (9.7)
Median	-9	-10.5	-8
Minimum, maximum	-26, 12	-27, 12	-34, 16
95% CI	-10.9, -5.6	-11.5, -5.9	-10.9, -5.1
Last visit on treatment			
Observed			
n	58	52	52
Mean (SD)	7.2 (7.3)	6.5 (6.0)	5.0 (3.8)
Median	5	5	4
Minimum, maximum	0, 36	0, 25	0, 21
95% CI	5.3, 9.1	4.8, 8.2	3.9, 6.1
DC Week 1			
Change from last visit on treatment			
n	58	52	49
Mean (SD)	1.9 (7.3)	1.4 (4.5)	2.3 (6.6)
Median	1	1	1
Minimum, maximum	-27, 30	-11, 22	-10, 25
95% CI	-0.1, 3.8	0.2, 2.7	0.4, 4.2
DC Week 2			
Change from last visit on treatment			
n	54	49	44
Mean (SD)	2.1 (6.1)	2.0 (5.5)	1.6 (6.3)
Median	0.5	1	0
Minimum, maximum	-9, 23	-9, 20	-9, 24
95% CI	0.4, 3.7	0.5, 3.6	-0.3, 3.6

Cohort 2: All subjects who discontinued between Weeks 9 and 15 or who switched to placebo at the end of Week 12, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; n = number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Table 12. Physicians Withdrawal Checklist (PWC) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 3 (6-Month Last Visit), Per Protocol Analysis Set

	PGB_H → PGB_H (N=109)	PGB_H → PBO (N=30)	PGB_L → PGB_L (N=94)	PGB_L → PBO (N=29)	LOR → LOR (N=100)	LOR → PBO (N=30)
Baseline						
Observed						
n	109	30	94	29	99	30
Mean (SD)	17.8 (8.4)	17.8 (7.8)	16.1 (7.5)	17.4 (9.3)	16.8 (8.9)	14.9 (7.6)
Median	17.0	18.5	16.0	18.0	17.0	14.5
Minimum, maximum	0, 40	0, 32	0, 31	0, 45	0, 47	0, 29
95% CI	16.2, 19.4	14.9, 20.7	14.6, 17.6	13.9, 20.9	15.0, 18.5	12.1, 17.8
DC Week 1						
Change from Baseline						
n	109	30	94	29	98	30
Mean (SD)	-11.0 (9.5)	-12.9 (7.9)	-11.0 (8.1)	-9.9 (11.0)	-8.7 (10.8)	-10.4 (7.6)
Median	-10	-14	-10.5	-11	-9	-9
Minimum, maximum	-36, 16	-30, 2	-28, 16	-35, 16	-45, 20	-23, 5
95% CI	-12.8, -9.2	-15.8, -9.9	-12.7, -9.4	-14.1, -5.8	-10.9, -6.6	-13.2, -7.5
DC Week 2						
Change from Baseline						
n	106	29	84	26	92	30
Mean (SD)	-9.8 (10.3)	-13.8 (8.3)	-10.8 (8.4)	-10.2 (8.6)	-9.6 (9.7)	-10.3 (7.5)
Median	-9	-15	-11	-9	-10	-8.5
Minimum, maximum	-36, 22	-30, 2	-28, 7	-29, 9	-43, 11	-23, 5
95% CI	-11.8, -7.8	-17.0, -10.6	-12.6, -8.9	-13.7, -6.8	-11.6, -7.6	-13.1, -7.5
Last visit on treatment						
Observed						
n	109	30	93	29	100	30
Mean (SD)	5.2 (5.6)	4.9 (7.2)	3.9 (4.1)	6.5 (6.7)	5.3 (6.7)	4.7 (4.5)
Median	4.0	2.5	2.0	5.0	4.0	4.0
Minimum, maximum	0, 28	0, 36	0, 16	0, 26	0, 41	0, 15
95% CI	4.1, 6.2	2.3, 7.6	3.1, 4.8	3.9, 9.0	3.9, 6.6	3.0, 6.3
DC Week 1						
Change from last visit on treatment						
n	109	30	93	29	99	30
Mean (SD)	1.7 (4.9)	0.0 (2.2)	1.1 (3.5)	1.0 (4.4)	3.0 (6.8)	-0.1 (3.2)

Table 12. Physicians Withdrawal Checklist (PWC) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 3 (6-Month Last Visit), Per Protocol Analysis Set

	PGB_H → PGB_H (N=109)	PGB_H → PBO (N=30)	PGB_L → PGB_L (N=94)	PGB_L → PBO (N=29)	LOR → LOR (N=100)	LOR → PBO (N=30)
Median	1.0	0.0	0.0	1.0	2.0	0.0
Minimum, maximum	-15, 26	-10, 3	-6, 16	-12, 16	-22, 26	-8, 7
95% CI	0.7, 2.6	-0.8, 0.8	0.4, 1.9	-0.7, 2.6	1.7, 4.4	-1.3, 1.1
DC Week 2						
Change from last visit on treatment						
n	106	29	84	26	93	30
Mean (SD)	2.8 (6.0)	-1.0 (5.7)	1.7 (4.8)	1.8 (5.1)	2.2 (6.0)	-0.1 (3.6)
Median	1.0	0.0	0.0	0.0	1.0	0.0
Minimum, maximum	-9, 26	-29, 6	-6, 19	-6, 20	-13, 19	-11, 9
95% CI	1.6, 3.9	-3.2, 1.1	0.7, 2.8	-0.2, 3.9	1.0, 3.5	-1.4, 1.3

Cohort 3: All subjects who either completed the study or discontinued after Week 15, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; n = number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = Standard deviation.

Rebound Anxiety: HAM-A total score, change from Baseline and change from last day of treatment for Cohort 1 (<3-month last visit), Cohort 2 (3-month last visit) and Cohort 3 (6-month last visit); PP analysis set is summarized in Table 13, Table 14, and Table 15.

Table 13. Hamilton Rating Scale for Anxiety (HAM-A) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 1 (<3-Month Last Visit), Per Protocol Analysis Set

	PGB_H (N=15)	PGB_L (N=19)	LOR (N=21)
Baseline			
Observed			
n	15	19	21
Mean (SD)	25.8 (4.2)	24.9 (4.2)	24.4 (4.9)
Median	25	25	23
Minimum, Maximum	21, 35	20, 32	18, 39
95% CI	23.5, 28.1	22.9, 26.9	22.2, 26.6
DC Week 1			
Change from Baseline			
n	15	19	18
Mean (SD)	-7.7 (6.8)	-5.9 (7.2)	-9.9 (10.8)
Median	-7	-5	-9
Minimum, maximum	-19, 3	-20, 4	-39, 12
95% CI	-11.5, -4.0	-9.4, -2.4	-15.3, -4.6
DC Week 2			
Change from Baseline			
n	14	15	16
Mean (SD)	-12.0 (7.2)	-5.9 (5.5)	-9.7 (11.1)
Median	-11.5	-5	-8
Minimum, maximum	-26, -3	-20, 1	-38, 13
95% CI	-16.2, -7.8	-8.9, -2.8	-15.6, -3.8
Last visit on treatment			
Observed			
n	15	18	20
Mean (SD)	16.1 (8.5)	21.6 (6.2)	16.1 (10.1)
Median	14	23	14
Minimum, maximum	1, 32	8, 34	0, 43
95% CI	11.4, 20.8	18.5, 24.6	11.4, 20.8
DC Week 1			
Change from last visit on treatment			
n	15	18	18
Mean (SD)	2.0 (11.5)	-2.3 (4.6)	-2.4 (3.3)
Median	1	-1.5	-1
Minimum, maximum	-16, 29	-13, 8	-10, 1
95% CI	-4.3, 8.3	-4.6, -0.0	-4.1, -0.8
DC Week 2			
Change from last visit on treatment			
n	14	15	16
Mean (SD)	-2.3 (9.5)	-3.5 (5.3)	-2.2 (4.2)
Median	0	-3	-0.5
Minimum, maximum	-20, 16	-14, 2	-13, 4
95% CI	-7.8, 3.2	-6.4, -0.5	-4.4, 0.0

Cohort 1: All subjects who discontinued prior to Week 9, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; n = number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Table 14. Hamilton Rating Scale for Anxiety (HAM-A) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 2 (3-Month Last Visit), Per Protocol Analysis Set

	PGB_H (N=58)	PGB_L (N=52)	LOR (N=52)
Baseline			
Observed			
n	58	52	52
Mean (SD)	25.0 (5.4)	24.7 (3.9)	24.6 (4.8)
Median	23.5	24	23.5
Minimum, Maximum	18, 49	18, 35	18, 40
95% CI	23.6, 26.4	23.6, 25.8	23.2, 25.9
DC Week 1			
Change from Baseline			
n	58	52	48
Mean (SD)	-15.3 (7.8)	-15.3 (6.7)	-15.8 (7.9)
Median	-17	-16	-16
Minimum, maximum	-35, 4	-31, -1	-34, 7
95% CI	-17.4, -13.3	-17.2, -13.5	-18.1, -13.5
DC Week 2			
Change from Baseline			
n	54	49	44
Mean (SD)	-15.6 (7.4)	-14.9 (7.1)	-16.0 (8.0)
Median	-17	-15	-17
Minimum, maximum	-36, 2	-31, 5	-34, 6
95% CI	-17.7, -13.6	-16.9, -12.8	-18.5, -13.6
Last visit on treatment			
Observed			
n	58	52	50
Mean (SD)	8.0 (6.6)	8.5 (6.5)	6.7 (4.3)
Median	7	7	6
Minimum, maximum	0, 33	0, 28	0, 18
95% CI	6.2, 9.7	6.7, 10.3	5.4, 7.9
DC Week 1			
Change from last visit on treatment			
n	58	52	48
Mean (SD)	1.7 (6.7)	0.9 (4.0)	2.3 (5.7)
Median	1	0	0
Minimum, maximum	-26, 24	-13, 16	-7, 20
95% CI	-0.1, 3.4	-0.3, 2.0	0.6, 4.0
DC Week 2			
Change from last visit on treatment			
n	54	49	44
Mean (SD)	1.5 (5.6)	1.5 (6.4)	1.5 (5.4)
Median	1	1	0.5
Minimum, maximum	-11, 20	-13, 28	-10, 17
95% CI	-0.0, 3.0	-0.3, 3.4	-0.1, 3.2

Cohort 2: All subjects who discontinued between Week 9-15 or who switched to placebo at the end of Week 12, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; n = number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

Table 15. Hamilton Rating Scale for Anxiety (HAM-A) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 3 (6-Month Last Visit), Per Protocol Analysis Set

	PGB_H → PGB_H (N=109)	PGB_H → PBO (N=30)	PGB_L → PGB_L (N=94)	PGB_L → PBO (N=29)	LOR → LOR (N=100)	LOR → PBO (N=30)
Baseline						
Observed						
n	109	30	94	29	100	30
Mean (SD)	25.5 (3.9)	24.2 (4.6)	24.7 (3.9)	24.9 (3.8)	24.6 (4.4)	24.9 (3.9)
Median	26.0	23.0	24.0	25.0	24.0	25.0
Minimum, maximum	18, 37	18, 36	18, 34	19, 32	18, 40	19, 34
95% CI	24.8, 26.3	22.4, 25.9	23.9, 25.5	23.4, 26.3	23.7, 25.5	23.4, 26.3
DC Week 1						
Change from Baseline						
n	109	30	94	28	99	30
Mean (SD)	-17.6 (7.3)	-18.7 (5.4)	-18.4 (6.3)	-16.5 (7.3)	-16.2 (8.1)	-19.1 (6.7)
Median	-19.0	-19.0	-19.0	-17.0	-17.0	-19.0
Minimum, maximum	-33, 4	-36, -6	-32, -3	-31, -1	-39, 8	-33, -6
95% CI	-19.0, -16.2	-20.7, -16.7	-19.7, -17.1	-19.3, -13.7	-17.9, -14.6	-21.6, -16.6
DC Week 2						
Change from Baseline						
n	107	29	84	26	94	30
Mean (SD)	-16.6 (8.5)	-19.1 (5.8)	-18.3 (7.1)	-16.0 (8.2)	-16.7 (7.5)	-18.7 (7.4)
Median	-17.0	-19.0	-18.0	-17.0	-16.5	-19.0
Minimum, maximum	-34, 7	-36, -6	-32, -1	-31, 6	-39, 2	-33, -2
95% CI	-18.3, -15.0	-21.3, -16.9	-19.8, -16.7	-19.3, -12.7	-18.2, -15.1	-21.5, -16.0
Last visit on treatment						
Observed						
n	109	30	93	29	100	30
Mean (SD)	6.3 (5.9)	5.5 (6.1)	5.6 (5.0)	8.3 (6.5)	5.6 (6.2)	5.5 (4.7)
Median	5.0	4.0	4.0	7.0	4.0	4.5
Minimum, maximum	0, 37	0, 30	0, 20	0, 22	0, 36	0, 15
95% CI	5.2, 7.4	3.2, 7.8	4.6, 6.6	5.9, 10.8	4.4, 6.9	3.8, 7.2
DC Week 1						
Change from last visit on treatment						
n	109	30	93	28	99	30
Mean (SD)	1.6 (4.4)	-0.0 (2.3)	0.7 (3.1)	0.6 (2.7)	3.0 (5.7)	0.3 (3.0)

Table 15. Hamilton Rating Scale for Anxiety (HAM-A) Total Score, Change From Baseline and Change From Last Day of Treatment - Cohort 3 (6-Month Last Visit), Per Protocol Analysis Set

	PGB_H → PGB_H (N=109)	PGB_H → PBO (N=30)	PGB_L → PGB_L (N=94)	PGB_L → PBO (N=29)	LOR → LOR (N=100)	LOR → PBO (N=30)
Median	0.0	0.0	0.0	0.0	1.0	0.0
Minimum, maximum	-11, 17	-11, 4	-6, 13	-6, 8	-7, 21	-6, 8
95% CI	0.8, 2.5	-0.9, 0.8	0.0, 1.3	-0.5, 1.6	1.9, 4.2	-0.8, 1.4
DC Week 2						
Change from last visit on treatment						
n	107	29	84	26	94	30
Mean (SD)	2.5 (5.7)	-0.8 (5.3)	1.2 (3.9)	1.5 (5.1)	2.2 (5.4)	0.6 (3.8)
Median	1.0	0.0	0.0	0.0	1.0	0.0
Minimum, maximum	-7, 24	-27, 6	-5, 15	-5, 21	-10, 18	-9, 11
95% CI	1.4, 3.6	-2.8, 1.3	0.3, 2.0	-0.5, 3.6	1.1, 3.3	-0.8, 2.0

Cohort 3: All subjects who either completed the study or discontinued after Week 15, and had a corresponding DC week assessment.
CI = confidence interval; DC = discontinuation; LOR = lorazepam; N = total number of subjects; number of subjects; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SD = standard deviation.

The incidence of rebound anxiety is summarized in Table 16 and Table 17.

Table 16. Incidence of Rebound Anxiety - Cohort 1 and Cohort 2, Per Protocol Analysis Set

	PGB_H	PGB_L	LOR
Cohort 1			
Number assessed	15	19	18
Number with rebound anxiety	1 (6.7%)	5 (26.3%)	1 (5.6%)
Cohort 2			
Number assessed	58	52	48
Number with rebound anxiety	3 (5.2%)	1 (1.9%)	2 (4.2%)

Rebound Anxiety: HAM-A total score at Discontinuation Week 1 or Week 2 that was greater than the HAM-A total score at Baseline (Visit 2).
LOR = lorazepam; PGB_H = pregabalin high; PGB_L = pregabalin low.

Table 17. Incidence of Rebound Anxiety - Cohort 3, Per Protocol Analysis Set

	PGB_H → PGB_H (N=109)	PGB_H → PBO (N=30)	PGB_L → PGB_L (N=94)	PGB_L → PBO (N=29)	LOR → LOR (N=100)	LOR → PBO (N=30)
Number assessed	109	30	94	28	100	30
Number with rebound anxiety	4 (3.7%)	0	0	1 (3.6%)	6 (6.0%)	0

Rebound Anxiety: HAM-A total score at Discontinuation Week 1 or Week 2 that was greater than the HAM-A total score at Baseline (Visit 2).
LOR = lorazepam; N = total number of subjects; PGB_H = pregabalin high; PGB_L = pregabalin low.

Discontinuation Emergent Signs and Symptoms:

In Cohort 1, the incidence of DESS was higher in the pregabalin high and lorazepam treatment groups (reported by 3 and 2 subjects, respectively) than in the pregabalin low treatment group (no DESS reported). Overall, 6 events were reported in the pregabalin high treatment group (1 event each of asthenia, irritability, pyrexia, insomnia, tension and pollakiuria) and 3 events in the lorazepam treatments group (1 event each of asthenia, cystitis and vaginal infection). With the exception of 1 subject in the pregabalin high treatment group who reported severe irritability, no subjects reported serious adverse events (SAEs), severe AEs or discontinued due to AEs.

In Cohort 2, the incidence of DESS was similar across the treatment groups (36.2%, 32.7%, and 32.7% subjects in the pregabalin high, pregabalin low and lorazepam treatment groups, respectively). No subjects experienced SAEs. Severe AEs were reported by 6.9%, 5.8% and 3.8% subjects in the pregabalin high, pregabalin low and lorazepam treatment groups, respectively. The most frequently reported (≥5% subjects) DESS by preferred term were nausea, decreased appetite, dizziness, headache, anxiety and insomnia.

In Cohort 3, 1 subject in the pregabalin high-pregabalin high group reported a serious DESS of anxiety disorder and 1 subject in the lorazepam-lorazepam group reported a serious DESS of food poisoning. The incidence of DESS was higher in the pregabalin high-pregabalin high treatment group (31.2%) compared with the pregabalin high-placebo treatment

group (13.3%). Similarly, the incidence of DESS was higher in the lorazepam-lorazepam treatment group (28.0%) compared with the lorazepam-placebo treatment group (13.3%). However, the incidence of DESS was lower in the pregabalin low-pregabalin low treatment group (22.3%) compared with the pregabalin low-placebo treatment group (31.0%). The most frequently reported (≥5% subjects) DESS by preferred term were headache, anxiety and insomnia.

Safety Results: Overviews of treatment-emergent AEs (TEAEs) are presented for all causality and treatment related events in Table 18 and Table 19, respectively.

Table 18. Treatment-Emergent Adverse Events (All Causalities)

Number (%) of Subjects	PGB_H → PGB_H	PGB_H → PBO	PGB_L → PGB_L	PGB_L → PBO	LOR → LOR	LOR → PBO
Subjects evaluable for adverse events	154	52	154	52	153	50
Number of adverse events	543	166	404	213	435	155
Subjects with adverse events	121 (78.6)	42 (80.8)	121 (78.6)	43 (82.7)	115 (75.2)	39 (78.0)
Subjects with serious adverse events	2 (1.3)	0	5 (3.2)	2 (3.8)	4 (2.6)	0
Subjects with severe adverse events	27 (17.5)	4 (7.7)	21 (13.6)	6 (11.5)	22 (14.4)	3 (6.0)
Subjects discontinued due to adverse events	13 (8.4)	9 (17.3)	22 (14.3)	6 (11.5)	13 (8.5)	7 (14.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	5 (3.2)	0	8 (5.2)	3 (5.8)	11 (7.2)	3 (6.0)

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.
LOR = lorazepam; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low.

Table 19. Treatment-Emergent Adverse Events (Treatment-Related)

Number (%) of Subjects	PGB_H → PGB_H	PGB_H → PBO	PGB_L → PGB_L	PGB_L → PBO	LOR → LOR	LOR → PBO
Subjects evaluable for adverse events	154	52	154	52	153	50
Number of adverse events	350	111	230	119	272	96
Subjects with adverse events	108 (70.1)	37 (71.2)	90 (58.4)	36 (69.2)	99 (64.7)	33 (66.0)
Subjects with serious adverse events	1 (0.6)	0	1 (0.6)	0	0	0
Subjects with severe adverse events	23 (14.9)	3 (5.8)	10 (6.5)	3 (5.8)	12 (7.8)	3 (6.0)
Subjects discontinued due to adverse events	11 (7.1)	9 (17.3)	15 (9.7)	4 (7.7)	8 (5.2)	5 (10.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	5 (3.2)	0	5 (3.2)	2 (3.8)	8 (5.2)	3 (6.0)

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.
LOR = lorazepam; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low.

Adverse Events (All Causalities): The most frequently reported TEAEs (all causalities, reported by ≥5% of subjects in any treatment group) are summarized in Table 20.

Table 20. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA (v15.0) Preferred Term	PGB_H → PGB_H (N=154) n (%)	PGB_H → PBO (N=52) n (%)	PGB_L → PGB_L (N=154) n (%)	PGB_L → PBO (N=52) n (%)	LOR → LOR (N=153) n (%)	LOR → PBO (N=50) n (%)
Ear and labyrinth disorders	4 (2.6)	1 (1.9)	5 (3.2)	4 (7.7)	3 (2.0)	1 (2.0)
Vertigo	4 (2.6)	1 (1.9)	5 (3.2)	4 (7.7)	3 (2.0)	1 (2.0)
Gastrointestinal disorders	39 (25.3)	12 (23.1)	22 (14.3)	16 (30.8)	28 (18.3)	11 (22.0)
Abdominal pain	1 (0.6)	1 (1.9)	2 (1.3)	3 (5.8)	1 (0.7)	0
Constipation	10 (6.5)	1 (1.9)	4 (2.6)	2 (3.8)	2 (1.3)	1 (2.0)
Diarrhoea	10 (6.5)	3 (5.8)	8 (5.2)	5 (9.6)	9 (5.9)	1 (2.0)
Dry mouth	13 (8.4)	3 (5.8)	5 (3.2)	2 (3.8)	8 (5.2)	4 (8.0)
Nausea	17 (11.0)	7 (13.5)	12 (7.8)	8 (15.4)	18 (11.8)	7 (14.0)
General disorders and administration site conditions	21 (13.6)	7 (13.5)	19 (12.3)	12 (23.1)	22 (14.4)	6 (12.0)
Fatigue	16 (10.4)	6 (11.5)	15 (9.7)	11 (21.2)	15 (9.8)	5 (10.0)
Irritability	6 (3.9)	1 (1.9)	4 (2.6)	2 (3.8)	8 (5.2)	1 (2.0)
Infections and infestations	21 (13.6)	4 (7.7)	14 (9.1)	5 (9.6)	15 (9.8)	4 (8.0)
Influenza	8 (5.2)	3 (5.8)	7 (4.5)	0	7 (4.6)	0
Nasopharyngitis	13 (8.4)	2 (3.8)	7 (4.5)	5 (9.6)	8 (5.2)	4 (8.0)
Investigations	5 (3.2)	1 (1.9)	7 (4.5)	3 (5.8)	4 (2.6)	0
Weight increased	5 (3.2)	1 (1.9)	7 (4.5)	3 (5.8)	4 (2.6)	0
Metabolism and nutrition disorders	6 (3.9)	1 (1.9)	3 (1.9)	4 (7.7)	6 (3.9)	3 (6.0)
Decreased appetite	6 (3.9)	1 (1.9)	3 (1.9)	4 (7.7)	6 (3.9)	3 (6.0)
Musculoskeletal and connective tissue disorders	17 (11.0)	5 (9.6)	8 (5.2)	2 (3.8)	13 (8.5)	6 (12.0)
Arthralgia	4 (2.6)	1 (1.9)	3 (1.9)	0	3 (2.0)	3 (6.0)
Back pain	9 (5.8)	1 (1.9)	1 (0.6)	0	4 (2.6)	2 (4.0)
Myalgia	5 (3.2)	4 (7.7)	4 (2.6)	2 (3.8)	9 (5.9)	1 (2.0)
Nervous system disorders	87 (56.5)	31 (59.6)	75 (48.7)	29 (55.8)	74 (48.4)	24 (48.0)
Disturbance in attention	12 (7.8)	1 (1.9)	3 (1.9)	2 (3.8)	6 (3.9)	1 (2.0)
Dizziness	37 (24.0)	17 (32.7)	28 (18.2)	14 (26.9)	20 (13.1)	10 (20.0)
Headache	38 (24.7)	13 (25.0)	36 (23.4)	17 (32.7)	33 (21.6)	10 (20.0)
Paraesthesia	6 (3.9)	0	3 (1.9)	3 (5.8)	5 (3.3)	2 (4.0)
Sedation	6 (3.9)	2 (3.8)	5 (3.2)	0	10 (6.5)	1 (2.0)

Table 20. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA (v15.0) Preferred Term	PGB_H → PGB_H (N=154) n (%)	PGB_H → PBO (N=52) n (%)	PGB_L → PGB_L (N=154) n (%)	PGB_L → PBO (N=52) n (%)	LOR → LOR (N=153) n (%)	LOR → PBO (N=50) n (%)
Somnolence	25 (16.2)	7 (13.5)	31 (20.1)	9 (17.3)	35 (22.9)	13 (26.0)
Tremor	5 (3.2)	2 (3.8)	1 (0.6)	3 (5.8)	6 (3.9)	0
Psychiatric disorders	41 (26.6)	19 (36.5)	37 (24.0)	12 (23.1)	40 (26.1)	15 (30.0)
Anxiety	14 (9.1)	6 (11.5)	10 (6.5)	1 (1.9)	19 (12.4)	5 (10.0)
Generalised anxiety disorder	4 (2.6)	2 (3.8)	9 (5.8)	2 (3.8)	6 (3.9)	2 (4.0)
Insomnia	31 (20.1)	15 (28.8)	24 (15.6)	12 (23.1)	23 (15.0)	13 (26.0)
Tension	8 (5.2)	1 (1.9)	4 (2.6)	0	2 (1.3)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	1 (1.9)	2 (1.3)	0	2 (1.3)	4 (8.0)
Cough	1 (0.6)	1 (1.9)	2 (1.3)	0	2 (1.3)	4 (8.0)

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.
LOR = lorazepam; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with adverse events; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low.

Adverse Events (Treatment-Related): The most frequently reported TEAEs (treatment-related, reported by ≥5% of subjects in any treatment group) are summarized in Table 21.

Table 21. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Treatment-Related) For Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA (v15.0) Preferred Term	PGB_H → PGB_H (N=154) n (%)	PGB_H → PBO (N=52) n (%)	PGB_L → PGB_L (N=154) n (%)	PGB_L → PBO (N=52) n (%)	LOR → LOR (N=153) n (%)	LOR → PBO (N=50) n (%)
Ear and labyrinth disorders	6 (3.9)	2 (3.8)	5 (3.2)	3 (5.8)	3 (2.0)	4 (8.0)
Vertigo	3 (1.9)	1 (1.9)	5 (3.2)	3 (5.8)	3 (2.0)	1 (2.0)
Gastrointestinal disorders	31 (20.1)	12 (23.1)	23 (14.9)	15 (28.8)	34 (22.2)	15 (30.0)
Constipation	8 (5.2)	1 (1.9)	4 (2.6)	1 (1.9)	2 (1.3)	1 (2.0)
Diarrhoea	4 (2.6)	3 (5.8)	4 (2.6)	2 (3.8)	7 (4.6)	1 (2.0)
Dry mouth	13 (8.4)	3 (5.8)	5 (3.2)	2 (3.8)	8 (5.2)	3 (6.0)
Nausea	13 (8.4)	6 (11.5)	11 (7.1)	7 (13.5)	18 (11.8)	7 (14.0)
General disorders and administration site conditions	36 (23.4)	8 (15.4)	21 (13.6)	15 (28.8)	23 (15.0)	9 (18.0)
Fatigue	15 (9.7)	5 (9.6)	14 (9.1)	11 (21.2)	13 (8.5)	5 (10.0)
Investigations	6 (3.9)	1 (1.9)	7 (4.5)	3 (5.8)	5 (3.3)	1 (2.0)
Weight increased	5 (3.2)	1 (1.9)	7 (4.5)	3 (5.8)	2 (1.3)	0
Metabolism and nutrition disorders	11 (7.1)	4 (7.7)	3 (1.9)	4 (7.7)	7 (4.6)	2 (4.0)
Decreased appetite	4 (2.6)	0	2 (1.3)	3 (5.8)	5 (3.3)	2 (4.0)
Nervous system disorders	84 (54.5)	29 (55.8)	67 (43.5)	27 (51.9)	72 (47.1)	23 (46.0)
Disturbance in attention	10 (6.5)	0	2 (1.3)	1 (1.9)	5 (3.3)	0
Dizziness	35 (22.7)	17 (32.7)	27 (17.5)	14 (26.9)	18 (11.8)	10 (20.0)
Headache	26 (16.9)	9 (17.3)	17 (11.0)	11 (21.2)	20 (13.1)	5 (10.0)
Sedation	5 (3.2)	2 (3.8)	4 (2.6)	0	10 (6.5)	1 (2.0)
Somnolence	25 (16.2)	7 (13.5)	31 (20.1)	9 (17.3)	35 (22.9)	13 (26.0)
Psychiatric disorders	38 (24.7)	17 (32.7)	25 (16.2)	10 (19.2)	34 (22.2)	11 (22.0)
Anxiety	12 (7.8)	5 (9.6)	5 (3.2)	0	11 (7.2)	4 (8.0)
Insomnia	20 (13.0)	14 (26.9)	10 (6.5)	7 (13.5)	14 (9.2)	8 (16.0)

AEs and SAEs are not separated out.
MedDRA (v15.0) coding dictionary applied.
AE = adverse event; LOR = lorazepam; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with adverse events; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low; SAE = serious adverse event.

Deaths: One subject died during the study; a 65-year-old female in the pregabalin low-pregabalin low treatment group, died during the post-treatment phase. The cause of death was reported as metastasis of unknown origin. The event was not considered related to study drug. The subject also had infectious disease of unknown origin at the time of death.

Serious Adverse Events: All SAEs are summarized in Table 22. A total of 20 SAEs were reported for 15 subjects. All, except 2 of the SAEs, were considered not related to study drug. Six subjects were permanently withdrawn due to SAEs.

Table 22. Serious Adverse Events

Serial Number	Treatment Group	Suspect Drug / Dose	Event (Preferred Term)	Action Taken	Investigator Causality / Sponsor Causality	Clinical Outcome
1	LOR → LOR	Lorazepam 3 mg	Typhoid fever	Permanently withdrawn	Unrelated / unrelated	Recovered
2	LOR → LOR	Lorazepam 4 mg	Myocardial infarction	Permanently withdrawn	Unrelated / unrelated	Resolved with sequel
			Myocardial ischaemia	Permanently withdrawn	Unrelated / unrelated	Not recovered
3	LOR → LOR	Lorazepam 4 mg	Anxiety	Permanently withdrawn	Unrelated / unrelated	Recovered
4[a]	LOR → LOR	Lorazepam 4 mg	Food poisoning	Dose not changed	Unrelated / unrelated	Recovered
5[b]	PGB_H → PGB_H	Pregabalin 450 mg	Anxiety disorder	No action taken due to post therapy	Related / unrelated	Recovered
6	PGB_H → PGB_H	Pregabalin 600 mg	Subdural haematoma	Temporarily withdrawn	Unrelated / unrelated	Recovered
7	PGB_L → PBO	Placebo / Pregabalin 300 mg	Diabetes mellitus inadequate control	Not applicable	Unrelated / unrelated	Recovered
			Hyperglycaemia	Not applicable	Unrelated / unrelated	Recovered
			Ketoacidosis	Not applicable	Unrelated / unrelated	Recovered
8	PGB_L → PBO	Pregabalin 150 mg	Abdominal hernia	Dose not changed	Unrelated / unrelated	Recovered
9	PGB_L → PGB_L	Pregabalin 150 mg	Infection	Dose not changed	Unrelated / unrelated	Recovered
			Metastasis	Dose not changed	Unrelated / unrelated	Fatal
10	PGB_L → PGB_L	Pregabalin 150 mg	Suicidal ideation	Permanently withdrawn	Related / related	Recovered
			Depression	Permanently withdrawn	Related / related	Recovered
11	PGB_L → PGB_L	Pregabalin 150 mg	Anxiety disorder	Permanently withdrawn	Unrelated / unrelated	Recovered
12	PGB_L → PGB_L	Pregabalin 150 mg	Cerebral haemorrhage	Permanently withdrawn	Unrelated / unrelated	Recovered
13	PGB_L → PGB_L	Pregabalin 300 mg	Inguinal hernia	No action taken due to post therapy	Unrelated / unrelated	Recovered
14	Pre-randomization	Pre-randomization	Gastritis	Not applicable	Not applicable	Recovered
15	Pre-randomization	Pre-randomization	Tension headache	Not applicable	Not applicable	Recovering

DESS = Discontinuation-emergent signs and symptoms; LOR = lorazepam; PBO = placebo; PGB_H = pregabalin high; PGB_L = pregabalin low.

a. Subject in the lorazepam-lorazepam treatment group reported serious DESS of food poisoning.

b. Subject in the pregabalin high-pregabalin high group reported a serious DESS of anxiety disorder.

Discontinuations Due to Adverse Events: Overall, 70 subjects permanently discontinued from the study due to AEs. Of these; 13 (8.4%) subjects were in the pregabalin high-pregabalin high, 9 (17.3%) subjects in the pregabalin high-placebo, 22 (14.3%) subjects in the pregabalin low-pregabalin low, 6 (11.5%) subjects in the pregabalin low-placebo, 13 (8.5%) subjects in the lorazepam-lorazepam and 7 (14%) subjects in the lorazepam-placebo treatment groups. The reasons for discontinuation were similar across the treatment groups and the most frequently reported AEs leading to discontinuation were GAD (9 [12.9%] subjects), anxiety (8 [11.4%] subjects), insomnia (6 [8.6%] subjects), dizziness (6 [8.6%] subjects) and somnolence (5 [7.1%] subjects).

CONCLUSIONS:

The primary objective of this study was to investigate whether discontinuation of pregabalin after short- and long-term (3 months or 6 months) treatment in subjects with GAD was associated with the development of discontinuation symptoms, including rebound anxiety. To investigate the possible contribution of dose to discontinuation symptoms, subjects were randomly assigned to a high dose pregabalin group (450-600 mg/day) or a low dose pregabalin group (150-300 mg/day). The benzodiazepine lorazepam at a dose of 3-4 mg/day was used as an active-control. Subjects were tapered over 1 week, following either 3 months of treatment (Cohort 2) or 6 months of treatment (Cohort 3). For Cohort 3, there was a double-blind placebo comparison group consisting of subjects who had been blindly tapered off either pregabalin or lorazepam after 3 months, and who had received placebo treatment for 3 months.

There were no clinically meaningful differences in PWC, rebound anxiety or DESS between the pregabalin treatment groups compared to placebo or lorazepam, which is supportive of the utilization of a 1 week taper to manage the potential of rebound anxiety and discontinuation symptoms. The current study used a 4 mg maximum dose of lorazepam consistent with product labelling and current clinical practice today. The subjects included in the current study differed from subjects included in earlier studies of discontinuation symptoms in that, subjects included in the previous studies had been treated with benzodiazepines on average for 5 years and received higher maximum daily doses of lorazepam (1-16 mg). In the previous studies, subjects had higher rates of prior benzodiazepine use than in the current study. In the present study fewer subjects (approximately 10%) had a prior history of daily benzodiazepine use, and only subjects who were able to taper off benzodiazepines prior to randomization were eligible for the study. These differences between subjects in the previous studies and those in the current study may explain why marked discontinuation effects were not observed following lorazepam after a 1 week taper.

The results of this study indicate that 6 months of treatment with pregabalin in the dosage range of 150-600 mg/day is not associated with a clinically meaningful drug withdrawal syndrome as measured by the validated rating scales of the HAM-A, PWC, and DESS. A small proportion of subjects (approximately 3-5%) experienced a return of anxiety symptomatology to a level that was equal-or-higher than their pre-treatment level of anxiety. The efficacy results also confirm that pregabalin low dose (150-300 mg/day), pregabalin high dose (450-600 mg/day), or lorazepam (3-4 mg/day) are effective in the treatment of subjects

with GAD. The efficacy was consistent with published reports; efficacy was generally maintained after 3 months, with a slight continued improvement in symptoms over 6 months of treatment.

The results of this randomized, double-blind, discontinuation study confirms the safety and efficacy of pregabalin and lorazepam in subjects with GAD.