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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI).

NATIONAL CLINICAL TRIAL NO.: NCT00368745

PROTOCOL NO.: A0081092

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Pregabalin in Subjects with Generalized Anxiety Disorder (GAD) Switching from Benzodiazepine Therapy

Study Centers: Spain (4 centers), Mexico (3 centers), France (5 centers), Italy (2 centers), Costa Rica (1 center), Czech Republic (4 centers) and Guatemala (1 center). Five additional centers in France (1 center), Spain (1 center), Italy (1 center) and the Czech Republic (2 centers) did not enroll any subjects.

Study Initiation and Completion Dates: 04 September 2006 to 14 August 2008

Phase of Development: Phase 3

Study Objectives: Primary: To evaluate the efficacy of pregabalin in maintaining the benzodiazepine–free state in subjects with prior stable alprazolam use.

Secondary: To obtain additional data on the efficacy of pregabalin in reducing the severity of symptoms of GAD, rebound anxiety, benzodiazepine withdrawal, and titration regimen in comparison to placebo after switching from a stable therapeutic dose of alprazolam to treatment with pregabalin or placebo.

METHODS

Study Design: This was a randomized, double blind, placebo-controlled study. After screening, subjects were stabilized on a therapeutic dose of open label alprazolam, for 2 weeks if they entered the study on a stable alprazolam dose or for up to 4 weeks if they entered taking a different benzodiazepine. Visits to the study center were weekly (7±3 days) during this phase or more frequent if necessary. Subjects were randomized to pregabalin or placebo at baseline. After a baseline visit, there were then 3 phases to the study:

- Alprazolam taper phase: subjects reduced their daily open label alprazolam dose by at least 25% per week, over 3 to 6 weeks (depending on the starting dose), until the subject

discontinued alprazolam under supervision of the investigator. Subjects could take alprazolam as rescue medication during this phase. At the start of this phase, subjects began treatment with either pregabalin or placebo in a double-blind fashion.

- Alprazolam-free double-blind phase: subjects continued taking double blind pregabalin or placebo.

- Pregabalin taper phase: subjects ending the study or terminating early took end of study taper study drug (placebo or pregabalin) for 1 week.

Number of Subjects (Planned and Analyzed): Approximately 120 subjects on stable alprazolam use for GAD were planned to be screened in order to have 80 randomized subjects, with 40 subjects per treatment arm. Subjects were planned to be randomized in a 1:1 ratio; 40 subjects randomized to pregabalin, 40 subjects randomized to placebo. One hundred and thirty-eight subjects were screened; 57 were assigned to pregabalin treatment and 51 were assigned to placebo treatment. Enrolment was extended due to GCP violations at 2 of the sites. Fifty-six subjects received pregabalin treatment and 50 subjects received placebo treatment. One subject in each group was randomized but did not receive study treatment. Of the 106 subjects who received study treatment (pregabalin or placebo from Day 1 of the study), 30 subjects (52.6%) in the pregabalin group and 19 subjects (37.3%) in the placebo group completed the study.

Diagnosis and Main Criteria for Inclusion: Male and female subjects of ages 18 to 65 years with a primary lifetime diagnosis of GAD with stable use of a benzodiazepine (between 8 and 52 weeks prior to the screening visit).

Study Treatment: Randomization occurred at the beginning of the alprazolam taper phase and began with the baseline visit. Between the baseline visit and Week 1 subjects received capsules of pregabalin 75 mg twice daily (BID) or matching placebo. For Week 2, subjects received pregabalin 150 mg BID or matching placebo. During Weeks 3 through the remaining 3 weeks of the alprazolam taper period, subjects took an adjusted dose of pregabalin (75 mg BID to 300 mg BID) or its placebo equivalent. The dose could continue to be adjusted during the subsequent 6 week alprazolam-free phase. From the baseline visit, subjects also took their stabilized alprazolam dose which was reduced by 25% each week during the up to 6 week alprazolam taper phase.

Efficacy Evaluations: ***Primary Endpoint***

Benzodiazepine free: A subject was considered benzodiazepine-free if they met all of the following conditions:

1. The subject reported taking less than 2 doses of rescue medication

2. The subject tested negative for all substances listed in the Statistical Analysis Plan (1 positive benzodiazepine test was allowed.). The benzodiazepine tests for the first week of the benzodiazepine-free phase were not included in this algorithm, however, all other listed drugs and metabolites were included.

3. The subject tested negative on the alcohol breath test.

Investigator Rated Scales

Hamilton Anxiety Scale (HAM-A): The HAM-A is sensitive to treatment-related changes in generalized anxiety symptoms. The scores for each of the 14 items range from 0 for not present to 4 for very severe.

Hamilton Depression Rating Scale (HAM-D): The HAM-D is a clinician–rated, semi-structured interview measuring the presence of depressive symptoms in 17 areas and produces a score from 0 to 52.

Clinical Global Impression - Improvement (CGI-I) and Clinical Global Impression - Severity (CGI-S): The CGI-I is a 7-point scale ranging from (1) very much improved to (7) very much worse, used to assess global change in patient condition compared to baseline at each visit. The CGI-S is a 7-point scale ranging from (1) no evidence of illness to (7) among the most ill.

Physician's Withdrawal Checklist (PWC): The PWC is a 20-item physician-rated interview measuring the presence of anxiolytic drug withdrawal-related signs and symptoms in the areas of gastrointestinal, mood, sleep, motor, somatic, perception and cognition. The 20 questions are measured from 0 (not present) to 3 (severe) to produce a score ranging from 0 to 60.

Subject Completed Scales

Patient Global Impression of Improvement (PGI-I): The PGI-I is a subject-rated instrument that measures change in overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 is a screening and monitoring tool for depression, well validated and documented in a variety of populations, used to diagnose and rate depression severity.

Digital Symbol Substitution Test (DSST): The DSST is a subject-rated instrument designed to evaluate aspects of cognition including attending to directions, processing speed, sustained attention, visual-motor integration, learning and psychomotor speed. Specifically, the DSST involves using a 'number-symbol key' to complete a form consisting of rows of symbols on a test page. The subject matches each symbol in a row with its appropriate number (provided by the key at the top of the test page) and writes that number under the symbol on the test page. The number of correct symbol-number pairs completed by the subject over a 90 second test period determines the DSST score.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: No pharmacokinetic, pharmacodynamic or other evaluations were planned.

Safety Evaluations: Safety evaluations were performed at each study visit and included vital signs (heart rate, blood pressure), adverse events (AEs) and safety laboratory tests (at screening and final visit only).

Statistical Methods: The safety population included all subjects who had received at least 1 dose of study medication (pregabalin or placebo) and was analyzed as assigned to treatment.

The intent-to-treat (ITT) population consisted of all subjects who had received at least 1 dose of study medication (pregabalin or placebo). For the primary outcome, benzodiazepine-free status, all treated subjects were included in the population. For analyses of the subject- and physician-rated scales, subjects additionally must have had a baseline and at least 1 post-baseline HAM-A measurement to be included in the efficacy population (using as assigned treatment). Any sites closed due to GCP violations were excluded from the ITT population. Additional sets of efficacy tables were planned to include any sites that closed due to GCP violations.

The per protocol (PP) population consisted of the ITT population with the subjects omitted who had failed certain inclusion and exclusion criteria as well as any subject who was improperly tapered from alprazolam (<3 weeks or >6 weeks of taper).

In order to test the primary hypothesis, a Cochran-Mantel Haenszel (CMH) test was performed to compare the proportion of successes between the pregabalin and placebo groups, controlling for country, with significance determined using a two-tailed significance level of 0.05.

The secondary endpoints were analyzed using an analysis of covariance model (ANCOVA or mixed model) with treatment as the main effect and country and baseline as the covariates. This was done for each visit using the observed cases (OC) model and also last observation carried forward (LOCF) at endpoint.

Country was a covariate in all models. Baseline was used as a covariate in all models which used change from baseline to any visit as the outcome variable. PWC, PGI-I and CGI-I did not use change from baseline as the outcome and therefore, baseline was not used as a covariate when these variables were the outcome.

For the PWC, the rates of change were estimated using a random change-point model was found using the visits from Week 1 post-randomization to Week 12, with each phase estimated separately. The rates of change between the 2 treatment groups were compared in each phase and across both phases.

The proportion of subjects who took rescue medication was compared using CMH tests. Significance was determined using a two-tailed significance level of 0.05. This was done under 3 sets of conditions: at any point in the study, at each visit and at LOCF endpoint.

Log-rank tests were used with treatment as the strata, in order to analyze time until use of first rescue medication and time until discontinuation.

RESULTS

Subject Disposition and Demography: One hundred and thirty-eight subjects were screened; 57 were assigned to pregabalin treatment and 51 were assigned to placebo treatment. Fifty-six subjects received pregabalin treatment and 50 subjects received placebo treatment. Subject disposition and reasons for discontinuation are summarized in Table S1. Data sets analyzed are summarized in Table S2. Subject demographics are summarized in Table S3.

Table S1. Subject Disposition and Reasons for Discontinuation

Number of Subjects (%)	Pregabalin	Placebo
Subjects screened 138		
Assigned to Study Treatment	57	51
Treated	56	50
Completed	30 (52.6)	19 (37.3)
Discontinued	26 (45.6)	31 (60.8)
Discontinuations – Safety Population	**N=56**	**N=50**
Total	26 (46.4)	31 (62.0)
Related to Study Drug	13 (23.2)	20 (40.0)
Adverse Event	6 (10.7)	4 (8.0)
Lack of Efficacy	7 (12.5)	16 (32.0)
Not Related to Study Drug	13 (23.2)	11 (22.0)
Adverse Event	0	2 (4.0)
Lost to Follow-up	1 (1.8)	0
Other[a]	7 (12.5)	6 (12.0)
Subject no Longer Willing to Participate in Study	5 (8.9)	3 (6.0)

[a] Other reasons for discontinuation included: No way to get a treatment from computerized randomization system – study terminated; one visit forgotten by investigator; subject withdrawn due to unblinding in error; 2 subjects came to a visit without having received treatment in time; and protocol violations.

Table S2. Data Sets Analyzed

Number of Subjects (%)	Pregabalin N=57	Placebo N=51
Analyzed for Efficacy		
ITT Population[a]	46 (80.7)	41 (80.4)
Per-Protocol Population	27 (47.4)	24 (47.1)
ITT plus GCP Violators	53 (93.0)	47 (92.2)
Analyzed for Safety		
Adverse Events	56 (98.2)	50 (98.0)
Laboratory Data	48 (84.2)	44 (86.3)

GCP=good clinical practice, ITT=intent-to-treat, N=total subjects
[a] All subjects enrolled in the 2 sites closed due to GCP violations were excluded from the ITT population.

Table S3. Subject Demographics (Safety Population)

Number of Subjects	Pregabalin N=56	Placebo N=50
Sex		
Male	14 (25.0%)	16 (32.0%)
Female	42 (75.0%)	34 (68.0%)
Age (years)		
Mean (SD)	40.1 (10.6)	43.5 (11.3)
Range	20-64	22-65
Race		
White	48 (80.4%)	41 (82.0%)
Other	11 (19.6%)	9 (18.0%)
Weight (kg)		
Mean (SD)	66.8 (16.1)	71.0 (14.7)
Range	45.6-110.5	40.7-11.0
Body Mass Index (kg/m^2)		
Mean (SD)	25.1 (6.4)	26.5 (5.1)
Range	17.3-47.7	18.6-42.2
Height (cm)		
Mean (SD)	163.5 (8.7)	163.6 (10.9)
Range	145.5-187.0	141.0-194.0

SD=standard deviation, N=total subjects

Efficacy Results: The primary analysis used the ITT population and further analyses were also performed using the PP population and the ITT population plus subjects from GCP violator sites. The majority of the results from these analyses were in line with those from the primary ITT analysis.

The primary efficacy variable for this study was the proportion of subjects who were able to remain benzodiazepine-free from the end of the alprazolam taper phase until the end of study. Of the 37 subjects (80.4%) in the pregabalin group who entered the alprazolam-free phase, 20 subjects (54.1%) were able to complete the study benzodiazepine-free; whereas, of the 27 subjects (65.9%) in the placebo group who entered the alprazolam-free phase, 10 subjects (37.0%) were able to complete the study benzodiazepine-free. There was no significant difference between the 2 treatment groups ($p=0.28$).

For HAM-A, at each visit there was a numerical superiority in the pregabalin group as compared to the placebo group. Furthermore, during most of the alprazolam taper phase, the placebo group showed an increase in anxiety symptoms. There was a significant difference ($p<0.05$) in favor of pregabalin at alprazolam taper Week 2, alprazolam-free Week 1 and LOCF endpoint; with a trend toward significance ($p<0.1$) at alprazolam taper Weeks 1, 3, 4 and 6.

For HAM-D at each visit, apart from alprazolam-free Week 4, there was a numerical superiority in the pregabalin group as compared to the placebo group. There were no significant differences ($p<0.05$) between the groups although there was a trend toward significance ($p<0.1$) in favor of pregabalin at alprazolam-free Week 1.

For the Physician Withdrawal Checklist (PWC) at each visit, apart from alprazolam-free Week 4, there was a numerical superiority in the pregabalin group as compared to the placebo group; with significant differences ($p<0.05$) at alprazolam taper Weeks 2, 4, and 6 and alprazolam-free Weeks 1 and 6 and the LOCF endpoint. The placebo subjects showed an (almost significant) increase in symptoms from the beginning until the end of the alprazolam taper phase ($p=0.08$) followed by a significant decrease in symptoms from the beginning of the alprazolam-free phase to the end of study ($p=0.04$). In the pregabalin subjects, however, there was no significant change in symptoms either during the alprazolam taper phase ($p=0.86$) or during the alprazolam-free phase ($p=0.64$). There was a significant difference in favor of pregabalin between the rates of change during each phase ($p=0.006$ for the alprazolam taper phase and $p=0.04$ for the alprazolam-free phase). Furthermore, there was a significant difference in favor of pregabalin between the mean number of symptoms in the pregabalin and placebo groups ($p<0.01$). The PWC was not measured at baseline (randomization), thus all hypotheses which required a baseline for the PWC were restated or eliminated.

For the CGI-S at each visit except baseline there was a numerical superiority in the pregabalin group as compared to the placebo group; with significant differences ($p<0.05$) at alprazolam taper Weeks 1 and 2, alprazolam-free Weeks 1 and 3 and LOCF endpoint, and a trend toward significance ($p<0.1$) at alprazolam taper Week 3 and alprazolam-free Week 2.

For the CGI-I at each visit, apart from alprazolam taper Week 4, there was a numerical superiority in the pregabalin group as compared to the placebo group for the ITT population analysis. There was a significant difference ($p<0.05$) in favor of pregabalin at alprazolam taper Week 2, alprazolam-free Weeks 1, 2 and 3 and LOCF endpoint; with a trend toward significance ($p<0.1$) at alprazolam taper Week 6.

For the PGI-I at each visit, apart from alprazolam taper Week 4, there was a numerical superiority in the pregabalin group as compared to the placebo group for the ITT population analysis. There was a significant difference ($p<0.05$) in favor of pregabalin at alprazolam taper Weeks 1 and 2, alprazolam-free Week 6 and LOCF endpoint; with a trend toward significance ($p<0.1$) at alprazolam-free Weeks 2 and 3.

Eleven subjects (23.9%) in the pregabalin group and 17 subjects (41.5%) in the placebo group used rescue medication prior to the completion of the study (Table S4). Two pregabalin subjects and 9 placebo subjects used rescue medication during the alprazolam taper phase; and 9 pregabalin and 11 placebo subjects used rescue medication during the alprazolam-free phase. At alprazolam taper Week 2 and alprazolam-free Weeks 3 and 4 there were significantly more subjects who were relapse-free in the pregabalin group compared to the placebo group. Twenty subjects (43.5%) in the pregabalin group and 19 subjects (46.3%) in the placebo group used benzodiazepine or psychoactive substances prior to the completion of the study. The median times to first use of benzodiazepine or psychoactive substances were 89 days (95% confidence interval [CI]: 63 with no estimable upper limit) in the pregabalin group and 70 days (95% CI: 46, 89) in the placebo group. There was no significant difference ($p=0.18$) between the 2 groups in the time until first use of benzodiazepine or psychoactive substances.

Nineteen (41.3%) of the pregabalin subjects and 24 (58.5%) of the placebo subjects discontinued (all causes) prior to the completion of the study. The median time to discontinuation for the pregabalin group could not be estimated since 50% of the subjects did not discontinue, and the placebo group median time until discontinuation was 54 days. The 25th percentile time until discontinuation could be estimated in both groups (51 days [95% CI: 44 to 65] for the pregabalin group and 33 days [95% CI: 21 to 46] for the placebo group); showing a trend towards later discontinuation in the pregabalin group as compared to the placebo group (p=0.06).

There were no significant differences between treatments for the mean DSST and PHQ scores at baseline or at the LOCF endpoint. There was a 13 point increase in DSST scores for both groups.

Table S4. Proportion of Subjects who Took Rescue Medication by Visit (ITT Population)

	Pregabalin (46)			Placebo (41)			
Week	**N**	**n**	**%**	**N**	**n**	**%**	**p-value**
Alprazolam Taper Phase							
Week 1	46	0	(0)	41	1	(2.4)	0.37
Week 2	45	0	(0)	40	3	(7.5)	0.04
Week 3	45	1	(2.2)	38	3	(7.9)	0.19
Week 4	37	1	(2.7)	29	1	(3.4)	0.75
Week 5	25	0	(0)	14	1	(7.1)	0.32
Week 6	14	0	(0)	5	0	(0)	NE
Alprazolam-Free Phase							
Week 1	42	4	(9.5)	30	2	(6.7)	0.89
Week 2	37	1	(2.7)	26	2	(7.7)	0.47
Week 3	36	2	(5.6)	25	4	(16.0)	0.30
Week 4	32	0	(0)	23	2	(8.7)	0.11
Week 5	31	2	(6.5)	20	1	(5.0)	0.63
Week 6	23	0	(0)	14	0	(0)	NE
Pregabalin Taper Phase							
Week 1	28	1	(3.6)	24	0	(0)	0.32
Week 2	2	0	(0)	4	0	(0)	NE

ITT=intent to treat, N=number of subjects taking study drug during each week, n=number of subjects taking rescue concomitant drug. NE=not estimable. Subjects were counted only once per week. The p-values were determined using a Cochran-Mantel-Haenszel test with country as covariate.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: There were no pharmacokinetics, pharmacodynamic or other analyses planned for this study.

Safety Results: In the pregabalin group, 40/56 subjects (71.4%) experienced 137 all causality AEs and in the placebo group, 33/50 subjects (66.0%) experienced 111 all causality AEs (Table S5). The most commonly reported all causality AEs in the pregabalin group (>10%) were dizziness (12 subjects, 21.4%), anxiety (11 subjects, 19.6%), headache (7 subjects, 12.5%) and paresthesia (6 subjects, 10.7%) (Table S6). Dizziness (19.6%), headache (10.7%) and paresthesia (10.7%) were considered treatment-related in >10% of subjects. The most commonly reported all causality AEs in the placebo group (>10%) were headache (13 subjects, 26.0%), anxiety (10 subjects, 20.0%), nausea (7 subjects, 14.0%) and

insomnia (7 subjects, 14.0%). Only nausea (12.0%) was considered treatment-related in >10% of subjects. Most AEs occurred during the alprazolam taper phase. Dizziness and paresthesia were the AEs which were reported in >10% of subjects in the pregabalin group and with a higher incidence than in the placebo group.

No subject experienced death or a treatment-emergent serious AE (SAE), although 2 subjects experienced SAEs before receiving study treatment (diarrhea and overdose, both unrelated to treatment).

- A 55 year old Caucasian female, experienced severe diarrhea from Day -8 to Day -5 of the study before the beginning of double blind treatment, while taking alprazolam. This resolved after treatment was given (aluminum magnesium silicate). The subject continued in the study and was randomized to pregabalin. She later discontinued due to a protocol violation: she self-medicated with prazepam and zopiclone.

- A 58 year old Caucasian female, experienced an overdose of 49 capsules of venlafaxine hydrochloride before randomization, while being treated with 20 mg prazepam.

Most AEs were of mild or moderate severity. Three subjects (5.4%) in the pregabalin group and 4 subjects (8.0%) in the placebo group experienced severe AEs: paresthesia, asthenia and dizziness in the pregabalin group; and post-traumatic stress disorder, libido decreased, anxiety and 1 subject experienced headache, insomnia and erectile dysfunction in the placebo group. For these 7 subjects, severe paresthesia, asthenia, and dizziness experienced in the pregabalin group and libido decreased, headache and erectile dysfunction in the placebo group were considered treatment related. Six subjects (10.7%) in the pregabalin group and 6 subjects (12.0%) in the placebo group discontinued due to AEs (Table S7). Four subjects (7.1%) in the pregabalin group and 2 subjects (4.0%) in the placebo group had dose reductions due to AEs. For the pregabalin group, Nervous System Disorders, Gastrointestinal Disorders and Psychiatric Disorders were the system organ classes (SOCs) in which there were >20% incidences of all causality AEs.

Of the 48 subjects in the pregabalin group and 44 subjects in the placebo group evaluable for laboratory test abnormalities without regard for normal or abnormal baseline, 3 subjects (6.3%) in the pregabalin group and 7 subjects (15.9%) in the placebo group had laboratory test abnormalities. Median changes from baseline in laboratory test result values were similar for the pregabalin and placebo groups.

Mean changes from baseline for vital signs and weight were small and similar for placebo and pregabalin groups.

Table S5. Summary of All Causality Treatment-Emergent Adverse Events (Safety Population)

Number of Subjects (%)	Pregabalin N=56	Placebo N=50
Number of Adverse Events	137	111
Subjects with Adverse Events	40 (71.4%)	33 (66.0%)
Subjects with Serious Adverse Events	0	0
Subjects with Severe Adverse Events	3 (5.4%)	4 (8.0%)
Subjects who Discontinued Due to Adverse Events	6 (10.7%)	6 (12.0%)
Subjects with Dose Reduced or Temporary Discontinuation due to Adverse Events	4 (7.1%)	2 (4.0%)

N=total number of subjects evaluable
Except for the number of adverse events, subjects are counted only once per treatment in each row.

Table S6. All Causality Treatment-Emergent Adverse Events Experienced by >5% Subject in Either Group (Safety Population)

Number of Subjects (%)	Pregabalin N=56	Placebo N=50
Dizziness	12 (21.4%)	3 (6.0%)
Anxiety	11 (19.6%)	10 (20.0%)
Headache	7 (12.5%)	13 (26.0%)
Paraesthesia	6 (10.7%)	0
Vision Blurred	5 (8.9%)	2 (4.0%)
Oedema Peripheral	5 (8.9%)	0
Nausea	5 (8.9%)	7 (14.0%)
Insomnia	4 (7.1%)	7 (14.0%)
Diarrhoea	3 (5.4%)	5 (10.0%)
Vomiting	3 (5.4%)	0
Asthenia	3 (5.4%)	5 (10.0%)
Hyperacusis	3 (5.4%)	1 (2.0%)
Pain in Extremity	3 (5.4%)	0
Somnolence	3 (5.4%)	2 (4.0%)
Hyperhidrosis	3 (5.4%)	0
Tremor	2 (3.6%)	4 (8.0%)
Fatigue	2 (3.6%)	3 (6.0%)
Irritability	0	4 (8.0%)

N=total number of subjects evaluable
Except for the number of adverse events, subjects were counted only once per treatment in each row.

Table S7. Permanent Discontinuations Due to Adverse Events

Sex/Age/Race	Adverse Event	Adverse Event Start/Stop day[a]	Severity	Causality
Pregabalin				
F/36/W	Paraesthesia	38/44	Moderate	Related
F/34/W	Weight increased	1/>16 (present at end of study)	Mild	Related
F/53/W	Oedema peripheral	6/53	Mild	Related
	Dizziness	12/50	Moderate	Related
F/33/W	Tachycardia	27/34	Moderate	Related
	Insomnia	28/34	Moderate	Related
M/64/W	Accommodation Disorder	6/10	Moderate	Related
	Asthenia	3/13	Severe	Related
	Musculoskeletal stiffness	6/6	Moderate	Related
F/48/W	Ataxia	31/32	Moderate	Related
Placebo				
F/33/W	Generalized Anxiety Disorder	4/8	Mild	Related
F/22/Other	Anxiety	15/26	Moderate	Related
M/37/W	Libido Decreased	1/>7 (present at end of study)	Moderate	Related
F/55/W	Nausea	22/32	Mild	Related
	Sleep Disorder	18/39	Moderate	Related
F/42/W	Post-traumatic Stress Disorder	41/59	Severe	Unrelated
M/38/Other	Anxiety	20/33	Severe	Unrelated

[a] Day from start of therapy
F=female, M=male, W=white

CONCLUSIONS: In this study of the ability of pregabalin to allow chronically treated GAD patients to discontinue use of benzodiazepine, pregabalin was compared to placebo in a downward titration of alprazolam followed by an alprazolam-free phase. More subjects in the pregabalin group (54.1% versus 37.0% in placebo) were able to complete the study benzodiazepine-free; however, this result was not significant. Furthermore, there was a trend toward a significant difference in favor of pregabalin in the time until all cause discontinuation.

For HAM-A, at each time point, there was a numerical superiority in the pregabalin group as compared to the placebo group. Furthermore, during most of the alprazolam taper phase, the placebo group showed an increase in anxiety symptoms. At several time points there was either a significant difference or a trend toward a significant difference in favor of pregabalin for HAM-A, CGI-S, CGI-I and PGI-I total score.

There was no difference between the pregabalin and placebo groups in the change from baseline to endpoint in DSST, with both groups showing a 13 point decrease showing a positive impact of discontinuing benzodiazepines and no impact of pregabalin on cognition (as measured by the DSST).

The use of pregabalin allowed the subjects to discontinue alprazolam without an overall increase in benzodiazepine withdrawal symptoms (as indicated by the PWC) throughout the study. The placebo subjects not only showed a significantly higher rate of overall withdrawal symptoms with an increase (trend toward significance) during the alprazolam taper phase, but also a significant decrease in withdrawal symptoms during the alprazolam-free phase.

The most commonly reported AEs in the pregabalin group were dizziness, anxiety, headache and paresthesia. The most commonly reported AEs in the placebo group were headache, anxiety, nausea and insomnia. No treatment-emergent SAEs were observed during this study.