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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00413010

PROTOCOL NO.: A0081103

PROTOCOL TITLE: An 8-Week, Double-Blind, Placebo-Controlled, Phase 3 Trial of Pregabalin (150-600 mg/day) in the Adjunctive Treatment of Patients with Generalized Anxiety Disorder (GAD) Who Have Not Optimally Responded to Existing Therapies

Study Center(s): 55 centers randomized subjects in 8 countries (27 sites in the United States, 7 sites in the Russian Federation, 6 sites in the Czech Republic, 5 sites in Ukraine, 4 sites in Serbia, 3 sites in Hungary, 2 sites in Finland, and1 site in Estonia).

Study Initiation and Completion Dates: 01 December 2006 to 18 March 2008.
This study was terminated prematurely.

Phase of Development: Phase 3

Study Objective(s): The primary objective of this study was to evaluate the efficacy of pregabalin as compared to placebo as an adjunctive treatment in subjects with Generalized Anxiety Disorder (GAD) who partially responded to a standard GAD treatment. Efficacy was measured by the improvement in the total Hamilton Rating Scale for Anxiety (HAM-A) scores from Baseline (Visit 8, Week 0) following 8 weeks of double-blind treatment (Visit 15, Week 8 or at early termination during the double-blind treatment phase) and was analyzed using a mixed linear model for repeated measures.

The secondary objectives were the following:

- To evaluate the efficacy of pregabalin as compared to placebo in time-to-onset as measured by time to achieve sustained response and remission at any point in the double-blind study phase or at termination of the double-blind phase (Visit 15, Week 8).

- To evaluate response and remission rates of adjunctive pregabalin as compared to placebo using the following definitions:

- Responder definition: ≥50% reduction in HAM-A total score from Baseline of the double-blind phase to termination of the double-blind phase.

- Remission definition: HAM-A ≤7 at any time during double-blind phase or at termination of the double-blind phase.

- To evaluate the efficacy of pregabalin as compared to placebo in improving scores on the HAM-A Psychic Anxiety and Somatic subscales, the Hamilton Depression Rating Scale (HAM-D), the Daily Diary (DD) (a measure combining Daily Assessment of Symptoms-Anxiety [DAS-A] and Global Anxiety-Visual Analogue Scale [GA-VAS]), the Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I) scales, and the Sheehan Disability Scale (SDS).

- To evaluate the safety of pregabalin as compared to placebo in combination with background GAD treatment based on frequency and severity of treatment-emergent adverse events (AEs), changes in vital signs, laboratory analyses, and electrocardiograms (ECGs).

METHODS

Study Design: This was a randomized (1:1), double-blind, placebo-controlled, parallel group, multi-center trial consisting of 4 phases: screening phase (Period 1), open-label treatment optimization phase (Period 2), double-blind active treatment phase (Period 3), and a double-blind taper and follow-up phase (Period 4) as follows:

Study Period 1 consisted of a 2-7 day screening phase to determine subject eligibility. Study Period 2 consisted of an 8-week prospective open-label treatment optimization phase in which subjects received or continued treatment for GAD with escitalopram, paroxetine, or venlafaxine extended release (XR). During the first 6 weeks of this period, dosing with these agents was flexible within the respective approved dose range, to permit identification of the optimal dose for the subject. For the final 2 weeks of this period, the optimal dose was required to be fixed and was required to remain so for the duration of Study Period 3. Study Period 3 consisted of an 8-week randomized double-blind placebo-controlled active treatment phase using flexible dosing of pregabalin (150-600 mg/day). Only those subjects who partially responded during the open-label treatment optimization phase (Study Period 2) were eligible for randomization. Subjects were randomized to pregabalin or placebo at Baseline (Visit 8) in a 1:1 ratio while continuing to receive the optimized, fixed-dose regimen of escitalopram, paroxetine, or venlafaxine XR determined at the end of Study Period 2. Subjects who did not meet the randomization eligibility criteria were discontinued from the study at randomization and continued to receive treatment outside of the trial in the framework of general medical care. Study Period 4 consisted of a 1-week double-blind taper and follow-up phase. Subjects tapered off pregabalin or placebo over a 7-day period.

Number of Subjects (Planned and Analyzed):
Planned: A total of 346 subjects, 173 subjects per double-blind treatment group (pregabalin and placebo) were planned.

Actual: 180 subjects were randomized to the pregabalin treatment group and 176 subjects were randomized to the placebo group.

Diagnosis and Main Criteria for Inclusion: Subjects had to have a primary diagnosis of GAD (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV), as confirmed by the Mini International Neuropsychiatric Interview (MINI) structured interview. In addition, all subjects were required to have a total HAM-A score ≥22 at screening. Subjects who initiated GAD treatment prior to entering the study were required to have CGI-I ≥3 (minimally improved or worse) as determined by the physician's assessment of a subject's response to the treatment (ie, escitalopram, paroxetine, or venlafaxine XR [extended release]) at study enrollment (Visit 1). Subjects who initiated the GAD treatment at enrollment (Visit 1) were required to have CGI-S ≥4 at screening (Visit 0) and enrollment (Visit 1). All subjects were to have had an historical failure to respond optimally to a GAD treatment (CGI-I ≥3 – ie, minimally improved or worse) that was different from the one used during the open-label optimization phase of this study.

Only those subjects who partially responded to background GAD treatment (escitalopram, paroxetine, or venlafaxine XR) and who met all inclusion/exclusion criteria were eligible for randomization at the end of Period 2. For randomization, all subjects were required to have a total HAM-A score ≥16 at randomization (Visit 8). Subjects who initiated the GAD treatment at enrollment (Visit 1) must have demonstrated no more than 50% reduction in the HAM-A total score from entrance into the study (Visit 1) to randomization (Visit 8), and had CGI-I ≤3 at randomization (Visit 8). Subjects must have had predominance of anxiety symptoms over depression symptoms in the clinical picture at Baseline (Visit 8), as evidenced by Covi Anxiety Scale total score ≥9 and Raskin Depression Scale score ≤7.

Study Treatment: *Study Period 2 (Open-Label Phase):* Subjects enrolled in the open-label phase completed an 8-week prospective treatment optimization phase using one of the following medications: escitalopram, paroxetine, or venlafaxine XR. Dosing of these agents was either initiated at the enrollment visit (Visit 1; Study Period 2) or continued from prior treatment initiated prior to the screening visit (Visit 0). During the initial 6 weeks of the open-label optimization phase (Study Period 2), flexible dosing of the GAD treatment was permitted to achieve dose optimization. Based on toleration in Study Period 2, the dose of these agents was to be escalated weekly per product label instructions. During the final 2 weeks of the optimization phase, the subject was required to be at a stable dose.

Study Period 3 (Double-Blind Phase): Subjects meeting all enrollment criteria for Study Period 3 were randomized in a 1:1 ratio to receive either oral pregabalin starting at 150 mg/day or matching placebo while continuing on open-label treatment with escitalopram, paroxetine, or venlafaxine XR, as established in Study Period 2. The blinded study medication (pregabalin or placebo) was administrated orally, BID with or without food. Flexible dosing of pregabalin was allowed during the first 6 weeks of Study Period 3; fixed dosing was required for the last 2 weeks of this period. Pregabalin doses of 150 mg/day, 300 mg/day, 450 mg/day, and 600 mg/day were used during the double-blind phase.

At each weekly visit during the first 6 weeks of the double-blind treatment phase, subjects with HAM-A ≥8 who were tolerating the current dose level were to have their pregabalin

dose escalated by 150 mg/day. Subjects in remission (ie, with a HAM-A ≤7) were not to have their pregabalin dose escalated. These subjects were to remain at their current dose unless they could not tolerate it, in which case the pregabalin dose should have been reduced by 150 mg/day or the subject should have been discontinued from the study. Subjects should have remained at the reduced dose level for a minimum of 1 week unless clinically contraindicated. Subjects requiring a dose reduction of more than 150 mg/day within 1 week should have been discontinued due to an inability to tolerate study medication. The dose of pregabalin or placebo was required to remain constant for the final 2 weeks of the double-blind treatment phase. Subjects were also required to remain on a stable dose of their concurrent GAD treatment (ie, escitalopram, paroxetine, or venlafaxine XR) during the entire double-blind treatment phase of the study.

Study Period 4 (Double-blind Taper and Follow-up Phase): At the end of the double-blind treatment phase (Visit 15, Week 8), all subjects were required to enter the 1-week double-blind taper phase. During the taper phase, changing the dose of the concurrent GAD treatment was not permitted unless it was necessary for clinical management of the subject.

Efficacy Evaluations: *Hamilton Rating Scale for Anxiety:* The HAM-A is a clinician-rated, semi-structured interview measuring the presence of anxiety-related symptoms in 14 areas. This scale measures a range of symptoms related to anxiety: anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, and restlessness. The total score ranges from 0 to 56; a higher score indicates greater anxiety. This scale was administered at every visit by the same rater throughout the study whenever possible. Two 7-item subscales were also assessed: the HAM-A Subscale Anxiety (items 1-6 and 14 of the HAM-A) and the HAM-A Subscale Somatic (items 7–13 of the HAM-A).

Hamilton Rating Scale for Depression: The HAM-D is a clinician-rated, semi-structured interview measuring the presence of depressive symptoms in 17 areas. Questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss. The total score ranges from 0 to 52 and higher scores indicate more depression. This scale was administered at every visit by the same rater throughout the study whenever possible.

Mini International Neuropsychiatric Interview: The MINI is a short diagnostic structured interview that contains 120 questions and screens 17 DSM-IV axis I diagnoses with a focus on current diagnoses. The MINI was only administered at the screening visit to confirm the primary diagnosis of GAD.

Covi Anxiety Scale: The Covi Anxiety Scale is a 3-item scale that measures the extent of anxiety based on clinician ratings of a subject's verbal report, behavior, and somatic complaints. Possible scores range from 3 to 15 where higher scores are indicative of greater anxiety. The Covi Anxiety Scale was administered only once at Visit 8 (randomization) to assist in confirming a predominance of anxiety symptoms over depression symptoms as per the randomization criteria.

Raskin Depression Scale: The Raskin Depression Scale is a 3-item scale that measures the extent of depression or despondency from clinician ratings of a subject's verbal report,

behavior, and somatic complaints. Possible scores range from 3 to 15 where higher scores are indicative of more depression. The Raskin Depression Scale rating was assessed only once at Visit 8 (randomization) to assist in confirming a predominance of anxiety symptoms over depression symptoms at randomization.

Sheehan Disability Scale: The SDS is a patient-rated instrument that measures functional impairment in 3 domains: work impairment, social impairment, and impairment of family life/home responsibilities. Disability scores are reported for each of the domains and a total disability score is calculated as the sum of scores for each domain. Higher scores reflect greater impairment. The SDS was performed at Visit 0 (screening) and at every visit from Visit 8 (randomization) through Visit 16 (taper and follow-up phase).

Clinical Global Impression of Severity: The CGI-S is a clinician-rated instrument measuring the severity of a subject's symptoms on a 7-point scale. Scores range from 1 (not at all ill) to 7 (among the most extremely ill patients). This scale was performed at every visit and was administered by the same rater throughout the study whenever possible.

Clinical Global Impression of Improvement: The CGI-I is a clinician-rated instrument that measures change in subject's overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). This scale was performed at every visit and was administered by the same rater throughout the study whenever possible.

Daily Diary: The DD is a patient-rated scale that consists of the 8-item DAS-A, a Likert-like questionnaire, and a single item GA-VAS. All 9 items have been developed to assess the onset of anxiety symptom relief. Each item in the diary uses a 24-hour recall period. Subjects were to complete the DD daily starting at Baseline (randomization visit, Visit 8) and were to continue to complete the DD, just before going to bed, for the first week of the double-blind treatment phase and then at the last clinic visit of the double-blind phase (Visit 15).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Standard pharmacogenomic methods were applied to using the samples. No pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Evaluations: Adverse events (AEs) were monitored throughout the study period. Safety endpoints included standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), 12-lead ECG, and physical examinations, which were performed at screening (Visit 0) and termination (Visit 15). Vital signs were monitored at every study visit. In addition, serum pregnancy testing was performed for women of childbearing potential (at Visit 0, Visit 8 [randomization], and Visit 15), and urine drug testing was performed at Visit 0 and Visit 8.

Statistical Methods: The primary population for the efficacy analysis was the Intent-to-Treat analysis set (ITT). The ITT population included all randomized subjects who had received at least 1 dose of the double-blind treatment. All efficacy analyses included the ITT subjects who had a Baseline and a post-Baseline assessment of the respective efficacy endpoints. No Per Protocol analysis set was used for this study.

Statistical inferences for making treatment group comparisons for the primary endpoint were performed using a two-sided test at a level of significance which took into consideration one interim analysis and a change in the number of subjects at the end of the study from the targeted sample size. The results are indicated as the adjusted 95% confidence intervals and the adjusted p-values.

Primary Efficacy Analysis: The primary endpoint analysis was conducted on the ITT analysis set. The change in the HAM-A total score from Baseline to termination of the double-blind phase (Visit 15, Week 8 or at early termination if withdrawn from the study during the double-blind phase) was analyzed using a linear mixed model for repeated measures using the method of restricted maximum likelihood estimation with treatment, pooled center, baseline HAM-A total score, time (classification variable), and treatment-by-time as fixed effects; and between and within subject errors as random effects. Treatment group comparisons were made using the least squares mean that averages over the weekly measurements for each of the subjects using the linear mixed model described above. The least squares means and appropriate standard errors based on the between subject error term in the model were used as the definitive measures to summarize treatment group means and differences between treatment group means. The covariance matrix for the within subject error term in the linear mixed model was a heterogeneous auto-regressive structure.

Since an interim analysis was performed on the primary endpoint only, a conservative alpha spending function corresponding to an O'Brien-Fleming boundary was used for the possibility of rejecting the null hypothesis early. Significance testing for the primary endpoint using the primary analysis model was conducted at the nominal $\alpha = 0.0007$ for the interim analysis, with a final statistical test performed at the nominal $\alpha = 0.049$.

Other descriptive statistics including sample size, sample mean, and sample standard deviation were used to further summarize the data by treatment group. In addition to performing hypothesis testing, 2-sided 95% CIs were constructed for the true difference between treatment group means using the least squares means and appropriate standard errors. Sensitivity analyses were conducted to assess the robustness of the primary analysis for the primary endpoint, but were not substituted for the primary analysis in order to avoid the issue of possibly experiencing either an inflated type I error or type II error.

Secondary Efficacy Analyses: The changes from Baseline in the HAM-A total score at each week in the double-blind phase (Weeks 1, 2, 3, 4, 5, 6, and 8) were analyzed using the same linear mixed model used for the primary analysis. However, inferences for comparing treatment groups at each weekly assessment incorporated a Satterthwaite adjustment for the degrees of freedom.

Changes in the HAM-A Subscale Psychic Anxiety, HAM-A Subscale Somatic, HAM-D, and SDS were each analyzed in the same manner as the HAM-A total score data (Weeks 1, 2, 3, 4, 5, 6, and 8). The linear mixed model for these analyses was the same as the primary analysis, with the exception that the Baseline covariates corresponded to the response that was measured.

Changes in DAS-A total score and GA-VAS were each analyzed over Days 1, 2, 3, 4, 5, and 6 of Week 0 (double-blind phase) using a repeated measures model. The linear mixed model for these analyses were the same as for the primary analysis, with the exception that the repeated measures were in terms of days instead of weeks, and the Baseline covariates corresponded to the response being measured. Changes in the DAS-A total score and the GA-VAS were also analyzed separately at the last study visit using a linear model with the fixed effect terms for treatment, pooled center, and continuous Baseline covariate that corresponded to the response being measured.

The CGI-S score was analyzed using a proportional odds model for ordinal data with treatment group and pooled center in the model.

The HAM-A responders (defined as subjects with ≥50% decrease in total HAM-A scores from double-blind Baseline to last study week), HAM-A Remission rate (defined as HAM-A ≤7 at last study week), and CGI-I responders (defined as subjects much improved or very much improved at last study week) were analyzed using a logistic regression model for binary data with treatment group and pooled center in the model.

Time to onset of sustained HAM-A improvement was analyzed using the Kaplan-Meier survival method. The Kaplan-Meier survival estimate, the two-sided nominal 95% CI of the Kaplan-Meier estimate, number at risk, number of events, and number of censored observations were summarized, by treatment, at each observed time point, and were presented graphically. Differences in the survival distributions between treatment groups were assessed using 2-sided log-rank tests at the nominal $\alpha = 0.05$ level of significance. The median time to onset, as well as the 25^{th} and 75^{th} percentiles was presented with the nominal 95% confidence limits.

Sustained HAM-A improvement was defined as a ≥50% reduction in HAM-A total score from Baseline (at the start of the double-blind randomized phase) that was sustained for the remainder of the study and was measured in study days. The distribution of time to onset of sustained HAM-A improvement was summarized for each treatment group using the Kaplan-Meier product limit estimates.

Subjects who did not achieve sustained HAM-A improvement during the course of the study, or did not drop-out of the study without sustained HAM-A improvement, were treated as right-censored observations at the last visit date available.

Interim analysis:
An independent Data Monitoring Committee (DMC, independent of the sponsor and study sites) conducted an interim analysis of the primary efficacy endpoint in order to assess sample size re-estimation or the possibility of stopping the trial early. Stopping the trial early could be based on meeting the conditions of futility or overwhelming efficacy in favor of pregabalin. The analysis was conducted when 138 subjects (68 in the pregabalin group and 70 in the placebo group) had both a HAM-A total score at Baseline (start of double-blind phase, Visit 8, Week 0) and at termination of the double-blind phase (Visit 15, Week 8, or early termination).

To protect the integrity of the study, a conservative alpha spending function corresponding to an O'Brien-Fleming boundary was used for the possibility of stopping the study early for overwhelming efficacy in favor of pregabalin (nominal $\alpha = 0.0007$ for the interim analysis and nominal $\alpha = 0.049$ for the final analysis). The interim analysis also allowed the study to stop early if the test statistic exceeded the critical value of 3.3569 indicating efficacy in favor of pregabalin. This critical value corresponded to an observed p-value of approximately 0.0008 using a two-sided test.

Further enrollment in this study was stopped on 28 January 2008 based on the recommendation of an independent DMC. Based on an interim analysis involving 40% enrollment, the data did not suggest the potential for robust efficacy. The study was not stopped for any safety findings. The sponsor accepted the recommendation—further enrollment was terminated and subjects were discontinued at their next planned visit. At the time the DMC recommendation was implemented, the study population was fully recruited (N=356), compared with the original targeted sample size (N=346). The results presented in the clinical study report represent all the data collected in the study using preplanned statistical analyses.

RESULTS

Subject Disposition and Demography: A total of 964 subjects were screened for this study, of whom 180 subjects received pregabalin but only 177 had a post-baseline measure of efficacy; 176 subjects were randomized to the placebo group in Period 3. Subjects completing the study totaled 108 (60.0%) in the pregabalin group and 113 (64.2%) in the placebo group. Seventy-two (40.0%) subjects in the pregabalin group and 63 (35.8%) subjects in the placebo group were discontinued from the study. The majority of early discontinuations (those subjects who did not have a Week 8 assessment) were due to the decision to stop the study.

The demographic characteristics were similar between the two treatment groups. Subjects' ages ranged from 19 to 76 years, with a mean age between 41 and 44 years for men and women in each treatment group. The population was predominantly white, with approximately twice as many women as men. Subjects' heights and weights were similar between the treatment groups.

Efficacy Results: The primary endpoint in this study measured efficacy by the change in the mean HAM-A total score from Baseline following 8 weeks of double-blind treatment with pregabalin or placebo using a mixed-linear model for repeated measures. (Baseline measurements were obtained after completion of open-label phase immediately before randomization for Period 3.) The HAM-A scale measures the presence of anxiety-related symptoms in 14 areas; a higher score indicates greater anxiety. The results of the primary analysis are summarized in Table S1.

Table S1. HAM-A Total Score: Change from Baseline Averaging Across Visits Using Heterogeneous Auto-Regressive Covariance Structure – ITT Population

Statistics	Pregabalin N=180	Placebo N=176	Treatment Difference (Pregabalin - Placebo)
n	177[a]	176	
LS mean (SE)	-7.6 (0.35)	-6.4 (0.36)	
Difference			-1.2
[95% CI for difference][†]			[-2.15, -0.27]

[†] Since an interim analysis was conducted and the sample size was larger than the targeted 173 subjects per group, a critical t-value adjustment as per the Statistical Analysis Plan was 1.9772, which yielded an adjusted 95% CI of [-2.16, -0.26].

HAM-A = Hamilton Anxiety Rating Scale; ITT = intent-to-treat; N = subjects that were randomized and received at least 1 dose of double-blind treatment; n=subjects that were randomized, received at least 1 dose of double-blind treatment, and have Baseline and at least 1 post-Baseline HAM-A scores; LS =least squares; SE=standard error; CI=confidence interval.

[a].Three of the 180 subjects who received pregabalin did not have a postbaseline measure of efficacy.

Mean HAM-A total score was similar at Baseline for both treatment groups with mean values of 20.7 for pregabalin and 21.4 for placebo. For the primary analysis of the primary endpoint, the mean change in the HAM-A total score was significantly greater for pregabalin compared with that for placebo, with the respective least squares mean values (standard error [SE]) of -7.6 (0.35) and -6.4 (0.36) and a treatment difference in favor of pregabalin (-1.2, adjusted 95% CI: -2.16, -0.26).

Sensitivity analyses for the primary endpoint included the primary analysis model with a robust variance estimator, a Week 8 only analysis using the primary analysis model, and a Week 8 last observation carried forward (LOCF) analysis. The results of these analyses are presented in Table S2.

Table S2. HAM-A Total Score: Change from Baseline Sensitivity Analyses – ITT Population

Analysis Statistics	Pregabalin (N = 180)	Placebo (N = 176)	Treatment Difference (Pregabalin – Placebo)
Primary model with RVE			
n	177[a]	176	
LS mean (SE)	-7.6 (0.40)	-6.4 (0.37)	
Difference [95% CI] †			-1.2 [-2.22, -0.21]
Primary model at Week 8			
n	126	127	
LS mean (SE)	-9.3 (0.56)	-8.0 (0.56)	
Difference [95% CI] †			-1.3 [-2.9, 0.2]
Week 8 LOCF			
n	177 [a]	176	
LS mean (SE)	-8.7 (0.53)	-7.3 (0.54)	
Difference [95% CI] †			-1.5 [-2.89, -0.09]

† Since an interim analysis was conducted and the sample size for each of the sensitivity analyses was not at its targeted 173 subjects per group, adjusted t-critical value, [corresponding 95% CIs] for RVE, Week 8, and Week 8 LOCF were -1.9783, [-2.22, -0.20]; 1.8116, [-2.74, 0.04]; and 1.9845, [-2.90, -0.08], respectively.
HAM-A = Hamilton Anxiety Rating Scale; ITT = intent-to-treat; N = subjects that were randomized and received at least 1 dose of double-blind treatment; n = subjects that were randomized, received at least 1 dose of double-blind treatment, and have Baseline and at least 1 post Baseline HAM-A score at the time-point of interest; RVE = robust variance estimator; LS = least squares; SE = standard error; CI = confidence interval; LOCF = last observation carried forward.
[a] Three of the 180 subjects who received pregabalin did not have a postbaseline measure of efficacy.

In all analyses, a larger decrease in mean HAM-A total score from Baseline to Week 8 was observed for pregabalin as compared with placebo. The analysis using the robust variance estimator and the Week 8 LOCF analysis were statistically significant with a mean difference in favor of pregabalin (-1.2, adjusted 95% CI: [-2.22, -0.20] and -1.5, adjusted 95% CI: [-2.90, -0.08], respectively). Although the Week 8 LOCF analysis was not found to be statistically significant, the difference was in favor of pregabalin (-1.3, adjusted 95% CI: [-2.74, 0.04]).

The changes from Baseline in the HAM-A total score at each week in the double-blind phase (Weeks 1, 2, 3, 4, 5, 6, and 8) showed a consistent difference between treatments with no treatment-by week-interaction. Because of this consistency in the treatment differences across weeks, the pre-specified primary analysis is valid.

Key secondary efficacy endpoints included HAM-A changes from Baseline at each week, HAM-A responders, HAM-A remission rate, time to onset of sustained HAM-A improvement, CGI-I responders, and CGI-S score. Larger decreases from Baseline in the mean HAM-A total scores were observed for pregabalin as compared with placebo at all visits in Period 3. At each weekly assessment, the percentage of responders and of subjects who remitted was greater for pregabalin compared with that for placebo. Time to onset of sustained HAM-A improvement (defined as a ≥50% reduction in HAM-A total score from Baseline, sustained for the remainder of the study) was analyzed using Kaplan-Meier

survival methods. Subjects receiving pregabalin had an earlier time to onset of sustained HAM-A improvement compared with those receiving placebo. At each weekly assessment, the number and percentage of CGI-I responders was greater among subjects receiving pregabalin compared with those receiving placebo. Following treatment, the number and percentage of subjects in the less severe categories of CGI-S scores was greater among those receiving pregabalin compared with those receiving placebo.

For additional secondary efficacy endpoints, larger decreases from Baseline in the mean HAM-A Psychic Anxiety Subscale score, the mean HAM-A Somatic Subscale score, and the HAM-D total score were observed for subjects receiving pregabalin compared with those receiving placebo at each weekly assessment. The exception to this was at Week 5 when the mean change in the HAM-A Somatic Subscale score was similar for both treatment groups.

For other secondary endpoints such as the Sheehan Disability Scale (SDS), Daily Assessment of Symptoms - Anxiety (DAS-A), and Global Anxiety Visual Analogue Scale (GA-VAS), the data generally showed greater positive changes for pregabalin as compared with those for placebo.

Safety Results: A higher percentage of subjects in the pregabalin group experienced AEs compared with subject in the placebo group (53.9% versus 46.0%), and a higher percentage of subjects in the pregabalin group (42.8%) experienced treatment-related AEs compared with subjects in the placebo group (29.5%).

Dizziness (11.7%), headache (9.4%), somnolence (8.3%), and nausea (7.2%) were the most commonly reported all-causality AEs in subjects receiving pregabalin. Dizziness (5.7%), nausea (4.5%), headache (4.0%), and sedation (4.0%) were the most frequently occurring AEs in subjects receiving placebo.

The only severe adverse events that occurred in more than 1 subject in the pregabalin group were nausea (3 subjects), dizziness (2 subjects), and anxiety (2 subjects). In the placebo group, 2 subjects had adverse severe events of nausea; any other severe events in this group were experienced by single subjects.

One death occurred in the study; the subject died prior to being randomized in the double-blind phase. The investigator considered the causality of the event not related to the study drug. The number and percentage of subjects who reported treatment-emergent SAEs during the study was low: 1 (0.6%) subject in the pregabalin group and 3 (1.7%) subjects in the placebo group. None of the SAEs were considered to be related to study drug.

Eight (4.4%) subjects in the pregabalin group discontinued from the study due to AEs; the events were considered treatment-related for 5 (2.8%) of these subjects. In the placebo group, 3 (1.7%) subjects discontinued from the study due to treatment-emergent AEs; the events were considered treatment-related for 2 (1.1%) of these subjects. Sixteen (8.9%) subjects in the pregabalin group and 15 (8.5%) subjects in the placebo group temporarily discontinued study drug or had their dose reduced due to AEs. In all cases for both groups, the events were considered to be related to study drug.

Treatment with pregabalin was generally well-tolerated by this population. No serious clinical laboratory abnormalities or safety concerns were identified.

CONCLUSION: Pregabalin was shown to be safe and effective adjunctive therapy for subjects with GAD who have not optimally responded to existing GAD therapies.