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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00151450

PROTOCOL NO.: A0081012

PROTOCOL TITLE: An 8-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Flexible Dose Study of Pregabalin (300-600 mg/Day) and Venlafaxine XR (75-225 mg/Day) for the Acute Treatment of DSM-IV Generalized Anxiety Disorder in Outpatients

Study Center(s): Forty-five study centers randomized subjects in Belgium (4 centers), Canada (5 centers), France (12 centers), Ireland (1 center), Italy (4 centers), Netherlands (5 centers), Spain (7 centers) and Sweden (7 centers)

Study Initiation and Completion Dates: 29 March 2005 to 30 November 2006

Phase of Development: Phase 3b

Study Objective(s): The primary objective of the trial was to evaluate the efficacy of pregabalin and venlafaxine XR compared to placebo in the treatment of generalized anxiety disorder (GAD).

The secondary objectives of the trial were:

- to evaluate onset of activity of pregabalin in comparison to placebo and venlafaxine XR in the treatment of GAD symptoms at Day 4 of double-blind treatment and to evaluate, through a subject-rated global scale, the efficacy of pregabalin in decreasing GAD symptoms, on a daily basis during the first week of double-blind treatment;

- to evaluate the effect of pregabalin in the treatment of GAD, on improvement in quality of life, sexual satisfaction, disability, sleep and pain;

- to evaluate the effect of pregabalin and venlafaxine XR in the treatment of depressive symptoms experienced by subjects diagnosed with GAD;

- to evaluate the safety of pregabalin and venlafaxine XR in GAD, including overall tolerability, effects on sexual functioning, discontinuations due to adverse events, and discontinuation-emergent symptoms.

METHODS

Study Design: This was an 8-week, multicenter, randomized, double-blind, placebo-controlled, flexible dose study of pregabalin (300-600 mg/day) and venlafaxine XR (75-225 mg/day) for the acute treatment of DSM-IV-TR™, (2000) GAD in outpatients.

A one week, lead-in, wash-out phase was followed by a one week randomized, double-blind, placebo-controlled, parallel group treatment phase (pregabalin 300 mg/day, venlafaxine XR 75 mg/day), followed by 7 weeks of flexible dose treatment (pregabalin between 300 and 600 mg/day; venlafaxine XR between 75 and 225 mg/day). For subjects on pregabalin 600 mg or venlafaxine XR 225 mg per day, there was a two week tapering phase. For subjects on pregabalin 450mg or venlafaxine XR 150 mg per day, there was a one week tapering phase. There was no tapering phase for subjects on pregabalin 300 mg or venlafaxine XR 75 mg per day.

Number of Subjects (planned and analyzed): Approximately 600 subjects were to be screened to randomize 390 subjects. Approximately 130 subjects were to be randomized 1:1:1 into one of the three treatment groups. Each group received pregabalin 300 to 600 mg daily, venlafaxine XR 75-225 mg daily or matching placebo capsules.

Due to the slow enrollment of the trial, the sample size was reevaluated and it was determined that decreasing the sample size to 369 (123 per group) would only decrease the power to 88%. However, due to multiple sites enrolling, the final number of subjects randomized was 374.

Diagnosis and Main Criteria for Inclusion: Male or female outpatients with a primary diagnosis of GAD, with a Hamilton Anxiety Rating Scale (HAM-A) total score ≥20 **and** a score of ≥10 on both the psychic and somatic factor scores at screening and baseline, and at least 4 Global Anxiety Visual Analogue Scale and 4 Daily Pain Rating Scale assessments completed between screening and baseline

Study Treatment: During the double-blind treatment phase, pregabalin was administered twice daily (in the morning and in the evening) and venlafaxine XR was taken once daily in the morning.

There were three types of medication kits; low dose, medium dose and high dose. Each kit type contained sufficient drug for 7 days of treatment, plus three days overage, and were used across all medication visits from baseline to Week 8. The low dose kit consisted of pregabalin 300 mg/day or venlafaxine XR 75 mg/day or placebo. The medium dose kit consisted of pregabalin 450 mg/day or venlafaxine XR 150 mg/day or placebo. The high dose kit consisted of pregabalin 600 mg/day or venlafaxine XR 225 mg/day or placebo.

At Weeks 2, 3, 4, and 6, subjects exhibiting a satisfactory treatment response were instructed to continue taking the same dose of medication. Subjects who were not exhibiting a

satisfactory treatment response, in the absence of dose-limiting adverse events, increased the dose level and were assigned the next higher dose kit via the web/telephone telerandomization system.

At Week 8, subjects on the low dose kit discontinued study medication and returned for an end of taper closeout visit (Week 10). Subjects on the medium dose kit were assigned the low dose kit for the first week of tapering and then discontinued study medication and returned for the end of taper closeout visit (Week 10). Subjects on the high dose kit were assigned the medium dose kit for the first week of tapering and the low dose kit for the second week of tapering. Study medication was discontinued at the end of taper closeout visit (Week 10).

Efficacy Evaluations: The primary efficacy parameter was the Hamilton Anxiety Scale Total Score (HAM-A). The secondary efficacy evaluations included both Investigator-rated and Subject-rated scales. Investigator-rated scales included HAM-A: psychic anxiety factors and somatic anxiety factors, Clinical Global Impression-Severity Scale (CGI-S), Clinical Global Impression-Improvement Scale (CGI-I), and Hamilton Depression Rating Scale (HAM-D). Subject-rated scales included Hospital Anxiety and Depression Scale (HADS including HADS-A, HADS-D), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Sheehan Disability Scale (SDS), EuroQol (EQ-5D) Health State Questionnaire and Visual Analogue Scale (VAS), Changes in Sexual Functioning Questionnaire [CSFQ - (CSFQ-M-C; CSFQ-F-C)], Global Anxiety Visual Analogue Scale (GA-VAS), Daily Pain Rating Scale (DPRS), and Medical Outcomes Study (MOS) Sleep Scale.

Safety Evaluations: Safety evaluations included adverse events (AEs), serious adverse events (SAEs), clinical laboratory assessments, vital signs and physical examination.

Statistical Methods: The intent-to-treat (ITT) population was the primary population. Efficacy analyses were performed using the intent-to-treat population defined as all randomized subjects who took at least one dose of study medication and had at least one post-randomization efficacy assessment on any efficacy scale. The per protocol population excluded subjects with major protocol violations including baseline HAM-A total score <20 at baseline, HAM-A psychic score <10 at baseline, HAM-A somatic score <10 at baseline, HAM-D total score $\geq$15 at baseline (if baseline not present use screening value), HAM-D item 1 $\geq$2 at baseline (if baseline not present use screening value), duration since first diagnosis is <6 months for certain diagnoses, and use of certain concomitant medications during the active treatment phase of study. The safety evaluable population was defined as all subjects who took at least one dose of study drug and for whom follow-up safety data was obtained.

The primary null hypotheses were that the mean change from baseline to endpoint on the HAM-A total scale was approximately equal for pregabalin and placebo, and that the mean change from baseline to endpoint on the HAM-A total scale was approximately equal for venlafaxine XR and placebo. The primary research hypotheses were that the mean change from baseline to endpoint on the HAM-A total scale for pregabalin was significantly different from placebo, and that the mean change from baseline to endpoint on the HAM-A total scale for venlafaxine XR was different from placebo.

The primary analysis was comparison of the mean change from baseline to endpoint in HAM-A total score for the pregabalin and venlafaxine XR groups and placebo. The analysis was based on the last observation carried forward (LOCF) ITT dataset. An analysis of covariance (ANCOVA) model with center and baseline as covariates and test for center by treatment and treatment by baseline interactions were used. In addition, the two active treatment groups were compared to placebo using Dunnett's tests comparisons.

For the secondary efficacy analyses, comparison of pregabalin versus venlafaxine XR was added to the comparisons of active treatment and placebo on Day 4 of double-blind treatment based on the HAM-A total score was performed if the primary comparisons were significant. With the exception of the MOS Sleep Optimal Sleep Score all outcomes were evaluated with an ANCOVA model (no baseline covariate was included in the CGI-I model). The MOS Sleep Optimal Sleep Score was analyzed using a logistic regression model similar to the ANCOVA model.

Other variables for secondary analysis included the following:

- HAM-A: total score, psychic anxiety factor and somatic anxiety factor; anxious mood item (item 1) and tension (item 2)
- CGI-S and CGI-I
- HAM-D-total score
- HADS: HADS-A, and HADS-D
- Global Anxiety Visual Analogue Scale (GA-VAS)
- Daily Pain Rating Scale
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score, expressed as a percentage of 70, items 15 and 16 separately expressed as a percentage of 4
- Sheehan Disability Scale (SDS)
- EuroQol (EQ-5D)
- Changes in Sexual Functioning Questionnaire [CSFQ - (CSFQ-M-C; CSFQ-F-C)]
- Medical Outcomes Study (MOS) Sleep Scale

Secondary tests were two-sided with α=0.05. Hierarchical testing was used to control overall type I error at α=0.05. The hierarchy of hypotheses tests used in the primary tests and key secondary tests were applied at the α=0.05 level for each hypothesis test. All efficacy and outcomes variables were tested at each acute treatment period time point where they were collected (including the telephone interview).

RESULTS

Subject Disposition and Demography:

Table 1. Subject Disposition

	Pregabalin n (%)	Venlafaxine XR n (%)	Placebo n (%)
Assigned to Study Treatment N=374			
Treated	121	125	128
Completed	88 (72.7)	84 (67.2)	93 (72.7)
Discontinued	33 (27.3)	41 (32.8)	35 (27.3)
Analyzed for Efficacy			
ITT	121 (100.0)	125 (100.0)	128 (100.0)
Per Protocol	86 (71.1)	94 (75.2)	95 (74.2)
Analyzed for Safety			
Adverse events (AEs)	121 (100.0)	125 (100.0)	126 (98.4)
Laboratory data	114 (94.2)	120 (96.0)	115 (89.8)
Vitals	121 (100.0)	124 (99.2)	128 (100.0)

Note: Two subjects in the placebo group were listed as not being included in the adverse event population. One of these subjects discontinued on study Day 11 due to a protocol violation, and the other subject completed the study. The CRFs of both subjects did not include an AE log. These subjects were included in AE tables as having no AEs.

The most common reason for discontinuation was adverse event in the pregabalin and venlafaxine XR groups (12.4% and 16.8%, respectively), and lack of efficacy in the placebo group (9.4%).

In the pregabalin, venlafaxine XR and placebo groups there were more females (63.6%, 57.6% and 60.9%, respectively) than males (36.4%, 42.4% and 39.1%, respectively). The mean age in the pregabalin, venlafaxine XR and placebo groups was 39.5 years, 42.6 years and 40.2 years, respectively. The majority of subjects in the 3 treatment groups were white.

Efficacy Results: The primary analysis compared the mean change from baseline to endpoint in HAM-A for the pregabalin, venlafaxine XR, and placebo groups. The comparison of the 3 treatment groups for mean change from baseline to endpoint was statistically significant (p=0.0266). Treatment with pregabalin compared to placebo resulted in a statistically significant larger mean decrease from baseline to endpoint in HAM-A (p=0.0276). The comparison between venlafaxine XR and placebo was not statistically significant. The results were similar in the per protocol population.

The comparison of the 3 treatment groups was statistically significant for mean change in HAM-A from baseline to Day 4 and Weeks 1, 2, 3, and 4. Treatment with pregabalin compared to placebo resulted in a statistically significant larger mean decrease in HAM-A

from baseline to Day 4 through Week 4. The comparison between venlafaxine XR and placebo was not statistically significant at any timepoint, although there was a trend towards significance at Week 4 (p=0.0518).

For GA-VAS, the comparison of the 3 treatment groups was statistically significant for mean change from baseline to Day 4 and Weeks 1, 3 and 4, but not at endpoint. Treatment with pregabalin compared to placebo resulted in a statistically significant larger mean decrease in GA-VAS from baseline to Day 4 and Weeks 1, 3 and 4. The comparison between venlafaxine XR and placebo was statistically significant at Weeks 3 and 4.

For CGI-S, the comparison of the 3 treatment groups was statistically significant for mean change from baseline to Weeks 1, 2, 3, 4, and 8. Treatment with pregabalin compared to placebo resulted in a statistically significant larger mean decrease in CGI-S from baseline to Weeks 1, 2, 3, 4, and 8. The comparison between venlafaxine XR and placebo was not statistically significant at any timepoint, with the exception of Week 4 (p=0.0242).

For CGI-I, the comparison of the 3 treatment groups was statistically significant for mean change from baseline at Weeks 1, 2 and 4. Treatment with pregabalin compared to placebo resulted in a statistically significant lower mean CGI-I score at Weeks 1, 2 and 4. The comparison between venlafaxine XR and placebo was not statistically significant at any timepoint, with the exception of Week 4 (p=0.0156).

For the HAM-A psychic score, the comparison of the 3 treatment groups was statistically significant for mean decrease from baseline to Day 4, Weeks 1, 2, 3, 4 and endpoint (p<0.0001, 0.0007, 0.0096, 0.0217, 0.0030 and 0.0184, respectively). Treatment with pregabalin compared to placebo resulted in a statistically significant mean decrease in HAM-A psychic score at each of the timepoints significant in the overall comparison, however, the comparison between venlafaxine XR and placebo was statistically significant only at Week 4.

For the HAM-A somatic score, the comparison of the 3 treatment groups was statistically significant for mean decrease from baseline to Weeks 1 and 2 (p=0.0251 and 0.0504, respectively). Treatment with pregabalin compared to placebo resulted in a statistically significant mean decrease in HAM-A somatic score at each of the time-points significant in the overall comparison, however, the comparison between venlafaxine XR and placebo was not statistically significant.

For the HADS anxiety score, the comparison of the 3 treatment groups was statistically significant for mean change from baseline to Week 4 and endpoint (p=0.0052 and 0.0300, respectively). Treatment with pregabalin compared to placebo resulted in a statistically significant mean decrease in HADS anxiety score from baseline to Week 4 and endpoint (p=0.0049 and 0.0274, respectively). The comparison between venlafaxine XR and placebo resulted in a statistically significant mean decrease in HADS anxiety score from baseline to Week 4 (p=0.0267) and a marginally significant score at endpoint (p=0.0688).

For the HADS depression score, the comparison of the 3 treatment groups was statistically significant for mean change from baseline to Week 4 (p=0.0404), with a statistically

significant difference in the comparison of pregabalin and placebo (p=0.0229). The difference between venlafaxine XR and placebo was not statistically significant.

For the Q-LES-Q, the comparison of the 3 treatment groups was statistically significant for mean change from baseline to Week 4 and Week 8 (p=0.0343 and 0.0397, respectively), and was marginally significant at endpoint (p=0.0530). Comparisons between pregabalin and placebo were not statistically significant. The comparison between venlafaxine XR and placebo resulted in a statistically significant mean increase in Q-LES-Q from baseline to Weeks 4, 8 and endpoint (p=0.0329, 0.0301 and 0.0381, respectively).

There was generally no difference among the treatment groups for sexual functioning scores, daily pain rating, EuroQol health state profile score and EuroQol VAS score.

For all efficacy parameters, the results in the per protocol population were generally similar to the ITT population.

Safety Results: An overview of adverse events is summarized in Table 2.

Table 2. Overview of All Causality and Treatment Related Adverse Events

	All Causality			Treatment Related		
	Pregabalin N=121	Venlafaxine XR N=125	Placebo N=128	Pregabalin N=121	Venlafaxine XR N=125	Placebo N=128
No of AEs	265	284	167	216	229	117
Subjects with:						
-AEs	85 (70.2)	88 (70.4)	67 (52.3)	78 (64.5)	79 (63.2)	53 (41.4)
-SAEs	0	0	0	0	0	0
-Severe AEs	11 (9.1)	25 (20.0)	10 (7.8)	11 (9.1)	23 (18.4)	8 (6.3)
-DC due to AEs	15 (12.4)	22 (17.6)	7 (5.5)	15 (12.4)	21 (16.8)	6 (4.7)
-Dose reduced or temporary DC due to AEs	11 (9.1)	3 (2.4)	5 (3.9)	11 (9.1)	2 (1.6)	3 (2.3)

For the pregabalin, venlafaxine XR and placebo groups, the percentage of subjects with AEs was larger in the pregabalin and venlafaxine XR groups than the placebo group for both all causality (70.2% and 70.4% compared to 52.3%, respectively) and treatment related (64.5% and 63.2% compared to 41.4%, respectively) AEs.

All causality AEs reported by ≥5% subjects in any treatment group are summarized in Table 3.

Table 3. Incidence of All Causality Adverse Events Reported by ≥5% of Subjects in Any Treatment Group

	Pregabalin N=121		Venlafaxine XR N=125		Placebo N=128	
AE Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Vertigo	1	(13.2)	10	(8.0)	4	(3.1)
Dry mouth	13	(10.7)	15	(12.0)	5	(3.9)
Nausea	15	(12.4)	32	(25.6)	11	(8.6)
Constipation	5	(4.1)	7	(5.6)	4	(3.1)
Fatigue	12	(9.9)	16	(12.8)	5	(3.9)
Disturbance in attention	6	(5.0)	1	(0.8)	0	(0.0)
Dizziness	25	(20.7)	12	(9.6)	8	(6.3)
Headache	21	(17.4)	20	(16.0)	15	(11.7)
Somnolence	11	(9.1)	6	(4.8)	3	(2.3)
Anxiety	6	(5.0)	5	(4.0)	5	(3.9)
Generalized anxiety disorder	6	(5.0)	3	(2.4)	3	(2.3)
Insomnia	5	(4.1)	12	(9.6)	6	(4.7)
Hyperhidrosis	3	(2.5)	10	(8.0)	7	(5.5)

The most common AEs in the pregabalin group were dizziness (20.7%), headache (17.4%) and vertigo (13.2%). The most common AEs in the venlafaxine XR group were nausea (25.6%), headache (16.0%) and fatigue (12.8%). The most common AEs in the placebo group were headache (11.7%) and nausea (8.6%). More severe events were reported in the venlafaxine XR group (39/284 [13.7%]), than in the pregabalin or placebo groups (17/265 [6.4%], and 13/167 [7.8%], respectively).

Treatment related AEs reported by ≥5% of subjects in any treatment group are summarized in Table 4.

Table 4 Incidence of Treatment Related Adverse Events Reported by ≥5% of Subjects in Any Treatment Group

	Pregabalin N=121		Venlafaxine XR N=125		Placebo N=128	
AE Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Dizziness	24	(19.8)	12	(9.6)	8	(6.3)
Headache	18	(14.9)	14	(11.2)	11	(8.6)
Vertigo	16	(13.2)	10	(8.0)	3	(2.3)
Dry mouth	12	(9.9)	14	(11.2)	4	(3.1)
Nausea	12	(9.9)	31	(24.8)	7	(5.5)
Fatigue	12	(9.9)	16	(12.8)	5	(3.9)
Somnolence	11	(9.1)	6	(4.8)	3	(2.3)
Disturbance in attention	6	(5.0)	1	(0.8)	0	(0.0)
Insomnia	4	(3.3)	7	(5.6)	5	(3.9)
Hyperhidrosis	2	(1.7)	10	(8.0)	6	(4.7)

The most common treatment related AEs in the pregabalin group were dizziness (19.8%), headache (14.9%) and vertigo (13.2%). The most common treatment related AEs in the venlafaxine XR group were nausea (24.8%), fatigue (12.8%), headache (11.2%) and dry

mouth (11.2%). The most common treatment related AEs in the placebo group were headache (8.6%) and nausea (5.5%).

Fifteen subjects (12.4%) in the pregabalin group, 22 subjects (17.6%) in the venlafaxine XR group and 7 subjects (5.5%) in the placebo group discontinued due to adverse events. Adverse events that resulted in withdrawal of at least 2 subjects in any treatment group are summarized in Table 5.

Table 5. Adverse Events That Resulted in Withdrawal from the Study of at Least Two Subjects in Any Treatment Group

AE Preferred Term	Pregabalin N=121 n (%)	Venlafaxine XR N=125 n (%)	Placebo N=128 n (%)
Total withdrawals due to AEs	16 (13.2)	22 (17.6)	7 (5.5)
Agitation	0 (0.0)	2 (1.6)	1 (0.8)
Dizziness	4 (3.3)	2 (1.6)	0 (0.0)
Drowsiness	2 (1.7)	0 (0.0)	0 (0.0)
Insomnia	1 (0.8)	2 (1.6)	2 (1.6)
Nausea	1 (0.8)	7 (5.6)	0 (0.0)
Panic attack	0 (0.0)	3 (2.4)	0 (0.0)
Sedation	2 (1.7)	0 (0.0)	0 (0.0)

The most common reason for withdrawal in the pregabalin group was dizziness (4 subjects), followed by drowsiness and sedation (2 subjects each). The most common reason for withdrawal in the venlafaxine XR group was nausea (7 subjects), followed by panic attack (3 subjects each), and agitation, dizziness and insomnia (2 subjects each). The most common reason for withdrawal in the placebo group was insomnia (2 subjects).

There were no deaths or serious AEs.

In general, laboratory abnormalities were infrequent and comparable between the pregabalin, venlafaxine XR and placebo treatment groups.

CONCLUSIONS: The study results support the following conclusions:

- Pregabalin 300-600 mg/day was effective in reducing anxiety. As early as Day 4 there was a significant relief of GAD symptoms (as measured by both the HAM-A and the GA-VAS) in the pregabalin group as compared to the placebo group. This difference was observed at most timepoints up to and including LOCF endpoint.

- Venlafaxine-XR 75-225 mg/day was not statistically significantly superior to placebo in reducing anxiety in this study.

- Pregabalin and venlafaxine XR were both generally well tolerated. The most frequent AEs reported in the pregabalin group were dizziness, headache and vertigo. The most frequent AEs in the venlafaxine XR group were nausea, headache and fatigue. No SAEs were reported.