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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: Not applicable

PROTOCOL NO.: A0080090-A0080152

PROTOCOL TITLE: A Placebo-Controlled Study of Pregabalin in Elderly Patients with Generalized Anxiety Disorder (Protocols 1008-090, 1008-152)

Study Center(s):

Study 1008-090: Twenty-six (26) centers in United States

Study 1008-152: Sixty-nine (69) centers in Europe: United Kingdom (26), France (17), Spain (12), Ukraine (4), Estonia (3), Latvia (3), Portugal (3), Germany (1)

Study Initiation and Completion Dates:

Study 1008-152: 01 August 2000 to 04 March 2005

Study 1008-090: 25 July 2000 to 01 March 2001 (this study terminated prematurely due to a partial clinical hold on pregabalin in the United States)

Phase of Development: Phase 3

Study Objective(s):
Primary

- Evaluate the efficacy of pregabalin versus placebo in relieving the symptoms of Generalized Anxiety Disorder (GAD) as measured by the Hamilton Anxiety Rating Scale (HAM-A)
- Evaluate the safety of pregabalin versus placebo based upon the nature, incidence, and severity of adverse events (AEs)

Secondary

- Evaluate response rates (defined as ≥ 50% improvement in HAM-A total score from baseline to last observation on double-blind treatment) between pregabalin and placebo

- Compare the effects of pregabalin and placebo in relieving the symptoms of depression as measured by the 17-item Hamilton Depression Rating Scale (HAM-D)
- Compare the effects of pregabalin and placebo on the clinician-rated Clinical Global Impression of Change (CGIC)
- Compare the effects of pregabalin and placebo on symptoms of psychopathology and psychological distress using the 90-Item Symptom Checklist-Revised (SCL-90-R) total score and subscales
- Compare the effects of pregabalin and placebo on cognition using the Mini-Mental State Examination (MMSE)

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of pregabalin in elderly subjects with GAD. The study consisted of 3 phases: a 1-week screening phase, an 8-week double-blind treatment phase, and a 1-week double-blind taper and follow-up visit. Visits took place on Week -1 (pre-screening), Week 0 (baseline), Weeks 1, 2, 4, 6, and 8, and Week 9 (follow-up). The HAM-A was completed at all visits except follow-up. The HAM-D, MMSE and SCL-90-R were performed at baseline and the final on-treatment visit, and the CGIC was performed at all visits during which the subject received treatment. This study was carried out at US centers under Protocol 1008-090 and at non-US centers under Protocol 1008-152. Due to study procedures at the time this study was planned, US and non-US sites were given separate protocol numbers; however, these 2 protocols were part of the same study from the planning stage onward. Data from both US and non-US centers were combined to provide a single data set.

Number of Subjects (Planned and Analyzed):

Planned: The original protocol specified a total of 200 subjects. However, a blinded evaluation of available data revealed that the sample size needed to be increased to 261.

Analyzed: Data from both protocols were combined for the analyses. A total of 366 subjects were screened, 277 subjects were randomized to treatment and 273 subjects received treatment. Of these, 177 subjects received pregabalin and 96 received placebo.

Diagnosis and Main Criteria for Inclusion: Study subjects were male or non-fertile female outpatients, aged 65 years or older, who had a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of GAD confirmed using the Mini International Neuropsychiatric Interview (MINI). Subjects had to have a HAM-A score of ≥ 20 at screening and randomization and a MMSE of Folstein total score ≥ 24. They could not use any psychotropic medications or initiate any formal psychodynamic, cognitive, or behavioral psychotherapy within 3 months of beginning this study and were not to be at risk of suicide per the investigator's clinical judgment nor have had previous exposure to pregabalin.

Study Treatment:

- Oral pregabalin capsules (50 mg or 100 mg) or matching placebo
- A 1-week titration phase followed by a 5-week flexible dosing phase, a 2-week fixed dose phase, and a 1-week taper phase
- Dosing and duration: 50 mg/day titrated to 150 mg/day by Day 5 (twice daily [BID] or 3 times daily [TID])
    - During the flexible dosing phase, the dose could be adjusted to up to 600 mg/day based on clinical status (CGIC) and tolerability. During the fixed dose phase treatment was to be maintained as at the end of the flexible dosing phase.
- During the initial 2 weeks after randomization subjects could use zolpidem 5 to 10 mg per night or zaleplon 5 to 10 mg per night for extreme sleeplessness. Use of zolpidem or zaleplon was restricted to no more than 2 nights per week and was not to be taken the night before a scheduled clinic appointment.

Efficacy Evaluations:
Primary: Change from baseline to end point (Week 8 or last observation carried forward in double-blind phase) in the HAM-A total score

Secondary: HAM-A responders, baseline to end point change in the 17-item HAM-D total score, CGIC responders, and SCL-90-R total and subscale scores

Safety Evaluations: Adverse event data (occurrence, nature, intensity, and relationship to study drug), clinical laboratory data, and the results of vital signs, and electrocardiograms (ECGs) were used to evaluate safety.

Statistical Methods:

The ITT population included all subjects who had taken 1 dose of study medication. This population was also used for the evaluation for safety.

Analyses were performed on data that were pooled from US (Study 1008-090) and non-US (Study 1008-152) centers. Subjects with no post-randomization observation were assigned a

missing value for end point. Only subjects with at least 1 post baseline observation were included in the primary and secondary efficacy analyses.

The primary analysis was performed on data from the ITT population using an analysis of covariance (ANCOVA) model with treatment and center in the model, and the HAM-A score at baseline as the covariate. All secondary analyses were performed on data from the ITT population. All secondary variables, with the exception of HAM-A responders and CGIC responders, were analyzed using ANCOVA. The HAM-A and CGIC responders were analyzed using logistic regression. In centers in the UK, France, Netherlands, and Spain (study 1008-152), descriptive statistics were performed for Digit-Symbol Substitution Test of the Wechsler Adult Intelligence Scale (WAIS-III), the Digit Span Test, and the Set Test.

RESULTS

Patient Disposition and Demography:

A summary of subject disposition is given in Table S1.

Table S1 Subject Disposition and Subjects Analyzed

Number of Subjects		Placebo	Pregabalin	All Subjects
Planned	261			
Screened	366			
Entered Double-blind Phase		96	181	277
Intent-To-Treat		96	177	273
Discontinued During Double-blind		27 (28.1%)	44 (24.9%)	71 (26.0%)
Lack of Efficacy		7 (7.3%)	7 (4.0%)	14 (5.1%)
Adverse Event		9 (9.4%)	19[a] (10.7%)	28 (10.3%)
Other		6 (6.3%)	10 (5.6%)	16 (5.9%)
Lost to Follow-Up		1 (1.0%)	0 (0.0%)	1 (0.4%)
Subject Withdrew Consent		3 (3.1%)	7 (4.0%)	10 (3.7%)
Lack of Compliance		1 (1.0%)	1 (0.6%)	2 (0.7%)
Completed Double-Blind		69 (71.9%)	133 (75.1%)	202 (74.0%)
Entered Taper Phase		70 (72.9%)	129 (72.9%)	199 (72.9%)
Discontinued from Taper Phase		0	0	0
Entered OL Safety Study (1008-100)		41 (42.7%)	84 (47.5%)	125 (45.8%)

[a] Includes 1 subject with a non-treatment-emergent signs and symptoms AE

Treatment groups were well balanced in terms of demographic characteristics (Table S2).

Table S2. Demographic Characteristics

Characteristics	Placebo N = 96	Pregabalin N= 177	All Subjects N = 273
Gender, n (%)			
Male	24 (25.0)	37 (20.9)	61 (22.3)
Female	72 (75.0)	140 (79.1)	212 (77.7)
Race, n (%)			
White	95 (99.0)	173 (97.7)	268 (98.2)
Black	1 (1.0)	4 (2.3)	5 (1.8)
Age (years)			
Mean (SD)	72.2 (6.4)	72.4 (5.6)	72.3 (5.9)
Range	62 to 89	64 to 91	62 to 91
Height (cm)	n = 96	n = 175	n = 271
Mean (SD)	161.8 (9.3)	160.0 (9.6)	160.7 (9.5)
Median (range)	161 (145 to 185)	159 (137 to 185)	160 (137 to 185)
Weight (kg)	n = 96	n = 175	n = 271
Mean (SD)	74.4 (17.2)	70.7 (12.2)	72.0 (14.2)
Median (range)	74.3 (45.5 to144.6)	69.3 (45.4 to 113.7)	70.3 (45.4 to 144.6)

Efficacy Results:

Results of the primary analysis indicated that pregabalin was significantly superior ($p < 0.05$) to placebo in reducing the symptoms of GAD as measured by the change in HAM-A score from baseline to endpoint (Table S3).

Table S3. Change from Baseline at Week 8 (LOCF) in HAM-A Total Score

Treatment	Least Squares			Treatment Comparisons	
	N	Mean	SE	Difference From Placebo	p Value
Placebo					
Baseline Score	96[a]	26.2	0.4	--	
Change From Baseline	95[b]	-10.6525	0.89	--	
Pregabalin					
Baseline Score	177[a]	26.7	0.4	--	
Change From Baseline	171[b]	-12.8355	0.70	-2.183 (-4.3036, -0.0625)	0.0437

Effect of gender and severity of disease were evaluated for the primary efficacy measure. There were no treatment-by-gender ($p = 0.7551$) or treatment-by-severity of disease interactions ($p = 0.8194$).

Results of several secondary efficacy analyses supported the superiority of pregabalin over placebo in the treatment of GAD in an elderly population.

Pregabalin-treated subjects showed a significant ($p < 0.05$) reduction in mean HAM-A total score at Weeks 2, 4, 6, and 8 compared with placebo-treated subjects. Fifty-three percent of pregabalin-treated subjects and 41% of placebo-treated subjects qualified as responders (50% improvement [decrease] from baseline in HAM-A total score at the final evaluation) ($p = 0.071$). Pregabalin-treated subjects had a significant ($p = 0.0414$) decrease in mean HAM-D score at Week 8 compared with placebo-treated subjects. Pregabalin-treated

subjects had a mean change in HAM-D score of -5.5 compared with a mean change of -4.0 for placebo-treated subjects.

The CGIC responders were defined as subjects rated as "much improved" or "very much improved" by the clinician at the end of treatment. Fifty-eight percent of pregabalin-treated subjects were considered responders compared with 48% of placebo-treated subjects ($p = 0.117$).

The mean SCL-90-R total score decreased from baseline for both pregabalin- and placebo-treated subjects; there was no significant difference ($p = 0.657$) in the mean change in total score between the treatment groups. All SCL-90-R subscale scores followed this same pattern with the exception of the anxiety subscale; pregabalin-treated subjects had a significantly greater decrease ($p = 0.0412$) in mean SCL-90-R at Week 8 compared with placebo-treated subjects.

Mean change from baseline in MMSE total score was < 1 (on a scale of 1 to 30) for pregabalin- and placebo-treated subjects; mean change from baseline in MMSE – Attention and Calculation subscale score was also < 1 (on a scale of 1 to 5). There was no significant difference in total or subscale score between treatment groups. The MMSE – Immediate Recall subscale score, which had a scale of 1 to 3, had no change from baseline on 95% of the pregabalin subjects and on 99% of the placebo subjects. Therefore, no meaningful conclusion could be drawn from the analysis.

In centers in the UK, France, Netherlands, and Spain (study 1008-152), there were no meaningful changes in mean DSST score or in mean Set Test total score for pregabalin- or placebo-treated subjects. The subset of subjects who were administered the Digit Span Test also showed no meaningful change in total score.

Safety Results:

Seventy-two percent of subjects treated with pregabalin experienced AEs compared with 56% of subjects treated with placebo. Adverse events associated with study medication showed the same pattern; 51% of pregabalin-treated subjects and 33% of placebo-treated subjects had AEs considered associated with study medication. The AEs most frequently associated with pregabalin treatment were dizziness (16%), somnolence (13%), and headache (6%). Dizziness (10%), headache (7%), and somnolence (6%) were also frequently associated with placebo treatment.

A greater percentage of men treated with pregabalin (84%) experienced AEs compared with women treated with pregabalin (69%). The majority of AEs were mild to moderate in intensity. The incidence of severe AEs was similar across treatment groups (8% of placebo-treated subjects; 9% of pregabalin-treated subjects). The incidence of serious (nonfatal) AEs (3%) and withdrawals due to AEs (9% placebo; 11% pregabalin) was also similar across both treatment groups. One pregabalin-treated subject died during the study due to a cerebral hemorrhage. This event was considered not to be related to study medication by the study investigator.

The most frequently occurring treatment-emergent AEs are summarized in Table S4.

Table S4. Adverse Events that Occurred in ≥ 2% of Pregabalin-Treated Subjects by Decreasing Frequency, ITT

Preferred Term	Placebo N = 96 n (%)	Pregabalin 150 600 mg/day N = 177 n (%)
Subjects with at least 1 AE	54 (56.3)	127 (71.8)
Dizziness	11 (11.5)	36 (20.3)
Somnolence	7 (7.3)	23 (13.0)
Headache	8 (8.3)	18 (10.2)
Nausea	6 (6.3)	16 (9.0)
Infection	3 (3.1)	10 (5.6)
Abdominal Pain	3 (3.1)	7 (4.0)
Accidental Injury	1 (1.0)	7 (4.0)
Hypertension	1 (1.0)	7 (4.0)
Peripheral Edema	3 (3.1)	7 (4.0)
Dry Mouth	2 (2.1)	6 (3.4)
Amblyopia	1 (1.0)	5 (2.8)
Asthenia	3 (3.1)	5 (2.8)
Ataxia	0 (0.0)	5 (2.8)
Back Pain	4 (4.2)	5 (2.8)
Constipation	2 (2.1)	5 (2.8)
Insomnia	6 (6.3)	5 (2.8)
Paresthesia	0 (0.0)	5 (2.8)
Weight Gain	0 (0.0)	5 (2.8)
Diarrhea	5 (5.2)	4 (2.3)
Dyspepsia	0 (0.0)	4 (2.3)
Pain	1 (1.0)	4 (2.3)
Vertigo	0 (0.0)	4 (2.3)

Sorted by decreasing frequency by pregabalin treatment.

Adverse events related to vision, weight gain, dizziness, somnolence, cognition (speech disorder, thinking abnormal, amnesia, confusion), peripheral edema, and accidental injury were considered to be clinically important based on experience in earlier clinical studies with pregabalin. The incidence of these events is shown in Table S5.

Table S5. Clinically Important Adverse Events, ITT

Preferred Term	Placebo N = 96 n (%)	Pregabalin 150-600 mg/day N = 177 n (%)
Dizziness	11 (11.5)	36 (20.3)
Somnolence	7 (7.3)	23 (13.0)
Accidental Injury	1 (1.0)	7 (4.0)
Peripheral Edema	3 (3.1)	7 (4.0)
Amblyopia	1 (1.0)	5 (2.8)
Weight Gain	0 (0.0)	5 (2.8)
Vertigo	0 (0.0)	4 (2.3)
Incoordination	0 (0.0)	2 (1.1)
Abnormal Dreams	0 (0.0)	1 (0.6)
Abnormal Vision	0 (0.0)	1 (0.6)
Malaise	0 (0.0)	1 (0.6)
Thinking Abnormal	2 (2.1)	1 (0.6)
Confusion	1 (1.0)	0 (0.0)

Twenty-seven subjects withdrew from the study due to a treatment-related AE: 18 (10%) pregabalin-treated subjects and 9 (9%) placebo-treated subjects**.** Dizziness (4.5%), somnolence (1.1%), and vomiting (1.1%) were the only AEs that resulted in withdrawal of more than 1 pregabalin-treated subject (Table S6).

Table S6. Withdrawals Due to Adverse Events, ITT

Preferred Term	Placebo N = 96	Pregabalin 150-600 mg/day N = 177
Dizziness	1 (1.0)	8 (4.5)
Vomiting	1 (1.0)	2 (1.1)
Somnolence	0 (0.0)	2 (1.1)
Abdomen Enlarged	0 (0.0)	1 (0.6)
Abdominal Pain	0 (0.0)	1 (0.6)
Accidental Injury	0 (0.0)	1 (0.6)
Asthenia	0 (0.0)	1 (0.6)
Headache	0 (0.0)	1 (0.6)
Neck Pain	0 (0.0)	1 (0.6)
Cerebral Hemorrhage	0 (0.0)	1 (0.6)
Constipation	0 (0.0)	1 (0.6)
Diarrhea	1 (1.0)	1 (0.6)
Gastritis	0 (0.0)	1 (0.6)
Nausea	3 (3.1)	1 (0.6)
Abnormal Gait	0 (0.0)	1 (0.6)
Ataxia	0 (0.0)	1 (0.6)
Hypotonia	0 (0.0)	1 (0.6)
Vertigo	0 (0.0)	1 (0.6)
Amblyopia	0 (0.0)	1 (0.6)
Impotence	0 (0.0)	1 (0.6)
Myocardial Infarct	1 (1.0)	0 (0.0)
Peripheral Edema	1 (1.0)	0 (0.0)
Leg Cramps	1 (1.0)	0 (0.0)
Dysarthria	1 (1.0)	0 (0.0)
Nervousness	1 (1.0)	0 (0.0)
Thinking Abnormal	1 (1.0)	0 (0.0)
Rash	1 (1.0)	0 (0.0)

One subject died during Study 1008-152. An 82-year-old woman treated with pregabalin (for a total of 7 days), died after experiencing a cerebral hemorrhage (2 days post-last dose). The event was not considered to be related to the study medication. The incidence of serious adverse events (SAEs) was similar for both treatment groups; 3% of placebo-treated subjects and 4% of pregabalin-treated subjects (includes 1 unrelated death) had 1 or more SAEs (Table S7). No particular event occurred in more than 1 subject.

The majority of SAEs were unrelated to study medication; however, anxiety, somnolence, and accidental injury (fractured arm) experienced by subjects treated with pregabalin were considered possibly or probably related to study medication.

Table S7. Serious Adverse Events

Preferred Term	Placebo N = 96 n (%)	Pregabalin 150-600 mg/day N = 177 n (%)
Accidental Injury	0 (0.0)	1 (0.6)
Chest Pain	0 (0.0)	1 (0.6)
Cerebral Hemorrhage	0 (0.0)	1 (0.6)
Palpitation	0 (0.0)	1 (0.6)
Vascular Disorder	0 (0.0)	1 (0.6)
Ventricular Tachycardia	0 (0.0)	1 (0.6)
AV Block Second Degree	1 (1.0)	0 (0.0)
Myocardial Infarct	1 (1.0)	0 (0.0)
Duodenal Ulcer	1 (1.0)	0 (0.0)
Rectal Hemorrhage	1 (1.0)	0 (0.0)
Anemia	1 (1.0)	0 (0.0)
Anxiety	0 (0.0)	1 (0.6)
Dizziness	0 (0.0)	1 (0.6)
Somnolence	0 (0.0)	1 (0.6)
Skin Ulcer	0 (0.0)	1 (0.6)
Number of Subjects With AEs	**3 (3.1)**	**7 (4.0)**

Regarding laboratory results, there were no findings of clinical concern. For ECG and vital signs, there were no differences between the pregabalin and placebo groups.

CONCLUSION(S):

Pregabalin was effective in reducing the symptoms of GAD as measured by the HAM-A and supportive measures. Pregabalin is generally well tolerated in this elderly population. No new safety concerns for pregabalin were identified in this study.

- Pregabalin significantly reduced mean HAM-A scores versus placebo in this trial at flexible doses from 150-600 mg/day dosed either BID or TID.
- Pregabalin significantly reduced mean HAM-A scores versus placebo after 1 week of treatment with 150 mg per day (Week 2 in this study).
- The HAM-A and CGIC responder analyses were not statistically significant. However, the percentage of responders was higher in pregabalin-treated subjects than placebo-treated subjects using either HAM-A or CGIC criteria (HAM-A: 41% placebo, 53% pregabalin; and CGIC 48% placebo, 58% pregabalin).
- No increase was observed in the severity or frequency of AEs in this elderly population versus the existing pregabalin safety database. The safety profile of pregabalin in elderly GAD subjects was similar to that observed in the previous non-elderly controlled GAD studies and in elderly subjects treated with pregabalin in other indications. Titration for this study began at a low dose and increased over a 1-week period to reduce the chance of AEs in this elderly population.