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**PROPRIETARY DRUG NAME/INN:** Pregabalin

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** see USPI

**NCT #:** NCT00245609

**PROTOCOL NO.:** PROTOCOL A0081072

**PROTOCOL TITLE:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial of the Anxiolytic Efficacy of Pregabalin and Alprazolam IR in Subjects with Anxiety Prior to Dental Procedure

**Study Center(s):** Nine centers; 6 centers in Germany and 3 centers in the United Kingdom

**Study Initiation and Completion Dates:** 9 January 2006 to 25 October 2006

**Phase of Development:** Phase 2

**Study Objective(s):** The primary objective of the trial was to assess the anxiolytic efficacy at 4 hours post-dose of pregabalin and alprazolam IR versus placebo in subjects experiencing anxiety prior to dental procedure.

The secondary objective of the trial was to document the safety and tolerability profile of pregabalin and alprazolam IR versus placebo in subjects treated for dental anxiety. Sedation status was actively assessed.

**METHODS**

**Study Design:** This was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group trial of the anxiolytic efficacy of pregabalin and alprazolam IR in subjects experiencing anxiety while awaiting a dental procedure.

Subjects who had an appointment for a dental procedure at one of these sites, fulfilling all inclusion and exclusion criteria, and signing informed consent, were recruited to this trial.

**Number of Patients (planned and analyzed):** Approximately 90 subjects (30 per group) were planned for recruitment. A total of 27, 31 and 31 subjects, respectively, were randomly assigned and treated in the pregabalin, alprazolam and placebo groups.

**Diagnosis and Main Criteria for Inclusion:** Healthy male or female subjects 18 years of age or older with a total score of 12 points or more on the Dental Anxiety Scale at the screening and baseline evaluations and a scheduled appointment for an elective minor dental procedure.

**Study Treatment:** Subjects were randomized to receive 1 dose of either pregabalin 150 mg, alprazolam IR 0.5 mg, or placebo equivalent using a double-dummy design 4 hours ( $\pm 5$  minutes) prior to the scheduled dental procedure. Study medication was administered at the clinic. No other treatment doses were administered.

**Efficacy Evaluations:** Efficacy assessments were made at Screening (1-4 weeks prior to baseline), at Baseline (prior to dosing on the day of procedure), and at 2, 2.5, 3, 3.5, and 4 hours after single-dose intake, with the exception of the Dental Anxiety Scale which was administered at Screening, Baseline and 4 hours post-dose. The efficacy evaluations included:

Primary measure:

- Visual Analog Scale for Anxiety (VAS-A) - In this study, the VAS measures used were rated on 0 to 100-mm scale where 0 means none of the symptom and 100 represents the worst rating of the symptom.

Secondary measures:

- Time-to-Onset of Action Scale (TOAS) - The TOAS is a subject-rated scale that records the degree (on a 0 to 10 point scale) of anxiolytic benefit that the subject received from a dose of medication. The scores are plotted against a Good Benefit Threshold, defined as the score, on a 0 to 10 point scale, the subject would choose as "acceptable" where 10 represents maximal possible improvement for that subject.
- Visual Analog Scale for Sedation (VAS-S) - In this study, the VAS measures used were rated on 0 to 100-mm scale where 0 means none of the symptom and 100 represents the worst rating of the symptom.
- Dental Anxiety Scale - The Dental Anxiety Scale is a subject-rated scale for the assessment of dental anxiety. The scale consists of four multiple choice questions relating to the subject's subjective feelings regarding going to the dentist, waiting in the dentist's office, waiting in the dentist's chair for drilling, and waiting in the dentist's chair for scraping. The total score ranges from 4 to 20, with 20 representing the greatest level of dental anxiety.

**Safety Evaluations:** Safety evaluations included assessment of adverse events throughout the study, a urine toxicology screen, weight, sitting blood pressure, heart rate and a urine pregnancy test in all females of childbearing potential at the Screening and Baseline visits, and a physical examination and height at the Screening visit.

**Statistical Methods:** The primary efficacy endpoint was the VAS-A. The primary analysis compared the mean change from baseline to endpoint in VAS-A between the pregabalin, alprazolam, and placebo groups. For this analysis, the method of last observation carried forward (LOCF) was used for any missing post-baseline measurements. An ANCOVA model as was used with country and baseline as covariates and test for country-by-treatment and treatment-by-baseline interactions were examined. The two active treatment groups were compared to placebo using Dunnett's test. A secondary endpoint for the VAS-A was the area under the curve (AUC), from baseline to endpoint. The AUC was calculated for each subject and then the mean AUC was analyzed using an ANCOVA model, similar to that used for the primary efficacy analysis, to compare the 3 treatment groups.

The secondary endpoints included the TOAS, VAS-S and Dental Anxiety Scale. The mean change from baseline to each time point measured for VAS-S and the Dental Anxiety Scale was analyzed using an ANCOVA model as done for the primary analysis, with Dunnett's tests conducted for the treatment group comparisons. The TOAS score at each time point was analyzed in the same manner.

Additional secondary endpoints were derived from the TOAS. Benefit of treatment was defined as a score of 7 or more on the TOAS. Time to benefit of treatment (time to onset of action) was defined as the first time point that the subject had a score of 7 or greater on the TOAS. Sustained benefit was defined as achieving a score of 7 or more on the TOAS and maintaining a score of 7 or more at each subsequent time point (this variable was assessed at Hours 2, 2.5, 3, and 3.5). The proportions of subjects with benefit of treatment and sustained benefit of treatment were analyzed using a Cochran-Mantel-Haenszel (CMH) test controlling for country. Kaplan-Meier estimates of the time to benefit of treatment (time to onset of action) were compared between the 3 treatment groups using the log-rank statistic.

## RESULTS

**Subject Disposition and Demography:** All treated subjects in the pregabalin, alprazolam and placebo groups (27, 31 and 31 subjects, respectively) completed the study and were analyzed for efficacy and safety (Table 1).

**Table 1 Subject Disposition**

	<b>Pregabalin</b>	<b>Alprazolam</b>	<b>Placebo</b>
Screened N=134			
Assigned to Study Treatment N=91 <sup>a</sup>			
Treated	27	31	31
Completed	27	31	31
Discontinued	0	0	0
Analyzed for Efficacy	27	31	31
Analyzed for Safety	27	31	31

<sup>a</sup> Subjects 10091019 and 10091023 were randomized to placebo and alprazolam treatments, respectively, but not treated.

There were more males in the alprazolam group (48.4%) than in the placebo or pregabalin groups (35.5% and 29.6%, respectively) and thus, fewer females (51.6%, 64.5% and 70.4%, respectively). The mean age of the pregabalin, alprazolam and placebo groups was 35.1 years, 41.8 years and 36.8 years, respectively. The majority of subjects in the 3 treatment groups were white.

**Efficacy Results:**

Efficacy results are summarized in Table 2.

**Table 2 Overview of Efficacy Results**

Hour 4/ Endpoint	Treatment	LS Mean (SE)	Overall p-value	Treatment vs Placebo			
				Difference (SE)	95% CI	p-value	
<b>Primary Efficacy Endpoint</b>							
VAS-A <sup>a</sup>	Pregabalin	-11.98 (5.47)	0.0102	-4.89 (7.42)	(-21.60, 11.82)	0.7380	
	Alprazolam	-28.57 (5.10)		-21.48 (7.17)			(-37.64, -5.33)
	Placebo	-7.08 (5.05)					
<b>Secondary Efficacy Endpoints</b>							
TOAS <sup>b</sup>	Pregabalin	5.11 (0.55)	0.0005	2.37 (0.74)	(0.69, 4.05)	0.0040	
	Alprazolam	5.44 (0.51)		2.70 (0.72)			(1.08, 4.32)
	Placebo	2.74 (0.51)					
VAS-S <sup>a</sup>	Pregabalin	27.51 (5.12)	0.0035	18.30 (6.90)	(2.75, 33.86)	0.0182	
	Alprazolam	31.08 (4.77)		21.88 (6.77)			(6.63, 37.12)
	Placebo	9.21 (4.75)					
DAS <sup>a</sup>	Pregabalin	-2.49 (0.61)	0.2164	-0.83 (0.82)	(-2.69, 1.02)	0.4995	
	Alprazolam	-3.06 (0.58)		-1.41 (0.81)			(-3.23, 0.40)
	Placebo	-1.65 (0.55)					

Pregabalin N=27, alprazolam N=31, placebo N=31

<sup>a</sup>Change from baseline to endpoint

<sup>b</sup>Endpoint value

VAS-A=visual analog scale-anxiety; TOAS=time-to-onset of action scale; VAS-S=visual analog scale-sedation; DAS=dental anxiety scale; LS Mean=Least squares mean of change from baseline, SE=Standard error of change from baseline.

LS Means from ANCOVA model with main effects of treatment and country and baseline as covariate.

Overall p-value=p-value from the type III Sums of Squares for treatment from the ANCOVA model.

95% CI and p-value are adjusted for 2 comparisons using Dunnett's test.

Endpoint value is LOCF.

For the primary analysis, the mean change from baseline to endpoint in VAS-A comparing the 3 treatment groups (pregabalin, alprazolam, and placebo groups) was statistically significant (p=0.0102). The Dunnett's test comparing pregabalin and placebo was not statistically significant (p=0.7380), however, the comparison of alprazolam and placebo was statistically significant in favor of alprazolam (p=0.0069).

For the additional anxiety outcome measure of TOAS, there was a significant difference between the alprazolam and placebo groups, and between the pregabalin and placebo groups at endpoint. These significant differences began at Hour 2 between the alprazolam and placebo groups, and at Hour 3 between the pregabalin and placebo groups.

The change from baseline to the end of study in the Dental Anxiety Score was not statistically significant in the overall comparison of the 3 treatment groups.

The overall comparison of the 3 treatment groups for mean change from baseline in VAS-S at Hour 2, 2.5, 3, 3.5 and 4/endpoint was statistically significant (p=0.0397, 0.0047, 0.0007, 0.0199 and 0.0035, respectively). Beginning at Hour 2 there was a significant difference between alprazolam and placebo, and beginning at Hour 2.5 there was a significant difference between the pregabalin and placebo groups in perceived sedation.

The proportion of subjects with benefit of treatment (defined as a score of 7 or greater on the TOAS scale) was larger in the pregabalin than either the alprazolam or placebo groups beginning at Hour 3.0 (40.74% in the pregabalin group vs. 32.26% and 16.13% in the alprazolam and placebo groups, respectively); the proportion of subjects reporting benefit of treatment was statistically different among the three treatment groups (overall  $p=0.0402$ , pregabalin vs. placebo  $p=0.0395$ ) and was maintained until endpoint. At endpoint, the proportion of subjects with benefit of treatment was 44.4% in the pregabalin group, 32.3% in the alprazolam group and 16.1% in the placebo group (overall  $p=0.0172$ ). Pairwise comparison showed that the proportion of pregabalin subjects was significantly higher than the proportion of placebo subjects who reported benefit of treatment ( $p=0.0163$ ); whereas, the proportion of alprazolam subjects was not different from placebo ( $p=0.1503$ ).

The proportion of subjects with sustained benefit of treatment (defined as a score of 7 or greater on the TOAS scale at specified time points until the end of the study) was slightly larger (but not significantly) in the pregabalin than the alprazolam or placebo groups from Hour 2.5 onward; the difference among the 3 treatment groups became greater at Hour 3 and was of borderline statistical significance from Hour 3 and 3.5 forward (specifically this difference can be attributed to the difference between the pregabalin and placebo groups).

**Safety Results:** For the pregabalin, alprazolam and placebo groups, the proportion of subjects with adverse events (AEs) was 48.1%, 38.7% and 22.6%, respectively; all subjects who reported AEs had at least one AE that was considered treatment related. There were no treatment emergent serious AEs (SAEs), severe AEs or discontinuations due to AEs in any treatment group. There was one SAE (retinal detachment) that occurred pre-randomization.

The most common AEs in the pregabalin, alprazolam, and placebo groups were fatigue (25.9%, 22.6% and 9.7%, respectively) and dizziness (22.2%, 9.7% and 3.2%, respectively). Somnolence was reported in 3 subjects (11.1%) in the pregabalin group and no subjects in the alprazolam or placebo groups. All cases of dizziness in the pregabalin and alprazolam groups were mild in severity. Somnolence was considered mild in severity in 2 of the 3 subjects who reported it (the other case was judged as moderate). Overall, the majority of adverse events reported in all 3 groups were considered mild by the investigators. No adverse events in any treatment group were considered severe.

## CONCLUSION(S):

In this single-dose study of pregabalin (150 mg) and alprazolam (0.5 mg) versus placebo, the differences in the mean change from baseline to endpoint in VAS-A (the primary analysis) between the pregabalin, alprazolam, and placebo groups were statistically significant. Statistical significance between the pregabalin and placebo groups was not demonstrated in the primary analysis; the comparison between the alprazolam and placebo groups was statistically significant in favor of alprazolam.

For the additional anxiety endpoint measured by the TOAS (Time-to-Onset of Action Scale), there was a statistically significant difference between alprazolam and placebo beginning at Hour 2, and between the pregabalin and placebo groups beginning at Hour 3. These differences were sustained until endpoint.

The subjects in the pregabalin and alprazolam groups reported more sedation, as measured by the VAS-S, than those in the placebo group. Consistent with this finding, the most common treatment emergent AE was fatigue in the pregabalin and alprazolam groups.

Due the nature of this study, pregabalin was administered as a single dose of 150 mg (the recommended administration is twice or three times daily). Dizziness and somnolence, common side effects of pregabalin, occurred at a greater frequency in the pregabalin group versus the alprazolam or placebo group, but the incidence of these events was within the expected rate as described in the product labeling. Overall, pregabalin and alprazolam were safe and well tolerated in this single-dose study.