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

PROTOCOL NO.: 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 Centers: Nine centers took part in the study and enrolled subjects; 6 in Germany and 3 in the United Kingdom (UK).

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

Phase of Development: Phase 2

Study Objectives: The primary objective of the trial was to assess the anxiolytic efficacy at 4 hours post-dose of pregabalin and alprazolam immediate release (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: 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.

Approximately 90 subjects were consecutively recruited at 9 sites and were randomized 1:1:1 into each of the 3 treatment groups: 150 mg pregabalin, 0.5 mg alprazolam IR, or placebo. Subjects, who had an appointment for a dental procedure at 1 of these sites, fulfilling all inclusion and exclusion criteria, and signing informed consent, were recruited to this trial.

Screening: One to 4 weeks prior to the dental appointment, subjects had a screening visit to provide informed consent and establish inclusion/exclusion criteria. This visit included a physical examination including vital signs, a medical/psychiatric history including a Mini International Neuropsychiatric Interview (M.I.N.I.), a urine toxicology screen, and a urine pregnancy test for females of childbearing potential. Prior and concomitant medications and nondrug treatments/procedures were recorded. Subjects completed the Dental Anxiety Scale, Visual Analog Scale for Anxiety (VAS-A), and Visual Analog Scale for Sedation (VAS-S).

Baseline: Subjects arrived at the clinic for baseline evaluations at least 4.5 hours prior to the scheduled dental procedure to allow adequate time to complete all pre-dose activities so that the dose was taken 4 hours (±5 minutes) prior to the scheduled dental procedure. The medical/psychiatric history was updated. Prior and concomitant medications and nondrug treatments/procedures and vital signs were recorded. Subjects provided a urine toxicology sample and females of childbearing potential completed a urine pregnancy test.

Five minutes prior to the dose, subjects completed the Dental Anxiety Scale, VAS-A, and VAS-S. Subjects who still met the entrance criteria were randomized to receive 1 dose of either 150 mg pregabalin, 0.5 mg alprazolam IR or placebo equivalent using a double-dummy design. Subjects ingested the single dose of randomized study medication under the supervision of site personnel at 4 hours (±5 minutes) prior to the scheduled dental procedure. No other treatment doses were administered.

Double-Blind Treatment Phase: Assessments of efficacy (VAS-A, VAS-S, and Time-to-Onset of Action Scale [TOAS]) and collection of safety and tolerability parameters were done at 2, 2.5, 3, 3.5, and 4 hours after drug intake (study endpoint at 4 hours after dosing, and just prior to the scheduled dental procedure). At the 4-hour time point, the Dental Anxiety Scale was also assessed. No assessments other than that for follow-up adverse events (AEs) and for concomitant medication were conducted after the 4-hour endpoint.

A schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activity	Screening	Baseline (0 Hour)	2 Hours	2.5 Hours	3 Hours	3.5 Hours	4 Hours
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Physical examination	X						
General medical/psychiatric history (updated at baseline)	X	X					
Vital signs	X	X					
M.I.N.I. (mini international neuropsychiatric interview)	X						
Dental Anxiety Scale	X	X					X
Urine toxicology screen	X	X					
Urine pregnancy test	X	X					
Randomization and trial treatment		X					
Visual analog scale for anxiety (VAS-A)	X	X	X	X	X	X	X
Visual analog scale for sedation (VAS-S)	X	X	X	X	X	X	X
Time to onset-to-action scale (TOAS)			X	X	X	X	X
Adverse event assessment		X	X	X	X	X	X
Prior and concomitant medication and non-drug treatment/procedures	X	X					X

Number of Subjects (Planned and Analyzed): Approximately 90 subjects (30 per group) were planned for recruitment. A total of 91 subjects were randomized; 27, 31, and 31 subjects were randomly assigned to the pregabalin, alprazolam, and placebo groups, respectively. Two subjects were randomized to placebo and alprazolam treatments, respectively, but not treated.

Of the 91 subjects, 39 were randomized in the UK and 52 were randomized in Germany.

Diagnosis and Main Criteria for Inclusion: Both male or female outpatients 18 years of age or older who scored 12 points or more on the Dental Anxiety Scale at screening and baseline evaluations and have a scheduled appointment for an elective dental procedure were included in the study. Subjects with current diagnosis of any of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) anxiety disorders and/or current diagnosis of major depressive disorder, dysthymia, schizophrenia or any other psychotic disorder, bipolar disorder, and eating disorders as assessed by the M.I.N.I. at screening, or current diagnosis of delirium, dementia, or body dysmorphic disorder were excluded from the study.

Study Treatment: Pregabalin (150 mg) and its matching placebo were supplied as capsules. Alprazolam (0.5 mg) and its placebo were supplied as tablets.

Subjects were randomized to receive 1 dose of either 150 mg pregabalin, 0.5 mg alprazolam IR, or placebo equivalent orally using a double-dummy design 4 hours (±5 minutes) prior to the scheduled dental procedure. Study medication was administered at the clinic. No other treatment doses were administered. Since the 0.5 mg alprazolam tablets and the corresponding placebo tablets did not match in appearance, subjects were blindfolded for dosing and not allowed to see or touch the study medication.

Efficacy Endpoints: The primary efficacy endpoint was to assess VAS-A, and the secondary efficacy endpoints were the assessments of TOAS, VAS-S, and the Dental Anxiety Scale.

Safety Evaluations: Safety evaluations included assessment of all observed or volunteered AEs (including adverse drug reactions, illnesses with onset during the study, exacerbation of previous illnesses, any clinically significant changes in physical examination findings, and abnormal objective test findings), severity of AEs (mild, moderate, or severe), relationship AE to study treatment, seriousness of AEs, significant events for laboratory evaluations (including any positive findings from urine toxicology tests at the screening and baseline visits with the substances of abuse, including alcohol, amphetamines, barbiturates, opiates, methadone, cocaine, phencyclidine, cannabinoids, and benzodiazepines. A urine pregnancy test was performed in all females of childbearing potential.

Statistical Methods:

Full Analysis Set: The full analysis data set was the intent-to-treat (ITT) dataset. Efficacy analyses were performed using the ITT population defined as all randomized subjects who took at least 1 dose of study medication and had at least 1 postrandomization efficacy assessment on any efficacy scale. The ITT population was the primary efficacy evaluation population.

Safety Analysis Set: The safety evaluable population was defined as containing all subjects who took at least 1 dose of study drug and for whom follow-up safety data was obtained.

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 analysis of covariance (ANCOVA) model was used with country and baseline as covariates and test for country-by-treatment and treatment-by-baseline interactions were examined. The 2 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 the 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 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: Table 2 presents a summary of subject disposition. A total of 134 subjects were screened and 91 were randomized. One subject randomized to alprazolam and 1 subject randomized to placebo was not treated. 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 2. Subject Disposition

	Pregabalin	Alprazolam	Placebo
Screened N=134			
Assigned to study treatment N=91[a]			
Treated	27	31	31
Completed	27	31	31
Discontinued	0	0	0
Analyzed for efficacy	27	31	31
Analyzed for safety	27	31	31

N = number of subjects.
a. Two subjects were randomized to placebo and alprazolam treatments, respectively, but were not treated.

Demographic characteristics are summarized in Table 3. 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.

Table 3. Demographic Characteristics, Treated Subjects

	Pregabalin N=27	Alprazolam N=31	Placebo N=31
Sex, n (%)			
Male	8 (29.6)	15 (48.4)	11 (35.5)
Female	19 (70.4)	16 (51.6)	20 (64.5)
Age			
Categories, n (%)			
18-44	22 (81.5)	17 (54.8)	23 (74.2)
45-64	4 (14.8)	14 (45.2)	7 (22.6)
≥65	1 (3.7)	0 (0.0)	1 (3.2)
Mean ± SD	35.1±12.2	41.8±12.4	36.8±12.7
Range	22-67	20-63	18-67
Race, n (%)			
White	26 (96.3)	29 (93.5)	30 (96.8)
Black	0 (0.0)	1 (3.2)	0 (0.0)
Asian	1 (3.7)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (3.2)	1 (3.2)
Weight (kg)			
Mean ± SD	74.9±18.4	86.6±18.8	82.1±22.8
Height (cm)			
Mean ± SD	169.1±8.2	173.8±9.4	173.0±9.5

N = number of subjects in each treatment group; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results: Efficacy results are summarized in Table 4.

Table 4. Overview of Efficacy Results

Hour 4/ Endpoint	Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
				Difference (SE)	95% CI	p-value
Primary Efficacy Endpoint						
VAS-A[a]	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)	0.0069
	Placebo	-7.08 (5.05)				
Secondary Efficacy Endpoints						
TOAS[b]	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)	0.0006
	Placebo	2.74 (0.51)				
VAS-S[a]	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)	0.0034
	Placebo	9.21 (4.75)				
DAS[a]	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)	0.1484
	Placebo	-1.65 (0.55)				

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 sum 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.
ANCOVA = analysis of covariance; CI = confidence interval; DAS = dental anxiety scale; LOCF = last observation carried forward; LS Mean = least squares mean of change from baseline; SE = standard error of change from baseline; TOAS = time-to-onset of action scale; VAS-A = visual analog scale-anxiety; VAS-S = visual analog scale-sedation.
a. Change from baseline to endpoint.
b. Endpoint value.

Visual Analog Scale for Anxiety: The primary analysis compared the mean change from baseline to endpoint in VAS-A for the pregabalin, alprazolam, and placebo groups. Baseline and the change from baseline to Hour 2, 2.5, 3, 3.5, and 4/endpoint are summarized in Table 5. The comparison of the 3 treatment groups for mean change from baseline at Hour 3, 3.5 and 4/endpoint was statistically significant (p-value =0.0395, 0.0417 and 0.0102, respectively). The comparisons between pregabalin and placebo at Hour 3, 3.5 and 4/endpoint were not statistically significant (p-value =0.4480, 0.3171 and 0.7380, respectively); however, statistical significance in favor of alprazolam was shown in the comparisons between alprazolam and placebo (p-value =0.0216, 0.0230 and 0.0069, respectively).

Table 5. Change from Baseline to Each Visit: Visual Analog Scale - Anxiety

Visit	Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
				Difference (SE)	95% CI	p-value
Baseline	Pregabalin	70.21 (5.08)	0.1837	6.09 (6.93)	(-9.52, 21.70)	0.5881
	Alprazolam	57.35 (4.75)		-6.77 (6.69)	(-21.84, 8.30)	0.4997
	Placebo	64.12 (4.74)				
Hour 2	Pregabalin	-14.74 (3.93)	0.2672	-1.03 (5.34)	(-13.06, 10.99)	0.9734
	Alprazolam	-21.59 (3.67)		-7.88 (5.16)	(-19.51, 3.74)	0.2265
	Placebo	-13.70 (3.63)				
Hour 2.5	Pregabalin	-22.27 (4.42)	0.0605	-7.03 (6.00)	(-20.55, 6.49)	0.4025
	Alprazolam	-29.21 (4.13)		-13.97 (5.80)	(-27.04, -0.90)	0.0343
	Placebo	-15.24 (4.08)				
Hour 3	Pregabalin	-23.73 (4.56)	0.0395	-6.79 (6.19)	(-20.73, 7.16)	0.4480
	Alprazolam	-32.44 (4.26)		-15.49 (5.98)	(-28.97, -2.01)	0.0216
	Placebo	-16.95 (4.21)				
Hour 3.5	Pregabalin	-22.50 (4.85)	0.0417	-8.75 (6.58)	(-23.58, 6.09)	0.3171
	Alprazolam	-30.07 (4.53)		-16.32 (6.36)	(-30.66, -1.98)	0.0230
	Placebo	-13.76 (4.48)				
Hour 4/endpoint	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)	0.0069
	Placebo	-7.08 (5.05)				

Pregabalin N=27; alprazolam N=31; placebo N=31.
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.
ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean of change from baseline, LOCF = last observation carried forward; N = number of subjects in each group; SE = standard error of change from baseline.

The distribution of subject mean AUC for the VAS-A scale "a measure of total anxiety burden" is summarized in Table 6. Lower VAS-A; AUC scores indicate lessening of the total anxiety burden for the 4 hour study period. No difference was observed between pregabalin and placebo. Alprazolam demonstrated a significant difference versus placebo. There was no planned comparison of pregabalin and alprazolam.

Table 6. Distribution of Subject Mean Area Under the Curve for VAS-A Scale

Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
			Difference (SE)	95% CI	p-value
Pregabalin	197.00 (11.55)	0.0448	-13.80 (15.67)	(-49.10, 21.50)	0.5884
Alprazolam	172.69 (10.78)		-38.11 (15.14)	(-72.24, -3.98)	0.0260
Placebo	210.80 (10.66)				

Pregabalin N=27; alprazolam N=31; placebo N=31.
LS Means from ANCOVA model with main effects of treatment and country 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.
ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean of change from baseline; N = number of subjects in each group; SE = standard error of change from baseline; VAS-A = visual analog scale for anxiety.

Time-to-Onset of Action Scale: The TOAS is summarized at Hour 2, 2.5, 3, 3.5 and 4/endpoint in Table 7. The comparison of the 3 treatment groups for TOAS at Hours 2, 2.5,

3, 3.5 and 4/endpoint were statistically significant (p-value =0.0453, 0.0177, 0.0109, 0.0035, and 0.0005, respectively). Beginning at Hour 2, there was a significant difference between alprazolam and placebo, and beginning at Hour 3 there was a significant difference between the pregabalin and placebo groups in TOAS. These differences were sustained until endpoint.

Table 7. Time-to-Onset of Action Scale (TOAS) at Each Visit

Visit	Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
				Difference (SE)	95% CI	p-value
Hour 2	Pregabalin	3.96 (0.53)	0.0453	1.25 (0.72)	(-0.38, 2.88)	0.1551
	Alprazolam	4.43 (0.50)		1.72 (0.70)	(0.14, 3.29)	0.0302
	Placebo	2.71 (0.50)				
Hour 2.5	Pregabalin	4.69 (0.52)	0.0177	1.54 (0.71)	(-0.05, 3.13)	0.0597
	Alprazolam	5.02 (0.49)		1.87 (0.68)	(0.33, 3.41)	0.0143
	Placebo	3.15 (0.48)				
Hour 3	Pregabalin	5.17 (0.50)	0.0109	1.73 (0.68)	(0.20, 3.26)	0.0238
	Alprazolam	5.24 (0.47)		1.81 (0.66)	(0.33, 3.28)	0.0137
	Placebo	3.44 (0.46)				
Hour 3.5	Pregabalin	5.15 (0.52)	0.0035	1.86 (0.70)	(0.27, 3.44)	0.0188
	Alprazolam	5.51 (0.48)		2.22 (0.68)	(0.69, 3.75)	0.0031
	Placebo	3.29 (0.48)				
Hour 4/endpoint	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)	0.0006
	Placebo	2.74 (0.51)				

Pregabalin N=27; alprazolam N=31; placebo N=31.
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.
ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean of change from baseline; N = number of subjects in each group; SE = standard error of change from baseline.

Benefit of Treatment: The proportion of subjects with benefit of treatment at each time point (defined as a score of 7 or greater on the TOAS scale) is summarized in Table 8. The percentage of subjects achieving a benefit of treatment (defined as a score of 7 or greater on the TOAS scale at any point in the 4 hour study period) in the pregabalin, alprazolam, and placebo groups was 51.9%, 48.4%, and 22.6%, respectively. Of these subjects, the median time to benefit of treatment in the pregabalin, alprazolam, and placebo groups was 3, 3, and 2.5 hours, respectively.

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; the proportion of subjects reporting benefit of treatment was statistically different among the 3 treatment groups. By 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-value =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-value =0.0163), whereas, the proportion of alprazolam subjects was not different from placebo (p-value =0.1503).

Table 8. Proportion of Subjects with Benefit of Treatment

					p-values	
Time	**Pregabalin N=27**	**Alprazolam N=31**	**Placebo N=31**	**Overall p-value**	**Pregabalin Versus Placebo**	**Alprazolam Versus Placebo**
2.0 hours	4 (14.81)	7 (22.58)	4 (12.90)	0.814	0.834	0.324
2.5 hours	7 (25.93)	8 (25.81)	6 (19.35)	0.553	0.558	0.563
3.0 hours	11 (40.74)	10 (32.26)	5 (16.13)	0.040	0.040	0.147
3.5 hours	12 (44.44)	11 (35.48)	5 (16.13)	0.020	0.018	0.090
4.0 hours/endpoint	12 (44.44)	10 (32.26)	5 (16.13)	0.017	0.016	0.150

Benefit of Treatment was defined as a score of 7 or greater on the Time-to-Onset of Action Scale.
p-value was from a Cochran-Mantel-Haenszel test of treatment benefit controlling for country.
N = number of subjects in each group.

Sustained Benefit of Treatment: The proportion of subjects with sustained benefit of treatment (defined as a score of 7 or greater on the TOAS scale from Hour 2 until the end of the study) in the pregabalin, alprazolam and placebo groups was 14.81%, 12.90% and 6.45%, respectively (p-value =0.314).

The proportion of subjects with sustained benefit of treatment from Hour 2.5 onward is summarized in Table 9. 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).

Table 9. Proportion of Subjects with Sustained Benefit of Treatment from 2.5 Hours Forward

					p-values	
Time	**Pregabalin N=27**	**Alprazolam N=31**	**Placebo N=31**	**Overall p-value**	**Pregabalin Versus Placebo**	**Alprazolam Versus Placebo**
Sustained benefit from Hour 2.5 forward	5 (18.52)	5 (16.13)	4 (12.90)	0.562	0.564	0.753
Sustained benefit from Hour 3.0 forward	9 (33.33)	6 (19.35)	4 (12.90)	0.060	0.065	0.521
Sustained benefit from Hour 3.5 forward	10 (37.04)	8 (25.81)	5 (16.13)	0.068	0.070	0.374

Benefit of Treatment was defined as a score of 7 or greater on the Time-to-Onset of Action Scale from visit forward until end of study.
p-value was from a Cochran-Mantel-Haenzel test of treatment benefit controlling for country.
N = number of subjects in each group.

Visual Analog Scale for Sedation: Baseline and the change from baseline to Hour 2, 2.5, 3, 3.5, and 4/endpoint are summarized for VAS-S in Table 10. The 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-value =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 significantly more sedation in the

pregabalin group than in the placebo group; similarly, there was more sedation in the alprazolam group than in the placebo group.

Table 10. Change from Baseline to Each Visit: Visual Analog Scale-Sedation

Visit	Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
				Difference (SE)	95% CI	p-value
Baseline	Pregabalin	11.02 (3.52)	0.1050	-1.71 (4.81)	(-12.54, 9.13)	0.9134
	Alprazolam	20.56 (3.30)		7.84 (4.64)	(-2.62, 18.30)	0.1679
	Placebo	12.73 (3.29)				
Hour 2	Pregabalin	28.02 (4.76)	0.0397	12.27 (6.41)	(-2.17, 26.70)	0.1069
	Alprazolam	31.06 (4.43)		15.31 (6.28)	(1.15, 29.47)	0.0319
	Placebo	15.75 (4.41)				
Hour 2.5	Pregabalin	37.40 (4.79)	0.0047	19.73 (6.45)	(5.19, 34.27)	0.0058
	Alprazolam	34.80 (4.46)		17.14 (6.33)	(2.88, 31.39)	0.0157
	Placebo	17.66 (4.44)				
Hour 3	Pregabalin	37.15 (4.93)	0.0007	22.14 (6.64)	(7.16, 37.11)	0.0025
	Alprazolam	37.69 (4.59)		22.68 (6.51)	(8.00, 37.36)	0.0016
	Placebo	15.01 (4.57)				
Hour 3.5	Pregabalin	31.28 (5.14)	0.0199	15.59 (6.92)	(-0.02, 31.19)	0.0503
	Alprazolam	33.47 (4.78)		17.77 (6.79)	(2.48, 33.07)	0.0200
	Placebo	15.70 (4.77)				
Hour 4/endpoint	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)	0.0034
	Placebo	9.21 (4.75)				

Pregabalin N=27; alprazolam N=31; placebo N=31.
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 sum of squares for treatment from the ANCOVA model.
95% CI and p-value are adjusted for 2 comparisons using Dunnett's test.
ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean of change from baseline; N = number of subjects in each group; SE = standard error of change from baseline.

Dental Anxiety Scale: The change in the Dental Anxiety Score from baseline to Hour 4/endpoint is summarized in Table 11. The change from baseline to the end of the study in the Dental Anxiety Score was not statistically significant in the overall comparison of the 3 treatment groups.

Table 11. Change from Baseline to End of Study: Dental Anxiety Score

Visit	Treatment	LS Mean (SE)	Overall p-value	Treatment Versus Placebo		
				Difference (SE)	95% CI	p-value
Baseline	Pregabalin	16.82 (0.47)	0.3113	0.49 (0.64)	(-0.95, 1.94)	0.6619
	Alprazolam	17.28 (0.44)		0.95 (0.62)	(-0.44, 2.34)	0.2215
	Placebo	16.33 (0.44)				
Hour 4/endpoint	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)	0.1484
	Placebo	-1.65 (0.55)				

Pregabalin N=27; alprazolam N=31; placebo N=31.
At Hour 4, 25 subjects in the pregabalin, 29 subjects in the alprazolam, and 31 subjects in the placebo group had data for analysis.
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 sum of squares for treatment from the ANCOVA model.
95% CI and p-value are adjusted for 2 comparisons using Dunnett's test.
ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean of change from baseline; N = number of subjects in each group; SE = standard error of change from baseline.

Safety Results: An overview of AEs is presented in Table 12. For the pregabalin, alprazolam, and placebo groups, the proportion of subjects with AEs was 48.1%, 38.7%, and 22.6%, respectively; all subjects who reported AEs had at least 1 AE that was considered treatment-related. There were no treatment-emergent serious AEs, severe AEs, or discontinuations due to AEs in any treatment group.

Table 12. Overview of All Causality and Treatment Related Adverse Events

	All Causality			Treatment Related		
	Pregabalin N=27	Alprazolam N=31	Placebo N=31	Pregabalin N=27	Alprazolam N=31	Placebo N=31
Number of adverse events	28	24	17	28	24	17
Subjects (%) with adverse events	13 (48.1)	12 (38.7)	7 (22.6)	13 (48.1)	12 (38.7)	7 (22.6)

N = number of subjects in each treatment group.

Treatment-Emergent Adverse Events: All causality and treatment-related AEs reported by at least 2 subjects in any treatment group are summarized in Table 13 (in all of these cases, the events were considered treatment-related).

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 (11.1%) subjects 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).

There were no severe AEs in any treatment group. The majority of events in the pregabalin, alprazolam, and placebo groups were mild (24/28 [85.7%], 22/24 [91.7%], and 11/17 [64.7%], respectively) or moderate (4/28 [14.3%], 2/24 [8.3%], and 6/17 [35.3%], respectively).

Table 13. All Causality and Treatment-Related Adverse Events Reported by at Least Two Subjects in Any Treatment Group

AE Preferred Term	Pregabalin N=27 n (%)	Alprazolam N=31 n (%)	Placebo N=31 n (%)
Fatigue	7 (25.9)	7 (22.6)	3 (9.7)
Dizziness	6 (22.2)	3 (9.7)	1 (3.2)
Disturbance in attention	3 (11.1)	1 (3.2)	0 (0.0)
Somnolence	3 (11.1)	0 (0.0)	0 (0.0)
Dry mouth	2 (7.4)	0 (0.0	0 (0.0)
Feeling abnormal	0 (0.0)	2 (6.5)	0 (0.0)
Balance disorder	0 (0.0)	2 (6.5)	0 (0.0)

The number of subjects with all causality and treatment-related AEs was the same for the AEs summarized in this table; however, not all AEs were treatment related.
AE = adverse event; N = number of subjects in each treatment group; n = number of subjects with adverse events.

Serious Adverse Events: There were no treatment-emergent SAEs during the study.

Death: There were no deaths during the study.

Discontinuations due to Adverse Events: No subjects permanently discontinued due to AEs. There were no dose reductions or temporary discontinuations due to AEs.

Other Safety Related Findings: There were no laboratory tests performed during the study.

CONCLUSIONS:

In this single-dose study of 150 mg pregabalin and 0.5 mg alprazolam 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, 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 to the nature of this study, pregabalin was administered in a single dose at 150 mg (the recommended administration is twice or 3 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 product labeling. Overall, pregabalin and alprazolam were safe and well tolerated in this single-dose study.