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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Neurontin[®]/Gabapentin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00666770

PROTOCOL NO.: A9451139

PROTOCOL TITLE: A Randomized, Double-Blind, Single-Dose, Placebo-Controlled, Multicenter, Polysomnographic Study of Gabapentin 250 mg and 500 mg in Transient Insomnia Induced by a Sleep Phase Advance

Study Centers: Four centers in the United States enrolled subjects.

Study Initiation and Completion Dates: 20 October 2004 – 15 November 2004

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To assess the effect of gabapentin 250 mg and 500 mg on polysomnographic (PSG) assessments in transient insomnia induced by a sleep phase advance

Secondary Objectives:

- To assess the effect of gabapentin 250 mg and 500 mg on subjective sleep assessments in transient insomnia induced by a sleep phase advance
- To assess the effect of gabapentin 250 mg and 500 mg on memory and psychomotor performance in transient insomnia induced by a sleep phase advance

METHODS

Study Design: This was a randomized, double-blind, single-dose, placebo-controlled, multicenter, PSG study of gabapentin (250 mg and 500 mg) in subjects with transient insomnia induced by a sleep phase advance. The study included the following 2 visits:

- Screening Visit (Visit 1): Evaluations done at this visit included a brief medical history, concomitant medication history, vital signs (pulse rate, blood pressure and respiratory

rate), height and weight. A urine sample was also collected for drug screening. Eligible subjects at this visit were scheduled for Visit 2.

- Randomization Visit (Visit 2): Subjects returned to the clinic 5 to 14 days after Visit 1 at approximately 1:00 pm. Subjects completed the Epworth Sleepiness Scale (ESS). Vital signs (pulse rate, blood pressure and respiratory rate) were recorded, and an alcohol breathalyzer test and urine pregnancy test (for women of childbearing potential) were conducted for each subject. Eligible subjects were randomized and prepared for PSG recording. Subjects were dosed at 4:30 pm (\pm 3 minutes), went to bed 30 minutes later and were awakened 8 hours later. PSG was conducted during this sleep period. Fifteen minutes (\pm 5 minutes) after awakening, subjects were instructed to begin completing the following subjective sleep assessments:
 - Subjective Sleep Latency
 - Subjective Number of Awakenings
 - Subjective Wake After Sleep Onset
 - Subjective Total Sleep Time
 - Subjective Assessment of Sleep Refreshment
 - Subjective Assessment of Sleep Quality
 - Karolinska Sleep Diary (KSD)

After completion of the subjective sleep assessments, psychomotor performance was assessed using the Digit Symbol Substitution Test (DSST). Memory was then assessed using the Buschke Selective Reminding Test (BSRT). The BSRT was completed within 1 hour of awakening. Vital signs (pulse rate, blood pressure and respiratory rate) were then recorded. Subjects remained awake until 5 hours after awakening (\pm 10 minutes), when sleepiness was assessed using the Stanford Sleepiness Scale (SSS).

Number of Subjects (Planned and Analyzed):

Planned: Sufficient subjects were to be enrolled to ensure approximately 300 subjects completed the study (100 subjects in each treatment group).

Analyzed: A total of 309 subjects were randomized (103 subjects to each treatment group). All subjects were analyzed for efficacy and safety with the exception of 1 subject in the gabapentin 500 mg group who was excluded from the efficacy analysis (evaluable subjects) because he was suffering from a chronic painful condition.

Diagnosis and Main Criteria for Inclusion: Males or females at least 18 years of age with typical and consistent duration of sleep, bed time hours, and time of awakening were included in the study. Females of childbearing potential had to have been using a medically-acceptable method of birth control for at least 1 month prior to Visit 1.

Study Treatment: Gabapentin was provided as 250 mg capsules with matching placebo. Subjects in the gabapentin 500 mg treatment group took two 250 mg capsules. All subjects took 2 identically appearing capsules orally 30 minutes prior to bedtime.

Efficacy Evaluations: The primary efficacy variable was PSG-determined Latency to Persistent Sleep recorded over the 8 hour sleep period at the clinics. Subjective sleep assessments, including the KSD, and the DSST, were completed by the subjects approximately 15 minutes after awakening. The BSRT was administered to subjects by the staff at the clinic within 1 hour of awakening. The SSS was completed by subjects approximately 5 hours after awakening.

Safety Evaluations: Vital signs were measured pre- and post-dose by the clinic staff. Adverse event (AE) information (if any) was collected at each visit.

Statistical Methods: Unless otherwise specified, between-treatment comparisons were based on pairwise t-tests from an analysis of variance (ANOVA) with treatment and center as factors. The interactions between treatment and center were examined. The assumption of normality was examined using the Shapiro-Wilk test and normal probability plots. If normality assumption was rejected at the 0.05 level, nonparametric analyses was performed. All statistical comparisons were performed at a significance level of 0.05, 2-sided. Summary statistics or frequency counts by treatment group were provided for all variables. Standard errors (SEs) were calculated for means. The primary statistical inference for the primary efficacy variable was based on a step-down (SD2L) procedure.

RESULTS

Subject Disposition and Demography: A total of 427 subjects were screened for this study. At Visit 1, 416 subjects met the inclusion/exclusion criteria. Of the 416 subjects who qualified for Visit 2, 309 subjects were randomized equally amongst the 3 treatment groups (107 subjects were not randomized for various reasons). No subjects discontinued from the study. Subject disposition is presented in Table S1.

Table S1. Subject Disposition and Subjects Analyzed

Number of Subjects	Placebo	Gabapentin 250 mg	Gabapentin 500 mg
Planned		300 completed subjects	
Screened		427	
Assigned to study treatment		309	
Treated	103	103	103
Completed	103	103	103
Discontinued	0	0	0
Analyzed for Efficacy			
ITT subjects	103	103	103
Evaluable subjects	103	103	102 ^a
Analyzed for safety	103	103	103

^a One subject with chronic painful condition was excluded from the evaluable analysis set.

ITT=Intent-to-treat

The mean age of subjects treated was 29.3 years (range, 18–76 years). The majority of subjects were males (177 subjects, 57.3%) and white (212 subjects, 68.6%). There were no

statistically significant differences among treatment groups in demographic characteristics with the exception of height. However, height was deemed not to have a meaningful impact on the results of the study. Demographic characteristics are summarized in Table S2.

Table S2. Demographic Characteristics (ITT Population)

Variables	Placebo (N=103)	Gabapentin 250 mg (N=103)	Gabapentin 500 mg (N=103)	p-value
Age (years)				0.274 ^a
Mean	28.4	30.4	29.2	
Range	18–58	18–76	18–66	
Sex, n (%)				0.080 ^b
Male	65 (63.1)	50 (48.5)	62 (60.2)	
Female	38 (36.9)	53 (51.5)	41 (39.8)	
Height (inches)				0.011 ^a
Mean (Range)	68.1 (60–76)	66.8 (59–76)	68.2 (60–79)	
Weight (lb)				0.526 ^a
Mean (Range)	163.9 (110–302)	168.8 (111–281)	167.7 (108–277)	

^a p-values are based on ANOVA model with terms for treatment and center

^b p-value are based on Cochran-Mantel-Haenszel general association test, stratified by center
 N=Total number of subjects

The mean ESS Total Score was 4.0 for placebo, 4.8 for gabapentin 250 mg, and 3.7 for gabapentin 500 mg, respectively. The difference was statistically different and may suggest subjects in the gabapentin 250 mg treatment group on average had a higher level of sleep propensity prior to randomization compared to subjects in the gabapentin 500 mg and placebo treatment groups.

Efficacy Results: There were significant improvements in total sleep time and all sleep maintenance measures, both subjective and PSG, for both gabapentin 250 mg and 500 mg, compared to placebo. Neither gabapentin dose was significantly different than placebo for objectively- or subjectively-measured sleep latency. This lack of effect on sleep latency may be due in part to subjects' excessive nascent sleep drive as roughly half of placebo-treated subjects fell asleep within 15 minutes of going to bed at 5:00 pm. PSG assessments were consistent with subjective assessments. Significant increases in slow wave sleep (Stages 3 plus 4) were seen only in the gabapentin 500 mg treatment group. There were significant improvements in sleep quality and sleep refreshment assessments for both gabapentin 250 mg and 500 mg, compared to placebo. Results for the PSG and subjective sleep assessments are summarized in Table S3.

Table S3. Polysomnographic and Subjective Sleep Assessments

Assessment	PSG/Subjective	Placebo (N=103)	Gabapentin 250 mg (N=103)	Gabapentin 500 mg (N=103)
Latency to persistent sleep (minutes) ¹	PSG	34.51 (5.79)	36.85 (5.81) ^a	37.75 (5.80) ^a
Sleep Onset Latency (minutes)	PSG	19.26 (3.74)	19.92 (3.75) ^a	16.65 (3.75) ^a
	Subjective	56.5 (8.0)	56.9 (8.0)	43.6 (8.0)
Total Sleep Time (minutes)	PSG	309.6 (9.2)	362.0 (9.2) ^{a***}	374.0 (9.3) ^{b***}
	Subjective	318.9 (10.8)	371.8 (10.8) ^{a***}	379.0 (10.8) ^{a***}
Sleep Efficiency	PSG	64.50 (1.91)	75.41 (1.91) ^{a***}	77.91 (1.93) ^{b***}
	Subjective ^a	10.6 (0.7) ^a	7.4 (0.7) ^{a***}	6.8 (0.7) ^{b***}
Number of Awakenings	PSG	4.7 (0.3) ^b	3.1 (0.3) ^{c***}	2.8 (0.3) ^{***}
	Subjective ^a	151.24 (8.46)	98.41 (8.49) ^{a***}	89.51 (8.55) ^{b***}
Wake After Sleep Onset (minutes)	PSG	115.2 (8.6) ^b	53.7 (8.6) ^{c***}	54.6 (8.4) ^{***}
	Subjective	142.30 (8.21)	87.22 (8.19) ^{***}	73.74 (8.25) ^{***}
Wake After Persistent Sleep Onset (minutes)	PSG	93.4 (7.5) ^a	54.2 (7.5) ^{a***}	46.9 (7.5) ^{b***}
Maximum Duration of Awakenings	PSG	143.23 (9.73) ^a	133.22 (9.71) ^a	126.66(9.81) ^b
Latency to REM	PSG	207.9 (9.1)	153.5 (9.1) ^{a***}	139.8 (9.2) ^{b***}
Total Wake Time + Stage 1 Sleep (minutes)	PSG	12.82 (0.72)	10.60 (0.72) ^{a*}	9.67 (0.72) ^{b**}
Stage 1 Sleep (%)	PSG	56.50 (0.98)	57.77 (0.98) ^a	55.34 (0.99) ^b
Stage 2 Sleep (%)	PSG	7.19 (0.43)	6.97 (0.43) ^a	8.35 (0.44) ^b
Stage 3 Sleep (%)	PSG	8.41 (0.76)	7.07 (0.76) ^a	10.02 (0.77) ^b
Stage 4 Sleep (%)	PSG	15.60 (0.88)	14.04 (0.88) ^a	18.37 (0.89) ^{b*}
Slow Wave Sleep (%)	PSG	15.08 (0.57)	17.58 (0.57) ^{a***}	16.62 (0.57) ^{b*}
REM Sleep (%)	PSG			

Results are presented as adjusted mean (± SE). Means are adjusted for centre.

¹ Primary endpoint

^an=102, ^bn=101, ^cn=100

*p<0.05 versus placebo, **p<0.01 versus placebo, ***p<0.001 versus placebo

PSG=Polysomnographic; REM=Rapid Eye Movement

N=Total number of subjects

Results for the Sleep Quality Assessments are summarized in Table S4. As shown in Table S5, results for the KSD sleep quality index (KSD-SQI) were well correlated to PSG for many variables. This indicates that KSD-SQI is a good predictor of some objective measures of PSG.

Table S4. Sleep Quality Assessments

Assessment	Placebo N=103	Gabapentin 250 mg N=103	Gabapentin 500 mg N=103
Assessment of Sleep Quality	1.6 (0.1)	2.3 (0.1)***	2.5 (0.1)***
Assessment of Sleep Refreshment	1.7 (0.1)	2.0 (0.1)*	2.0 (0.1)*
Karolinska Sleep Diary Sleep Quality Index	2.7 (0.1)	3.4 (0.1)***	3.5 (0.1)***
Karolinska Sleep Diary-Sleep Quality	2.7 (0.1)	3.3 (0.1)***	3.4 (0.1)***
Karolinska Sleep Diary-Calm Sleep	2.7 (0.1)	3.2 (0.1)***	3.6 (0.1)***
Karolinska Sleep Diary-Ease Falling Asleep	3.2 (0.1)	3.2 (0.1)	3.3 (0.1)
Karolinska Sleep Diary-Slept Throughout	2.4 (0.2)	3.7 (0.2)***	3.8 (0.2)***
Karolinska Sleep Diary-Ease Awakening	4.1 (0.1)	3.8 (0.1)*	3.8 (0.1)*
Karolinska Sleep Diary-Well-Rested	2.8 (0.1)	3.5 (0.1)***	3.3 (0.1)**
Karolinska Sleep Diary- Sufficient Sleep	3.0 (0.1)	3.6 (0.1)***	3.6 (0.1)***

All numbers presented are adjusted mean (\pm SE)

*p<0.05 versus placebo, **p<0.01 versus placebo, ***p<0.001 versus placebo

N=Total number of subjects

Table S5. Correlations of PSG Variables With KSD-SQI

Assessment	Pearson Correlation with KSD-SQI Intent-to-Treat Subjects		
	Overall (All Treatment Groups Combined)		
	P	n	p-value
Latency to Persistent Sleep (min)	-0.29168	307	0.0000
Sleep Onset Latency (min)	-0.24455	307	0.0000
Latency to REM (min)	-0.30972	304	0.0000
Number of Awakenings	-0.00465	304	0.9356
Wake After Sleep Onset (min)	-0.51136	305	0.0000
Wake After Persistent Sleep Onset (min)	-0.46139	304	0.0000
Total Wake Time Plus Stage 1 Sleep (min)	-0.55639	305	0.0000
Maximum Duration of Awakenings (min)	0.45437	304	0.0000
Total Sleep Time (min)	0.56623	305	0.0000
Sleep Efficiency (%)	0.56622	305	0.0000
Stage 1 Sleep (%)	-0.23193	305	0.0000
Stage 2 Sleep (%)	0.10741	305	0.0610
Stage 3 Sleep (%)	-0.00606	305	0.9161
Stage 4 Sleep (%)	-0.13640	305	0.0172
Slow Wave Sleep (%)	-0.12087	305	0.0349
REM Sleep (%)	0.30354	305	0.0000

KSD-SQI=Karolinska Sleep Diary - Sleep Quality Index; REM=Rapid Eye Movement

N=Total number of subjects; n=Nnumber of subjects

Results for BSRT, DSST and SSS are summarized in Table S6. There were no significant differences between subjects who received gabapentin 250 mg or 500 mg in any score on the BSRT or the DSST test score compared to subjects who received placebo. However, subjects who received gabapentin 500 mg reported less daytime sleepiness as measured by SSS 5 hours after wakening compared to subjects who received placebo.

Table S6. Other Assessments

Assessment	Placebo N=103	Gabapentin 250 mg N=103	Gabapentin 500 mg N=103
Buschke Selective Reminding Test			
Immediate Recall Score	53.3 (0.9)	53.3 (0.9)	54.0 (0.9)
Long Term Storage Score	47.6 (1.3)	48.2 (1.3)	49.6 (1.3)
Total Number of Intrusions	0.7 (0.1)	0.8 (0.1)	0.6 (0.1)
Delayed Recall Score	8.6 (0.2)	8.5 (0.2)	8.7 (0.2)
Digit Symbol Substitution Test	76.9 (1.7)	76.5 (1.7)	75.1 (1.7)
Stanford Sleepiness Scale	2.8 (0.1)	2.5 (0.1)	2.5 (0.1)*

All numbers presented are adjusted mean (\pm SE)

*p<0.05 versus placebo

N=Total number of subjects

Safety Results: There were no deaths or serious adverse events (SAEs) during the study and no subjects discontinued due to AEs.

Of those randomized, 10 subjects (3.2%) reported at least 1 AE after dosing; 4 (3.9%), 4 (3.9%), and 2 (1.9%) subjects in the placebo, gabapentin 250 mg, and gabapentin 500 mg groups, respectively. A total of 12 AEs were reported (6, 4 and 2 in the placebo, gabapentin 250 mg and gabapentin 500 mg groups, respectively). The majority of these were mild; no severe AEs were reported. No single AE was reported by more than 3 subjects in any treatment group. The incidence of AEs (all causalities) is presented in Table S7.

Table S7. Incidence of All Causality Adverse Events

Preferred Term	Placebo (N=103) N (%)	Gabapentin 250 mg (N=103) n (%)	Gabapentin 500 mg (N=103) n (%)
Subjects with at least 1 AE	4 (3.9)	4 (3.9)	2 (1.9)
Headache	2 (1.9)	3 (2.9)	1 (<1.0)
Dizziness	0 (0.0)	0 (0.0)	1 (<1.0)
Dyspepsia	0 (0.0)	1 (<1.0)	0 (0.0)
Lethargy	1 (<1.0)	0 (0.0)	0 (0.0)
Sensory disturbance	1 (<1.0)	0 (0.0)	0 (0.0)
Thirst	1 (<1.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (<1.0)	0 (0.0)	0 (0.0)

AE=Adverse Event

N=Total number of subjects, n=Number of subjects

Eight subjects (2.6%) reported at least 1 treatment related AE after dosing; 2 (1.9%), 4 (3.9%), and 2 (1.9%) subjects in the placebo, gabapentin 250 mg, and gabapentin 500 mg groups, respectively. A total of 10 treatment related AEs were reported (4, 4 and 2 in the placebo, gabapentin 250 mg and gabapentin 500 mg groups, respectively). The incidence of AEs (treatment related) is presented in Table S8.

Table S8. Incidence of Treatment Related Adverse Events

Preferred Term	Placebo (N=103) N (%)	Gabapentin 250 mg (N=103) n (%)	Gabapentin 500 mg (N=103) n (%)
Subjects with at least 1 AE	2 (1.9)	4 (3.9)	2 (1.9)
Headache	1 (<1.0)	3 (2.9)	1 (<1.0)
Dizziness	0 (0.0)	0 (0.0)	1 (<1.0)
Dyspepsia	0 (0.0)	1 (<1.0)	0 (0.0)
Lethargy	1 (<1.0)	0 (0.0)	0 (0.0)
Sensory disturbance	1 (<1.0)	0 (0.0)	0 (0.0)
Thirst	1 (<1.0)	0 (0.0)	0 (0.0)

AE=Adverse Event

N=Total number of subjects, n=Number of subjects

Vital Signs, Physical Findings, and Other Observations Related to Safety: There were no meaningful differences among the 3 treatment groups in terms of vital signs. Mean changes from predose in pulse rate, blood pressure and respiratory rate are presented in Table S9.

Table S9. Vital Signs: Mean Changes from Predose

Vital Sign	Placebo N=103	Gabapentin 250 mg N=103	Gabapentin 500 mg N=103
Systolic Blood Pressure	-1.0	-0.6	-0.5
Diastolic Blood Pressure	0.8	0.9	1.0
Respiratory Rate	-0.7	-0.4	-0.2
Pulse Rate	-3.2	-4.0	-3.9

There was 1 other observation related to safety. One subject, a 21 year old female, reported a positive urine pregnancy test result 4 days after completion of the study. The subject had had a negative urine pregnancy test result prior to randomization. The same subject reported a diagnosis of thyroid cancer 55 days after completion of the study. This was not considered related to the investigational product by the investigator. The subject later reported a healthy birth.

Conclusions: This study demonstrated gabapentin's positive effects on improving sleep and the impact of these improvements on perceptions of overall sleep quality as well as the refreshing and restorative qualities of sleep. Specifically, gabapentin demonstrated improvement on all aspects of sleep maintenance (number of awakenings, wake after sleep onset, wake after persistent sleep onset, maximum duration of awakenings, total sleep time, and sleep efficiency). This study did not demonstrate an effect on sleep latency using this model of transient insomnia possibly due to subjects' excessive nascent sleep drive. The study model as conducted may be more sensitive at discriminating effects on sleep maintenance than sleep latency. Alternatively, a given dose of gabapentin may have a more pronounced effect on sleep maintenance than sleep latency. A large portion of the population in the United States has sleep complaints, the majority of which relate to sleep maintenance rather than sleep latency; the number of awakenings is a particularly common

complaint. Therefore, the preferential effect of gabapentin on sleep maintenance in this model addresses a substantial need.

Both doses of gabapentin were well-tolerated. No deaths or SAEs were reported and there were no discontinuations from the study. Of the 309 subjects randomized, only 3.9% of subjects who received placebo or gabapentin 250 mg and 1.9% of subjects who received gabapentin 500 mg reported AEs.

Overall, this study demonstrated that gabapentin 250 and 500 mg were effective in improving sleep maintenance in subjects who underwent phase advance, a model of transient insomnia. Indices reflecting sleep quality and next-day refreshment were also significantly improved, compared to placebo. Neither gabapentin dose had an adverse impact on memory or next-day performance. Daytime sleepiness was significantly improved by gabapentin 500 mg, compared to placebo. Based on these results, both gabapentin 250 and 500 mg are safe and effective treatments of impaired sleep maintenance due to transient insomnia.