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**PROPRIETARY DRUG NAME<sup>®</sup>/GENERIC DRUG NAME:** Neurontin<sup>®</sup>/Gabapentin

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

**NCT NO:** NCT00667108

**PROTOCOL NO.:** A9451140

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

**Study Centers:** Eight centers in the United States enrolled subjects

**Study Initiation and Completion Dates:** 21 October 2004 to 21 January 2005

**Phase of Development:** Phase 3

**Study Objective:**

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

*Secondary Objective:* 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 study of gabapentin 250 mg and 500 mg in subjects with transient insomnia induced by a sleep phase advance. Subjects stayed overnight (sleep period) in a sleep facility and subjective assessments were conducted at the end of the sleep period.

The study included the following 2 visits:

- **Screening Visit (Visit 1):** Evaluations performed 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). At this visit, vital signs (pulse rate, blood pressure and respiratory rate) were recorded. An alcohol

breathalyzer test and urine pregnancy test (for women of childbearing potential) were conducted for each subject. . Subjects were dosed at 4:30 pm ( $\pm$  3 minutes), went to bed 30 minutes later and were awakened 8 hours later. . Fifteen minutes ( $\pm$  5 minutes) after awakening, subjects were instructed to begin completing the following subjective sleep assessments:

- Sleep Latency
- Number of Awakenings
- Wake After Sleep Onset
- Total Sleep Time
- Assessment of Sleep Refreshment
- 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:* A total of 756 subjects were planned (252 in each treatment group).

*Analyzed:* A total of 784 subjects were randomized (262 subjects to placebo and 261 subjects each to gabapentin 250 mg and gabapentin 500 mg). All subjects were analyzed for efficacy except 3 subjects who discontinued (1 per treatment group). All 784 subjects were analyzed for safety.

**Diagnosis and Main Criteria for Inclusion:** Males or females at least 18 years of age with typical and consistent duration of sleep, bedtime hours, and time of awakening were enrolled 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:** 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:** All adverse events (AEs) and serious events (SAEs) that occurred during the study were recorded in the case record form. Vital signs were measured pre- and postdose.

**Statistical Methods:** Unless otherwise specified, between-treatment comparisons were based on pairwise t-tests from ANOVA (Analysis of Variance) 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 were 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. The primary statistical inference for each of the primary efficacy variable was based on a step-down (SD2L) procedure.

## RESULTS

**Subject Disposition and Demography:** A total of 1047 subjects were screened for this study. At Visit 1, 999 subjects met inclusion/exclusion criteria. Of the 999 subjects who qualified for Visit 2, 784 subjects were randomized (215 subjects were not randomized for various reasons).

Three subjects discontinued from the study after randomization (1 from each treatment group). Reasons for discontinuation were withdrawal of consent, protocol violation and an AE. Subject disposition is summarized in Table S1.

**Table S1 Subject Disposition and Subjects Analyzed**

<b>Number of Subjects</b>	<b>Placebo N=262 n (%)</b>	<b>Gabapentin 250 mg N=261 n (%)</b>	<b>Gabapentin 500 mg N=261 n (%)</b>
Subjects Randomized	262 (100)	261 (100)	261 (100)
Randomized, Not Meeting Criteria <sup>a</sup>	7 (2.7)	8 (3.1)	12 (4.6)
Randomized Subjects, Discontinued	1 (0.4)	1 (0.4)	1 (0.4)
Randomized Subjects, Completed	261 (99.6)	260 (99.6)	260 (99.6)
Analyzed for Efficacy			
ITT	261 (99.6)	260 (99.6)	261 (100)
Subjects Evaluable <sup>b</sup>	252 (96.2)	251 (96.2)	254 (97.3)
Analyzed for Safety	262 (100)	261 (100)	261 (100)

<sup>a</sup> Subjects not meeting inclusion/exclusion/randomization criteria regardless of randomization (not including subjects with a pre-existing medical condition that was later determined to be a protocol deviation).

<sup>b</sup> No analysis was performed based on evaluable subjects

ITT+ Intent to Treat

The mean age of subjects was 31.8 years (range 18 to 71 years). The majority of subjects were female (58.4%) and white (58.3%). There were statistically significant differences among treatment groups for gender and weight. However, these were deemed not to have a meaningful impact on the study results. Demographic and baseline characteristics are summarized in Table S2.

**Table S2 Demographic and Baseline Characteristics (All randomized subjects)**

Variables	Placebo (N=262)	Gabapentin 250 mg (N=261)	Gabapentin 500 mg (N=261)	Total (N=784)	Overall p-value
<b>Age (years)</b>					
Mean (Range)	31.4 (18-71)	31.8 (18-69)	32.1 (18-66)	31.8 (18-71)	0.738 <sup>a</sup>
<b>Sex</b>					
Male (%)	107 (40.8)	124 (47.5)	94 (36.0)	325 (41.5)	0.030 <sup>b</sup>
Female (%)	155 (59.2)	137 (52.5)	167 (64.0)	459 (58.5)	
<b>Race</b>					
White (%)	149 (56.9)	151 (57.9)	157 (60.2)	457 (58.3)	0.812 <sup>b</sup>
Black (%)	53 (20.2)	49 (18.8)	53 (20.3)	155 (19.8)	
Hispanic (%)	38 (14.5)	45 (17.2)	36 (13.8)	119 (15.2)	
Asian or Pacific Islander (%)	15 (5.7)	13 (5.0)	12 (4.6)	40 (5.1)	
Other (%)	7 (2.7)	3 (1.1)	3 (1.1)	13 (1.7)	
<b>Height (inches)</b>					
Mean (Range)	66.8 (51-76)	67.4 (58-78)	66.9 (60-78)	67.0 (51-78)	
<b>Body weight (lb)</b>					
Mean (Range)	170.6 (98-324)	178.7 (94-356)	180.1 (101-374)	176.5 (94-374)	

<sup>a</sup>p-value are based on ANOVA model with terms for treatment and center

<sup>b</sup>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 4.2 for placebo, 4.2 for gabapentin 250 mg, and 4.4 for gabapentin 500 mg. There were no statistically significant differences between treatment groups for ESS Total Score.

**Efficacy Results:** There were statistically significant improvements in subjective total sleep time and both subjective sleep maintenance measures of wake after sleep onset and number of awakenings for gabapentin 250 mg and 500 mg treatment groups compared to the placebo treatment group. Though both gabapentin treatment groups did better than placebo for subjectively-measured sleep latency, there were no statistically significant differences for either gabapentin dose from placebo, although the value for gabapentin 500 mg approached statistical significance (p=0.057). There were statistically significant differences in the qualitative assessments of sleep for both gabapentin 250 mg and 500 mg treatment groups, compared to placebo. The results of primary and secondary efficacy variables are summarized in Table S3.

**Table S3 Primary and Secondary Efficacy Parameters**

Assessment	Placebo N=261	Gabapentin 250 mg N=260	Gabapentin 500 mg N=261
Sleep Latency (minutes) <sup>†</sup>	64.1(5.7)	51.4 (5.7)	49.9 (5.7)
Number of Awakenings	3.6 (0.2) <sup>a</sup>	3.3 (0.2) <sup>c</sup>	2.7 (0.2) <sup>b***</sup>
Wake After Sleep Onset (minutes)	96.1 (5.5) <sup>a</sup>	72.7 (5.5) <sup>b***</sup>	47.6 (5.5) <sup>***</sup>
Total Sleep Time (minutes)	321.86 (7.24)	359.72 (7.24) <sup>***</sup>	382.58 (7.22) <sup>***</sup>
Assessment of Sleep Refreshment	1.7 (0.07)	1.9 (0.07) <sup>*</sup>	1.9 (0.07) <sup>*</sup>
Assessment of Sleep Quality	1.9 (0.07)	2.2 (0.07) <sup>***</sup>	2.5 (0.07) <sup>***</sup>
Karolinska Sleep Diary-Sleep Quality Index	2.89 (0.06) <sup>c</sup>	3.22 (0.06) <sup>d***</sup>	3.57 (0.06) <sup>d***</sup>
Karolinska Sleep Diary-Sleep Quality	2.9 (0.07) <sup>c</sup>	3.2 (0.07) <sup>d***</sup>	3.6 (0.07) <sup>d***</sup>
Karolinska Sleep Diary-Calm Sleep	2.9 (0.08)	3.2 (0.08) <sup>d***</sup>	3.6 (0.08) <sup>d***</sup>
Karolinska Sleep Diary-Ease Falling Asleep	3.1 (0.08)	3.2 (0.08) <sup>b</sup>	3.5 (0.08) <sup>d***</sup>
Karolinska Sleep Diary-Slept Throughout	2.7 (0.11)	3.2 (0.11) <sup>***</sup>	3.6 (0.11) <sup>d***</sup>
Karolinska Sleep Diary-Ease Awakening	4.1 (0.06) <sup>c</sup>	4.1 (0.06) <sup>b</sup>	4.0 (0.06) <sup>d</sup>
Karolinska Sleep Diary-Well-Rested	2.9 (0.08) <sup>c</sup>	3.3 (0.08) <sup>b***</sup>	3.4 (0.08) <sup>d***</sup>
Karolinska Sleep Diary-Sufficient Sleep	3.1 (0.08) <sup>c</sup>	3.5 (0.08) <sup>b***</sup>	3.6 (0.08) <sup>d***</sup>

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

<sup>†</sup>Primary endpoint

KSD-SQI (Sleep Quality Index) is a composite score comprised of KSD-Sleep Quality, KSD-Calm Sleep, KSD-Ease Falling Sleep and KSD Slept Throughout

<sup>a</sup>n = 256 <sup>b</sup>n = 257 <sup>c</sup>n = 258 <sup>d</sup>n = 259 <sup>e</sup>n = 260

\* p<0.05 vs. placebo; \*\*p<0.01 vs. placebo; \*\*\*p<0.001 vs. placebo

Subjects who received gabapentin 500 mg had a statistically significantly better BSRT delayed recall score compared to subjects who received placebo. There were no other statistically significant differences in BSRT scores between the treatment groups. There were also no statistically significant differences in DSST score between the treatment groups. However, subjects who received gabapentin 500 mg reported less daytime sleepiness as measured by the SSS 5 hours after awakening compared to subjects who received placebo. Results for BSRT, DSST and SSS are summarized in Table S4.

**Table S4 Other Assessments**

Assessment	Placebo N=261 n (%)	Gabapentin 250 mg N=260 n (%)	Gabapentin 500 mg N=261 n (%)
Buschke Selective Reminding Test			
Immediate Recall Score	46.7 (0.69)	47.7 (0.69)	47.3 (0.69)
Long Term Storage Score	39.1 (1.05)	41.3 (1.05)	41.3 (1.05)
Total Number of Intrusions	1.2 (0.11)	1.1 (0.11)	1.2 (0.11)
Delayed Recall Score	8.0 (0.16)	8.3 (0.16)	8.4 (0.16) <sup>*</sup>
Digit Symbol Substitution Test	71.1 (1.10)	73.3 (1.10)	71.8 (1.10)
Stanford Sleepiness Scale	2.5 (0.09)	2.4 (0.09)	2.3 (0.09) <sup>*</sup>

All numbers presented are adjusted mean (SE) \* p<0.05 vs. placebo

**Safety Results:** There were no deaths or SAEs reported during the study. One subject (a 27 year old female) discontinued due to an AE (worsening menstrual cramps). The menstrual cramps resolved 2 days later. The investigator deemed the worsening of menstrual cramps unlikely to be related to the investigational product.

Of those randomized, 54 subjects (6.9%) reported at least 1 AE after dosing; 14 (5.3%), 14 (5.4%), and 26 (10.0%) subjects in the placebo, gabapentin 250 mg and gabapentin 500 mg groups, respectively. The majority of AEs were mild and 2 severe AEs were reported: worsening menstrual cramps in the gabapentin 250 mg group and headache in the gabapentin 500 mg group. The incidence of AEs reported by > 3 subjects in any treatment group are presented in Table S5.

**Table S5 Incidence of All Causality Adverse Events (Reported by > 3 Subjects in Any Treatment Group)**

Adverse Event	Placebo N=262 n (%)	Gabapentin 250 mg N=261 n (%)	Gabapentin 500 mg N=261 n (%)
Subjects with at Least 1 AE	14 (5.3)	14 (5.4)	26 (10.0)
Headache	10 (3.8)	6 (2.3)	12 (4.6)
Dizziness	2 (<1.0)	1 (<1.0)	10 (3.8)
Nausea	1 (<1.0)	2 (<1.0)	6 (2.3)

A total of 43 subjects (5.5%) reported at least 1 treatment-related AE after dosing; 10 (3.8%), 10 (3.8%) and 23 (8.8%) in the placebo, gabapentin 250 mg and gabapentin 500 mg treatment groups, respectively. The incidence of treatment-related AEs reported by > 3 subjects in any treatment group are presented in Table S6.

**Table S6 Incidence of Treatment-Related Adverse Events (Reported by > 3 Subjects in Any Treatment Group)**

Adverse Event	Placebo N=262 n (%)	Gabapentin 250 mg N=261 n (%)	Gabapentin 500 mg N=261 n (%)
Subjects with at Least 1 Event	10 (3.8)	10 (3.8)	23 (8.8)
Headache	7 (2.7)	5 (1.9)	10 (3.8)
Dizziness	2 (<1.0)	1 (<1.0)	10 (3.8)
Nausea	0	2 (<1.0)	6 (2.3)

**Vital Signs, Physical Findings and Other Observations Related to Safety:** There were no meaningful differences among treatment groups for any vital sign. Mean changes from predose in pulse rate, blood pressure and respiratory rate are presented in Table S7.

**Table S7 Vital Signs: Mean Changes from Predose**

Vital Sign	Placebo N=262	Gabapentin 250 mg N=261	Gabapentin 500 mg N=261
Systolic Blood Pressure	-3.4	-4.6	-2.9
Diastolic Blood Pressure	1.4	0.7	1.6
Respiratory Rate	-0.3	-0.6	-0.2
Pulse Rate	-6.8	-6.5	-6.3

**Conclusions:** This study demonstrated gabapentin's positive effects on sleep in this transient insomnia model. Furthermore, the study demonstrated gabapentin's positive effect on the overall qualitative aspects of sleep, including the refreshing and restorative qualities of sleep. However, a statistically significant effect on sleep latency was not demonstrated although the effect of gabapentin 500 mg on this parameter did approach statistical significance. This lack of effect on sleep latency may possibly be 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, compared to a drug that would primarily affect sleep latency and not sleep maintenance.

Gabapentin 500 mg also reduced next day sleepiness. Neither dose of gabapentin had an adverse impact on memory or next day performance.

Both doses of gabapentin were well tolerated. No deaths or SAEs were reported and only 1 subject discontinued from the study due to an AE. This AE was not considered to be related to study treatment by the investigator.

Based on these results, both gabapentin 250 mg and 500 mg are safe and effective treatments of impaired sleep maintenance due to transient insomnia.