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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.:** NCT00666796

**PROTOCOL NO.:** A9451149

**PROTOCOL TITLE:** A Randomized, Double-Blind, 4-Way Crossover, Placebo-Controlled, Single Center Trial to Evaluate the Potential Pharmacodynamic Interaction Between Gabapentin 500 mg and Ethanol in Healthy Volunteers

**Study Centers:** One center in the United States enrolled subjects.

**Study Initiation and Completion Dates:** 01 April 2005 – 19 May 2005

**Phase of Development:** Phase 3

**Study Objectives:**

Primary Objective: To measure and compare psychometric responses, influences on memory, and sleepiness before and after an oral single dose of gabapentin 500 mg (2 capsules of 250 mg) or placebo (2 placebo capsules) and either oral ethanol 0.7 g/kg or placebo ethanol 0.4%

Secondary Objective: To summarize the adverse event (AE) profile reported after an oral single dose of gabapentin 500 mg (two 250 mg capsules) or placebo (2 placebo capsules) in combination with oral ethanol 0.7 g/kg or placebo ethanol 0.4%

**METHODS**

**Study Design:** This was a randomized, double-blind, 4-way crossover, placebo-controlled, single-center trial to evaluate the potential pharmacodynamic interaction between gabapentin 500 mg and ethanol 0.7 g/kg in healthy volunteers. Subjects were randomized to 1 of 4 treatment sequences to receive either gabapentin or placebo and ethanol or placebo ethanol at 4 separate treatment periods. The washout between the 4 treatment periods was 1 week. Psychometric tests, including assessment of psychomotor performance, influence on memory and learning, cognition and motor speed, and sleepiness were performed before dosing and repeated at 2 and 6 hours after the dose of gabapentin or placebo. Sleepiness was also assessed at 7.5 hours after the dose of gabapentin or placebo. The study comprised of the following

visits: Screening Visit (Visit 1), Visit 2, Visit 3, Visit 4, and Visit 5. The assessments made are given below:

**Screening Visit:** Subjects were screened for trial participation at Visit 1. Evaluations done at this visit included medical history, demography, vital signs, physical examination, serum and urine pregnancy test (if female and of child bearing potential), laboratory tests, Psychomotor Vigilance Task (PVT), Buschke Selective Reminding Test (BSRT), and Digit Symbol Substitution Test (DSST). Subjects who met all inclusion/exclusion criteria were randomized to one of the treatment sequences between days 5–14 from Visit 1.

**Visit 2:** At Visit 2, subjects were administered a breath ethanol concentration test, a urine pregnancy test (if female and of childbearing potential), and completed the Epworth Sleepiness Scale. The continuation criteria were assessed and any new concomitant medication or change in this medication was reviewed. Eligible subjects were randomized to 1 of the 4 treatment sequences. Subjects then completed the assessments overnight and were discharged the following morning.

**Visits 3, 4, and 5:** The above-mentioned procedures at Visit 2 were repeated at Visits 3, 4 and 5. The washout period between Visits 2, 3, 4 and 5 was at least 1 week.

#### **Number of Subjects (Planned and Analyzed):**

*Planned:* The study plan was to enroll enough subjects to ensure that 16 subjects completed the study.

*Analyzed:* A total of 16 subjects were analyzed for efficacy. Up to 20 subjects were analyzed for safety.

**Diagnosis and Main Criteria for Inclusion:** Healthy volunteers aged 21–50 years, weighing between 50–100 kg (110–220 lbs) with mild to moderate alcohol use (ie, maximum 14 units of alcoholic drinks per week) were included.

**Study Treatment:** Subjects were administered 4 treatments according to pre-specified sequences at least 7 days apart on days 1, 8, 15 and 22 at Visits 2 through 5 according to a randomized dosing schedule.

The following treatments were administered in the study:

- A. Placebo + placebo ethanol
- B. Gabapentin 500 mg + ethanol 0.7 g/kg
- C. Placebo + ethanol 0.7 g/kg
- D. Gabapentin 500 mg + placebo ethanol

Each treatment consisted of 2 oral capsules of either gabapentin 250 mg or placebo with 8 oz of water 120 minutes before the first assessment time point, followed by either oral ethanol 0.7 g/kg or placebo ethanol 0.4% in 300 mL as an orange juice cocktail 60 minutes after gabapentin dosing. The entire cocktail was consumed within 15 minutes under the supervision of the research site staff.

**Efficacy Evaluations:** All subjects performed a psychomotor vigilance task (PVT) for 10 minutes at 0.5 hours before and 2 and 6 hours after investigational product administration to assess reaction time. Subjects used a commercially available instrument, the PVT-192 (Ambulatory Monitoring, Inc; Ardsley, NY), to record simple reaction time to a visual stimulus, a bright red light. Subjects were instructed to press a response button as soon as they saw the stimulus. The interstimulus interval varied randomly from 2 to 10 seconds over the 10-minute task duration with approximately 80 to 90 responses per trial. Response times longer than 500 milliseconds were counted as lapses.

Subjects assessed their sleepiness at 0.5 hours before and 2, 6, and 7.5 hours after investigational product administration using the self-administered Stanford Sleepiness Scale. The scale describes 7 levels of sleepiness varying from “1 - feeling active, vital, alert, or wide awake” to “7 - no longer fighting sleep, sleep onset soon; having dream-like thoughts.”

All subjects were administered the Buschke Selective Reminding Test (BSRT) at 0.5 hours before and 2 and 6 hours after investigational product administration. The BSRT consisted of 6 trials performed consecutively and 1 delayed recall trial performed 15 minutes after the completion of the first 6 trials. Subjects listened to a list of words read at a rate of one word per 2 seconds, after which subjects attempted to recall all the words in any order (free recall). Subjects were then selectively reminded only those words that were missed and requested to recall the entire word list again. This sequence was repeated 5 more times unless the subject recalled all the words twice in a row.

All subjects were administered the Digit Symbol Substitution Test (DSST) 0.5 hours before and 2 and 6 hours after investigational product administration. The DSST was administered on a paper form using rows of numbers from 1 to 9 in random sequence. Subjects were instructed to match the number in the box to a symbol in a key at the top of the form and write in the symbol. Subjects were given 2 minutes to write as many correct symbols as possible in the blank square below each number. The score assigned was the number of correctly completed items.

Breath ethanol concentration (B<sub>r</sub>AC) was measured using the Draeger Alcotest<sup>®</sup> 6510 (Draeger Safety Diagnostics, Inc., Irving, TX) alcohol specific sensor technology starting 15 minutes after the consumption of the orange juice-ethanol cocktail or placebo ethanol cocktail until the first assessment time point and every 30 minutes thereafter until the 7.5 hour assessment.

Before each investigational product administration, subjects completed the Epworth Sleepiness Scale (ESS) as part of the continuation criteria. The ESS is a simple, self-administered, paper-based questionnaire that quantifies level of sleepiness in eight situations that subjects rate on sleep propensity from 0 (would never doze) to 3 (high chance of dozing). The score is the total of eight individual scores ranging from 0 to 24.

**Safety Evaluations:** Safety evaluations included AEs recorded throughout the study period and vital signs (blood pressure [BP], pulse, and respirations) taken before and prior to cocktail at 1 pm, prior to psychomotor test battery at 3 pm and 7 pm and after SSS at 8.30 pm at specified times (Visits 1–5) after trial treatment administration.

**Statistical Methods:** The primary efficacy variable was the change from pre-dose in the PVT at the first assessment time point (2 hours post-dose) in subjects who completed all 4 treatment visits.

All secondary efficacy variables were pharmacodynamic variables and included the change from pre-dose in the following:

- PVT 6 hours post-dose (completed subjects)
- PVT at 2 hours (ITT subjects)
- PVT at 6 hours (ITT subjects)
- BSRT at 2 hours post-dose (completed subjects)
- BSRT at 6 hours post-dose (completed subjects)
- BSRT at 2 hours post-dose (ITT subjects)
- BSRT at 6 hours post-dose (ITT subjects)
- DSST at 2 hours post-dose (completed subjects)
- DSST at 6 hours post-dose (completed subjects)
- DSST at 2 hours post-dose (ITT subjects)
- DSST at 6 hours post-dose (ITT subjects)
- SSS at 2 hours post-dose (completed subjects)
- SSS at 6 hours post-dose (completed subjects)
- SSS at 7.5 hours post-dose (completed subjects)
- SSS at 2 hours post-dose (ITT subjects)
- SSS at 6 hours post-dose (ITT subjects)
- SSS at 7.5 hours post-dose (ITT subjects)

The primary analysis for pharmacodynamic variables was based on subjects who completed all treatment visits of the trial. In addition, subjects were required to have PVT data at all treatment periods. The secondary analysis for pharmacodynamic variables was based on the ITT subjects, defined as all randomized subjects who took investigational product and had any post-treatment pharmacodynamic assessment data.

The change from pre-dose scores was analyzed using an ANCOVA model that included Sequence, Period, Treatment, Time (2 levels, 2 hours, and 6 hours post-dose), Period\*Time, and Treatment\*Time as fixed effects, subject within sequence as random effect, and pre-dose score as a covariate. The covariance matrix of compound symmetry was used.

To evaluate the effect of gabapentin on psychomotor performance relative to ethanol, the following comparisons were made for all variables on the change-from-pre-dose scores:

- Gabapentin + Ethanol 0.7 g/kg vs. Placebo + Ethanol 0.7 g/kg

- Gabapentin + Ethanol 0.7 g/kg vs. Gabapentin + Placebo ethanol
- Gabapentin + Ethanol 0.7 g/kg vs. Placebo + Placebo ethanol
- Placebo ethanol vs. Placebo + Ethanol 0.7 g/kg
- Gabapentin + Placebo ethanol vs. Placebo + Placebo ethanol
- Placebo + Ethanol 0.7 g/kg vs. Placebo + Placebo ethanol

All statistical comparisons were performed at a significance level of 0.05, two-sided.

Safety data was summarized for all randomized subjects. AEs occurring prior to the treatment period (onset prior to the first dosing date) were also summarized for all subjects (randomized and non-randomized subjects). AEs were summarized by Primary System Organ Class and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) dictionary and by treatment, giving the number of subjects (incidence), the percentage of subjects (incidence rate) and the total number of events reported. Vitals signs were summarized by treatment and assessment time (actual value and change from pre-dose) using descriptive statistics (mean, median, standard deviation [SD], minimum and maximum).

## RESULTS

**Subject Disposition and Demography:** A total of 23 subjects were screened, 20 of whom were randomized and treated. Of the 23 subjects, 2 subjects did not meet inclusion/exclusion criteria (screen failures), and a third subject discontinued before randomization. The 20 randomized subjects received at least 1 treatment with investigational product, 19 of whom completed double-blind treatment. Three subjects did not have PVT data for all treatment periods as required and were excluded from complete subject analysis.

- Completed Subjects: The 16 subjects who completed the study, ranged in age from 21–49 years (mean 36.5 years). Of these, 8 subjects were males and 8 subjects were females.
- The ITT Subjects: The ITT subject population ranged in age from 21–49 years (mean 36.1 years). Of these, 9 subjects were males and 11 subjects were females.

The demographic and baseline characteristics for the completed and ITT subjects are presented in Tables S1 and S2.

**Table S1. Demographic and Baseline Characteristics – Complete Subjects**

Variables	Complete subjects <sup>a</sup> Treatment sequence <sup>b</sup>					p-value
	ABDC (N=5)	BCAD (N=3)	CDBA (N=5)	DACB (N=3)	Total (N=16)	
Age (years)						
Mean	36.0	46.0	35.0	30.0	36.5	0.306 <sup>c</sup>
Range	23–48	40–49	26–47	21–37	21–49	
Race (No.(%) of subjects)						
Black	2(40.0)	2(66.7)	2(40.0)	1(33.3)	7(43.8)	0.855 <sup>d</sup>
Hispanic	3(60.0)	1(33.3)	3(60.0)	2(66.7)	9(56.3)	
Sex(No.(%) of subjects)						
Male	2(40.0)	2(66.7)	3(60.0)	1(33.3)	8(50.0)	0.801 <sup>d</sup>
Female	3(60.0)	1(33.3)	2(40.0)	2(66.7)	8(50.0)	
Weight (lb)						
Mean	157.4	175.7	165.2	182.3	167.9	0.791 <sup>c</sup>
Range	124–181	154–194	134–216	116–247	116–247	
Height (in)						
Mean	64.2	66.7	67.2	65.0	65.8	0.737 <sup>c</sup>
Range	60–70	64–68	63–72	59–73	59–73	

<sup>a</sup> Subjects who had PVT data at pre-dose and at least one post-dose time point for all 4 periods.

<sup>b</sup> A = Placebo + Placebo Ethanol, B = Gabapentin 500 mg + Ethanol 0.7 g/kg, C= Placebo + Ethanol 0.7 g/kg, D = Gabapentin 500 mg + Placebo Ethanol

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

<sup>d</sup> p-value based on Cochran-Mantel-Haenszel, stratified by center

**Table S2. Demographic and Baseline Characteristics - ITT Subjects**

Variables	Complete Subjects <sup>a</sup> Treatment Sequence <sup>b</sup>					p-value
	ABDC (N=5)	BCAD (N=5)	CDBA (N=5)	DACB (N=5)	Total (N=20)	
Age(years)						
Mean	36.0	41.2	35.0	32.2	36.1	0.633 <sup>c</sup>
Range	23–48	25–49	26–47	21–49	21–49	
Race(No.(%) of subjects)						
White	0	0	0	1(20.0)	1(5.0)	0.525 <sup>d</sup>
Black	2(40.0)	4(80.0)	2(40.0)	2(40.0)	10(50.0)	
Hispanic	3(60.0)	1(20.0)	3(60.0)	2(40.0)	9(45.0)	
Sex(No.(%) of subjects)						
Male	2(40.0)	2(40.0)	3(60.0)	2(40.0)	9(45.0)	0.902 <sup>d</sup>
Female	3(60.0)	3(60.0)	2(40.0)	3(60.0)	11(55.0)	
Weight(lb)						
Mean	157.4	172.4	165.2	172.4	166.9	0.875 <sup>c</sup>
Range	124–181	144–194	134–216	116–247	116–247	
Height (in)						
Mean	64.2	65.4	67.2	65.0	65.7	0.718 <sup>c</sup>
Range	60–70	63–68	63–72	59–73	59–73	

<sup>a</sup> Subjects who had PVT data at pre-dose and at least 1 post-dose time point for all four periods.

<sup>b</sup> A = Placebo + Placebo Ethanol, B = Gabapentin 500 mg + Ethanol 0.7 g/kg, C= Placebo + Ethanol 0.7 g/kg, D = Gabapentin 500 mg + Placebo Ethanol

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

<sup>d</sup> p-value based on Cochran-Mantel-Haenszel, stratified by center

There were no clinically meaningful differences among the subjects in each of the 4 treatment sequences with respect to demographics for the complete subjects and the ITT population.

**Efficacy Results:** There were no statistically significant differences among treatment groups in the adjusted mean change from pre-dose at 2 hours post-dose in the primary pharmacodynamic variable PVT - Mean of the Slowest 10% of Reciprocal Reaction Time (PVT-Mean SRRT) for subjects who completed all 4 treatment visits. The addition of gabapentin to ethanol did not appear to potentiate ethanol's impairment such that it could be detected in this model. Findings were similar for 6 hours post-dose.

Primary Efficacy Evaluation: The primary variable, PVT - Mean SRRT, adjusted mean change from pre-dose at 2 hours post-dose for complete subjects is presented in Table S3.

**Table S3. Psychomotor Vigilance Task: Mean Slowest 10% Reciprocal Reaction Time, Change from Pre-dose (Complete Subjects)**

PVT Mean slowest 10% RRT 2 hour change from baseline	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Mean	-0.38	-0.29	-0.24	-0.39
Standard deviation	0.498	0.658	0.616	0.482
Median	-0.26	-0.45	-0.18	-0.41
(Min, Max)	(-1.5, 0.2)	(-1.1, 0.9)	(-1.3, 0.6)	(-1.5, 0.2)
Adjusted mean	-0.31	-0.35	-0.30	-0.43
Pairwise comparisons				
vs placebo + placebo ethanol	–	0.802 <sup>a</sup>	0.946 <sup>a</sup>	0.484 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.751 <sup>a</sup>	0.649 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.433 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.788 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.465 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate. PVT=Psychomotor Vigilance Task; RRT=Reciprocal Reaction Time  
 N=Total Number of Subjects

There was no significant difference in the PVT - Mean SRRT adjusted mean change from pre-dose at 2 hours post-dose for complete subjects between the 4 treatment groups. Results were similar for adjusted mean change from pre-dose at 6 hours post-dose.

Secondary Efficacy Evaluations:

*Psychomotor Vigilance Task:* The adjusted mean change from pre-dose at 2 and 6 hours post-dose for the secondary PVT variables for complete subjects is presented in Tables S4 and S5.

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**Table S4. Psychomotor Vigilance Task: Secondary Variables Adjusted Mean Change from Pre-dose to 2 Hours Post-dose (Complete Subjects)**

PVT Variables	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
<b>Mean Fastest 10% Reaction Time</b>				
Adjusted mean (s.e.)	5.78 (7.181)	24.06 (7.176)	8.23 (7.179)	18.55 (7.178)
vs placebo + placebo ethanol	–	0.030 <sup>a</sup>	0.771 <sup>a</sup>	0.132 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.062 <sup>a</sup>	0.513 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.216 <sup>a</sup>
<b>Median Reaction Time</b>				
Adjusted mean (s.e.)	42.37 (26.814)	129.61 (26.835)	34.85 (26.845)	59.56 (27.101)
vs placebo + placebo ethanol	–	0.011 <sup>a</sup>	0.827 <sup>a</sup>	0.620 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.007 <sup>a</sup>	0.046 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.471 <sup>a</sup>
<b>Number of Lapses</b>				
Adjusted mean (s.e.)	6.9 (3.28)	11.6 (3.29)	6.8 (3.28)	8.6 (3.30)
vs placebo + placebo ethanol	–	0.249 <sup>a</sup>	0.969 <sup>a</sup>	0.682 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.241 <sup>a</sup>	0.472 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.649 <sup>a</sup>
<b>Transformed Number of Lapses</b>				
Adjusted mean (s.e.)	1.46 (0.765)	2.25 (0.764)	1.28 (0.764)	2.16 (0.766)
vs placebo + placebo ethanol	–	0.352 <sup>a</sup>	0.828 <sup>a</sup>	0.418 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.257 <sup>a</sup>	0.919 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.295 <sup>a</sup>
<b>Reciprocal Reaction Time - slope</b>				
Adjusted mean (s.e.)	-0.0032 (-0.01973)	0.0243 (0.01974)	0.0016 (0.1976)	0.0725 (0.01983)
vs placebo + placebo ethanol	–	0.284 <sup>a</sup>	0.854 <sup>a</sup>	0.005 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.388 <sup>a</sup>	0.070 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.007 <sup>a</sup>
<b>Reciprocal Reaction Time - intercept</b>				
Adjusted mean (s.e.)	-0.28 (0.156)	-0.67 (0.156)	-0.29 (0.156)	-0.90 (0.156)
vs placebo + placebo ethanol	–	0.052 <sup>a</sup>	0.974 <sup>a</sup>	0.003 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.061 <sup>a</sup>	0.261 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.003 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

PVT=Psychomotor Vigilance Task

N=Total Number of Subjects

*Mean Fastest 10% Reaction Time:* Significant difference in the Mean Fastest 10% Reaction Time adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was seen for placebo + placebo ethanol (5.78) and placebo + ethanol (24.06) treatment groups. The placebo + placebo ethanol treatment group had a significantly faster mean fastest 10% reaction time than the placebo + ethanol treatment group. The Mean Fastest 10% Reaction Time adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was 24.06 for placebo + ethanol and 18.55 for gabapentin 500 mg + ethanol treatment groups. There was no significant difference between these two treatment groups. There were no significant differences between the other treatment groups.

*Median Reaction Time:* Significant difference in the Median Reaction Time adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was seen for placebo + placebo ethanol (42.37) group and placebo + ethanol (129.61) treatment groups. The placebo + placebo ethanol treatment group had a significantly faster median reaction time than the placebo + ethanol treatment group. The Median Reaction Time adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was 129.61 for placebo + ethanol and 59.56 for gabapentin 500 mg + ethanol treatment groups. There was a significant difference between these 2 treatment groups. The gabapentin 500 mg + placebo ethanol treatment group had a significantly faster median reaction time than the placebo + ethanol treatment group. There were no significant differences between the other treatment groups.

*Number of Lapses and Transformed Number of Lapses:* There was no significant difference between the 4 treatment groups in Number of Lapses adjusted mean change and the Transformed Number of Lapses adjusted mean change from pre-dose at 2 hours post-dose for complete subjects.

*Reciprocal Reaction Time Slope:* The Reciprocal Reaction Time Slope adjusted mean change from pre-dose at 2 hours post-dose was significantly different between the placebo + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups; and the gabapentin 500 mg + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups. There was a significant difference between the 2 ethanol treatment groups and the 2 placebo ethanol treatment groups. There was no significant difference between other treatment groups.

*Reciprocal Reaction Time Intercept:* The Reciprocal Reaction Time Intercept adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was -0.28 for placebo + placebo ethanol and -0.67 for placebo + ethanol treatment groups. There was no significant difference between these two treatment groups though the difference approached significance ( $p=0.052$ ). The Reciprocal Reaction Time Intercept adjusted mean change from pre-dose at 2 hours post-dose was significantly different between the placebo + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups. The Reciprocal Reaction Time Intercept adjusted mean change from pre-dose at 2 hours post-dose was significantly different between the gabapentin 500 mg + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups. There was a significant difference between the 2 ethanol treatment groups and the 2 placebo ethanol treatment groups. There was no significant difference between other treatment groups.

**Table S5. Psychomotor Vigilance Task: Secondary Variables Adjusted Mean Change from Pre-dose to 6 Hours Post-dose (Complete Subjects)**

PVT Variables	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
<b>Mean Fastest 10% Reaction Time</b>				
Adjusted mean (s.e.)	-3.70(7.181)	0.39 (7.176)	-11.56 (7.179)	-7.19 (7.178)
vs placebo + placebo ethanol	–	–	0.353 <sup>a</sup>	0.679 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.062 <sup>3a</sup>	0.158 <sup>a</sup>	0.370 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.599 <sup>a</sup>
<b>Median Reaction Time</b>				
Adjusted mean (s.e.)	1.06 (26.814)	17.36 (26.835)	-16.71 (26.845)	-2060 (27.101)
vs placebo + placebo ethanol	–	–	0.606 <sup>a</sup>	0.533 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.629 <sup>a</sup>	0.323 <sup>a</sup>	0.276 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.910 <sup>a</sup>
<b>Number of Lapses</b>				
Adjusted mean (s.e.)	1.0 (3.28)	5.2 (3.29)	-2.4 (3.28)	-2.8 (3.30)
vs placebo + placebo ethanol	–	–	0.402 <sup>a</sup>	0.360 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.303 <sup>a</sup>	0.066 <sup>a</sup>	0.057 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.934 <sup>a</sup>
<b>Transformed Number of Lapses</b>				
Adjusted mean (s.e.)	0.72 (0.765)	1.12 (0.764)	-0.67 (0.764)	-0.20 (0.766)
vs placebo + placebo ethanol	–	0.633 <sup>a</sup>	0.107 <sup>a</sup>	0.288 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.038 <sup>a</sup>	0.126 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.575 <sup>a</sup>
<b>Reciprocal Reaction Time - slope</b>				
Adjusted mean (s.e.)	0.0513 (0.01973)	-0.0016 (0.01974)	-0.0085 (0.01976)	0.0015 (0.01983)
vs placebo + placebo ethanol	–	–	0.025 <sup>a</sup>	0.061 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.041 <sup>a</sup>	0.791 <sup>a</sup>	0.906 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.695 <sup>a</sup>
<b>Reciprocal Reaction Time - intercept</b>				
Adjusted mean (s.e.)	-0.37 (0.156)	-0.15 (0.156)	0.21 (0.156)	0.05 (0.156)
vs placebo + placebo ethanol	–	–	0.005 <sup>a</sup>	0.040 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.270 <sup>a</sup>	0.082 <sup>a</sup>	0.326 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.432 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

PVT=Psychomotor Vigilance Task

N=Total Number of Subjects

Buschke Selective Reminding Test (BSRT): The adjusted mean change from pre-dose at 2 and 6 hours post-dose for the BSRT is presented in Tables S6 and S7.

**Table S6. Buschke Selective Reminding Test Scores: Change from Pre-dose at 2 Hours Post dose (Complete Subjects)**

BSRT Variables	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
<b>Immediate Recall Score</b>				
Adjusted mean	-3.2	-5.2	-3.0	-9.3
vs placebo + placebo ethanol	–	0.579 <sup>a</sup>	0.959 <sup>a</sup>	0.089 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.547 <sup>a</sup>	0.242 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.074 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.438 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.097 <sup>a</sup>
<b>Delayed Recall Score</b>				
Adjusted mean	-1.3	-2.4	-1.4	-3.5
vs placebo + placebo ethanol	–	0.071 <sup>a</sup>	0.883 <sup>a</sup>	<0.001 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.103 <sup>a</sup>	0.069 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	<0.001 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.170 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				<0.001 <sup>a</sup>
<b>Total Number of Intrusions</b>				
Adjusted mean	-0.4	0.6	-0.5	1.5
vs placebo + placebo ethanol	–	0.366 <sup>a</sup>	0.929 <sup>a</sup>	0.095 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.337 <sup>a</sup>	0.438 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.077 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.634 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.065 <sup>a</sup>
<b>Long-Term Storage Score</b>				
Adjusted mean	-3.1	-4.5	-3.8	-10.2
vs placebo + placebo ethanol	–	0.766 <sup>a</sup>	0.878 <sup>a</sup>	0.130 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.888 <sup>a</sup>	0.220 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.165 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.336 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.232 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

BSRT=Buschke Selective Reminding Test

N=Total Number of Subjects

*BSRT Scores, Change From Pre-Dose At 2 Hours Post Dose (Complete Subjects):* No significant difference was observed for the 4 treatment groups in terms of the Immediate Recall Score, Long-Term Storage Score, and Total Number of Intrusions. The Delayed Recall Score adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was significantly different between the placebo + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups and was significantly different between the gabapentin 500 mg + placebo ethanol and gabapentin 500 mg + ethanol treatment groups. There was a significant difference between the 2 ethanol treatment groups and the 2 placebo ethanol treatment groups. There was no significant difference between the other treatment groups.

**Table S7. Buschke Selective Reminding Test Scores: Change from Pre-dose at 6 Hours Post dose (Complete Subjects)**

BSRT Variables	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
<b>Immediate Recall Score</b>				
Adjusted mean	3.1	-0.3	-0.4	-3.1
vs placebo + placebo ethanol	–	–	0.329 <sup>a</sup>	0.084 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.328 <sup>a</sup>	0.985 <sup>a</sup>	0.438 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.443 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.223 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.216 <sup>a</sup>
<b>Delayed Recall Score</b>				
Adjusted mean	0.0	-0.6	-1.3	-0.7
vs placebo + placebo ethanol	–	–	0.028 <sup>a</sup>	0.218 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.290 <sup>a</sup>	0.240 <sup>a</sup>	0.843 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.321 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.096 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.964 <sup>a</sup>
<b>Total Number of Intrusions</b>				
Adjusted mean	-0.7	0.4	-0.2	1.7
vs placebo + placebo ethanol	–	0.366 <sup>a</sup>	0.686 <sup>a</sup>	0.040 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.631 <sup>a</sup>	0.246 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.096 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.279 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.073 <sup>a</sup>
<b>Long-Term Storage Score</b>				
Adjusted mean	5.8	-0.0	2.3	-3.3
vs placebo + placebo ethanol	–	0.211 <sup>a</sup>	0.458 <sup>a</sup>	0.056 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	–	0.621 <sup>a</sup>	0.490 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.230 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.318 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.083 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

BSRT=Buschke Selective Reminding Test

N=Total Number of Subjects

Digit Symbol Substitution Test: The adjusted mean change from pre-dose at 2 and 6 hours post-dose for the DSST for complete subjects is presented in Tables S8 and S9.

**Table S8. Digit Symbol Substitution Test, Change from Pre-dose at 2 Hours Post dose (Complete Subjects)**

DSST Score	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Adjusted mean	-5.1	-17.6	-9.2	-6.8
vs placebo + placebo ethanol	-	<0.001 <sup>a</sup>	0.284 <sup>a</sup>	0.650 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	-	-	0.026 <sup>a</sup>	0.005 <sup>a</sup>
vs Gaba + placebo ethanol	-	-	-	0.528 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.221 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.054 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

DSST=Digit Symbol Substitution Test

N=Total Number of Subjects

The DSST adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was -5.1 for placebo + placebo ethanol and -17.6 for placebo + ethanol treatment groups. There was a significant difference between these two treatment groups. The placebo + placebo ethanol was significantly better than the placebo + ethanol treatment group.

The DSST adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was -17.6 for placebo + ethanol and - 6.8 for gabapentin 500 mg + ethanol treatment groups. There was a significant difference between these 2 treatment groups. The gabapentin 500 mg + ethanol treatment group was significantly better than the placebo + ethanol treatment group.

The DSST was significantly different between the placebo + ethanol and the gabapentin 500 mg + placebo ethanol treatment groups. The gabapentin 500 mg + placebo ethanol treatment group was significantly better than the placebo + ethanol treatment group. There was no significant difference between the 2 ethanol treatment groups and the 2 placebo ethanol treatment groups though the difference approached significance (p=0.054). There was no significant difference between the other treatment groups.

**Table S9. Digit Symbol Substitution Test, Change from Pre-dose at 6 Hours Post dose (Complete Subjects)**

DSST Score	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Adjusted mean	-6.2	-7.5	-4.7	-1.9
vs placebo + placebo ethanol	-	-	0.695 <sup>a</sup>	0.267 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	-	0.175 <sup>a</sup>	0.451 <sup>a</sup>	0.140 <sup>a</sup>
vs Gaba + placebo ethanol	-	-	-	0.454 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.197 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.787 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

DSST=Digit Symbol Substitution Test

N=Total Number of Subjects

Stanford Sleepiness Scale: The adjusted mean change from pre-dose at 2 and 6 hours post-dose for the SSS for complete subjects is presented in Tables S10 and S11.

**Table S10. Stanford Sleepiness Scale, Change from Pre-dose at 2 Hours Post-dose (Complete Subjects)**

SSS Score	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Adjusted mean	0.0	1.3	0.0	1.2
vs placebo + placebo ethanol	-	<0.001 <sup>a</sup>	0.965 <sup>a</sup>	<0.001 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	-	-	<0.001 <sup>a</sup>	0.774 <sup>a</sup>
vs Gaba + placebo ethanol	-	-	-	<0.001 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.866 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				<0.001 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

SSS=Stanford Sleepiness Scale

N=Total Number of Subjects

The SSS adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was 0.0 for placebo + placebo ethanol and 1.3 for placebo + ethanol. There was a significant difference between these 2 treatment groups. The placebo + placebo ethanol was significantly less sleepy than the placebo + ethanol treatment group.

The SSS adjusted mean change from pre-dose at 2 hours post-dose for complete subjects was 1.3 for placebo + ethanol and 1.2 for gabapentin 500 mg + ethanol treatment groups. There was no significant difference between these 2 treatment groups.

The SSS was significantly different between the placebo + ethanol and the gabapentin 500 mg + placebo ethanol treatment groups and the gabapentin 500 mg + placebo ethanol and the gabapentin 500 mg + ethanol treatment groups. All the ethanol treatment groups reported greater sleepiness.

There was a significant difference seen between the 2 ethanol treatment groups and the 2 ethanol placebo treatment groups; the ethanol treatment groups reported greater sleepiness. There was no significant difference between other treatment groups.

**Table S11. Stanford Sleepiness Scale, Change from Pre-dose at 6 Hours Post-dose (Complete Subjects)**

SSS Score	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Adjusted mean	0.3	1.0	0.4	0.8
vs placebo + placebo ethanol	–	–	0.810 <sup>a</sup>	0.092 <sup>a</sup>
vs placebo + ethanol 0.7 g/kg	–	0.029 <sup>a</sup>	0.053 <sup>a</sup>	0.628 <sup>a</sup>
vs Gaba + placebo ethanol	–	–	–	0.139 <sup>a</sup>
Comparison of 2 groups with gabapentin vs 2 groups with placebo				0.866 <sup>a</sup>
Comparison of 2 groups with ethanol 0.7 g/kg vs 2 groups with placebo ethanol				0.010 <sup>a</sup>

<sup>a</sup> p-values are based on an ANCOVA model with Sequence, Period, Treatment, Time, Period\*Time, and Treatment\*Time as fixed effects, subjects within sequence as random effects, and pre-dose score as covariate.

SSS=Stanford Sleepiness Scale

N=Total Number of Subjects

Breath Ethanol Concentration Measurements: Table S12 shows the highest mean breath ethanol concentration at 1.25 hours after gabapentin dosing (15 minutes after consumption of the orange juice-ethanol cocktail) in completed subjects.

**Table S12. Breath Ethanol Concentration Measurements (g/dL) by Treatment, Trial Hour 1.25 (Completed Subjects)**

Breath Ethanol Concentration (g/dL) Trial Hour 1.25	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Mean	0.0000	0.0501	0.0000	0.0412
Standard deviation	0.00000	0.08713	0.00000	0.01920
Median	0.0000	0.0325	0.0000	0.0395
(Min, Max)	(0.000, 0.000)	(0.000, 0.368)	(0.000, 0.000)	(0.000, 0.077)

N=Total Number of Subjects

The highest mean breath ethanol concentrations were seen at the 1.25 hour time point (15 minutes after consumption of the orange juice-ethanol cocktail), 0.0501 g/dL for placebo + ethanol 0.7 g/kg and 0.0412 g/dL for gabapentin + ethanol 0.7 g/kg. In general, the breath ethanol values were lower than expected with a wide range of values obtained. In the placebo + ethanol 0.7 g/kg group, 2 subjects had no detectable ethanol.

No ethanol was detected in subjects who received placebo ethanol with either gabapentin or placebo, except 1 subject who had detectable ethanol reported for Period 1 when gabapentin + placebo ethanol was administered.

Table S13 shows the mean breath ethanol concentration at 2.0 hours after gabapentin dosing (1 hour after consumption of the orange juice-ethanol cocktail) in completed subjects.

**Table S13. Breath Ethanol Concentration Measurements (g/dL) by Treatment, Trial Hour 2.0 (Completed Subjects)**

Breath Ethanol Concentration (g/dL) Trial Hour 1.25	Placebo + Placebo Ethanol (N=16)	Placebo + Ethanol 0.7 g/kg (N=16)	Gabapentin 500 mg + Placebo Ethanol (N=16)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=16)
Mean	0.0000	0.0451	0.0000	0.0511
Standard deviation	0.00000	0.02514	0.00000	0.01711
Median	0.0000	0.0525	0.0000	0.0520
(Min, Max)	(0.000, 0.000)	(0.000, 0.083)	(0.000, 0.000)	(0.000, 0.076)

N=Total Number of Subjects

The mean breath ethanol concentrations at 2.0 hours after gabapentin dosing (1 hour after consumption of the orange juice-ethanol cocktail) was 0.0451 g/dL for placebo + ethanol 0.7 g/kg and 0.0511 g/dL for gabapentin + ethanol 0.7 g/kg. No ethanol was detected in subjects who received placebo ethanol with either gabapentin or placebo.

No interim analyses was conducted for this study and due to small sample size, no subgroup analysis was performed. Results of the ITT analysis were similar to those for complete subjects at all time points for all variables.

Epworth Sleepiness Scale: The mean baseline Epworth Sleepiness Scale was between 1.9 and 2.9 for the groups. There were no statistically significant differences between the groups with regards to the baseline Epworth Sleepiness Scale (p=0.357).

**Safety Results:** No deaths or SAEs were reported during the study. No subjects discontinued as a result of an AE.

Overall, 6 of 20 subjects who received at least one dose of investigational product reported 15 AEs. Of the 6 subjects reporting AEs, 3 subjects accounted for 12 of the 15 reported events.

Crying was the most frequent AE (experienced by 4 subjects). The most frequently reported AEs by system organ class were psychiatric disorders (5 subjects); these included crying (4 subjects) and hallucination (1 subject) reported during treatments with the presence of ethanol. Table S14 shows the incidence of AEs for all randomized subjects reported during the double-blind treatment period.

**Table S14. Summary of AEs During Double-Blind Treatment Period**

Preferred Term	Placebo + Placebo Ethanol (N=19)	Placebo + Ethanol 0.7 g/kg (N=19)	Gabapentin 500 mg + Placebo Ethanol (N=19)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=20)
	n (%)	n (%)	n (%)	n (%)
<b>Subjects with at least 1 AE</b>	<b>2 (10.5)</b>	<b>4 (21.2)</b>	<b>0</b>	<b>4 (20.0%)</b>
Crying	0	2 (10.5)	0	2 (10.0)
Hallucination	0	1 (5.3)	0	0
Flushing	0	0	0	2 (10.0)
Lacrimation increased	0	0	0	1 (5.0)
Nausea	0	0	0	1 (5.0)
Oesophageal pain	0	1 (5.3)	0	0
Periorbital hematoma	1 (5.3)	0	0	0
Headache	1 (5.3)	1 (5.3)	0	0
Rash	0	1 (5.3)	0	0
Urticaria	0	1 (5.3)	0	0

N=Total Number of Subjects; n=Number of Subjects; AE=Adverse Event

No AEs were related to treatment with gabapentin alone. AEs related to ethanol consisted of crying which occurred in 2 subjects during both placebo + ethanol 0.7 g/kg and gabapentin 500 mg + ethanol 0.7 g/kg treatment. One of these subjects reported an AE of crying on both occasions when she drank ethanol. No specific AEs can be attributed to the combination of ethanol and gabapentin. Table S15 shows the incidence of treatment-related AEs for all randomized subjects reported during the double-blind treatment period.

**Table S15. Incidence of Treatment-Related AEs During Double-Blind Treatment Period**

Preferred Term	Placebo + Placebo Ethanol (N=19)	Placebo + Ethanol 0.7 g/kg (N=19)	Gabapentin 500 mg + Placebo Ethanol (N=19)	Gabapentin 500 mg + Ethanol 0.7 g/kg (N=20)
	n (%)	n (%)	n (%)	n (%)
<b>Subjects with at least 1 AE</b>	<b>1 (5.3)</b>	<b>3 (15.8)</b>	<b>0</b>	<b>4 (20.0)</b>
Crying	0	2 (10.5)	0	2 (10.0)
Hallucination	0	1 (5.3)	0	0
Flushing	0	0	0	2 (10.0)
Lacrimation increased	0	0	0	1 (5.0)
Nausea	0	0	0	1 (5.0)
Headache	1 (5.3)	1 (5.3)	0	0
Rash	0	1 (5.3)	0	0
Urticaria	0	1 (5.3)	0	0

N=Total Number of Subjects; n=Number of Subjects; AE=Adverse Event

No AE was reported more than twice. All AEs were mild or moderate and did not require intervention. No trends were seen for changes in BP, pulse, or respirations during the trial.

No clinical laboratory evaluations were performed after the screening examinations. No trends were identified in vital signs and no new or clinically meaningful safety issues arose during the conduct of the trial. One subject was discontinued from the trial at Visit 2 prior to administration of any investigational product because of elevated BP and tachycardia. Vital signs were obtained at admission to the unit instead of prior to dispensing of any treatment as specified in the protocol. Since no treatment was administered, the elevated BP and tachycardia were not recorded as AEs.

**Conclusions:** In this randomized, double-blind, 4-way crossover, placebo-controlled, single center trial of the potential pharmacodynamic interaction between gabapentin 500 mg and ethanol in healthy volunteers, gabapentin did not appear to significantly potentiate ethanol-induced impairment of psychomotor performance, memory and learning, and cognition and motor speed as measured by the PVT, BSRT, and DSST. A subjective measure of sleepiness, the Stanford Sleepiness Scale, was strongly significant for differences between ethanol-treated subjects and non-treated subjects. Gabapentin did not potentiate the effect of ethanol for subjectively-rated sleepiness.

The incidence of AEs did not increase when gabapentin was administered in conjunction with ethanol. Neither any specific AE nor the overall frequency of AEs increased with the addition of gabapentin in any treatment group. No trends were identified in vital signs and no new or clinically meaningful safety issues arose during the conduct of the trial.

Gabapentin in combination with ethanol did not produce significant additional decrements in the pharmacodynamic parameters measured, as compared to ethanol alone, in this subject population under the conditions of the trial.