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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00603473

PROTOCOL NO.: A9451162

PROTOCOL TITLE: An Open-Label, Multicenter Study Evaluating, the Efficacy, Safety and Pharmacokinetics of Gabapentin as Adjunctive Therapy in Pediatric Patients With Partial Seizures When Other Antiepileptic Drugs Do Not Provide Satisfactory Effects

Study Center(s): Twenty-seven (27) centers in Japan

Study Initiation and Completion Dates: 10 January 2008 to 24 December 2009

Phase of Development: Phase 3

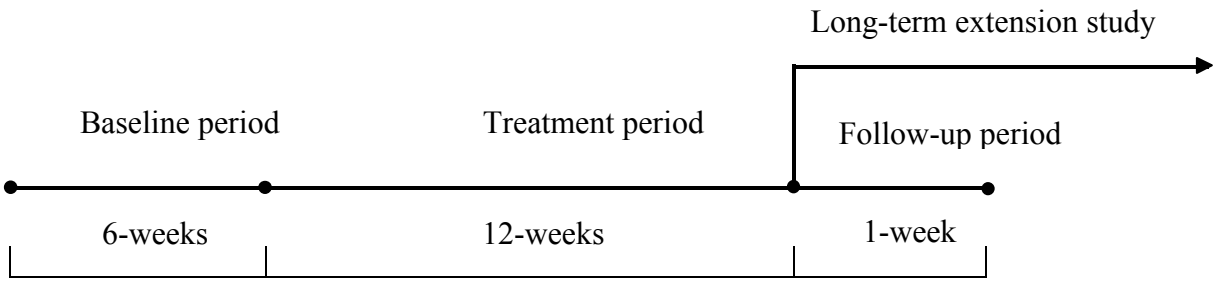
Study Objective(s): The study evaluated the efficacy, safety and pharmacokinetics of gabapentin administered for 12 weeks as adjunctive therapy in pediatric epilepsy patients with partial seizures (with or without secondarily generalized seizures) without a satisfactory response to other antiepileptic drugs. To demonstrate the efficacy, it was confirmed that the upper limit of the 95% confidence interval (CI) of the Response Ratio (R Ratio) (mean) for gabapentin in the present study would be below the R Ratio (least squares mean) for placebo in an international study (Protocol No. 945-86/186) conducted outside of Japan.

METHODS

Study Design: This study was an open-label, non-controlled multicenter study in pediatric epilepsy patients with partial seizures without a satisfactory response to other antiepileptic drugs.

Subject's participation consisted of a 6-week baseline period, a 12-week treatment period, and a 1-week follow-up period. Subjects who had completed the treatment period and wanted to continue gabapentin therapy were provided with an opportunity of entering a 52-week long-term extension study (Protocol No. A9451165). Subjects who had completed the treatment period and did not want to continue gabapentin therapy or who were withdrawn from the study entered the follow-up period, where the study treatment was tapered off over 1 week to complete it 1 week after the end of treatment period or withdrawal. The study design is outlined in Figure 1.

Figure 1. Study Design



Number of Subjects (Planned and Analyzed):

Planned: 95 subjects to be enrolled and 85 subjects to be included in the primary efficacy analysis population (modified intent-to-treat [MITT] population).

Analyzed: 90 subjects were enrolled, 89 subjects were treated and 86 subjects were included MITT population.

Diagnosis and Main Criteria for Inclusion: To be enrolled in the study, subjects were required to be aged between 3 and 15 years, have partial seizures (defined by the International League Against Epilepsy; with or without secondary generalized seizures) which could not be controlled satisfactorily with existing antiepileptic drugs, to have experienced at least 4 seizure episodes within the 6-week baseline period and at least 1 episode for each 2 weeks of the baseline period, and to be receiving 1 to 3 antiepileptic drugs at screening.

Study Treatment:

(1) Treatment period

As shown in Table 1, subjects received gabapentin three times daily for a duration of 12 weeks (each dosing interval should not exceed 12 hours). The dosage of oral solution for subjects aged 3 to 12 years was calculated based on their body weight. As shown in Table 2, the dose was titrated for the first 3 days of the treatment period. After Day 3, the dose was adjusted if necessary within the range of maintenance doses. As a general rule, dose adjustment was done at planned visits. The maximum daily dose was 600 mg for Day 1, 1200 mg for Day 2, and 1800 mg for Day 3 and thereafter.

Table 1. Study Drug

Drug	Potency	Formulation
gabapentin	250 mg/5 mL	Oral solution containing 250 mg of gabapentin per 5 mL
	200 mg	Film-coated tablets containing 200 mg of gabapentin per tablet

Table 2. Formulation and Dosage of Gabapentin by Age

Age	3, 4 years	5 to 12 years	13 to 15 years
Formulation	250 mg/5 mL Oral solution		200 mg tablet
Day 1	10 mg/kg/day[a]	10 mg/kg/day[a]	600 mg/day
Day 2	20 mg/kg/day[b]	20 mg/kg/day[b]	1200 mg/day
After Day 3 (maintenance doses)	40 mg/kg/day[c]	25 to 35 mg/kg/day[c]	1200 mg or 1800 mg/day

a: The daily dose should not exceed 600 mg.
b: The daily dose should not exceed 1200 mg.
c: The daily dose should not exceed 1800 mg.

(2) Follow-up period

Subjects who had completed the treatment period and did not want to continue gabapentin therapy or who were withdrawn from the study entered the follow-up period, where the study treatment was tapered off over 1 week to complete it 1 week after the end of treatment period or withdrawal.

(3) Entry into the long-term extension study (A9451165)

Subjects who had completed the treatment period and wanted to continue gabapentin therapy entered the 52-week long-term extension study (A9451165). These subjects entering the long-term study started to receive study drugs for the long-term study at Week 12 visit.

Efficacy Evaluations:

(1) Primary endpoint

The R Ratio calculated by the following equation was assessed as the primary endpoint:

R Ratio = (T−B) / (T+B)

T = seizure frequency per 28 days (i.e., the number of seizures per 28 days) calculated from the total number of seizures for the 12-week treatment period

B = seizure frequency per 28 days (i.e., the number of seizures per 28 days) calculated from the total number of seizures for the 6-week baseline period

(2) Secondary endpoints

The following 3 variables were assessed as secondary endpoints:

- Responder rate (defined as the proportion of subjects with a 50% or greater reduction in the seizure frequency per 28 days for the 12-week treatment period in comparison with the frequency per 28 days for the 6-week baseline period)

- Percent change in seizure frequency (PCH)
  PCH = 100 (T−B) / B

• R Ratio and PCH for individual types of partial seizures

Pharmacokinetic Evaluations: Pharmacokinetics of gabapentin in pediatric subjects were evaluated as secondary endpoint, based on gabapentin concentrations in plasma samples collected at Weeks 4 (Visit 4), 8 (Visit 5), 12 (Visit 6) / Early termination visit.

Safety Evaluations: As secondary endpoint, adverse events, serious adverse events, withdrawals due to adverse events, results of clinical laboratory tests, blood pressure, pulse rate, body weight, and 12-lead electrocardiogram (ECG).

Statistical Methods:

Efficacy analysis

In the study, the MITT and intent-to-treat (ITT) populations were used as primary and secondary efficacy analysis populations, respectively. Each population was defined as follows:

MITT population: Subjects who have received the study medication for at least 28 days and in whom the number of epileptic seizures used for efficacy assessment has been counted for at least 28 days in both the baseline and treatment periods.

ITT population: Subjects who have received at least 1 dose of the study medication and in whom the number of epileptic seizures used for efficacy assessment has been counted in both the baseline and treatment periods.

In the analysis of the primary efficacy endpoint, it was confirmed that the upper limit of the 95% CI of the R Ratio (mean) for gabapentin in the present study would be below the R Ratio (least squares mean) of −0.072 for placebo in the international study (945-86/186). The MITT population was used as the primary efficacy analysis population. The same analysis was done in the ITT population used as the secondary efficacy analysis population to assess the robustness of analytical results from the MITT population. The secondary endpoints were also analyzed in both the MITT and ITT populations. For the PCH regarded as a continuous variable, summary statistics (five-number summary, mean, standard deviation, and 95% CI) were calculated. The responder rate and its 95% CI were estimated, with whether or not the responder criteria were met as a binary variable.

Pharmacokinetic analysis

To assess the pharmacokinetics of gabapentin in pediatric subjects, a population pharmacokinetic analysis was performed in pediatric subjects with at least 1 measurement of plasma gabapentin concentration after the start of study treatment.

Safety analysis

The safety analysis population consisted of subjects who received at least 1 dose of the study medication. Safety data and other observations were summarized and tabulated for clinical review in accordance with the sponsor's in-house standards, "Pfizer Data Standard (PDS)."

For adverse events, the incidences were tabulated by system organ class and by event. The incidences were also tabulated by causal relationship with the study drug and by severity of adverse event. Furthermore, data were summarized for clinical laboratory tests, blood pressure, pulse rate, body weight, height, 12-lead ECG, physical examination, and neurological examination.

RESULTS

Subject Disposition and Demography: Ninety (90) subjects were screened and enrolled in the study. Of them, 89 received the study treatment, while 1 withdrew consent. Of those enrolled, 80 subjects (88.9%) completed the study, whereas 9 (10.0%) were withdrawn from the study. The reason for withdrawal was reported as adverse events in 4 subjects, lack of efficacy in 4, and other in 1 (Table 3).

Among the subjects enrolled, 1 subject who did not receive the study medication because of consent withdrawal was excluded from the ITT and safety analysis populations. Eighty-six (86) subjects were included in the MITT population; those excluded from the population were 1 subject excluded from the ITT population, 2 subjects withdrawn from the study because of adverse events, and 1 subject meeting any exclusion criterion, with the duration of study treatment or epileptic seizure counting less than 28 days.

Table 3. Disposition of Patients (Number of Subjects [%])

Number of Subjects	
Assigned to Study Treatment	90
Treated	89
Completed	80 (88.9)
Discontinued	9 (10.0)
Related to Study Drug	7
Adverse event	3
Lack of efficacy	4
Not Related to Study Drug	2
Adverse event	1
Other[a]	1
Analyzed for Efficacy	
Intent to Treat (ITT)	89 (98.9)
Modified Intent to Treat (MITT)	86 (95.6)
Analyzed for Safety	
Adverse events	89 (98.9)
Laboratory data	89 (98.9)

a: A subject meeting any exclusion criterion.

Among the 89 subjects who received the study medication, the mean age was 8.7 years (range, 3 to 15 years), the mean body weight was 30.5 kg (range, 11.4 to 85.6 kg), the mean duration of disease was 6.6 years (range, 1.0 to 15.2 years), and 49 were males and 40 were females. The most common type of epileptic seizure was complex partial seizure in 91.0% of subjects. Simple partial and secondarily generalized seizures were found in 41.6% and 51.7%, respectively. Most subjects were using 3 (44.9%) or 2 (43.8%) concomitant

antiepileptic drugs. The highest proportion of the subjects (41.6%) had tried and failed 5 or more antiepileptic drugs on the baseline characteristics.

Efficacy Results: In the MITT population, the upper limit of the 95% CI for the mean R Ratio (Weeks 1 to 12), which was assessed as the primary endpoint, was −0.096; it was below the R Ratio (least squares mean) of −0.072 for placebo in the international study (945-86/186). The mean R Ratio for partial seizures by assessment period was −0.158 (95% CI, −0.221 to −0.096) for Weeks 1 to 12 (Table 4). Analytical results of R Ratio in the ITT population were the same as those in the MITT population and supported the MITT results.

Table 4. Response Ratio (MITT)

Number of Evaluable Subjects	86
R Ratio (Week 1 to Week 12, Mean)	−0.158
Standard deviation	0.2915
95% confidence interval [Lower Limit, Upper Limit]	[−0.221, −0.096]

In the MITT population, the responder rate for partial seizures by assessment period was 19.8% (17 responders) for Weeks 1 to 12 (Table 5). Analytical results of responder rate in the ITT population were the same as those in the MITT population and supported the MITT results.

Table 5. Responder Rate (MITT)

Number of Evaluable Subjects	86
Responder rate (Week 1 to Week 12, Mean)	19.8%
The Number of Responder	17
95% confidence interval [Lower Limit, Upper Limit]	[12.0, 29.8]

In the MITT population, the median PCH for partial seizures by assessment period was −24.4% for Weeks 1 to 12 (Table 6). Analytical results of PCH in the ITT population were the same as those in the MITT population and supported the MITT results.

Table 6. PCH [%] (MITT)

Number of Evaluable Subjects	86
PCH (Week 1 to Week 12)	
Median	−24.4
Range (Min, Max)	(−100.0, 192.9)

Analytical results of R Ratio, responder rate, and PCH by type of epileptic seizure (simple partial, complex partial, and secondarily generalized seizures) indicate a reduction in seizure frequency after treatment with gabapentin for all types of seizures. These effects were sustained throughout the treatment period.

Safety Results: In the study, 218 all-causality adverse events were reported in 78 of 89 subjects treated. Of them, 73 events in 47 subjects were assessed as treatment-related (Table 7). These adverse events were classified as mild or moderate in severity. No subject died in this study. All-causality serious adverse events occurred in 3 subjects, but no treatment-related serious adverse events were reported in the study. All-causality adverse events resulted in study withdrawal in 4 subjects and dose reduction or treatment interruption in 4 subjects. All of these events, except 1 resulting in study withdrawal, were assessed as treatment-related.

Table 7. Summary of Adverse Events

	All-causality	Treatment-related
Number of Subjects Analyzed for Safety	89	89
Number of subjects with an AE (%)	78 (87.6)	47 (52.8)
Number of AEs	218	73
Number of subjects with an SAE[a]	3	0
Number of subjects with a severe AE	0	0
Number of subjects withdrawn due to AEs (%)	4 (4.5)	3 (3.4)
Number of subjects with dose reduction or temporary interruption due to AEs (%)	4 (4.5)	4 (4.5)

a: The number of subjects with any serious adverse event was based on information from the safety database.

All-causality adverse events observed in ≥ 3% of subjects are presented in Table 8. Common all-causality adverse events (with an incidence of 10% or higher) were somnolence in 35 subjects (39.3%), nasopharyngitis in 24 subjects (27.0%), and influenza in 9 subjects (10.1%).

Table 8. All-causality Adverse Events (Incidence ≥ 3%)

Number of Subjects Analyzed for Safety MedDRA (version 12.1) Preferred Term	89
Number of subjects with an AE (%)	78 (87.6)
Somnolence	35 (39.3)
Nasopharyngitis	24 (27.0)
Influenza	9 (10.1)
Pharyngitis	7 (7.9)
Fall	7 (7.9)
Diarrhoea	6 (6.7)
Contusion	6 (6.7)
Pyrexia	5 (5.6)
Rash	5 (5.6)
Upper respiratory tract infection	4 (4.5)
Conjunctivitis	3 (3.4)
Nausea	3 (3.4)
Rhinitis	3 (3.4)
Excoriation	3 (3.4)
Increased appetite	3 (3.4)
Ataxia	3 (3.4)
Convulsion	3 (3.4)

Treatment-related adverse events observed in ≥ 2% of subjects are presented in Table 9. Common treatment-related adverse event was somnolence reported in 35 subjects (39.3%). Other treatment-related adverse events occurred in 3 subjects (3.4%) or less.

Table 9. Treatment-related Adverse Events (Incidence ≥ 2%)

Number of Subjects Analyzed for Safety	89
MedDRA (version 12.1) Preferred Term	
Number of subjects with an AE (%)	47 (52.8)
Somnolence	35 (39.3)
Convulsion	3 (3.4)
Increased appetite	3 (3.4)
Nausea	2 (2.2)
Salivary hypersecretion	2 (2.2)
Weight increased	2 (2.2)
Ataxia	2 (2.2)
Affect lability	2 (2.2)
Mood altered	2 (2.2)
Rash	2 (2.2)

A list of subjects who discontinued due to adverse events is presented in Table 10. Adverse events resulting in study withdrawal were reported in 4 subjects: rash in 1 subject, attention deficit/hyperactivity disorder in 1 subject, convulsion in 1 subject, and increased appetite and mood altered in 1 subject (2 events in 1 subject). These events were classified as mild or moderate, and none of them were assessed as serious. The rash, convulsion, and increased appetite and mood altered in 3 subjects were assessed as treatment-related. All the adverse events reported in the 4 subjects resolved with the discontinuation of treatment.

Table 10. Discontinuations Due to Adverse Events

Age/Sex	MedDRA (version 12.1) Preferred Term	Causality	Severity	Outcome
6/Female	Rash	Related	Moderate	Recovered
9/Female	Attention deficit/hyperactivity disorder	Unrelated	Moderate	Recovered
11/Male	Convulsion	Related	Moderate	Still present[a]
10/Female	Increased appetite	Related	Mild	Recovered
	Mood altered	Related	Mild	Recovered

a: Confirmed recovered at a follow-up.

No subject died in this study. Other serious adverse events are presented in Table 11. In the study, serious adverse events occurred in 3 subjects: pharyngitis reported during the treatment period in 1 subject, gastroenteritis reported before the start of study treatment in 1 subject, and bacterial infection reported after the completion of the study in 1 subject. All the events were assessed as not related to the study drug.

Table 11. Serious Adverse Events

Age/Sex	MedDRA (version 12.1) Preferred Term	Latest dose	Causality	Outcome
4/Male	Gastroenteritis	Predose	Not applicable	Recovered
13/Male	Pharyngitis	1800 mg/day	Not-related	Recovered
9/Male	Bacterial infection	100 mg/day	Not-related	Recovered

No severe or serious adverse events related to laboratory abnormalities were reported. No adverse events related to laboratory abnormalities resulted in treatment withdrawal, dose reduction, or treatment interruption.

CONCLUSION(S): An open-label, non-controlled multicenter study was conducted in Japan to evaluate the efficacy, safety and pharmacokinetics of gabapentin administered for 12 weeks as adjunctive therapy with other antiepileptic drugs in pediatric epilepsy subjects with partial seizures without a satisfactory response to other antiepileptic drugs.

In the MITT population, the mean R Ratio for partial seizures for the 12-week treatment period was −0.158 (95% CI, −0.221 to −0.096). This confirms that the upper limit of the 95% CI is below the R Ratio (least squares mean) of −0.072 for placebo in the international study (945-86/186).

Adverse events were reported in 78 of 89 subjects treated with gabapentin. These adverse events were classified as mild or moderate in severity. Common adverse events were somnolence, nasopharyngitis, and influenza. Adverse events resulting in study withdrawal were reported in 4 subjects (rash, attention deficit/hyperactivity disorder, convulsion, and increased appetite and mood altered). All the events resolved with the discontinuation of treatment. A serious adverse event (pharyngitis) was reported during the treatment period in 1 subject. The event was assessed as not related to the study drug.

Gabapentin was efficacious in this study as adjunctive therapy in pediatric epilepsy patients aged from 3 to 15 years old with other antiepileptic drugs. Gabapentin was safe and well tolerated in pediatric epilepsy patients in Japan.