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

PROTOCOL NO.: A9451165

PROTOCOL TITLE: A 52 weeks, open-label, multicenter study evaluating the efficacy and safety of gabapentin as adjunctive therapy in pediatric patients who have completed the 12 weeks treatment in Study A9451162 (Final report)

Study Center(s): 22 centers in Japan (excluding the center with no subject enrolled)

Study Initiation and Final Completion Dates: 28 May 2008 (date of the first informed consent) to 22 December 2010 (date of last observation)

Phase of Development: Phase 3

Study Objective(s): To evaluate the safety and efficacy of gabapentin administered for 52 weeks as concomitant therapy for the treatment of partial seizures (including secondarily generalized seizures) in pediatric epilepsy subjects who completed the treatment period of Study A9451162 and chose to continue gabapentin therapy.

METHODS

Study Design: This study was conducted in Japan as a multicenter, open-label, clinical study in pediatric epilepsy subjects who have completed the treatment period of the preceding Study A9451162 and who chose to continue gabapentin therapy. The present study consisted of a 52-week treatment period and a 1-week follow-up period. Subjects who completed the 52-week treatment period or were withdrawn from the study entered the 1-week follow-up period, where the study treatment was tapered off before it was completely terminated.

Study schedule is presented in Table 1.

Table 1. Study Schedule

Procedures	Treatment Period						Follow-Up Period
	Baseline Week 0	Week 8	Week 16	Week 24	Week 36	Week 52 or Withdrawal	1 week after Week 52 or Withdrawal
	Visit 1 [a)]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Acceptable Time Frame	-	±14 days	±14 days	±14 days	±14 days	±14 days	0 to +3 days
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Complications	(X)						
Body Temperature, Pulse Rate, Blood Pressure	(X)	X	X	X	X	X	X
Height	(X)	X	X	X	X	X	
Weight	(X)	X	X	X	X	X	X
Physical Examinations	(X)					X	X
Neurological Tests	(X)					X	X
Clinical Laboratory Test							
Hematology	(X)	X	X	X	X		X
Urinalysis	(X)	X	X	X	X		X
Pregnancy Test (urine) [b)]	(X)						X
Plasma Gabapentin Concentration [c)]		←				→	
Concomitant Medication, Therapy	(X)	X	X	X	X	X	X
Treatment Compliance		X	X	X	X	X	X
Evaluation of Seizures [d)]		X	X	X	X	X	
Adverse Events [e)]	←						→
Serious Adverse Events [f)]	←						→

(X): Test results conducted on Visit 6 of Study A9451162 was used.
a) Visit 6 of Study A9451162.
b) Only conducted on females of childbearing potential.
c) To be performed every visit if subject was given higher doses than those given in Study A9451162.
d) Baseline symptom characteristics of Study A9451162 were used as the baseline symptom characteristics for the present study.
e) Adverse events were reported from the first dose of study drug to 7 days after the last dose of study drug.
f) Serious adverse events were reported from the date of informed consent to 28 days after the last dose of study drug.

Number of Subjects (Planned and Analyzed):

Planned: Not Applicable

Analyzed: 65 subjects

Diagnosis and Main Criteria for Inclusion: Pediatric epilepsy subjects who chose to continue gabapentin therapy after completing the treatment period of Study A9451162, and were consented to participate in the present study by their parents or legal guardians were enrolled. Female subjects of childbearing potential were also required to have a negative urine pregnancy test result at baseline visit. Subjects with any of the following at baseline were excluded from the study: drug-related seizures or acute-phase disease; aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, blood

urea nitrogen (BUN), or creatinine level greater than or equal to twice the upper limit of normal; white blood cell counts below 3000/mm3; or neutrophil counts below 1500/mm3.

Study Treatment: Subjects received gabapentin three times daily for a duration of 52 weeks with dosing intervals not exceeding 12 hours. The doses were adjusted within the range of maintenance doses as shown in Table 2. However, they could be increased up to the maximum dose of 2400 mg per day, according to need.

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
Maintenance doses	40 mg/kg/day [a)]	25 to 35 mg/kg/day [a)]	1200 or 1800 mg/day
Maximum doses	50 mg/kg/day [b)]	50 mg/kg/day [b)]	2400 mg/day

a) The daily dose should not exceed 1800 mg.
b) The daily dose should not exceed 2400 mg.

Subjects who had completed the treatment period or who were discontinued from study entered the 1-week follow-up period, where the study treatment was tapered off before it was completely terminatd.

Efficacy Endpoints: As secondary endpoints, the Response Ratio (R Ratio), the responder rate, and the percent change in seizure frequency (PCH) were assessed at each visit during the 52-week treatment period in the study.

Pharmacokinetic Endpoints: As secondary endpoints, pharmacokinetics of gabapentin in pediatric subjects was evaluated.

Safety Evaluations: As the primary endpoint, the safety of gabapentin (adverse events, serious adverse events, discontinuation due to adverse events, results of clinical laboratory tests, blood pressure, pulse rate, and body weight) was assessed:

- Serious and non-serious adverse event monitoring (throughout study)
- Clinical laboratory testing/measurements (Weeks 8, 16, 24 and 36, and 1 week after completion/discontinuation)
- Blood pressure, pulse rate, and body weight measurements [Weeks 8, 16, 24, 36 and 52, at discontinuation (if applicable), and 1 week after completion/discontinuation]

Statistical Methods:

Efficacy Analysis: The intent-to-treat (ITT) population used as the efficacy analysis population consisted of subjects who received at least 1 dose of the study medication and in whom the number of seizures used for efficacy assessment had been counted in both the baseline and treatment periods. In order to assess the time course of seizure frequency, secondary endpoints (R Ratio and responder rate) were calculated at every visit from Week 1 to Week 52, which corresponds to 13 and 64 weeks from the start of gabapentin treatment, counting from the preceding Study (A9451162). The baseline symptom characteristics recorded at Study A9451162 was used as the baseline symptom characteristics for the present study.

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 according to formats and algorithms defined in Pfizer Data Standard. The baseline data recorded at Study A9451162 was used as the baseline data for the present study. Any adverse events occurring after start of treatment in the present study, or existing adverse events from preceding study increasing in severity after start of treatment in this study, will be counted as treatment emergent adverse events. 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 adverse event severity. Furthermore, data were summarized for clinical laboratory tests, blood pressure, pulse rate, body weight, physical examination and neurological examination.

RESULTS

Subject Disposition and Demography: Of the subjects who completed the treatment period in Study A9451162, all 65 subjects eligible for screening were enrolled to the present study and were treated with the study medication. Table 3 presents a summary of subject disposition and subjects analyzed.

Table 3. Subject Disposition and Subjects Analyzed

	Number of Subjects (%)
Enrolled	65
Treated	65
Completed	44 (67.7)
Discontinued	21 (32.3)
Adverse event	
Related to Study Drug	2 (3.1)
Not Related to Study Drug	2 (3.1)
Ineligibility based on the inclusion/exclusion criteria	2 (3.1)
Insufficient clinical response	12 (18.5)
Study consent withdrawal	1 (1.5)
Other [a)]	2 (3.1)
Analyzed for Efficacy	
Intent to Treat (ITT)	65 (100)
Analyzed for Safety	
Adverse events	65 (100)
Laboratory data	65 (100)

a) One chose to receive other treatment and another failed to make scheduled visit

Demographics and baseline characteristics are presented in Table 4.

Table 4. Demographics and Baseline Characteristics

Number of subjects evaluated		N=65
Sex, n	Males	38
	Females	27
Age (years), n (%)	3-4 years	8 (12.3)
	5-12 years	42 (64.6)
	≥13 years	15 (23.1)
	Mean (SD)	9.1 (3.6)
	Range	3-16
Weight (kg)	Mean (SD)	32.8 (16.8)
	Range	12-88
Duration of Disease (years)	Mean	6.8
	Range	1.4-15.5
Epileptic Seizure Type, n (%)	Simple Partial	27 (41.5)
	Complex Partial	59 (90.8)
	Secondarily Generalized	35 (53.8)
Number of Concomitant Antiepileptic Drugs, n (%)	1	7 (10.8)
	2	25 (38.5)
	3	33 (50.8)
Number of Concomitant Antiepleptic Drug History, n (%)	0	5 (7.7)
	1	7 (10.8)
	2	15 (23.1)
	3	12 (18.5)
	4	7 (10.8)
	≥5	19 (29.2)

Efficacy Results: In the ITT population, the mean R Ratio for partial seizures at each assessment time point ranged from −0.327 to −0.256 during the treatment periods, and there was no great fluctuation in the response (Table 5).

Table 5. R Ratio (ITT)

Period	Week 1 to 8	Week 9 to 16	Week 17 to 24	Week 25 to 36	Week 37 to 52
Number of Subjects	65	60	58	54	47
Mean	–0.263	–0.256	–0.300	–0.280	–0.327
Standard deviation	0.3141	0.3513	0.3671	0.3753	0.3712
95% CI [Lower Limit, Upper Limit]	[–0.341, –0.185]	[–0.347, –0.166]	[–0.396, –0.203]	[–0.382, –0.177]	[–0.436, –0.218]

R Ratio = (T−B) / (T＋B)
T = the total number of seizures at each assessment time point converted to seizure frequency per 28 days (i.e., the number of seizures per 28 days)
B = the total number of seizures for the 6-week baseline period converted to seizure frequency per 28 days (i.e., the number of seizures per 28 days)
CI= confidence interval

In the ITT population, the responder rate for partial seizures was maintained in the range of 35.4% to 46.8% throughout the treatment period after the start of treatment (Table 6).

Table 6. Responder Rate (ITT)

Period	Week 1 to 8	Week 9 to 16	Week 17 to 24	Week 25 to 36	Week 37 to 52
Number of Subjects	65	60	58	54	47
Number of Responder	23	24	23	22	22
Responder Rate (%)	35.4	40.0	39.7	40.7	46.8
95% CI [Lower Limit, Upper Limit]	[23.9, 48.2]	[27.6, 53.5]	[27.1, 53.4]	[27.6, 55.0]	[32.1, 61.9]

CI= confidence interval

In the ITT population, the median PCH resulted in the range of –49.2 to –33.0 during the treatment period (Table 7).

Table 7. PCH (ITT)

Period	Week 1 to 8	Week 9 to 16	Week 17 to 24	Week 25 to 36	Week 37 to 52
Number of Subjects	65	60	58	54	47
Median	–34.2	–33.0	–42.0	–41.6	–49.2
Range (Min, Max)	(–100.0, 63.1)	(–100.0, 99.8)	(–100.0, 112.5)	(–100.0, 110.7)	(–100.0, 131.7)

PCH = 100(T−B) / B
T = the total number of seizures at each assessment time point converted to seizure frequency per 28 days (i.e., the number of seizures per 28 days)
B = the total number of seizures for the 6-week baseline period converted to seizure frequency per 28 days (i.e., the number of seizures per 28 days)

Pharmacokinetic Results: Pharmacokinetic results are described in the report prepared separately.

Safety Results: In this study, 207 all-causality adverse events were reported in 58 (89.2%) of 65 subjects, and 17 treatment-related adverse events were reported in 13 (20.0%) of 65 subjects. An overview of adverse events is presented in Table 8.

Table 8. Summary of Adverse Events

	All-Causality	Treatment-Related
Subjects evaluable for safety	65	65
Number of subjects with an AE (%)	58 (89.2)	13 (20.0)
Number of AEs	207	17
Number of subjects with a serious AE	2 (3.1)	0
Number of subjects with a severe AE	1 (1.5)	0
Number of subjects withdrawn due to AEs (%)	4 (6.2)	2 (3.1)
Number of subjects with dose reduction or temporary interruption due to AEs (%)	2 (3.1)	2 (3.1)

All-causality adverse events (with an incidence of 5 % or higher), not including serious adverse events, are presented in Table 9. The most common all-causality adverse events were nasopharyngitis in 28 subjects (43.1%), somnolence in 10 subjects (15.4%), influenza in 9 subjects (13.8%), pyrexia in 8 subjects (12.3%), and diarrhoea in 7 subjects (10.8%). Of all adverse events (207 events), most of them were classified as mild (190 events) or moderate (15 events) in severity.

Table 9. All-Causality Non-Serious Adverse Events (Incidence ≥5%)

MedDRA System Organ Classs Preferred Term (ver.13.1)	N (%)
Subjects evaluable for adverse events	65
Gastrointestinal Disorders	
Dental caries	5 (7.7)
Diarrhoea	7 (10.8)
Vomiting	4 (6.2)
General Disorders and Administration Site Conditions	
Pyrexia	8 (12.3)
Infections and Infestations	
Bronchitis	4 (6.2)
Influenza	9 (13.8)
Nasopharyngitis	28 (43.1)
Pharyngitis	4 (6.2)
Upper respiratory tract infection	4 (6.2)
Injury, Poisoning and Procedural Complications	
Arthropod bite	4 (6.2)
Fall	4 (6.2)
Nervous system Disorders	
Somnolence	10 (15.4)
Skin and Subcutaneous Tissue Disorders	
Eczema	4 (6.2)

Treatment-related adverse events, not including serious adverse events, are presented in Table 10. All the events were classified as mild or moderate in severity.

Table 10. Treatment-Related Non-Serious Adverse Events

MedDRA System Organ Classs Preferred Term (ver.13.1)	N (%)
Subjects evaluable for adverse events	65
Gastrointestinal Disorders	
Salivary hypersecretion	1 (1.5)
Infections and Infestations	
Nasopharyngitis	1 (1.5)
Investigations	
Blood alkaline phosphatase increased	1 (1.5)
Metabolism and Nutrition Disorders	
Decreased appetite	1 (1.5)
Nervous System Disorders	
Convulsion	1 (1.5)
Somnolence	7 (10.8)
Psychiatric Disorders	
Aggression	1 (1.5)

No deaths were reported in this study. Serious adverse events occurred in 2 subjects in this study (Table 11). All the events were assessed as not related to the study drug.

Table 11. Serious Adverse Events

	Age/Sex	MedDRA (version 13.1) Preferred Term	Latest dose	Causality	Outcome
1	9/Female	Encephalopathy	765 mg	Unrelated	Recovered
		Status epilepticus	765mg	Unrelated	Recovered
2	10/Male	Bronchopneumonia	600 mg	Unrelated	Recovered

Adverse events that resulted in treatment discontinuation are presented in Table 12. The adverse events considered not related to the study drug were mild convulsion in 1 subject, severe and serious encephalopathy and status epilepticus in 1 subject. Moderate agitation (1 subject) and mild aggression (1 subject) were considered related to the study drug. All aforementioned events resolved after treatment discontinuation.

Table 12. Discontinuations Due to Adverse Events

	Age/Sex	MedDRA (version 13.1) Preferred Term	Causality	Severity	Outcome
1	3/Male	Convulsion	Unrelated	Mild	Recovered
2	9/Female	Encephalopathy	Unrelated	Severe	Recovered
		Status epilepticus	Unrelated	Severe	Recovered
3	10/Female	Agitation	Related	Moderate	Unrecovered [a)]
4	9/Male	Aggression	Related	Mild	Unrecovered [a)]

a) Confirmed recovered at a follow-up.

Two subjects experienced adverse events related to study drug (mild somnolence and mild insomnia) and underwent dose reduction. Both events resolved after dose reduction.

No severe or serious adverse events related to laboratory abnormalities were reported. No adverse events related to laboratory abnormalities resulted in treatment discontinuation, dose reduction, or treatment interruption. The results of physical examination showed gingival swelling in 1 subject; the event was assessed as not related to the study drug. No clinically significant abnormal findings were noted for other safety-related tests.

CONCLUSION(S): This study was conducted to evaluate the safety and efficacy of gabapentin administered for 52 weeks as concomitant therapy in pediatric epilepsy subjects with partial seizures (including secondarily generalized seizures) who completed the treatment period of the preceding Study A9451162 and chose to continue gabapentin therapy.

In the study, all 65 subjects received the study medication. Of these 65 subjects, 44 (67.7%) completed the study, and 21 (32.3%) were discontinued from the study.

The mean R Ratio and responder rate for all partial seizures at each assessment point were in the range of −0.327 to −0.256 and 35.4% to 46.8%, respectively. The median PCH for all partial seizures at each assessment point were in the range of −49.2 to −33.0. These results suggest that long-term administration has no significant influence on the effect of gabapentin.

All-causality adverse events were reported in 58 of the 65 subjects enrolled. Common adverse events were nasopharyngitis, somnolence, influenza, pyrexia, and diarrhoea. Serious adverse events occurred in 2 subjects. These events were considered not related to the study drug. Other adverse events reported in the study were classified as mild or moderate in severity. Treatment-related adverse events were reported in 13 of the 65 subjects enrolled. The most common treatment-related adverse event was somnolence. Treatment-related adverse events were all classified as mild in severity, except for somnolence, convulsion and agitation all experienced in 1 subject each, which were classified to be moderate. Four adverse events resulted in treatment discontinuation, and all of such events resolved after treatment discontinuation. No new safety and tolerability related concerns about long-term gabapentin administration was indicated from the study results; the adverse event profiles observed in this study showed no significant difference to those seen in overseas study (Study 945-86/186) or the preceding study (Study A9451162).

These study results demonstrate the safety, tolerability and efficacy of long-term administration of gabapentin in pediatric epilepsy patients with partial seizures.