2 STUDY SYNOPSIS

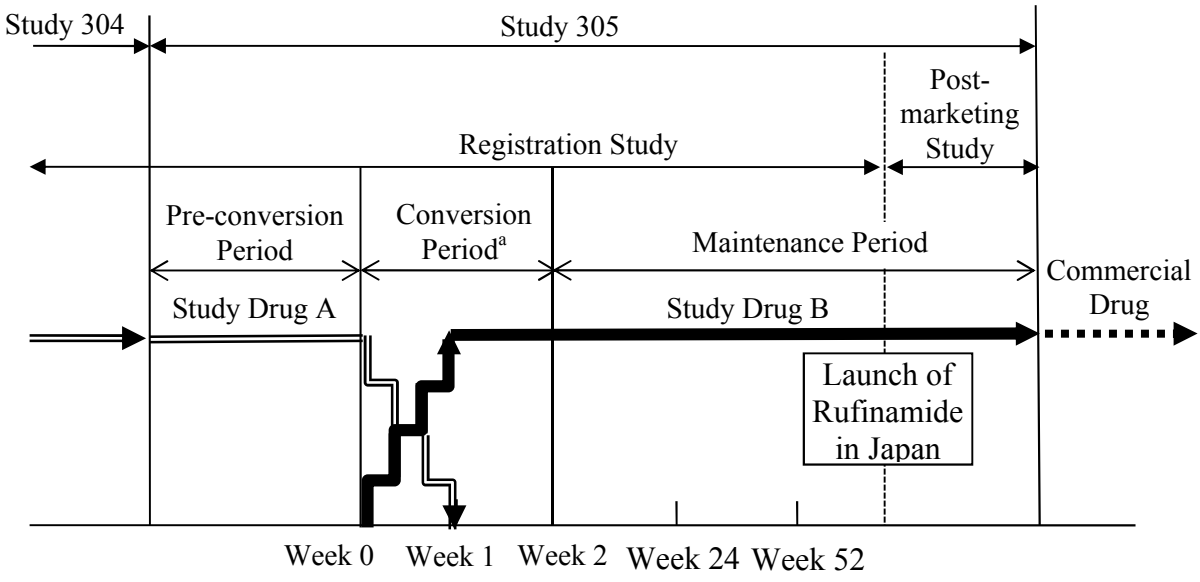
Name of Company: Eisai Co., Ltd	INDIVIDUAL STUDY TABLE		(For National Authority Use Only)
Name of Finished Product: Rufinamide Tablets 100 mg and 200 mg	Referring to Module 5 of the Dossier		
Name of Active Ingredient: Rufinamide	Volume:	Page:	
Study Title A long term extension study of E2080 in patients with Lennox-Gastaut syndrome			
Investigator(s)/Site(s) Makiko Osawa, MD, et al. Multicenter: 22 sites in Japan (refer to Appendix 16.1.4 for the list of investigators and sites)			
Publication (Reference) None			
Study Period 19 Nov 2010 to 09 Aug 2013			
Phase of Development Phase 3			
Objective(s) **Primary Objective:** To evaluate the long term safety and tolerability of rufinamide under the open-label treatment in patients with Lennox-Gastaut syndrome (LGS) who completed the phase 3 placebo-controlled, double-blind, comparative study (E2080-J081-304 study, herein after as Study 304). **Secondary Objective:** To evaluated the long term efficacy of rufinamide under the open-label treatment in patients with LGS who completed the Study 304.			
Methodology This was a multicenter study, which included the Pre-conversion Period, the Conversion Period, and the Maintenance Period. The Pre-conversion Period was designed to avoid breaking the blindness in the preceding Study 304 and to prevent any data obtained in the open-label treatment in Study 305 from affecting the evaluation in the Study 304. Under double-blind condition, subjects were treated with the same study drug as in the Study 304 (the Study Drug A; rufinamide or placebo) until the evaluation data of the Study 304 for each subject were fixed.			

In the Conversion Period, subjects who were on placebo were titrated to the appropriate dose of rufinamide (the Study Drug B) within 2 weeks under double-blind condition.

The long term safety and efficacy of rufinamide were evaluated under the open-label treatment in the Maintenance Period. The daily dose at the end of the Conversion Period was used as the initial dose for the Maintenance Period. Treatment of rufinamide (the Study Drug B) was allowed to be continued as long as the subject and legally authorized representative desired to keep receiving rufinamide and the investigator permitted that.

The Maintenance Period was allowed to continue until rufinamide was launched in Japan and was to be commercially available in the respective study sites. This study was conducted as a registration study before the launch and as a post-marketing study after that. The study was to finish within around 3 months after the price listing of rufinamide.

In case subjects discontinued the study, the study drug was to be tapered (Follow-up Period), but subjects who completed Study 305 were allowed to continue receiving rufinamide as a commercial drug without tapering.



a: In the Conversion Period, Study Drug A (double-blind; rufinamide or placebo tablets) was switched to the Study Drug B (open-label; rufinamide tablets) in a step-by-step manner.

Number of Subjects (Planned and Enrolled)

Planned: up to 50

Analyzed (number of subjects by treatment group in Study 304 was shown in parentheses):

Enrolled and entered Study 305: 54 (25 in the rufinamide group, 29 in the placebo group)

Efficacy Analysis Set: 46 (23 in the rufinamide group, 23 in the placebo group)

Safety Analysis Set: 54 (25 in the rufinamide group, 29 in the placebo group)

Diagnosis and Main Criteria for Inclusion

The subjects of this study were the patients with LGS who completed the phase 3 placebo-controlled, double-blind, comparative study of rufinamide (Study 304) and who fulfill all

the following criteria.

Inclusion criteria

1. Patients who had completed the 304 Study
2. Male patients with reproductive ability and female patients with child-bearing potential, or their partners, had to be able to take medically appropriate contraceptive measures.
3. Patients who had provided a written informed consent to participate in this clinical study until the evaluation of the end of Treatment Period in the Study 304 (subject's informed consent should be obtained if feasible. The consent of the legally authorized representative* was mandatory).

   *Note: A legally authorized representative is a person who is authorized to provide informed consent on behalf of a subject who is not fully capable of giving informed consent. The legally authorized representative included subject's spouse, a person in parental authority, a guardian, or an equivalent individual who was able to look after the subject's best interest, as judged by their actual living conditions or emotional ties.
4. Patients who had a family member or a caregiver (as for hospitalized patients, it might be nurses) capable of recording the reporting diary, providing patient information necessary for the study, assisting treatment compliance, and accompanying the patient on scheduled visit days during the study period.

Patients who met any of the following criteria were excluded from this study.

Exclusion criteria

1. Patients who were judged by investigators that they were not appropriate to participate in this clinical study for safety reasons based on the subject information etc. collected up to the evaluation of the end of Treatment Period in the Study 304
2. Patients who were highly likely to be noncompliant with treatment during the study period.
3. Patients judged to be inappropriate for study participation.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Test drug: Rufinamide

Dose and mode of administration:

The study drug was administered orally twice daily after breakfast and dinner.

1. Pre-conversion Period

   Under double-blind condition, subjects were treated with the same study drug as in the Study 304 (the Study Drug A; rufinamide or placebo). As a general rule, the dose was to be maintained at the dose of the final evaluation (Week 12) in the Study 304.

   When the investigator judged dose reduction was necessary to attempt for safety concerns on a subject who completed the Study 304 at the target maintenance dose, a 1-step reduction from the target maintenance dose was allowed. This reduction was performed from the next morning of the judgment, if feasible. Returning to the previous dose (ie, the target maintenance dose) after the reduction was prohibited.

In subjects for whom the dose had been reduced from the target maintenance dose by the completion of the Study 304, further dose reduction was prohibited under any circumstances. Subjects were to be withdrawn from the study if further dose reduction was judged to be necessary for safety reasons by the investigator

For reference, dose steps to the target maintenance dose depended on the subject's weight in the Study 304 are shown in Table 1.

Table 1 Dose steps to the target maintenance dose in Study 304

Body weight	15.0 to 30.0 kg	30.1 to 50.0 kg	50.1 to 70.0 kg	70.1 kg or above
Tablet	100 mg tablet	200 mg tablet	200 mg tablet	200 mg tablet
Step 1 (Day 1 to 2)	200 mg/day	400 mg/day	600 mg/day	
Step 2 (Day 3 to 4)	400 mg/day	800 mg/day	1200 mg/day	
Step 3 (Day 5 to 6)	800 mg/day	1200 mg/day	1800 mg/day	
Step 4 (Day 7 or after)	1000 mg/day[a]	1800 mg/day[a]	2400 mg/day[a]	2400 mg/day
Step 5 (Day 9 or after)	–	–	–	3200 mg/day[a]

a: Target maintenance dose for each body weight category.

2. Conversion Period

Under double-blind conditions, subjects who were on placebo were titrated to the appropriate dose of rufinamide within 2 weeks in a manner similar to the dose steps shown above. Study Drug A (double-blind; rufinamide or placebo tablets) was switched to the Study Drug B (open-label; rufinamide tablets) in a step-by-step manner by 2 days.

Daily number of tablets on the final day of the Pre-conversion Period (constant)
= Daily number of tablets of the Study Drug A (taper off by 2 days)
+ Daily number of tablets of the Study Drug B (gradual increase by 2 days)

If a safety problem was observed during conversion, the conversion could be suspended and daily numbers of tablets of the Study Drug A and Study Drug B were maintained temporarily. Even in such a case, the conversion was to be completed by 2 days before the end of the Conversion Period.

When the investigator judged dose reduction was necessary to attempt for safety concerns on a subject who had completed the conversion, a 1-step reduction was allowed only for subjects who had administered at the target maintenance dose. This reduction was performed from the next morning of the judgment, if feasible. Returning to the previous dose (ie, the target maintenance dose) after the reduction was prohibited.

3. Maintenance Period

As a general rule, the dose of rufinamide (Study Drug B) at the end of the Conversion Period was to be maintained throughout the Maintenance Period.

When the investigator judged dose reduction was necessary to attempt for safety concerns, a 1-step reduction from the target maintenance dose was allowed. This reduction was performed from the next morning of the judgment, if feasible.

In subjects for whom the dose had been reduced 1-step from the target maintenance dose by the end of the Conversion Period, further dose reduction during the Maintenance Period was prohibited. Subjects were to be withdrawn from the study if further dose reduction was judged to be necessary for safety reasons by the investigator.

Dose increase to the target maintenance dose was allowed only when the investigator judged necessary. Administrations at a higher dose than the target maintenance dose was prohibited under any circumstances.

Even when the body weight changed during the study period, dose adjustment based on the new weight category was not to be conducted in the registration study part. However, since rufinamide had been launched in Japan, the maintenance dose was to follow the approved dosage. In such a case, dose adjustment based on the new weight category might be allowed as long as same tablet form (100 mg tablet or 200 mg tablet) was used.

In subjects who completed Study 305 and continued receiving rufinamide as a commercial drug, tapering of rufinamide and the Follow-up Period were not required.

4. Follow-up Period (Tapering; when discontinuing the study)

   As a general rule, the dose was reduced by step-by-step every 2 days. The dose reduction was started from the next morning of the study discontinuation decided by the investigator, if feasible.

   Dose reduction could be postponed and the current dose maintained temporarily by the judgment of the investigator only if there was a safety problem. Even in this case, study drug administration was to be terminated at least by 12 days after start tapering.

   Dose steps for tapering rufinamide are shown in Table 2.

Table 2 Dose Steps for Tapering in the Follow-up Period

Body weight	15.0 to 30.0 kg	30.1 to 50.0 kg	50.1 to 70.0 kg	70.1 kg or above
Tablet	100 mg tablet	200 mg tablet	200 mg tablet	200 mg tablet
Step 1	800 mg/day[a]	1200 mg/day[a]	1800 mg/day[a]	2400 mg/day[a]
Step 2	400 mg/day	800 mg/day	1200 mg/day	1800 mg/day
Step 3	200 mg/day	400 mg/day	600 mg/day	1200 mg/day
Step 4	0 mg/day	0 mg/day	0 mg/day	600 mg/day
Step 5	–	–	–	0 mg/day

a: Target maintenance dose for each body weight category.

Batch (Lot) numbers:

- Rufinamide 100 mg tablets: P95011ZZC, P95011ZZD, P95011ZZE, P95011ZZF, and P95011ZZG
- Rufinamide 200 mg tablets: P99015ZZE, P99015ZZF, P99015ZZG, P99015ZZH, P99015ZZI, and P99015ZZK

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Control drug: None; however, during the Pre-conversion Period and the Conversion Period, placebo tablets were orally administered twice daily after breakfast and dinner to the subjects who were on placebo group in the Study 304 (See the above section for details).

Batch (Lot) numbers:

- Placebo 100 mg tablets: P99013ZZC
- Placebo 200 mg tablets: P99014ZZE and P99014ZZF

Duration of Treatment

Pre-conversion Period: for a maximum of 4 weeks

Conversion Period: 2 weeks

Maintenance Period: allowed to continue until rufinamide was launched in Japan and became commercially available in the respective study sites.

Follow-up Period (when discontinuing the study): 2 weeks

Concomitant Drug and Therapy

Concomitant Antiepileptic Drug (AED)

Patients were allowed to take 1 to 3 AEDs among predefined AEDs in the protocol. Concomitant AEDs were not to be changed during the Pre-conversion and Conversion Periods (ie, subjects were kept receiving the AEDs administered at the start of the Pre-conversion Period). It was prohibited to change the dosage of existing AEDs or to start taking new AEDs during those periods.

During the Maintenance Period, concomitant AEDs were not to be changed in principle; however it was allowed to discontinue the existing AEDs or to start new AEDs as far as number of AEDs to be kept within 1 to 3.

Concomitant AEDs were not to be changed during the Follow-up (Tapering) Period. It was prohibited to change the dosage of existing AEDs or to start taking new AEDs during tapering.

Emergency AED for Status Epilepticus

Only when subjects had status epilepticus and required emergency treatment, the following drugs were allowed to be used as rescue drugs (Note: the restriction of emergency AED was removed at the last protocol amendment on 24 Oct 2012 after completing all efficacy assessments).

diazepam (injection or suppository), flunitrazepam (injection), midazolam (injection), phenytoin (injection), phenobarbital (injection or suppository), chloral hydrate (injection or suppository), fosphenytoin (injection)

Prohibited Concomitant Drug

Other study drugs and unapproved drugs in Japan

Prohibited Concomitant Therapy

The following therapies were prohibited to conduct concomitantly throughout the study.

ketogenic diet, adrenocorticotropic hormone (ACTH) therapy, high-dose vitamin B_6 therapy, brain surgery, vagal nerve stimulation, investigational medical devices and unapproved medical devices

Assessments

Schedule of procedures/assessments is provided in Table 11.

Efficacy

Percent change in tonic-atonic seizure frequency, percent change in the total seizure frequency, percent change in the frequency of seizures other than tonic-atonic seizures, and 25%, 50%, 75%, 100% responder, and aggravated subjects in tonic-atonic seizure frequency (see protocol [Appendix 16.1.1] Section 8.5.1.3 and statistical analysis plan [Appendix 16.1.9.1] for more detailed information).

Safety

Adverse events, clinical laboratory tests, blood pressure, pulse rate, physical examination, and 12-lead ECG (see protocol Section 8.5.1.5 for more detailed information).

Statistical Methods

Efficacy

For percent change in tonic-atonic seizure frequency, the total seizure frequency, and the frequency of seizures other than tonic-atonic seizures, the summary statistics were calculated for the entire Efficacy Analysis Set and for each treatment group in Study 304. For 25%, 50%, 75%, 100% responder, and aggravated subjects in tonic-atonic seizure frequency, responder (or aggravated) rates were calculated for the entire Efficacy Analysis Set and for each treatment group in Study 304. For percent change in tonic-atonic seizure frequency and the total seizure frequency, median percent change was plotted by visit for each treatment group in Study 304.

Safety

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0. Treatment-emergent adverse events (TEAEs) and treatment related TEAEs were summarized for the entire Safety Analysis Set and for each treatment group in Study 304, the number and percent of subjects having any adverse event in each primary system organ class (SOC) and having each preferred term (PT). In addition, TEAEs and treatment related TEAEs were tabulated by causal relationship with the study drug or by severity. For laboratory tests (hematology, blood chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and body weight), and 12-lead ECG (heart rate, PR interval, QRS amplitude, QT interval, and QTc), the summary statistics of the observed value at each assessment time point, and changes from the end of the Observation Period in Study 304 (baseline) were calculated for the entire Safety Analysis Set and for each treatment group. Urinalysis data were subjected to cross-tabulation between the end of the Observation Period in Study 304 (baseline) and each assessment time point after the start of treatment.

Results

Subject Disposition/Analysis Sets

Subject disposition and reason for discontinuation from Study 305 are shown in Table 14.1.1 and Listing 16.2.1. All of the 54 subjects who entered Study 305 received at least 1 dose of the study drug. Of the 54 treated subjects, 41 subjects (75.9%) completed the study (ie, kept administered rufinamide in Study 305 until commercial drug of rufinamide was prescribed) and 13 subjects (24.1%) discontinued the study. Primary reason for discontinuation was withdrawal of consent due to insufficient therapeutic effect (7 subjects), withdrawal of consent for a reason other than insufficient effect (2 subjects), and adverse event (4 subjects).

Analysis sets are shown in Section 16.1.9.2 (Table 14.1.2) and Listing 16.2.3. The Safety Analysis Set consists of all the 54 treated subjects, whereas the Efficacy Analysis Set consists of 46 subjects, excluding 8 subjects who have no evaluable efficacy data in Study 305.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics collected during screening or Observation Period of Study 304 are shown in Section 16.1.9.2 (Table 14.1.3 and Table 14.1.4) and Listing 16.2.3. In the Efficacy Analysis Set (46 subjects), 65.2% (30 subjects) were males and 34.8% (16 subjects) were females. The mean age was 15.2 years, and 39.1% (18 subjects) were younger than 12 years old. The mean weight was 39.45 kg, and more than 40% of the subjects were in the range of 15.0 to 30.0 kg. The mean duration of LGS was 10.61 years. The subjects experienced a median of 268.20 seizures, including 220.85 tonic-atonic seizures, per 28 days.

Concomitant AEDs

Concomitant AEDs are shown in Table 14.1.7.1.1 to Table 14.1.7.4.2, and Listing 16.2.4.4. Concomitant AEDs actually used by at least 20% of subjects in the Efficacy Analysis Set (46 subjects) during Study 304 and Study 305 were sodium valproate (44 subjects; 95.7%), lamotrigine (29 subjects; 63.0%), clobazam (16 subjects; 34.8%), and phenytoin (11 subjects; 23.9%).

Efficacy

Efficacy was evaluated until the timepoint at Week 52 (ie. the last efficacy evaluation was conducted for 7 days starting from the next day of the Week 52 visit [Visit 12]). Previous study report (data cut-off at Week 52) issued on 28 Dec 2012 includes efficacy results up to Week 40 (ie, efficacy data at Week 52 is provided only in this report).

Summary of percent change in tonic-atonic seizure frequency per 28 days relative to baseline (Observation Period in Study 304) is provided in Table 3. The median percent changes in tonic-atonic seizure frequency relative to baseline were –39.30%, –40.60%, –46.80%, –47.60%, and –36.05% in Weeks 12, 24, 32, 40, and 52, respectively. A reduction in median tonic-atonic seizure frequency occurred at every time point for around 1 year. The median percent change in tonic-atonic seizure frequency is shown in Figure 14.2.1.

Table 3 Summary of Percent Change in Tonic-atonic Seizure Frequency per 28 Days Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	median (min, max)	N	median (min, max)	N	median (min, max)
Seizure frequency per 28 days at baseline in Study 304	23	256.10 (28.0, 22469.5)	23	183.60 (8.3, 2046.2)	46	220.85 (8.3, 22469.5)
% Change in Week 12	23	–34.60 (–92.1, 114.3)	23	–59.90 (–100.0, 125.2)	46	–39.30 (–100.0, 125.2)
% Change in Week 24	22	–32.75 (–85.7, 85.7)	21	–51.30 (–100.0, 70.0)	43	–40.60 (–100.0, 85.7)
% Change in Week 32	21	–44.20 (–88.6, 63.8)	21	–50.90 (–100.0, 75.0)	42	–46.80 (–100.0, 75.0)
% Change in Week 40	20	–29.75 (–94.4, 833.2)	21	–52.50 (–100.0, 65.0)	41	–47.60 (–100.0, 833.2)
% Change in Week 52	19	–48.90 (–91.3, 31.1)	21	–23.70 (–100.0, 101.7)	40	–36.05 (–100.0, 101.7)
% Change in Week 52 (LOCF)	23	–48.50 (–91.3, 31.1)	23	–27.10 (–100.0, 101.7)	46	–39.25 (–100.0, 101.7)

min = minimum, max = maximum, LOCF = last observation carried forward.
Source: Table 14.2.1

Summary statistics of subjects who responded to treatment with at least a 50% reduction in tonic-atonic seizure frequency relative to baseline is provided in Table 4. The 50% responder rates in tonic-atonic seizure frequency were 43.5%, 39.5%, 47.6%, 48.8%, and 37.5% in Weeks 12, 24, 32, 40, and 52, respectively. There was no evidence of tolerance developing to the anticonvulsant effect of the therapy including rufinamide. Categorized percent change (25%, 50%, 75%, 100% responder, and aggravated subjects) in tonic-atonic seizure frequency relative to baseline is provided in Table 14.2.2.

Table 4 Summary Statistics of Subjects Who Responded to Treatment with at Least a 50% Reduction in Tonic-atonic Seizure Frequency Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	n (%)	N	n (%)	N	n (%)
50% Responders in Week 12	23	6 (26.1)	23	14 (60.9)	46	20 (43.5)
50% Responders in Week 24	22	6 (27.3)	21	11 (52.4)	43	17 (39.5)
50% Responders in Week 32	21	9 (42.9)	21	11 (52.4)	42	20 (47.6)
50% Responders in Week 40	20	8 (40.0)	21	12 (57.1)	41	20 (48.8)
50% Responders in Week 52	19	9 (47.4)	21	6 (28.6)	40	15 (37.5)
50% Responders in Week 52 (LOCF)	23	10 (43.5)	23	8 (34.8)	46	18 (39.1)

min = minimum, max = maximum, LOCF = last observation carried forward.
Source: Table 14.2.2

Summary of percent change in total seizure frequency per 28 days relative to baseline is provided in Table 5. The median percent changes in total seizure frequency relative to baseline were –47.70%, –48.90%, –50.60%, –52.00%, and –47.35% in Weeks 12, 24, 32, 40, and 52, respectively. A reduction in median total seizure frequency occurred at every time point for around 1 year. The median percent change in total seizure frequency is shown in Figure 14.2.2.

Table 5 Summary of Percent Change in Total Seizure Frequency per 28 Days Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	median (min, max)	N	median (min, max)	N	median (min, max)
Seizure frequency per 28 days at baseline in Study 304	23	256.10 (95.4, 22499.4)	23	273.00 (79.9, 2125.9)	46	268.20 (79.9, 22499.4)
% Change in Week 12	23	–46.80 (–93.6, 101.5)	22	–56.00 (–100.0, 37.0)	45	–47.70 (–100.0, 101.5)
% Change in Week 24	22	–42.40 (–85.9, 30.0)	21	–51.30 (–97.0, 116.6)	43	–48.90 (–97.0, 116.6)
% Change in Week 32	21	–50.10 (–90.8, 30.0)	21	–50.90 (–84.4, 209.2)	42	–50.60 (–90.8, 209.2)
% Change in Week 40	20	–46.75 (–95.5, 833.2)	21	–52.00 (–86.9, 168.6)	41	–52.00 (–95.5, 833.2)
% Change in Week 52	19	–53.60 (–91.4, 16.7)	21	–34.00 (–94.3, 340.8)	40	–47.35 (–94.3, 340.8)
% Change in Week 52 (LOCF)	23	–49.40 (–91.4, 16.7)	23	–34.00 (–100.0, 340.8)	46	–46.30 (–100.0, 340.8)

min = minimum, max = maximum, LOCF = last observation carried forward.
Source: Table 14.2.3

As to other seizure types, summary of percent change in frequency per 28 days relative to baseline (Observation Period in Study 304) by seizure type is provided in Table 14.2.4.

Subgroups analyses were performed by sex, age, weight, total number of concomitant AEDs, type of concomitant AEDs, or presence/absence of dose reduction. Results showed no subgroups that evidently affected the activity of rufinamide in suppressing tonic-atonic seizure frequency (see Table 14.2.5.1 to Table 14.2.5.10). Rufinamide was effective even in subjects treated at doses 1-step lower than the target maintenance dose.

Safety

Extent of Exposure

Extent of exposure is shown in Table 14.3.1.1.1 to Table 14.3.1.1.7, and Listing 16.2.5.1 to Listing 16.2.5.3. The median duration of exposure to rufinamide was 818.00 days (range 13.5 to 1042.5 days), and 70.4% (38/54 subjects) received rufinamide for 2 years or more. The median durations of exposure to rufinamide by treatment group in Study 304 were 888.50 days (range 139.0 to 1042.5 days) and 762.50 days (range 13.5 to 930.5 days) in rufinamide and placebo group, respectively.

Adverse Events

Following analyses were conducted on treatment-emergent adverse events (TEAEs) occurred in Study 304 and Study 305 for Safety Analysis Set. The term “treatment” here means rufinamide treatment, thus AEs occurred during placebo treatment are not included in the statistical analyses.

As to serious TEAEs and TEAEs leading to study drug withdrawal, those TEAEs occurred only in Study 305 were summarized.

Overview of Adverse Events

Table 6 presents an overview of TEAEs. All of the 54 subjects who received rufinamide experienced TEAEs, and 38 subjects (70.4%) experienced TEAEs that were considered possibly or probably related to administration of study drug. Severe TEAEs were reported in 3 subjects (5.6%) and severe treatment-related TEAEs were also reported in the same subjects. Serious TEAEs were reported in 9 subjects (16.7%) with no subjects died within Study 305. TEAEs leading to study drug withdrawal were reported in 3 subjects (5.6%) in Study 305.

Table 6 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Category	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
TEAEs	25 (100.0)	29 (100.0)	54 (100.0)
Treatment-related TEAEs[a]	17 (68.0)	21 (72.4)	38 (70.4)
Severe TEAEs	1 (4.0)	2 (6.9)	3 (5.6)
Severe Treatment-related TEAEs[a]	1 (4.0)	2 (6.9)	3 (5.6)
Serious TEAEs[b,c]	4 (16.0)	5 (17.2)	9 (16.7)
Serious Treatment-related TEAEs[a,b,c]	1 (4.0)	1 (3.4)	2 (3.7)
TEAEs leading to study drug withdrawal[b]	0 (0.0)	3 (10.3)	3 (5.6)
Treatment-related TEAEs leading to study drug withdrawal[a,b]	0 (0.0)	3 (10.3)	3 (5.6)

TEAE = treatment-emergent adverse event.
Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs.
For each row category, a subject with 2 or more TEAEs in that category is counted only once.
a: Includes TEAEs considered by the investigator to be possibly or probably related to study drug.
b: Only includes TEAEs occurred after the first dose of rufinamide in Study 305.
c: Serious criterion was an adverse event which required inpatient hospitalization or prolongation of existing hospitalization for all serious TEAEs.
Source: Table 14.3.1.2.1

Common Adverse Events

Common TEAEs (≥5%) of total subjects and common treatment-related TEAEs are summarized by MedDRA SOC and PT in Table 7 and Table 8, respectively. The most frequently reported TEAEs (≥30%) in total subjects (N=54) were nasopharyngitis (29 subjects; 53.7%), status epilepticus (23 subjects; 42.6%), and somnolence (18 subjects; 33.3%). The most frequently reported treatment-related TEAEs (≥10%) in total subjects were somnolence (11 subjects; 20.4%), decreased appetite (9 subjects; 16.7%), status epilepticus (7 subjects; 13.0%), constipation, and vomiting (6 subjects each; 11.1%).

Table 7 Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
Subjects with any TEAEs	25 (100.0)	29 (100.0)	54 (100.0)
Eye disorders			
Conjunctivitis allergic	1 (4.0)	2 (6.9)	3 (5.6)
Gastrointestinal disorders			
Vomiting	8 (32.0)	7 (24.1)	15 (27.8)
Constipation	4 (16.0)	5 (17.2)	9 (16.7)
Dental caries	7 (28.0)	2 (6.9)	9 (16.7)
Stomatitis	1 (4.0)	5 (17.2)	6 (11.1)
Nausea	2 (8.0)	3 (10.3)	5 (9.3)
Diarrhoea	2 (8.0)	1 (3.4)	3 (5.6)
General disorders and administration site conditions			
Pyrexia	5 (20.0)	1 (3.4)	6 (11.1)
Infections and infestations			
Nasopharyngitis	15 (60.0)	14 (48.3)	29 (53.7)
Influenza	4 (16.0)	8 (27.6)	12 (22.2)
Upper respiratory tract infection	5 (20.0)	3 (10.3)	8 (14.8)
Bronchitis	4 (16.0)	2 (6.9)	6 (11.1)
Gastroenteritis	3 (12.0)	2 (6.9)	5 (9.3)
Pneumonia	2 (8.0)	3 (10.3)	5 (9.3)
Pharyngitis	2 (8.0)	2 (6.9)	4 (7.4)
Injury, poisoning and procedural complications			
Contusion	5 (20.0)	7 (24.1)	12 (22.2)
Skin laceration	4 (16.0)	1 (3.4)	5 (9.3)
Eyelid injury	3 (12.0)	1 (3.4)	4 (7.4)
Fall	2 (8.0)	2 (6.9)	4 (7.4)
Mouth injury	1 (4.0)	3 (10.3)	4 (7.4)
Investigations			
Platelet count decreased	0 (0.0)	3 (10.3)	3 (5.6)
Weight decreased	1 (4.0)	2 (6.9)	3 (5.6)
Metabolism and nutrition disorders			
Decreased appetite	5 (20.0)	6 (20.7)	11 (20.4)
Nervous system disorders			
Status epilepticus	10 (40.0)	13 (44.8)	23 (42.6)
Somnolence	11 (44.0)	7 (24.1)	18 (33.3)
Dizziness	0 (0.0)	3 (10.3)	3 (5.6)

Table 7 Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set (continued)

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
Psychiatric disorders			
Insomnia	4 (16.0)	2 (6.9)	6 (11.1)
Agitation	1 (4.0)	4 (13.8)	5 (9.3)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	3 (12.0)	3 (10.3)	6 (11.1)
Skin and subcutaneous tissue disorders			
Dry skin	2 (8.0)	2 (6.9)	4 (7.4)
Dermatitis contact	1 (4.0)	2 (6.9)	3 (5.6)
Rash	2 (8.0)	1 (3.4)	3 (5.6)

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
TEAE = treatment-emergent adverse event.
Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs. Subject with two or more TEAEs in the same preferred term is counted only once for that preferred term.
Source: Table 14.3.1.2.2

Table 8 Treatment-Related Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
Subjects with any Treatment-related, TEAEs	17 (68.0)	21 (72.4)	38 (70.4)
Gastrointestinal disorders			
Constipation	3 (12.0)	3 (10.3)	6 (11.1)
Vomiting	4 (16.0)	2 (6.9)	6 (11.1)
Metabolism and nutrition disorders			
Decreased appetite	5 (20.0)	4 (13.8)	9 (16.7)
Nervous system disorders			
Somnolence	6 (24.0)	5 (17.2)	11 (20.4)
Status epilepticus	4 (16.0)	3 (10.3)	7 (13.0)
Dizziness	0 (0.0)	3 (10.3)	3 (5.6)

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
TEAE = treatment-emergent adverse event.
Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs. This table includes TEAEs considered by the investigator to be possibly or probably related to study drug. Subject with two or more treatment-related TEAEs in the same preferred term is counted only once for that preferred term.
Source: Table 14.3.1.2.3

A subject listing of all TEAEs is provided in Listing 16.2.7.2. Subject Listings of AEs occurred before the first dose of rufinamide (ie, not treatment-emergent) are provided in Listing 16.2.7.1 (those occurred in Study 305) and Listing 16.2.7.3 (those occurred in Study 304 and continued at the enrollment of Study 305) for subjects who received placebo in Study 304 and Pre-conversion Period of Study 305. Coding list of all AEs is provided in Listing 16.2.7.4.

Analysis of Adverse Events

Summaries of TEAEs and treatment-related TEAEs by SOC, PT, and maximum severity are provided in Table 14.3.1.2.9 and Table 14.3.1.2.10, respectively. Severe TEAEs were reported in 3 subjects (5.6%) and severe treatment-related TEAEs were also reported in the same subjects. Severe TEAE was status epilepticus (3 subjects; 5.6%).

Summary of TEAEs by SOC, PT, and relationship to study drug is provided in Table 14.3.1.2.8.

Summaries of TEAEs by SOC, PT, and time to first onset are provided in Table 14.3.1.2.11 (categorical) and Table 14.3.1.2.12 (summary statistics). Median time to onset from the first administration of rufinamide for the most frequently reported TEAEs (≥30%) was 54.0 days (range 1 to 876 days, n=29) for nasopharyngitis, 138.0 days (range 4 to 672 days, n=23) for status epilepticus, and 105.5 days (range 1 to 621 days, n=18) for somnolence. Summaries of treatment-related TEAEs by SOC, PT, and time to first onset are provided in Table 14.3.1.2.13 (categorical) and Table 14.3.1.2.14 (summary statistics).

Subgroups analyses were performed by sex, age, weight, mean daily dose, or mean daily dose per weight (see Table 14.3.1.2.15.1 to Table 14.3.1.2.15.5). There were no notable difference in the incidence of the most frequently reported TEAEs (≥30%; nasopharyngitis, status epilepticus, and somnolence) by age group.

Summary of TEAEs and treatment-related TEAEs by SOC, PT in the Follow-up Period is provided in Table 14.3.1.2.16.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

An overview of serious TEAEs and TEAEs leading to study drug withdrawal is presented in Table 6. Subject listings of AEs leading to deaths, SAEs, and AEs leading to study drug withdrawal, treatment-emergent or otherwise, are provided in Table 14.3.2.1, Table 14.3.2.2, and Table 14.3.2.3, respectively.

No subjects died or had AEs that resulted in deaths within Study 305.

Summaries of serious TEAEs and serious treatment-related TEAEs by SOC and PT are provided in Table 14.3.1.2.4 and Table 14.3.1.2.5, respectively.

Serious TEAEs were reported in 9 subjects (16.7%) in Study 305. Serious TEAEs were pneumonia (4 subjects; 7.4%), status epilepticus (2 subjects; 3.7%), dental caries, gastroenteritis viral, influenza, upper respiratory tract infection, and contusion (1 subject each; 1.9%).

Listing of SAEs is shown in Table 9 and narratives for subjects with SAE are provided in Table 14.3.3.

Table 9 Listing of Serious Adverse Events in Study 305– Safety Analysis Set

Subject ID Age (year) Sex	Study Phase Daily Dose of Rufinamide[a]	MedDRA Preferred Term	Start Day[b] Severity Serious criteria	Duration Outcome	Relationship to Study Drug Study Drug Action Taken Other Action Taken
Treatment Group in Study 304: Rufinamide					
PPD 9, PPD	Maintenance 1000.0 mg	Status epilepticus	Day 207 Severe Hospitalization[c]	17 days Recovered	Possibly related Study drug continued Treatment given, dose reduction of phenobarbital, dose increase of valproic acid
	Maintenance 1000.0 mg	Status epilepticus	Day 506 Moderate Hospitalization[c]	11 days Recovered	Possibly related Study drug continued Treatment given
	Maintenance 1000.0 mg	Status epilepticus	Day 807 Moderate Hospitalization[c]	18 days Recovered	Possibly related Study drug continued Treatment given
PPD 14, PPD	Maintenance 1000.0 mg	Pneumonia	Day 175 Moderate Hospitalization[c]	33 days Recovered	Not related Study drug continued Treatment given
PPD 20, PPD	Maintenance 1779.2 mg	Upper respiratory tract infection	Day 187 Moderate Hospitalization[c]	18 days Recovered	Not related Study drug continued Treatment given
	Maintenance 1800.0 mg	Pneumonia	Day 725 Moderate Hospitalization[c]	39 days Recovered	Not related Study drug continued Treatment given
PPD 15, PPD	Maintenance 1800.0 mg	Dental caries	Day 237 Mild Hospitalization[c]	231 days Recovered	Not related Study drug continued Dental procedure
Treatment Group in Study 304: Placebo					
PPD 13, PPD	Maintenance 1800.0 mg	Pneumonia	Day 206 Moderate Hospitalization[c]	16 days Recovered	Not related Study drug continued Treatment given, cooling
	Maintenance 1800.0 mg	Pneumonia	Day 357 Moderate Hospitalization[c]	9 days Recovered	Not related Study drug continued Treatment given, aspiration, cooling
	Maintenance 1800.0 mg	Pneumonia	Day 440 Moderate Hospitalization[c]	13 days Recovered	Not related Study drug continued Treatment given, aspiration, cooling

Table 9 Listing of Serious Adverse Events in Study 305– Safety Analysis Set (continued)

Subject ID Age (year) Sex	Study Phase Daily Dose of Rufinamide[a]	MedDRA Preferred Term	Start Day[b] Severity Serious criteria	Duration Outcome	Relationship to Study Drug Study Drug Action Taken Other Action Taken
Treatment Group in Study 304: Placebo (continued)					
PPD 18, PPD	Maintenance 1800.0 mg	Contusion	Day 662 Moderate Hospitalization[c]	11 days Recovered	Not related Study drug continued Treatment given
	Maintenance 1800.0 mg	Status epilepticus	Day 717 Severe Hospitalization[c]	17 days Recovered	Possibly related Study drug continued Treatment given
PPD 9, PPD	Maintenance 988.1 mg	Pneumonia	Day 540 Moderate Hospitalization[c]	7 days Recovered	Not related Study drug continued Treatment given
PPD 6, PPD	Follow-up 800.0 mg	Influenza	Day 57 Moderate Hospitalization[c]	5 days Recovered	Not related Study drug continued Treatment given
PPD 12, PPD	Maintenance 1000.0 mg	Gastroenteritis viral	Day 309 Moderate Hospitalization[c]	10 days Recovered	Not related Study drug continued Treatment given

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
Subject ID = subject identification number.
a: Mean daily dose (mg/day) of the prescription period in which the event occurred (in case the event occurred after discontinuation of administration, the mean daily dose of the last prescription period).
b: Onset date of the event – date of the first administration of rufinamide + 1 (day).
c: An adverse event which requires inpatient hospitalization or prolongation of existing hospitalization.
Source: Table 14.3.2.2, 14.3.3

Summaries of TEAEs and treatment-related TEAEs leading to study drug withdrawal by SOC and PT are provided in Table 14.3.1.2.6 and Table 14.3.1.2.7, respectively.

TEAEs leading to study drug withdrawal were reported in 3 subjects in Study 305. TEAEs leading to study drug withdrawal were decreased appetite (2 subjects; 3.7%) and drug eruption (1 subject; 1.9%).

Listing of TEAEs leading to study drug withdrawal is shown in Table 10.

Another subject (Subject PPD also discontinued the study treatment in Study 305 due to an AE (autism); however the autism was not included in Table 10 since the event occurred in Study 304 and did not get worse during Study 305.

Table 10 Listing of Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal in Study 305– Safety Analysis Set

Subject ID Age (year) Sex	Study Phase Daily Dose of Rufinamide[a]	MedDRA Preferred Term	Start Day[b] Severity Seriousness	Duration Outcome	Relationship to Study Drug Study Drug Action Taken Other Action Taken
Treatment Group in Study 304: Placebo					
PPD 19, PPD	Conversion 1200.0 mg	Decreased appetite	Day 7 Moderate Not serious	57 days Recovered	Probably related Study drug withdrawn Treatment given
PPD 6, PPD	Maintenance 1000.0 mg	Drug eruption	Day 13 Moderate Not serious	28 days Recovered	Possibly related Study drug withdrawn None
PPD 19, PPD	Maintenance 2400.0 mg	Decreased appetite	Day 20 Moderate Not serious	192 days Recovered	Possibly related Study drug withdrawn Treatment given, dose reduction of valproic acid, withdrawn of pyridoxal

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
Subject ID = subject identification number.
a: Mean daily dose (mg/day) of the prescription period in which the event occurred (in case the event occurred after discontinuation of administration, the mean daily dose of the last prescription period).
b: Onset date of the event – date of the first administration of rufinamide + 1 (day).
Source: Table 14.3.2.3

Laboratory Results

A listing of all individual laboratory results by subject with reference (normal) ranges and Common Terminology Criteria Grades is provided in Listing 16.2.8.1.

Laboratory Parameters Over Time

Summary statistics for all laboratory test results are provided in Table 14.3.4.1. Box plots of laboratory parameters by visit are shown in Figure 14.3.4.1. There were no changes of clinical importance in mean laboratory values over time.

Individual Subject Changes: Shifts from Baseline

A summary of subject shifts from baseline by visit for categorical urinalysis parameters is provided in Table 14.3.4.2. A summary of subject LNH (low, normal, or high) shifts from baseline by visit for hematology, clinical chemistry, and urinalysis parameters is provided in Table 14.3.4.3. The shift analysis revealed no shifts of clinical concern for hematology, clinical chemistry, or urinalysis parameters.

Markedly Abnormal Laboratory Values

TEAEs related to clinical laboratory results reported in more than one subject were platelet count decreased (3 subjects; 5.6%) and blood lactate dehydrogenase increased (2 subjects; 3.7%). No serious TEAEs or TEAEs leading to study drug withdrawal related to clinical laboratory results were reported.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs and Weight

Summary statistics for all vital signs and weight are provided in Table 14.3.5.1. A listing of all individual vital signs and weight by subject is provided in Listing 16.2.8.2. There were no changes of clinical importance in mean vital signs or mean weight over time.

Summary of clinically notable changes in weight is provided in Table 14.3.5.2. Clinically notable changes were defined as 13% increase (for subjects under 12 years old), 7% increase (for subjects with 12 years old or over), or 7% decrease at any post-baseline visit relative to the baseline. Clinically notable weight decrease and increase were observed in 22 subjects (40.7%) and 21 subjects (38.9%), respectively. More subjects experienced clinically notable weight increase in compared with the previous report (data cut-off at Week 52), probably due to normal growth as children during long-term administration of rufinamide (median duration of exposure 818.00 days).

TEAEs related to vital signs or weight reported in more than one subject were weight decreased (3 subjects; 5.6%). No serious TEAEs or TEAEs leading to study drug withdrawal related to vital signs or weight were reported, although 2 subjects discontinued the study due to decreased appetite.

Electrocardiograms

Summary statistics for all ECG values is provided in Table 14.3.6.1. A listing of all individual ECG results by subject is provided in Listing 16.2.8.3. There were no changes of clinical importance in mean ECG parameters over time.

A summary of subject shifts (normal or abnormal) from baseline by visit for ECG finding is provided in Table 14.3.6.2. Abnormal ECG findings were reported in 3 subjects; incomplete right bundle branch block, Q wave abnormal, and left atrial hypertrophy V1 in Subject PPD without clinical symptoms (those abnormalities were not considered to be AEs), ventricular arrhythmia and sinus arrhythmia in Subject PPD and QTc prolongation in Subject PPD Thus, TEAEs related to ECG findings were ventricular arrhythmia, sinus arrhythmia, and electrocardiogram QT prolonged (1 subject each; 1.9%).

Conclusions

- Rufinamide given twice daily for long term (more than 2 years of median duration of exposure) was safe and well-tolerated in Japanese patients with LGS.
- There was no tendency to develop tolerance to the efficacy for 52-week administration of rufinamide.
- Therapeutic benefit of rufinamide as an add-on therapy with conventional AEDs in Japanese patients with LGS was maintained for long term.

Date of Report

17 Mar 2014