Rufinamide as an adjunctive therapy for Lennox–Gastaut syndrome: A randomized double-blind placebo-controlled trial in Japan

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Rufinamide; Lennox–Gastaut syndrome; Randomized double-blind placebo-controlled trial; Efficacy; Tolerability; Pharmacokinetics

Summary
Purpose: To evaluate the efficacy, safety, and pharmacokinetics of rufinamide as an adjunctive therapy for patients with Lennox–Gastaut syndrome (LGS) in a randomized, double-blind, placebo-controlled trial.
Methods: We conducted a multicenter clinical trial with a 4-week baseline, a 2-week titration, a 10-week maintenance, and either a follow-up visit or entry into an open-label extension. Patients with LGS (4 to 30 years old) taking between one and three antiepileptic drugs were recruited. After the baseline period, patients were randomly assigned to rufinamide or placebo. The primary efficacy variable was the percent change in the tonic–atonic seizure frequency per 28 days.
Key findings: Of the 59 patients, 29 were randomized to the rufinamide group and 30 to the placebo group. The frequency of epileptic seizures was significantly decreased in the rufinamide group than in the placebo group; the median percent change in frequency of tonic–atonic seizures

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seizures was $-24.2\%$ and $-3.3\%$, respectively, ($p = 0.003$) and that of total seizures was $-32.9\%$ and $-3.1\%$, respectively ($p < 0.001$). Subgroup analyses indicated that the efficacy of rufinamide was consistent independent of clinical background characteristics. The common treatment-related adverse events in the rufinamide group were decreased appetite ($17.2\%$), somnolence ($17.2\%$), and vomiting ($13.8\%$). Transient seizure aggravations were observed in 13 ($22.0\%$) of the 59 patients, though a causal relationship with rufinamide was suspected in only one patient. All adverse events were mild to moderate in severity. The mean plasma concentration of rufinamide between 1 and 9 within 12 h after administration was $17.2 \mu g/mL$.

**Significance:** The present results showed a favorable risk-benefit profile for rufinamide as an adjunctive therapy for patients with LGS.

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**Introduction**

Lennox–Gastaut syndrome (LGS) is one of the most severe forms of childhood-onset epileptic encephalopathy. This syndrome is characterized by various types of epileptic seizures (mainly tonic seizures), diffuse slow spike-and-wave complex patterns on electroencephalogram (EEG), and impairment of cognitive function (Arzimanoglou et al., 2009; Beaumanoir, 1985). The long-term mental and seizure prognoses are generally devastating (Arzimanoglou et al., 2009; Beaumanoir, 1985; Blatter-Arifi, 1991; Oguni et al., 1996; Ohtsuka et al., 1990; Yagi, 1996), and appropriate and early intervention is crucial for the treatment of patients with LGS to prevent mental deterioration.

However, therapeutic evidence for antiepileptic drugs (AEDs) in LGS treatment is not sufficiently established due to its complex symptoms and low prevalence rate (less than $1.0$ per $10,000$ population) (Cowan et al., 1989; Eriksson and Koivikko, 1997; Oka et al., 2006; Olafsson and Hauser, 1999), though several randomized controlled clinical trials have been conducted with some AEDs: felbamate (The Felbamate Study Group in Lennox–Gastaut Syndrome, 1993), lamotrigine (Motte et al., 1997), topiramate (Sachdeo et al., 1999), and clobazam (Ng et al., 2011). Rufinamide is a recently developed AED that is being used for the treatment of LGS in many countries on the basis of the results of a randomized, controlled trial conducted in Europe, North America, and Brazil (Glauser et al., 2008), but no other randomized, controlled study of rufinamide for LGS has been reported. The Cochrane Epilepsy Group concluded that the optimum treatment for LGS remains uncertain (Hancock and Cross, 2013).

Therefore, we conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of rufinamide as an adjunctive therapy for patients with LGS.

**Methods**

**Study design**

This was a multicenter, randomized, double-blind, placebo-controlled trial in Japan.

The study design of this trial basically referred to the previous trial of rufinamide for LGS (Glauser et al., 2008). Eligible patients were aged 4–30 years, weighing 15 kg or more. LGS was diagnosed based on a history of tonic and/or atonic seizures and atypical absence seizures and slow spike-and-wave complex patterns on EEG within 6 months before the baseline period. The patients should have experienced at least 90 seizures during the 28 days before the baseline period. Patients were excluded from the study if they experienced tonic–clonic status epilepticus during the baseline period. Patients were also excluded if they had other clinically severe diseases or electrocardiographic/laboratory abnormalities.

This study consisted of the following four periods: a 4-week baseline, a 2-week titration, a 10-week maintenance, and either a follow-up visit or entry into an open-label extension. Patients were randomized to either rufinamide or placebo in a 1:1 ratio according to body weight. Seizure frequency data were obtained using a diary recorded by caregivers (mainly parents, including schoolteachers and childcare workers). All caregivers underwent standardized training about seizure classification and the rules for diary recording prior to the baseline period. In addition, a nationwide meeting of the investigators was held to standardize the methods applied to the evaluation of rufinamide efficacy and safety.

Seizures were classified according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (Commission on Classification and Terminology of the ILAE, 1981). Amelioration of tonic seizures and/or atonic seizures is essential for LGS patients, since these seizures often result in sudden falls and disturb the patients’ quality of life. Referring to the previous study, the sum of frequencies of tonic seizures and atonic seizures was defined as the frequency of tonic–atonic seizures, and the percent change in the frequency per 28 days was used as the primary efficacy variable in this study. Percent change in seizure frequency was defined as $[(D - B)/B] \times 100$, where $D$ and $B$ were the seizure frequencies per 28 days in the double-blind period and the baseline period, respectively. The double-blind period included the titration and the maintenance periods.

Secondary efficacy variables were: percent change in the total seizure frequency; 50% responder rate for the tonic–atonic seizure frequency; percent change in the frequency of seizures other than tonic–atonic seizures; and clinical global impression of the patient’s condition. The 50% responder rate was defined as the percentage of patients with at least 50% reduction in seizure frequency. The
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clinical global impression of the patient’s condition, including seizure status, was evaluated by investigators at Day 84 using a 7-point scale (markedly improved, improved, slightly improved, unchanged, slightly worsened, worsened, and markedly worsened).

We classified the patients into subgroups based on patient demographics and baseline characteristics: sex, age, time since LGS diagnosis, underlying causes, transition from West syndrome, seizure types, baseline frequency of the tonic–atonic seizures, and concomitant AEDs taken by at least 25% of patients in rufinamide and/or placebo groups at baseline period. In each subgroup, we estimated the intergroup difference between the rufinamide and the placebo groups with regards to tonic–atonic seizure frequency.

We evaluated the number of patients who experienced adverse events (AEs) and treatment-related AEs, and their incidences after administration of the blinded study drug. A causal relationship with the blinded study drug was categorized as “not related”, “possibly related”, or “probably related” by investigators. Treatment-related AEs were defined as AEs for which the causality was “possibly related” or “probably related”.

Rufinamide was supplied as 100- and 200-mg tablets, with corresponding matching placebo tablets. Doses were titrated according to a predetermined schedule based on body weight (Table 1). The corresponding target dose was maintained during the maintenance period. One-step dose reduction was allowed only when investigators judged it necessary due to safety concerns. A rescue treatment (e.g. intravenous injection or rectal suppository of diazepam) was permitted for transient seizure aggravation including status epilepticus. One to three AEDs were allowed to be administered concomitantly, but they had to remain unchanged throughout the trial. Blood samples for pharmacokinetic analyses were collected at Day 0 (for baseline concentrations of concomitant AEDs), and at Days 28, 56, and 84 in the maintenance period. The plasma concentrations of rufinamide and concomitant AEDs were measured using liquid chromatography-mass spectrometry.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice for trials on medical products and was approved by the ethical committee of each hospital. Written informed consent was obtained from patients and/or their guardians prior to screening.

Statistical methods

Sample size was determined on the basis of the results of the previous trial of rufinamide for LGS (Glauser et al., 2008). We predefined the statistical significance level as 0.1 (two-sided) because we thought that it would be difficult to recruit a sufficient number of LGS patients for about a year. Due to an expected irregular distribution of the seizure frequency, we calculated the statistical power by using the simulation-based approach known as a resampling method, which directly re-samples the existing data without any assumption about the underlying distribution of the sampled population. As the result of this simulation, a sample size of 23 patients in each group was considered sufficient for a >80% power to detect a significant difference in percent change in the tonic–atonic seizure frequency between the rufinamide group and the placebo group. Considering the possibility of early discontinuations, we set the target number of patients to 50 in total.

The intergroup comparisons of the seizure frequency between the rufinamide and the placebo groups were made using the Mann–Whitney U test. Subgroup analyses based on patient demographics and baseline characteristics were made by the point estimate of the median group difference and its 90% confidence interval (CI) calculated by the Hodges-Lehmann method. To evaluate subgroup difference, we also made the multiple regression analysis. Intergroup comparison of the 50% responder rate in tonic–atonic seizure frequency was made by Fisher’s exact test and by calculating an odds ratio with 90% CI. Intergroup comparison of the clinical global impression of the patients’ condition was made by the Mann–Whitney U test.

Statistical analysis was performed using SAS for Windows (version 9.2, SAS Institute Inc., Cary, North Carolina). The significance level of all statistical analyses was <0.1 (two-sided) as noted above.

Results

Patients’ characteristics

Sixty-six Japanese patients were enrolled during the baseline period, 59 of whom were randomized to the treatment groups (29 for rufinamide, 30 for placebo) (Fig. 1). Safety and tolerability were assessed in these 59 patients. One patient assigned to the rufinamide group was excluded from the efficacy analysis due to inappropriate diagnosis. Patients in both groups had similar demographic and baseline

![Figure 1 Patient disposition. Safety and tolerability were assessed in all 59 randomized patients. *: One of the 29 patients in the rufinamide group was excluded from the efficacy analysis due to inappropriate diagnosis. Accordingly, the efficacy analyses were performed in 58 patients (28 in the rufinamide group and 30 in the placebo group).](image-url)
Rufinamide was partially different between the rufinamide and placebo groups (Table 2). Approximately 40% of patients had underlying causes: for example, tuberous sclerosis and cerebral palsy in five patients each; cerebral dysgenesis, encephalitis and bacterial meningitis in three patients each.

**Efficacy**

The median percent change in the frequency of tonic–atonic seizures was −24.2% in the rufinamide group and −3.3% in the placebo group (p = 0.003), and that of total seizures was −32.9 and −3.1%, respectively (p < 0.001) (Fig. 2). Rufinamide adjunctive therapy significantly reduced the frequency of tonic seizures (p = 0.031), myoclonic seizures (p = 0.021), and partial seizures (p = 0.025) compared with placebo (Table 3).

The 50% responder rate for the tonic–atonic seizures was 25.0% in the rufinamide group and 6.7% in the placebo group (p = 0.074) (Fig. 3). The odds ratio was 4.67 (90%CI: 1.15, 18.95). No patient became free from seizures during the study.

The percent change in the tonic–atonic seizure frequency was greater in the rufinamide group than in the placebo group in all subgroups based on patient demographics and baseline characteristics (Table 4). Although the percentage of the patients on three AEDs was higher in the rufinamide group (Table 2), the number of concomitant AEDs did not affect group difference between rufinamide and placebo groups (Table 4).

| Table 1 | Dose titration schedule. |
|---------|--------------------------|
| Trial day | Daily dose by body weight (mg/day) |
| 15.0–30.0 kg | 30.1–50.0 kg | 50.1–70.0 kg | ≥70.1 kg |
| Day 1–2 | 200 | 400 | 600 | 600 |
| Day 3–4 | 400 | 800 | 1200 | 1200 |
| Day 5–6 | 800 | 1200 | 1800 | 1800 |
| Day 7–8 | 1000 | 1800 | 2400 | 2400 |
| Day 9 | 1000 | 1800 | 2400 | 3200 |

| Table 2 | Patients’ demographics and baseline characteristics. |
|---------|--------------------------------------------------|
| | Rufinamide (n = 28) | Placebo (n = 30) |
| Male, n (%) | 17 (60.7) | 19 (63.3) |
| Mean age (SD), year | 16.0 (7.1) | 13.9 (6.1) |
| 4 to <12, n (%) | 10 (35.7) | 13 (43.3) |
| 12 to <17, n (%) | 6 (21.4) | 6 (20.0) |
| ≥17, n (%) | 12 (42.9) | 11 (36.7) |
| Mean weight (SD), kg | 39.0 (19.5) | 40.9 (18.0) |
| Mean time since LGS diagnosis (SD), year | 10.5 (7.1) | 9.3 (5.8) |
| Underlying causes, n (%) | 12 (42.9) | 13 (43.3) |
| Transition from West syndrome, n (%) | 15 (53.6) | 15 (50.0) |
| Seizure type, n (%) | | |
| Multiple seizure types | 19 (67.9) | 24 (80.0) |
| Tonic–atonic seizure only | 9 (32.1) | 6 (20.0) |
| Tonic–atonic seizure frequency<sup>a</sup> | | |
| Median (range) | 234.9 (28.0–22,469.5) | 187.8 (8.3–5388.4) |
| Total seizure frequency<sup>a</sup> | | |
| Median (range) | 253.0 (95.4–22,499.4) | 296.7 (63.0–5759.7) |
| No. of concomitant AEDs, n (%) | | |
| One | 2 (7.1) | 1 (3.3) |
| Two | 3 (10.7) | 9 (30.0) |
| Three | 23 (82.1) | 20 (66.7) |
| Type of concomitant AEDs<sup>b</sup>, n (%) | | |
| Valproic acid | 25 (89.3) | 28 (93.3) |
| Lamotrigine | 13 (46.4) | 22 (73.3) |
| Clobazam | 12 (42.9) | 5 (16.7) |

LGS: Lennox–Gastaut syndrome, AED: antiepileptic drug.
<sup>a</sup> Seizure frequency per 28 days.
<sup>b</sup> Concomitant AEDs taken by at least 25% of patients in rufinamide and/or placebo groups at baseline period.
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Regarding the subgroup comparison, the multiple regression analysis (response variable: frequency change in tonic–atonic seizures, explanatory variables: sex, age, transition from West syndrome, seizure type, baseline frequency of tonic–atonic seizures, and concomitant AEDs) revealed that no factors independently affected the rufinamide efficacy (Supplementary Table).

Table 3
Percent change in the frequency of seizures other than tonic–atonic seizures per 28 days relative to baseline.

| Seizure type | Rufinamide | | Placebo | | p Value |
|--------------|------------|------------------|------------------|----------|
|              | n=28 | Median (range) | n=30 | Median (range) | |
| Tonic seizures | | | | | |
| Baseline frequency | 28 | 225.1 (21.8–22,469.5) | 28 | 124.2 (8.3–5388.4) | |
| Double-blind frequency | 28 | 136.2 (3.1–18,550.5) | 28 | 97.0 (3.4–4828.8) | |
| Median % reduction | 28 | -24.2 | 28 | -3.6 | 0.031 |
| Atonic seizures | | | | | |
| Baseline frequency | 10 | 21.7 (5.8–2503.4) | 12 | 17.7 (1.0–1284.9) | |
| Double-blind frequency | 10 | 17.9 (0.0–733.1) | 12 | 29.0 (0.0–1626.7) | |
| Median % reduction | 10 | -63.1 | 12 | -6.1 | 0.221 |
| Atypical absence seizures | | | | | |
| Baseline frequency | 12 | 40.9 (2.8–377.5) | 19 | 64.3 (1.0–549.6) | |
| Double-blind frequency | 12 | 15.2 (0.0–384.6) | 19 | 28.7 (0.3–753.8) | |
| Median % reduction | 12 | -59.0 | 19 | -21.1 | 0.128 |
| Myoclonic seizures | | | | | |
| Baseline frequency | 10 | 26.5 (4.7–3324.7) | 10 | 171.6 (1.0–1092.0) | |
| Double-blind frequency | 10 | 10.4 (0.0–863.9) | 10 | 120.2 (3.7–1470.5) | |
| Median % reduction | 10 | -52.4 | 10 | 6.6 | 0.021 |
| Tonic–clonic seizures | | | | | |
| Baseline frequency | 2 | 6.4 (5.2–7.5) | 10 | 4.9 (1.0–93.0) | |
| Double-blind frequency | 2 | 3.2 (0.0–6.4) | 10 | 5.9 (1.3–81.8) | |
| Median % reduction | 2 | -57.4 | 10 | 2.4 | 0.107 |
| Generalized clonic seizures | | | | | |
| Baseline frequency | 1 | 11.7 | 0 | — | |
| Double-blind frequency | 1 | 2.2 | 0 | — | |
| Median % reduction | 1 | -81.2 | 0 | — | |
| Partial seizures | | | | | |
| Baseline frequency | 4 | 103.1 (7.0–578.7) | 6 | 164.9 (24.9–252.0) | |
| Double-blind frequency | 4 | 13.0 (2.2–426.4) | 6 | 148.2 (27.7–342.5) | |
| Median % reduction | 4 | -52.2 | 6 | 4.5 | 0.025 |

*a Number of patients who experienced a given type of seizure during the baseline period.
Figure 3  Percentage of patients with ≥75% reduction, ≥50% reduction, ≥25% reduction, unchanged, and increase in the frequency of tonic–atonic seizures.

Table 4  Subgroup analyses of percent change in tonic–atonic seizure frequency.

|                     | Rufinamide |                     | Placebo |                     | Group difference (90%CI) |
|---------------------|------------|---------------------|---------|---------------------|--------------------------|
|                     | n          | Median              | n       | Median              |                          |
| All patients        | 28         | −24.2               | 30      | −3.3                | −26.7 (−40.3 to −11.8)   |
| Sex                 |            |                     |         |                     |                          |
| Male                | 17         | −37.5               | 19      | 5.1                 | −37.8 (−56.1 to −20.5)   |
| Female              | 11         | −13.2               | 11      | −10.4               | −5.9 (−41.4 to 14.9)     |
| Age (year)          |            |                     |         |                     |                          |
| 4 to <12            | 10         | −24.2               | 13      | −10.4               | −27.6 (−45.4 to −7.0)    |
| 12 to <17           | 6          | −25.4               | 6       | −5.1                | −23.4 (−127.6 to 26.0)   |
| ≥17                 | 12         | −22.1               | 11      | 1.2                 | −29.9 (−56.1 to −5.2)    |
| Time since LGS diagnosis (year) |          |                     |         |                     |                          |
| <9.9                | 14         | −21.7               | 16      | −2.6                | −27.5 (−48.2 to −5.9)    |
| >9.9                | 14         | −34.5               | 14      | −3.3                | −28.1 (−48.6 to 5.2)     |
| Underlying causes   |            |                     |         |                     |                          |
| Yes                 | 12         | −23.3               | 13      | −7.0                | −28.5 (−46.4 to −4.7)    |
| No                  | 16         | −27.1               | 17      | 0.5                 | −27.1 (−47.4 to −5.8)    |
| Transition from West syndrome |          |                     |         |                     |                          |
| Yes                 | 15         | −20.8               | 15      | 0.5                 | −20.2 (−40.1 to −0.3)    |
| No                  | 13         | −37.4               | 15      | −8.0                | −32.0 (−59.1 to −5.2)    |
| Seizure type        |            |                     |         |                     |                          |
| Multiple seizure types | 19       | −25.8               | 24      | −7.5                | −23.7 (−39.9 to −8.3)    |
| Tonic–atonic seizure only | 9        | −12.5               | 6       | 5.5                 | −28.4 (−75.2 to 1.2)     |
| Baseline seizure frequency |          |                     |         |                     |                          |
| ≤225.1 (tonic–atonic seizures) | 12      | −25.5               | 17      | 5.1                 | −30.0 (−60.2 to −8.3)    |
| >225.1 (tonic–atonic seizures) | 16     | −24.2               | 13      | −10.4               | −20.9 (−37.9 to −1.3)    |
| Number and type of concomitant AEDs |          |                     |         |                     |                          |
| 1 or 2 AEDs         | 5          | −17.4               | 10      | −4.6                | −14.9 (−39.8 to 7.8)     |
| 3 AEDs              | 23         | −37.4               | 20      | −3.3                | −29.5 (−48.4 to −11.4)   |
| Valproic acid       | 25         | −31.6               | 28      | −3.3                | −27.9 (−44.0 to −12.2)   |
| Clobazam            | 12         | −48.4               | 5       | −25.5               | −22.9 (−57.9 to 10.9)    |
| Lamotrigine         | 13         | −22.6               | 22      | −9.2                | −22.5 (−41.7 to −2.1)    |

LGS: Lennox–Gastaut syndrome, CI: confidence interval, AED: antiepileptic drug.
Table 5  Numbers of patients with common treatment-related adverse events by age.

| Age (year) | Rufinamide | Placebo |
|------------|------------|---------|
|            | 4 to <12   | 12 to <17 | ≥17      | 4 to <12 | 12 to <7 | ≥17 |
| All patients | 10        | 6       | 13      | 13       | 6       | 11 |
| Decreased appetite | 1 (10.0) | 0 (0.0) | 4 (30.8) | 0 (0.0) | 0 (0.0) | 1 (9.1) |
| Somnolence | 0 (0.0) | 1 (16.7) | 4 (30.8) | 1 (7.7) | 0 (0.0) | 0 (0.0) |
| Vomiting | 1 (10.0) | 1 (16.7) | 2 (15.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Number of patients (%).

Safety

AEs occurred in 93.1% of patients in the rufinamide group and 70.0% in the placebo group. All AEs were mild to moderate in severity.

Treatment-related AEs occurred in 62.1% of patients in the rufinamide group and 16.7% in the placebo group. The common treatment-related AEs in the rufinamide group were decreased appetite (17.2% for rufinamide, 3.3% for placebo), somnolence (17.2% for rufinamide, 3.3% for placebo), and vomiting (13.8% for rufinamide, 0% for placebo) (Table 5).

Transient seizure aggravations were observed in 13 (22.0%) of the 59 patients [eight (27.6%) in the rufinamide group and five (16.7%) in the placebo group]. All events required rescue medication, and all medications actually used were diazepam suppositories. When we defined status epilepticus as "the situation in which a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between seizures does not occur", seven (11.9%) of the 59 patients [five (17.2%) in the rufinamide group and two (6.7%) in the placebo group] were diagnosed as having status epilepticus in the double-blind period. The remaining patients experienced seizure-clustering. Four patients experienced transient seizure aggravations several times during this trial, but all events were the same type of events in a given patient.

Regarding the causal relationship with the blinded study drug, only one of the 13 patients was thought to have a treatment-related AE. This patient belonged to the rufinamide group. He experienced status epilepticus on Day 74 while receiving 2400 mg/day of rufinamide. He completed the study after resolution of this event. Causality in the other 12 patients was ruled out by the investigator because these patients had experienced transient seizure aggravations before participating in this trial.

Rash was reported in three patients (two in the rufinamide group and one in the placebo group). An 11-year-old boy in the rufinamide group experienced a rash on Day 13, but he continued the study based on the clinical judgment of the investigator, because his seizures had markedly decreased and his skin symptoms were not severe. His skin symptoms improved gradually 1 week after onset as a result of tentative cessation of rufinamide and administration of an anti-allergic drug. He completed the study without early discontinuation. The other patient, a 9-year-old boy in the rufinamide group, developed a rash on Day 14, and he then discontinued the study due to the event.

Fifty-four (91.5%) patients completed the trial, and five (8.5%) discontinued early due to AEs. AEs that resulted in discontinuation were reported in four (13.8%) patients in the rufinamide group and in one (3.3%) in the placebo group. The AEs responsible for withdrawal in the rufinamide group were rash, purpura, and decreased appetite (one patient each), and vomiting, dizziness, and headache (one patient experienced all three AEs). Among the patients who completed the trial, seven (25.0%) in the rufinamide group and one (3.3%) in the placebo group underwent a one-step dose reduction of the blinded study drug due to safety concerns.

AEs related to laboratory tests were experienced by a few patients in each treatment group, but no differences were apparent between the two groups. No electrocardiographic abnormalities were observed in either group.

Pharmacokinetics

Plasma concentrations [mean ± standard deviation (SD)] of rufinamide between 1 and 9 h after administration were 17.2 ± 6.2 μg/mL; no effect was found in relation to body weight (Fig. 4), and no differences were detected in relation to age. The highest concentration was 39.9 μg/mL approximately 2 h after administration, and the corresponding patient (an 18-year-old woman) discontinued the study due to decreased appetite, though her seizures had very much improved.

Rufinamide had no effect on the plasma concentrations of valproate, lamotrigine, or clobazam. Due to the small number of patients, we were unable to evaluate the effects of rufinamide on the plasma concentrations of other concomitantly administered AEDs or the effects of concomitantly administered AEDs on the plasma concentrations of rufinamide.
Discussion

Therapeutic evidence for rufinamide in the treatment of LGS has been scarce because large-scale clinical trials are difficult to conduct due to the low prevalence rate of LGS. Furthermore, it is not easy to accurately evaluate the efficacy of AEDs for LGS due to the multiple seizure types and the high seizure frequency in this syndrome. It also might be difficult for caregivers to identify all seizures throughout the day. To obtain accurate data about seizures, we provided all caregivers who recorded a seizure diary with standardized training before the start of the baseline period. In particular, we gave priority to consistency in seizure recording throughout the clinical study, because it is essential for valid evaluation of change in seizure frequency.

Compared with the previous study (Glauser et al., 2008), the percent change in the frequency of total seizures was compatible (−32.9% vs −32.7%), while the percent change in the tonic–atomic seizure frequency was smaller (−24.2% vs −42.5%) in the present study. In the present study, one-step dose reduction due to safety concerns was permitted; this might have affected the efficacy evaluation, considering the dose-dependent effect of rufinamide in a clinically relevant concentration range (Perucca et al., 2008). In addition, the small sample size of the study might have affected efficacy assessment. Meanwhile, the odds ratio of the 50% responder rate for the tonic–atomic seizure frequency was greater in the present study than in the previous study (4.67 vs 3.81). This fact provides further supportive evidence of rufinamide’s effectiveness.

In the present clinical trial, significant intergroup differences were found in tonic seizures, myoclonic seizures, and partial seizures. However, this result was somewhat different from that of the previous study (Glauser et al., 2008), in which absence seizures and atomic seizures were significantly improved by rufinamide. Nevertheless, all types of seizures were improved in the rufinamide group of both studies as far as the median values were concerned. This fact suggests that rufinamide can be effective for various types of seizure associated with LGS, as also indicated by other studies (Kim et al., 2012; Olson et al., 2011).

LGS is an epilepsy syndrome associated with various underlying causes and a relatively wide age-range at onset of seizures. The clinical course of LGS is also variable, and a certain number of patients have a history of West syndrome (Arzimanoglou et al., 2009; Beaumanoir, 1985; Ohtahara et al., 1995; Ohtsuka et al., 1990). We performed subgroup analyses of percent change in tonic–atomic seizure frequency to evaluate the effect of patient characteristics on the efficacy of rufinamide. Although the number of patients in each subgroup was too small to make statistical comparisons, the efficacy of rufinamide seemed to be consistent independent of clinical background characteristics. The multivariate analysis revealed that all clinical background characteristics including sex and concomitant AEDs were not independently related to the efficacy of rufinamide.

In this study, rufinamide was well tolerated, and AEs or treatment-related AEs were mostly similar to those reported in other studies (Brodie et al., 2009; Glauser et al., 2008; Kluger et al., 2009, 2010; Wheless and Vazquez, 2010). All transient seizure aggravations including status epilepticus in this trial were not severe and were able to be controlled by diazepam suppositories alone. The ratio of their occurrence was higher in the rufinamide group than in the placebo group; however, of the 13 patients, a causal relationship was considered likely in only one patient in the rufinamide group. It is well known that status epilepticus, especially nonconvulsive status epilepticus, is sometimes observed during the clinical course of LGS (Arzimanoglou et al., 2009; Beaumanoir, 1985; Hoffmann-Riem et al., 2000). Almost all patients with transient seizure aggravations in the present trial also had experienced similar events before participating in this trial. Although seizure aggravations were also reported during other clinical trials of rufinamide, their causal relationships with rufinamide were not clearly proven (Coppola et al., 2010; Glauser et al., 2008; Kim et al., 2012; Lee et al., 2013; Olson et al., 2011). Considering all these facts, it is not likely that rufinamide was the main cause of transient seizure aggravations in the present clinical trial. Nevertheless, we should carefully monitor the changes in frequency and severity of seizures after administration of rufinamide, because aggravation of seizures by AEDs is generally known, especially in patients with childhood refractory epilepsy such as LGS (Ohtsuka et al., 2006; Perucca et al., 1998; Sazgar and Bourgeois, 2005).

The limitation of the present clinical trial was that the sample size was relatively small, which could have affected the evaluations of efficacy and safety. However, the distribution of responders was obviously different between the rufinamide and placebo groups, and the analyses of multiple efficacy variables indicated that rufinamide was robustly beneficial as an adjunctive therapy for LGS. The other limitation was that this was a short-term clinical trial. In order to elucidate the long-term efficacy and safety of rufinamide, we are conducting an open-label extension study following the present study.

Conclusion

To evaluate the efficacy, safety, and pharmacokinetics of rufinamide as an adjunctive therapy for patients with LGS, we performed a multicenter randomized, double-blind
placebo-controlled trial in Japan. The results of this clinical trial demonstrated that rufinamide was an efficacious and well-tolerated adjunctive therapy in patients with LGS across a wide age range.

**Disclosure**

Yoko Ohtsuka serves as a consultant for Eisai Co., Ltd. Hiroki Takano is an employee of Eisai Co., Ltd. The remaining authors were involved as study investigators. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Eisai Co., Ltd. (Tokyo, Japan) was solely responsible for the design and conduct of the study as well as the collection, management, and analysis of the data. This study was also supported by grant from Japanese government which was specifically aimed to resolve ‘Drug Lag’ problem in Japan.

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