


Novel seizure outcomes in patients with Lennox-Gastaut syndrome: Post hoc analysis of seizure-free days in rufinamide Study 303

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Summary

Objective: Drug development for patients with Lennox-Gastaut syndrome (LGS) is based on clinical trials that use drop seizure counts. However, such counts do not assess total seizure burden and affect a patient's quality of life (QoL). In this post hoc analysis, we evaluated two novel seizure efficacy parameters related to QoL in pediatric patients with LGS, using seizure diary data from rufinamide Study 303 (NCT01405053).

Methods: Study 303 was a phase III, multicenter, randomized, controlled, open-label study involving patients aged ≥ 1 to < 4 years with inadequately controlled LGS. Patients were randomized 2:1 to receive add-on therapy with rufinamide or any other approved antiseizure drug (ASD), in addition to their existing treatment of 1-3 ASDs, across a 106-week treatment phase. Seizure diaries, completed by parents or caregivers, recorded seizure occurrence, and were used in this post hoc analysis to evaluate two novel efficacy parameters comparing baseline vs postbaseline mean number of seizure-free days and assessing time to reach the number of prerandomization seizures for patients receiving rufinamide or any other ASD.

Results: Patients received rufinamide ($n = 25$) or any other ASD ($n = 12$). For rufinamide, mean number of seizure-free days was 42.2% greater postbaseline compared with baseline ($P < 0.0001$); only one rufinamide patient experienced a decrease in number of seizure-free days postbaseline. Median time to reach the baseline number of seizures increased by 10.5 days for rufinamide and 0.5 days for the any-other-ASD group during the treatment phase, to 46.0 and 54.0 days, respectively.

Significance: Both of these novel and contrasting endpoints demonstrated potential improvements in seizure outcomes in patients receiving rufinamide postbaseline vs baseline. Although these parameters should be investigated in larger patient populations, our initial findings suggest that they could be applied as predefined primary endpoints for seizure assessment in future clinical trials for LGS drug development.

KEYWORDS

antiseizure drug, children, epilepsy, Lennox-Gastaut syndrome, rufinamide

1 | INTRODUCTION

Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy resulting in cognitive impairment, with onset usually occurring before the age of 8 years.^{1–3} Effective treatment and management of LGS depends on an accurate and early diagnosis.⁴ Although there is no precise definition of LGS, no biologic marker, and a heterogeneous etiology,⁵ LGS is characterized by multiple seizure types, including tonic, atonic, and atypical absence seizures, and key abnormal electroencephalography features consisting primarily of an interictal pattern of slow spike-wave complexes at <3 Hz that occur during wakefulness.⁵ Although commonly observed in LGS and initially considered to be indicative of the syndrome,⁶ intellectual disability and behavioral problems are not necessarily present in all patients with LGS at diagnosis, and hence are not included in the diagnostic criteria.⁵ In addition, the diagnostic signs of LGS are not pathognomonic of the syndrome and can develop over time, causing uncertainty in distinguishing LGS from other epilepsy syndromes.^{2,4,5}

Drug development for LGS is based on randomized controlled trials using drop seizure counts (both tonic and atonic seizures resulting in falls) as a primary outcome. This is because drop seizures are reliably countable and considered one of the most clinically significant outcomes in LGS because of the physical damage they can cause, including recurrent injuries.⁷ However, assessment of drop seizures alone does not allow for evaluation of drug efficacy on other seizure types, such as tonic-clonic, focal-onset, atypical absences, and epileptic spasms,⁷ or the assessment of total seizure burden. Although seizures resulting in falls affect the quality of life (QoL) of a patient with LGS, the total number of seizures affect patient's QoL more globally, as seizure frequency appears to be correlated with cognitive function.^{7,8} Consequently, developing novel endpoints that consider all LGS seizure types and account for total seizure burden may provide a more complete assessment of drug efficacy in patients with LGS.

Rufinamide (1-[(2,6-difluorophenyl) methyl]-1H-1,2,3-triazole-4 carboxamide) is a triazole derivative structurally unrelated to other currently approved antiseizure drugs (ASDs). As of October 2018, rufinamide is approved for adjunctive treatment of seizures associated with LGS in patients ≥ 1 year of age in >30 countries, and in patients ≥ 4 years of age in >45 countries. Rufinamide received initial US Food and Drug Administration approval in 2008, and as of October 2018, it is indicated in the United States for adjunctive treatment of seizures associated with LGS in patients ≥ 1 year of age and in adults.⁹

Study 303 (ClinicalTrials.gov identifier: NCT01405053) was a multicenter, randomized, open-label, phase III study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and behavioral effects of adjunctive rufinamide in

Key Points

- Lennox-Gastaut syndrome (LGS) trials rely on drop seizure counts as a primary outcome, but do not account for other seizure types or assess total seizure burden
- This post hoc analysis applied two novel endpoints to assess seizure-free days in pediatric patients with LGS from rufinamide Study 303
- For patients treated with rufinamide, the mean number of seizure-free days was 42.2% greater postbaseline compared with baseline
- An increase in median time to reach baseline number of seizures was observed during the treatment phase for rufinamide vs any other antiseizure drug (ASD)
- These parameters potentially represent new primary endpoints for seizure assessment in patients with LGS in future clinical trials

pediatric patients (≥ 1 to <4 years of age) with inadequately controlled seizures associated with LGS. A 6-month interim analysis of safety and PK outcomes from Study 303 has been previously reported¹⁰; the results of this interim analysis led to the expansion of the rufinamide indication in 2015 to include pediatric patients ≥ 1 year of age in the United States.⁹ The final 2-year safety, tolerability, and behavioral outcomes from Study 303 were recently published and found that long-term treatment with rufinamide was well tolerated in pediatric patients with LGS.¹¹ Herein we report the results of an initial post hoc analysis, based on the final data from Study 303, to explore two novel seizure efficacy parameters and assess if they could be investigated further in larger clinical trials. These parameters were the number of days without a seizure and the time taken during treatment to reach the number of seizures at baseline.

2 | METHODS

2.1 | Study design

Study 303 was a multicenter, randomized, controlled, open-label, phase III study conducted between June 2011 and November 2015 at 19 centers across Canada, France, Greece, Italy, Poland, and the United States. Study 303 adheres to the principles of the Declaration of Helsinki, the European Agency for the Evaluation of Medicinal Products, the United States Code of Federal Regulations, and the European Good Clinical Practice and Clinical Trial Directives, and it was approved by the institutional review boards at all sites.¹⁰ Written informed consent was obtained from each patient's guardian or legal representative.

The study design has been described previously.^{10,11} Briefly, eligible patients were ≥ 1 to < 4 years of age, with inadequately controlled LGS, and receiving fixed doses of 1-3 ASDs for a minimum of 4 weeks prior to randomization. Following the prerandomization phase (screening period and baseline visit; 1-8 weeks ["baseline"]), patients were randomized 2:1 to receive add-on therapy with rufinamide oral suspension or any other approved ASD of the investigator's choice for a 106-week treatment period (titration period and maintenance period ["postbaseline"]) defined as treatment start date to treatment end date. Titration of rufinamide began at a 10 mg/kg/day dose. The dose was increased by 10 mg/kg/day every 3 days to 40 mg/kg/day, at which point the dose was increased by 5 mg/kg/day to a target maintenance dose of 45 mg/kg/day, given in two equally divided doses. In response to tolerability issues, titration and target doses of rufinamide could be adjusted at the investigator's discretion, and the dose achieved at the end of the titration phase was to be maintained throughout the maintenance phase. The administration of other ASDs was undertaken according to the investigator's usual practice by allowing the investigator to add any other approved add-on ASD of their choice. Rufinamide or the selected add-on ASD could have been discontinued and replaced with another add-on ASD if either rufinamide or the selected add-on ASD were not well tolerated by the patient, according to the investigator's opinion. This could have been repeated if the selected add-on ASD was not tolerated or if there was a lack of efficacy. The Safety Analysis Set included all enrolled patients who had received at least one dose of rufinamide or any other approved add-on ASD of the investigator's choice, and who had at least one postdose safety assessment.

2.2 | Seizure-free days analyses

Throughout Study 303, seizures were assessed by parents or caregivers and occurrences were recorded in seizure diaries on a daily basis. Every effort was made to have the same person record seizures in a consistent manner throughout the study and to enter seizure information to the best of their ability. Data for the current analyses were obtained from these seizure diaries, and patients with both recorded baseline information and seizure data were included in the seizure-free days analysis. Days with no seizure records were considered to be seizure free. Percentages of seizure-free days were calculated based on the number of seizure-free days at baseline or postbaseline divided by the total number of days at baseline or postbaseline, respectively, multiplied by 100. Comparisons between baseline and postbaseline for mean number of seizure-free days was performed for both the rufinamide and any-other-ASD groups, and significance was tested with parametric (*t* test) and nonparametric (sign and signed-rank) tests.

Time-to-event analysis was performed on both treatment groups to assess the median number of days that it took during treatment (postbaseline) to reach the number of seizures at baseline.

3 | RESULTS

3.1 | Patients

Overall, 43 patients were enrolled in Study 303. Of these, 37 patients were randomized to rufinamide ($n = 25$) or any other ASD ($n = 12$), and all were included in the Safety Analysis Set. Demographic and baseline characteristics for the 37 randomized patients are shown in Table 1; the two treatment groups were generally well balanced for age and weight. For the any-other-ASD group, those selected by the investigators at randomization were lamotrigine (41.7%), clobazam and topiramate (16.7% each), and phenobarbital, valproic acid, and zonisamide (8.3% each). Mean (standard deviation [SD]) postbaseline durations were 103.6 (32.3) weeks for the rufinamide group and 73.6 (33.9) weeks for the any-other-ASD group.

3.2 | Percentage of seizure-free days at baseline and postbaseline

The analysis of seizure-free days included 24 patients who received treatment with rufinamide and 8 patients who received treatment with any other ASD. The mean percentage of seizure-free days recorded at baseline was 19.1% for the rufinamide group and 32.1% for the any-other-ASD group. These increased postbaseline, for both treatment groups, to 61.3% and 53.4% for rufinamide and any other ASD, respectively.

3.3 | Baseline vs postbaseline comparisons of seizure-free days for rufinamide and the any-other-ASD group

For rufinamide, the mean number of seizure-free days was 42.2% greater postbaseline compared with baseline ($P < 0.0001$ by *t* test). Due to a slightly skewed distribution in the data (not shown), this comparison was also tested and found to be significant ($P < 0.0001$) by nonparametric (sign and signed-rank) tests. Only one patient receiving rufinamide experienced a decrease in the number of seizure-free days postbaseline, as indicated by the comparison of percent seizure-free days for rufinamide-treated patients during baseline vs postbaseline (Figure 1A). For the any-other-ASD group, the mean number of seizure-free days was 21.3% greater postbaseline compared with baseline (Figure 1B); however, this comparison was not found to be significant (*t* test, sign and signed-rank tests).

TABLE 1 Patient demographics and baseline characteristics (Safety Analysis Set)

Category	Rufinamide (n = 25) ¹¹	Any other ASD (n = 12) ¹¹	Total (n = 37) ¹¹
Mean age, ^a ¹¹ months (SD)	28.3 (10.0)	29.8 (9.9)	28.8 (9.8)
Female, ¹¹ n (%)	11 (44.0)	2 (16.7)	13 (35.1)
Race, n (%)			
Caucasian	23 (92.0)	9 (75.0)	32 (86.5)
Black or African American	2 (8.0)	2 (16.7)	4 (10.8)
Other	0 (0.0)	1 (8.3)	1 (2.7)
Mean weight, ¹¹ kg (SD)	12.5 (3.2)	13.4 (2.8)	12.8 (3.1)
Mean time since diagnosis, ¹¹ months (SD)	19.9 (9.9)	23.0 (9.5)	20.9 (9.8)
Seizure type, ^b ¹¹ n (%)			
Partial	15 (60.0)	7 (58.3)	22 (59.5)
Absence	5 (20.0)	4 (33.3)	9 (24.3)
Atypical absence	12 (48.0)	6 (50.0)	18 (48.6)
Myoclonic	15 (60.0)	10 (83.3)	25 (67.6)
Clonic	6 (24.0)	4 (33.3)	10 (27.0)
Tonic-atonic	15 (60.0)	8 (66.7)	23 (62.2)
PGTC	6 (24.0)	3 (25.0)	9 (24.3)
Other	9 (36.0)	1 (8.3)	10 (27.0)

ASD, antiseizure drug; PGTC, primary generalized tonic-clonic; SD, standard deviation.

Permissions have been requested to reproduce data previously reported in Arzimanoglou et al (Eur J Paediatr Neurol 2019;23:126-135).

^aAge was calculated at date of informed consent.¹¹

^bPatients could have had ≥1 type of seizure.¹¹

3.4 | Time to baseline number of seizures for rufinamide vs any other ASD

The median number of seizure-diary data-collection days at baseline (consent date to randomization date) was 35.5 for the rufinamide group and 53.5 for the any-other-ASD group (Table 2). Postbaseline, the median time to reach the baseline number of seizures increased during the treatment phase by 10.5 days (29.6%) for the rufinamide group and 0.5 days (0.9%) for the any-other-ASD group, to 46.0 days and 54.0 days, respectively (Table 2).

4 | DISCUSSION

For patients with LGS, there is an unmet need to develop endpoints for clinical trials that assess total seizure burden. The post hoc analysis reported here was performed

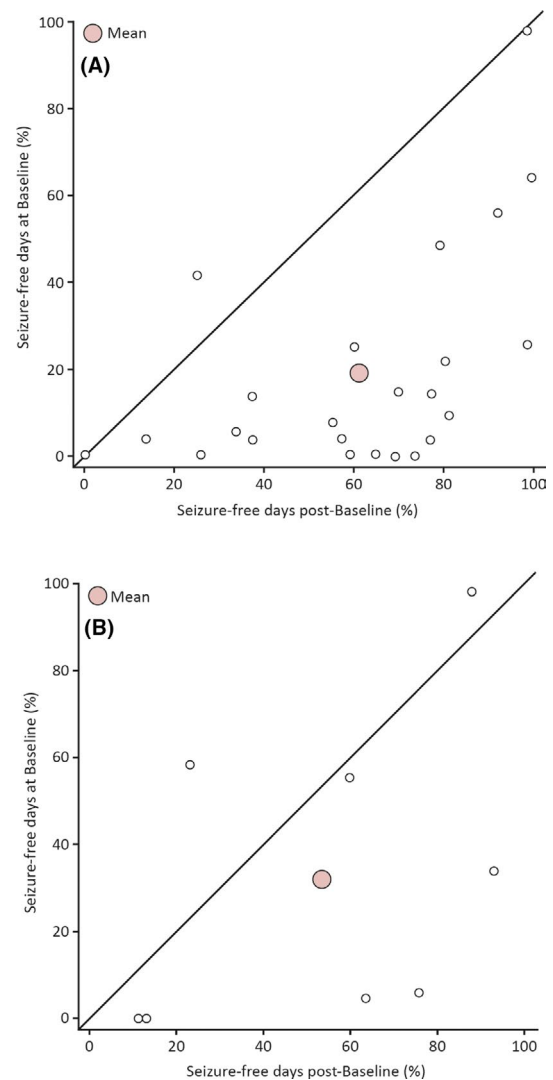


FIGURE 1 Comparison of percent frequency of seizure-free days for patients treated with rufinamide (A) and any other ASD (B) during baseline and postbaseline phases

to evaluate the potential of two novel endpoints for the assessment of ASD efficacy in pediatric patients with LGS, using seizure diary data from the phase III, randomized, open-label Study 303. These endpoints were the comparisons of baseline vs postbaseline seizure-free days following treatment with either rufinamide or any other ASD, and time-to-event analysis to compare the time taken to reach the baseline number of seizures in both the rufinamide and any-other-ASD groups.

Both endpoints indicated a change from baseline after randomization in seizure burden for patients receiving rufinamide. Rufinamide was associated with improved outcomes in pediatric patients with LGS, and the 42.2% increase in mean number of seizure-free days from baseline observed in patients treated with rufinamide may represent a significant benefit for this patient population. The robustness of this comparison between baseline and postbaseline number

TABLE 2 Summary of number of days postbaseline to reach baseline number of seizures

	Treatment	
	Rufinamide (n = 24)	Any other ASD (n = 8)
Median (min, max) number of seizure-diary data-collection days at baseline (consent to randomization)	35.5 (9, 56)	53.5 (21, 84)
Median (95% CI) number of days postbaseline to reach baseline number of seizures	46.0 (24.0-58.0)	54.0 (0-385.0)
Increase postbaseline vs baseline, days (%)	10.5 (29.6)	0.5 (0.9)

ASD, anti-seizure drug; CI, confidence interval; max, maximum; min, minimum.

of seizure-free days was indicated by similar outcomes with parametric and nonparametric tests. In addition, a time-to-event analysis indicated that the increase in median time to reach the baseline number of seizures was considerably greater for the rufinamide group than for the any-other-ASD group (10.5 vs 0.5 days, respectively).

These endpoints were applied together to counterbalance each other's limitations. A potential limitation of assessing the mean number of seizure-free days is the occurrence of cluster seizures, as counting seizure-free days may not capture a reduction or an increase in the overall frequency of seizures. To overcome this, we analyzed the time taken to reach the baseline number of seizures to indicate any potential relationship between increased number of seizure-free days and lower seizure frequency. Further limitations of these analyses include the fact that this was a post hoc analysis involving a small population of patients with highly refractory seizures. In addition, LGS is not a single disease and patients have varied clinical characteristics, involving many different etiologies and seizure types,^{2,12} hence responses to ASDs may differ greatly. The seizure diaries used in Study 303 allowed only for seizures to be recorded on a daily basis, and there was no option for recording seizure frequency over shorter time intervals. For future clinical trials, seizure diaries could be made more appropriate for seizure-free analyses by containing a question for parents or caregivers to specifically confirm that no seizures were observed during the defined time period or to record information over a shorter period.

Although the study population may not be representative of a typical LGS population, most notably due to the relatively young age of the patients involved (mean age, 28.8 months), the availability of daily seizure diary data from Study 303 permitted this type of analysis to be performed in a patient population that fulfilled the accepted regulatory inclusion criteria for an LGS study. Additional limitations of Study 303 are the lack of blinding and the low number of patients included in the any-other-ASD group compared with the rufinamide group; however, these study limitations should have little influence on use of the Study 303 dataset in this post hoc analysis to assess seizure-free

days as a potential endpoint. Conceivably, these endpoints could be used for any LGS population and could enable a move toward a clinical trial endpoint that accounts for total seizure burden. In addition, the time-to-event analysis may identify worsening seizure outcomes earlier, therefore, allowing discontinuation of treatment and shorter involvement in trials for those patients who are not benefiting from treatment. Evaluation of novel primary endpoints such as these do require further study, including analysis in a randomized, controlled trial involving a larger and more typical LGS population.

As far as we are aware, this is the first reported application of a seizure-free days analysis to study ASD efficacy in patients with LGS. More commonly used seizure assessments tend to be quantitative variables and may be considered to be only partially reliable. In contrast, evaluating a day as seizure-free or not represents a binary clinical outcome. Here, our assessment of seizure-free days relied on the assumption that seizure diary days with no recorded seizure were seizure-free; future application of seizure-free days as an endpoint should entail the recording of days on which no seizure occurred, to produce a confirmed binary outcome. The parameters reported here might represent new primary endpoints in clinical trials for seizure assessment in patients with LGS that may be clinically significant and allow greater evaluation of drug efficacy on other LGS seizure types and assessment of total seizure burden. With further evaluation, we anticipate that these could be applied as predefined endpoints in future trials for LGS drug development.

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CONFLICTS OF INTEREST

Stéphane Auvin has served as a consultant for Biocodex, Eisai, GW Pharma, Novartis, Nutricia, Shire, UCB Pharma, Ultragenyx, and Zogenix. Betsy Williams is a former employee of Eisai Inc. and has carried out consultancy work for Eisai Inc. Rob McMurray is an employee of Eisai Ltd. Dinesh Kumar, Carlos Perdomo, and Manoj Malhotra are employees of Eisai Inc. 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.

AUTHOR CONTRIBUTIONS

All authors were involved in the study design, interpretation of the results, and the reviewing and approval of the manuscript, and in the decision to submit the article for publication. All authors also confirm accountability for the accuracy and integrity of the work. Dinesh Kumar and Carlos Perdomo conducted the data analysis.

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