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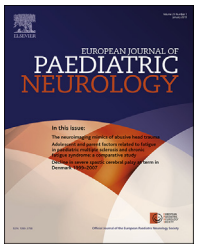

Original article

Evaluation of long-term safety, tolerability, and behavioral outcomes with adjunctive rufinamide in pediatric patients (≥1 to <4 years old) with Lennox-Gastaut syndrome: Final results from randomized study 303

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ABSTRACT

Objective: Evaluate the long-term safety, tolerability, and behavioral effects of adjunctive rufinamide in pediatric patients (≥1 to <4 years old) with inadequately controlled seizures associated with Lennox-Gastaut syndrome (LGS).

Methods: Study 303 (ClinicalTrials.gov identifier NCT01405053) was a multicenter, randomized, open-label, Phase III trial. Patients were randomized (2:1) to oral suspension rufinamide (≤45 mg/kg/day) or any other investigator-chosen antiepileptic drug (AED) for a 2-year treatment period. Primary safety/tolerability assessments included monitoring of treatment-emergent adverse events (TEAEs) and serious TEAEs. Behavioral effects were assessed via the Child Behavior Checklist (CBCL) using the Total Problems score and change from baseline in CBCL Total Problems score. CBCL subscores were also evaluated.

Results: The Safety Analysis Set included 37 patients (rufinamide: $n = 25$; any other AED: $n = 12$). TEAE incidence was similar between the rufinamide (88.0%) and any-other-AED groups (83.3%); serious TEAE incidence was also similar between treatment groups

Abbreviations: AE, adverse event; AED, antiepileptic drug; CBCL, child behavior checklist; ECG, electrocardiogram; EEG, electroencephalogram; EXC, exclusion; INC, inclusion; LDS, language development survey; LGS, Lennox-Gastaut syndrome; max, maximum; min, minimum; PK, pharmacokinetic; QoLCE, quality of life in childhood epilepsy; SD, standard deviation; TEAE, treatment-emergent adverse event.

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(40.0% and 41.7%, respectively). Between treatment groups, the difference in the least squares mean CBCL Total Problems score across time was not significant ($p = 0.7083$), behavior outcomes were similar across all endpoints, and there were no consistent trends in CBCL subscores.

Significance: Long-term (2 years) adjunctive rufinamide was well tolerated in pediatric patients with LGS. Behavioral outcomes were comparable between the rufinamide and any-other-AED groups, however the small sample size and difficulties assessing behavior in this population should be noted. The challenges of this study raise the issue of revising how studies in very young children with rare and complex epilepsies are performed.

1. Introduction

Lennox-Gastaut syndrome (LGS) is a severe epileptic and development encephalopathy that typically has an onset between 3 and 7 years of age (most commonly between 3 and 5 years of age).[1–3] LGS is characterized by multiple seizure types (tonic, atypical absence, and atonic), abnormal electroencephalogram (EEG) patterns (slow spike–wave complex), cognitive impairment, and behavioral problems (hyperactivity, aggression, and autistic traits).[1,2,4] However, due to the lack of a biological marker, the heterogeneous etiology of LGS, and the fact that in most cases the full clinical picture is not understood at disease onset,[5] an accurate diagnosis of LGS can be difficult to achieve, particularly in very young children.[1,6] Furthermore, the final prognosis of LGS remains poor due to difficulties in maintaining long-term seizure control, and persistent cognitive impairments and behavioral problems.[2,4]

Rufinamide (1-[(2,6-difluorophenyl) methyl]-1H-1,2,3-triazole-4 carboxamide) is a triazole derivative structurally unrelated to other currently approved antiepileptic drugs (AEDs).[7] Rufinamide received initial Food and Drug Administration approval in 2008, and is currently indicated in the United States for adjunctive treatment of seizures associated with LGS in patients ≥1 year of age and in adults.[8] At present, rufinamide is approved in 53 countries, including Canada and the European Union, for adjunctive treatment of seizures associated with LGS in patients ≥4 years of age. The approval of adjunctive rufinamide was primarily based on the results of Study 022, a double-blind, placebo-controlled study in patients ≥4–30 years of age with inadequately controlled LGS.[9] In this study, and compared with placebo, rufinamide was associated with greater median percent reductions in total and tonic–atonic seizure frequency per 28 days relative to baseline ($p = 0.0015$ and $p < 0.0001$, respectively), and greater improvements in seizure severity ($p = 0.0041$).[9]

There is currently little information available regarding the safety and tolerability of AEDs in very young patients with LGS, and as treatment options are limited in this patient population, it is important to continue to investigate the safety and efficacy of AEDs in these very young patients.[6] Furthermore, and given that LGS develops progressively, evidence that an AED known to be efficacious in LGS can also be tolerated in very young children may help to improve the overall prognosis of LGS.[6]

Study 303 was a multicenter, randomized, open-label, Phase III study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and behavioral effects of adjunctive rufinamide in 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 reported.[6] The PK profile of rufinamide in patients ≥1 to <4 years of age was shown to be comparable to that observed in previous studies in patients ≥4 years of age, indicating that dose adjustments in the younger patient group are not required based on body weight.[6] The results of the interim analysis led to the expansion of the rufinamide indication in 2015 to include pediatric patients ≥1 year of age in the United States.[8] Here, we report the final 2-year safety, tolerability, and behavioral outcomes from Study 303.

2. Materials and methods

2.1. Standard protocol approvals, registration, and patient consents

Study 303 (Eisai Inc. protocol E2080-G000-303; ClinicalTrials.gov identifier: NCT01405053) 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, European Agency for the Evaluation of Medicinal Products, United States Code of Federal Regulations, and European Good Clinical Practice and Clinical Trial Directives, and was approved by the institutional review boards at all sites.[6] Written informed consent was provided by parent(s) or legal representative(s) of the patients.

2.2. Patients

Eligible patients were ≥1 to <4 years of age with a clinical diagnosis of LGS, which might have included presence of a slow background EEG rhythm, slow spike–wave pattern (<3 Hz), and/or the presence of polyspikes. Patients were receiving stable doses of 1–3 concomitant AEDs for a minimum of 4

weeks prior to randomization with an inadequate response, and had consistent seizure documents with no uncertainty of the presence of seizures during the prerandomization phase. Patients were excluded if they had familial short QT syndrome or any significant disease that could affect the conduct of the study or the patient's safety. Detailed inclusion/exclusion criteria are provided in Supplementary Table 1.

2.3. Study design

The design of Study 303 has been previously described.[6] Briefly, after screening for eligibility, patients were randomized 2:1 to receive add-on therapy with rufinamide oral suspension or any other approved AED of the investigator's choice for a 106-week treatment period, including an initial 2-week titration phase and a 104-week maintenance phase (Fig. 1). Patients were assigned to treatment groups (rufinamide or any other AED) using a computer-generated random allocation sequence, which was approved and locked by an independent statistician. Randomization and dose dispensing at each visit was performed centrally by an Interactive Voice Response System. The 40 mg/ml oral suspension of rufinamide used in this study has been shown to be bioequivalent to the 400-mg oral tablet formulation previously used in Study 022.[10]

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 2 equally divided doses. If tolerability issues arose, titration could occur more slowly and/or conclude at a lower maintenance dose. Once the maintenance dose of rufinamide was reached, further dose adjustments were permitted according to the investigator's discretion. The administration of other AEDs was undertaken according to the investigator's usual practice by allowing the investigator to add any other approved add-on AED of their choice. A follow-up visit occurred 4 weeks after the last dose of rufinamide or other add-on AED at the end of the maintenance phase or after withdrawal from the study.

2.4. Safety/tolerability assessments

Routine safety/tolerability assessments consisted of monitoring and recording all treatment-emergent adverse events (TEAEs) and serious TEAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); and performance of physical examinations. An adverse event (AE) was considered treatment-emergent if the AE was: (a) absent at baseline and emerged during treatment; (b) present at baseline but stopped before treatment and re-emerged during treatment; or (c) continuous from baseline but became more severe during treatment relative to its pretreatment state.

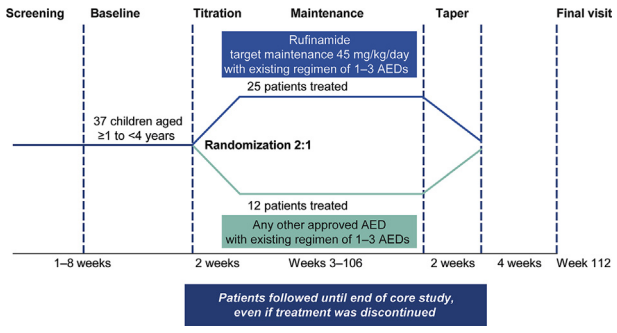

Fig. 1 – Study 303 design. AED = antiepileptic drug.

2.5. Behavioral assessments

Behavior was assessed via the Child Behavior Checklist (CBCL), which has previously been used to evaluate behavior in children as young as 1.5 years of age.[11,12] The CBCL is a 99-item questionnaire, completed by the patient's parent or guardian, that rates 8 problem areas: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behavior, and other problems; and additionally produces 3 summary scores: Internalizing, Externalizing, and Total Problems. The Total Problems score is the sum of all problem areas plus 1 additional item and higher scores indicate more problems. In Study 303, the primary efficacy endpoint was the CBCL Total Problems score at the end of the 2-year treatment period. Change from baseline in CBCL subscores was also assessed as an exploratory endpoint.

2.6. Statistical methods

2.6.1. Sample size

The final Study 303 protocol used a sample size of 75 patients (50 randomized to rufinamide and 25 to any other AED), to provide 84% power to detect a mean difference of approximately 23 (standard deviation [SD] = 25) in CBCL scores between children with documented psychopathological issues and those without. However, due to the difficulties in enrolling patients in this age group, the sample size was reduced to 37 patients (25 randomized to rufinamide and 12 to any other AED) during the interim analysis. A sample size of 37 patients provided 72% power. Overall, a total of 24 patients receiving rufinamide and 9 patients receiving any other AED had CBCL assessments at various times by the end of the study. A sample size of 24 patients had 70% power to detect events with a frequency of 5% and over 90% power to detect events with a frequency of 10%. Given that rufinamide is already approved for adjunctive treatment of LGS in patients ≥4 years old (≥1 year old in the United States), and population PK analyses have shown that no dose changes are required in patients ≥1 to <4 years old compared with those ≥4 years old,[6] these sample sizes were deemed acceptable by regulatory authorities to assess safety in this patient population.

2.6.2. Statistical analyses

All safety/tolerability analyses were based on the Safety Analysis Set, which included all enrolled patients who received at least 1 dose of rufinamide or any other approved add-on AED of the investigator's choice, and had at least 1 post-dose safety assessment. Safety/tolerability data, presented by treatment group, were summarized on an "as treated" basis. Study Day 1 for all safety/tolerability analyses was defined as the date of the first dose of study drug. Unless otherwise specified, all safety/tolerability summaries only included data from the period during which patients received

the initial randomized drug (from date of first dose until 7 days after date of last dose). Time to withdrawal from treatment due to occurrence of AEs or lack of efficacy was summarized by treatment group and analyzed using Kaplan–Meier curves.

Primary efficacy analyses were based on the Full Analysis Set for primary efficacy variables, which included all randomized patients who received rufinamide or any other approved add-on AED of the investigator's choice, and had baseline and at least 1 post-dose behavior measurement. CBCL Total Problems scores at the end of treatment were analyzed for the rufinamide and any-other-AED groups using an analysis of covariance model with last observation carried forward; baseline score and age were included as covariates, and sex and treatment were included as factors. To test the effect of time (weeks), treatment groups were compared by excluding treatment by week interaction. Treatment groups were declared significantly different if the p-value was less than 0.05 using a 2-sided test, and if the least squares mean of the rufinamide group was less than that of the any-other-AED group over time.

3. Results

3.1. *Patient allocation and demographics*

Between June 2011 and November 2015, a total of 43 patients were screened for entry into the study (Fig. 2). Of these, 6 patients failed screening, and 37 were randomized to treatment (rufinamide: $n = 25$; any other AED: $n = 12$) and included in the Safety Analysis Set. The Full Analysis Set for primary efficacy variables comprised 33 patients (rufinamide: $n = 24$; any other AED: $n = 9$). Overall, 18 patients discontinued from the study (rufinamide: $n = 10$ [40%]; any other AED: $n = 8$ [67%]; Fig. 2). Primary reasons for discontinuation were: AEs and withdrawal of consent (both $n = 3$ [12%]), and inadequate therapeutic effect and patient choice (both $n = 2$ [8%]) in the rufinamide group; and withdrawal of consent ($n = 4$ [33%]), and inadequate therapeutic effect, lost to follow-up, patient choice, and other (all $n = 1$ [8%]) in the any-other-AED group. There was 1 additional patient in the rufinamide group who discontinued rufinamide treatment but completed the study.

Demographic and baseline characteristics for the 37 randomized patients are shown in Table 1. The 2 treatment groups were generally well balanced for age, weight, and height. Approximately two-thirds of patients (67.6%) were 12–35 months old and 32.4% were 36–48 months old. Mean (SD) time since diagnosis was 19.9 (9.9) months in the rufinamide group and 23.0 (9.5) in the any-other-AED group.

Among patients in the Safety Analysis Set, 8.1% were taking 1 AED at baseline, 37.8% were taking 2 AEDs, 45.9% were taking 3 AEDs, 2.7% were taking 4 AEDs, and 5.4% were taking 5 AEDs. At baseline, the most common concomitant AEDs (≥20% in either treatment group) were valproic acid, levetiracetam, topiramate, diazepam, vigabatrin, clobazam, and lamotrigine

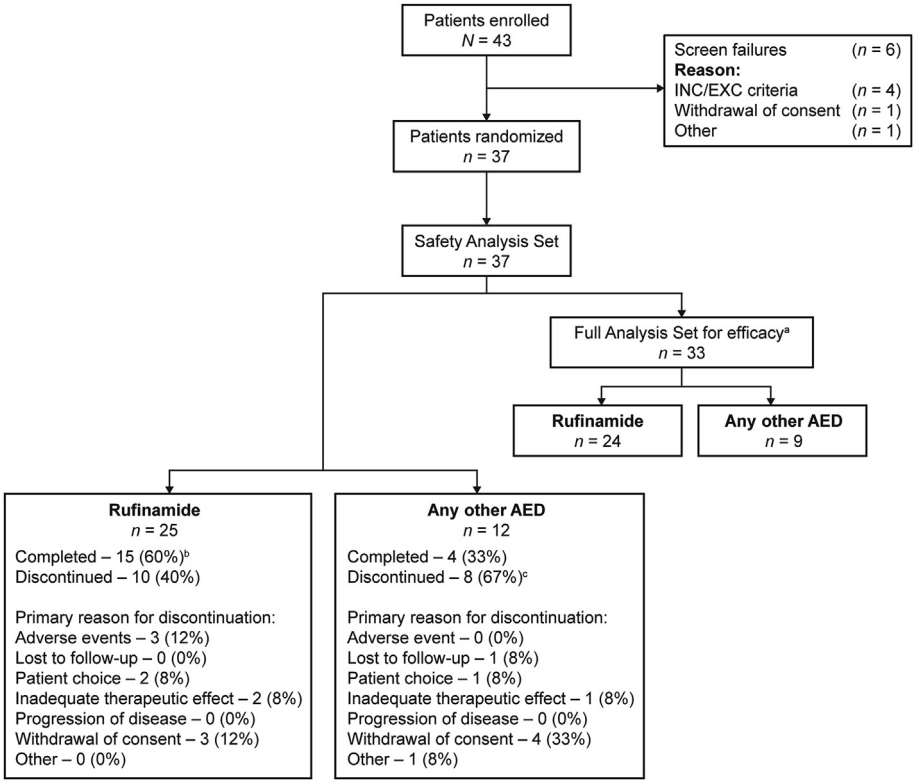

Fig. 2 – Patient flow. AED = antiepileptic drug; INC/EXC = inclusion/exclusion. [a]Four patients did not have post-baseline data and were thus not included in the Full Analysis Sets (rufinamide, $n = 1$; any other AED, $n = 3$). [b]One patient in the rufinamide group discontinued rufinamide treatment due to inadequate therapeutic effect but completed the study. [c]Six patients in the any-other-AED group simultaneously discontinued from treatment and the study, and 2 patients in this group discontinued randomized treatment before discontinuing from the study.

Table 1 – Demographic and baseline characteristics – safety analysis set.

Category	Rufinamide (N = 25), n (%)	Any other AED (N = 12), n (%)	Total (N = 37), n (%)
Age, months[a]			
Mean (SD)	28.3 (10.0)	29.8 (9.9)	28.8 (9.8)
Median	28.0	30.5	30.0
Min, max	12, 46	13, 47	12, 47
Age group, n (%)			
12–35 months	17 (68.0)	8 (66.7)	25 (67.6)
36–48 months	8 (32.0)	4 (33.3)	12 (32.4)
Sex, n (%)			
Male	14 (56.0)	10 (83.3)	24 (64.9)
Female	11 (44.0)	2 (16.7)	13 (35.1)
Ethnicity, n (%)			
Hispanic or Latino	5 (20.0)	3 (25.0)	8 (21.6)
Not Hispanic or Latino	20 (80.0)	9 (75.0)	29 (78.4)
Weight, kg			
Mean (SD)	12.5 (3.2)	13.4 (2.8)	12.8 (3.1)
Median	12.0	13.0	12.3
Min, max	7.0, 19.0	9.0, 19.0	7.0, 19.0
Height, cm			
Missing	1	0	1
Mean (SD)	91.4 (9.7)	92.7 (8.8)	91.8 (9.3)
Median	90.8	95.2	93.8
Min, max	72.0, 111.0	80.0, 106.6	72.0, 111.0
Mean time since diagnosis, months (SD)	19.9 (9.9)	23.0 (9.5)	20.9 (9.8)
Seizure type,[b] 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)
Primary generalized tonic–clonic	6 (24.0)	3 (25.0)	9 (24.3)
Other	9 (36.0)	1 (8.3)	10 (27.0)

AED = antiepileptic drug; Max = maximum; Min = minimum; SD = standard deviation.
[a] Age was calculated at date of informed consent.
[b] Patients could have had more than one type of seizure.

(Table 2). The add-on AEDs selected by investigators at randomization for the any-other-AED group were lamotrigine (41.7%), clobazam and topiramate (16.7% each), and phenobarbital, valproic acid, and zonisamide (8.3% each; Table 2).

3.2. *Safety/tolerability outcomes*

Overall, TEAEs were reported in 22 (88.0%) patients in the rufinamide group and 10 (83.3%) patients in the any-other-AED group (Table 3). The most common TEAEs were upper respiratory tract infection, vomiting, somnolence, and pneumonia in the rufinamide group, and upper respiratory tract infection, diarrhea, seizure, and pyrexia in the any-other-AED group (Table 3). The majority of patients in both treatment groups had TEAEs that were considered mild (rufinamide: $n = 4$ [16.0%]; any other AED: $n = 4$ [33.3%]) or moderate (rufinamide: $n = 14$ [56.0%]; any other AED: $n = 4$ [33.3%]); severe TEAEs were reported in 4 (16.0%) patients in the rufinamide group and 2 (16.7%) patients in the any-other-AED group. Approximately half of all patients in both groups experienced TEAEs that were deemed possibly or probably related to the study drug(s) by the investigator. Treatment-related TEAEs that occurred in ≥2 patients were vomiting ($n = 5$ [20.0%]) and somnolence ($n = 4$ [16.0%]) in the rufinamide group, and pyrexia and upper respiratory tract infection (both $n = 2$ [16.7%]) in the any-other-AED group.

Serious TEAEs were reported in 10 (40.0%) patients in the rufinamide group and 5 (41.7%) patients in the any-other-AED group (Table 3). Serious TEAEs reported in ≥1 patient included seizure (1 rufinamide patient, 3 any-other-AED patients), respiratory distress (2 rufinamide patients, 1 any-other-AED patient), status epilepticus (2 rufinamide patients), and bronchopneumonia (1 patient in each group). Serious TEAEs that were considered to be treatment-related by investigators included 3 cases in the rufinamide group (bronchopneumonia, pneumonia aspiration, and status epilepticus) and 2 cases in the any-other-AED group (seizure and lethargy). There was 1 death due to pneumonia that occurred in the rufinamide group after 994 days of treatment, which was determined to be unrelated to the study drug.

TEAEs leading to discontinuation were rare in both groups, occurring in 2 (8.0%) patients in the rufinamide group (vomiting and decreased appetite in 1 patient and vomiting in another patient) and 1 (8.3%) patient in the any-other-AED group (rash). All TEAEs that led to discontinuation of study drug were attributed to the study drug by the investigator. The Kaplan–Meier estimate of the median overall survival time to withdrawal from treatment due to the occurrence of a TEAE or lack of seizure

Table 2 – Baseline AED use in the rufinamide group, and baseline and add-on AED use in the any-other-AED group – safety analysis set.

Drug name	Rufinamide (N = 25)	Any other AED (N = 12)		
	Baseline, n (%)	Baseline, n (%)	Randomization,[a] n (%)	Total, n (%)
Valproic acid	17 (68.0)	6 (50.0)	1 (8.3)	7 (58.3)
Levetiracetam	6 (24.0)	9 (75.0)	0 (0.0)	9 (75.0)
Topiramate	9 (36.0)	2 (16.7)	2 (16.7)	4 (33.3)
Diazepam	4 (16.0)	3 (25.0)	0 (0.0)	3 (25.0)
Vigabatrin	7 (28.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clobazam	3 (12.0)	3 (25.0)	2 (16.7)	5 (41.7)
Lamotrigine	5 (20.0)	1 (8.3)	5 (41.7)	6 (50.0)
Clonazepam	3 (12.0)	1 (8.3)	0 (0.0)	1 (8.3)
Nitrazepam	2 (8.0)	1 (8.3)	0 (0.0)	1 (8.3)
Oxcarbazepine	2 (8.0)	1 (8.3)	0 (0.0)	1 (8.3)
Ethosuximide	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)
Phenobarbital	1 (4.0)	1 (8.3)	1 (8.3)	2 (16.7)
Zonisamide	1 (4.0)	1 (8.3)	1 (8.3)	2 (16.7)
Ergenyl chrono	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)
Lacosamide	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)
Lorazepam	0 (0.0)	1 (8.3)	0 (0.0)	1 (8.3)
Midazolam	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primidone	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)

Patients with 2 or more medications within a class level and drug name were counted only once within that class level and drug name. AEDs at baseline were defined as AEDs starting prior to first dose date and ending on or after first dose date.
AED = antiepileptic drug.
[a] Add-on AEDs chosen by the investigator at the time of randomization for patients in the any-other-AED group.

efficacy was 142.0 weeks for patients in the rufinamide group and 28.0 weeks for patients in the any-other-AED group. There were no clinically important mean changes in laboratory values, vital signs, or ECG parameters in either treatment group.

3.3. *Behavioral outcomes*

At baseline, the mean (SD) Total Problems scores were 56.6 (11.3) and 62.8 (13.1) in the rufinamide and any-other-AED groups, respectively (least squares mean difference: −5.43; $p = 0.3262$). The mean and mean change from baseline in CBCL Total Problems scores are shown in Fig. 3A and B, respectively. The difference in the least squares mean (95% confidence interval) CBCL Total Problems score across time (based on the means across Weeks 24, 56, 88, and 106) was not significantly different between treatment groups (−1.197 [−7.6, 5.3; $p = 0.7083$]; Fig. 3A). Similarly, no significant differences between treatment groups were observed for mean change from baseline in CBCL Total Problems score at any week during the study (Fig. 3B). Furthermore, the least squares mean differences between treatment groups were comparable during each week of the study, including Week 106 following 2 years of treatment (Supplementary Table 2). No consistent trends were found in mean and mean change from baseline in CBCL subscores between treatment groups (Supplementary Table 3).

4. Discussion

Study 303 was designed to evaluate the safety, tolerability, PK, and behavioral effects of adjunctive rufinamide in a pediatric population (≥1 and <4 years of age) with seizures associated with LGS. The 6-month interim safety and PK analyses from Study 303 have been previously reported[6] and we now expand on this by reporting the final 2-year safety/tolerability and behavioral outcomes from Study 303.

Consistent with safety/tolerability outcomes from the 6-month interim analysis,[6] adjunctive rufinamide (≤45 mg/kg/day) was shown to be well tolerated in pediatric patients (≥1 to <4 years of age) following 2 years of treatment. Similar TEAE incidence rates were observed in the rufinamide and any-other-AED groups, and the frequency of severe and serious TEAEs was also comparable between the 2 groups. Although certain TEAEs were more common in the rufinamide group (vomiting, pneumonia, somnolence), and others were more common in the any-other-AED group (diarrhea, pyrexia, seizure), there was no clear pattern of TEAEs that distinguished the 2 treatment groups, and upper respiratory tract infection was 1 of the most common TEAEs in both groups. The safety/tolerability profile of rufinamide reported here for patients ≥1 to <4 years of age is comparable with that previously reported in patients 1–50 years of age,[9,13,14] and is consistent with the known safety profile of rufinamide.[8]

Based on the CBCL Total Problems scores and CBCL subscores, the behavior of patients treated with rufinamide appeared to be comparable with that in patients treated with any other AED. However, caution is recommended when interpreting these data due to the limitations of small sample sizes, high disease severity of many of the patients during baseline, the relatively high dropout rates across both treatment groups, and the difficulties in obtaining direct responses from patients included in this study given their age group. The inability to monitor data up to study completion and limited ability to detect subtle differences also hindered behavioral assessments in this patient population. In addition, long-term safety and behavioral data are lacking in the literature for this

Table 3 – Overview of TEAEs – safety analysis set.

Category	Rufinamide (N = 25), n (%)	Any other AED (N = 12), n (%)	Total (N = 37), n (%)
TEAEs[a]	22 (88.0)	10 (83.3)	32 (86.5)
Severe TEAEs	4 (16.0)	2 (16.7)	6 (16.2)
Serious TEAEs[b]	10 (40.0)	5 (41.7)	15 (40.5)
Deaths	1 (4.0)	0 (0.0)	1 (2.7)
Other SAEs	10 (40.0)	5 (41.7)	15 (40.5)
Life threatening	0 (0.0)	0 (0.0)	0 (0.0)
Required inpatient hospitalization or prolongation of existing hospitalization	10 (40.0)	5 (41.7)	15 (40.5)
Important medical events	1 (4.0)	1 (8.3)	2 (5.4)
TEAEs leading to study-drug dose adjustment			
Withdrawal	2 (8.0)	1 (8.3)	3 (8.1)
Reduction	7 (28.0)	0 (0.0)	7 (18.9)
Interruption	0 (0.0)	2 (16.7)	2 (5.4)
Other TEAEs of special interest			
Skin reactions	5 (20.0)	1 (8.3)	6 (16.2)
Somnolence	5 (20.0)	0 (0.0)	5 (13.5)
Weight loss	2 (8.0)	0 (0.0)	2 (5.4)
Fatigue	1 (4.0)	1 (8.3)	2 (5.4)
Overdose of study medication	0 (0.0)	0 (0.0)	0 (0.0)
TEAE occurring in ≥10% of patients in any treatment group by preferred term			
Upper respiratory tract infection	7 (28.0)	4 (33.3)	11 (29.7)
Vomiting	7 (28.0)	1 (8.3)	8 (21.6)
Pneumonia	5 (20.0)	0 (0.0)	5 (13.5)
Somnolence	5 (20.0)	0 (0.0)	5 (13.5)
Diarrhea	4 (16.0)	3 (25.0)	7 (18.9)
Pyrexia	4 (16.0)	3 (25.0)	7 (18.9)
Cough	4 (16.0)	2 (16.7)	6 (16.2)
Sinusitis	4 (16.0)	1 (8.3)	5 (13.5)
Seizure	2 (8.0)	3 (25.0)	5 (13.5)
Otitis media	4 (16.0)	0 (0.0)	4 (10.8)
Rash	3 (12.0)	1 (8.3)	4 (10.8)
Irritability	3 (12.0)	1 (8.3)	4 (10.8)
Decreased appetite	3 (12.0)	1 (8.3)	4 (10.8)
Constipation	3 (12.0)	1 (8.3)	4 (10.8)
Bronchitis	3 (12.0)	0 (0.0)	3 (8.1)
Nasal congestion	3 (12.0)	0 (0.0)	3 (8.1)

Percentages are based on the total number of patients in the Safety Analysis Set dosed with the relevant treatment.
AED = antiepileptic drug; TEAE = treatment-emergent adverse event.
[a] A TEAE was defined as an adverse event that had an onset date, or a worsening in severity from baseline (pretreatment), on or after the first dose of study drug and up to 7 days following study drug discontinuation.
[b] A serious adverse event was considered treatment-emergent if the onset date or worsening in severity occurred within 30 days after study drug discontinuation.

patient population, meaning that comparisons and conclusions based on the behavioral data reported here cannot be made at present. A more sensitive behavior scale may be required to assess behavior in this patient population in future studies.

Efficacy outcomes (median percent change in total seizure frequency per 28 days and worsening of seizures), the Language Development Survey (LDS), and the Quality of Life in Childhood Epilepsy (QoLCE) questionnaire were included as exploratory endpoints in this study. These data are not reported here because they were not sufficient to suggest any differences in seizure frequency between treatment groups, and the majority of patients in this trial exhibited severe deficits in language development that may have limited the ability to detect changes. Furthermore, the LDS and QoLCE[15] have not been validated in this patient population.

Additional limitations of Study 303 include its open-label design and the fact that dose adjustments for rufinamide and other AEDs were permitted over the course of the study. This included discontinuation of the selected add-on AED or replacement with another add-on AED if the initial add-on AED selected was not well tolerated (in the investigator's opinion) by the patient. These design features were necessary for inclusion of these markedly impaired patients, all of whom required intensive treatment. Moreover, it was difficult to recruit patients from this population into the trial due to the difficulties in diagnosing LGS in very young children, including the lack of a biological marker and multiple etiologies underlying LGS. In addition, LGS is characterized by seizure types and EEG patterns that can also be attributed to other epilepsy disorders, and the features of LGS can change over time.[2]

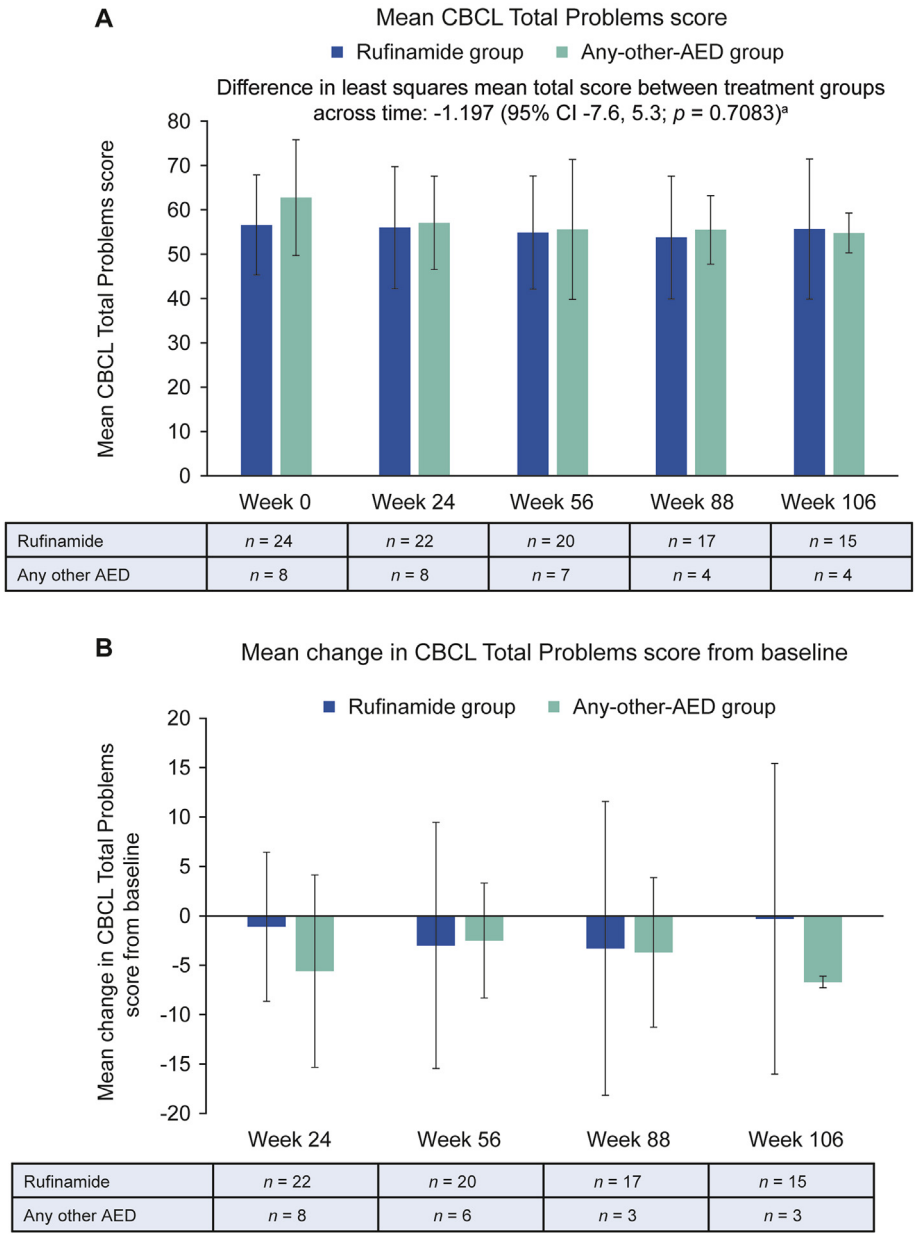

Fig. 3 – CBCL total problems score: (A) mean score by week and (B) mean change from baseline by week – full analysis set for primary efficacy variables. AED = antiepileptic drug; CBCL = Child Behavior Checklist; CI = confidence interval. The Total Problems score is the sum of all the problem areas plus 1 additional item. [a]The difference in the least squares mean CBCL Total Problems score between treatment groups was based on the means across Weeks 24, 56, 88, and 106.

Indeed, the full clinical picture of LGS is usually reached progressively by the ages of 3–5 years old.[2,16]

Despite these limitations, this study provided valuable insights into treatment responses in this patient population and these preliminary data suggest there are no consistent trends over time between the 2 treatment groups in terms of behavioral effects. The consistent lack of notable differences in any of the safety assessments between the 2 treatment groups suggests that treatment with adjunctive rufinamide is likely to be comparable to other AEDs used in young children with LGS with regard to adverse effects on childhood behavior. Study 303 is the first study to evaluate rufinamide in patients as young as 1 year of age, and the safety/tolerability and behavioral outcomes reported here provide preliminary evidence to suggest that rufinamide is a viable treatment option for this young patient population. Considering that early treatment may positively influence the prognosis of LGS, substantial progress could be achieved in the effective management of seizures in these very young patients.[1] However, the challenges encountered in this study raise the issue of completely revising how studies in very young children with rare and complex epilepsies are performed, and suggest that specialized study protocols may be required for these patient populations.

5. Conclusions

The 2-year findings of Study 303 are consistent with those reported in the interim publication,[6] and confirm the tolerability of rufinamide as an adjunctive therapy in the treatment of inadequately controlled seizures associated with LGS in patients ≥1 to <4 years old.

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Conflict of interests

A. Arzimanoglou has been an advisor for Eisai, GW Pharmaceuticals, Shire, Takeda, UCB, Upsher-Smith, and Zogenix, and his institution has received grants from CAIXA Bank Spain, Eisai, and UCB.

J. Ferreira serves on the speaker bureau for Eisai, Lundbeck, and Supernus Pharmaceuticals; is a consultant for Eisai; has received grants from LivaNova and Supernus Pharmaceuticals; and provides contracted research for Eisai.

A. Satlin, F. Bibbiani, and O. Olhaye are former employees of Eisai Inc.

D. Kumar and S. Dhadda are employees of Eisai Inc.

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.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2018.09.010.

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