The secondary efficacy variables were:

1) response to treatment (i.e., experiencing at least a 50% reduction in tonic-atonic seizure frequency during the double-blind phase relative to the baseline phase);
2) percent change in the frequency per 28 days for seizure subtypes other than tonic-atonic; and
3) the composite score for the Global Evaluation of the patient's condition.

Sample size

Approximately 128 patients were necessary to perform efficacy analyses in this study. This sample size was calculated based on the percent change in seizure frequency in the double-blind phase relative to the baseline phase.

No information was available on the performance of rufinamide in this population. It was assumed that rufinamide could deliver a percent reduction in seizure frequency 22.5% greater than that of placebo. Results from a similar trial with felbamate suggested a population standard deviation of no more than $\sigma = 35$.

Conditional on these assumptions and assuming a normal distribution, a two-sided t-test with a significance level of 0.025 has a statistical power of 91.3% to reject the null hypothesis of no treatment difference with approximately 64 randomized patients per treatment group. However, to guard against departures from normality, Wilcoxon rank-sum tests were used for this and the other two joint analyses of the primary efficacy variables.

Randomisation

Randomization was performed by the applicant using a validated system that automates the random assignment of treatment groups to randomisation numbers. Randomisation was in block of four at the country/centre level. The randomisation scheme was reviewed by the Company's trial statistician and was locked after approval.

Blinding (masking)

Study drugs were supplied as 100, 200, and 400 mg tablets with corresponding matching placebo tablets. The investigator, study site personnel and the Company's personnel involved in the monitoring or conduct of the study were blinded to the study drug codes. The codes were not available to the above personnel until the core study was completed and the final data review and database lock were performed, except in the case of an emergency.

Statistical methods

The data set used in all efficacy analyses was the intent-to-treat patient population, which consisted of all randomized patients who received double-blind study drug and provided seizure diary data during the double-blind phase. The data set used for all other analyses was the all-treated-patients population, which consisted of all patients who received at least one dose of study drug.

All tests performed by the Applicant to show statistical significance on the primary efficacy variables were two-tailed with a probability level of 0.025; a probability level of 0.05 was used to show statistical significance for the secondary efficacy variables.

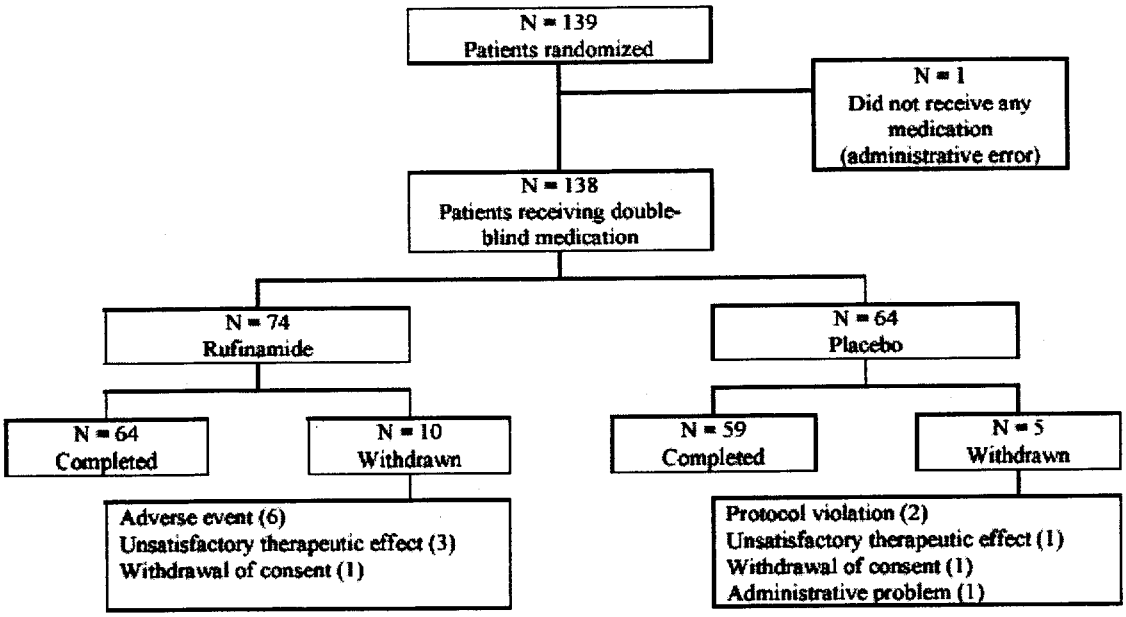
A pooling scheme of countries was used for analyses that examined country effect due to the small enrolment at many centres and within countries, and the expected large variability in seizure frequency between patients. As a result, a factor "Region" consisting of three levels (USA, Brazil, Europe) was fitted in the analysis of response to treatment and in the exploratory analyses.

A data listing of the study-drug dosage administered to each patient during the Double-blind
Phase was provided by treatment group. The number and percent of patients exposed to study drug over distinct time intervals were calculated, and descriptive statistics were provided to summarize the duration of exposure to study drug by treatment group. In addition, descriptive statistics of the dose administered during the Maintenance Period (Visits 4 through 6) were provided. No interim analyses were planned.

RESULTS

Participant flow

The participant flow was the following:



Recruitment

A total of 43 centres in the following countries participated in the study: Belgium (2), Brazil (3), Germany (9), Hungary (3), Italy (3), Norway (1), Poland (2), Spain (2), and United States (18). Patients were enrolled in 36 of the centres.

Conduct of the study

Patient disposition for each treatment group

	Rufinamide		Placebo		All treatments	
	n	%	n	%	n	%
Number of patients randomized	75	100.0	64	100.0	139	100.0
Number of patients treated	74	98.7	64	100.0	138	99.3
Number of patients in intent-to-treat	74	98.7	64	100.0	138	99.3
Number for efficacy analysis						
primary variable 1	74	98.7	64	100.0	138	99.3
primary variable 2	73	97.3	60	93.8	133	95.7
primary variable 3	73	97.3	62	96.9	135	97.1
Number completed	64	85.3	59	92.2	123	88.5
Number discontinued						
- total	11[b]	14.7	5	7.8	16	11.5
- death	0	0.0	0	0.0	0	0.0
- for adverse events	6	8.0	0	0.0	6	4.3
- other[a]	5[b]	6.7	5	7.8	10	7.2

Primary variable 1 - percent reduction in total seizure frequency
Primary variable 2 - percent reduction in tonic-atonic seizure frequency
Primary variable 3 - seizure severity rating from the Global Evaluation of patient's condition
[a]Discontinued due to protocol violation, unsatisfactory therapeutic effect, withdrawal of consent, administrative problems
[b]Includes Patient USA/3054/2101 who was randomized but did not receive study drug.

There were no particular problems with the conduct of the study.
One randomized patient did not receive double-blind study drug due to an administrative error. The remaining 138 treated patients were included in the intent-to-treat population for percent change in total seizure frequency per 28 days (primary variable 1). One patient in the rufinamide group and four patients in the placebo group did not have any tonic-atonic seizures during the Baseline Phase and thus were excluded from the analyses for primary variable 2. One patient in the rufinamide group and two patients in the placebo group did not have an end-of-study seizure severity rating from the Global Evaluation of patient's condition and were thus excluded from the analyses for primary variable 3.
No patients were prematurely withdrawn from the study due to non-compliance.
Safety analyses were based on data from all 138 treated patients, including those who were excluded from the intent-to-treat populations for primary variables 2 and 3.
The study blind was not broken during the study for any treated patient. Thus, for all patients treated in this study, study blinding was preserved until all patients had completed the study, patient validity was determined, and the database was locked.

Baseline data

Demographic and baseline characteristics by treatment (All treated patients)

Characteristic	Rufinamide (N=74)		Placebo (N=64)		All treatments (N=138)	
	n	%	n	%	n	%
Sex						
Male	46	62.2	40	62.5	86	62.3
Female	28	37.8	24	37.5	52	37.7
Race						
White/Caucasian	62	83.8	53	82.8	115	83.3
Black	6	8.1	4	6.3	10	7.2
Other	6	8.1	7	10.9	13	9.4
Age (years)						
Mean (Range)	14.5 (4, 35)		13.6 (4, 37)		14.1 (4, 37)	
4 - <12	31	41.9	33	51.6	64	46.4
12 - <17	19	25.7	17	26.6	36	26.1
≥17	24	32.4	14	21.9	38	27.5
Weight (kgs)						
Mean (Range)	44.1 (15.5, 138.5)		40.2 (16.2, 86.0)		42.3 (15.5, 138.5)	
18 – 29.0	24	32.4	24	37.5	48	34.8
29.1 – 50.0	25	33.8	20	31.3	45	32.6
50.1 – 70.0	13	17.6	14	21.9	27	19.6
≥70.1	12	16.2	6	9.4	18	13.0

There were no notable differences between the two treatment groups with respect to sex, race, age, body weight.

Summary statistics of seizures in baseline phase (All treated patients)

	Rufinamide (N=74)			Placebo (N=64)		
	n	Median	Range	n	Median	Range
All types of seizures	74	290.0	48, 53760	64	205.0	21, 109714
Tonic-atonic seizures[a]	73	92.0	5, 14304	60	92.5	1, 13122
Atypical absence seizures	59	76.0	1, 2171	55	52.0	1, 4009
Tonic seizures	52	66.3	1, 14304	43	49.0	1, 1066
Atonic seizures	45	56.0	1, 4037	33	49.0	2, 13122
Myoclonic seizures	37	80.0	1, 38928	31	50.8	1, 92583
Tonic-clonic seizure	37	18.0	1, 336	27	15.0	1, 788
Unclassified	12	17.5	1, 202	13	16.0	1, 72
Partial seizures	11	49.0	1, 4195	9	41.0	3, 723
Absence seizures	8	31.0	1, 192	5	22.0	3, 84
Clonic seizures	7	36.0	1, 6021	1	51.0	

The median number of seizures of any type that occurred during the baseline phase was higher in the rufinamide group than in the placebo group due to median number for atypical absence, tonic, myoclonic, partial, and absence seizures higher in the rufinamide group. The median numbers of other types of seizures that occurred during the baseline phase were comparable in both groups.

The mean duration of LGS, defined as the time between diagnosis and baseline of the study, was 9.9 years for the rufinamide group and 9.6 years for the placebo group.

Summary of treatment exposure (All treated patients)

Cumulative exposure (units)	Rufinamide		Placebo	
	n	%	n	%
1 day	74	100.0	64	100.0
1 week	74	100.0	64	100.0
2 weeks	74	100.0	64	100.0
4 weeks	72	97.3	62	96.9
8 weeks	71	95.9	61	95.3
12 weeks	65	87.8	58	90.6
Summary Statistics (in days)				
Mean	79.2		81.0	
Median	84.0		84.0	
Range	(13, 112)		(13, 103)	

The target dosage was approximately 45 mg/kg/day of rufinamide (or placebo equivalent) or the maximum recommended daily dose in milligrams for the patient's weight, whichever was less.
In both treatment groups, more than 87% of patients received at least 12 weeks of treatment with the study drug. The median duration of exposure to study drug (84 days in both treatment groups) was consistent with the planned duration of the double-blind phase (84 days).

Summary of total number of concomitant AEDs used by patients in either treatment group (All treated patients)

Total Number of Concomitant AEDs	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
One	8	10.8	8	12.5
Two	38	51.4	35	54.7
Three	28	37.8	21	32.8

Valproate, lamotrigine, and topiramate were the most frequently used concomitant AEDs for both rufinamide- and placebo-treated patients during the study.

Summary of concomitant AEDs used by at least 10% of the patients in either treatment group during the double-blind phase (All treated patients)

Concomitant AED	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
Valproate	44	59.5	35	54.7
Lamotrigine	30	40.5	19	29.7
Topiramate	20	27.0	17	26.6
Clonazepam	14	18.9	7	10.9
Carbamazepine	12	16.2	12	18.8
Clobazam	10	13.5	8	12.5
Phenytoin	10	13.5	12	18.8
Phenobarbital	6	8.1	9	14.1

The types of concomitant AEDs used were generally comparable for the two treatment groups.

Outcomes and estimation

Primary efficacy results

The primary efficacy analysis showed statistically significant results in favour of rufinamide for all 3 primary variables ($p \leq 0.0041$), as shown below.

Primary efficacy variable 1: percentage change in total seizure frequency per 28 days

Primary efficacy variable 1 showed a significant difference between the 2 treatment groups in favour of rufinamide (p=0.0015). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency, as shown in the table below.

Summary of percent change in total seizure frequency per 28 days relative to baseline (ITT)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	74	290.0	(48.0, 53760.0)	64	205.0	(21.0, 109714.0)
Double-blind seizure frequency per 28 days	74	204.1	(5.4, 43262.3)	64	205.4	(50.7, 113165.0)
Percentage change in seizure frequency per 28 days from baseline[a]	74	-32.7	(-92.3, 381.4)	64	-11.7	(-82.8, 550.6)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0015

Cross-reference: Table 9-1 in the CSR for Study 022.

No significant treatment-by-region interaction was observed (p=0.7373). Rufinamide remained significantly superior to placebo after adjusting for the number of AEDs used at baseline (p=0.0021).

Primary efficacy variable 2: percentage change in tonic-atonic seizure frequency per 28 days

Primary efficacy variable 2 showed a significant difference between the 2 treatment groups in favour of rufinamide (p<0.0001). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 days, as shown in the following table:

Summary of percent change in tonic-atonic seizure frequency per 28 days relative to baseline (ITT patients)

	Rufinamide			Placebo		
	n[a]	Median	Range	n[a]	Median	Range
Baseline tonic-atonic seizure frequency per 28 days	73	92.0	(5.0, 14304)	60	92.5	(1.0, 13122)
Double-blind tonic-atonic seizure frequency per 28 days	73	60.7	(0.0, 12036.1)	60	76.2	(0, 17500)
Percentage change in tonic-atonic seizure frequency per 28 days from baseline[b]	73	-42.5	(-100, 1190.8)	60	1.4	(-100, 709.6)

[a] 5 patients (1 rufinamide, 4 placebo) did not experience tonic-atonic seizures during the Baseline Phase.

[b] Between-group comparison using Wilcoxon rank-sum test p-value < 0.0001.

Cross reference: Table 9-2 in the CSR for Study 022.

Primary efficacy variable 3: seizure severity subscale of Global Evaluation of patient's condition

Primary efficacy variable 3 showed a significant difference between the 2 treatment groups in favour of rufinamide (p=0.0041). An improvement in seizure severity was observed in 39 (53.4%) of the 73 rufinamide-treated patients compared to 19 (30.6%) of the 62 placebo-treated patients, as shown in the table below:

Summary of seizure severity rating of the Global evaluation of the patients' condition (ITT population)

	Rufinamide (N=73)		Placebo (N=62)	
Seizure severity	n[a]	%	n[a]	%
Very much worse	0	0.0	0	0.0
Much worse	3	4.1	4	6.5
Minimally worse	3	4.1	4	6.5
No change	28	38.4	35	56.5
Minimally improved	14	19.2	10	16.1
Much improved	16	21.9	8	12.9
Very much improved	9	12.3	1	1.6

Wilcoxon rank-sum test p-value = 0.0041

[a] 3 patients (1 rufinamide, 2 placebo) did not have a seizure severity evaluation.

Cross reference: Table 9-3 in the CSR for Study 022.

Secondary efficacy results

Response to treatment

The percent of patients who experienced at least a 50% reduction in tonic-atonic seizure frequency per 28 days, relative to baseline, was significantly higher in the rufinamide group (42.5%) than in the placebo group (16.7%) (p = 0.0020).

Summary statistics of patients who responded to treatment with at least a 50% reduction in tonic-atonic seizure frequency relative to baseline (Intent-to-treat patients)

	Rufinamide		Placebo			
Responder Rate	**n**	**%**	**n**	**%**	**Odds Ratio[a]**	**P-value[b]**
50%	31/73	42.5	10/60	16.7	3.81	0.0020

[a]The odds of a rufinamide-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days relative to the odds of a placebo-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days.

[b] p-value based on logistic regression model with treatment, region, sex, and age as explanatory variables.

Nevertheless, the percentage of seizure (tonic-atonic) free patients is low and not different in both arms (4.1% versus 3.3%). The median reduction in different isolated seizure type frequency is significant only for absences and atonic seizures.

In the composite score for the Global Evaluation of the patient's condition, the difference between the groups was not statistically significant (p = 0.3492).

Ancillary analyses

The applicant has performed additional exploratory analyses which do not indicate any association of age with the results of the primary efficacy analyses. Children, adolescents, and adult populations showed similar treatment effects. There was no association of age or weight at baseline with the results of the primary efficacy analyses. The number or type of concomitant AEDs a patient received was not associated with the results of the primary efficacy analyses. The efficacy of rufinamide could be observed when it was given in combination with commonly used AEDs in LGS, including valproate, lamotrigine, and topiramate. No evidence was found that rufinamide treatment caused an increase in the total seizure frequency, or that there was any development of short-term tolerance.

- Analysis performed across trials (pooled analyses and meta-analysis)

The patients within each age subgroup who received rufinamide had larger median decreases in seizure frequency than did the patients who received placebo. The only exceptions to this were noted in subgroups with very low numbers of patients.

The results for total seizure frequency, revealed that the median decreases became larger over the course of treatment and the persistence of the response in the rufinamide group but not in the placebo group. The large difference between rufinamide and placebo could be seen as early as Week 2.

In all cohorts, reduction in seizure frequency did not diminish over time, suggesting that at least a subpopulation of treated patients had seizure control maintained during long-term therapy. There appeared to be no development of tolerance to the anticonvulsant effect of rufinamide when cohorts with different lengths of drug exposure were analyzed.

In Study 022, the proportions of patients with increases in seizure frequency of 25% or less and with increases of more than 25% but less than 100% were lower in the rufinamide group than in the placebo group. The proportion of patients with 100% or greater increases in seizure frequency was small and no different between the 2 groups. In patients with primary generalized tonic-clonic seizures (Study 018), the proportion of patients with increases in seizure frequency was not different in the rufinamide-treated group compared to the placebo-treated group.

- Supportive studies

All the supportive placebo-controlled studies provide efficacy of rufinamide in patients with different types of epilepsy and of various age ranges.

1. Double-blind placebo-controlled adjunctive therapy studies in adults with partial seizures

Study AE/PT2

A multi-centre double-blind placebo-controlled randomized parallel group study.

The study was a 'proof of concept' study performed in a limited number of patients for duration of 4 weeks. The study included patients with primary generalised as well partial seizures. For the primary efficacy variable, seizure frequency ratio, and for response rate, there were trends for an improvement with rufinamide vs. placebo but no statistically significant differences. There was an unexpected worsening of seizure frequency in the placebo group for the (i) population.

The data used in the efficacy analyses are summarised below:

Median seizure frequency per 28 days in the Baseline and double-blind phases (All analysis populations in Study AE/PT2)

			Median seizure frequency		Median % change
Data set[a]	Treatment	No. of patients	Baseline Phase	Double-blind Phase	relative to Baseline Phase
(i)	Rufinamide	23	4.00	3.11	-41
	Placebo	21	6.46	8.30	+52
(ii)	Rufinamide	23	4.00	3.11	-41
	Placebo	19	8.62	9.33	+8
(iii)	Rufinamide	25	3.69	3.11	0[b]
	Placebo	25	4.62	5.19	0[b]

[a] Data set (i) included all patients who received treatment, except those who were seizure-free for the duration of both the Baseline and Double-blind Phases.
Data set (ii) included all patients who received treatment, except those who were seizure-free during the Baseline Phase.
Data set (iii) included all patients who received treatment (intent-to-treat population).

[b] Although the median seizure frequencies during the Baseline and Double-blind Phases differed, the median percentage change was 0% in both groups.

Study 021A

A multi-centre, double-blind, placebo-controlled, randomized, parallel-group study.

In this study, which included patients with inadequately controlled partial seizures that were being treated with 1 or 2 concomitant fixed-dose AEDs, the percentage reduction in total seizure frequency/28 days (primary variable) was significantly higher in the active group. However, no statistically significant difference was observed between the placebo and rufinamide groups with regard to partial seizure frequency per 28 days. The responder analysis demonstrated a significant difference for 50 and 25 % responder criteria in favour of rufinamide. Among patients who experienced secondarily generalized seizures during the baseline phase, there was no difference between the treatment groups in the percentage change in the frequency of this type of seizure during the double-blind phase.

The results of the primary efficacy variable: percentage change in total seizure frequency per 28 days are summarised in the table below:

Table 42. Summary of percentage change in partial seizure frequency per 28 days relative to baseline (ITT, Study 021A).

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	156	8.5	(3.0, 275.0)	156	8.0	(2.5, 578.5)
Double-blind seizure frequency per 28 days	156	7.6	(0.0, 552.2)	156	8.7	(0.0, 416.3)
Percentage change in seizure frequency per 28 days from baseline[a]	156	-20.4	(-100.0, 987.5)	156	1.6	(-100.0, 6837.8)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0158

Cross reference: Table 9-1 in the CSR for Study 021A.

Study 039

This was a multi-centre, double-blind randomised placebo-controlled parallel group monotherapy study in untreated patients 12 years of age or older with recent onset partial seizures. The study consisted of three phases: a 56-day baseline phase, a 56-day double-blind phase and an extension phase. Approximately 18 patients were planned but only 29 patients were randomised into the study, 14 to rufinamide and 15 to placebo. The study was terminated early due to the lack of enrolment. The number of enrolled patients was inadequate to obtain interpretable efficacy information, and no efficacy analysis was performed.

2. Double-blind, controlled studies of monotherapy and monotherapy substitution in patients with partial seizures

Study 038

Design: This was a multicentre, double-blind, placebo-controlled, randomized, parallel-group study of rufinamide as monotherapy in patients with refractory partial seizures who had completed an inpatient presurgical diagnostic examination. The study consisted of a 48-hour baseline phase and a 10-day double-blind treatment phase during which patients were randomized to receive either rufinamide or placebo. Patients who completed the study were allowed to enter an open-label Extension Phase.

Results: The median time to exit criteria (primary efficacy variable) was twice as along for rufinamide as for placebo, which was statistically significant. The results provide evidence for short-tem efficacy in monotherapy when the drug is tested in an extremely refractory population. However, the results may not be relevant for longer term clinical use.
The data are summarised in the table below:

Table 43. Summary statistic for time to seizure (ITT, Study 0389)

Study	Treatment	Time to	No. of events	Median (days)	(95% CI)	p-value
038	RUF 3200 mg/day	1st seizure	45	0.64	(0.50, 1.72)	0.0248[a]
	PLA		49	0.54	(0.19, 0.85)	
	RUF 3200 mg/day	2nd seizure	37	2.51	(0.98, 3.86)	0.0348[a]
	PLA		44	1.18	(0.80, 1.60)	
	RUF 3200 mg/day	3rd seizure	34	3.54	(2.60, 5.17)	0.0300[a]
	PLA		41	1.55	(1.26, 2.35)	
	RUF 3200 mg/day	4th seizure	30	4.39	(3.41, 7.64)	0.0509[a]
	PLA		34	2.37	(1.61, 3.67)	

[a] Based on Wald test from Prentice-Williams-Peterson proportional hazards regression model.

Cross reference: Appendix 5.1, Table 7 of the CSR for Study 038.

Study 016

A multicenter, double-blind, controlled, and randomized, parallel-group study.

The study compared the efficacy of treatment with rufinamide in monotherapy at a therapeutic dose with a subtherapeutic dose of rufinamide after gradual down titration of the baseline AED. No difference was observed for the primary efficacy variable percentage of patients meeting one of the exit criteria. For the secondary efficacy parameter median time to meeting one of the exit criteria, there was a trend for a better result with rufinamide 3200 mg/day but the difference was not statistically significant.

3. Double-blind placebo-controlled adjunctive therapy study in primary generalised epilepsy

Study 018

A multicenter, double-blind, placebo-controlled, randomized, parallel-group study.

In this study of primary generalised tonic-clonic seizures, there was a numerical trend for seizure reduction with rufinamide, but no statistically significant differences. This is consistent with the results in the pivotal study where no statistically significant effects were observed on primary generalised tonic-clonic seizures.

The primary efficacy variable data (percentage change in PGTC seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase) are shown in the table below:

Responder rates for Study 018.

Responder Rate	Rufinamide 800 mg/day n	%	Placebo n	%	Odds Ratio[a]	Confidence interval	p-value[b]
50%	30/74	40.5	24/74	32.4	1.44	0.72, 2.88	0.2966
75%	16/74	21.6	12/74	16.2	1.53	0.65, 3.59	0.3298
100%	4/74	5.4	7/74	9.5	0.57	0.16, 2.05	0.3871

[a] The odds of a rufinamide-treated patient experiencing a reduction in PGTC seizure frequency per 28 days from baseline relative to the odds of a placebo-treated patient experiencing a reduction in PGTC seizure frequency per 28 days relative to baseline.

[b] p-value based on logistic regression model.

4. Adjunctive therapy study in children with partial seizures

Study 021P

Design: A multicenter, double-blind, placebo-controlled, randomized, parallel-group study.

Results: This study failed to demonstrate any significant difference for the primary variable with rufinamide versus placebo in children and adolescents aged 4-16 years with inadequately controlled partial seizures. as shown in the table below.

Summary of percentage change in partial seizure frequency per 28 days relative to baseline (ITT, Study 021P)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	136	13.0	(3.0, 910.0)	131	14.5	(2.0, 243.0)
Double-blind seizure frequency per 28 days	136	11.7	(0.0, 1436.8)	131	14.0	(0.3, 307.7)
Percentage change in seizure frequency per 28 days from baseline[a]	136	-7.0	(-100.0, 758.1)	131	-12.8	(-97.2, 1293.0)

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.6214

Cross reference: Table 9-1 in the CSR for Study 021P.

For 50 % responders, however, there was a strong trend for superiority with rufinamide. The target dose of rufinamide was the same as used in the pivotal study in LGS, 45 mg/kg and day.

A summary of these results is presented in the following table.

Response to treatment in Study 021P

	Rufinamide		Placebo		Odds Ratio[a]	
Responder Rate	n	%	n	%	(Wald CI)	p-value[b]
25%	56/136	41.2	48/131	36.6	1.25 (0.76, 2.06)	0.3796
50%	37/136	27.2	24/131	18.3	1.77 (0.98, 3.19)	0.0596
75%	18/136	13.2	12/131	9.2	1.56 (0.72, 3.40)	0.2619
100%	6/136	4.4	0/131	0.0	259[9] (---)	---

[a] The odds of a rufinamide-treated patient experiencing at least the given level of reduction in partial seizure frequency relative to the odds of a placebo-treated patient experiencing at least that level of reduction in partial seizure frequency.

[b] p-value based on logistic regression model with treatment, region, sex, and age as explanatory variables.

Cross reference: Table 9-4 in the CSR for Study 021P.

4. Open-label extension studies

Efficacy data were obtained during the open label extension phases of Studies 022, AE/ET1 and 021 A.

Study 022E

Design: a multicentre, open-label extension of study 022.

Inclusion criteria: Patients who had completed the 84- day Double-blind Phase of Study 022 were eligible to participate in the extension phase if the investigators thought they might benefit from treatment with rufinamide.

Treatment: The extension phase consisted of 2 periods: a double-blind conversion period and an open-label period. During the double-blind conversion period, patients who had received placebo in Study 022 began receiving rufinamide at a dose of approximately 10 mg/kg/day. The dose was titrated to approximately 45 mg/kg/day over a period of 14 days. Patients who had received rufinamide during Study 022 continued to receive the same dose of rufinamide during the double-blind conversion phase. The daily dose at the end of the conversion phase was used as the initial dose for open-label phase. During open-label treatment, the rufinamide dose could range from 10-45 mg/kg/day in 2 or 3 divided doses at the investigator's discretion. The newer FMI formulation of rufinamide was used in this study. The extension phase continued in a participating country until rufinamide was registered and launched in that country or until its development was terminated in that country.

Primary and secondary efficacy variables: The protocol did not define any efficacy variables for the extension phase, although the patients were required to record the occurrence of seizures in diaries. The following efficacy variables were identified by the Company after the study was completed:

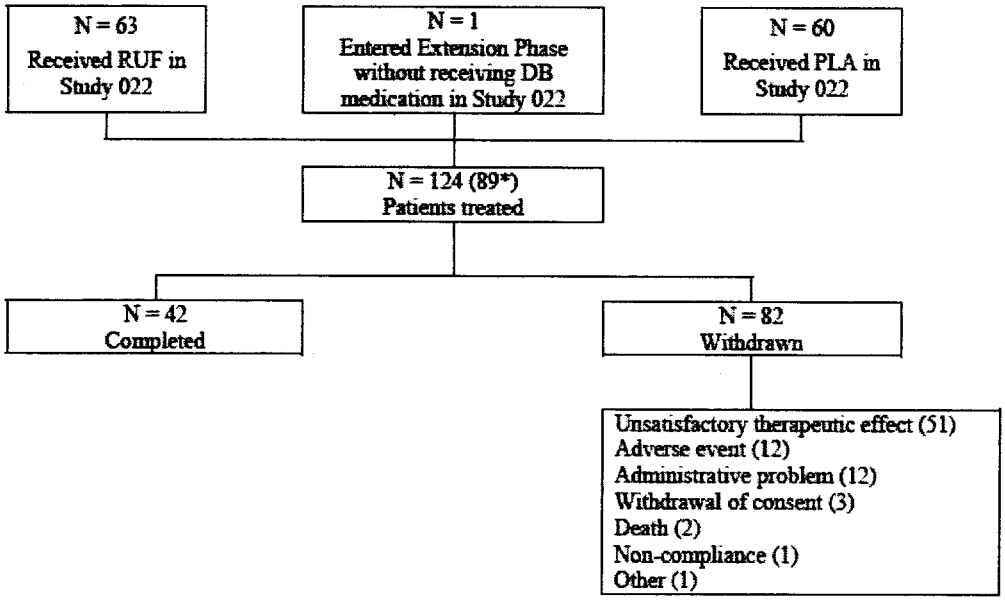
• Variable 1 - The percentage change in seizure frequency (total and tonic-atonic) per 28 days relative to baseline. This was determined for 2 cohorts: patients who had received rufinamide during both the double-blind phase (Study 022) and the extension phase (022E), and patients who had received placebo during the double-blind phase and rufinamide during the extension phase.

• Variable 2 - Response to treatment, defined as experiencing at least a 50% or 75% reduction in seizure frequency for the overall study period, the last 6 months, or the last 12 months of the study. This variable was determined for total seizure frequency and for tonic-atonic seizure frequency.

Tolerance to effectiveness was also evaluated using those 2 efficacy variables. If there were an initial percentage reduction in seizure frequency, followed by a lessening of the reduction or an increase in frequency, this would have suggested that patients were developing tolerance to the antiepileptic effect of rufinamide.

The disposition of the 124 patients treated in this study is illustrated in Figure 11.

Fig. 11. The disposition of the 124 patients treated in the extension study 022E



* Number of patients who were 16 years or younger.

Exposure to study drug in Study 022E

One patient was randomized to receive double-blind treatment in Study 022 but did not receive any study drug due to an administrative error. He was allowed to enter the Extension Phase directly. Of the remaining 123 patients, 63 had received rufinamide during the double-blind

Phase of Study 022 and 60 had received placebo. The median cumulative duration of exposure to rufinamide for patients who entered the Extension Phase was 432 days, with a range of 10 to 1149 days. Eighty-three (66.9%) of 124 patients received rufinamide for 1 year or more, 74 (59.7%) received rufinamide for 18 months or more, and 51 (41.1%) received rufinamide for 2 years or more. The median dose of rufinamide was approximately 1800 mg/day in the Open-label Period.

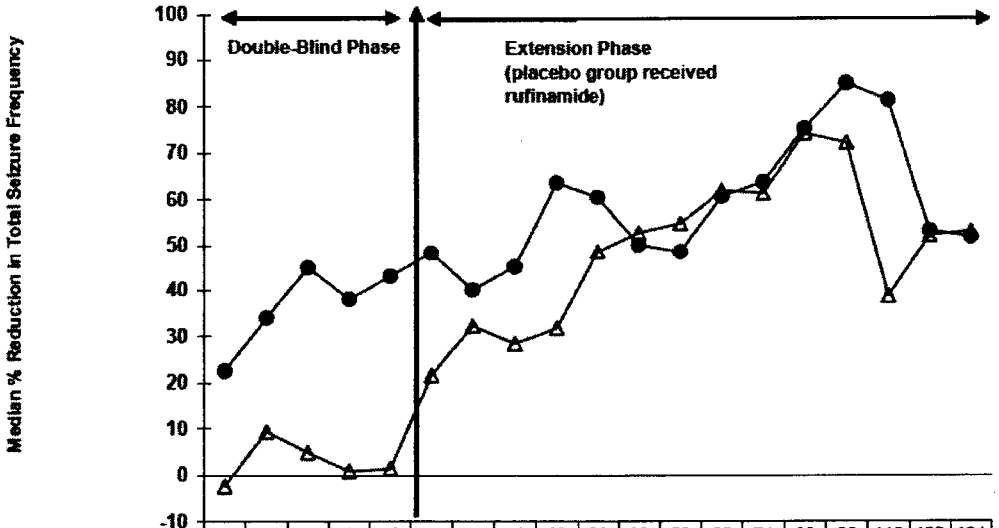
Results

Efficacy variable 1: Percentage change in seizure frequency per 28 days

Total seizures

Figure 12 illustrates the median percentage reduction from baseline in total seizure frequency for the rufinamide and placebo groups during the double-blind and extension phases.

Fig. 12. Median percentage reduction from baseline in total seizure frequency (Patients in Study 022E)



(Week)	1	2	4	8	12	14	16	18	22	26	38	50	62	74	86	98	110	122	134
%Reduction-Placebo	-2.3	9.4	4.9	0.9	1.5	21.7	32.3	28.5	31.8	48.6	52.7	54.6	62.0	61.3	74.2	72.2	38.7	52.1	53.1
%Reduction-Rufinamide	22.6	34.1	45.1	38.1	43.1	48.3	40.1	45.2	63.6	60.5	50.0	48.5	60.7	63.8	75.2	85.0	81.4	53.1	51.8
Placebo (N)	60	60	60	59	59	59	56	54	51	48	45	40	35	26	21	19	14	10	6
Rufinamide (N)	63	63	63	63	63	63	62	56	49	47	47	41	39	31	22	18	12	6	3

Patients who received rufinamide in both phases demonstrated preserved reduction in total seizure frequency as the group continued from the double-blind phase into the extension phase. Patients who received placebo during the double-blind phase and then switched to rufinamide in the extension phase had a reduction in seizure frequency once they started receiving rufinamide. However, it should be noted that only 42 patients completed the study whereas 82 patients withdrew. As much as 51 patients withdrew due to insufficient therapeutic effect. It is therefore not possible to conclude whether there was tolerance development during the extension phase.

Efficacy variable 2: Response to treatment
Total seizures
The responder rates based on total seizure frequency are summarized in Table 47.

Table 47. Response to treatment based on total seizure frequency (Patients in Study 022E)

Responder Rate	Period	Responded/ Treated	% Response
50%	Overall	45/122	36.9
	Last 12 months	50/122	41.0
	Last 6 months	55/122	45.1
75%	Overall	26/122	21.3
	Last 12 months	29/122	23.8
	Last 6 months	34/122	27.9
100% (Seizure free)	Overall	0/122	0.0
	Last 12 months	0/122	0.0
	Last 6 months	2/122	1.6

Cross reference: Table 9-3 in the CSR for Study 022E.

Forty-five percent (45%) of the patients had at least a 50% reduction in total seizure frequency during the last 6 months of treatment. The percentage of patients with a 50% response during the last 12 months was 41.0%. The 50% response rate for total seizure was 36.9% overall. For at least a 75% reduction in total seizures, the response rates were lower but the pattern was similar. Two of 122 patients (1.6%) were seizure-free for the last 6 months of treatment.

In summary, the patients who switched from double-blind placebo to open-label rufinamide responded to treatment with decreases in seizure frequency. However, only 42 of 124 patients completed the study, whereas 82 withdrew and of these, 51 patients withdrew due to insufficient therapeutic effect. It is possible that a proportion of these 51 patients withdrew due to tolerance development with reduced efficacy. The results from the extension study do not answer the question whether there is development of tolerance to the anticonvulsant effect of rufinamide during long-term treatment.

Studies AE/ET1 E and 021AE

Efficacy date were obtained during the open-label phase of Studies AE/ET1 and 021A. Patients who had completed the double-blind phase of the studies were eligible to participate in the Extension Phase (395 patients were treated in study AE/ET1E and 240 in study 021AE).
The Extension Phase consisted of 2 periods: an open-label Conversion Period and an Open-label Period. During the Conversion Period, all patients received rufinamide according to a recommended titration schedule based on the dose of study drug (rufinamide or placebo) they had received during the double-blind phase. After completion of the Conversion Period, each patient entered the Open-label Period.

The following efficacy variables were identified after the study was completed:

• Variable 1 - The percentage change in partial seizure frequency per 28 days relative to the baseline phase. This was determined for 2 cohorts: patients who had received rufinamide during both the double-blind phase (Study 021A) and the Extension Phase (021AE), and patients who had received placebo during the double-blind phase and rufinamide during the Extension Phase.

• Variable 2 - Response to treatment, defined as experiencing at least a 50% or 75% reduction in seizure frequency for the overall study period, the last 6 months, or the last 12 months of the study. This variable was determined for total seizure frequency and for tonic-atonic seizure frequency.

The results were similar in the 2 extensions, so only study 021AE is presented.

Efficacy variable 1: Percentage change in seizure frequency per 28 days
Patients who received placebo during the core study and then switched to open-label rufinamide showed decreases in seizure frequency, which, over time, became similar to those experienced by patients who received both double-blind and open-label rufinamide.