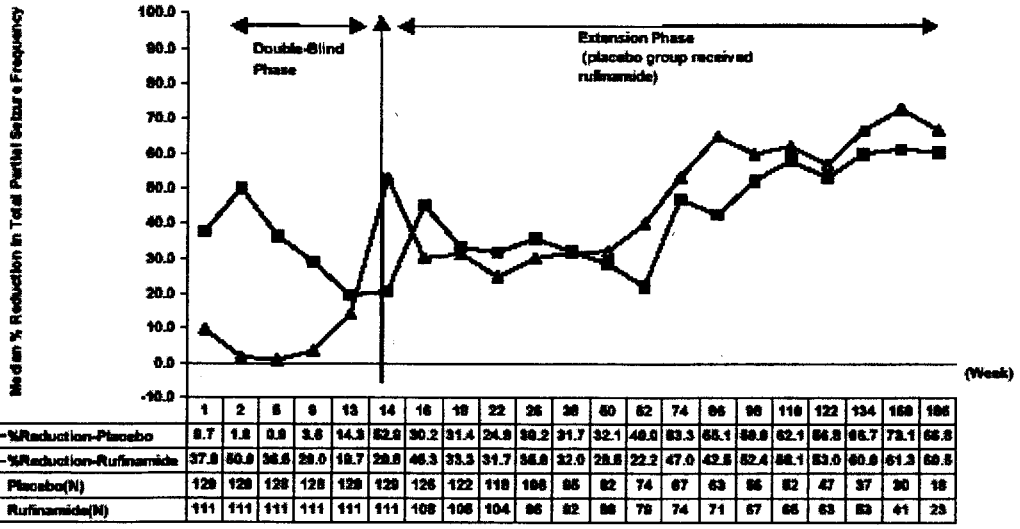

	1	2	5	9	13	14	16	18	22	26	30	50	52	74	96	98	110	122	134	158	186
%Reduction-Placebo	8.7	1.8	0.9	3.6	14.3	52.9	30.2	31.4	24.9	30.2	31.7	32.1	40.0	53.3	65.1	59.9	62.1	64.8	66.7	73.1	66.8
%Reduction-Rufinamide	37.8	50.9	36.6	29.0	19.7	29.8	46.3	33.5	31.7	36.8	32.0	29.8	22.2	47.0	42.5	52.4	56.1	53.0	60.8	61.3	60.5
Placebo(N)	129	129	128	128	128	129	126	122	118	106	95	82	74	67	63	56	52	47	37	30	18
Rufinamide(N)	111	111	111	111	111	111	108	106	104	86	82	80	76	74	71	67	66	63	53	41	23

Efficacy variable 2: Response to treatment

Approximately 22% of the patients maintained at least a 50% reduction in total seizure frequency during treatment with rufinamide. The rate was approximately 29% for those who had at least a 50% reduction during the last 6 or 12 months of treatment. For at least a 75% reduction in total seizures, the response rates were lower but the pattern was similar. Five (2.1%) patients were seizure-free for the last 6 months of treatment.

Response to treatment based on partial seizure frequency

Responder Rate	Period	Responded/ Treated	% Response
50%	Overall	53/238	22.3
	Last 12 months	69/238	29.0
	Last 6 months	70/238	29.4
75%	Overall	18/238	7.6
	Last 12 months	35/238	14.7
	Last 6 months	42/238	17.6
100% (Seizure free)	Overall	2/238	0.8
	Last 12 months	4/238	1.7
	Last 6 months	5/238	2.1

In summary, approximately half of the 635 patients who participated in these studies received rufinamide for a cumulative duration of at least 2 years. The group of patients who had received rufinamide in the double-blind phase and entered the Extension Phase continued to show reductions in seizure frequency. The group of patients who switched from double-blind placebo to open-label rufinamide quickly responded with improvement in seizure frequency, which eventually matched that attained by rufinamide-treated patients. The median reduction in seizure frequency did not diminish over time in the open-label Extension Phase in patients who had received rufinamide or placebo during the double-blind phase.

- Discussion on clinical efficacy

There is a single pivotal clinical trial conducted in Lennox-Gastaut syndrome (study 022 and its extension 022E). Study 022 is a multicenter, randomised, double-blind, placebo-controlled, parallel study comparing the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome. The study design was in accordance with current standards to determine efficacy of antiepileptic drug and design is comparable to published study design supporting the approval of felbamate, topiramate and lamotrigine in this indication.

The diagnosis of LGS was based on the International League Against Epilepsy (ILAE) and confirmed with direct 6- to 24-hour video-EEG recordings.
The patient population, as chosen on the basis of the inclusion/exclusion criteria, was appropriate and representative of patients with LGS, due to the substantial proportion of children included in the present trial (more than 2/3).

The percent change in total seizure frequency per 28 days during the double-blind phase relative to the baseline phase (Primary efficacy variable 1), showed a significant difference between the two 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.
The percent change in tonic-atonic seizure frequency per 28 days during the double-blind phase relative to the baseline phase, showed a significant difference between the two 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.
The seizure severity rating at the end of the double-blind phase, showed a significant difference between the two 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.

Nevertheless, there was a systematic strong baseline imbalance with respect to one of the two primary endpoints: i.e. the total seizure frequency at baseline. This strong imbalance also occurred for some seizure subtypes. The baseline total seizure frequency median was 290 in patients treated with rufinamide and only 205 in patients treated with placebo. Hence, patients treated with placebo were less severe at baseline than those treated with rufinamide. The medians estimated over the double-blind period were similar between the two treatments: i.e. 204.1and 205.4 in the rufinamide and placebo groups respectively. Thus, it cannot be excluded that the treatment effect might be explained entirely from this strong baseline imbalance.
At the request of the CHMP further analysis have been performed by the applicant.
Hodges-Lehmann estimators and 95% confidence intervals of the treatment effect for all seizure types using percent change from baseline in seizure frequency, change from baseline in seizure frequency, and post-baseline seizure frequency (including baseline seizure frequency as covariate) were performed. Unfortunately, as baseline unadjusted analysis are missing, it is not possible to exclude that results of primary efficacy variable 1 (the percent change in total seizure frequency per 28 days during the double-blind phase relative to the baseline phase) might be explained entirely from this strong baseline imbalance.
Nevertheless, primary efficacy variable 2 (the percent change in tonic/atonic seizure frequency per 28 days during the double-blind phase relative to the baseline phase) (where there was no imbalance observed at baseline) and primary efficacy variable 3 (the seizure severity rating at the end of the double-blind phase), showed a highly significant difference between the two treatment groups in favour of rufinamide on quantitative and responder analysis.
These results are consistent and robust as confirmed by the results obtained in the sensitivity analysis.

The PK-PD analysis showed that reduction in total seizure frequency, reduction in tonic-atonic seizure frequency, and improvement in seizure severity were related to the rufinamide serum concentration, i.e., higher exposure to rufinamide was related to seizure improvement.

Children, adolescents, and adult patients of either sex showed similar treatment effects.

The open-label study (study 022E) showed that the group of patients who switched from double-blind rufinamide to open-label rufinamide continued to respond to treatment with decreases in seizure frequency that were as large as, or larger, than the responses during double-blind treatment. The group of patients who switched from double-blind placebo to open-label rufinamide quickly responded to treatment with marked decreases in seizure frequency. As open-label treatment continued, these patients eventually attained levels of seizure reduction that were comparable to those in patients who had received both double-blind and open-label rufinamide.

A satisfactory maintenance of effect was seen at more than 18 months, without any obvious sign of tolerance. However long-term efficacy and absence of tolerance have not been demonstrated convincingly. A statement has been included in the SPC.

Rufinamide showed a moderate efficacy on partial seizures in adults and adolescents as adjunctive therapy (studies. AE/PT2, AE/ET1 and 021A) and as monotherapy of substitution in adults and adolescents (studies 016 and 038), but not in children with refractory partial seizures (study 021P). In addition, there was no significant efficacy found on partial seizures in adults as monotherapy comparing high versus low doses, as well as in primary generalized epilepsy in adults and children over 4 years (study 018), and the effect on associated seizure types, absence and myoclonic seizures, was inferior to placebo. It is true that this population included was very small for these seizure types, and subject to high individual variations. Thus, study 018 failed to bring supportive notion of efficacy in generalized syndromes. No antiepileptic mechanism is known for rufinamide that could explain a better effect of rufinamide in LGS than in the major types of epilepsy. This was a concern for the external validity of efficacy.
Therefore, further information was requested by the CHMP including data about titration, maintenance dose, dose- response relationship, pharmacokinetics and short term safety in these supportive studies.
In the response by the applicant, overall the efficacy of rufinamide as an antiepileptic drug is supported by three positive trials in adults with partial seizures in which significant differences in seizure frequency were seen versus placebo. The trial in paediatric patients with partial seizures did not meet the primary efficacy endpoints. However, the responder rate approached significance (p=0.0596).
In patients with primary generalized seizures rufinamide efficacy has not been demonstrated. Nevertheless, relatively low rufinamide dose (800 mg/day) have been used. Thus these data give some reassurance for the external validity of the results.

Clinical safety

The population of all patients with epilepsy who have received at least 1 dose of rufinamide in a controlled or open-label clinical study or in an open-label extension includes a total of 1,978 patients. In addition to safety documentation for all patients with epilepsy, the applicant has submitted analyses of different subpopulations of patients who have been exposed to rufinamide. The different subpopulations for which safety data have been provided are listed below:

- Double-blind, adjunctive therapy study in LGS: This population includes all patients who received at least 1 dose of rufinamide or placebo in the pivotal study, Study 022 (N=74 rufinamide-treated patients and N=64 placebo-treated patients).

- Double-blind, adjunctive therapy study in LGS (with open-label extension): This population includes all patients who 1) received double-blind rufinamide in the pivotal study, Study 022, and did not enter the Extension Phase (Study 022E), 2) received double-blind rufinamide in Study 022, entered the Extension Phase, and received at least 1 dose of open-label rufinamide; and 3) received double-blind placebo in Study 022, entered the Extension phase, and received at least 1 dose of open-label rufinamide (N=135 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

- Double-blind studies in paediatric patients: This population includes all patients who received at least 1 dose of rufinamide or placebo and either were enrolled in double-blind Study 021P (paediatric patients only) or were ≤16 years old and enrolled in another double-blind study in epilepsy, including the LGS study (N=212 rufinamide-treated patients and N=197 placebo-treated patients).

- Double-blind, adjunctive therapy study in paediatric patients (with open-label extension): This population includes all patients in the preceding population who 1) received double-blind rufinamide only, 2) received double-blind rufinamide, entered an Extension Phase, and received at least 1 dose of open-label rufinamide; and 3) received double-blind placebo, entered an Extension

Phase, and received at least 1 dose of open-label rufinamide (N=391 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

- All treated patients with epilepsy (double-blind studies): This population includes all patients with epilepsy who received at least 1 dose of study drug in a double-blind clinical study (N=1,240 rufinamide-treated patients and N=635 placebo-treated patients).

- All treated patients with epilepsy: This population includes all patients with epilepsy who received at least 1 dose of rufinamide in a controlled or open-label clinical study or in an open-label extension (N=1,978 rufinamide-treated patients). Data obtained only while patients were receiving rufinamide are included in this pool.

The number of patients in each analysis population, by study is summarised in the table below. The largest population, "All treated patients with epilepsy", included a total of 1,978 patients. In this assessment report, focus is on the two largest safety populations, "All treated patients with epilepsy (double-blind studies)" [n=1875] and "All treated patients with epilepsy" [n=1978].

Table. Number of patients in each analysis population, by study

	Number of patients										
	DB, adjunctive therapy study in LGS		DB, adjunctive therapy study in LGS (with OL extension)		DB studies in pediatric patients		DB studies in pediatric patients (with OL extensions)		All treated patients with epilepsy (double-blind studies)		All treated patients with epilepsy
Study	RUF	PLA	RUF	PLA	RUF	PLA	RUF	PLA	RUF	PLA	RUF
AE/ET1					8		8		514	133	514
AE/ET1E[a]											83[b]
AE/PT2									50[c]		50[c]
016									142		142
016E[a]											NA
018					14	11	14	11	78	75	78
018E[a]							10				64
021A					1		1		156	157	156
021AE[a]											129
021P					136	132	136	132	136	132	136
021PE[a]							119				119
022	74	64	74	64	50	50	50	50	74	64	74
022E[a]			61[b]				47				61[b]
027											16
027E[a]											NA
038					3	3	3	3	52	52	52
038E[a]							2				44
039						1		1	14	15	14
039E[a]							1				13
0101											209
2301											(73[d])
AE/PT1									15[e]	4	15
AE/PT3									9	3[f]	9
Total	74	64	135	64	212	197	391	197	1,240	635	1,978

[a] E indicates an open-label extension of a double-blind study. The number of patients shown in the rows for extension studies represent patients who received placebo during the double-blind study and rufinamide during the open-label study.

[b] Includes 1 patient who did not receive study drug in a double-blind study due to administrative problems and was allowed to enter the extension of the study directly.

[c] This was a double-blind, placebo-controlled study in which 25 patients received rufinamide and 25 patients received placebo for up to 4 weeks. In addition, the study included 2 pharmacokinetic evaluation periods in which all patients in both treatment groups received single doses of rufinamide 800 mg.

[d] These patients had received rufinamide in an open-label study that was terminated, and were allowed to continue receiving the drug in this compassionate-use study. These 73 patients are counted once in the total for this column.

[e] 12 patients with epilepsy and 3 healthy volunteers.

[f] These 3 patients also received a single-dose of rufinamide; they were included only in the placebo group.

The following table summarizes the demographic characteristics of all treated patients with epilepsy. Approximately half of the 1,978 patients exposed to rufinamide were males. The mean age was 31.3 years, and 77.6% of the patients were between the ages of 17 and 64 years. The mean weight was 66.8 kg, and 78.4% of the patients weighed more than 50 kg.

Table. Patient demographics for all treated patients with epilepsy (n=1,978).

Characteristic	Rufinamide[a] (N=1,978) n	(%)
Sex		
Male	999	(50.5)
Female	979	(49.5)
Race[b]		
White/Caucasian	1,139	(57.6)
Black	86	(4.3)
Oriental	6	(0.3)
Other	100	(5.1)
Not reported[c]	647	(32.7)
Age, years		
Mean (Range)	31.3 (1-81)	
<12	234	(11.8)
≥12 – 16	183	(9.3)
≥17 – 64	1,534	(77.6)
≥65	27	(1.4)
Weight, kg		
Mean (Range)	66.8 (13.2-158.3)	
≤29	152	(7.7)
>29 – 50	275	(13.9)
>50	1,551	(78.4)

[a] Includes all patients who received rufinamide during open-label studies, double-blind studies, and extension studies, including patients who received placebo during a double-blind study and then received rufinamide during an extension study.

[b] The possible choices for race on the rufinamide CRFs that collected this information were white/Caucasian, black, oriental, or other.

[c] Information about race was not collected in all studies.

- Patient exposure

The extent of exposure to study drug for all rufinamide-treated patients with epilepsy is summarized by median daily dose in Table 50. Median doses were less than 1,600 mg/day for 939 (47.5%) patients, 1,600 to less than 2,400 mg/day for 381 (19.3%) patients, 2,400 to 3,200 mg/day for 598 (30.2%) patients, and more than 3,200 mg/day for 60 (3.0%) patients. The duration of exposure to these median daily doses ranged from less than 1 month to 4 years or more. More than half of the 939 patients with median doses of less than 1,600 mg/day were treated for at least 6 months. More than half of the 1,039 patients with median doses of 1,600 mg/day or more were treated for at least 12 months.

Table. Duration of exposure to rufinamide by median daily dose in mg/day
(All treated patients with epilepsy)

Cumulative Duration of Exposure[b,c]	Median dose[a] (mg/day) <400 (N=117) N	(%)	400 - <1,600 (N=822) N	(%)	1,600 - <2,400 (N=381) N	(%)	2,400 - ≤3,200 (N=598) N	(%)	>3,200 (N=60) N	(%)	All doses (N=1,978) N	(%)
0 - <1 month	117	(100)	822	(100)	381	(100)	598	(100)	60	(100)	1,978	(100)
1 - <3 months	104	(89)	751	(91)	361	(95)	562	(94)	60	(100)	1,838	(93)
3 - <6 months	75	(64)	571	(69)	293	(77)	516	(86)	58	(97)	1,513	(76)
6 - <12 months	41	(35)	467	(57)	227	(60)	451	(75)	53	(88)	1,239	(63)
12 - <24 months	11	(9)	316	(38)	173	(45)	376	(63)	46	(77)	922	(47)
24 - <36 months	1	(1)	125	(15)	86	(23)	206	(34)	27	(45)	445	(22)
36 - <48 months	0		54	(7)	43	(11)	92	(15)	14	(23)	203	(10)
≥48 months	0		23	(3)	12	(3)	31	(5)	1	(2)	67	(3)

[a] Median daily dose starting in the Maintenance Period. Dose calculations do not include titration information.
[b] 1 month = 30 days
[c] Includes patients with exposure to rufinamide during any open-label, double-blind, and/or extension phases.

- Adverse events

Events that were expected due to the trial indication (such as seizures in patients with epilepsy) were not treated as adverse events or serious adverse events, unless the event represented a significant worsening of the symptom (e.g., new seizure type, clinically significant increase in seizure severity, status epilepticus or hospitalization, etc.). The investigators were instructed to record adverse events using standard medical terminology. For the CSRs, the specific terms that the investigators recorded were coded to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. To maintain consistency in terminology for this safety summary, all investigator terms from all studies were recoded using MedDRA.

Adverse events data were pooled using the analysis populations defined in Section IV.1

An overview of all adverse events, deaths, serious adverse events, and adverse events leading to discontinuation of therapy is presented in the next table.

Table. Overview of adverse events, deaths, non-fatal serious adverse events, and adverse events leading to discontinuation of therapy

	Double-blind, adjunctive study in LGS		Double-blind studies in pediatric patients		Double-blind studies in patients with epilepsy		All treated patients with epilepsy
	RUF (N=74) N (%)	PLA (N=64) N (%)	RUF (N=212) N (%)	PLA (N=197) N (%)	RUF (N=1,240) N (%)	PLA (N=635) N (%)	RUF (N=1,978) N (%)
Any adverse event	60 (81.1)	52 (81.3)	177 (83.5)	147 (74.6)	975 (78.6)	497 (78.3)	1,761 (89.0)
Maximum severity							
Mild	17 (23.0)	31 (48.4)	65 (30.7)	82 (41.6)	394 (31.8)	240 (37.8)	466 (23.6)
Moderate	33 (44.6)	15 (23.4)	93 (43.9)	52 (26.4)	448 (36.1)	199 (31.3)	884 (44.7)
Severe	10 (13.5)	6 (9.4)	19 (9.0)	13 (6.6)	133 (10.7)	58 (9.1)	411 (20.8)
Deaths	0	0	0	1 (0.5)	2 (0.2)	4 (0.6)	18 (0.9)
Any non-fatal serious adverse event	3 (4.1)	2 (3.1)	16 (7.5)	11 (5.6)	78 (6.3)	25 (3.9)	261 (13.2)
Adverse event leading to discontinuation	6 (8.1)	0	15 (7.1)	4 (2.0)	100 (8.1)	27 (4.3)	259 (13.1)

All treated patients with epilepsy (double-blind studies)

The adverse events which occurred in more than 10 % of the patients are displayed by severity in the table below. The most common adverse events were headache (22.9 % for rufinamide vs. 18.9 % for placebo), dizziness (15.5 % vs. 9.4 %), fatigue (13.6 % vs. 9.0 %), somnolence (11.8 % vs. 9.1 %) and nausea (11.4 % vs. 7.6 %).

Table. Number (%) of patients with adverse events by preferred term (10 % of greater for either treatment group) by severity. All treated patients with epilepsy, double-blind studies)

	Rufinamide		Placebo	
	n	(%)	n	(%)
Total number of patients studied	1,240		635	
Total number of patients with an adverse event	975	(78.6)	497	(78.3)
Mild	394	(31.8)	240	(37.8)
Moderate	448	(36.1)	199	(31.3)
Severe	133	(10.7)	58	(9.1)
Headache - Total	284	(22.9)	120	(18.9)
Mild	166	(13.4)	74	(11.7)
Moderate	98	(7.9)	34	(5.4)
Severe	20	(1.6)	12	(1.9)
Dizziness - Total	192	(15.5)	60	(9.4)
Mild	117	(9.4)	46	(7.2)
Moderate	67	(5.4)	13	(2.0)
Severe	8	(0.6)	1	(0.2)
Fatigue - Total	169	(13.6)	57	(9.0)
Mild	100	(8.1)	39	(6.1)
Moderate	57	(4.6)	13	(2.0)
Severe	12	(1.0)	5	(0.8)
Somnolence - Total	146	(11.8)	58	(9.1)
Mild	98	(7.9)	44	(6.9)
Moderate	43	(3.5)	12	(1.9)
Severe	5	(0.4)	2	(0.3)
Nausea - Total	141	(11.4)	48	(7.6)
Mild	93	(7.5)	37	(5.8)
Moderate	44	(3.5)	11	(2.7)
Severe	4	(0.3)	0	

Note: Patient-years of exposure = 291.51 for rufinamide and 149.60 for placebo.

The analysis of incidence of adverse events that occurred in 10 % or more of the rufinamide-treated patients shows a general tendency for an increased incidence with increasing dose.

A safety review of eye disorders shows that such events were reported in 18, 7% of all patients who received at least 1 dose of rufinamide. The most commonly occurring eye disorders were diplopia(8,9%), vision blurred(6%) and visual disturbance among all treated patients The rate of eye disorder based on patient –years of exposure to rufinamide was higher in adults than in paediatric patients or patients with LGS. As there was a higher incidence of diplopia and blurred vision in the rufinamide group compared to placebo in controlled clinical studies and as the occurrence of diplopia and other eye disorders are common with AEDs, these findings are mentioned in the SPC (section 4.8)

- Serious adverse event/deaths/other significant events

Double-blind, adjunctive therapy study in LGS (Study 022)[n=138]

In the pivotal study in LGS, three (4.1%) rufinamide-treated patients experienced a total of 5 serious adverse events, and 2 (3.1%) placebo-treated patients experienced a total of 2 serious adverse events. Serious adverse events led to discontinuation of treatment in 1 patient, who was in the rufinamide group and had serious adverse events of vomiting, fatigue, and rash.

No patient in either treatment group died during or within 30 days of discontinuing treatment in the double-blind LGS study (Study 022).

All treated patients with epilepsy (double-blind studies)[n=1875]

Seventy-eight (6.3%) rufinamide-treated patients experienced a total of 98 serious adverse events, and 25 (3.9%) placebo-treated patients experienced a total of 28 serious adverse events. The most frequently reported serious events in the rufinamide group were related to general disorders, eye disorders and epilepsy. Fatigue was reported for 6 patients (0.5 %) in the rufinamide groups versus 0 in the placebo group. Convulsion was reported for 7 patients (0.6 %) in the active groups vs. 4 (0.6 %) in the placebo group. Status epilepticus was reported for 4 (0.3 %) in the active group vs. 0 in the placebo group.
Twenty-three serious adverse events in the rufinamide group and 7 serious adverse events in the placebo group led to discontinuation of treatment.

All treated patients with epilepsy [n=1978]
Two hundred sixty-one (13.2%) patients experienced a total of 327 serious adverse events. The estimated exposure to rufinamide in this population was 2,552.96 patient-years. The rate of serious adverse events was therefore 10.22 per 100 patient-years. The most frequently reported serious events with rufinamide were related to epilepsy: convulsion (43 patients), status epilepticus (19 patients), grand mal convulsion (11 patients), partial seizures with secondary generalization (8 patients), complex partial seizures (4 patients), epilepsy (4 patients), and partial seizures (1 patient). The most frequently occurring non-epilepsy related serious adverse events with rufinamide were pneumonia (15 patients) and vomiting (11 patients). Fifty-three serious adverse events led to discontinuation of treatment.

Deaths
Twenty-two patients (18 who received rufinamide and 4 who received placebo) died during one of the clinical studies or within 30 days after receiving the last dose of study drug in one of the studies. Six patients (2 who received rufinamide and 4 who received placebo) died during double-blind studies, and 16 died while taking rufinamide during open-label studies or open label extension studies. For all treated patients with epilepsy, the rate of deaths was 0.71 per 100 patient-years of exposure to rufinamide. The rates were 0.69 per 100 patient-years of exposure to rufinamide and 2.67 per 100 patient-years of exposure to placebo for all patients with epilepsy who received study drug in double-blind studies.
Only 1 death was suspected by the investigators of being related to study drug: cardiac arrest in Patients 0001-03008 (Study AE/ET1) who received placebo.

0101	Rufinamide	0052-00011	65/M	Death	1,200	119	Not suspected
0101	Rufinamide	0052-00016	33/M	Death	800	86	Not suspected
0101	Rufinamide	0507-00003[b]	61/F	Pneumonia, small cell carcinoma of bronchus, urinary tract infection	3,200	273	Not suspected
AE/ET1E	Rufinamide	0001-06005	64/M	Prostate cancer	1,600	NA	Not suspected
AE/ET1E	Rufinamide	0001-09009	34/F	Epilepsy	1,200	406	Not suspected
AE/ET1E	Rufinamide	0002-02056	33/F	Asphyxia	400	193	Not suspected
AE/ET1E	Rufinamide	0002-07029	48/F	Adenocarcinoma	400	504	Not suspected
AE/ET1E	Rufinamide	0008-01159	24/M	Death	1,400	173	Not suspected

[a] Dose expressed as equivalents of rufinamide.
[b] This death occurred more than 30 days after the patient received his or her last dose of rufinamide and is therefore not included in any tabulations or analyses related to deaths. A narrative is included in the CSR.

Sudden unexplained death in epilepsy (SUDEP)
The applicant has reviewed all available information concerning each of the deaths to determine which represented sudden deaths, i.e., deaths without any obvious cause (except for seizures), regardless of the investigators' terms for cause of death. Eight deaths among rufinamide-treated patients, all during open-label treatment, and the four deaths among placebo treated patients were considered sudden deaths. All deaths in the rufinamide-treated patients were considered not related to rufinamide.

- Discontinuation due to adverse events

In the double-blind studies, discontinuations due to adverse events occurred in higher percentages of rufinamide- patients (approximately 7% to 8%) than placebo-treated patients (0% to 4.3%). Discontinuations were more frequent (approximately 13%) with longer duration of rufinamide

exposure as in the open-label extensions. Of the 1,978 patients with received at least 1 dose of rufinamide, 13.1% discontinued treatment because of adverse events with the most common events being fatigue, headache, nausea, and dizziness. The reasons for discontinuations due to adverse events are reviewed below for the pivotal study 022, all double-blind studies, and for all treated patients with epilepsy.

Double-blind, adjunctive therapy study in LGS, Pivotal study 022
Six (8.1%) rufinamide-treated patients and no placebo-treated patients discontinued study drug during the double-blind study in LGS due to adverse events. The events leading to discontinuation of more than 1 patient were vomiting (3 patients), somnolence (2 patients), and rash (2 patients). No patient had laboratory abnormalities as a primary reason for discontinuation.
No patient discontinued in the placebo group.

All treated patients with epilepsy (double-blind studies)
In the population of all patients with epilepsy who received study drug in double-blind studies,
100 (8.1%) of 1,240 rufinamide-treated patients and 27 (4.3%) of 635 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 1.8% of the patients. The events most frequently leading to discontinuation of rufinamide were dizziness (22 patients), fatigue (20 patients), headache (14 patients), nausea (13 patients), and diplopia (12 patients). Rash was the cause of discontinuation for 6 (0.5%) rufinamide-treated patients and 1 (0.2%) placebo-treated patient.

The following table displays the adverse events leading to the discontinuation of more than 1 patient in either treatment group:

Table. Adverse events leading to discontinuation of more than 1 patient per treatment group (All treated patients with epilepsy, double-blind studies)

SOC	Preferred term	Rufinamide (N=1,240) N (%)	Placebo (N=635) N (%)
Any		100 (8.1)	27 (4.3)
Ear and labyrinth disorders	Vertigo	7 (0.6)	0
Eye disorders	Diplopia	12 (1.0)	1 (0.2)
	Vision blurred	3 (0.2)	1 (0.2)
	Accommodation disorder	2 (0.2)	0
Gastrointestinal disorders	Nausea	13 (1.0)	0
	Vomiting	5 (0.4)	1 (0.2)
	Abdominal pain upper	4 (0.3)	1 (0.2)
	Diarrhea	2 (0.2)	1 (0.2)
General disorders and administration site conditions	Fatigue	20 (1.6)	3 (0.5)
	Asthenia	4 (0.3)	0
	Malaise	4 (0.3)	0
	Gait disturbance	3 (0.2)	1 (0.2)
Metabolism and nutrition disorders	Anorexia	5 (0.4)	0
Nervous system disorders	Dizziness	22 (1.8)	3 (0.5)
	Headache	14 (1.1)	4 (0.6)
	Ataxia	11 (0.9)	0
	Convulsion	10 (0.8)	4 (0.6)
	Somnolence	8 (0.6)	2 (0.3)
	Nystagmus	5 (0.4)	1 (0.2)
	Paresthesia	4 (0.3)	0
	Disturbance in attention	3 (0.2)	0
	Sedation	3 (0.2)	0
	Tremor	2 (0.2)	2 (0.3)
	Hemiparesis	2 (0.2)	1 (0.2)
	Sensory disturbance	2 (0.2)	1 (0.2)
	Lethargy	2 (0.2)	0
	Grand mal convulsion	1 (0.1)	3 (0.5)
	Memory impairment	1 (0.1)	2 (0.3)
Psychiatric disorders	Anxiety	4 (0.3)	1 (0.2)
	Irritability	4 (0.3)	1 (0.2)
	Confusional state	3 (0.2)	1 (0.2)
	Apathy	3 (0.2)	0
	Aggression	2 (0.2)	1 (0.2)
	Affect lability	2 (0.2)	0
Skin and subcutaneous tissue disorders	Rash	6 (0.5)	1 (0.2)
	Face edema	2 (0.2)	0
	Rash papular	2 (0.2)	0
	Urticaria	2 (0.2)	0

Note: Patient-years of exposure = 291.51 for rufinamide and 149.60 for placebo.

All treated patients with epilepsy (n=1,978)

In the population of all treated patients with epilepsy, 259 (13.1%) of 1,978 patients treated with rufinamide discontinued study drug due to adverse events. The events most often leading to discontinuation of rufinamide were fatigue (38 patients), headache (32 patients), nausea (31 patients), dizziness (31 patients), rash (17 patients), convulsion (24), diplopia (19), somnolence (18), vomiting (13).

- Laboratory findings

Clinical laboratory data were summarized using descriptive statistics for values obtained at baseline and at the last post-baseline visit, and for the difference between those two evaluations.

Hepatic laboratory parameters

In the double-blind studies, increases in hepatobiliary parameters occurred in $\leq$ 3.4 % of the rufinamide-treated patients and in $\leq$ 6.0 % of the placebo-treated patients. For most individual parameters, the percentages of patients with upward of downward shifts were similar for rufinamide and placebo. A total of 22 cases reporting of increased liver enzymes with a value over 3N were

analysed. Although the causal role of rufinamide is difficult to establish due to confounding factors this adverse reaction will be mention inn the SPC. There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. One rufinamide-treated patient (in Study 022) discontinued due to hepatic enzymes increased. In other studies, one patient had a serious adverse event related to the hepatobiliary system (cholecystitis, Study 0101) and another patient in Study 021PE discontinued due to suspicion of hepatitis toxic, the origin of which was not confirmed later on.

Renal laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for all renal parameters, and were comparable in the rufinamide and placebo groups in the double-blind studies.

Adverse events related to renal laboratory tests or renal disorders occurred in less than 1% of all rufinamide-treated patients. One patient had a serious adverse event of renal failure acute after a prolonged seizure, which resulted in rhabdomyolysis and dehydration. Renal experts at the hospital attributed the event to the prolonged seizure, which resulted in dehydration. The patient was subsequently restarted on rufinamide.

Haematology laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable in the rufinamide and placebo groups for every population that compared results from the double-blind studies.

Thyroid laboratory parameters
Rufinamide does not appear to have a clinically or statistically significant effect on thyroid although there were individual cases of changes of T3 or TSH and individual cases of hypothyroidism.

- Other adverse effects of interest

Status epilepticus
Status epilepticus did not occur in any patient who received placebo in any of the double-blind studies in the rufinamide clinical development program. As shown in the following table, status epilepticus was an adverse event in 1.4% of all patients who received at least 1 dose of rufinamide, a serious adverse event in 1.0%, and an event that led to discontinuation of treatment in 0.3%. The incidence of status epilepticus as an adverse event was higher in patients with LGS (3.7%) and in paediatric patients (2.6%) than in adult patients (1.1%). Serious status epilepticus occurred in ≤2.0% of the patients in any subgroup, and this event led to the discontinuation of <1.0% of those in any subgroup. No patient had a status epilepticus that lead to death.

Table 7. Overview of Occurrence of Status Epilepticus in Rufinamide Clinical Studies

	Double-blind plus open-label			
	All patients with epilepsy (N=1978)	**Patients with LGS (N=135)**	**Paediatric patients (N=391)**	**Adults patients (N=1561)**
Incidence of status epilepticus	27 (1.4%)	5 (3.7%)	10 (2.6%)	17 (1.1%)
Discontinuation due to status epilepticus	6 (0.3%)	1 (0.7%)	2 (0.5%)	4 (0.3%)
Status epilepticus as non-fatal serious adverse event	19 (1.0%)	2 (1.5%)	8 (2.0%)	11 (0.7%)

Note: he population "all patients with epilepsy" includes all patients who received at least 1 dose of rufinamide in any Phase II or III double-blind study, open-label extension of a double-blind study, or open-label study. The remaining 3 populations shown in this table include all patients who received at least 1 dose of rufinamide in a Phase II or III double-blind study or its open-label extension (patients enrolled only in Phase II or III open-label studies are not included). Patients included in the population "patients with LGS" are also included in the populations "paediatric patients" and "adult patients" depending on whether their age at baseline was ≤16 years (paediatric patients) or >16 years (adult patients).
Cross reference: Appendix 3, Tables 2.2.2, 2.2.4, 2.2.6, 3.1.2, 3.2.4, 3.2.6, 5.1.1, 22.2.1, 22.4.1, 22.6.1