EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulations (EC) NO 1901/2006

Inovelon

International non-proprietary name: RUFINAMIDE

Procedure No. EMEA/H/C/000660/P46/030.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. INTRODUCTION

On March 31th 2014, the MAH submitted the synoptic clinical study report for study E2080-J081-305 for INOVELON (rufinamide), in accordance with Article 46 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH stated that the submitted paediatric study does not influence the benefit risk for INOVELON and that there is no consequential regulatory action.

On August 11th 2014, as requested, Eisai Ltd submits to the EMA the responses to the Outstanding Questions.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study

The study was conducted using Inovelon tablet formulation since an alternative paediatric formulation was not available at this time. Eisai Limited had since been granted a marketing approval for a line extension MAA for an oral suspension formulation for use in children (Commission decision issued on 21/11/2011).

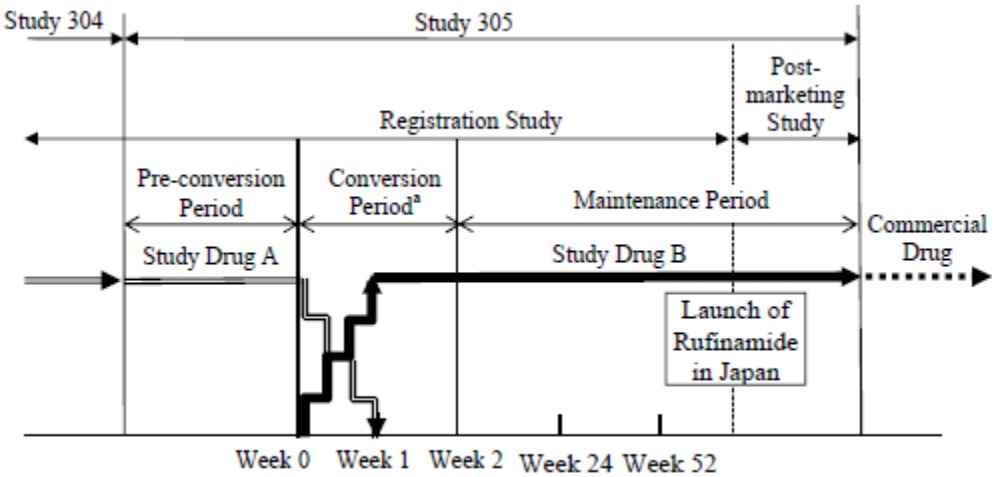
II.2 Clinical aspects

1. Introduction

Study E2080-J081-305 was a multicentre long term extension study, to evaluate the long term safety and tolerability of rufinamide under the open-label treatment in patients with Lennox-Gastaut syndrome (LGS) who completed the phase 3 placebo-controlled, double-blind, comparative study (study E2080-J081-304).

2. Clinical study

Methods



a: In the Conversion Period, Study Drug A (double-blind; rufinamide or placebo tablets) was switched to the Study Drug B (open-label; rufinamide tablets) in a step-by-step manner.

The Pre-conversion Period was designed to avoid breaking the blindness in the preceding Study 304 and to prevent any data obtained in the open-label treatment in Study 305 from affecting the evaluation in the Study 304. Under double-blind condition, subjects were treated with the same

study drug as in the Study 304 (the Study Drug A; rufinamide or placebo) until the evaluation data of the Study 304 for each subject were fixed.

In the Conversion Period, subjects who were on placebo were titrated to the appropriate dose of rufinamide (the Study Drug B) within 2 weeks under double-blind condition.

The long term safety and efficacy of rufinamide were evaluated under the open-label treatment in the Maintenance Period. The daily dose at the end of the Conversion Period was used as the initial dose for the Maintenance Period. Treatment of rufinamide (the Study Drug B) was allowed to be continued as long as the subject and legally authorized representative desired to keep receiving rufinamide and the investigator permitted that.

The Maintenance Period was allowed to continue until rufinamide was launched in Japan and was to be commercially available in the respective study sites. This study was conducted as a registration study before the launch and as a post-marketing study after that.

The study was to finish within around 3 months after the price listing of rufinamide. In case subjects discontinued the study, the study drug was to be tapered (Follow-up Period), but subjects who completed Study 305 were allowed to continue receiving rufinamide as a commercial drug without tapering.

The study drug was administered orally twice daily after breakfast and dinner.

1. Pre-conversion Period

Under double-blind condition, subjects were treated with the same study drug as in the Study 304 (the Study Drug A; rufinamide or placebo). As a general rule, the dose was to be maintained at the dose of the final evaluation (Week 12) in the Study 304.
When the investigator judged dose reduction was necessary to attempt for safety concerns on a subject who completed the Study 304 at the target maintenance dose, a 1- step reduction from the target maintenance dose was allowed. This reduction was performed from the next morning of the judgment, if feasible. Returning to the previous dose (ie, the target maintenance dose) after the reduction was prohibited.

In subjects for whom the dose had been reduced from the target maintenance dose by the completion of the Study 304, further dose reduction was prohibited under any circumstances. Subjects were to be withdrawn from the study if further dose reduction was judged to be necessary for safety reasons by the investigator

For reference, dose steps to the target maintenance dose depended on the subject's weight in the Study 304 are shown in Table 1.

Table 1 Dose steps to the target maintenance dose in Study 304

Body weight	15.0 to 30.0 kg	30.1 to 50.0 kg	50.1 to 70.0 kg	70.1 kg or above
Tablet	100 mg tablet	200 mg tablet	200 mg tablet	200 mg tablet
Step 1 (Day 1 to 2)	200 mg/day	400 mg/day	600 mg/day	
Step 2 (Day 3 to 4)	400 mg/day	800 mg/day	1200 mg/day	
Step 3 (Day 5 to 6)	800 mg/day	1200 mg/day	1800 mg/day	
Step 4 (Day 7 or after)	1000 mg/day[a]	1800 mg/day[a]	2400 mg/day[a]	2400 mg/day
Step 5 (Day 9 or after)	–	–	–	3200 mg/day[a]

a: Target maintenance dose for each body weight category.

2. Conversion Period

Under double-blind conditions, subjects who were on placebo were titrated to the appropriate dose of rufinamide within 2 weeks in a manner similar to the dose steps shown above. Study Drug A (double-blind; rufinamide or placebo tablets) was switched to the Study Drug B (open-label; rufinamide tablets) in a step-by-step manner by 2 days.

Daily number of tablets on the final day of the Pre-conversion Period (constant)
= Daily number of tablets of the Study Drug A (taper off by 2 days)
+ Daily number of tablets of the Study Drug B (gradual increase by 2 days)

If a safety problem was observed during conversion, the conversion could be suspended and daily numbers of tablets of the Study Drug A and Study Drug B were maintained temporarily.

Even in such a case, the conversion was to be completed by 2 days before the end of the Conversion Period.
When the investigator judged dose reduction was necessary to attempt for safety concerns on a subject who had completed the conversion, a 1-step reduction was allowed only for subjects who had administered at the target maintenance dose. This reduction was performed from the next morning of the judgment, if feasible. Returning to the previous dose (ie, the target maintenance dose) after the reduction was prohibited.

3. Maintenance Period
As a general rule, the dose of rufinamide (Study Drug B) at the end of the Conversion Period was to be maintained throughout the Maintenance Period.
When the investigator judged dose reduction was necessary to attempt for safety concerns, a 1-step reduction from the target maintenance dose was allowed. This reduction was performed from the next morning of the judgment, if feasible.

In subjects for whom the dose had been reduced 1-step from the target maintenance dose by the end of the Conversion Period, further dose reduction during the Maintenance Period was prohibited. Subjects were to be withdrawn from the study if further dose reduction was judged to be necessary for safety reasons by the investigator.

Dose increase to the target maintenance dose was allowed only when the investigator judged necessary. Administrations at a higher dose than the target maintenance dose was prohibited under any circumstances.

Even when the body weight changed during the study period, dose adjustment based on the new weight category was not to be conducted in the registration study part.
However, since rufinamide had been launched in Japan, the maintenance dose was to follow the approved dosage. In such a case, dose adjustment based on the new weight category might be allowed as long as same tablet form (100 mg tablet or 200 mg tablet) was used.

In subjects who completed Study 305 and continued receiving rufinamide as a commercial drug, tapering of rufinamide and the Follow-up Period were not required.

4. Follow-up Period (Tapering; when discontinuing the study)
As a general rule, the dose was reduced by step-by-step every 2 days. The dose reduction was started from the next morning of the study discontinuation decided by the investigator, if feasible.
Dose reduction could be postponed and the current dose maintained temporarily by the judgment of the investigator only if there was a safety problem. Even in this case, study drug administration was to be terminated at least by 12 days after start tapering.
Dose steps for tapering rufinamide are shown in Table 2.

Table 2 Dose Steps for Tapering in the Follow-up Period

Body weight	15.0 to 30.0 kg	30.1 to 50.0 kg	50.1 to 70.0 kg	70.1 kg or above
Tablet	100 mg tablet	200 mg tablet	200 mg tablet	200 mg tablet
Step 1	800 mg/day[a]	1200 mg/day[a]	1800 mg/day[a]	2400 mg/day[a]
Step 2	400 mg/day	800 mg/day	1200 mg/day	1800 mg/day
Step 3	200 mg/day	400 mg/day	600 mg/day	1200 mg/day
Step 4	0 mg/day	0 mg/day	0 mg/day	600 mg/day
Step 5	–	–	–	0 mg/day

a: Target maintenance dose for each body weight category.

- **Study Participants**

Patients were included if they had completed the 304 study:
The key criteria for inclusion in study 304 were as follows
• Patients who were diagnoses with LGS with tonic-atonic seizures and typical absence seizures)
• Male and female subjects between 12 and 30 years of age, inclusive;
• Patients whose body weight at the start of the Observation Period was at least 15 kg;
• At least 90 seizures episodes during the 28 days before the start of the Observation Period;
• Current treatment with 1 to 3 approved AEDs, within 28 days prior to the Observation Period and had not changed the drug type;
• Patients who had a slow spike-and-wave pattern in an EEG within 6 months prior to the Observation Period.

Exclusion criteria were: Patients who were judged by investigators that they were not appropriate to participate in this clinical study for safety reasons based on the subject information etc. collected up to the evaluation of the end of Treatment Period in the Study 304, patients who were highly likely to be noncompliant with treatment during the study Period, patients judged to be inappropriate for study participation.

- **Objectives**

PRIMARY OBJECTIVE
• To evaluate the long term safety and tolerability of rufinamide under the open-label treatment in patients with Lennox-Gastaut syndrome (LGS) who completed the phase 3 placebo-controlled, double-blind, comparative study (E2080-J081-304 study, herein after as Study 304).

SECONDARY OBJECTIVES
• To evaluated the long term efficacy of rufinamide under the open-label treatment in patients with LGS who completed the Study 304.

- **Outcomes/endpoints**

Primary efficacy outcome: Percent change in tonic-atonic seizure frequency, percent change in the total seizure frequency, percent change in the frequency of seizures other than tonic-atonic seizures, and 25%, 50%, 75%, 100% responder, and aggravated subjects in tonic-atonic seizure frequency.

Safety outcomes:
Adverse events, clinical laboratory tests, blood pressure, pulse rate, physical examination, and 12-lead ECG.

• **Statistical methods**

Efficacy
For percent change in tonic-atonic seizure frequency, the total seizure frequency, and the frequency of seizures other than tonic-atonic seizures, the summary statistics were calculated for the entire Efficacy Analysis Set and for each treatment group in Study 304.

For 25%, 50%, 75%, 100% responder, and aggravated subjects in tonic-atonic seizure frequency, responder (or aggravated) rates were calculated for the entire Efficacy Analysis Set and for each treatment group in Study 304. For percent change in tonic-atonic seizure frequency and the total seizure frequency, median percent change was plotted by visit for each treatment group in Study 304.

Safety
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0. Treatment-emergent adverse events (TEAEs) and treatment related TEAEs were summarized for the entire Safety Analysis Set and for each treatment group in Study 304, the number and percent of subjects having any adverse event in each primary system organ class (SOC) and having each preferred term (PT). In addition, TEAEs and treatment related TEAEs were tabulated by causal relationship with the study drug or by severity. For laboratory tests (hematology, blood chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and body weight), and 12-lead ECG (heart rate, PR interval, QRS amplitude, QT interval, and QTc), the summary statistics of the observed value at each assessment time point, and changes from the end of the Observation Period in Study 304 (baseline) were calculated for the entire Safety Analysis Set and for each treatment group. Urinalysis data were subjected to cross-tabulation between the end of the Observation Period in Study 304 (baseline) and each assessment time point after the start of treatment.

Results

- **Participant flow**

Fifty subjects were planned. 54 (25 in the rufinamide group, 29 in the placebo group) were enrolled and entered in the study.

	E2080/ E2080	Placebo/ E2080	Total
Subjects who were enrolled in Study 305, n	25	29	54
Not Treated, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Treated, n (%)	25 (100.0)	29 (100.0)	54 (100.0)
Completed the Study 305, n (%)	20 (80.0)	21 (72.4)	41 (75.9)
Discontinued from the Study 305, n (%)	5 (20.0)	8 (27.6)	13 (24.1)
Primary reason for discontinuation, n (%)			
Withdrawal of Consent due to Insufficient Therapeutic Effect	3 (12.0)	4 (13.8)	7 (13.0)
Withdrawal of Consent for a reason other than Insufficient Effect	1 (4.0)	1 (3.4)	2 (3.7)
Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event[a]	1 (4.0)	3 (10.3)	4 (7.4)

All of the 54 subjects who entered Study 305 received at least 1 dose of the study drug. Of the 54 treated subjects, 41 subjects (75.9%) completed the study (ie, kept administered rufinamide in Study 305 until commercial drug of rufinamide was prescribed) and 13 subjects (24.1%) discontinued the study.
Primary reason for discontinuation was withdrawal of consent due to insufficient therapeutic effect (7 subjects), withdrawal of consent for a reason other than insufficient effect (2 subjects), and adverse event (4 subjects).

Efficacy Analysis Set: 46 (23 in the rufinamide group, 23 in the placebo group), 8 subjects have no evaluable efficacy data.
Safety Analysis Set: 54 (25 in the rufinamide group, 29 in the placebo group).

Demographic and other baseline characteristics
In the Efficacy Analysis Set (46 subjects), 65.2% (30 subjects) were males and 34.8% (16 subjects) were females. The mean age was 15.2 years, and 39.1% (18 subjects) were younger than 12 years old. The mean weight was 39.45 kg, and more than 40% of the subjects were in the range of 15.0 to 30.0 kg. The mean duration of LGS was 10.61 years. The subjects experienced a median of 268.20 seizures, including 220.85 tonic-atonic seizures, per 28 days.

Assessor's comments:
Patients aged ≥ 4 to < 17 years were considered as the paediatric population. Taking into account that the definition of paediatric population included children until 18 years old. The number of patients between 17 and 18 years old in each arm should be provided and the MAH should discuss the impact of these patients in the different results.
Tables with demographic and other baseline characteristics (age, sex, body weight, duration of LGS,….) and summary of seizure frequency and type of seizure should be submitted.
Issue resolved after further clarification was provided (see section III)

Number of concomitant AEDs (FAS)

	E2080/ E2080 (N=23) n (%)	Placebo/ E2080 (N=23) n (%)	Total (N=46) n (%)
Total number of concomitant AEDs after first dosing of E2080			
1	0 (0.0)	1 (4.3)	1 (2.2)
2	3 (13.0)	6 (26.1)	9 (19.6)
3	17 (73.9)	11 (47.8)	28 (60.9)
>=4	3 (13.0)	5 (21.7)	8 (17.4)

	E2080/ E2080 (N=23) n (%)	Placebo/ E2080 (N=23) n (%)	Total (N=46) n (%)
Subjects with any Concomitant AEDs	23 (100.0)	23 (100.0)	46 (100.0)
SODIUM VALPROATE	21 (91.3)	23 (100.0)	44 (95.7)
LAMOTRIGINE	13 (56.5)	16 (69.6)	29 (63.0)
CLOBAZAM	11 (47.8)	5 (21.7)	16 (34.8)
PHENYTOIN	6 (26.1)	5 (21.7)	11 (23.9)
CARBAMAZEPINE	5 (21.7)	3 (13.0)	8 (17.4)
CLONAZEPAM	4 (17.4)	3 (13.0)	7 (15.2)
TOPIRAMATE	3 (13.0)	0 (0.0)	3 (6.5)
ETHOSUXIMIDE	2 (8.7)	3 (13.0)	5 (10.9)
ACETAZOLAMIDE	1 (4.3)	0 (0.0)	1 (2.2)
DIAZEPAM	1 (4.3)	0 (0.0)	1 (2.2)
LEVETIRACETAM	1 (4.3)	1 (4.3)	2 (4.3)
PHENOBARBITAL	1 (4.3)	3 (13.0)	4 (8.7)
ZONISAMIDE	1 (4.3)	1 (4.3)	2 (4.3)
GABAPENTIN	0 (0.0)	1 (4.3)	1 (2.2)
SULTIAME	0 (0.0)	3 (13.0)	3 (6.5)

Assessor's comments:
All subjects used at least 1 AED, with the majority in each group using 3 concomitant AEDs. Sodium valproate was the most frequently used AED in both groups. The next most frequently used AED was lamotrigine.

- **Outcomes and estimation**

Primary efficacy results

Table 3 Summary of Percent Change in Tonic-atonic Seizure Frequency per 28 Days Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	median (min, max)	N	median (min, max)	N	median (min, max)
Seizure frequency per 28 days at baseline in Study 304	23	256.10 (28.0, 22469.5)	23	183.60 (8.3, 2046.2)	46	220.85 (8.3, 22469.5)
% Change in Week 12	23	–34.60 (–92.1, 114.3)	23	–59.90 (–100.0, 125.2)	46	–39.30 (–100.0, 125.2)
% Change in Week 24	22	–32.75 (–85.7, 85.7)	21	–51.30 (–100.0, 70.0)	43	–40.60 (–100.0, 85.7)
% Change in Week 32	21	–44.20 (–88.6, 63.8)	21	–50.90 (–100.0, 75.0)	42	–46.80 (–100.0, 75.0)
% Change in Week 40	20	–29.75 (–94.4, 833.2)	21	–52.50 (–100.0, 65.0)	41	–47.60 (–100.0, 833.2)
% Change in Week 52	19	–48.90 (–91.3, 31.1)	21	–23.70 (–100.0, 101.7)	40	–36.05 (–100.0, 101.7)
% Change in Week 52 (LOCF)	23	–48.50 (–91.3, 31.1)	23	–27.10 (–100.0, 101.7)	46	–39.25 (–100.0, 101.7)

min = minimum, max = maximum, LOCF = last observation carried forward.

Assessor's comments:
The median percent changes in tonic-atonic seizure frequency relative to baseline were –39.30%, –40.60%, –46.80%, –47.60%, and –36.05% in Weeks 12, 24, 32, 40, and 52, respectively.

Table 4 Summary Statistics of Subjects Who Responded to Treatment with at Least a 50% Reduction in Tonic-atonic Seizure Frequency Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	n (%)	N	n (%)	N	n (%)
50% Responders in Week 12	23	6 (26.1)	23	14 (60.9)	46	20 (43.5)
50% Responders in Week 24	22	6 (27.3)	21	11 (52.4)	43	17 (39.5)
50% Responders in Week 32	21	9 (42.9)	21	11 (52.4)	42	20 (47.6)
50% Responders in Week 40	20	8 (40.0)	21	12 (57.1)	41	20 (48.8)
50% Responders in Week 52	19	9 (47.4)	21	6 (28.6)	40	15 (37.5)
50% Responders in Week 52 (LOCF)	23	10 (43.5)	23	8 (34.8)	46	18 (39.1)

min = minimum, max = maximum, LOCF = last observation carried forward.

Assessor's comments:
The 50% responder rates in tonic-atonic seizure frequency were 43.5%, 39.5%, 47.6%, 48.8%, and 37.5% in Weeks 12, 24, 32, 40, and 52, respectively. There was no evidence of tolerance developing to the anticonvulsant effect of the therapy including rufinamide.

Table 5 Summary of Percent Change in Total Seizure Frequency per 28 Days Relative to Baseline – Efficacy Analysis Set

	Treatment Group in Study 304				Total	
	Rufinamide		Placebo			
	N	median (min, max)	N	median (min, max)	N	median (min, max)
Seizure frequency per 28 days at baseline in Study 304	23	256.10 (95.4, 22499.4)	23	273.00 (79.9, 2125.9)	46	268.20 (79.9, 22499.4)
% Change in Week 12	23	–46.80 (–93.6, 101.5)	22	–56.00 (–100.0, 37.0)	45	–47.70 (–100.0, 101.5)
% Change in Week 24	22	–42.40 (–85.9, 30.0)	21	–51.30 (–97.0, 116.6)	43	–48.90 (–97.0, 116.6)
% Change in Week 32	21	–50.10 (–90.8, 30.0)	21	–50.90 (–84.4, 209.2)	42	–50.60 (–90.8, 209.2)
% Change in Week 40	20	–46.75 (–95.5, 833.2)	21	–52.00 (–86.9, 168.6)	41	–52.00 (–95.5, 833.2)
% Change in Week 52	19	–53.60 (–91.4, 16.7)	21	–34.00 (–94.3, 340.8)	40	–47.35 (–94.3, 340.8)
% Change in Week 52 (LOCF)	23	–49.40 (–91.4, 16.7)	23	–34.00 (–100.0, 340.8)	46	–46.30 (–100.0, 340.8)

min = minimum, max = maximum, LOCF = last observation carried forward.

Assessor's comments:
The median percent changes in total seizure frequency relative to baseline were –47.70%, –48.90%, –50.60%, –52.00%, and –47.35% in Weeks 12, 24, 32, 40, and 52, respectively.

Overall assessor's comments on efficacy:
The MAH provided a synoptic clinical study report. Results of clinical efficacy outcome showed a therapeutic benefit of long-term use of rufinamide in japanese patients with LGS. Nevertheless, these data should be completed. Summary of percent change in the frequency of seizures other than tonic-atonic seizures, summary of aggravated subjects in tonic-atonic seizure frequency as well as subgroups analyses performed should be submitted.
Issue resolved after further clarification was provided (see section III)

II.3 Safety evaluation

1. Patient exposure

The median duration of exposure to rufinamide was 818.00 days (range 13.5 to 1042.5 days), and 70.4% (38/54 subjects) received rufinamide for 2 years or more.
The median durations of exposure to rufinamide by treatment group in Study 304 were 888.50 days (range 139.0 to 1042.5 days) and 762.50 days (range 13.5 to 930.5 days) in rufinamide and placebo group, respectively.

Table 14.3.1.1.7
Duration of Exposure to E2080
Safety Analysis Set

Statistic	E2080/ E2080 (N=25)	Placebo/ E2080 a (N=29)	Total (N=54)
Duration of Exposure (day)			
n	25	29	54
Mean (SD)	785.08 (288.34)	601.40 (335.90)	686.44 (325.28)
Median	888.50	762.50	818.00
Min, Max	139.0, 1042.5	13.5, 930.5	13.5, 1042.5
Duration of Exposure Categories, n (%)			
0 month =<	25 (100.0)	29 (100.0)	54 (100.0)
1 month =<	25 (100.0)	28 (96.6)	53 (98.1)
3 month =<	25 (100.0)	23 (79.3)	48 (88.9)
6 month =<	23 (92.0)	22 (75.9)	45 (83.3)
9 month =<	22 (88.0)	21 (72.4)	43 (79.6)
12 month =<	21 (84.0)	21 (72.4)	42 (77.8)
18 month =<	20 (80.0)	21 (72.4)	41 (75.9)
24 month =<	20 (80.0)	18 (62.1)	38 (70.4)

a: For subjects previously assigned to the Placebo group in Study 304, the data on or after the Conversion Phase in Study 305 were used in this table.

Safety analysis set was performed on 54 patients aged between 4 and 30 years old: 25 patients were in the rufinamide group and 29 in the placebo group in study 304. All the patients were treated with rufinamide in study 305 until rufinamide was registered in the country.

The table below shows the summary of age and sex in the analysis set in study 304.

Category		Rufinamide (N = 29)	Placebo (N = 30)	Total (N = 59)
Age (year) [a]	Mean ± SD	16.3 ± 7.1	13.9 ± 6.1	15.1 ± 6.7
	Median	14.0	13.0	13.0
	Min, Max	5, 30	4, 29	4, 30
	≥4 to <12	10 (34.5)	13 (43.3)	23 (39.0)
	≥12 to <17	6 (20.7)	6 (20.0)	12 (20.3)
	≥17	13 (44.8)	11 (36.7)	24 (40.7)
Sex	Male	18 (62.1)	19 (63.3)	37 (62.7)
	Female	11 (37.9)	11 (36.7)	22 (37.3)

Number of subjects (%)
a) Age at the start of the Observation Period

Summary of age of the 54 patients who were in study 305 (***assessor table***)	
mean (year)	15,0
median	13
min (year)	4
max (year)	30
number of patient ≥ 4 to < 12	22
number of patient≥ 12 to < 18	14
number of patien> 18	18

Assessor's comments:
The MAH did not transmit a summary of the number, age and sex of the enrolled paediatric patients for study 305. All the patients included in the study 305 had completed study 304 before. The population is slightly older as expected.
Of note, some demographics data were transmitted in Japanese language and with no synthetic table for study 305. In the next potential PAM, all the documents should be translated in English. Only English language is requested.
The MAH provided all safety analysis data into 3 categories of age: ≥4 - <12, ≥12 - <17 and ≥17. However paediatric population should have included all patients younger than 18 years. This data presentation risked to slightly underestimate the number of AEs in paediatric population.
The MAH should provide AEs experienced by patients between 17 and 18 years old in each arms and discuss the impact of these patients on the safety analysis.
Issue resolved after further clarification was provided (see section III)

2. Adverse events

Table 6 presents an overview of TEAEs. All of the 54 subjects who received rufinamide experienced TEAEs, and 38 subjects (70.4%) experienced TEAEs that were considered possibly or probably related to administration of study drug in study 304. Severe TEAEs were reported in 3 subjects (5.6%) and severe treatment-related TEAEs were also reported in the same subjects.

Table 6 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Category	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
TEAEs	25 (100.0)	29 (100.0)	54 (100.0)
Treatment-related TEAEs[a]	17 (68.0)	21 (72.4)	38 (70.4)
Severe TEAEs	1 (4.0)	2 (6.9)	3 (5.6)
Severe Treatment-related TEAEs[a]	1 (4.0)	2 (6.9)	3 (5.6)
Serious TEAEs[b,c]	4 (16.0)	5 (17.2)	9 (16.7)
Serious Treatment-related TEAEs[a,b,c]	1 (4.0)	1 (3.4)	2 (3.7)
TEAEs leading to study drug withdrawal[b]	0 (0.0)	3 (10.3)	3 (5.6)
Treatment-related TEAEs leading to study drug withdrawal[a,b]	0 (0.0)	3 (10.3)	3 (5.6)

TEAE = treatment-emergent adverse event.

Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs.

For each row category, a subject with 2 or more TEAEs in that category is counted only once.

a: Includes TEAEs considered by the investigator to be possibly or probably related to study drug.

b: Only includes TEAEs occurred after the first dose of rufinamide in Study 305.

c: Serious criterion was an adverse event which required inpatient hospitalization or prolongation of existing hospitalization for all serious TEAEs.

Common TEAEs (≥5%) of total subjects and common treatment-related TEAEs are summarized by MedDRA SOC and PT in Table 7 and Table 8, respectively. The most frequently reported TEAEs (≥30%) in total subjects (N=54) were nasopharyngitis (29 subjects; 53.7%), status epilepticus (23 subjects; 42.6%), and somnolence (18 subjects; 33.3%). The most frequently reported treatment-related TEAEs (≥10%) in total subjects were somnolence (11 subjects; 20.4%), decreased appetite (9 subjects; 16.7%), status epilepticus (7 subjects; 13.0%), constipation, and vomiting (6 subjects each; 11.1%).

Table 7 Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304		Total N=54 n (%)
	Rufinamide N=25 n (%)	Placebo N=29 n (%)	
Subjects with any TEAEs	25 (100.0)	29 (100.0)	54 (100.0)
Eye disorders			
Conjunctivitis allergic	1 (4.0)	2 (6.9)	3 (5.6)
Gastrointestinal disorders			
Vomiting	8 (32.0)	7 (24.1)	15 (27.8)
Constipation	4 (16.0)	5 (17.2)	9 (16.7)
Dental caries	7 (28.0)	2 (6.9)	9 (16.7)
Stomatitis	1 (4.0)	5 (17.2)	6 (11.1)
Nausea	2 (8.0)	3 (10.3)	5 (9.3)
Diarrhoea	2 (8.0)	1 (3.4)	3 (5.6)
General disorders and administration site conditions			
Pyrexia	5 (20.0)	1 (3.4)	6 (11.1)
Infections and infestations			
Nasopharyngitis	15 (60.0)	14 (48.3)	29 (53.7)
Influenza	4 (16.0)	8 (27.6)	12 (22.2)
Upper respiratory tract infection	5 (20.0)	3 (10.3)	8 (14.8)
Bronchitis	4 (16.0)	2 (6.9)	6 (11.1)
Gastroenteritis	3 (12.0)	2 (6.9)	5 (9.3)
Pneumonia	2 (8.0)	3 (10.3)	5 (9.3)
Pharyngitis	2 (8.0)	2 (6.9)	4 (7.4)
Injury, poisoning and procedural complications			
Contusion	5 (20.0)	7 (24.1)	12 (22.2)
Skin laceration	4 (16.0)	1 (3.4)	5 (9.3)
Eyelid injury	3 (12.0)	1 (3.4)	4 (7.4)
Fall	2 (8.0)	2 (6.9)	4 (7.4)
Mouth injury	1 (4.0)	3 (10.3)	4 (7.4)
Investigations			
Platelet count decreased	0 (0.0)	3 (10.3)	3 (5.6)
Weight decreased	1 (4.0)	2 (6.9)	3 (5.6)
Metabolism and nutrition disorders			
Decreased appetite	5 (20.0)	6 (20.7)	11 (20.4)
Nervous system disorders			
Status epilepticus	10 (40.0)	13 (44.8)	23 (42.6)
Somnolence	11 (44.0)	7 (24.1)	18 (33.3)
Dizziness	0 (0.0)	3 (10.3)	3 (5.6)

Table 7 Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set (continued)

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304 Rufinamide N=25 n (%)	Treatment Group in Study 304 Placebo N=29 n (%)	Total N=54 n (%)
Psychiatric disorders			
Insomnia	4 (16.0)	2 (6.9)	6 (11.1)
Agitation	1 (4.0)	4 (13.8)	5 (9.3)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	3 (12.0)	3 (10.3)	6 (11.1)
Skin and subcutaneous tissue disorders			
Dry skin	2 (8.0)	2 (6.9)	4 (7.4)
Dermatitis contact	1 (4.0)	2 (6.9)	3 (5.6)
Rash	2 (8.0)	1 (3.4)	3 (5.6)

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
TEAE = treatment-emergent adverse event.
Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs. Subject with two or more TEAEs in the same preferred term is counted only once for that preferred term.
Source: Table 14.3.1.2.2

Table 8 Treatment-Related Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects by System Organ Class and Preferred Term – Safety Analysis Set

MedDRA System Organ Class Preferred Term	Treatment Group in Study 304 Rufinamide N=25 n (%)	Treatment Group in Study 304 Placebo N=29 n (%)	Total N=54 n (%)
Subjects with any Treatment-related, TEAEs	17 (68.0)	21 (72.4)	38 (70.4)
Gastrointestinal disorders			
Constipation	3 (12.0)	3 (10.3)	6 (11.1)
Vomiting	4 (16.0)	2 (6.9)	6 (11.1)
Metabolism and nutrition disorders			
Decreased appetite	5 (20.0)	4 (13.8)	9 (16.7)
Nervous system disorders			
Somnolence	6 (24.0)	5 (17.2)	11 (20.4)
Status epilepticus	4 (16.0)	3 (10.3)	7 (13.0)
Dizziness	0 (0.0)	3 (10.3)	3 (5.6)

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
TEAE = treatment-emergent adverse event.
Adverse events occurred during the first dose of rufinamide (in Study 304 for rufinamide group and in Study 305 for placebo group) and the last visit were defined as TEAEs. This table includes TEAEs considered by the investigator to be possibly or probably related to study drug. Subject with two or more treatment-related TEAEs in the same preferred term is counted only once for that preferred term.
Source: Table 14.3.1.2.3

Serious TEAEs were reported in **9 subjects (16.7%) in study 305. No cases of death were reported in Study 305. The 9 TAES are summarised herafter and concern 2 cases of satus epilepticus, one case of dental caries, and the other were infection cases (pneumonia, influenza and gastroenteral viral)**. TEAEs leading to study drug withdrawal were reported in 3 subjects (5.6%) in Study 305.

- Subject ID10021002 9 yo Male
Treatment Group in Study 304: rufinamide
Event (preferred term): **status epilepticus** (3 times)
On 15 Dec 2010, informed consent for rufinamide double-blind clinical study (Study 304) was obtained and Observation Period started. Concomitant antiepilepsy drugs included 400 mg/day of Selenica-R granules (sodium valproate) 40%, 140 mg/day of Excegran powder (zonisamide) 20%, and 70 mg/day of Phenobal powder 10%. Number of seizures: tonic seizure, 47 per 30 days; partial seizure, 170 per 30 days; atonic seizure, 28 per 30 days; myoclonic seizure, 7 per 30 days.
On 12 Jan 2011, rufinamide was initiated. Number of seizures: tonic seizure, 4 per week; partial seizure, 18 per week; atonic seizure, 1 per week; myoclonic seizure, 1 per week.
On 06 Apr 2011, informed consent for rufinamide long-term study (Study 305) was obtained. Number of seizures: tonic seizure, 5 per week; partial seizure, 2 per week; atonic seizure, 2 per week; myoclonic seizure, 6 per week.
The 1st SAE of status epilepticus was reported on August 2011, 8 months after the start of Rufinamide), recovered after treatment (midazolam). The investigator reported that the interaction between the study drug and the antiepilepsy drugs was believed to have increased PB (Phenobal) level followed by decreased VPA (Selenica-R) level, resulting in atypical absence status epilepticus.
The second SAE of status epilepticus was reported on June 2012, 18 months after the start of rufinamide, recovered after treatment (midazolam). According to the investigator, It was likely to be caused by the seasonal reason and the blood ammonia elevation caused by VPA. However, the possibility of the relationship with the study drug cannot be ruled out completely
The third SAE of status epilepticus was reported on March 2014, 27 months after the start of rufinamide. The patient was not doing well after suffering from influenza type B which appeared on Mar 2013, a decreased blood concentration of VPA was observed at the time of the SAE.

- Subject ID10061001 14 yo Male
Treatment Group in Study 304: rufinamide
Event (preferred term): **pneumonia**
On 23 Nov 2010, rufinamide was initiated. On 14 Feb 2011, informed consent for rufinamide long-term study (Study 305) was obtained. Pneumonia was reported 8 months after the start of rufinamide and recovered after antibiotics.

- Subject ID10111001 20 yo Female
Treatment Group in Study 304: rufinamide
Event (preferred term): **upper respiratory tract infection**, **pneumonia**, 7 months after the start of rufinamide on April 2011.

- Subject ID10231001 15 yo Female
Treatment Group in Study 304: rufinamide
Event (preferred term): **dental caries**, 10 months after the start of rufinamide on April 2011.

- Subject ID10011001 13 yo Female
Treatment Group in Study 304: rufinamide
Event (preferred term): **pneumonia** (3 times), 12 months (oct), 17 months (Feb) and 20 months (May) after the start of rufinamide on April 2011, all the 3 events were recovered after antibiotics treatment.

- Subject ID10041006 18 yo Female
Treatment Group in Study 304: placebo
Event (preferred term): contusion, **status epilepticus**.
On 10 Feb 2011, rufinamide was initiated. The status epilepticus was reported on Jan 2013, 23 months after the start of rufinamide that recovered.

- Subject ID10091004 9 yo Male
Treatment Group in Study 304: placebo

Event (preferred term): **pneumonia**, 6 months after the start of rufinamide recovered following antibiotic treatments.

- Subject ID10111003, 6 yo Male
Treatment Group in Study 304: placebo
Event (preferred term): **influenza** 3 months after the start of rufinamide that recovered.

Subject ID10111003, 12 yo Female
Treatment Group in Study 304: placebo
Event (preferred term): **gastroenteritis viral** 11 months after the start of rufinamide that recovered.

Listing of TEAEs leading to study drug withdrawal is shown in Table 10.

Another subject (Subject 10041009) also discontinued the study treatment in Study 305 due to an AE (autism); however the autism was not included in Table 10 since the event occurred in Study 304 and did not get worse during Study 305.

Table 10 Listing of Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal in Study 305– Safety Analysis Set

Subject ID Age (year) Sex	Study Phase Daily Dose of Rufinamide[a]	MedDRA Preferred Term	Start Day[b] Severity Seriousness	Duration Outcome	Relationship to Study Drug Study Drug Action Taken Other Action Taken
Treatment Group in Study 304: Placebo					
10101001 19, Female	Conversion 1200.0 mg	Decreased appetite	Day 7 Moderate Not serious	57 days Recovered	Probably related Study drug withdrawn Treatment given
10131010 6, Female	Maintenance 1000.0 mg	Drug eruption	Day 13 Moderate Not serious	28 days Recovered	Possibly related Study drug withdrawn None
10141004 19, Male	Maintenance 2400.0 mg	Decreased appetite	Day 20 Moderate Not serious	192 days Recovered	Possibly related Study drug withdrawn Treatment given, dose reduction of valproic acid, withdrawn of pyridoxal

MedDRA (Medical Dictionary for Regulatory Activities) Version 13.0.
Subject ID = subject identification number.
a: Mean daily dose (mg/day) of the prescription period in which the event occurred (in case the event occurred after discontinuation of administration, the mean daily dose of the last prescription period).
b: Onset date of the event – date of the first administration of rufinamide + 1 (day).

Assessor's comments:
The most frequently reported TAES in total subjects (during both studies) were nasopharyngitis (29 subjects; 53.7%), status epilepticus (23 subjects; 42.6%), and somnolence (18 subjects; 33.3%). The most frequently reported treatment-related TEAEs (≥10%) in total subjects were somnolence (11 subjects; 20.4%), decreased appetite (9 subjects; 16.7%), status epilepticus (7 subjects; 13.0%), constipation, and vomiting (6 subjects each; 11.1%). In study 305 3 cases of status epilepticus were reported. Status epilepticus, constipation and nasopharyngitis are listed in the Eu Smpc. Vomiting, somnolence and Status epilepticus are considered important identified risks under close monitoring in the PSUR.

No new safety concerns were emerged from this analysis.

III. ADDITIONAL CLARIFICATIONS REQUESTED

Efficacy

Question 1
Tables of demographic and baseline characteristics of patient included should be submitted (age, sex, weight, duration of LGS, type and number of seizures during each phase).

MAH's response

Study E2080-J081-305 (Study 305) was an extension study of Study E2080-J081-304 (Study 304).

Therefore demographic information was not newly collected at the start of Study 305. Table 1 shows summary of demographic and other baseline characteristics for 46 patients in Efficacy Analysis Set in Study 305. The paediatric population was reconsidered involving patients up to and including 18 years of age. There were 2 patients in the 17 and 18 years old group (both of them were in placebo group in Study 304). Table 2 shows summary of seizure frequency during the baseline phase and type of seizure in Efficacy Analysis Set in Study 305. There is no impact to the previous conclusion.

Table 1 Summary of demographic and other baseline characteristics (Efficacy Analysis Set)

Category		Treatment Group in Study 304		Total
		Rufinamide (N = 23)	Placebo (N = 23)	(N = 46)
Age (year)	Mean ± SD	16.0 ± 7.5	14.4 ± 6.2	15.2 ± 6.9
	Median	13.0	13.0	13.0
	Min, Max	5, 30	4, 29	4, 30
	≥4 to <12	9 (39.1)	9 (39.1)	18 (39.1)
	≥12 to <19	5 (21.7)	8 (34.8)	13 (28.3)
	≥19	9 (39.1)	6 (26.1)	15 (32.6)
Sex	Male	14 (60.9)	16 (69.6)	30 (65.2)
	Female	9 (39.1)	7 (30.4)	16 (34.8)
Height (cm)	Mean ± SD	144.80 ± 19.73	146.34 ± 20.73	145.57 ± 20.02
	Median	151.20	153.40	151.85
	Min, Max	105.0, 181.2	107.2, 173.0	105.0, 181.2
Body weight (kg)	Mean ± SD	37.00 ± 14.91	41.90 ± 19.85	39.45 ± 17.53
	Median	35.70	38.50	37.15
	Min, Max	17.5, 66.8	18.9, 90.0	17.5, 90.0
	15.0 – 30.0 kg	9 (39.1)	10 (43.5)	19 (41.3)
	30.1 – 50.0 kg	9 (39.1)	6 (26.1)	15 (32.6)
	50.1 – 70.0 kg	5 (21.7)	5 (21.7)	10 (21.7)
	≥70.1 kg	0 (0.0)	2 (8.7)	2 (4.3)
Disease duration (years)	Mean ± SD	11.35 ± 7.35	9.88 ± 5.86	10.61 ± 6.62
	Median	10.80	10.00	10.25
	Min, Max	0.8, 29.5	0.3, 24.5	0.3, 29.5

Assessor's comments:

Main demographic characteristics are comparable in both groups.

Issue resolved

Table 2 Summary of seizure frequency (per 28 days) during the Baseline Phase in Study 304 (Efficacy Analysis set)

Type of seizures	Treatment Group in Study 304						Total		
	Rufinamide (N = 23)			Placebo (N = 23)			(N = 46)		
	n	Median	Min, Max	n	Median	Min, Max	n	Median	Min, Max
Tonic-atonic seizure frequency [a]	23	256.10	28.0, 22469.5	23	183.60	8.3, 2046.2	46	220.85	8.3, 22469.5
Total seizure frequency	23	256.10	95.4, 22499.4	23	273.00	79.9, 2125.9	46	268.20	79.9, 22499.4
Partial seizure frequency	2	103.10	29.9, 176.3	5	159.70	24.9, 252.0	7	159.70	24.9, 252.0
Absence seizure frequency	1	65.30	65.3, 65.3	0	–	–	1	65.30	65.3, 65.3
Atypical absence seizure frequency	10	31.10	2.8, 377.5	14	64.80	1.0, 549.6	24	50.30	1.0, 549.6
Myoclonic seizure frequency	7	39.20	7.3, 3324.7	7	23.90	1.0, 1092.0	14	30.60	1.0, 3324.7
Clonic seizure frequency	0	–	–	0	–	–	0	–	–
Tonic seizure frequency	23	229.20	21.8, 22469.5	22	120.10	8.3, 2046.2	45	167.00	8.3, 22469.5
Tonic-clonic seizure frequency	1	7.50	7.5, 7.5	7	6.20	1.0, 93.0	8	6.85	1.0, 93.0
Atonic seizure frequency	8	58.15	6.2, 2503.4	8	13.50	1.0, 1284.9	16	18.15	1.0, 2503.4
Frequency of unclassified seizures	1	6.20	6.2, 6.2	0	–	–	1	6.20	6.2, 6.2

[a] Sum of tonic seizures and atonic seizures

Assessor's comments:
During the Observation Period slightly higher frequency were observed in the rufinamide group for tonic-atonic seizures and for tonic and atonic seizure frequency. The median frequencies of partial seizures and atypical absence seizure were higher in the placebo group. Overall, no imbalance in the frequency distribution between the 2 groups were observed in the median frequency (per 28 days) of other seizures.
Issue resolved.

Question 2

Complete results of primary efficacy outcomes and results of subgroups analyses performed should be submitted. Summary of percent change in the frequency of seizures other than tonic-atonic seizures, summary of aggravated subjects in tonic-atonic seizure frequency as well as subgroups analyses performed should be submitted.

MAH's response

The synoptic clinical study report is the final report of Study 305, which includes the completed efficacy data. The required data are shown in Table 3 and Table 4.

Table 3 Percentage Change in Seizure Frequency per 28 Days other than Tonic-Atonic Seizure by Visit Relative to the Baseline Phase (Efficacy Analysis Set)

		Treatment Group in Study 304				Total	
		Rufinamide		Placebo			
		N	median (min, max)	N	median (min, max)	N	median (min, max)
Partial seizure	% Change in Week 12	2	-100.00 (-100.0, -100.0)	5	-35.10 (-100.0, 255.6)	7	-95.00 (-100.0, 255.6)
	% Change in Week 24	2	-98.85 (-100.0, -97.7)	3	-75.00 (-80.9, 303.2)	5	-80.90 (-100.0, 303.2)
	% Change in Week 32	2	-85.25 (-100.0, -70.5)	3	-54.20 (-72.4, 30.2)	5	-70.50 (-100.0, 30.2)
	% Change in Week 40	2	-96.60 (-100.0, -93.2)	3	-77.10 (-85.7, -42.4)	5	-85.70 (-100.0, -42.4)
	% Change in Week 52	2	-88.65 (-100.0, -77.3)	3	-62.40 (-100.0, -61.8)	5	-77.30 (-100.0, -61.8)
	% Change in Week 52 (LOCF)	2	-88.65 (-100.0, -77.3)	5	-62.40 (-100.0, 189.2)	7	-77.30 (-100.0, 189.2)
Absence seizure	% Change in Week 12	1	-87.70 (-87.7, -87.7)	0	-	1	-87.70 (-87.7, -87.7)
	% Change in Week 24	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 32	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 40	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 52	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 52 (LOCF)	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
Atypical absence seizure	% Change in Week 12	10	-95.00 (-100.0, 54.7)	14	-77.90 (-100.0, 28.3)	24	-86.70 (-100.0, 54.7)
	% Change in Week 24	10	-100.00 (-100.0, 185.7)	12	-50.55 (-100.0, 151.3)	22	-92.85 (-100.0, 185.7)
	% Change in Week 32	10	-78.25 (-100.0, 185.7)	12	-100.00 (-100.0, 209.2)	22	-92.30 (-100.0, 209.2)
	% Change in Week 40	9	-100.00 (-100.0, -1.5)	12	-96.90 (-100.0, 219.3)	21	-100.00 (-100.0, 219.3)
	% Change in Week 52	9	-100.00 (-100.0, 8.6)	12	-85.75 (-100.0, 737.2)	21	-100.00 (-100.0, 737.2)
	% Change in Week 52 (LOCF)	10	-100.00 (-100.0, 8.6)	14	-85.75 (-100.0, 737.2)	24	-100.00 (-100.0, 737.2)
Myoclonic seizure	% Change in Week 12	7	-27.10 (-100.0, 228.8) -	6	-100.00 (-100.0, 100.8)	13	-100.00 (-100.0, 228.8)
	% Change in Week 24	7	93.90 (-100.0, 64.4)	6	-100.00 (-100.0, 50.6)	13	-100.00 (-100.0, 64.4)
	% Change in Week 32	7	-100.00 (-100.0, 24.6)	6	74.85 (-100.0, 435.6)	13	-100.00 (-100.0, 435.6)
	% Change in Week 40	7	-100.00 (-100.0, 22.4)	6	-81.70 (-100.0, 117.6)	13	-100.00 (-100.0, 117.6)
	% Change in Week 52	7	-100.00 (-100.0, -18.4)	6	-63.20 (-100.0, 368.2)	13	-100.00 (-100.0, 368.2)
	% Change in Week 52 (LOCF)	7	-100.00 (-100.0, -18.4)	7	-100.00 (-100.0, 368.2)	14	-100.00 (-100.0, 368.2)

Clonic seizure	% Change in Week 12	0	-	0	-	0	-
	% Change in Week 24	0	-	0	-	0	-
	% Change in Week 32	0	-	0	-	0	-
	% Change in Week 40	0	-	0	-	0	-
	% Change in Week 52	0	-	0	-	0	-
	% Change in Week 52 (LOCF)	0	-	0	-	0	-
Tonic seizure	% Change in Week 12	23	-34.60 (-92.1, 175.2)	22	-58.25 (-100.0, 125.2)	45	-35.40 (-100.0, 175.2)
	% Change in Week 24	22	-25.35 (-88.3, 138.5)	20	-51.55 (-100.0, 70.0)	42	-37.85 (-100.0, 138.5)
	% Change in Week 32	21	-44.20 (-100.0, 83.5)	20	-51.25 (-100.0, 77.3)	41	-49.40 (-100.0, 83.5)
	% Change in Week 40	20	-23.80 (-94.4, 833.2)	20	-52.15 (-100.0, 65.0)	40	-47.05 (-100.0, 833.2)
	% Change in Week 52	19	-48.50 (-91.3, 47.8)	20	-21.30 (-100.0, 110.2)	39	-36.40 (-100.0, 110.2)
	% Change in Week 52 (LOCF)	23	-47.40 (-91.3, 47.8)	22	-31.40 (-100.0, 110.2)	45	-46.20 (-100.0, 110.2)
Tonic-clonic seizure	% Change in Week 12	1	113.30 (113.3, 113.3)	7	-70.40 (-100.0, 300.0)	8	-61.55 (-100.0, 300.0)
	% Change in Week 24	1	6.70 (6.7, 6.7)	6	-56.65 (-100.0, 300.0)	7	-44.10 (-100.0, 300.0)
	% Change in Week 32	1	60.00 (60.0, 60.0)	6	-31.65 (-100.0, 700.0)	7	-22.60 (-100.0, 700.0)
	% Change in Week 40	1	-46.70 (-46.7, -46.7)	6	-46.25 (-100.0, 1100.0)	7	-46.70 (-100.0, 1100.0)
	% Change in Week 52	1	6.70 (6.7, 6.7)	6	-38.10 (-100.0, 700.0)	7	-35.50 (-100.0, 700.0)
	% Change in Week 52 (LOCF)	1	6.70 (6.7, 6.7)	7	-40.70 (-100.0, 700.0)	8	-38.10 (-100.0, 700.0)
Atonic seizure	% Change in Week 12	8	-46.00 (-100.0, 29.0)	8	-62.40 (-100.0, -27.7)	16	-60.35 (-100.0, 29.0)
	% Change in Week 24	7	-69.00 (-100.0, -11.2)	8	-100.00 (-100.0, 189.2)	15	-84.30 (-100.0, 189.2)
	% Change in Week 32	6	-82.10 (-100.0, -20.4)	8	-100.00 (-100.0, 20.5)	14	-100.00 (-100.0, 20.5)
	% Change in Week 40	6	-60.00 (-100.0, -14.3)	8	-85.90 (-100.0, 261.4)	14	-67.20 (-100.0, 261.4)
	% Change in Week 52	6	-75.45 (-100.0, -2.1)	8	-59.35 (-100.0, 526.5)	14	-67.55 (-100.0, 526.5)
	% Change in Week 52 (LOCF)	8	-75.45 (-100.0, -2.1)	8	-59.35 (-100.0, 526.5)	16	-67.55 (-100.0, 526.5)
Unclassified seizures	% Change in Week 12	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 24	1	6932.30 (6932.3, 6932.3)	0	-	1	6932.30 (6932.3, 6932.3)
	% Change in Week 32	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 40	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 52	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)
	% Change in Week 52 (LOCF)	1	-100.00 (-100.0, -100.0)	0	-	1	-100.00 (-100.0, -100.0)

Table 4 Summary Statistics of Subjects Who Responded and Aggravated to Treatment in Tonic-Atonic Seizure Frequency Relative to Baseline (Efficacy Analysis Set)

		Treatment Group in Study 304				Total	
		Rufinamide		Placebo			
		N	n (%)	N	n (%)	N	n (%)
100% reduction	in Week 52	19	0 (0.0)	21	2 (9.5)	40	2 (5.0)
	in Week 52 (LOCF)	23	0 (0.0)	23	4 (17.4)	46	4 (8.7)
75% or greater reduction	in Week 52	19	5 (26.3)	21	3 (14.3)	40	8 (20.0)
	in Week 52 (LOCF)	23	5 (21.7)	23	5 (21.7)	46	10 (21.7)
50% or greater reduction	in Week 52	19	9 (47.4)	21	6 (28.6)	40	15 (37.5)
	in Week 52 (LOCF)	23	10 (43.5)	23	8 (34.8)	46	18 (39.1)
25% or greater reduction	in Week 52	19	14 (73.7)	21	10 (47.6)	40	24 (60.0)
	in Week 52 (LOCF)	23	17 (73.9)	23	12 (52.2)	46	29 (63.0)
Increase	in Week 52	19	4 (21.1)	21	5 (23.8)	40	9 (22.5)
	in Week 52 (LOCF)	23	4 (17.4)	23	5 (21.7)	46	9 (19.6)

Assessor's comments:
As observed for tonic-atonic seizure, the median percent change in frequency from the Observation Period to the Treatment Period in the FAS for other types of seizure, the frequency decreased significantly in the rufinamide group compared to the placebo group.
50% responder rate in tonic-atonic seizure frequency is higher in the rufinamide group.
Increase in tonic-atonic seizure frequency is higher in the placebo group.
Issue resolved.

Safety

The MAH should provide AEs experienced by patients between 17 and 18 years old in each arms and discuss the impact of these patients on the safety analysis.

MAH's response

Table 5 shows the incidence of all treatment-emergent AEs by age group. The paediatric population was reconsidered including subjects up to 18 years of age. There is no impact to the previous conclusion.

MedDRA System Organ Class	Treatment Group in Study 304						Total (N=54)		
Preferred Term	Rufinamide (N=25)			Placebo (N=29)					
Age group	≥4 – <12 years (N=9)	≥12 – <19 years (N=5)	≥19 years (N=11)	≥4 – <12 years (N=13)	≥12 – <19 years (N=9)	≥19 years (N=7)	≥4 – <12 years (N=22)	≥12 – <19 years (N=14)	≥19 years (N=18)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any AEs	9 (100.0)	5 (100.0)	11 (100.0)	13 (100.0)	9 (100.0)	7 (100.0)	22 (100.0)	14 (100.0)	18 (100.0)
Blood and lymphatic system disorders	0 (0.0)	1 (20.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (5.6)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (5.6)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Eye disorders	1 (11.1)	0 (0.0)	1 (9.1)	2 (15.4)	0 (0.0)	0 (0.0)	3 (13.6)	0 (0.0)	1 (5.6)
Gastrointestinal disorders	7 (77.8)	4 (80.0)	6 (54.5)	8 (61.5)	6 (66.7)	4 (57.1)	15 (68.2)	10 (71.4)	10 (55.6)
General disorders and administration site conditions	2 (22.2)	0 (0.0)	3 (27.3)	1 (7.7)	1 (11.1)	0 (0.0)	3 (13.6)	1 (7.1)	3 (16.7)
Infections and infestations	9 (100.0)	5 (100.0)	9 (81.8)	10 (76.9)	6 (66.7)	5 (71.4)	19 (86.4)	11 (78.6)	14 (77.8)
Injury, poisoning and procedural complications	6 (66.7)	4 (80.0)	3 (27.3)	3 (23.1)	6 (66.7)	2 (28.6)	9 (40.9)	10 (71.4)	5 (27.8)
Investigations	3 (33.3)	3 (60.0)	0 (0.0)	2 (15.4)	4 (44.4)	2 (28.6)	5 (22.7)	7 (50.0)	2 (11.1)
Metabolism and nutrition disorders	2 (22.2)	0 (0.0)	4 (36.4)	0 (0.0)	4 (44.4)	3 (42.9)	2 (9.1)	4 (28.6)	7 (38.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (20.0)	1 (9.1)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	1 (7.1)	2 (11.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)
Nervous system disorders	6 (66.7)	4 (80.0)	10 (90.9)	8 (61.5)	7 (77.8)	5 (71.4)	14 (63.6)	11 (78.6)	15 (83.3)
Psychiatric disorders	2 (22.2)	2 (40.0)	3 (27.3)	2 (15.4)	3 (33.3)	0 (0.0)	4 (18.2)	5 (35.7)	3 (16.7)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	1 (5.6)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (7.1)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (22.2)	1 (20.0)	1 (9.1)	2 (15.4)	3 (33.3)	1 (14.3)	4 (18.2)	4 (28.6)	2 (11.1)
Skin and subcutaneous tissue disorders	4 (44.4)	3 (60.0)	5 (45.5)	4 (30.8)	4 (44.4)	3 (42.9)	8 (36.4)	7 (50.0)	8 (44.4)

The AEs included in the safety analysis are ones occurred on or after the first dose of study drug up to the last visit of the follow-up phase.

Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

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IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submitted efficacy results of this study provides some evidence of the long-term efficacy of rufinamide in japanese patients with LGS.

The safety data coming from assessment of the open—labelled Study 305 were consistent with the known safety profile of rufinamide. Most frequently reported adverse events were comparable to the most frequent adverse reactions listed in the currently approved SmPC for INOVELON.