15 December 2016
EMA/18473/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inovelon

International non-proprietary name: rufinamide

Procedure No. EMEA/H/C/000660/II/0037

Note

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

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List of abbreviations

AE	adverse event
AED	antiepileptic drug
ALT	serum alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under concentration-time curve
BMI	body mass index
C_{av}	steady-state average plasma concentration
CBCL	Child Behavior Checklist
CI	confidence interval
CL/F	Apparent clearance
C_{max}	peak plasma concentration
CNS	central nervous system
CWRES	conditional weighted residuals
CYP	Cytochrome P450
DT_{50}	50% degradation/dissipation time
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
FDA	United States Food and Drug Administration
Fpen	market penetration factor
GCP	Good Clinical Practice
IIV	inter-individual variability
LDS	Language Development Survey
LGS	Lennox-Gastaut syndrome
LOCF	last observation carried forward
LS	least squares
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
NOAEL	no-observed-adverse-effect-level
PD	Pharmacodynamics
PEC	predicted environmental concentrations
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PND	Postnatal Day
PNEC	predicted no-effect concentrations
PT	preferred term
QoL	quality of life
QoLCE	Quality of Life in Childhood Epilepsy
SAE	serious adverse event
SE	standard error
SOC	system organ class
TEAEs	treatment-emergent adverse events
VPC	visual predictive checks

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai Ltd submitted to the European Medicines Agency on 10 February 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include treatment of seizures associated with Lennox-Gastaut Syndrome in paediatric patients 1 year of age and older, based on the results of study E2080-G000-303 (Study 303); a randomized, controlled, open-label study to evaluate the cognitive development effects and safety, and pharmacokinetics of adjunctive rufinamide treatment in paediatric subjects 1 to less than 4 years of age with inadequately controlled Lennox-Gastaut Syndrome. This study was conducted to fulfil the long-term (2 years) safety and efficacy objectives required as part of the Paediatric Investigation Plan (PIP) EMEA-000709-PIP01-09. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are proposed to be updated and the Package Leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes in the annexes, to implement changes in line with the latest QRD template and to combine the SmPCs, labelling and Package Leaflets for the three authorised strengths of the tablet formulation in line with the current version of the QRD template. The application included an updated RMP version 9.0.

The requested variation proposed amendments to the Summary of Product Characteristics, labelling and Package Leaflet and to the Risk Management Plan (RMP).

Inovelon was designated as an orphan medicinal product EU/3/04/240 on 20 October 2004 in the following indication: Treatment of Lennox-Gastaut syndrome.

The extended indication, which is the subject of this application, falls within the above mentioned orphan designation.

During the procedure the marketing authorisation holder revised the requested scope of the variation and no longer sought an extension of the indication, instead proposing inclusion of relevant paediatric data in the product information.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0116/2016 on the agreement of a paediatric investigation plan (PIP).

PIP P/0116/2016 is completed. The PDCO issued an opinion on compliance for the PIP P/0116/2016.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	10 February 2016
Start of procedure	18 June 2016
CHMP Rapporteur Assessment Report	9 August 2016
PRAC Rapporteur Assessment Report	19 August 2016
PRAC members comments	24 August 2016
Updated PRAC Rapporteur Assessment Report	25 August 2016
PRAC Outcome	2 September 2016
CHMP members comments	5 September 2016
Updated CHMP Rapporteur Assessment Report	8 September 2016
Request for supplementary information (RSI)	15 September 2016
CHMP Rapporteur response Assessment Report	17 November 2016
PRAC Rapporteur response Assessment Report	21 November 2016
PRAC members comments	28 November 2016
Updated PRAC Rapporteur response Assessment Report	28 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	28 November 2016
Updated CHMP Rapporteur response Assessment Report	28 November 2016
Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

Rufinamide is a triazole derivative that exhibits broad-spectrum anticonvulsant properties by elevating seizure threshold and preventing seizure spread. *In vitro* pharmacodynamic data indicate that rufinamide interacts with the inactivated state of sodium channels and slows conversion to the active state thereby reducing the frequency of sodium dependent action potentials.

Rufinamide is the active substance of Inovelon, which was approved in the European Union/European Economic Area through the Centralised Procedure by Commission Decision in 2007 for use as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 4 years of age and older. The product was granted orphan drug designation for the treatment of LGS in the European Union in 2004.

Inovelon is available as tablets (100, 200, and 400 mg formulations) as well as an oral suspension (40 mg/ml). The oral suspension was developed in accordance with a post-approval commitment to the initial marketing authorisation as a child-friendly formulation, which is more convenient for administration to young children and those unable to swallow tablets. In patients weighing 30 kg or more, treatment with Inovelon should be initiated at a daily dose of 400 mg. According to clinical response and tolerability, the dose may be increased by 400 mg/day increments. The maximum dose depends on weight. In patients < 30 kg, treatment should be initiated at a daily dose of 200 mg, which may be further increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1000 mg/day. Lower doses are recommended in the patients if they receive concomitant valproate. Inovelon should be taken together with food twice daily, in two equally divided doses.

LGS is rare and is one of the most severe forms of childhood epilepsy. The syndrome usually has its onset between the ages of 1 and 8 years (typically between 3 and 5 years), but occasionally it occurs in children who are more than 8 years old. LGS continues to manifest into adulthood in a large number of patients and is associated with significant morbidity and mortality. The hallmarks of the disease include the following triad:

- The presence of multiple seizure types: the most characteristic are tonic-atonic seizures and atypical absences, but tonic-clonic, myoclonic, and partial seizures are also frequently present. Tonic-atonic seizures often provoke sudden falls (commonly called drop attacks) and result in injuries.
- The presence of generalized discharges with slow spike-and-wave complexes in the electroencephalogram (EEG).
- The presence of mental retardation or a learning disability. In general, this is represented by a static encephalopathy, although the mental status may worsen in the course of the disease due to multiple causes, such as very frequent occurrence of seizures, sometimes subclinical, frequent head trauma from the falls associated with seizures (drop attacks), and undesirable cognitive effects of the high doses of antiepileptic drugs (AEDs) used to treat this very refractory type of epilepsy.

The aetiology of LGS remains unknown in about half of the cases, whereas in others, the syndrome results from obvious brain injury. The most common identifiable factor is a history of infantile spasms, occurring in up to one-third of the cases. Other causes include perinatal central nervous system (CNS) trauma, meningitis and encephalitis, tumour, and severe head trauma. However, the electro-clinical features are identical. The expression of LGS is similar in the younger population compared to older children and adults. However, at 1 year of age, the diagnosis of LGS can be very challenging in particular in children with a history of infantile spasms or West Syndrome.

As children with LGS grow older they may continue to have atypical absence seizures, generalized tonic-clonic seizures and atonic seizures through adolescence and into adulthood (van Rijckevorsel 2008). Most longitudinal studies consistently show that approximately 50% of LGS patients will retain the characteristic features of LGS if followed for 5-10 years into adulthood (Oguni 1996, Oller-Daurella 1973, and Beaumanoir 1982, referenced in Glauser and Morita, 2006).

With the present application, the MAH sought to extend the indication to include paediatric patients from 1 year to less than 4 years of age. The application was supported by data from an open label safety and pharmacokinetic (PK) study (study E2080-G000-303, hereafter referred to as study 303) in children aged 1 to less than 4 years of age with inadequately controlled LGS and a juvenile toxicity study in beagle dogs.

Both studies were part of the PIP. In addition, population pharmacokinetic (pop PK) simulations were conducted.

No additional study to establish efficacy of rufinamide in the new age group of 1-4 year olds was conducted. Instead, reference was made to the original pivotal study (Study CRUF331 0022), in which efficacy of rufinamide in the add-on treatment of LGS had been demonstrated in an older paediatric population. The MAH claimed that efficacy can be extrapolated to the younger patients because as the disorder is physiologically similar in both age ranges.

2.1. Non-clinical aspects

2.1.1. Introduction

The original marketing authorisation of Inovelon was supported by a nonclinical package including pharmacology studies, a battery of safety pharmacology studies, PK studies in rodents (mouse and rat) and non-rodents (dog, cynomolgus monkey, and baboon), and distribution, metabolism, and excretion studies. In addition, a comprehensive toxicology program was conducted that included repeated-dose toxicity studies in rats, dogs, and cynomolgus monkeys (including toxicokinetics), 2-year carcinogenicity studies in mice and rats, juvenile toxicity studies in rats and dogs, genotoxicity studies, and reproductive and embryo-foetal developmental toxicity studies.

To support the extension of the indication for the treatment of LGS in children aged 1 to less than 4 years old, a 14-week oral toxicity study in juvenile beagle dogs was conducted to complement the previously conducted 13-week oral toxicity study in juvenile dogs and the dose range finding study in rats.

2.1.2. Pharmacology

In vitro data suggest that rufinamide is involved in modulation of sodium channels by prolonging their inactive state. Anti-seizure activity has been shown in relevant *in vivo* models of seizure disorders. Behavioural and safety pharmacology studies showed that no unwanted pharmacological effects at doses exceeding those which confer anti-convulsant protection.

2.1.3. Toxicology

In previously conducted studies, rufinamide showed a low acute toxicity. In the repeated-dose toxicity studies, the main target organ was the liver. Rufinamide did not show genotoxic potential. There was no evidence of teratogenic potential in either rat or rabbit, but reproductive toxicity was observed at doses where maternal toxicity was seen.

Juvenile toxicity data from the rat and dog, submitted in support of the initial application, indicated that the target organs in juvenile and adult rats and dogs were the same, i.e. liver and kidney, and that juvenile animals were not more sensitive than adult animals to the toxic effects of rufinamide. Furthermore, no effect on behavioural and physical development were observed in juvenile rats.

Additional juvenile dog toxicity study (repeat dose toxicity)

To support the extension of indication to patients aged 1-4 years, the MAH submitted a 14-week juvenile toxicity study in dogs aged 6 weeks at initiation of treatment. This study was conducted to complement the previous pivotal juvenile dog toxicity study with dosing of dogs initiated from the age of 4 months.

The study is summarized in the table below.

Table 1 - Summary of the 14-week juvenile dog toxicity study 901629

Study title	Species/ Number/ group	Dose Route Duration	Measurements	Major findings
Study No. 901629: A 14-week Oral Gavage Toxicity Study in the Juvenile Beagle Dog Followed by a 4-week Recovery Period	Beagle dog Main:4/sex and dose Recovery: 3 or 4 (control and highest dose)	Dose: 0, 20, 60, 200 mg/kg/day Route of administration: Oral (gavage) Duration: 14 weeks (from PND 42 to PND 139) + 4 weeks of recovery	mortality and signs of ill health or reaction to treatment, detailed examination, body weight, food consumption, growth measurements, observational and neurological assessments, laboratory investigations, bone mineral density measurements – dual energy X-ray absorptiometry, radiographs and bone length measurements, toxicokinetics, brain measurements, organ weights, macroscopic pathology and microscopic pathology	**≥ 20 mg/kg**: Brown pigment deposition morphologically compatible with biliary pigment/thrombi in centrilobular bile canaliculi and less abundantly in centrilobular hepatocytes and Kupffer cells (partially reversible) **200 mg/kg**: ↓ body weight and body weight gain (starting PND 59) (reversible) ↓ height and length (starting PND 63) (reversible) ↓ food intake (generally btw PND 70 and 90) ↑ ALT (reversible in F) ↑ relative liver weight **NOAEL <20 mg/kg/day**

ALT: serum alanine aminotransferase, NOAEL: no-observed-adverse-effect-level; PND: Postnatal Day

At 200 mg/kg, a decrease in body weight and body weight gain associated with a decrease in height and length was observed. These effects were reported as being of slight magnitude, with increases in body weight and height and length values comparable to those of controls during the recovery period. In addition, there was no treatment-related effect on bone parameters.

The liver was a target organ. Rufinamide induced an increase in serum alanine aminotransferase (ALT) and relative liver weight at 200 mg/kg. The only histopathological finding consisted of pigment deposition in centrilobular bile canaliculi, centrilobular hepatocytes and Kupffer cells at ≥ 20 mg/kg, corresponding to an exposure below the therapeutic exposure.

There was no evidence of accumulation or gender-related differences in the toxicokinetics of rufinamide after 14 weeks. The differences in absorption and elimination at the dose levels tested resulted in an overall less than dose-proportional increase in exposure between 20 and 200 mg/kg. An overview of the exposure ratio between dogs and humans is provided in Table 2.

Table 2 - Dog-to-human exposure ratios in juvenile dogs

Time	Daily Dose (mg/kg)	Animal AUC_{0-24} (ng.h/ml)		Animal : Human Exposure Ratio*	
		M	F	M	F
Day 1	20	78743	111190	0.3	0.4
	60	287848	269187	1.0	0.9
	200	531238	526769	1.8	1.7
Week 4	20	76305	111357	0.3	0.4
	60	329120	344377	1.1	1.1
	200	601395	619805	2.0	2.0
Week 14	20	130218	150115	0.4	0.5
	60	362884	339308	1.2	1.1
	200	648283	669627	2.1	2.2

AUC: area under concentration-time curve, F: Female, M: Male

* taking into consideration the AUC of 1272 µmol/h/L in children aged 2 years and older at a dose of 45 mg/kg/day.

2.1.4. Ecotoxicity / environmental risk assessment

A revised environmental risk assessment (ERA) was presented by the MAH. As in previous ERAs, environmental exposure to rufinamide has been calculated from the combined uses of Inovelon tablets and Inovelon oral suspension. A refined value for market penetration (F_{pen}) was calculated at 0.0000115 based on information on the sales forecast for 2016-2019, resulting in a predicted environmental concentration in surfacewater ($PEC_{surfacewater}$) of 0.0184 µg/L, which is above the trigger value of 0.01 µg/L. Therefore, a Phase II environmental fate and effect analysis has been performed.

Phase II – Tier A: Initial environmental fate and effects analysis

Ratios of PECs and predicted no-effect concentrations (PNEC), i.e. $PEC_{surfacewater}/PNEC_{water}$, and $PEC_{groundwater}/PNEC_{groundwater}$, were all below 1, and thus no further testing in the aquatic compartment or the groundwater compartment was necessary. The ratio of $PEC_{surfacewater}/PNEC_{microorganism}$ was significantly below 0.1 so that a risk to micro-organisms was extremely unlikely.

The log Kow of rufinamide was significantly smaller than 3. Furthermore, rufinamide is not highly adsorptive, does not belong to a class of substances known to have a potential to accumulate in living organisms, and there are no indications from structural features for bioaccumulative potential. Therefore, a bioconcentration study is not indicated and the risk for bioaccumulation is considered to be negligible.

In an OECD 106 study, the adsorption-desorption behaviour of rufinamide was studied in 2 sludges and 3 soils. The adsorption coefficient values including Koc were below the trigger for Phase II Tier B assessment for the terrestrial compartment.

Ready biodegradability / Water-sediment study

Rufinamide was not readily biodegradable under the conditions of a modified Sturm test performed. However by Day 29 of this study, there was 7% to 9% biodegradation of rufinamide.

In an OECD 308 study, the aerobic degradation of rufinamide in 2 water/sediment systems was investigated. The study showed that rufinamide was rapidly degraded in the water layer and in sediment. Very low to non-detectable levels were present in both sediment types (less than 1.3% by Day 14 and 0.0% by Days 28, 64 and 99). The major transformation product and bound residues were observed in both sediment types. The transformation product has demonstrated significant shifting to the sediment (14% after 28 days and 22% after 14 days in each of the two systems investigated) and based on the 50% degradation/dissipation time [DT_{50} > 1 year at 12°C (196/473 d at 20°C)] was found as very persistent in water-sediment-system.

Table 3 – Summary of Main Study Results

Substance: Rufinamide			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	**0.65**	**Potential PBT: No**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.65	not B
	BCF	not avauilable	B/not B
Persistence	DT50 or ready biodegradability	7-9% at Day 29 in Modified Sturm Test	P
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or	0.0184	µg/L	> 0.01

refined (e.g. prevalence, literature)					threshold Yes
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 12.2 mL/g K_{oc} = 14.7 mL/g K_{oc} = 43.5 mL/g K_{oc} = 118.0 mL/g K_{oc} = 109.5 mL/g			Sludge Sludge Loamy sand soil Sandy loam soil Clay soil
Ready Biodegradability Test	OECD 301B	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	<u>Rufinamide</u> $DT_{50, water}$ = 3.1 -3.2 days $DT_{50, sediment}$ = Not significant $DT_{50, whole\ system}$ = 3.6 – 3.7 days % shifting to sediment =0.0-0.8% (SL system) and 0.0-1.3% (SW system) <u>Transformation product</u> $DT_{50, water}$ = 196 days $DT_{50, whole\ system}$ = 473 days % shifting to sediment = 14% (SL system after 28 days) and 22% (in SW system after 14 days)			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	>33	mg/L	*Species: Selenastrum capriconutum*
Daphnia sp., Acute toxicity test	OECD 202	NOEC	>100	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	16	mg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	25	mg/L	*Pimephales prometas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>100	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	species

2.1.5. Discussion on non-clinical aspects

To support the application for an extension of the target population for Inovelon to patients aged 1-4 years, the MAH provided the results of a 14-week juvenile toxicity study in dogs aged 6 weeks at initiation of treatment, which is equivalent to a 2-year old human. This study was conducted to complement the previous

pivotal juvenile dog toxicity studies including a study in dogs with dosing initiated from the age of 4 months and a study in rats, which were 7 days of age at treatment initiation. Thus, altogether, a total of 3 pivotal toxicity studies with rufinamide have been performed in juvenile animals. Based on an interspecies comparison of CNS and reproductive development, the CHMP considered that the paediatric age range from 1-4 years have been adequately covered by these studies.

The previous juvenile toxicity studies showed that the target organs in juvenile and adult animals were the same (liver in both species, and kidneys in rats) and that juvenile animals were no more sensitive than adult animals to the toxic effects of rufinamide. Furthermore, no effect on behavioural and physical development was observed in juvenile rats. No new toxicity findings were reported in the new study with 6-weeks old dogs, compared to studies in more mature animals. Reductions in body weight gain and slightly elevated serum ALT values were observed at doses of 200 mg/kg. Brown pigment deposition in the liver was observed in all treated groups. These histopathological findings were reversible after treatment cessation, and not unexpected since they were noted at ≥ 5 mg/kg in a previously conducted 13-week toxicity study performed in sexually mature dogs, and taking also into account the identification of liver as target organ in all tested species. Finally, there were no effects on neuro-behavioural, brain measurement or bone parameters. The toxicological profile of rufinamide in juvenile dogs was thus in line with that observed in previous studies in older juvenile and sexually mature dogs. Relevant information has been added to section 5.3 of the SmPC.

Environmental risk assessment

The updated ERA including the Phase II Tier A analysis were considered acceptable. All PEC/PNEC ratios were significantly below the trigger values. Even though the refined F_{pen} should have been higher if calculated according to the Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev.1 , May 2016), it would not have changed the conclusions. Log Kow and Koc were below the trigger values and no further study was required.

However, a transformation product of rufinamide was shown to significantly shift to the sediment. The results also showed that the transformation product of rufinamide was very persistent in water-sediment-system (DT_{50} > 1 year). Since, by the time of this report, the MAH had decided to no longer pursue the extension of the indication, no further action was required. However, if an extension of the target population was to be pursued in the future, a specifically designed water/sediment study should be conducted to identify this transformation product. In addition, the effects on sediment dwelling organisms should be investigated in an OECD 218 Sediment-Water Chironomid Toxicity Test Using Spiked Sediment with ^{14}C-radiolabelled rufinamide (parent compound) as the test substance.

2.1.6. Conclusion on the non-clinical aspects

The CHMP considered that the 3 toxicity studies performed with rufinamide in juvenile animals adequately covered the proposed paediatric target population of Inovelon. The latest study in dogs initiated at 6 weeks of age did not identify an increased sensitivity to the toxic effects of rufinamide, and showed that the target organs were the same as in more mature juvenile and adult animals.

The CHMP concluded that the available nonclinical data were acceptable to support this application.

2.2. Clinical aspects

2.2.1. Introduction

Good Clinical Practice (GCP)

The MAH confirmed that the clinical trials were performed in accordance with GCP.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were

carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4 - Tabular overview of clinical studies

Study ID	Study Design	Number of Study Centers and Location	Number of subjects by Arm: Entered/ Completed	Treatment (Dose, Route, Regimen	Primary Efficacy Endpoint(s)	Study Dates/ Duration
Study 303	A Phase 3, multicenter, randomized, controlled, open-label study to evaluate the cognitive development effects and safety, and PK of adjunctive rufinamide treatment in paediatric subjects 1 to less than 4 years of age with inadequately controlled LGS	19 (US, Canada, France, Greece, Italy, Poland)	Rufinamide: 25/1 Comparator (any other AED): 12/4	Rufinamide: Up to 45 mg/kg/day, in 2 divided doses, administered as oral suspension (40 mg/mL) Comparator: Any approved AED of the investigator's choice, dosed according to iusual practice, added to subject's existing regimen of 1 to 3 AEDs	Child Behaviour Checklist Total Problems Score at the end of the 2 year treatment period.	Jun 2011 to Nov 2015; 2 years
Study 022	A Phase 3, multicenter, randomized, double-blind, placebo controlled, parallel trial comparing the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in subjects aged 4 to 30 years with inadequately controlled LGS	43 (Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, US)	Rufinamide : 74/64 Placebo: 64/59	Rufinamide: administered orally as 100, 200, or 400 mg tablets in a twice daily dosage regimen. Dosing started at approximately 10 mg/kg/day, and the dose was titrated to approximately 45 mg/kg/day over a 1 to 2-week period Placebo: administered orally, as matching tablets in a twice daily dosage regimen, according to the same titration schedule as used for rufinamide.	#1: % change in total seizure frequency per 28 days during the double-blind Phase relative to Baseline. #2: % change in tonic-atonic seizure frequency per 28 days during the double-blind Phase relative to Baseline. #3: the seizure severity rating at the end of the double-blind Phase.	Mar 1998 to Sep 2000; 84 days
Study 304	A Phase 3, placebo controlled, double-blind, comparative study of rufinamide in Subjects aged 4 to 30 years with LGS	22 sites in Japan	Rufinamide: 29/25 Placebo: 30/29	Rufinamide: 100 mg and 200 mg tablets orally administered twice daily, after breakfast and after dinner. Placebo: 100 mg and 200 mg tablets orally administered twice daily, after breakfast and after dinner.	Percent change in tonic-atonic seizure frequency.	Jun 2010 to Aug 2011; 12 weeks

2.2.2. Pharmacokinetics

In study 303, sparse PK samples for the determination of plasma rufinamide concentrations were collected during the Maintenance Period of the study at a morning visit to the clinic in Weeks 2, 8, and 24 and at an afternoon visit to the clinic in Weeks 4 and 16. PK data from 24 subjects in study 303 were available.

The PK analysis for study 303 was conducted by pooling data with study 304 and 022 (see description of studies in Table 3 above; for a detailed summary of study 303, see section 2.3.2.). The results from the latter two studies had previously been presented with the initial marketing authorisation application for Inovelon. The integration of PK data from studies 304 and 022 was done in order to enable comparison of PK across age groups. A population modeling approach was used to characterize the PK of rufinamide and to identify intrinsic and extrinsic factors significantly affecting the exposure.

Previous PK evaluations for Inovelon had shown that maximum plasma levels of rufinamide are reached approximately 6 hours after administration. Peak plasma concentration (C_{max}) and area under concentration-time curve (AUC) of rufinamide increase less than proportionally with doses in both fasted and fed healthy subjects and in patients, probably due to dose-limited absorption behaviour. After single doses, food increases the bioavailability (AUC) of rufinamide by approximately 34% and the peak plasma concentration by 56%.

Only a small fraction of rufinamide (34%) was found to be bound to human serum proteins. Rufinamide is almost exclusively eliminated by metabolism. The main pathway of metabolism is hydrolysis of the carboxylamide group to the pharmacologically inactive acid derivative CGP 47292. The plasma elimination half-life is approximately 6-10 hours in healthy subjects and patients with epilepsy. Renal excretion was the predominant route of elimination for active substance related material, accounting for 84.7% of the dose.

2.2.3. Pharmacokinetic/Pharmacodynamic (PK/PD) modelling

2.2.3.1. Course Model based on LGS patient data

Population PK Methods

Population PK analysis was performed using non-linear mixed effect modelling in NONMEM v7.2. The final population PK model was evaluated for performance using graphical assessment, nonparametric bootstrapping and visual predictive checks (VPC). The resulting parameters from the final PK model were evaluated for fitness for calculation of individual derived values of rufinamide steady-state exposure C_{av} (average plasma concentration).

The main objective was to characterize the PK of rufinamide in subjects with inadequately controlled LGS, permitting to compare exposure to rufinamide in paediatric population aged 1 to less than 4 years to that in subjects aged 4 years and older, by testing age as a continuous covariate as well as a categorical covariate (1 to < 4 years versus ≥ 4years), and to identify any intrinsic or extrinsic factors with an impact on rufinamide PK and PK variability.

C_{av} values were also used in a graphical exploration of the PK/PD relationships for efficacy (cognitive/behavioural effects as measured by in Child Behavior Check List [CBCL] total problems score, and in relevant subscales, see section 2.3.2.1. for details on the CBCL questionnaire) and safety based on data from study 303 alone.

PK/PD Data Sets

The final PK dataset included 304 observations from a total of 115 subjects. For study 303, 110 rufinamide plasma concentrations from 24 subjects were available. Study 304 contributed 76 observations from a total of 26 subjects, while study 0022 contributed 118 observations from 65 subjects.

A summary of the demographics and co-administered AEDs are presented below.

Table 5 - Demographics

Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Dose (mg per day)	1315 (845)	1000	160 - 4400
Age (years)	12.6 (8.8)	11	1 - 35
Weight (kg)	28.8 (23.2)	18.1	7 – 138.5
Alkaline phosphatase (U/L)	318.2 (227.2)	229	103 - 1828
Bilirubin (U/L)	0.3 (0.1)	0.3	0.1 – 1.0
Creatinine Clearance (mL/min)*	68.7 (41.5)	53.4	23.3 – 289.7
Age (categorical)	1 to < 4 years = 24 (1 to < 2 years = 10) ≥ 4 years = 91		
Sex	Females=47; Males=68		
Race	Caucasian=75; Non-Caucasian=40		

* Creatinine clearance was capped at 150 mL/min as a reasonable value.

Table 6 – Concomitant Use of AEDs

Concomitant AED	CYP3A4 Inducer	Number of subjects in the PK population (%) (N=152)
Carbamazepine	Yes	15 (13.0)
Lamotrigine	No	37 (32.2)
Valproate	No	76 (66.1)
Phenytoin	Yes	16 (13.9)

CYP = Cytochrome P450, N = Number of subjects

PK/PD data for cognitive development and behaviour effects assessments at baseline and at visit 8/week 24, visit 10/week 56, visit 12/week 88 and visit 12/week 106 was available for a total of 25 subjects participating in study 303. Of these, 20 subjects received rufinamide.

Model Development

Base model structure

Scatter plots of the observed rufinamide concentration versus time after dose for the final PK dataset are presented below.

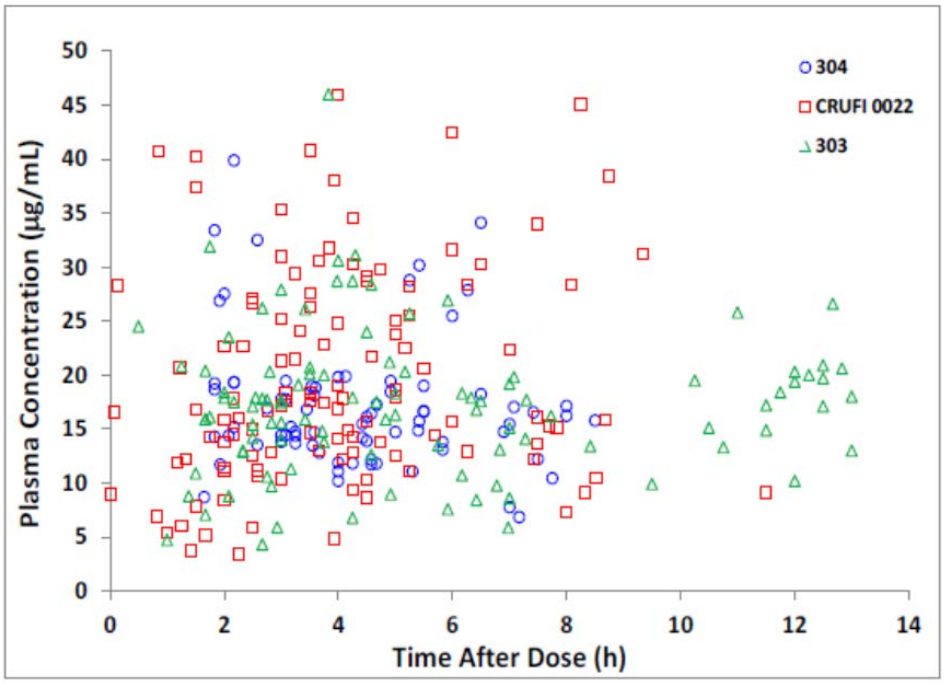


Figure 1 - Individual Observed Rufinamide Concentration versus Time after Dose by Study

The PK of rufinamide was best described by a constant input model parameterized in terms of clearance (CL/F) as follows: C_{av} = R / (CL/F), where R is the dose rate. The dose rate was defined as the given dose divided by the dosing interval. Dosing interval was set for every 12 hours, as the dosing was twice daily. The inter-individual variability (IIV) (η, ETA) was assessed using an exponential error structure, assuming normal distribution of this parameter. Inter-occasion variability by study visit was also tested on clearance. The residual variability (ε) was assessed by additive, proportional, and combined additive/proportional error structures. All permutations of inter-individual and residual variability error structures were tested systematically.

Covariate model:

The effect of the following covariates was investigated on rufinamide PK: demographics (sex, race, age [both as continuous and categorical], and body weight), renal function (creatinine clearance), and liver function (alkaline phosphatase, and bilirubin). Concomitant administration of other AEDs such as carbamazepine, lamotrigine, phenytoin, and valproic acid, were evaluated as categorical covariates. Plasma concentrations of valproate were also evaluated as a continuous covariate.

Population PK Results

Final model

Using a constant input model parameterized in terms of CL/F, the IIV for CL/F was adequately estimated while no significant effect of inter-occasion variability was observed. Body weight and plasma concentrations of valproic acid were found to statistically significantly affect rufinamide CL/F.

The estimate of basal CL/F from the final PK model was 2.19 L/h (95% Confidence Interval [CI]: 1.94; 2.44), while the estimate of the exponent for the effect of weight was 0.831 (95% CI: 0.704; 0.958). Plasma concentrations of valproic acid were associated with a linear decrease in rufinamide CL/F, with a slope of -0.496 (95% CI: -0.704; -0.288). As seen from the 95% CIs, all the parameters of the structural model were estimated with good precision (percent relative standard error of the estimate [%RSE] ≤21.5%). Inter-individual variability in CL/F was mild to moderate (33.3%) and estimated with good precision (%RSE

≤19.8). The additive residual error had an estimated standard deviation of 4.31 µg/mL, and was estimated with good precision (%RSE =11.7%).

Goodness-of-fit-plots for the final PK model were presented. The scatter plots of population predicted and individual predicted versus observed concentrations showed even distribution around the line of unity. Additionally, a scatter plot of conditional weighted residuals (CWRES) versus population predicted concentrations showed the CWRES to be roughly evenly distributed around zero, supporting the validity of the PK model.

Model evaluation

Visual predictive check (VPCs)

In order to evaluate the predictive performance of the final PK model for rufinamide, a VPC was performed based on the final PK model and the final PK dataset. Using the simulated data of 2300 patients and after stratifying rufinamide concentrations by visit, the 90 % prediction intervals were determined and plotted together with the observed rufinamide concentrations. VPC plots showed that the majority of observed concentrations were within the 90% prediction intervals for the model.

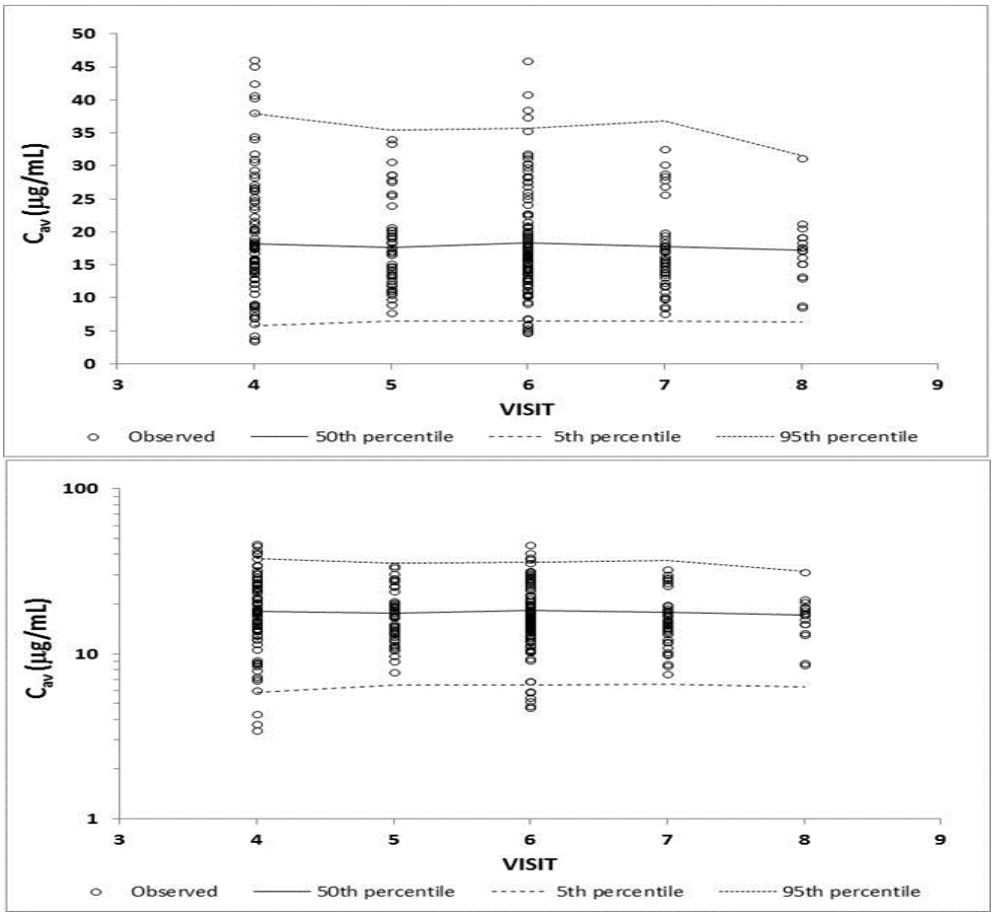


Figure 2 - Visual Predictive Check Plots for Rufinamide PK Model Evaluation

Bootstraps

A nonparametric bootstrap for the final PK model was conducted. The CIs were generally narrow and the median values of the distribution of bootstrapped parameter values were consistent with the original parameter estimates from the final PK model.

Predicted PK parameters

The PK of rufinamide was not significantly affected by age as a continuous covariate (1 – 35 years) or as a categorical covariate (age categories: 1 to < 4 years and ≥ 4 years) after body weight was taken into consideration. It was also not affected by sex, race (Caucasian versus non-Caucasian), hepatic function (alkaline phosphatase: 103 - 1828 IU/L, and bilirubin: 0.1 – 1.0 mg/dL), renal function (creatinine clearance: 23.3 to 298.7 mL/min) and total daily rufinamide dose (160 to 4400 mg).

A graphical presentation of predicted PK parameters by age group and valproate treatment status are depicted in figures below. Notably, plasma concentrations of valproic acid significantly decreased the CL/F of rufinamide in a linear relationship, with a slope of -0.496. This effect was more significant than the effect of valproic acid administration tested as a categorical covariate.

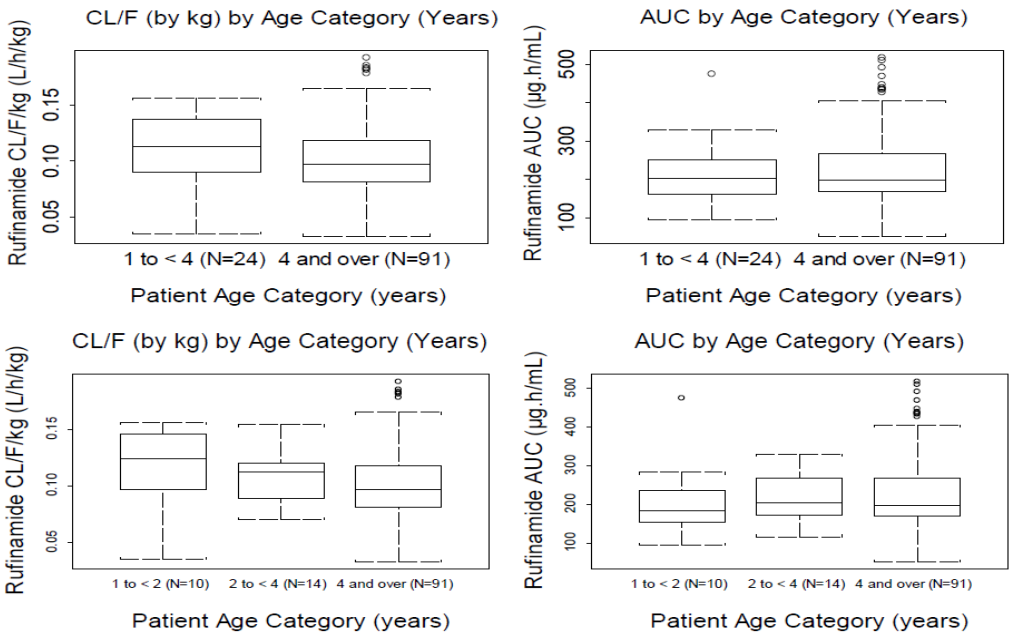


Figure 3 - Box Plots of CL/F/kg and AUC by Age Category

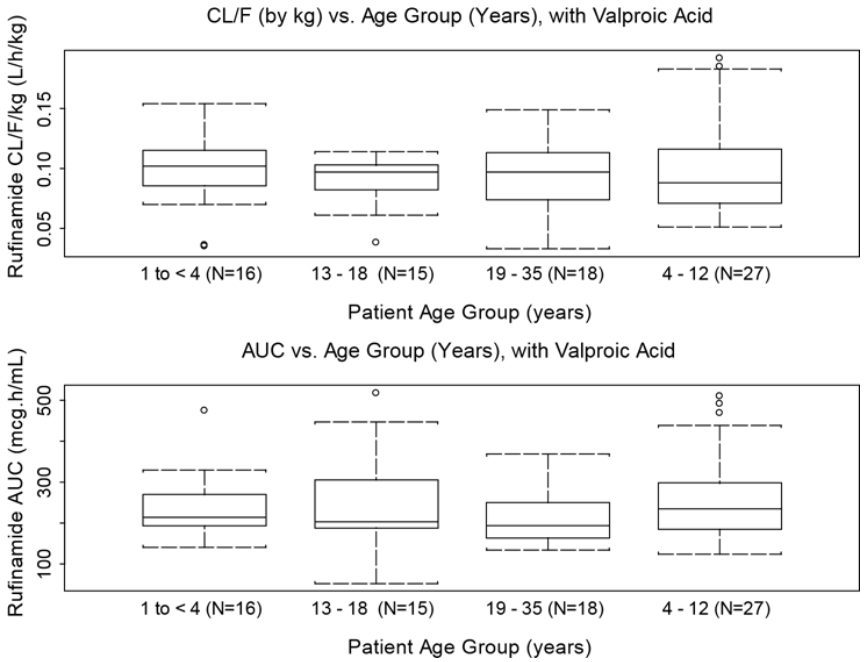


Figure 4 - Box Plots of Model Predicted Rufinamide PK Parameters by Age Group, with Valproic Acid Treatment

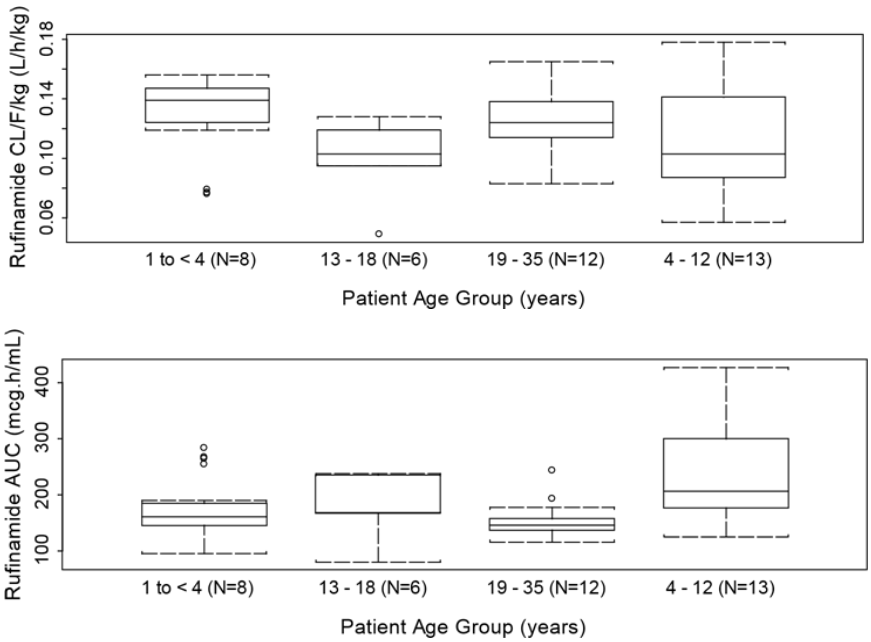


Figure 5 - Box Plots of Model Predicted Rufinamide PK Parameters by Age Group, without Valproic Acid Treatment

Model-Derived Exposure Predictions

Median model-derived rufinamide C_{av} and AUC values were comparable across the different age groups (see Table 7. Model-derived Cav and AUC values are 13.9% to 33.0% higher in subjects receiving valproic acid..

Table 7 - Summary of Final Model-Derived Exposure Estimates by Age Group

	1 to <4 years (N=24)		4 - 12 years (N=40)		13 -18 years (N=21)		19 - 35 years (N=30)	
	Cav (µg/mL)	AUC (µg.h/mL)	Cav (µg/mL)	AUC (µg.h/mL)	Cav (µg/mL)	AUC (µg.h/mL)	Cav (µg/mL)	AUC (µg.h/mL)
Mean	17.2	206.1	20.9	250.8	19.1	228.8	16.3	196.0
SD	4.9	59.3	7.7	92.4	8.3	99.3	5.4	64.8
Median	16.8	201.8	18.7	224.9	16.8	201.0	14.8	178.0
Min	7.9	95.3	10.3	124.1	4.4	52.2	9.6	115.7
Max	39.6	474.7	42.5	510.0	43.1	517.5	30.7	368.8

Exploratory Exposure-Response relationship

The relationship between rufinamide C_{av} and change from baseline in CBCL cognitive development and behavior effect scores at visits 8, 10, 12 and 13 were examined. Graphically, there was no clear trend to indicate for an effect of rufinamide exposure on CBCL total problems score and on each of the sub item CBCL scales: Emotionally Reactive, Anxious/Depression, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive behavior scores as well as internal and external scores.

There were 10 subjects receiving rufinamide treatment with available PK exposure data who experienced a total of 15 treatment related adverse events (AEs). The most common of these were somnolence (4 subjects) and nausea/vomiting (3 subjects). Due to the small numbers of subjects experiencing more than one AE, graphical PK/PD analysis of rufinamide C_{av} versus occurrence of treatment related AE could not be performed.

2.2.3.2. Revised Model based on extended PK data base

In response to CHMP concern on the adequacy of the coarse model, the MAH presented a new population PK analysis on rufinamide plasma steady-state concentration data pooled from ten studies in subjects with epilepsy, including data from studies 303, 022 and 304 and one bioequivalence study in healthy subjects between the suspension and marketed tablet. The new PK population for rufinamide consisted of 1182 subjects, of whom 11 were aged 1 to < 2 years, 19 were aged 2 to < 4 years old, 59 were aged 4 to < 8 years, 80 were aged 8 to < 12 years, 118 were aged 12 to < 18 years and 895were aged ≥18 years.

A one-compartment disposition model with first-order absorption and linear elimination adequately described rufinamide profiles from the pooled studies, parameterized for absorption rate constant, CL/F, apparent volume of distribution and relative bioavailability. Due to high shrinkage on absorption rate constant (66.9%) no covariate effects, including effect of age, could be examined. The model was qualified using goodness-of-fit plots and prediction-corrected visual predictive checks and validated using nonparameteric bootsrap.

2.2.4. Discussion on clinical pharmacology

A population modeling approach was used to characterize the PK of rufinamide in subjects with inadequately controlled LGS and to compare exposure to rufinamide in the paediatric population within the age range of 1 to less than 4 years in study 303 to that in subjects aged 4 years and older in study 022 and study 304 (see Table 4 for a brief description of the studies). Population PK analysis was performed using non-linear mixed effect modelling in NONMEM v7.2.

The final PK dataset included 304 observations from a total of 115 subjects aged 1 to 35 years. Amongst these were 110 rufinamide plasma concentrations from 24 subjects in study 303 (i.e. within the age range of 1 to less than 4 years). Ten (10) of these subjects were below 2 years of age. PK/PD data for cognitive development and behaviour effects assessments was available for a total of 25 subjects participating in study 303, of which 5 subjects received placebo and 20 received rufinamide.

Evaluation of concentration versus time profiles after dose showed neither a clearly identifiable absorption nor a clear elimination phase. A constant input model parameterized in terms of CL/F was found to best describe the PK profile of rufinamide. A one-compartment model assuming bolus administration was also tested, but it was considered not being appropriate to describe the data. Body weight and plasma concentrations of valproic acid were found to statistically significantly affect rufinamide CL/F. All the parameters of the final structural model were estimated with good precision and inter-individual variability in CL/F was mild to moderate (33.3%). Goodness-of-fit-plots supported the validity of the PK model.

Furthermore, according to the MAH, VPCs of the data for 2300 simulated patients suggested that the PK profile of rufinamide has been reasonably well defined by the final PK model with good predictive performance. However, VPCs suggested that the PK samples at visit 5 and 7 were over-predicted, which might indicate a model misspecification. Nonparametric bootstrap evaluation furthermore indicated that the final PK model for rufinamide was stable and produced a well estimated CL/F parameter.

Based on the final model, the PK of rufinamide in paediatric patients with inadequately controlled LGS was found to be dose-independent, and was not significantly affected by age either as a continuous covariate (within the age range of 1 to 35 years covered by the analysis) or as a categorical covariate (age categories: 1 to < 4 years and ≥ 4 years) after body weight was taken into consideration. As previously shown in subjects aged 4 years and above, CL/F increased significantly with body weight, as a power function. Further addition of age to the model with weight was shown to be not significant, suggesting that once subject body weight is taken into consideration for dosing there is no need for further adjustments due to subject age.

For the other evaluated covariates, no significant effect of sex, race, hepatic function, and renal function was seen. Co-administration of valproic acid significantly affected rufinamide clearance, in the 1 to < 4 year old subjects, similar to that in subjects 4 years and above. Co-administration of the other AEDs lamotrigine, carbamazepine, and phenytoin did not affect the PK of rufinamide PK. However, the validity of such finding was questionable, given the scarcity of data available in patients treated by carbamazepine, phenytoin and lamotrigine.

Notably, total daily rufinamide dose (160 to 4400 mg) was not found to affect rufinamide PK. This finding appeared to be at odds with previous studies which found a clear dose dependency of rufinamide.

The CHMP noted that the small amount of the data in patients with inadequately controlled LGS only allowed for building a coarse PK model. However, such model does not allow testing for differences in absorption, distribution and elimination upon age and would not lead to a comprehensive analysis of PK changes upon age. Thus, even if the outcome of the population PK analysis showed that age did not influence the PK of rufinamide and that exposure in younger and older patient was similar based on a comparison of rufinamide exposure (AUC and C_{av}) in patients aged 1 to <4 years to patients ≥4 years, no conclusions could be drawn from such findings due to the lack of sensitivity of the model.

Thus, due to the limitations of the original coarse population PK model, data from the model were not considered suitable to support dosing recommendations in the new proposed age group of 1 to less than 4 years old patients. Notably, with regards to the PK/PD analyses, no clear trend to indicate an effect of rufinamide exposure on CBCL total problems score and relevant sub item CBCL scale was seen. Thus, no exposure-response relationship could be established. It was unclear, if this was due to the scarcity of data, inadequacy of the model or the actual absence of correlation. Finally, due to the small numbers of subjects

experiencing more than one AE, graphical PK/PD analysis of rufinamide C_{av} versus occurrence of treatment related AE could not be performed.

In response to the CHMP concern on the adequacy of the coarse model, the MAH presented the results from a new population PK analysis on rufinamide plasma steady-state concentration data pooled from ten studies in subjects with epilepsy, including data from studies 303, 022 and 304 and one bioequivalence study in healthy subjects between the suspension and marketed tablet. The new PK population for rufinamide consisted of 1182 subjects including 11 and 19 patients younger than 2 years and 4 years, respectively. While in principle such enlarged model could bring useful information on rufinamide PK in children below the age of 4 years, the choice of model parameters and prediction power were questioned by the CHMP. While the absorbed fraction of rufinamide is known to be dependent upon the dose, this dose dependency was not accounted for in the new model. This issue was of importance as absorption features could be different in younger children (1-4 years). Furthermore, the prediction power of the model was questioned. Finally, a notable difference between basal CL/F compared to the coarse model was noted (5.34 L/h in the new model compared to 2.19 L/h in the former analysis). The new model was built upon data collected in heterogeneous subjects (healthy volunteers, LGS patient and other epilepsy patients) and the former analysis was performed with data exclusively collected in LGS patients. However, disease state was not identified as a covariate influencing rufinamide PK. At the time of this report, the above-mentioned concerns and discrepancies had not been satisfactorily addressed by the MAH and thus it was not possible to draw any conclusions from the new model.

The CHMP recommended for the MAH to address the outstanding issues and re-develop a qualified/validated population PK model with an adequate predictive power to describe the PK of rufinamide in children. The systemic exposure in young children 1-2 years and 2-4 years should be estimated accordingly and compared to that observed in older children to inform dose recommendation below 4 years of age.

2.2.5. Conclusions on clinical pharmacology

Overall, the available PK data and simulations at the time of this report were not considered suitable to support dosing recommendations in the new proposed age group of 1 to less than 4 year old LGS patients. The data used for the coarse population PK model from patient with inadequately controlled LGS were too limited to allow a reliable testing for differences in absorption, distribution and elimination by age. Furthermore, the choice of model parameters and prediction power of a new PK model including an enlarged data set from patients with LGS, other forms of epilepsy and from healthy subjects had not been sufficiently justified at the time of this report, thus not allowing to draw firm conclusion from the resulting PK predictions. Further development of a qualified/validated population PK model was recommended.

2.3. Clinical efficacy

Efficacy of rufinamide in the adjunctive therapy of LGS in patients older than 4 years of age has been previously established based on the results of the pivotal trial 022. Given that the disease expression of LGS is similar in adults, older and younger children, the MAH was of the view that efficacy as observed in the patients ≥4 years can be extrapolated to patients aged <4 years.

Supportive data were available from study 303, an open-label safety and PK study in children aged 1 to less than 4 years with inadequately controlled LGS. Efficacy was an exploratory objective.

2.3.1. Dose response study(ies)

No dose-response studies were conducted.

The MAH stated that the dose regimen of rufinamide used in Study 303 was shown to be well-tolerated and effective in subjects greater than or equal to 4 years of age, and is approved at these doses in the tablet form in the European Union and the United States of America, on the basis of results from Study 022, which was the pivotal trial for the initial approval of rufinamide, using the same dosing regimen (starting dose of 10 mg/kg/day and target maintenance dose of 45 mg/kg/day).

2.3.2. Main study

Title of Study 303: A Multicenter, Randomized, Controlled, Open-Label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to Less Than 4 Years of Age with Inadequately Controlled Lennox-Gastaut Syndrome.

2.3.2.1. Methods

This study was a 2-year evaluation of primarily the safety and PK of rufinamide as add-on treatment of seizures associated with LGS in subjects 1 to less than 4 years of age compared to any other approved add-on AED of the investigator's choice.

The study consisted of 2 phases (see also Figure 1):

- Pre-randomization Phase: Screening Period and a Baseline Visit (1 to 8 weeks)
- Randomization Phase: Titration + Maintenance (106 weeks), and Taper (2 weeks) Period.

Only subjects on rufinamide participated in the Taper Period and only those that completed the Taper Period at the end of the study had a Final or Follow-up Visit. Subjects that discontinued rufinamide early were tapered (if deemed necessary by the investigator) before starting another add-on AED.

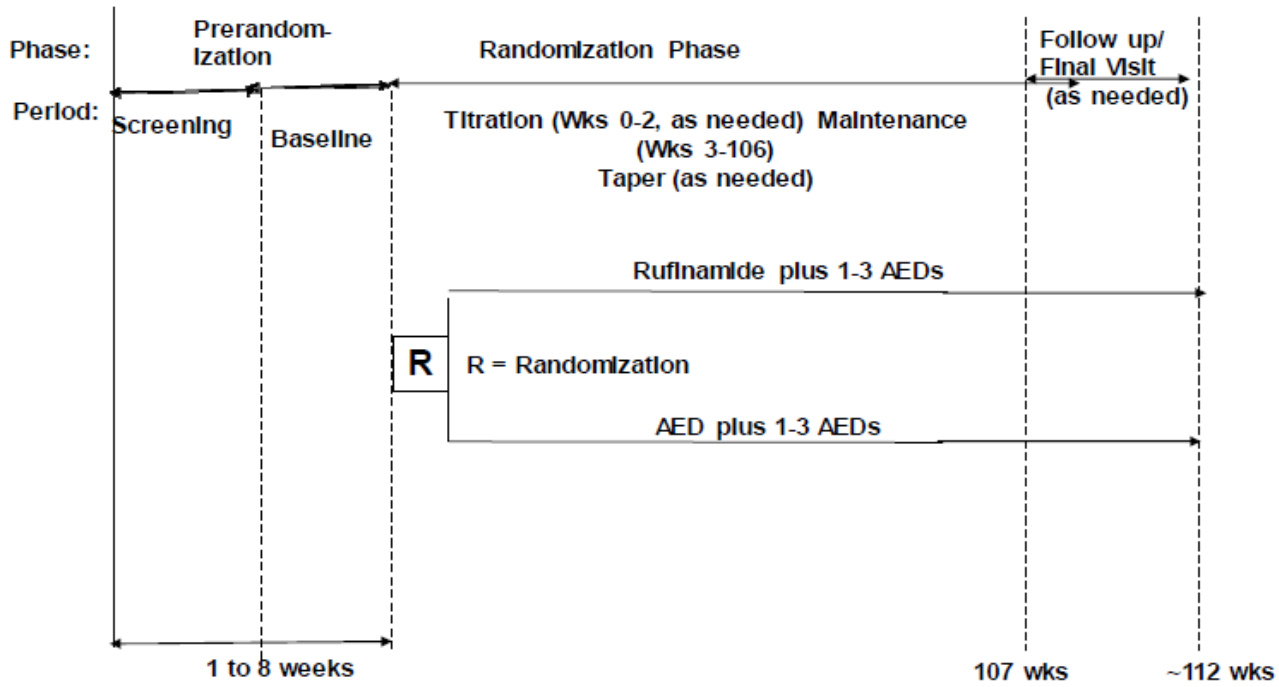


Figure 6 – Study 303 Diagram

Study participants

Diagnosis and Main Criteria for Inclusion

- Age 1 to less than 4 years.
- Clinical diagnosis of LGS at screening, which might have included the presence of a slow background electroencephalogram (EEG) rhythm, slow spikes-waves pattern (<3 Hz), the presence of polyspikes; care should have been taken not to include benign myoclonic epilepsy of infancy, subjects with a diagnosis of atypical benign partial epilepsy (pseudo-Lennox syndrome), or continuous spike-waves of slow sleep.
- On a fixed and documented dose of 1 to 3 concomitant regionally approved AEDs for a minimum of 4 weeks prior to randomization with an inadequate response to treatment.
- Consistent seizure documentation (ie, no uncertainty of the presence of seizures) during the Prerandomization Phase.

Exclusion Criteria

- Familial short QT syndrome.
- Prior treatment with rufinamide within 30 days of Baseline Visit or discontinuation of rufinamide treatment due to safety issues related to rufinamide.
- Any history of or concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.

Treatments

Subjects were randomized to 2 treatment groups in a ratio of 2:1 and received either rufinamide or any other approved AED of the investigator's choice as an add-on to the subject's existing regimen of 1 to 3 AEDs for 106 weeks (Titration plus Maintenance Period).

Test drug: Rufinamide oral suspension (40 mg/mL) was administered at a dose up to 45 mg/kg/day, in 2 equally divided doses. During the Titration Period, rufinamide was initially administered at 10 mg/kg/day. It was subsequently increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, and then further increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, the drug could be titrated more slowly or titrated to a lower dose at the investigator's discretion. The dose reached at the end of the Titration Period was the dose that the subject should have received during the entire Maintenance Period. However, during the Maintenance Period, the dose could have been adjusted according to the investigator's discretion. At the end of the Maintenance Period, rufinamide was discontinued. If deemed necessary by the investigator, discontinuation could have been done gradually over a period of 2 weeks.

Comparator: Administration of the add-on AED for subjects randomized to the any other AED treatment group was performed according to the investigator's usual practice. This included discontinuation of the selected add-on AED or replacement with another add-on AED if the initial add-on AED selected was not well tolerated. Tapering or discontinuation of the investigator selected add-on AED was performed according to the investigator's usual practice.

Objectives

Primary objectives

- To compare the effect of 2 drug regimens consisting of either rufinamide or any other approved AED of the investigator's choice as an add-on to the subject's existing regimen of 1 to 3 AEDs on the

overall safety and tolerability of rufinamide in subjects aged 1 to less than 4 years of age with inadequately controlled LGS,

- To characterize the age group-specific PK of rufinamide in a paediatric population, 1 to less than 4 years of age, with inadequately controlled LGS, using the population approach,
- To evaluate the effect of rufinamide as adjunctive treatment on the cognitive development and behavioural effects in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS.

Exploratory objectives

- To evaluate the effect of 2 drug regimens consisting of either rufinamide or any other approved AED of the investigator's choice as an add-on to the subject's existing regimen of 1 to 3 AEDs, on the language development in a paediatric population, 1 to less than 4 years of age, with inadequately controlled LGS,
- To evaluate the effect on quality of life (QoL) of rufinamide in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS,
- To evaluate the efficacy in terms of seizure reduction of rufinamide in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS,
- To explore the relationship between average exposure and most frequent adverse event (AE).

Outcomes / endpoints

Efficacy

The primary efficacy variables were Child Behavior Checklist (CBCL) Total Problems score and change from baseline in CBCL Total Problems score at the end of the 2-year (106 weeks) treatment period.

The CBCL is a 99-item questionnaire completed by a parent/legal guardian or appropriate caregiver (hereafter referred to as the rater) of the subject. Each item was rated with a 3-point scale indicating how often or characteristic it is of the subject. The 99 items were combined to produce scores for 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behaviour, and other problems) and 3 summary scores (internalizing, externalizing, and total problems). Each item should have been rated by the rater as best they can without providing any additional instructions other than to explain and clarify the wording of an item if needed. The purpose of the scale was to provide t-scores for all problem area scales and the summary scores to identify behavioural problems or developmental delays. The Total Problem score is the sum of all the problem areas plus 1 additional item. Internalization score is the sum of 4 problem areas that are problems within the self, and externalization consists of 2 problem areas involving conflict with other people and with their expectations of the child. The t-scores are standardized test scores that indicate the same degree of elevation in problems on each of the scales relative to the normative sample of peers. Higher scores are indicative of more problems.

Exploratory efficacy variables included time to withdrawal from treatment, seizure frequency, worsening of seizures, change from baseline in CBCL sub-scores, Language Development Survey (LDS) score, and Quality of Life in Childhood Epilepsy (QoLCE) total and subscores:

- Time to withdrawal from either rufinamide or investigator's choice of add-on AED because of occurrence of AEs or for lack of efficacy
- Percent change in total seizure frequency and in frequency by individual seizure type per 28 days by treatment group and in multiple cohorts of subjects. These cohorts included patients treated with

rufinamide or other-AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months. Seizures were assessed and recorded by the subject's parents (s)/caregiver(s).

Frequency per 28 days was defined as (S/D)*28 where, S = the sum of the seizures reported in the Subject Seizure Diary during the specified time interval and D = the number of days with non-missing seizure data in the Subject Seizure Diary for the specified study Phase.

- Worsening of seizures (doubling in total seizure frequency or in frequency of major seizures [generalized tonic-clonic, drop attacks] or occurrence of new seizure type) by treatment group and in multiple cohorts of patients. These cohorts included patients treated with rufinamide or other-AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months.
- Change from baseline in CBCL subscores
- Change from baseline in LDS score during Maintenance Period.

  The LDS consists of an 8-item questionnaire and a vocabulary list. The form was completed by a parent or caregiver who interacted with the subject on a consistent, daily basis. The LDS provided 2 scores, an average phrase length score and a number of endorsed vocabulary words score. Both raw scores were used to provide 2 normative scores based on the child's age in months. Higher scores are indicative of better language development
- Change from baseline in total and subscores of QoLCE scale

  The QoLCE is a 76-item questionnaire designed specifically to measure QoL in children with epilepsy. The form must have been completed by a parent or caregiver who interacted with the child on a consistent, daily basis. The items were combined into 13 scales and 3 of the items were used to represent an overall score in 3 separate areas.

Pharmacokinetics

Sparse blood sampling was performed for the determination of plasma rufinamide concentrations during the Maintenance Period at Visits 4, 5, 6, 7, and 8 (Weeks 2, 4, 8, 16, and 24, respectively). See section 2.2. for the results.

Safety

AEs and the results of clinical laboratory assessments, physical examinations, and vital signs were employed to assess safety. See section 2.4. for the results.

Sample size

Originally, 75 subjects (rufinamide: n=50, any-other-AED: n=25) were planned to be recruited.

Based on Achenbach System of Empirically Based Assessement Preschool Forms & Profiles (Achenbach and Rescorla, 2000), the mean raw scores of the Total Problems is 58.8 for referred (with documented psychopathological issues) children and 33.4 for non-referred (normal controls) children with standard deviations of 26.5 and 18.8 respectively. Using a standard deviation of 23, a total sample size of 75 (50 on rufinamide and 25 on non- rufinamide) would provide 84% power to detect a difference of 17, which is two thirds of the above difference of 58.8 and 33.4 (=25.4), using a two-sided t-test at alpha=0.05.

The planned number of subjects was later revised to allow a minimum of 21 rufinamide-treated subjects (25 rufinamide-treated patients as per the PIP).

Randomisation

Subjects were assigned to treatments on the basis of a computerized randomisation scheme. Subjects were randomized to either rufinamide or any other approved AED in a 2:1 ratio. Randomization was performed centrally by Interactive Voice Response System.

Blinding (masking)

Not applicable.

Statistical methods

Analysis Sets

The *Safety Set* included all enrolled subjects who received at least 1 dose of rufinamide or any other approved add-on AED of the investigator's choice and had at least 1 post-dose safety assessment. The Safety Set was based on actual treatment received.

The *PK Analysis Population* consisted of all treated subjects who received rufinamide and had at least 1 valid concentration measurement with adequately documented dosing history.

The *Full Analysis Set for primary efficacy variable* included all randomized subjects who received rufinamide or any other approved add-on AED of the investigator's choice and had baseline and at least 1 post-dose cognition measurement.

The *Full Analysis Set for other efficacy variable* included randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 post-baseline efficacy assessment.

The Full Analysis Sets were based on randomized treatment.

Efficacy Analyses

Evaluation of efficacy was performed on the Full Analysis Sets.

The 2 treatment groups were to be declared significantly different in favor of rufinamide, if the treatment effect p value was less than or equal to 0.05 using a 2-sided test, and if the least squares (LS) mean of the rufinamide group is less than the LS mean of the any-other-AED group over time (weeks).

The primary statistical model for comparing the 2 treatment groups was a repeated measures mixed model analysis of covariance (ANCOVA) with compound symmetric covariance structure, with baseline score, age, and sex as covariates, and treatment, week, and treatment by week interaction as factors. Unstructured covariance was also used to test the sensitivity of the model. Descriptive statistics of the mean change from baseline by treatment group and week were presented. LS means differences between the 2 treatment groups at each of the scheduled visits were computed.

To compare the 2 treatment groups at the End of Study, an ANCOVA model was used on the last observation carried forward (LOCF) with baseline score and age as covariates, and sex and treatment as factors. This was done to test the effects of drop-outs on the results. To test the effect of time (week) on treatment, treatment groups were compared by excluding treatment by week interaction.

The percent change in frequency of total seizures and by individual seizure types, per 28 days relative to baseline, was compared between treatment groups for each of the cohorts of subjects treated with rufinamide or any-other-AED using a Wilcoxon Rank Sum test with 2-sided 0.05 alpha level. The Hodges-Lehmann 95% CI of the difference between treatment groups was presented.

Incidence of worsening of seizures was summarized by treatment group.

LDS and QoLCE scores were analyzed similarly to the primary efficacy endpoint Total Problems Score. The repeated measure mixed ANCOVA model failed to converge with the unstructured covariance structure due to small sample sizes.

Time to withdrawal from treatment (excluding taper) because of occurrence of AEs or for lack of efficacy was summarized by treatment group and presented using Kaplan-Meier curves.

Safety Analyses

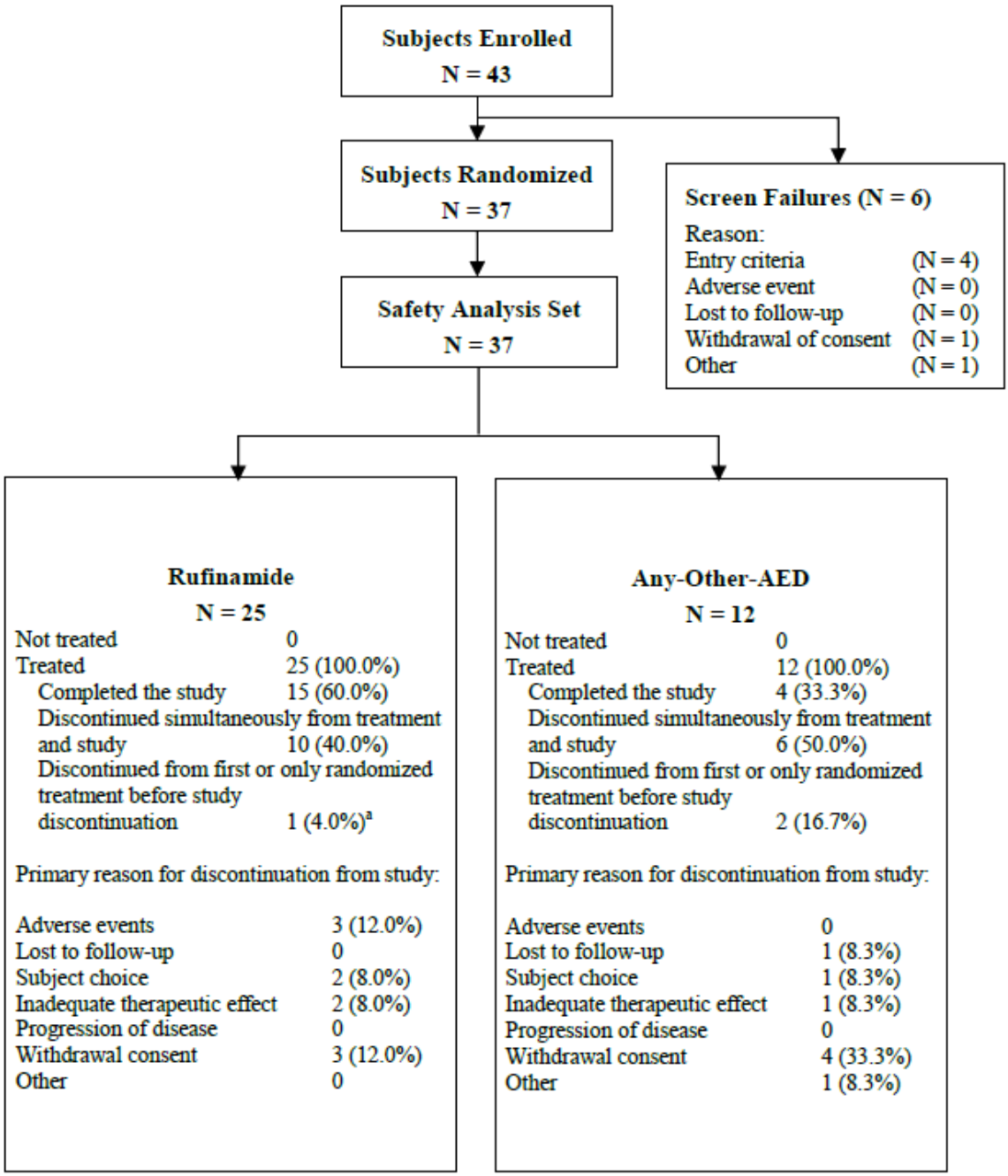
Evaluation of safety was performed on the Safety Population. Treatment-emergent adverse events (TEAEs) were summarized by presenting, for each treatment group, the incidence of AEs. Descriptive summary statistics (mean plus standard deviation, median, minimum, and maximum) of the laboratory, and vital signs, and changes from baseline were evaluated by treatment group. Details on the safety analyses are provided in section 2.4.

PK Analyses

The plasma sample concentration values from this study were merged with comparable data from other studies to permit population PK modeling. Details on the PK analyses are provided in section 2.2.

2.3.2.2. Results

Participant flow



A total of 43 subjects were screened for entry into the study. Of these 43 subjects, 6 were screening failures and 37 were randomized into the study. Of the 6 screen failures, 4 subjects failed to meet inclusion or exclusion criteria, 1 subject withdrew consent, and 1 subject was excluded for other reasons.

All 25 subjects randomized to rufinamide received at least 1 dose of study drug. Of the 25 rufinamide-treated subjects, 15 rufinamide-treated subjects completed the study. Ten subjects discontinued from the study and 1 subject discontinued from rufinamide treatment but completed the study (due to inadequate therapeutic effect). Primary reasons for discontinuation from study were due to AE (decreased appetite and vomiting, vomiting, SAE of pneumonia that resulted in death), withdrawal of consent, subject choice and inadequate therapeutic effect.

All 12 subjects randomized to the any-other-AED group received at least 1 dose of study drug. Four subjects in the any-other-AED group completed the study. Of the 12 subjects treated with any-other-AED, 8 subjects discontinued from the study. Primary reasons for discontinuation were withdrawal of consent, lost to follow-up, subject choice, inadequate therapeutic effect, and other reason.

Recruitment

The first subject was screened on 16 June 2011 and the last subject had the last visit on 2 November 2015. The study was conducted at 19 study sites in total; sites were in the US (8), Canada (1), France (1), Greece (2), Italy (4), and Poland (3).

Conduct of the study

There were 2 revisions and 2 amendments to the original protocol (24 Nov 2010, v1.0). The revisions corrected minor mistakes and typographical errors. A summary of the two amendments is provided below:

- 26 Oct 2011, v4.0 (Amendment 01): to satisfy health authority requests, added a minimum of 25% of rufinamide-treated subjects will be between 2 and 3 years of age and that every effort will be made to include a younger population (between 1 and 3 years of age); revised exclusion for prior use of rufinamide; added blood volume required; added instructions if screening visit is extended, added duplicate, consecutive electrocardiograms (ECGs) at Visit 2 and Visits 5, 6, and 7 for steady state and maximum observed concentration (Cmax); baseline ECG prior to dosing and Visits 5, 6, and 7 approximately 4 to 6 hours after drug administration; changed qualified designated reader to central reader and additional clarification for screening ECG; added measurement of head circumference at baseline, Visits 8, 10, 13, and at Follow-up/Final Visit or early discontinuation
- 03 Apr 2013, v5.0 (Amendment 02): reduced from 8 to 4 weeks the minimum required time on AEDs before randomization, and required that AED doses be documented; allowed historical seizure diaries to satisfy inclusion criteria in lieu of seizure diaries that would be compiled during the Screening Period, thus allowing the Screening Period to be shortened to expedite recruitment; changed criterion for interim analysis compilation to allow reporting of data within the time frame requested by regulators, even if fewer than 75 patients have completed 6 months of treatment; added amylase and lipase samples to list of laboratory tests per United States Food and Drug Administration (FDA) request for subject safety.

Baseline data

Most subjects were 12 to 35 months old (67.6%) and 32.4% were 36 to 48 months old; a similar distribution of age was present in the 2 treatment groups. Time to diagnosis and seizure type were also similar in both groups. Types of seizures were comparable in both groups, except for myoclonic seizures that were less frequent in percentage in rufinamide group (60.0%) compared to other-AED group (83.3%). The majority of subjects were white (86.5%); 10.8% were black or of African descent. The race and ethnicity of subjects randomized into this study was a reflection of the racial distribution of the patient population in the countries/sites participating in the study.

Table 8 - Demographic and Baseline Characteristics – Safety Analysis Set

	Rufinamide (N=25) n (%)	Any-Other-AED (N=12) n (%)	Total (N=37) n (%)
Age (months)[a]			
n	25	12	37

	Rufinamide (N=25) n (%)	Any-Other-AED (N=12) n (%)	Total (N=37) n (%)
Mean (SD)	28.3 (9.99)	29.8 (9.85)	28.8 (9.83)
Median	28.0	30.5	30.0
Min, Max	12, 46	13, 47	12, 47
Age group, n (%)			
12 to 35 months	17 (68.0)	8 (66.7)	25 (67.6)
36 to 48 months	8 (32.0)	4 (33.3)	12 (32.4)
Sex, n (%)			
Male	14 (56.0)	10 (83.3)	24 (64.9)
Female	11 (44.0)	2 (16.7)	13 (35.1)
Weight (kg)			
Mean (SD)	12.47 (3.236)	13.43 (2.805)	12.78 (3.097)
Median	12.00	13.00	12.30
Min, Max	7.0, 19.0	9.0, 19.0	7.0, 19.0
Time since diagnosis (months)			
n	25	12	37
Mean (SD)	19.89 (9.908)	22.97 (9.537)	20.89 (9.766)
Median	20.17	22.82	20.70
Min, Max	5.9, 37.1	2.4, 36.9	2.4, 37.1
Seizure type[b], n (%)			
Partial seizures	15 (60.0)	7 (58.3)	22 (59.5)
Absence seizures[c]	5 (20.0)	4 (33.3)	9 (24.3)
Atypical absence seizures	12 (48.0)	6 (50.0)	18 (48.6)
Myoclonic seizures	15 (60.0)	10 (83.3)	25 (67.6)
Clonic seizures	6 (24.0)	4 (33.3)	10 (27.0)
Tonic-atonic seizures	15 (60.0)	8 (66.7)	23 (62.2)
Primary generalized tonic-clonic seizures	6 (24.0)	3 (25.0)	9 (24.3)
Other	9 (36.0)	1 (8.3)	10 (27.0)

Percentages are based on the total number of subjects with non-missing values in relevant treatment group.
AED = antiepileptic drug, Max = maximum, Min = minimum.
a: Age was calculated at date of informed consent.
b: Subjects could have had more than 1 type of seizure.
c: Although not specifically categorized as such in the listings, all "absence seizures" were atypical.

Concomitant medication

Overall, 8.1% of subjects in the Safety Analysis Set were taking 1 AED, 37.8% were taking 2 AEDs, 45.9% were taking 3 AEDs, 2.7% were taking 4 AEDs, and 5.4% were taking 5 AEDs at baseline. The most commonly taken AEDs (≥25% of the subjects in any treatment group) were valproic acid, levetiracetam, topiramate, diazepam, vigabatrin, and clobazam. The 2 treatment groups appeared to have a similar treatment profile with respect to AEDs other than rufinamide. Differences in percentage should be interpreted with caution taking into account the small number of patients.

Add-on AEDs chosen by the investigator at the time of randomization for subjects in the any other AED group were lamotrigine (5 [41.7%] subjects), clobazam and topiramate (2 [16.7%] subjects each), phenobarbital, valproic acid, and zonisamide (1 [8.3%] subject each).

To compare the profile of AEDs (other than rufinamide) administered to subjects in both treatment groups, the add-on AEDs chosen by the investigator at the time of randomization were added to the baseline AEDs for subjects in the any-other-AED group, and compared to the baseline AEDs taken by subjects in the rufinamide group (see Table 5).

Table 9 - Comparison of Baseline AEDs in the Rufinamide Group to Baseline and Add-On AEDs in the Any-Other-AED Group

WHO Drug Name	Rufinamide (N=25)	Any-Other-AED (N=12)		
	Baseline n (%)	Baseline (n)	Randomization[a] (n)	Total n (%)
Valproic Acid	17 (68.0)	6 (50.0)	1 (8.3)	7 (58)
Levetiracetam	6 (24.0)	9 (75.0)	0	9 (75)
Topiramate	9 (36.0)	2 (16.7)	2 (16.7)	4 (33)
Diazepam	4 (16.0)	3 (25.0)	0	3 (25)
Vigabatrin	7 (28.0)	0	0	0
Clobazam	3 (12.0)	3 (25.0)	2 (16.7)	5 (42)
Lamotrigine	5 (20.0)	1 (8.3)	5 (41.7)	6 (50)
Clonazepam	3 (12.0)	1 (8.3)	0	1 (8)
Nitrazepam	2 (8.0)	1 (8.3)	0	1 (8)
Oxcarbazepine	2 (8.0)	1 (8.3)	0	1 (8)
Ethosuximide	2 (8.0)	0	0	0
Phenobarbital	1 (4.0)	1 (8.3)	1 (8.3)	2 (17)
Zonisamide	1 (4.0)	1 (8.3)	1 (8.3)	2 (17)
Ergenyl Chrono	0	1 (8.3)	0	1 (8)
Lacosamide	0	1 (8.3)	0	1 (8)
Lorazepam	0	1 (8.3)	0	1 (8)
Midazolam	1 (4.0)	0	0	0
Primidone	1 (4.0)	0	0	0

Subjects with 2 or more medications within a class level and drug name were counted only once within that class level and drug name.
AEDs at baseline were defined as AEDs starting prior to first dose date and ending on or after first dose date.
WHO Drug Dictionary March 2013, version 2.
AED = antiepileptic drug, WHO = World Health Organization.
a: Add-on AEDs chosen by the investigator at the time of randomization for subjects in the any-other-AED group.

Numbers analysed

A total of 37 subjects were randomized to receive either rufinamide (n=25) or any other AED (n=12). All subjects received at least 1 dose of study drug and had at least 1 post-dose safety assessment and were included in the Safety Analysis Set. The Full Analysis Set for the primary efficacy variable and the Full Analysis Set for other efficacy variables included 24 of 25 rufinamide-treated subjects and 9 of 12 treated

subjects in the any-other-AED group. One subject in the rufinamide group and 3 subjects in the in the any-other-AED group did not have post-baseline efficacy data and were thus not included.

Outcomes and estimation

- Primary Efficacy Results

The primary efficacy variable was CBCL Total Problems score at the end of the 2-year (106 weeks) treatment period. The CBCL Total Problems t-Scores mean and mean change from baseline are summarized by week in Table 10. The results of the CBCL Total Problems Score treatment comparison at Week 106, over time (based on means across Weeks 24, 56, 88, and 106) and the Final Visit using an ANCOVA model based on LOCF, with baseline score and age as covariates, and sex and treatment as factors are presented in Table 11.

Table 10 - CBCL/1.5-5 Total Problems T-Score: Mean and Mean Change From Baseline by Week (Full Analysis Set for Primary Efficacy Variable)

	Rufinamide[a] (N=24)		**Any-Other-AED[a] (N=9)**	
	Actual	*Change from Baseline (Week 0)*	*Actual*	*Change from Baseline (Week 0)*
Week 0 (Baseline)				
n	24		8	
Mean (SD)	56.6 (11.27)		62.8 (13.07)	
Median (Min, Max)	54.5 (38, 76)		65.0 (37, 82)	
Week 24				
n	22	22	8	8
Mean (SD)	56.0 (13.76)	-1.1 (7.56)	57.1 (10.53)	-5.6 (9.74)
Median (Min, Max)	57.5 (28, 86)	-1.5 (-18, 13)	59.0 (40, 72)	-4.0 (-25, 3)
Week 56				
n	20	20	7	6
Mean (SD)	54.9 (12.78)	-3.0 (12.45)	55.6 (15.78)	-2.5 (5.82)
Median (Min, Max)	55.5 (28, 74)	-4.0 (-29, 32)	59.0 (31, 74)	-2.5 (-9, 4)
Week 88				
n	17	17	4	3
Mean (SD)	53.8 (13.85)	-3.3 (14.86)	55.5 (7.72)	-3.7 (7.57)
Median (Min, Max)	50.0 (37, 79)	-1.0 (-39, 28)	57.0 (45, 63)	-7.0 (-9, 5)
Week 106				
n	15	15	4	3
Mean (SD)	55.7 (15.81)	-0.3 (15.72)	54.8 (4.50)	-6.7 (0.58)
Median (Min, Max)	54.0 (32, 81)	0.0 (-34, 38)	53.5 (51, 61)	-7.0 (-7, -6)

AED = antiepileptic drug, Max = maximum, Min = minimum.
[a] All randomized subjects who received rufinamide or any other approved add-on AED of the investigator's choice and had baseline and at least 1 post-dose cognition assessment.

Table 11 - CBCL/1.5-5 Total Problems T-Score: Treatment Comparison at Final Visit (Week 106), Across Time, and End of Study (Full Analysis Set for Primary Efficacy Variable)

Time (Week) Statistic	Rufinamide (N=24)	Any-Other-AED (N=9)
Week 106		
n	15	4
LS mean (SE)	56.346 (2.720)	53.746 (5.953)
95% CI	50.9, 61.8	41.9, 65.6
Treatment difference	2.601 (6.558)	
95% CI (*P* value)	-10.5, 15.7 (*P*=0.6928)	
Across time		
n	22	9
LS mean (SE)	41.497 (1.469)	42.694 (2.849)
95% CI	38.5, 44.5	36.9, 48.5
Treatment difference	-1.197 (3.172)	
95% CI (*P* value)	-7.6, 5.3 (*p*=0.7083)	
End of study		
n	23	9
LS mean (SE)	55.454 (2.469)	58.230 (4.561)
95% CI	50.4, 60.5	48.9, 67.6
Treatment difference	-2.776	
95% CI (*P* value)	-13.3, 7.8 (*p*=0.5939)	

The Baseline mean score for the any other AED group was higher compared with the rufinamide group (62.8 [n=8] vs. 56.6 [n=24] with LS mean difference of -5.43).

There was no consistent trend in change from baseline in CBCL Total Problems Score by week and overall. LS mean of the CBCL t-scores for subjects after 2 years of treatment were 53.75 for the any other AED group and 56.35 for the rufinamide group, suggesting slightly higher problem areas for the rufinamide subjects compared with the any other AED group (LS mean difference [95% CI] +2.60 [-10.5,15.7]; P=0.6928). The difference in the LS mean CBCL Total Problems Score between the 2 treatment groups across time and at the end of study (based on LOCF), though numerically slightly in favor of rufinamide with -1.20 (*95% CI*: -7.6, 5.3, P=0.7083) and -2.776 (*95% CI*: -13.3, 7.8*, P=0.5939*), respectively, were not statistically significant.

Exploratory Efficacy Results

- Time to withdrawal

The Kaplan-Meier estimate of the median overall survival time to withdrawal from treatment because of an AE or lack of efficacy was 142.0 weeks in the rufinamide group and 28.0 weeks in the any-other-AED group (Table 12).

Table 12 - Time to Withdrawal From Treatment Excluding Taper (Full Analysis Set for Other Efficacy Variables)

	Rufinamide[a] (N=24) n (%)	Any Other AED[a] (N=9) n (%)
Number of Subjects Who Withdrew During the Titration and Maintenance Phase, n (%)		
Withdrawal from treatment	5 (20.8)	4 (44.4)
Censored	19 (79.2)	5 (55.6)
Kaplan-Meier Estimate of Overall Survival (Weeks)		
1st quartile (95% CI)	142.0 (87.7, NC)	61.1 (17.7, NC)
Median (95% CI)	142.0 (142.0, NC)	NC (61.1, NC)
3rd quartile (95% CI)	NC (142.0, NC)	NC (62.9, NC)
Number of Subjects With an AE or Lack of Efficacy, n (%)		
Withdrawal from treatment	2 (8.3)	2 (22.2)
Censored	4 (16.7)	1 (11.1)
Kaplan-Meier Estimate of Overall Survival (weeks)		
1st quartile (95% CI)	142.0 (4.6, 142.0)	17.7 (17.7, NC)
Median (95% CI)	142.0 (NC, NC)	28.0 (17.7, NC)
3rd quartile (95% CI)	142.0 (NC, NC)	NC (17.7, NC)

AE = adverse event, AED = antiepileptic drug, CI = confidence interval, NC = not calculated.
Percentages are based on the total number of subjects in the group of randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 post-baseline efficacy assessment.
[a] The group of randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 postbaseline efficacy assessment.

- Change from Baseline CBCL sub-scores

The mean and mean change from baseline are summarized for the CBCL t-scores for problem scales (total emotional reactive scores, total anxious/depression scores, total somatic complaints scores, total withdrawn scores, total sleep problems scores, total attention problems scores, total aggressive behavior scores, total internalizing scores, and total externalizing scores).

Table 13 – CBCL/1.5-5 Sub-Scores – Mean and Mean Change from Baseline to Week 106 (Full Analysis Set for Primary Efficacy Variable)

	Rufinamide[a] (N=24)		Any-Other-AED[a] (N=9)	
	Actual	Change from Baseline (Week 0)	Actual	Change from Baseline (Week 0)
Total emotional Reactive Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	59.0 (8.13)		60.9 (8.64)	
Median	59.0		60.5	
Min, Max	50, 77		50, 77	

	Rufinamide[a] (N=24)		Any-Other-AED[a] (N=9)	
	Actual	Change from Baseline (Week 0)	Actual	Change from Baseline (Week 0)
Week 106				
n	15	15	4	3
Mean (SD)	58.1 (9.53)	-1.1 (9.30)	58.0 (6.83)	-6.7 (0.58)
Median	51.0	-1.0	57.0	0.0
Min, Max	50, 77	-20, 17	51, 67	-8.0, 4
Total Anxious/Depression Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	56.4 (7.48)		54.6 (6.67)	
Median	51.5		51.5	
Min, Max	50, 69		50, 69	
Week 106				
n	15	15	4	3
Mean (SD)	56.7 (8.19)	0.5 (8.87)	53.0 (4.08)	0.7 (1.15)
Median	50.0	0.0	51.5	0.0
Min, Max	50, 74	-19, 23	50, 59	0, 2
Total Somatic Complaints Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	59.4 (8.13)		54.9 (4.70)	
Median	58.0		55.5	
Min, Max	50, 76		50, 62	
Week 106				
n	15	15	4	3
Mean (SD)	59.5 (9.13)	0.1 (11.24)	55.8 (5.32)	-1.7 (2.89)
Median	58.0	0.0	55.5	0.0
Min, Max	50, 82	-16, 29	50, 62	-5, 0
Total Withdrawn Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	71.5 (11.72)		72.1 (11.03)	
Median	70.0		74.5	
Min, Max	50, 91		56, 85	
Week 106				
n	15	15	4	3
Mean (SD)	65.8 (10.32)	-2.2 (13.22)	65.8 (9.03)	-7.0 (9.54)

	Rufinamide[a] (N=24)		Any-Other-AED[a] (N=9)	
	Actual	Change from Baseline (Week 0)	Actual	Change from Baseline (Week 0)
Median	63.0	3.0	66.5	-12.0
Min, Max	51, 85	-25, 25	60, 70	-13, 4
Total Sleep Problems Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	57.8 (10.72)		62.4 (8.57)	
Median	52.0		63.0	
Min, Max	50, 94		50, 76	
Week 106				
n	15	15	4	3
Mean (SD)	56.7 (10.81)	-1.9 (12.30)	53.3 (2.06)	-5.7 (7.57)
Median	51.0	-1.0	53.0	-9.0
Min, Max	50, 88	-24, 21	51, 56	-11, 3
Total Attention Problems Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	59.3 (9.17)		65.9 (10.72)	
Median	57.0		68.5	
Min, Max	50, 80		50, 77	
Week 106				
n	15	15	4	3
Mean (SD)	58.8 (9.33)	-1.1 (4.65)	56.5 (4.93)	-7.7 (2.52)
Median	57.0	0.0	57.0	-8.0
Min, Max	50, 80	-11, 5	50, 62	-10, -5
Total Aggressive Behaviour Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	52.5 (5.01)		58.6 (12.07)	
Median	50.0		53.0	
Min, Max	50, 69		50, 84	
Week 106				
n	15	15	4	3
Mean (SD)	56.3 (9.72)	-3.2 (6.26)	52.5 (4.36)	-0.3 (2.89)
Median	51.0	0.0	50.5	-2.0
Min, Max	50, 82	-3, 19	50, 59	-2, 3
Total Internalizing Scores				

	Rufinamide[a] (N=24)		Any-Other-AED[a] (N=9)	
	Actual	Change from Baseline (Week 0)	Actual	Change from Baseline (Week 0)
Week 0 (Baseline)				
n	24		8	
Mean (SD)	61.6 (10.78)		60.6 (9.71)	
Median	63.0		60.0	
Min, Max	37, 79		43, 74	
Week 106				
n	15	15	4	3
Mean (SD)	57.9 (12.88)	-1.5 (13.73)	58.5 (4.36)	-2.7 (1.53)
Median	56.0	0.0	60.0	-3.0
Min, Max	37, 78	-31, 31	49, 65	-4, -1
Total Externalizing Scores				
Week 0 (Baseline)				
n	24		8	
Mean (SD)	47.5 (11.22)		58.1 (15.92)	
Median	46.5		57.0	
Min, Max	28, 74		28, 82	
Week 106				
n	15	15	4	3
Mean (SD)	52.4 (14.09)	4.7 (10.07)	50.3 (7.85)	-3.7 (3.51)
Median	50.0	4.0	51.0	-4.0
Min, Max	35, 83	-17, 28	40, 59	-7, 0

AED = antiepileptic drug, Max = maximum, Min = minimum, SD = Standard Deviation.
[a] All randomized subjects who received rufinamide or any other approved add-on AED of the investigator's choice and had baseline and at least 1 post-dose cognition assessment.

- Percent Change in Total Seizure Frequency

The percent change in total seizure frequency per 28 days was calculated for each cohort (i.e. patients treated with rufinamide or other-AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months) relative to baseline. Mean and median baseline seizure frequency was 752.02 and 449.54 in the rufinamide group (N=24) and 379.38 and 285.54 in the any other AED group (N=9). The overall median decrease (Min, Max) from baseline was 7.05% (79.2, 3644.1) in the rufinamide group and 20.15% (-83.3, 143.1) in the any other AED group. The median difference between the rufinamide group and the any other AED group was -14.4% (95%CI: -56.20, 15.50). The P value for the difference from the any-other-AED group was 0.2731.

Percent change in seizure frequency by individual seizure types (partial seizures, absences, typical absences, clonic seizures, tonic-atonic seizures, primary generalized tonic-clonic seizures and other seizures) per 28 days across all cohorts relative to baseline showed no statistically significant differences between the 2 treatments groups. However, sample sizes (7-12 patients receiving rufinamide and 1-5 patients receiving any other AED) were small, affecting the interpretability of these results.

- Worsening of seizures

Worsening of seizures was summarized by the incidence of subjects with doubling in total seizure frequency, doubling in frequency of major seizures (generalized tonic-clonic, drop attacks), or occurrence of new seizure type during each successive 3 to 4 month visit interval of the Maintenance Period relative to Baseline.

Across all cohorts in the rufinamide group, 4 of 24 (16.7%) subjects reported a doubling in total seizure frequency, 5 of 24 (20.8%) reported a doubling in frequency of major seizures (generalized tonic-clonic, drop attacks), and no subjects reported an occurrence of a new seizure type. Across all cohorts in the any-other-AED group, 1 of 9 (11.1%) subjects reported doubling in total seizure frequency and a doubling in frequency of major seizures (generalized tonic-clonic, drop attacks); no subjects reported an occurrence of a new seizure type.

- Change from baseline in LDS score during Maintenance Period

LDS Average Phrase Length

The LDS average phrase length can be categorized into delayed phrase development (≤20th percentile) or no delayed phrase development (>20th percentile). It is calculated by dividing the total number of words across all phrases by the number of phrases with greater than 0 words; for subjects with no words, the average is 0. At baseline, phrase development was delayed in all subjects. The delay in phrase development was severe; hence the baseline score was 0 for all except 3 subjects.

The LDS average phrase length did not change notably in either treatment group during the study, and was delayed in all except 3 subjects at the end of treatment; the end of treatment score was 0 for all except 5 subjects. When comparing LDS average phrase length between the 2 treatment groups at the End of Study using an ANCOVA model on the LOCF with baseline score and age as covariates and sex and treatment as factors, the resulting treatment difference was 0.194 (95% CI -0.4, 0.8), which is not statistically significant (P=0.5156). When compared across time using an ANCOVA mixed model for repeated measures with baseline score and age as covariates and sex, treatment, week, and treatment by week interaction as factors, the treatment difference of 0.222 (0.303) (95% CI -0.4, 0.8) is not statistically significant (P=0.4693)

LDS Vocabulary Score

The LDS vocabulary score can be categorized into delayed vocabulary development (≤15th percentile) or no delayed vocabulary development (>15th percentile). Vocabulary development was delayed in all except 1 subject at baseline, and all except 3 subjects at the end of treatment. The delay in development was severe, hence the baseline score was 0 for all except 7 subjects and the end of treatment score was 0 for all except 9 subjects.

The treatment difference of 12.450 (95% CI: -27.0, 51.9), when the 2 treatment groups was compared at the End of Study using an ANCOVA model on the LOCF with baseline score and age as covariates and sex and treatment as factors, was not statistically significant (P=0.5237). The LDS vocabulary score in the 2 treatment groups was also compared across time using an ANCOVA mixed model for repeated measures with baseline score and age as covariates and sex, treatment, week, and treatment by week interaction as factors. The treatment difference of 13.629 (95% CI: -10.0, 37.3) was not statistically significant (P=0.2497).

- Change from Baseline in Total and Sub-Scores of QoLCE Scale

At baseline, the mean total score of QoLCE was comparable between the 2 treatment groups. There were little changes from the baseline by the end of treatment, mean (SD) changes at the end of treatment were -0.3 (7.87) for rufinamide and 1.4 (1.81) for any other AED.

Ancillary analyses

Not applicable.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 - Summary of Efficacy for trial E2080-G000-303

Title: A Multicenter, Randomized, Controlled, Open-Label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to Less Than 4 Years of Age with Inadequately Controlled Lennox-Gastaut Syndrome			
Study identifier Company identifier	E2080-G000-303 EudraCT Number: 2010-023505-36		
Design	Multicentre, multiple-dose, open-label, randomized, controlled, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 weeks titration period (or as needed) 104 weeks maintenance period 2 weeks taper period (or as needed) Screening period and baseline visit up to 8 weeks n/a
Hypothesis	Superiority and Exploratory		
Treatments groups	Rufinamide		Titration Period: rufinamide 10 mg/kg/day (administered in 2 equally divided doses), increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level Target maintenance dose: 45 mg/kg/day. Added to existing regimen of 1 to 3 AEDs. 106 weeks Patients randomised: 24
	Any Other AED		Any approved AED of the investigator's choice, dosed according to investigator's usual practice, added to subject's existing regimen of 1 to 3 AEDs. 106 weeks Patients randomised: 12
Endpoints and definitions	Primary endpoint	CBCL Total Problems score	Child Behaviour Checklist (CBCL) Total Problems Score [combined score for 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behaviour, and other problems) and 3 summary scores (internalizing, externalizing, and total problems] and change from baseline.
	Exploratory endpoint	Time to withdrawal	Time to withdrawal from either rufinamide or investigator selected add-on AED because of occurrence of AEs or for lack of efficacy.
	Exploratory endpoint	Change in Seizure frequency	Percent change from baseline in total seizure frequency per 28 weeks.

	Exploratory endpoint	Worsening of seizures	Rate of subjects with doubling in total seizure frequency or in frequency of major seizures (generalized tonic-clonic, drop attacks), or occurrence of new seizure type during each successive 3 to 4 month visit interval of Maintenance Period relative to baseline.
Database lock	Last subject last visit: 15 January 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Full Analysis Set for primary efficacy variable: all randomized subjects who received rufinamide or any other approved add-on AED of the investigator's choice and had baseline and at least 1 post-dose cognition measurement. Full Analysis Set for other efficacy variable: randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 post-baseline efficacy assessment.		
Descriptive statistics and estimate variability	**Treatment group**	**Rufinamide**	**Any Other AED**
	Number of subjects	**24**	**9**
	CBCL Total Problems score – End of study LS mean	55.5	58.2
	95% CI	(50.4, 60.5)	(48.9, 67.6)
	Time to withdrawal Kaplan-Meier estimate for Median (weeks)	142.0	28.0
	95% CI	(NC, NC)	(17.7, NC)
	Percentage Change in Total Seizure Frequency Median	-7.05	-20.15
	Worsening of seizures Doubling in total seizure frequency	4	1
	Doubling in frequency of major seizures	5	1
	Occurrence of new seizure type	0	0
Effect estimate per comparison	Primary Endpoint: **CBCL Total Problems score**	Comparison groups	Rufinamide versus Any Other AED
		Treatment Difference	-2.776
		95% CI	-13.3, 7.8
		P-value	0.5939
	Exploratory endpoint: **Time to withdrawal**	No formal statistical comparison between groups was performed	
	Exploratory endpoint: **Percentage Change in Total Seizure**	Comparison groups	Rufinamide versus Any Other AED
		Median Difference	-14.4

	Frequency	95% CI	-56.20, 15.50
		P-value	0.2731
	Exploratory endpoint: **Worsening of seizures**	No formal statistical comparison between groups was performed.	

2.3.3. Discussion on clinical efficacy

In order to support the present application to expand the indication of Inovelon to paediatric patients from 1 year to less than 4 years of age, the MAH made reference to the established benefit-risk profile in patients 4 years of age and older and the fact that the clinical expression of LGS is similar in the younger population compared to older children and adults. Supportive data were available from a multicentre, multiple-dose, open-label, randomized, controlled, parallel group study (study 303), which provides a 2-year evaluation of the safety, PK, and cognitive/behavioural effects of rufinamide as add-on treatment for control of seizures associated with LGS in subjects 1 to less than 4 years of age compared to any other approved add-on AED of the investigator's choice.

Based on these data as well as pop PK modelling, extrapolation of the efficacy of rufinamide from older children and adults to younger children aged 1 to less than 4 years was proposed by the MAH. The CHMP agreed that the expression of LGS was similar in the younger population compared to older patients, and that there was no reason to expect that the effect of rufinamide on children between the ages of 1 and 4 years would differ from that in older children and adults, although it was noted that the diagnosis of LGS can be challenging in the very young children. Thus, in principle, extrapolation of efficacy as previously established in children > 4 years could be acceptable provided an adequate dose can be established (see discussion on this aspect in section 2.2.).

Design and conduct of clinical studies

Study 303 was included in the PIP of Inovelon and the design had previously been endorsed as appropriate to demonstrate the agreed objectives. The study aimed at to comparing the effect of 2 drug regimens consisting of either rufinamide or any other approved AED of the investigator's choice as an add-on to the subject's existing regimen of 1-3 AEDs on the overall safety and tolerability of rufinamide in subjects aged 1 to less than 4 years of age with inadequately controlled LGS. Other objectives were to characterize age group-specific PK and to evaluate cognitive development and behavioural effects and other exploratory efficacy variables.

In study 303, rufinamide was administered as oral suspension (40 mg/mL). During the Titration Period, rufinamide was administered at 10 mg/kg/day (administered in 2 equally divided doses) and the dose was increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. No dose finding study had been conducted. The choice of the dose in study 303 was the same as in study 022, the pivotal trial for the initial approval of rufinamide for use as adjunctive therapy in the treatment of seizures associated with LGS in patients 4 years of age and older.

The diagnosis of LGS was established according to the International League Against Epilepsy's Classification of Epileptic Seizures (ILAE, 2010) except for the EEG criteria. The ILAE criteria were adapted from the requirement of presence of slow spike-and-waves and burst of fast rhythms to 'a clinical diagnosis of at screening, which *might have included* the presence of a slow background EEG rhythm, slow spikes-waves pattern (<3 Hz), the presence of polyspikes (…)'. This widening of the inclusion criteria was done to account for the fact that at such an early age (1 to less than 4 years), diagnosis of LGS can be very difficult due to varying stages of brain maturation and disease development and not all the cardinal EEG signs and

symptoms may be present at the same time in this age group. While the CHMP acknowledged the difficulties in diagnosis, the lack of specific EEG requirements created uncertainties in the recruited patient population and if patients with other epileptic syndrome than LGS could have been enrolled. To address this concern, the MAH retrospectively requested participating study sites to provide EEG documentation. Information from 27 subjects (72% of all enrolled patients) was received. All of these subjects had EEG and clinical features consistent with LGS, which was considered reassuring by the CHMP.

The originally planned study size of 75 patients was reduced to a total of 37 patients (25 treated with rufinamide) due to difficulties in the recruitment related to the rarity of the condition, the diagnostic process specifically in the younger age group and the availability of the product on the market. The difficulties were acknowledged by the CHMP; however, the small number of study subjects randomised (and even smaller number of subjects completing the 2-year treatment period of 15/24 subjects in the rufinamide group and 4/12 subjects in the any-other-other AED group) made it difficult to interpret the study results, in particular with regards to efficacy.

Baseline distribution of age was similar in the 2 treatment groups; most subjects were 12 to 35 months old (67.6%) and 32.4% were 36 to 48 months old. Time to diagnosis and seizure type were also similar in both groups. Types of seizures were comparable in both groups, except for myoclonic seizures that were less frequent in percentage in rufinamide group (60.0%) compared to other-AED group (83.3%). In this context, the CHMP noted the high number of patients in the study with myoclonic seizures (68%) in the study which are not frequent in typical LGS syndrome. Finally, most patients were taking 2 (37.8%) and 3 (45.9%) concomitant AEDs at baseline. Both treatment groups appeared to have a similar treatment profile with respect to AEDs other than rufinamide.

Efficacy data and additional analyses

For the primary efficacy variable, LS mean difference in the CBCL Total Problems Score compared to baseline, the scores at the Final Visit (Week 106) were comparable in the rufinamide (56.35) and any other AED group (53.75) with slightly more problems for the rufinamide subjects compared with the any-other-AED group (LS mean difference [95% CI]: +2.60 [-10.5,15.7]; P=0.6928). Analyses across time (LS mean difference [95% CI]: -1.197 [95% -7.6, 5.3]; P=0.7083) and at the End of Study, based on LOCF (treatment difference [95% CI]: -2.776 [-13.3, 7.8]; P=0.5939) were not statistically significant either. The baseline mean score for the any other AED group was higher compared with the rufinamide group (62.8 [n=8] versus 56.6 [n=24] with LS mean difference of -5.43). Overall, there was no consistent trend for the change from baseline in CBCL Total Problems Score over time. There was also no major trend in mean CBCL sub-scores and mean change from baseline in CBCL sub-scores in the 2 treatment groups throughout the study.

Based on the sample size calculation, the CHMP noted that a minimum difference in CBCL Total Problem Score of at least 17 in favour of rufinamide was expected. This effect is rather large and a notable difference between the expected (-17) and observed (+2.6) outcome for the primary clinical endpoint was apparent. Based on the experience from other (not epilepsy) behavior health studies, this change in CBCL total score was assumed to bring down the rufinamide score closer to normal values compared to the any other AED arm where scores were expected to be relatively steady. However, it appears that due to the lack of experience with the use of the CBCL scale in the pediatric population recruited in study 303, this difference was overestimated and clearly out of reach. There was also a large variability in the scores of some patients in both treatment arms during and at the end of treatment. Due to the small size of the study, the results were considered inconclusive.

Exploratory efficacy endpoints included time to withdrawal from treatment because of an AE or lack of efficacy, which was 142.0 weeks (median Kaplan-Meier estimate of overall survival) in the rufinamide group and 28.0 weeks in the any-other-AED group. However, a time-to-withdrawal analysis taking into account

2 of the reasons for discontinuation (adverse event and lack of efficacy) was not considered reliable by the CHMP. Too few of the targeted events have been observed in the course of the trial (2 discontinuations in each arm). In response to a question by the CHMP, new analyses were performed including the taper period and considering all subjects who discontinued treatment for any reason (10 in the rufinamide arm and 5 in the any other AED arm). In this analysis, the median time-to-withdrawal in the any other AED arm was 62.9 weeks while it was not reached previously. On the contrary, when limiting the analysis again to AEs and lack of efficacy as withdrawal events (6 in the rufinamide arm and 3 in the any other AED arm), no median time-to-withdrawal was reached in the any other AED arm (i.e. less than half of the subjects experienced AE or lack of efficacy) while it was 28 weeks in the original analysis. The results were considered difficult to interpret and overall inconclusive due to the small size of the trial.

With regards to seizure outcomes, no statistically significant difference between the 2 treatments groups in the percent change in seizure frequency per 28 days relative to baseline was observed. The overall median decrease in total seizure frequency from baseline was lower in the rufinamide group (7.05%) than in the any other AED group (20.15%). The median difference between the rufinamide group and the any-other-AED group was -14.4% (P value= 0.2731). This finding was explained by the MAH by the small size of the trial and variability of seizure frequency among different time-points. A comparison of the number of variables between the two treatment groups such as individual characteristics, number and type of AEDs at baseline, frequency of seizures at baseline, and time in the study did not reveal any other possible cause that account for the observed difference. Due to the small size of the study, the results were considered inconclusive.

Concerning worsening of seizures, in the rufinamide group, 4 of 24 (16.7%) subjects reported a doubling in total seizure frequency, 5 of 24 (20.8%) reported a doubling in frequency of major seizures (generalized tonic-clonic, drop attacks), and no subjects reported an occurrence of a new seizure type. In the any other AED group, 1 of 9 (11.1%) subjects reported doubling in total seizure frequency and 1 of 9 (11.1%) subjects reported a doubling in frequency of major seizures (generalized tonic-clonic, drop attacks); no subjects reported an occurrence of a new seizure type.

The LDS average phrase length did not change notably in either treatment group during the study. At the end of the study, the treatment difference of 0.194 (95% CI -0.4, 0.8) was not statistically significant (P=0.5156). The treatment difference of 12.450 (95% CI -27.0, 51.9) at the End of study in the LDS vocabulary score was also not statistically significant (P=0.5237). Finally, there were no notable changes from baseline in total score of QoLCE.

2.3.4. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy results of study 303 were largely inconclusive and did not support a clinically relevant effect of rufinamide as adjunctive therapy in the treatment of seizures associated with LGS in patients aged 1 to less than 4 years. This was mainly due to the small study size and the fact that the study was not adequately powered for the performed efficacy analyses. Nevertheless, given that LGS disease expression is similar in younger and older children, extrapolation of efficacy from patients aged > 4 years might in principle be accepted. However, this is currently not possible as no adequate dose in patients has been established (see details in section 2.2.).

2.4. Clinical safety

Introduction

The primary safety data supporting the present application are data from study 303. Evaluation of safety was performed on the Safety Population. The Safety Set included all enrolled subjects who received at least 1 dose of rufinamide or any other approved add-on AED of the investigator's choice and had at least one post-dose safety assessment.

Pertinent safety data consisted of previously collected and reviewed data from study 022, the pivotal trial supporting the initial marketing authorisation for Inovelon and its use as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 4 years of age and older, and data from study 304, a Phase 3, controlled study in LGS conducted in Japan to support marketing application in that country (see Table 3 for an overview of clinical trials).

In these studies, rufinamide treatment has been associated with CNS adverse reactions including dizziness, somnolence, ataxia and gait disturbances. Other important identified risks in the RMP include status epilepticus, rash and hypersensitivity, decreased appetite and weight loss, diplopia and blurred vision and vomiting.In patients aged 4 years and older, the most common adverse reactions observed at a higher incidence than placebo in patients with LGS were somnolence and vomiting (both very commonly). The discontinuation rate in LGS due to adverse reactions was 8.2% for patients receiving rufinamide and 0% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from the rufinamide treatment group were rash and vomiting.

A summary of the key findings from study 303 is provided in this chapter. Safety data from study 303 are also compared to safety findings in older paediatric subjects 4 to less than 12 years of age from study 022. A brief summary of the safety data from study 304 is also given.

Safety assessments in study 303 consisted of monitoring and recording all AEs and serious AEs (SAEs); regular monitoring of haematology, blood chemistry (including amylase and lipase), and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations.

AEs were graded by seriousness and severity. Relationship to study treatment was assessed based on temporal relationship of the onset of the event to the initiation of the study treatment, the course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable, whether the event was known to be associated with the study treatment or with other similar treatments, the presence of risk factors in the study subject known to increase the occurrence of the event, and the presence of non-study, treatment-related factors that are known to be associated with the occurrence of the event. A related AE was considered an event for which a causal relationship between the study drug and the AE is a reasonable possibility.

Patient exposure

All of the 37 subjects randomized in study 303 received at least 1 dose of study drug and thus together constituted the Safety Set (25 subjects receiving rufinamide and 12 subjects receiving any other AED).

In the rufinamide arm, 22 (88%) of subjects had at least 16 weeks of exposure in the study, 21 (84%) subjects had at least 24 weeks of exposure, and 19 (76%) subjects had at least 56 weeks of exposure. The maximum exposure to rufinamide was 146.1 weeks. The total exposure to rufinamide was 2191.3 subject-weeks. In the any-other-AED arm, 9 (75%) of subjects had at least 16 weeks of exposure in the study, 8 (66.7%) subjects had at least 24 weeks of exposure, and 6 (50%) subjects had at least 56 weeks of exposure. The maximum exposure to any-other-AED was 107.9 weeks. The total exposure to any-other-AED was 653.7 subject-weeks.

A total of 11 (44%) subjects had 106 weeks of exposure in the rufinamide arm compared to 4 (33%) subjects in the any other AED group. The mean duration of exposure was higher in the rufinamide group (87.65 weeks) compared with the any other AED group (54.48 weeks).

The median average daily doses of rufinamide were 328.6 mg during the Titration Period, 518.1 mg during the Maintenance Period, and 213.9 mg during the Taper Period. During the Maintenance Period, 79.2% of subjects received rufinamide at a dose of greater than or equal to 40 mg/kg/day.

For an overview of demographic and baseline characteristics, including use of concomitant AEDs, see chapter 2.3.2.

Adverse events

Study 303

The overall incidence of treatment-emergent adverse events (TEAEs) was similar in the rufinamide group (22 of 25 subjects [88.0%]) and the any other AED group (10 of 12 subjects [83.3%]).

Common TEAEs (occurring in ≥10% of subjects in any treatment group) for subjects in study 303 are summarized in Table 10 by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), sorted by descending frequency in the rufinamide group.

Table 15 – TEAEs Occurring in at Least 10% of Subjects in Any Treatment Group by MedDRA SOC and PT by Decreasing Frequency

MedDRA System Organ Class Preferred Term	Rufinamide (N=25) n (%)	Any-Other-AED (N=12) n (%)	Total (N=37) n (%)
Subjects With Any TEAEa	22 (88.0)	10 (83.3)	32 (86.5)
Infections and Infestations	15 (60.0)	7 (58.3)	22 (59.5)
Upper respiratory tract infection	7 (28.0)	4 (33.3)	11 (29.7)
Pneumonia	5 (20.0)	0	5 (13.5)
Sinusitis	4 (16.0)	1 (8.3)	5 (13.5)
Otitis media	4 (16.0)	0	4 (10.8)
Bronchitis	3 (12.0)	0	3 (8.1)
Gastrointestinal Disorders	13 (52.0)	4 (33.3)	17 (45.9)
Vomiting	7 (28.0)	1 (8.3)	8 (21.6)
Diarrhoea	4 (16.0)	3 (25.0)	7 (18.9)
Constipation	3 (12.0)	1 (8.3)	4 (10.8)
Nervous System Disorders	11 (44.0)	4 (33.3)	15 (40.5)
Somnolence	5 (20.0)	0	5 (13.5)
Seizure	2 (8.0)	3 (25.0)	5 (13.5)
Respiratory, Thoracic and Mediastinal Disorders	8 (32.0)	4 (33.3)	12 (32.4)
Cough	4 (16.0)	2 (16.7)	6 (16.2)
Nasal congestion	3 (12.0)	0	3 (8.1)
Skin and Subcutaneous Tissue Disorders	7 (28.0)	2 (16.7)	9 (24.3)
Rash	3 (12.0)	1 (8.3)	4 (10.8)
Psychiatric Disorders	6 (24.0)	3 (25.0)	9 (24.3)
Irritability	3 (12.0)	1 (8.3)	4 (10.8)
General Disorders and Administration Site Conditions	5 (20.0)	4 (33.3)	9 (24.3)
Pyrexia	4 (16.0)	3 (25.0)	7 (18.9)
Metabolism and Nutrition Disorders	5 (20.0)	2 (16.7)	7 (18.9)

MedDRA System Organ Class Preferred Term	Rufinamide (N=25) n (%)	Any-Other-AED (N=12) n (%)	Total (N=37) n (%)
Decreased appetite	3 (12.0)	1 (8.3)	4 (10.8)

The most frequently reported TEAEs in the rufinamide treatment group (occurring in ≥10% of subjects) were vomiting (28.0%), upper respiratory tract infection (28.0%), pneumonia and somnolence (20.0% each), and sinusitis, otitis media, diarrhoea, cough, and pyrexia (16.0% each) and bronchitis, constipation, nasal congestion, rash, irritability, and decreased appetite (12.0% each).

In the any other AED group, upper respiratory tract infection (33.3%), diarrhea, seizure, and pyrexia (25.0% each), and cough (16.7%) were the most common TEAEs (occurring in >1 subject).

Approximately half of all subjects in both treatment groups (13 of 25 [52.0%] in the rufinamide group and 6 of 12 [50.0%] in the any other AED group) experienced TEAEs that were considered by the investigator to be possibly or probably related to study drug. Vomiting (5 of 25 [20.0%] subjects) and somnolence (4 of 25 [16.0%] subjects) were the only treatment-related TEAEs reported in more than 2 subjects in the rufinamide group. Pyrexia and upper respiratory tract infection (2 of 12 [16.7%] subjects each) were the only treatment-related TEAEs reported in more than 1 subject in the any-other-AED group.

The majority of subjects in both treatment groups had TEAEs that were considered mild (4 of 25 [16.0%] in the rufinamide group and 4 of 12 [33.3%] in the any other AED group) or moderate (14 of 25 [56.0%] in the rufinamide group and 4 of 12 [33.3%] in the any other AED group) by the investigators. Both groups had similar overall incidences of severe TEAEs: 4 subjects (16.0%) in the rufinamide group experienced severe TEAEs (1 bronchitis and pneumonia aspiration, 1 encephalitis and pneumonia influenzal, 1 pneumonia, and 1 weight decreased) and 2 subjects in the any other AED group (16.7%) (1 seizure and 1 rash).

Study 022 and study 304

Amongst the subjects 4 to less than 12 years of age in study 022, 28 of 31 (90.3%) subjects in the rufinamide group and 30 of 33 (90.9%) in the placebo group reported at least 1 TEAE.

The most frequently reported TEAEs in the rufinamide treatment groups were pyrexia (25.8%), vomiting (22.6%), somnolence (16.1%), and diarrhea (12.9%). The PK analyses revealed that patients who experienced somnolence, vomiting, pyrexia, or diarrhea did not have higher rufinamide exposure than patients who did not experience these AEs.

For study 304, the incidence of AEs was 93.1% (27 of 29 subjects) in the rufinamide group and 70.0% (21 of 30) in the placebo group. Frequent AEs that occurred in the rufinamide group were nasopharyngitis (9 of 29 [31.0%] subjects), status epilepticus (8 of 29 [27.6%] subjects), decreased appetite (6 of 29 [20.7%] subjects), somnolence (6 of 29 [20.7%] subjects), and vomiting (5 of 29 [17.2%] subjects).

Serious adverse event / deaths / other significant events

Serious AEs

Ten (10) of 25 (40.0%) subjects in the rufinamide group and 5 of 12 (41.7%) subjects in the any-other-AED group had SAEs. SAEs reported by more than 1 subject were bronchopneumonia (1 subject in each group), seizure (1 subject in the rufinamide group and 3 subjects in the any other AED group), status epilepticus (2 subjects in the rufinamide group), and respiratory distress (2 subjects in the rufinamide group and 1 subject in the any other AED group).

Treatment-related SAEs occurred in 3 subjects in the rufinamide group (pneumonia aspiration, status epilepticus, and bronchopneumonia) and 2 subjects in the any other AED group (seizure and lethargy).

Deaths

In Study 303, an AE leading to death (pneumonia) occurred in 1 subject in the rufinamide group. Study drug was taken until death (994 days of treatment). The subject was a 23-month old male child experiencing a cough, fever, and being described as sleepy. He was subsequently hospitalized owing to an SAE of severe pneumonia and subsequently died despite treatment. The event was considered not related to study drug.

Other significant AEs

Other significant AEs were defined as any AEs resulting in discontinuation of study drug, AEs requiring study drug dose adjustment or interruption, AEs resulting in significant treatment-emergent laboratory abnormality, AEs associated with overdose and other treatment-emergent events of interest (ie, cardiac and ECG).

A total of 2 of 25 (8.0%) subjects in the rufinamide group and 1 of 12 (8.3%) subjects in the any-other-AED group had TEAEs that resulted in discontinuation from study drug. In the rufinamide group, 1 subject discontinued treatment during the Maintenance Phase due to TEAEs of vomiting and decreased appetite and 1 subject discontinued treatment during the Titration Phase due to a TEAE of vomiting. In the any-other-AED group, 1 subject discontinued treatment during the Titration Phase due to a TEAE of rash. Discontinuation due to AE was more frequent in the rufinamide group.

A total of 8 out of the 25 (32.0%) subjects in the rufinamide group and 3 of the 12 (25.0%) subjects in the any other AED group had TEAEs requiring study drug dose adjustment or interruption. The most common TEAEs (occurring in more than 1 subject) in the rufinamide group resulting in dose adjustment or interruption were weight decreased (2 subjects) and decreased appetite (2 subjects). In the any other AED group, seizure (2 subjects) was the only TEAE that occurred in more than 1 subject and resulted in dose adjustment or interruption.

Furthermore, 4 of 25 (16.0%) subjects in the rufinamide group had TEAEs resulting in significant laboratory abnormalities, as defined by the statistical analysis plan: blood bicarbonate decreased (2 subjects), blood triglycerides increased (1 subject), haemoglobin decreased (1 subject), and hypoglycemia (1 subject). One of 12 (8.3%) subjects in the any other AED group had a TEAE of blood bicarbonate decreased.

Other reported TEAEs of special interest in the rufinamide group were weight loss (2 of 25 [8.0%] subjects), skin reactions (5 of 25 [20.0%] subjects), somnolence (5 of 25 [20.0%] subjects), and fatigue (1 of 25 [4.0%] subjects). Reported TEAEs of special interest in the any other AED group were skin reactions and fatigue (1 of 12 [8.3%] subjects each).

Study 022 and study 304

Amongst the subjects 4 to less than 12 years of age in study 022, non-fatal SAEs occurred in 1 subject in the rufinamide group (diarrhoea, upper respiratory tract infection, and vomiting) and 2 subjects in the placebo group (sinusitis in 1 subject and petit mal epilepsy in 1 subject). No SAEs reported in this age group were considered by the investigator to be related to study drug and none resulted in discontinuation from study treatment.

A total of 3 subjects in the rufinamide group (none in the placebo group) prematurely discontinued due to an AE: somnolence (related to study treatment), pneumonia (not related), and dermatitis (related).

For study 304, non-fatal SAEs of drug eruption occurred in 1 subject each in the rufinamide group and the placebo group, both of which were determined by the investigator to be related to study treatment. No other SAEs occurred during the study.

A total of 4 subjects in the rufinamide group and 1 subject in the placebo group had TEAEs that resulted in discontinuation of study treatment.

No data had been collected on TEAEs that required study drug dose adjustment or interruption from study and on AEs of special importance from either study 022 or study 304.

No deaths had been reported during study treatment in either study.

Laboratory findings

Findings related to marked abnormal laboratory values are summarized below. A markedly abnormal laboratory value was defined as, for phosphate, a post-baseline value with an increase from baseline to a grade of 3 or more and for all other parameters, a post-baseline value with an increase from baseline to a grade of 2 or more as defined in the statistical analysis plan.

Haematology

Notably low hemoglobin values were reported for 2 of 25 (8.0%) subjects in the rufinamide group and no subjects in the any other AED group. No other markedly abnormal hematology results were observed.

Clinical chemistry

Notably low values were observed for the parameters of bicarbonate (5 of 25 [20.0%] subjects in the rufinamide group, 4 of 12 [33.3%] subjects in the any other AED group) and glucose (1 of 25 [4.0%] subjects in the rufinamide group, no subjects in the any other AED group). Notably high values of potassium were observed in 2 of 25 (8.0%) subjects in the rufinamide group and no subjects in the any other AED group. No other markedly abnormal clinical chemistry results were observed.

Urinalysis

No changes of clinical importance were reported in mean urinalysis values over time, for any parameter.

Vital Signs, Weight, Physical Examination Findings, and Other Observations Related to Safety

- Vitals Signs

In the 25 rufinamide-treated subjects and 12 subjects treated in the any other AED group, notably low values for systolic blood pressure and diastolic blood pressure were observed for 8 (32.0%) and 7 (28.0%) subjects in the rufinamide group and 1 (8.3%) and 2 (16.7%) subjects in the any other AED group, respectively. Notably high pulse rates were observed for 12 (48.0%) subjects in the rufinamide group and no subjects in the any other AED group. Although there were single instances of clinically notable high and low values for systolic blood pressure, diastolic blood pressure, and pulse rates, occurring at a similar incidence in both treatment groups, none were sustained and none required additional treatment.

- Weight

Notably low and notably high weight values were observed for 7 (28.0%) and 17 (68.0%) subjects in the rufinamide group and 1 (8.3%) and 9 (75.0%) subjects in the any other AED group, respectively. Amongst the 7 cases of weight loss in the rufinamide group, 3 were considered by the MAH as possibly related to the rufinamide treatment. These events were all associated with decreased appetite and/or vomiting, mild or moderated in intensity and spontaneously resolved.

Mean (SD) weight values at baseline for subjects in the rufinamide group and any other AED group were 12.47 (3.24) kg and 13.43 (2.81) kg, respectively. Mean increases in weight from baseline to end of treatment were observed for subjects in the rufinamide group (2.50 [2.91] kg) and the any other AED group (2.79 [3.46] kg).

- ECG and Corrected QT Interval

There were no clinically important changes in mean ECG parameters from baseline to the end of treatment for any treatment group. There were no clinically significant results observed for corrected QT values.

Study 022 and study 304

For the subjects 4 to less than 12 years of age in study 022, mean and median changes in haematology, chemistry and urinalysis values and vital signs between baseline and the termination visit were small, similar in the 2 treatment groups, and not clinically meaningful. There were no data available on laboratory values reported as AEs from study 022. Vital sign-related AEs were observed in 1 of 29 subjects in the rufinamide group (blood pressure increased) and in 2 of 30 subjects in the placebo group (blood pressure increased and blood pressure decreased in 1 subject each). Results were similar between the rufinamide group and the placebo group.

For study 304, there were no serious or significant AEs related to laboratory values. AEs related to laboratory values were observed in 1 of 29 subjects in the rufinamide group (gamma-glutamyltransferase increased) and 3 of 30 subjects in the placebo group (blood lactate dehydrogenase increased, lymphocyte count decreased, platelet count decreased). Vital sign-related AEs were observed in 1 of 29 subjects in the rufinamide group (blood pressure increased) and in 2 of 30 subjects in the placebo group (blood pressure increased and blood pressure decreased in 1 subject each). There were no clinically relevant percent changes in any ECG variable in either treatment group. No ECG abnormalities were observed at any assessment time point.

Safety related to drug-drug interactions and other interactions

No new information in relation to drug-drug interactions was derived from study 303.Analyses from previous studies have shown decreased clearance of rufinamide when co-administered with valproic acid. The effect of valproic acid on the PK of rufinamide may be clinically relevant in extreme circumstances (e.g., in children on high doses of both compounds) and may lead to clinically significant elevation of rufinamide levels (by 70% or more).

Discontinuation due to adverse events

See ‘other significant events’.

Post marketing experience

Rufinamide was first approved via the Centralised Procedure on 16 January 2007 (International Birth Date) in the EU, for adjunctive therapy in the treatment of seizures associated with LGS in patients 4 years and older. Cumulatively, rufinamide 100 mg, 200 mg, and 400 mg tablets have been approved for marketing in over 40 countries, while rufinamide 40 mg/mL oral suspension has been approved for marketing in 34 countries. Rufinamide is sold under the trade names Inovelon and Banzel.

Using the available ex-factory sales data on the number of tablets sold and with the defined daily dose for rufinamide considered to be 1400 mg (World Health Organization daily average consumption estimate), it is estimated that from first product launch through January 2016, there have been approximately 31,000,000 patient-days of exposure in countries where rufinamide is marketed, including 29,000,000 patient-days of exposure to the tablet formulation and 2,050,000 for the oral suspension.

A cumulative search through 07 Jan 2015 of the Eisai rufinamide Global Safety Database (MedDRA version 8.1) was performed for reports of serious and non-serious adverse post-marketing events which occurred in children 4 to 17 years of age as compared to children less than 4 years of age. Since the International Birth Date, there have been 26 spontaneous reports of AEs associated with rufinamide in children less than 4 years of age and 260 reports in children 4 to 17 years of age.

Children 4 to Less than 17 Years of Age

The search returned a total of 260 individual case safety reports including 278 AEs. A total of 92 of the 163 reports met serious criteria. Most events were reported only once. The most frequently reported events

were convulsion (27 reports), vomiting (20 reports), rash (13 reports), nausea (9 reports), status epilepticus (7 reports), abnormal behavior and decreased appetite (6 reports each). The SAEs reported most frequently included convulsion (27 reports), vomiting (10 reports), status epilepticus (7 reports), and rash (5 reports). Most patients had a complete recovery from the event. In the reports where dosage was provided, 800 mg was the dose at which most patients experienced the event. Latency ranged from 1 day to 5 years.

Children 1 to Less Than 4 Years of Age

The search returned a total of 26 individual case safety reports with 49 AEs. A total of 13 of 26 reports met serious criteria. Most events were reported only once. The events reported more than once were convulsion (6 reports), rash (4 reports), decreased appetite (3 reports), and vomiting (2 reports). The only SAE reported more than once was convulsion (6 reports). Most patients had a complete recovery from the event. The majority of the reports did not report the dose administered. The latency ranged from 1 day to 420 days.

During the course of the procedure an update of post-marketing experience was provided for the period of 08 Jan 2015 through 31 August 2016. In the age group of < 4 year olds, the search revealed 8 reports (5 serious) describing 18 AEs. One case of rhabdomyolysis occurred in a 3-year old male patient with positive de-challenge. The investigator classified the event as possibly related to Inovelon therapy. However, due to a past medical history significant for myotonia and concomitant medications which have the potential to cause rhabdomyolysis, the role of rufinamide could not be confirmed. No other case of rhabdomyolysis has been reported with rufinamide.

2.4.1. Discussion on clinical safety

The safety of rufinamide use as adjunctive therapy in the treatment of seizures associated with LGS in patients 4 years of age and older at doses up to 1000 mg/day has previously been evaluated based on data from the pivotal trial 022 and was further supported by post-marketing data and data from study 304. The safety profile in the proposed extended target population of children aged 1 to 4 years with inadequately controlled LGS was evaluated in study 303. In this study, rufinamide was given at doses up to 45 mg/kg/day, which was compared to any other AED at the investigator's choice. The study provided long-term safety data up to 2 years of exposure. However, due to the small size of the trial, only limited support could be derived from the data.

In study 303, the overall incidence of TEAEs was similar in both treatment arms: 22 of 25 subjects (88.0%) in the rufinamide group and 10 of 12 subjects (83.3%) in the any other AED group reported TEAEs. The most frequently reported TEAEs in the rufinamide group (occurring in ≥10% of subjects) were vomiting (28.0%), upper respiratory tract infection (28.0%), pneumonia and somnolence (20.0% each), and sinusitis, otitis media, diarrhoea, cough, and pyrexia (16.0% each) as well as bronchitis, constipation, nasal congestion, rash, irritability, and decreased appetite (12.0% each). In the any other AED group, upper respiratory tract infection (33.3%), diarrhoea, seizure, and pyrexia (25.0% each), and cough (16.7%) were the most common TEAEs (occurring in >1 subject). Approximately half of all subjects in both treatment groups (13 of 25 [52.0%] in the rufinamide group and 6 of 12 [50.0%] in the any other AED group) TEAEs were considered to be possibly or probably related to study drug.

Reported TEAEs of special interest in the rufinamide group were weight loss (2 of 25 [8.0%] subjects), skin reactions (5 of 25 [20.0%] subjects), somnolence (5 of 25 [20.0%] subjects), and fatigue (1 of 25 [4.0%] subjects). Reported TEAEs of special interest in the any other AED group were skin reactions and fatigue (1 of 12 [8.3%] subjects each).

The majority of subjects in both treatment groups had TEAEs that were considered mild (4 of 25 in the rufinamide group and 4 of 12 in the any other AED group) or moderate (14 of 25 in the rufinamide group and 4 of 12 in the any-other-AED group) by the investigators. Both groups had similar overall incidences of

severe TEAEs including 4 subjects (16.0%) in the rufinamide group (1 bronchitis and pneumonia aspiration, 1 encephalitis and pneumonia influenza, 1 pneumonia, and 1 weight decreased). Except for the case that have presented encephalitis and pneumonia influenza, the other cases were considered possibly related to the study drug.

SAEs reported by more than 1 subject were bronchopneumonia (1 subject in each group), seizure (1 subject in the rufinamide group and 3 subjects in the any other AED group), status epilepticus (2 subjects in the rufinamide group), and respiratory distress (2 subjects in the rufinamide group and 1 subject in the any other AED group). Among the SAEs, 5 patients experienced SAEs considered possibly related or related to study drug, including 3 subjects in the rufinamide group (pneumonia aspiration, status epilepticus, and bronchopneumonia) and 2 subjects in the any other AED group (seizure and lethargy). One death occurred in the rufinamide group, but this event (pneumonia) was considered not related to study drug.

No new concerns arose from laboratory values, vital signs and ECGs conducted in patients receiving rufinamide.

Overall, the data from study 303 were consistent with the known safety profile of Inovelon. No new or unexpected risks were identified. Pneumonia and influenza were already listed in section 4.8 of the SmPC of Inovelon as common adverse reactions. Likewise, anorexia, eating disorder, weight decreased, decreased appetite and vomiting are known adverse reactions (common or very common) and listed in section 4.8 of the SmPC as well as in the RMP as important identified risks. The SmPC furthermore includes a warning in relation to status epilepticus and possible treatment discontinuation as cases of status epilepticus have previously been reported in the clinical development involving older children. Precautionary statements in the SmPC furthermore refer to CNS adverse reactions including dizziness, somnolence, ataxia and gait disturbances, as well as hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome. Status epilepticus, rash and hypersensitivity as well as CNS adverse reactions were also recognised as important identified risks in the RMP.

Post-marketing AEs reported in patients aged less than 4 years were consistent with those events that have been seen when rufinamide is used in older patients. Safety data from Study 304 in Japanese patients also did not differ from the known safety profile of rufinamide in LGS patients.

Finally, in study 303, patients received the approved rufinamide oral suspension, which contains 0.3 mg/mL propylparaben. The MAH took the opportunity of this application to address a previous recommendation of the CHMP to consider development of a paraben-free formulation due to concerns around the potential reproductive toxicity of propylparabens in the paediatric population. With reference to the Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use (EMA/CHMP/272921/2012, adopted by CHMP on 22 Oct 2015), and given that the daily doses of propylparaben in rufinamide oral suspension are 13% to 23% of the acceptable daily intake specified in the reflection paper, reformulation of the oral suspension was not considered necessary. This was considered acceptable by the CHMP in line with a previous PRAC recommendation (EMEA/H/C/PSUSA/00002671/201601)..

2.4.2. Conclusions on clinical safety

The results of study 303 showed that rufinamide was well tolerated in subjects aged 1 to less than 4 years. The safety profile of the younger paediatric subjects revealed no new safety concern compared to the known safety profile in older children, adolescents and adults. While the number of patients exposed was too limited to allow detection of rare event or realistic frequency estimations, the CHMP was of the view that the totality of the available safety data was sufficient to support the present application.

2.4.3. PSUR cycle

The PSUR cycle remains unchanged. The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.5. Risk management plan

The CHMP received the following PRAC opinion on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 9.0 with the following content:

Safety concerns

The safety concerns were updated as follows (in bold):

Table 16 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	•Status Epilepticus •Rash and Hypersensitivity •Decreased Appetite and Weight Loss •Coordination Abnormal (Ataxia) •Somnolence •Dizziness / Vertigo •Diplopia and Blurred Vision •Vomiting
Important potential risks	•Pregnancy and Associated Birth Defects •Hematological Dyscrasias including Myelofibrosis ~~**• Infection**~~ •Developmental and Maturation Impairment in Children and Adolescents •Adverse Effects on Cognition •Shortened QT interval on ECG •Suicide • Worsening of seizures and changes in seizure type including withdrawal seizures • Medication errors
Important missing information	• Elderly population • Concomitant medications • Hepatic Impairment

ECG = electrocardiogram, LGS = Lennox-Gastaut Syndrome, QT = Time interval from the onset of the QRS complex to the end of the T wave on an ECG tracing.

The PRAC considered that several preferred terms related to infections (i.e pneumonia, influenza, nasopharyngitis, ear infection, sinusitis and rhinitis) were already listed in section 4.8 of the SmPC with a common frequency. Based on this, the risk of infections was considered to be identified, rather than potential. However, at the same time, the PRAC considered that the types of infections currently described for Inovelon are not key to the benefit risk balance of the product and could be well managed by routine risk minimisation activities. It was thus concluded that infections should be removed from the safety concerns in

the Risk Management Plan. The MAH should continue to follow this risk, in particular severity and seriousness, through routine pharmacovigilance.

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies or activities in the Pharmacovigilance Plan.

Risk minimisation measures

The table of the risk minimisation measures has been updated to reflect the removal of infections from the list of safety concerns.

2.6. Update of the Product information

During the course of the procedure, the MAH decided to no longer pursue an extension to the indication. However, sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are still proposed to be updated to reflect relevant information in paediatric patients aged 1 to less than 4 years as well as data from juvenile animal toxicity studies. The MAH also updated section 5.1 to add additional details relevant to prescribers on the design of study 022, which had previously been assessed at the time of the initial marketing authorisation. In addition, editorial amendments are proposed in several sections of the Product Information.

The Package Leaflet has been updated accordingly.

Changes were also made to the Product Information to bring it in line with the current Agency/QRD template and the SmPC guideline, including the combination of the SmPCs, labelling and Package Leaflets for the three authorised strengths of the tablet formulation, which were reviewed and accepted by the CHMP.

Please refer to Attachment 1 which includes all agreed changes to the Product Information

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the present application did not result in major changes to the package leaflet that would affect formatting or readability of the Package Leaflet.

3. Benefit-Risk Balance

Therapeutic Context

Disease or condition and available therapies

LGS is a rare and severe form of childhood epilepsy with an onset typically between the ages of 3 and 5 years. The disease expression is similar in young children compared to older ones. Prognosis is poor and includes varying severity of epilepsy and cognitive deficits, usually in line with static encephalopathy but mental retardation may get worse with time. Seizure treatment consists of AED polytherapy, but often seizures remain refractory to treatment. The current management of LGS is still not satisfactory and there is a therapeutic need especially in younger patients.

Main clinical studies

Rufinamide is already authorised for the adjunctive treatment of LGS seizures in patients 4 years of age or older based on the result of study 022, which was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel trial comparing the safety and efficacy of rufinamide as add-on therapy relative to placebo in subjects aged 4 to 30 years with inadequately controlled LGS.

With the present application, results from study 303 were provided. Study 303 was a multicenter, randomized, controlled, open-label study including a 2-year evaluation of the safety, PK and efficacy of rufinamide as add-on treatment for control of seizures associated with LGS in subjects 1 to less than 4 years of age compared to any other approved add-on AED of the investigator's choice.

Benefits

Beneficial effects

The primary efficacy variables in study 303 aiming at investigating cognitive and behavioural effects of rufinamide were the Child Behavior Checklist (CBCL) Total Problems score and change from baseline in CBCL Total Problems score at the end of the 2-year (106 weeks) treatment period. LS mean of the CBCL Total Problems score for subjects after 2 years of treatment were 53.75 for the any other AED group and 56.35 for the rufinamide group (LS mean difference [95% CI] +2.60 [-10.5,15.7]; P=0.6928), and the difference between treatments was -2.776 (95% CI: -13.3, 7.8, P=0.5939).

Given that LGS disease expression is similar in younger and older children, there was no reason to expect that the effect of rufinamide on children with LGS between the ages of 1 and 4 would differ from that already demonstrated in older children and adults, although it was noted that the diagnosis of LGS can be challenging in the very young children. The efficacy of Inovelon in the adjunctive seizure therapy of LGS patients 4 years of age or older had already been demonstrated in study 022.

Uncertainty in the knowledge about the beneficial effects

The originally planned study size of 75 patients was reduced to a total of 37 patients (25 treated with rufinamide) due to difficulties in the recruitment related to the rarity of the condition, and the diagnostic process specifically in the younger age group.

In addition, the anticipated minimum difference in CBCL Total Problem Score of at least -17 in favor of rufinamide at the study planning stage was overestimated and clearly out of reach. A difference of +2.6 was in fact observed for the primary clinical endpoint.

The small number of study subjects randomised (and even smaller number of subjects completing the 2-year treatment period of 15/24 subjects in the rufinamide group and 4/12 subjects in the any-other-other AED group) made it difficult to interpret the study results, in particular with regards to efficacy, and the

efficacy results of study 303 were therefore largely inconclusive.

Extrapolation of efficacy from patients aged 4 years and older to the proposed extended age range of 1 to <4 year olds depended on the population PK analyses aiming at establishing a suitable dose in the latter age range. A coarse model was initially selected for the PK analysis based on data from LGS patients. While the CHMP appreciated that a more complex model was not feasible due to the scarcity of the underlying data (115 patients), such model did not allow testing for differences in absorption, distribution and elimination by age and would not lead to a comprehensive analysis of PK changes by age. Furthermore, no exposure-response relationship was evidenced in young children.

In response to these concerns, a new PK model based on a larger dataset (1182 subjects, including data from healthy volunteers and patients with other forms of epilepsy) was provided. However, while in principle such enlarged model could bring useful information on rufinamide PK in children below the age of 4 years, the model as presented at the time of this report was not considered mature enough for comparative dose-exposure analyses across age groups. Several issues with the final model including the lack of addressing dose dependency of absorption and prediction power had not been adequately addressed. Likewise, a discrepancy between the coarse and the new enlarged model with regards to CL/F was noted that could not be explained by differences in the two model population characteristics.

Risks

Unfavourable effects

Study 303 provided up to 2 years of exposure data and the safety evaluation revealed no new safety concern in patients aged 1 to less than 4 years with seizures associated with LGS compared to the established safety profile in older patients. In patients aged over 4 years, the most commonly reported adverse reactions were headache, dizziness, fatigue, and somnolence. The most common adverse reactions observed at a higher incidence than placebo in previous studied in LGS patients were somnolence and vomiting.

In study 303, the most frequently reported TEAEs in patients exposed to ralfinamide were vomiting (28.0%), upper respiratory tract infection (28.0%), pneumonia and somnolence (20.0% each), and sinusitis, otitis media, diarrhoea, cough, and pyrexia (16.0% each) as well as bronchitis, constipation, nasal congestion, rash, irritability, and decreased appetite (12.0% each). Similar to previous studies in patients aged 4 years and older, the majority of TEAEs in study 303 were mild to moderate in severity. Rufinamide was generally well tolerated. There were no new pertinent data concerning dermatological events and hypersensitivity or status epilepticus. Other important identified risks in the RMP also remained unchanged, including decreased appetite and weight loss, coordination abnormal (ataxia), somnolence, dizziness / vertigo, diplopia and blurred vision, and vomiting. Overall, adverse reactions observed in study 303 were already adequately covered by the current safety information in the product information and the RMP.

Uncertainty in the knowledge about the unfavourable effects

While the safety profile of rufinamide observed in study 303 was consistent with the previously established profile in older patients, the study size was very small, which is explained by the rarity of the disease. The number of patients exposed was thus too limited to allow detection of rare event or realistic frequency estimations.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

While the efficacy results of study 303 were difficult to interpret and largely inconclusive, mainly due to the small study size, the CHMP noted that LGS disease expression was similar in younger patients compared to older ones and thus, there was no reason to expect that the effect of rufinamide in children between the ages

of 1 and 4 years would differ from that already demonstrated in older children and adults. As a consequence, efficacy as established in the adjuvant therapy of seizures in patients ≥ 4 years affected by LGS could in principle be extrapolated to patients aged <4 years, provided the dose was established. A population modelling approach was used to characterize the PK profile of rufinamide in subjects with inadequately controlled LGS and to compare exposure in the paediatric population aged 1 to less than 4 years to older patients. However, the available models at the time of this report were not considered suitable to generate reliable exposure predictions, which would have been needed to derive sound dose recommendation in the new proposed age group. The CHMP recommended for the MAH to advance the knowledge of PK properties of the product and re-develop a qualified/validated population PK model with an adequate predictive power to describe the PK of rufinamide in children. The systemic exposure in young children 1-2 years and 2-4 years should be estimated accordingly and compared to that observed in older children to inform any dose recommendation below 4 years of age.

In terms of safety, rufinamide was well tolerated in subjects 1 to less than 4 years of age. The findings of the safety evaluation in study 303 were consistent with the known safety profile of rufinamide established in LGS patients aged 4 years and older. No new or unexpected risks were identified.

Benefit-risk balance

As a consequence of the outstanding concerns with the population PK simulations at the time of this report, the CHMP was of the view that the available comparative dose-exposure analyses across age groups were not reliable enough to derive sound dose recommendations in the new proposed age group of 1 to <4 year olds. For this reason and since the results of study 303 were largely inconclusive with regards to efficacy, the CHMP considered that a positive benefit-risk balance of rufinamide in the add-on treatment of seizures in LGS patients aged 1 to <4 years could not be concluded at this point in time.

In light of the CHMP view at the time of this report, the MAH decided to no longer pursue an extension of the indication and the outstanding issues with the model were not further addressed. However, the application to update the product information with relevant paediatric data was maintained, which was considered acceptable by the CHMP. The CHMP furthermore recommended that the MAH should re-develop a qualified/validated population PK model.

The benefit-risk balance of Inovelon in the approved indication in patients 4 years of age and older with LGS remained positive.

Discussion on the Benefit-Risk Balance

Not applicable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Update of sections 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC in order to include additional information relevant to the paediatric population based on the results of study 303 in patients aged 1 to less than 4 years with Lennox-Gastaut Syndrome and the results from toxicity studies in juvenile animals. Section 5.1 was furthermore updated to add additional information on the design of study 022 in LGS patients aged 4 years and older. Additional editorial amendments were made to SmPC sections 4.4 and 4.6. The Package Leaflet has been updated accordingly. Furthermore, the PI was brought in line with the latest QRD template and the SmPCs, Labelling and Package Leaflets for the three authorised strengths of the tablet formulation were combined. An updated RMP version 9.0 was agreed as part of the procedure.

The variation leads to amendments to the Summary of Product Characteristics, labelling and Package Leaflet and to the RMP.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0116/2016 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.