28 June 2018
EMA/491276/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inovelon

International non-proprietary name: rufinamide

Procedure No. EMEA/H/C/000660/II/0045

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
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CBCL	Child Behavior Checklist
CI	confidence interval
CRF	case report form (includes paper and electronic)
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GOF	Goodness-Of-Fit
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LDS	Language Development Survey
LGS	Lennox-Gastaut syndrome
LNH	low/normal/high
LOCF	last observation carried forward
LS	least squares
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mod	moderate
N	within laboratory parameter's reference range
NC	not calculated
NR	not related
PI	principal investigator
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
poss	possibly related
prob	probably related
PT	preferred term
QoL	quality of life
QoLCE	Quality of Life in Childhood Epilepsy
QTC	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
TESAE	treatment-emergent serious adverse event
Tx	treatment
WBC	white blood cell
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary
WR	Written Request

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 30 August 2017 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 the treatment of seizures associated with Lennox Gastaut syndrome in patients 1 year of age and older as adjunctive therapy; as a consequence sections 4.1, 4.2, 4.5, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 10.0) are updated accordingly. In addition the Marketing Authorisation Holder (MAH) took the opportunity to make small corrections with the Product Information and to update the name and contact details of the local representative in Belgium and Luxembourg. Furthermore, the Product Information is brought in line with the latest QRD template version 10.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and Risk Management Plan.

Information relating to orphan designation

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

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

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0116/2016 was completed.

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 and regulatory interactions

The applicant did not seek Protocol Assistance at the CHMP.

The MAH met the CHMP Co-rapporteur Team (MPA) within the framework of a Pre-submission Meeting on 12-May-17.

The purpose of the meeting was to discuss all outstanding issued listed as major objections in the CHMP Rapporteur's final assessment report for the Type II variation application procedure EMEA/H/C/000660/II/0037. This application was submitted in February 2016 to facilitate modification of the then (and presently) approved indication to extend the use of rufinamide from patients 4 years and above to 1 year and above.

From the discussions/minutes, it seems that the MPA supported the approach of using a sparse sampling design and agreed that it is not possible to fully elucidate rufinamide absorption.

It was acknowledged by MPA that exposures have been sufficiently demonstrated to be similar in the different age groups.

However, concerning the visual predictive checks (VPC), MPA was of the opinion that the PK analysis contained vague model prediction intervals and added they would like to see more elaborate VPCs with prediction intervals for the central tendency and outer percentiles. A minimum of 100 replicates of simulation were requested. Eisai pointed out that the prediction-corrected VPCs as presented in PPK Report CPMS-E2080-003R-v1, without prediction intervals for the central tendency and outer percentiles, alongside the goodness-of-fit plots and model validation results are adequate to support the qualification and validity on the final developed PPK model.

Pertaining to this request, Eisai pointed out that there appears to be some divergent opinions or misalignment in regard to requirements concerning data analysis/interpretation within the Agency (EMA). This is owing to the fact that the current prediction-corrected VPCs in the PPK report were performed in accordance with the request of the assessor from the rapporteur's team to perform VPCs as described in the publication: (Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models AAPS J. 2011; 13(2):143-51). This means any amendments made to satisfy MPA may not satisfy the assessors from ANSM. MPA advised they would raise this point at their upcoming working party meeting so steps can be taken to avoid this in the future.

Further, MPA requested Eisai provide an explanation as to why rufinamide exposure and relative viability was higher in the first model provided in CPMS-E2080-002R-v2 compared to that in the second model in CPMS-E2080-003R-v1. They also noted that exposure seemed to vary with body weight.

Finally, MPA advised Eisai to revisit the elementary scaling components which appear to be lower than 0.75 and in the steady state model about 0.83.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	30 August 2017
Start of procedure:	16 September 2017
CHMP Co-Rapporteur Assessment Report	10 November 2017
CHMP Rapporteur Assessment Report	13 November 2017
PRAC Rapporteur Assessment Report	17 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	6 December 2017
Request for supplementary information (RSI)	14 December 2017
CHMP Rapporteur Assessment Report	30 April 2018
PRAC Rapporteur Assessment Report	3 April 2018
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur Assessment Report	N/A
Request for supplementary information	31 May 2018
CHMP Rapporteur's preliminary assessment report circulated on:	15 June 2018
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	N/A
CHMP opinion:	28 June 2018

2. Scientific discussion

Rufinamide film-coated tablets were first approved in the EU via the Centralised Procedure in the European Commission (EC) decision dated 16 January 2007 for use as adjunctive therapy in the treatment of seizures associated with LGS in patients 4 years of age and older.

The purpose of this Type II variation is to expand the existing product label to include treatment of seizures associated with Lennox-Gastaut Syndrome in paediatric patients 1 year of age and older. The current extension of Indication was initially requested in application EMEA/H/C/000660/II/0037 submitted to the European Medicine's Agency (EMA) on 10 Feb 2016.

This new application is based on:

- Study CRUF331-0022: Study 022, a single, pivotal, multicenter, double-blind, placebo-controlled, randomized, parallel-group study) comparing the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in subjects 4 to 35 years of age with inadequately controlled LGS.
- Study E2080-G000-303: 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 LGS.

- A revised population PK analysis and Module 2.7.2 (CPMS-E2080-003R-v2 / Population Pharmacokinetics of Rufinamide in Subjects With Epilepsy Including Inadequately Controlled Lennox-Gastaut Syndrome (Studies E2080-G000-303, CRUF331 0022 and E2080-J081-304)) to address concerns highlighted in the Agency's final assessment report of initial application EMEA/H/C/000660/II/0037 relating to the indication extension.

Overall, at the time of the initial Application, 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. This was mainly due to the outstanding concerns with the population PK simulations and the largely inconclusive results of study 303 with regards to efficacy. Indeed, the available PK data and simulations 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. The CHMP furthermore recommended that the MAH should re-develop a qualified/validated population PK model.

In light of this CHMP view, the MAH decided to no longer pursue an extension of the indication and the outstanding issues with the model were not further addressed. Moreover, the decision to no longer pursue the extension of indication was also made as the applicant aimed to obtain an extension to the marketing exclusivity of rufinamide, which could not have been reached within the Application timeframe, as it was apparent a resolution could not be reached.

Thus, the scope of the current application is to fulfil the CHMP recommendation by submitting a revised population PK analysis (CPMS-E2080-003R-v2) to address concerns highlighted in the Agency's final assessment report of initial application EMEA/H/C/000660/II/0037. The current Type II variation includes among other things a graphical presentation of observed data from Study 303 superimposed with data from Studies 022 and 304 to demonstrate comparability in steady state exposure to rufinamide in LGS subjects from 1 to less than 4 years old to that in LGS subjects 4 years old and above.

For the Efficacy and Safety parts of rufinamide for the proposed paediatric population, the applicant considers that these parts has been extensively discussed during the initial application EMEA/H/C/000660/II/0037 and that conclusions should be drawn from it to support the efficacy and safety parts. Given that no additional efficacy/safety data have been submitted in the scope of the current application, the applicant proposal seems to be acceptable. Thus, CHMP discussion and conclusion from the initial application, especially those related to the efficacy and safety part, are included in the corresponding sections of this report.

Of note, from a regulatory point of view, the initial application to update the product information with relevant paediatric data was maintained, as this was considered as acceptable by the CHMP. Indeed, the benefit-risk balance of Inovelon in the approved indication in patients 4 years of age and older with LGS remained positive. The CHMP recommends the variation to the terms of the Marketing Authorisation concerning the change/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.

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.

2.2. Non-clinical aspects

2.2.1. Introduction

To support the application for an extension of the target population for Inovelon to patients aged 1-4 years, the MAH provided previously 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. These studies were evaluated during the previous variation EMEA/H/C/000660/II/0037.

A total of 3 pivotal toxicity studies were performed in juvenile animals, one in rats and two in dogs. Juvenile rats were 7 days of age at treatment initiation, which is equivalent to a human neonate based on an interspecies comparison of CNS and reproductive development. The youngest juvenile dogs were 6 weeks at treatment initiation, which is equivalent to a 2-year old human based on the same parameters. Therefore, it patients aged 1-4 years are covered by these studies. The latter did not identify an increased sensitivity of juvenile animals to the toxicity of rufinamide, and showed that the target organs were the same as in adults (liver in both species, and kidneys in rats). Overall, it is considered that the available nonclinical package supports the extension of indication to patients aged 1-4 years.

Concerning the Environmental risk Assessment, no new study has been included in this submission. The applicant proposed a new refined Fpen and consequently a new phase II ERA and he answered to CHMP request about the timeline on study concerning the sediment dwelling organism and classification of rufinamide as very persistent compound.

2.2.2. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): Rufinamide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	OECD107 or …	0.65			Potential PBT: **No**
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	0.65			not B
	BCF	not available			B/not B
Persistence	DT50 or ready biodegradability	DT50=196			vP
PBT-statement :					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*Koc = 12.2 mL/g* *Koc = 14.7 mL/g* *Koc = 43.5 mL/g* *Koc = 118.0 mL/g* *Koc = 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	Rufinamide $DT_{50, water}$ = 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) Transformation product $DT_{50, water}$ = 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/*Species*	OECD 201	NOEC	>33	µg/L	*Selenastrum capriconutum*
Daphnia sp., Acute toxicity test	OECD 202	NOEC	>100	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	16	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	25	µg/L	*Pimephales prometas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	100	µg/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

Phase 1: Estimation of exposure

Refined Fpen

The applicant submitted an estimation for the years 2017 to 2021 of the predicted amount of the drug substance (rufinamide) consumed in the EU-G5 and in the EU as a whole, as a result of the use of Inovelon Tablets and Inovelon Oral Suspension, both of which are indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 1 year and older.

The maximum total consumption of rufinamide in a single year in the EU-G5 (2017-2021) from the use of Inovelon Tablets and Inovelon Oral Suspension has been projected to be 3,093,013,066 mg + 14,741,256 mg = 3,107,754,322 mg for the year 2018.

Therefore, the refined market penetration Fpen (%) is calculated as:

Refined Fpen % = (Consumption x 100)/(DOSEai x EU-G5 inhabitants x 365)
Refined Fpen % = 3,107,754,322 mg x 100 / 3200 mg x 323,990,731 x 365

Refined Fpen % = 0.0008

PEC surface water calculation

According to the guideline, the PEC surfacewater is calculated as follows:

PECsurfacewater (mg/L) = (DOSEai x Refined Fpen)/(WASTEWinhab x DILUTION)
PECsurfacewater (mg/L) = (3200 x 0.000008)/(200 x 10)
PEC surface water (µg/L)=0.0128 µg/L

Table 1 Information Supporting the Estimates for the Years 2017 to 2021 of the Predicted Amount of the Drug Substance, Rufinamide, Consumed in the EU-G5 and in the EU as a Result of the Use of Inovelon Tablets and Inovelon Oral Suspension

	Input Fields	Reference	2017	2018	2019	2020	2021
INOVELON							
Total population EU-G5		1	322,750,999	323,990,731	325,087,195	326,087,790	327,013,133
Prevalence LGS	0.009%	2	0.009%	0.009%	0.009%	0.009%	0.009%
Prevalent Population LGS			29,048	29,159	29,258	29,348	29,431
Consultation rate for LGS	100%	3	100%	100%	100%	100%	100%
Number of consulting patients			29,048	29,159	29,258	29,348	29,431
Drug treated rates	100%	4	100%	100%	100%	100%	100%
Number of drug treated patients			29,048	29,159	29,258	29,348	29,431
Number of average treatment days per year per patient	250	5	250	250	250	250	250
Eisai product treatment days (EU-G5)			2,198,822	2,209,295	1,948,166	1,560,961	1,287,176
Eisai product market share (LGS)(EU-G5)		6	30.3%	30.3%	26.6%	21.3%	17.5%
Total mg Inovelon EU-G5			3,078,350,282	3,093,013,066	2,727,432,619	2,185,344,835	1,802,045,928
Total mg Inovelon Rest of Europe			1,251,336,254	1,459,655,606	1,357,686,605	1,177,630,356	945,800,379
Total mg Inovelon EU			4,329,686,536	4,552,668,672	4,085,119,224	3,362,975,191	2,747,846,307
Average dose per day (mg)	1400	7	3,092,633	3,251,906	2,917,942	2,402,125	1,962,747
Suspension share of daily doses		8	23%	25%	25%	25%	25%
INOVELON SUSPENSION substance amount in EU-G5 (mg)			708,020,565	773,253,267	681,858,155	546,336,209	450,511,482
INOVELON SUSPENSION substance amount in Rest of Europe (mg)			287,807,338	364,913,901	339,421,651	294,407,589	236,450,095

Inovelon Forecast of patients aged 1 - 3 years								
	Input Fields	Reference	2017	2018	2019	2020	2021	2022
INOVELON								
Total population EU-G5		1	9,730,910	9,749,508	9,798,930	9,828,708	9,864,179	9,864,386
Prevalence LGS	0.009%	2	0.009%	0.009%	0.009%	0.009%	0.009%	0.009%
Prevalent Population LGS			876	877	882	885	888	888
Consultation rate for LGS	100%	3	100%	100%	100%	100%	100%	100%
Number of consulting patients			876	877	882	885	888	888
Drug treated rates	100%	4	100%	100%	100%	100%	100%	100%
Number of drug treated patients			876	877	882	885	888	888
Number of average treatment days per year per patient	250	5	250	250	250	250	250	250
Eisai product treatment days (EU-G5)			10,509	10,529	10,583	10,615	10,653	10,654
Eisai product market share (LGS)(EU-G5)		6	4.8%	4.8%	4.8%	4.8%	4.8%	4.8%
Total mg Inovelon EU-G5			14,713,136	14,741,256	14,815,982	14,861,006	14,914,639	14,914,952
Total mg Inovelon Rest of Europe			8,276,139	8,291,957	8,333,990	8,359,316	8,389,484	8,389,660
Total mg Inovelon EU			22,989,275	23,033,213	23,149,972	23,220,323	23,304,123	23,304,612
Average dose per day (mg)	1400	7	16,420	16,452	16,535	16,585	16,645	16,646
Suspension share of daily doses		8	100%	100%	100%	100%	100%	100%
INOVELON SUSPENSION substance amount in EU-G5 (mg)			14,713,136	14,741,256	14,815,982	14,861,006	14,914,639	14,914,952
INOVELON SUSPENSION substance amount in Rest of Europe (mg)			8,276,139	8,291,957	8,333,990	8,359,316	8,389,484	8,389,660

[1] *Eurostat website (2017) http://ec.europa.eu/eurostat, with appropriate population growth rate applied*
[2] *EMEA/COMP Summary Report on an application for Orphan Medicinal Product Designation, COMP/390/03, 2004.*
[3] *Assumption based on market intelligence*
[4] *Assumption based on market intelligence*
[5] *Assuming ~70% adherence based on references Goodman MJ, Durkin M, Forlenza J, Ye X, Brixner DI. Assessing adherence-based quality measures in epilepsy, Int J Qual Health Care. 2012 Jun;24(3):293-300*
[6] *Estimate based on market intelligence*
[7] *WHO DDD dose, code: N03AF03, http://www.whocc.no/atc_ddd_index/?code=N03AF03&showdescription=yes*
[8] *Estimate based on Eisai internal sales data*

Table 2 Values Supporting the Calculation of Refined Fpen for Rufinamide from the Use of Inovelon Tablets and Inovelon Oral Suspension Combined

Input Value	Abbreviation	Value	Unit
Maximum Projected Consumption (Use) of Drug Substance in EU-G5 (at Year 2017)	-	3,107,754,322	mg/year
Maximum daily dose (according to SmPCs)	$DOSE_{ai}$	3200	mg/inh/day
Inhabitants (at Year 2017; based on EUROSTAT projection)	Inhab	323,990,731	EU-G5 inhabitants

As shown in Table 1 and **Table 2**, the maximum total consumption of rufinamide in a single year in the EU-G5 (2017-2021) from the use of Inovelon Tablets and Inovelon Oral Suspension has been projected to be 3,093,013,066 mg + 14,741,256 mg = 3,107,754,322 mg for the year 2018. EU-G5 member states are projected to have the highest per capita use/consumption in the EU, and therefore present a worst-case scenario for environmental exposure to rufinamide. The number of EU-G5 inhabitants at year 2018 is based on the EUROSTAT projection of 323,990,731 inhabitants.

Therefore, the refined market penetration Fpen (%) is calculated as:

$$\text{Refined } F_{pen}\ \% = \frac{\text{Consumption} \times 100}{\text{DOSEai} \times \text{EU-G5 inhabitants} \times 365}$$

$$\text{Refined } F_{pen}\ \% = \frac{3{,}107{,}754{,}322 \text{ mg} \times 100}{3200 \text{ mg} \times 323{,}990{,}731 \times 365}$$

$$\text{Refined } F_{pen}\ \% = 0.0008$$

$$\text{Refined } F_{pen} = 0.000008$$

The calculation of the $PEC_{SURFACEWATER}$ for rufinamide is shown below with the values supporting the calculation provided in Table 3.

$$PEC_{SURFACEWATER} = \frac{DOSE_{ai}}{WASTEW_{inhab}} \times \frac{\text{Refined } F_{pen}}{\text{DILUTION}}$$

$$PEC_{SURFACEWATER}\ (mg/L) = \frac{3200}{200} \times \frac{0.000008}{10}$$

$$PEC_{SURFACEWATER}\ (\mu g/L) = 0.0128\ \mu g/L$$

Table 3 Values Supporting the Calculation of $PEC_{SURFACEWATER}$ of Rufinamide in EU-G5, Based on Marketing Projections for Inovelon Oral Suspension.

Input Value	Abbreviation	Value	Unit
Maximum daily dose of rufinamide (based on SmPCs for Inovelon drug products)	$DOSE_{ai}$	3200	mg/inh/day
Refined market penetration factor	Refined F_{pen}	0.000008	-
Amount of waste water per inhabitant per day	$WASTE_{inhab}$	200	L [default value]
Dilution from Sewage Treatment Plant	DILUTION	10	[default value]

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

PNEC values are similar to that of the previous assessment report

Derivation of PNEC values

	Based on	Assessment factor	PNEC value (µg/L)
PNEC water	NOEC *Daphnia* reproduction test	10	1600
PNEC microorganism	NOEC respiration inhibition	10	10000
PNEC groundwater	NOEC *Daphnia* reproduction test	10	1600

PEC groundwater

PEC groundwater is calculated as:

PEC groundwater = 0.25 x PEC surfacewater (0.0128µg/L)

Hence, **PEC groundwater for rufinamide is 0.0032 µg/L**.

PEC/PNEC ratios

Ratio	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC	Trigger
PECsurfacewater/PNECwater	0.0128	1600	0.000008	1
PECsurfacewater/PNECmicroorganism	0.0128	10000	0.00000128	0.1
PECgroundwater/PNECgroundwater	0.0032	1600	0.000002	1

Outcome of Phase II Tier A fate and effect analysis.

Using the refined Fpen value for the PEC calculations,

All the PEC/PNEC ratio are all below the trigger value, therefore, it can be concluded that rufinamide and/or its metabolites are extremely unlikely to represent a risk to the aquatic environment, groundwater compartiment or for the microorganism.

The log Kow of rufinamide is significantly <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.

Koc : In a GLP-compliant OECD Guideline 106 study, the adsorption-desorption behavior 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.

Further water/sediment fate and effects investigations will be undertaken as a post authorization commitment. The transformation product observed in Project 500465 Aerobic Degradation of Rufinamide in Two Water/Sediment Systems will be identified in a specifically designed water/sediment study. This transformation product has already been quantified in the water layer and in the sediment in Project 500465 in both water/sediment systems over 99 days. Further quantification of this transformation product in OECD 308 water/sediment systems is not considered necessary for the environmental risk assessment.

In line with EMA Questions and answers on 'Guideline on the environmental risk 26 May 2016), the company plans to perform an OECD 218 Sediment-Water Chironomid Toxicity Test Using Spiked Sediment with 14C-radiolabelled rufinamide (parent compound) as the test substance. This is considered to be optimal for risk assessment purposes as the chironomid test organisms will be exposed to both rufinamide and the transformation product in the test system. As shown in Project 500465, the transformation product is rapidly formed in both the water layer and the sediment. In the OECD 218 study, it is planned that the water layer, pore water and sediment layer will be analysed for radioactivity, rufinamide and the identified transformation product.

As a post authorization commitment, the applicant proposed the following timelines for Conducting Studies

- 1Q FY2018: - synthesis of radiolabelled rufinamide
- 2Q FY2018 to 4Q FY2018: Conduct OECD 218 study along with associated investigations as detailed in Company Response
- Provide updated ERA with study report(s) from 4Q FY 2018

2.2.3. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

Juvenile toxicity studies in rats and dogs has previously been submitted and assessed in the initial MAA (EMEA/H/C/000660) and in a previous Type II variation (EMEA/H/C/000660/II/0037).

Altogether a total of 3 pivotal toxicity studies with rufinamide have been performed in juvenile animals; one 10-week study in rats aged 7 days at treatment initiation, one 13-week study in dogs aged 4 months at treatment initiation, and finally one 14-week study in dogs aged 6 weeks at initiation of treatment.

The 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. No effect on behavioural and physical development was observed in juvenile rats, and there were no effects on neuro-behavioural, brain measurement or bone parameters in juvenile dogs.

Based on an interspecies comparison of CNS and reproductive development, the paediatric age range from 1 to 4 years have been adequately covered by these studies.

Relevant information is included in section 5.3 of the SmPC and no further updates are needed.

Environmental risk assessment:

The updated ERA including the Phase II Tier A analysis are considered acceptable. All PEC/PNEC ratios were significantly below the trigger values. 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} effects on sediment dwelling organisms should be investigated in an OECD 218 Sediment-Water Chironomid Toxicity Test Using Spiked Sediment with 14> 1 year). Therefore, 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. The Applicant is recommended to perform these studies post approval.

According to the OECD 308 study, DT50, water = 196 days which is over the threshold of classification “very persistent”, therefore the CHMP considers that rufinamide has to be classified as very persistent in the environment.

2.2.4. Conclusion on the non-clinical aspects

The studies performed with rufinamide in juvenile animals adequately cover the proposed paediatric target population of Inovelon.

The results of the OECD 308 study clearly show that the major transformation product (Region 2, RT 17,90 min, HPLC, SL water, after 64 d) of rufinamide fulfils the criteria for very persistent in water-sediment-systems based on a DT50 >1 year at 12 °C (196/ 473 d at 20 °C). Consequently, in the CHMP’s view rufinamide has to be classified as very persistent in the environment. The information on the classification of rufinamide as very persistent in the environment is reflected in the SmPC section 5.3.

Furthermore, the following measures are considered necessary to address non-clinical issues:

Effects on sediment dwelling organisms should be investigated in an OECD 218 Sediment-Water Chironomid Toxicity Test Using Spiked Sediment with ^{14}a specifically designed water/sediment study should be conducted to identify this transformation product. In addition, the C-radiolabelled rufinamide (parent compound) as the test substance should be identified. The applicant is expected to submit the result of this study during 2018.

2.3. Clinical aspects

2.3.1. Introduction

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 Overview of clinical studies

Study ID	**Design; Control Type**	**Number of Study Centers (Locations)**	**# Subjects by Arm; Entered/ Completed**	**Gender Male/Female; Mean Age (Range); Race (if available)**	**Study and Control Drugs Dose, Route, Regimen**	**Primary Efficacy Endpoint(s)**
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 pediatric subjects 1 to less than 4 years of age with inadequately controlled LGS	19 (US, Canada, France, Greece, Italy, Poland)	rufinamide: 25/15 comparator (any-other-AED): 12/4	rufinamide: 14/11 28.3 months (12 to 46 months) 23 white, 2 black comparator (any-other-AED): 10/2 29.8 months (13 to 47 months) 9 white, 2 black, 1 other	rufinamide: up to 45 mg/kg/day, in 2 divided doses, administered as OS (40 mg/mL) comparator: 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	CBCL Total Problems Score at the end of the 2 year treatment period.
Study 022	A Phase 3, multicenter, randomized, double-blind, placebo controlled, parallel trial comparing the safety and efficacy of rufinamide as adjunctive therapy	43 (Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, US)	rufinamide: 74/64 placebo: 64/59	rufinamide: 46/28 14.5 years (4 to 35 years) 62 white, 6 black, 6 other placebo: 40/24 13.6 years (4 to 37 years) 53 white, 4 black, 7 other	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 dosage was titrated to approximately 45 mg/kg/day	1: the percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase 2: percent change in tonic-atonic

	relative to placebo in subjects with inadequately controlled LGS				over a 1to 2-week period placebo: administered orally, as matching tablets (to 100, 200, or 400 mg rufinamide) in a twice daily dosage regimen, according to the same titration schedule as that used for rufinamide.	seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase 3: the seizure severity rating at the end of the Double-blind Phase
Study 304	A Phase 3, placebo controlled, double-blind, comparative study of rufinamide in subjects with LGS	22 sites in Japan	rufinamide: 29/25 placebo: 30/29	rufinamide: 17/11 16.0 years (5 to 30 years) placebo: 19/11 13.9 years (4 to 29 years)	rufinamide: 100 and 200 mg tablets orally administered twice daily, after breakfast and after dinner placebo: 100 and 200 mg tablets orally administered twice daily, after breakfast and after dinner	Percent change in tonic-atonic seizure frequency

2.3.2. Pharmacokinetic Modelling

The current Type II variation includes the data from population PK Study 303 completed in subjects with LGS from 1 to less than 4 years old, and also makes comparisons with the PK data in subjects with LGS and other types of epilepsy 4 years old and above who were evaluated in previous clinical studies. Additionally, an update of the population-PK modelling including paediatric data (1-4 years) and other data collected in older children, adolescent and adults are also provided. For reminder, the basic scatter plot of concentrations observed in young and older children are reported and briefly commented as it was part of the earlier submission. However, the present report will focus on the new population-PK analysis (CPMS-E2080-003R-v2).

Studies included in the population PK and times for blood sampling for PK analysis are shown below:

- ***Study AE/ET1***: before the morning dose at all visits during the double-blind period and between 1-2, 2-4, 4-6, and 6-10 hours post morning dose, and before the evening dose at Visit 7 (Day 4).
- ***Study AE/PT2***: pre dose samples at all visits during the double-blind period and at pre-dose, and at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours, post dose at Visits 2 (Day 1) and 7 (Day 35) during the 2 single-dose periods.
- ***Study CRUF331 0016***: before the morning dose, and between 1-2 and 2-4 hours after the morning dose at Visits 3 (Day 14) and 6 (Day 63).
- ***Study CRUF331 0018***: anytime at Visits 2 (Day 14), 4 (Day 56), and 6 (Day 112).
- ***Study CRUF331 0021***: (adult and paediatric strata) anytime at Visits 3 (Day 14), 4 (Day 35), 5 (Day 63), and 6 (Day 91).
- ***Study CRUF331-0022***: anytime at Visits 4 (Day 28) and 6 (Day 84).
- ***Study CRUF331 0027***: before the morning dose, and at 2, 4, 6, 8, 10, 12 hours after the morning dose at Visits 3 (Day 7) and 4 (Day 14).
- ***Study E2080-G000-303***: Sparse PK samples were collected during the Maintenance Period as follow:
    - Visits 4, 6, and 8: one sample during a morning visit to the clinic during Weeks 2, 8, and 24.
    - Visits 5 and 7: one sample during an afternoon visit to the clinic during Weeks 4 and 16.
- ***Study E2080-J081-304:*** one sparse PK sample per visit was collected at any time on Days 28, 56, and 84 of treatment during the maintenance period, or when a subject was terminated from the study.
- ***Study E2080-E044-003:*** Blood samples were collected at pre-dose (within 60 minutes before dosing) and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48, and 72 hours after study drug administration.

The PK analysis was conducted using 7272 rufinamide plasma concentration observations from a total of 1182 subjects. For Studies 303, 304, and 022 in LGS subjects, 340 rufinamide plasma concentrations from 154 LGS subjects were available. Other studies contributed 6932 observations from 1028 subjects. Summaries of the demographics and other covariates are presented below in **Table 5**. A summary of the co-administered AED is given in Table 6.

Table 5 Summary of Demographics and Covariates in the Population PK Analysis of Rufinamide (N=1182)

Covariate (unit)	Mean (SD)	Median	Range (Min - Max)
Age (years)	30.1 (14.9)	30.7	1.0 – 76.9
1 to <2 (n=11)	*1.54 (0.4)*	*1.7*	*1.0 – 1.99*
2 to <4 (n= 19)	*3.1 (0.5)*	*3.1*	*2.2 – 3.95*
4 to <8 (n=59)	*6.0 (1.3)*	*6.0*	*4.0 – 7.97*
8 to <12 (n=80)	*9.8 (1.2)*	*9.9*	*8.0 – 11.92*
12 to <18 (n=118)	*14.6 (1.6)*	*14.4*	*12.0 – 17.93*
18 and older (n=895)	*36.5(10.9)*	*35.7*	*18 to 76.9*
Weight (kg)	64.0 (23.0)	65.6	7.0 – 140.9
1 to <2 (n=11)	*10.7 (2.0)*	*11.1*	*7.0 – 14.5*
2 to <4 (n=19)	*15.0 (2.9)*	*15.4*	*9.8 – 20.2*
4 to <8 (n=59)	*23.2 (5.67)*	*22.0*	*15.5 – 39.1*
8 to <12 (n=80)	*32.9 (9.4)*	*31.8*	*18.0 – 58.5*
12 to <18 (n=118)	*53.4 (21.0)*	*49.0*	*23.0 – 138.5*
18 and older (n=895)	*72.5 (16.1)*	*71.6*	*34.6 – 140.9*
Alanine transaminase[a] (IU/L)	18.2 (12.2)	16.0	0.05 -84
Alkaline Phosphatase[b] (IU/L)	238.3 (239.6)	165.0	1.5 – 1828
Aspartate transaminase[a] (IU/L)	18.9 (9.6)	18.0	0.15 – 95.4
Total bilirubin (mg/dL)[b]	0.60 (1.21)	0.35	0.1 – 10.3
Creatinine Clearance[b] (mL/min)	96.2 (35.9)	93.7	22.9 - 258
Daily Dose (mg)	1188.2 (870.3)	800	160 - 4400
Formulation	RC=537 ; WP=619; Suspension=48		
Sex	Females=584 Males = 598		
Race	Caucasian=522 Oriental/Japanese=69 Black/Afro-American=35 Other=34 Missing=522		

IU = international unit, RC = roller dry compaction tablet formulation; WP = wet granulation/predensification tablet formulation.
a: N=1069
b: N=1091

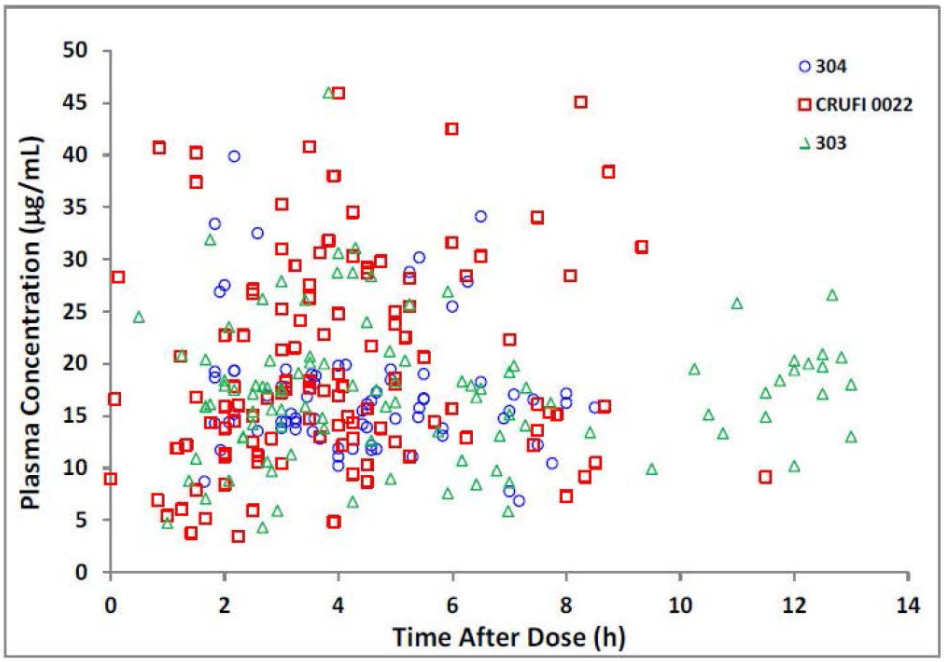
Table 6 Summary of Selected Co-Administered AEDs Included in the Population PK Analysis of Rufinamide

AED	CYP3A4 Inducers	Total PK Population (N=1182)	
		n	%
Carbamazepine	Yes	640	54.1
Phenytoin	Yes	291	24.6
Lamotrigine	No	145	12.3
Valproate	No	355	30.0

AED = antiepileptic drug PK = pharmacokinetics.

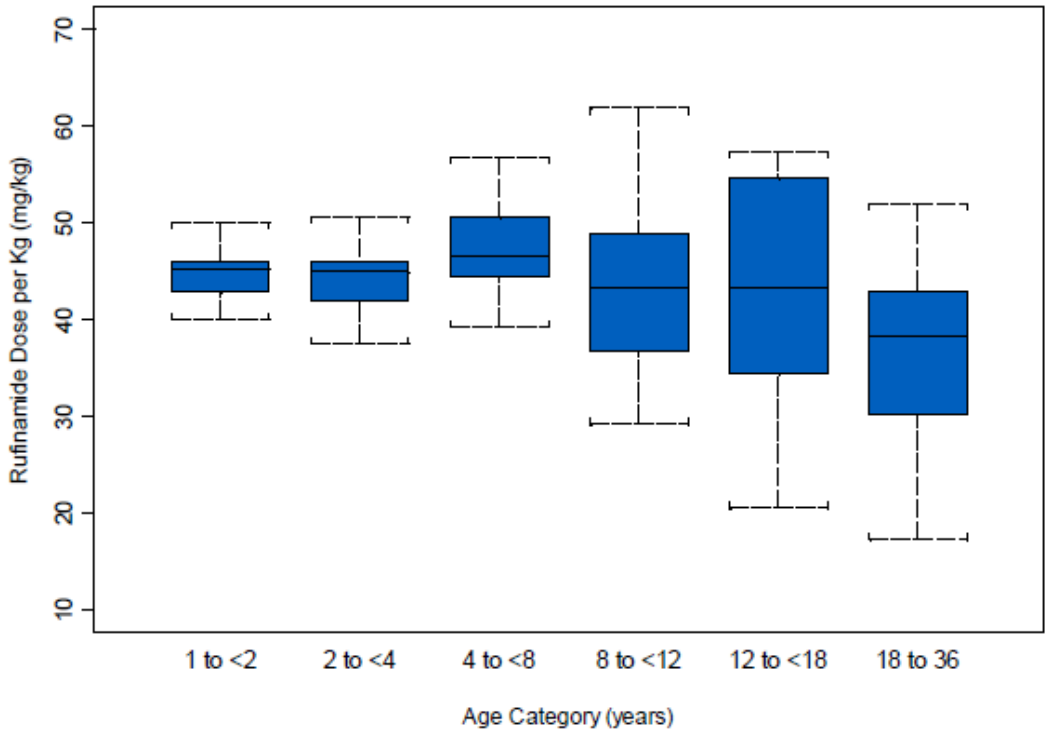
Observed rufinamide concentration versus time after dosing, the actual measured steady state rufinamide concentration data from Study 303 subjects from 1 to lessthan 4 years old, are visualised in the context of data from Studies 022 and 304 in LGS subjects 4 years old and above (Figure 1).

Figure 1 Individual Observed Rufinamide Concentration versus Time after Dose by Study in Subjects with LGS



The distribution of doses per age category in LGS patients is visualized in **Figure 2**.

Figure 2 Plot of Rufinamide Daily Dose per Kg by Age Category for LGS Patients Only (N=154)/All Visits



- **Model Development**

Base model structure

A one compartment disposition model with first-order absorption and linear elimination parameterized for clearance (CL/F), volume of distribution (V/F) and absorption rate constant (Ka) was fitted to the data. The inter-individual variability (IIV) (η, ETA) was assessed on all three parameters using an exponential error structure, assuming normal distribution for these parameters. A covariance between inter-individual variability terms for CL/F and V/F was assessed by application of the omega block. Inter-occasion variability (IOV) was assessed on CL/F, and V/F and Ka parameters. 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.

First-order condition estimation with interaction (FOCEI) was used.

Covariate model:

The effect of the following covariates was investigated on rufinamide PK: formulation (tablet: roller dry compaction tablet formulation [RC], wet granulation/predensification tablet formulation [WP], suspension), 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.

Final PK Model for Rufinamide:

A one-compartment disposition model with linear elimination from the central compartment adequately described rufinamide profiles from the pooled studies. The model was parameterized for absorption rate constant (Ka), apparent clearance (CL/F), apparent volume of distribution (V/F) and bioavailability for the roller dry compaction tablet (Old tablet) compared to the wet granulation/predensification tablet (Marketed) and oral suspension. The final population PK model for rufinamide contained the statistically significant effects of:

- Body weight on CL/F and on V/F
- Gender on V/F
- Daily dose per kg and formulation on Ka
- Daily dose per kg and roller dry compaction tablet on bioavailability
- Concomitant phenytoin, carbamazepine and valproate on CL/F

The final population PK model parameter estimates are presented in **Table 7** below.

Table 7 Intermediate Base Population PK Model Estimates of Rufinamide

	NONMEM Estimate		
Parameter	**Point Estimate**	**%RSE**	**95% CI**
$CL=\theta1*WGT/66)^{\theta10}$			
Basal CL/F (L/h)	6.02	4.10	5.54 – 6.50
Effect of body weight	1.10	2.94	1.04 – 1.16
$V=\theta2*(WGT/66)^{\theta11}$			
Basal V/F (L)	89.7	4.85	81.2 – 98.2
Effect of body weight	0.699	9.87	0.564 – 0.834
$Ka=(\theta3+\theta7*LOG(DDKG/1.96))*\theta8^{FOR}*\theta9^{FORR}$			
Basal Ka (1/h)	0.573	9.35	0.498 – 0.678
Effect of DDK	-0.0631	43.3	-0.117 - -0.00959
Effect of WP tablet	0.673	15.5	0.469 – 0.877
Effect of suspension	0.546	14.2	0.394 – 0.689
Relative bioavailability $F1=\theta4*(1+(\theta5*DDKG)/(\theta6+DDKG))$; RC $F2= 1+(\theta5*DDKG)/(\theta6+DDKG)$; WP/Suspension			
Relative F for roller compaction tablet (RC)	0.718	3.34	0.671 – 0.765
Emax effect of DDKG	-0.993	23.8	-1.46 - -0.530
DDKG for 50% of the effect (mg/kg)	60.6	46.7	5.13 - 116
Inter-individual variability			
CL/F (%CV)	43.2	4.33	-
Variance CL_V	0.678	7.42	-
V/F (%CV)	45.7	9.57	-
Ka (%CV)	39.7	17.3	-
Inter-occasion variability (%CV)			
CL/F	18.2	7.58	-
V/F	9.94	13.2	-
Ka	25.7	24.5	-
Residual variability (%CV)			
Proportional	21.1	1.08	-

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL/F = apparent clearance, V/F = apparent volume of distribution; Ka = absorption rate constant; DDKG = daily dose per kg; FOR = 1 for wet granulation/predensification tablet formulation; FORR = 1 for suspension; RC= Roller dry compaction tablet formulation; WP= Wet granulation/predensification tablet formulation; CI = confidence interval; %CV = Square root of variance *100.

Additionally, the effect of the following covariates was investigated on rufinamide PK: formulation (tablet: roller dry compaction tablet formulation [RC], wet granulation/predensification tablet formulation [WP], suspension), demographics (gender, race), renal function (creatinine clearance), liver function (alanine aminotransferase, aspartate amino transferase and total bilirubin) and concomitant carbamazepine, phenytoin, lamotrigine, valproic acid and valproate concentrations contained the statistically significant effects of:

- An increase in both clearance and volume with an increase in body weight (where scaling parameters for effect of body weight on CL/F and V/F have been estimated)
- A decrease in Ka with an increase in daily dose per kg: Ka decreases from 0.256 1/h to 0.202 1/h when increasing the suspension dose from 10 mg/kg/day to 45 mg/kg/day
- Lower bioavailability (0.78) for RC (Old formulation) relative to the WP (Marketed formulation) and suspension
- A decrease in bioavailability with an increase in daily dose per kg: bioavailability decreases from 0.85 to 0.57 when increasing the WP or suspension dose from 10 mg/kg/day to 45 mg/kg/day
- Lower absorption rate constant for the WP and suspension formulations compared to the
- RC

- Slightly lower (17%) volume of distribution in female compared to males
- 26% and 42% higher clearance with concomitant CARB and PHEN, respectively, and 24% lower clearance with concomitant valproate
- The final PK model was re-run by fixing scaling parameters to 0.75 for CL/F and 1 for V/F and there were no consequential difference observed in final model parameters using either estimated or fixed scaling parameters on CL/F and V/F.
- In the presence of the above significant effects none of the following covariates was found to be statistically significant:
- ***Clearance:*** age, gender, race, liver biomarkers, creatinine clearance and concomitant lamotrigine
- ***Volume:*** age and race
- This clearly indicates that in the presence of body weight effect on CL/F and V/F the PK of rufinamide is independent of sex, race, or age.
- The parameter estimates, precision of the estimate and 95% CI for the final PK model are presented below (**Table 8**).

Table 8 Final Population Pharmacokinetic Parameter Estimates of Rufinamide

		NONMEM Estimate	
Parameter	**Point Estimate**	**%RSE**	**95% CI**
$CL/F=\theta1*(WGT/66)^{\theta10}*\theta12^{PHEN}*\theta13^{VAL}*\theta14^{CARB}$			
Basal CL/F (L/h)	5.34	4.08	4.91 – 5.77
Effect of body weight	0.979	3.06	0.920 – 1.04
Effect of PHEN	1.42	2.48	1.35 – 1.49
Effect of VAL	0.760	2.63	0.721 – 0.799
Effect of CARB	1.26	2.43	1.20 – 1.32
$V/F=\theta2*(WGT/66)^{\theta11}*\theta15^{SEX}$			
Basal V/F (L)	105	5.31	94.1 – 116
Effect of body weight	0.591	12.1	0.451 – 0.731
Effect of gender	0.830	4.65	0.754 – 0.906
$Ka=(\theta3+\theta7*LOG(DDKG/1.96))*\theta8^{FOR}*\theta9^{FORR}$			
Basal Ka (1/h)	0.561	9.20	0.460 – 0.662
Effect of DDKG on Ka	-0.0648	40.6	-0.116 – -0.0133
Effect of WP tablet	0.694	15.1	0.488 – 0.900
Effect of suspension	0.563	13.8	0.411 – 0.715
Relative bioavailability $F1=\theta4*(1+(\theta5*DDKG)/(\theta6+DDKG))$; RC $F2= 1+(\theta5*DDKG)/(\theta6+DDKG)$; WP/Suspension			
Relative F for RC	0.776	3.09	0.729 – 0.823
E_{max} effect of DDKG	-0.902	18.6	-1.23 - -0.573
DDKG for 50% of the effect (mg/kg)	50.3	40.6	10.3 – 90.3
Inter-individual variability			
CL/F (%CV)	35.8	4.31	-
Variance CL_V	0.651	8.52	-
V/F (%CV)	45.1	10.2	-

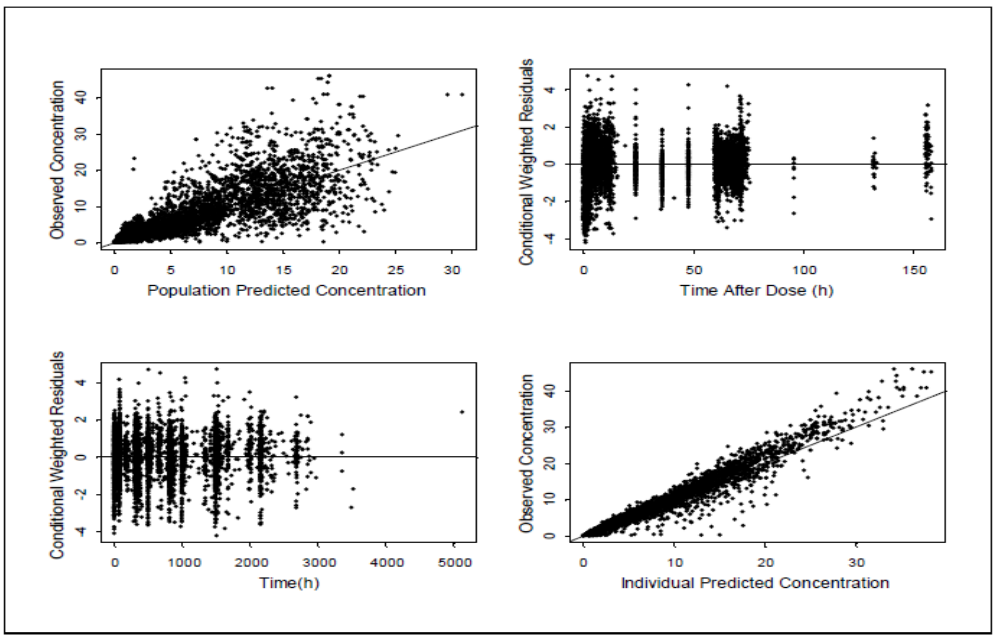
Ka (%CV)	38.7	18.2	-
Inter-occasion variability (%CV)			
CL/F	17.2	7.40	-
V/F	9.50	13.9	-
Ka	25.7	25.2	-
Residual variability (%CV)			
Proportional	21.2	1.10	-

*%CV = Square root of variance *100, %RSE = percent relative standard error of the estimate (ie, SE/parameter estimate * 100), CARB = Carbamazepine, CI = confidence interval, CL/F = apparent clearance, DDKG = daily dose per kg, F1 or F2 = relative bioavailability, FOR = wet granulation/predensification tablet formulation, FORR = suspension, Ka = absorption rate constant, PHEN = Phenytoin, RC = roller compaction tablet, VAL = Valproate, V/F = apparent volume of distribution, WGT = body weight, WP = wet granulation/predensification tablet formulation.*

The final PK model was qualified using goodness-of-fit plots and prediction corrected visual predictive check plots and formally validated using non-parametric bootsrap analysis.

Model evaluation

Figure 3 Goodness-of-fit Plot for Final Rufinamide PK model: All Studies



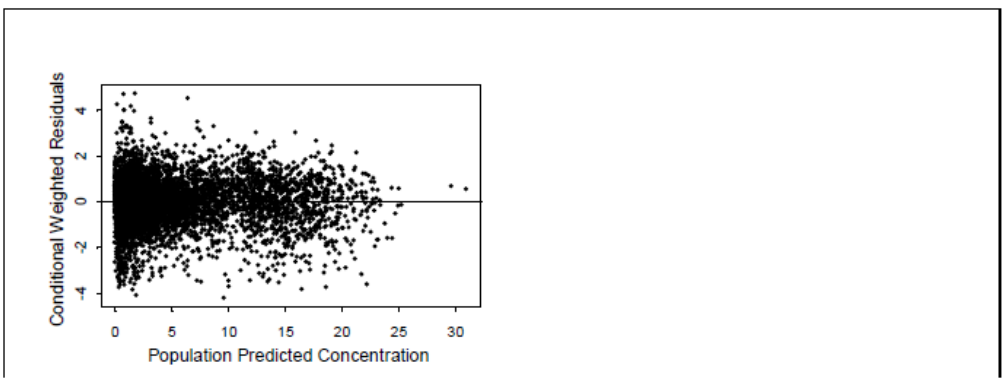
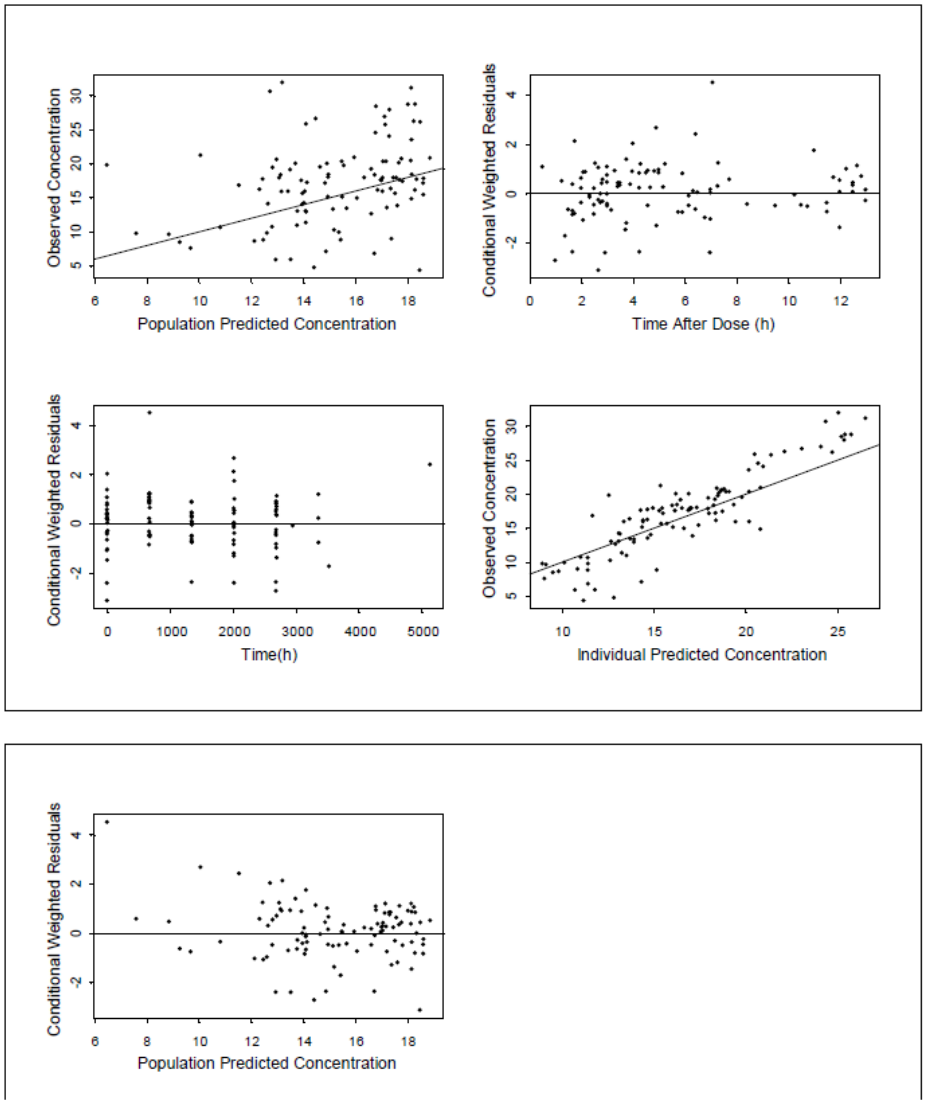


Figure 4 Goodness-of-fit Plot for Final Rufinamide PK model: Study 303



Goodness-of-fit

Goodness-of-fit-plots for the final PK model were presented. The scatter plots of population predicted and individual predicted versus observed concentrations showed reasonably well 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.

Visual predictive check (VPC)

In order to evaluate the predictive performance of the final PK model for rufinamide, prediction corrected visual predictive checks (pcVPCs) were performed by study. For each respective study 250 replicates were simulated using the final PK model. Using the simulated data corrected for typical model predictions, the 90% prediction intervals were determined and plotted together with observed rufinamide concentrations.

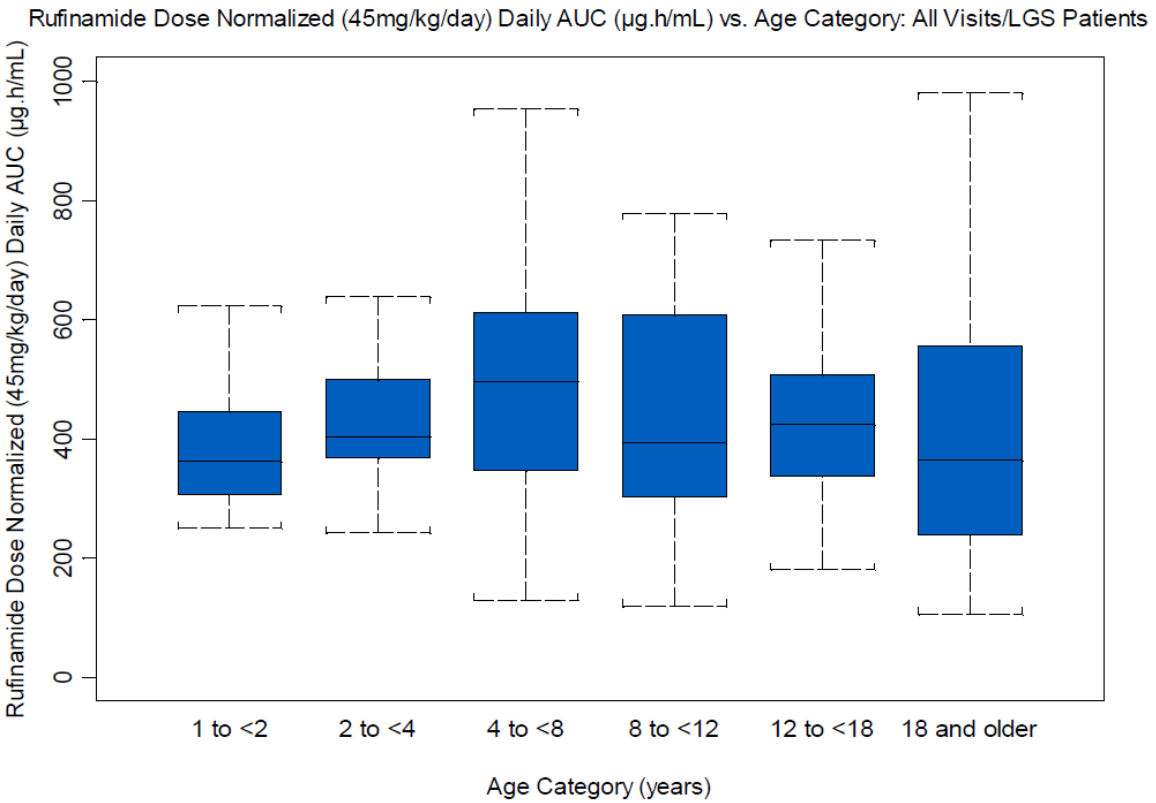
Bootstrap Method

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

Model-Derived Exposure Predictions

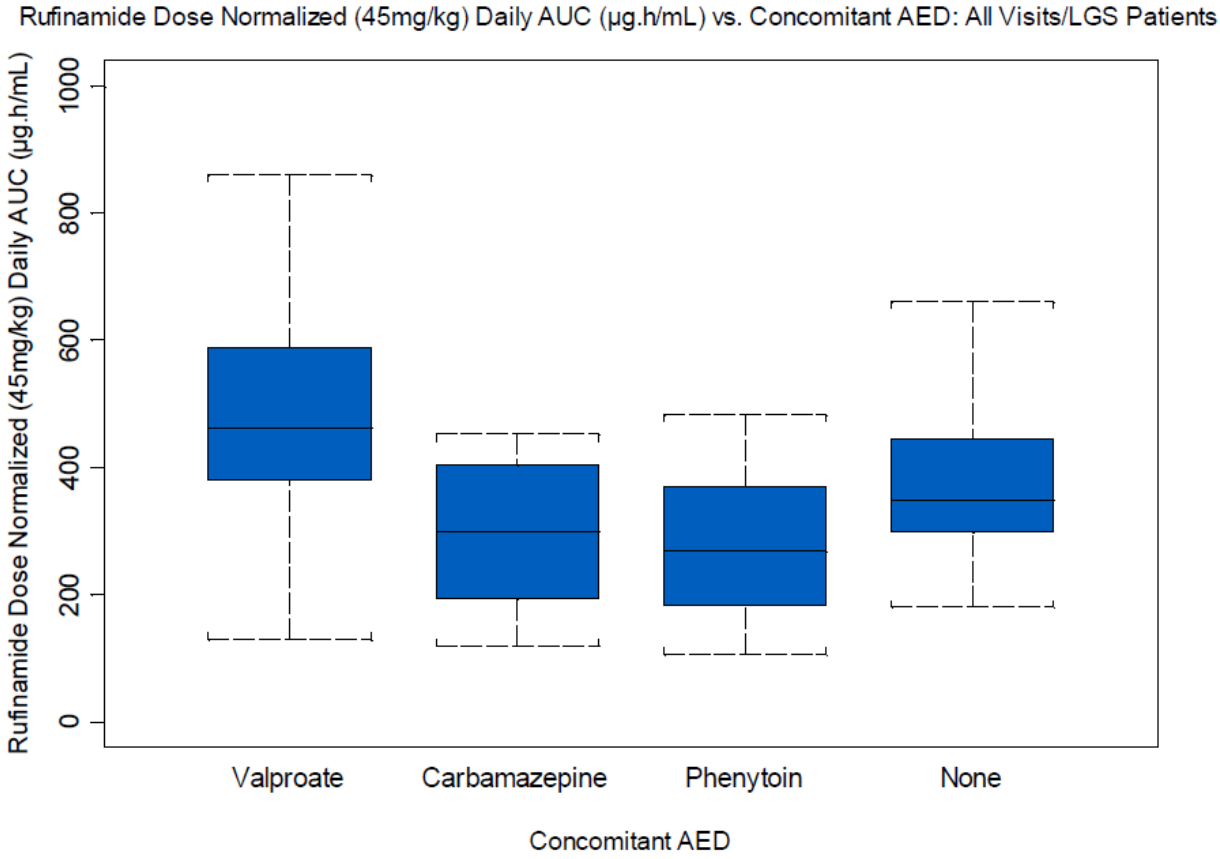
Boxplots of dose-normalized (45 mg/kg) steady-state daily AUC by age category are presented in **Figure 5** for LGS subjects only. In general, dose-normalized (45 mg/kg) steady-state daily AUC was comparable across all age groups at approximately 380 µg·h/mL in all subjects and for LGS-only subjects.

Figure 5 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State Across Different Age Groups in LGS Subjects Only (N=154)



Boxplots of dose-normalized (45 mg/kg) steady-state daily AUC by concomitant medication are presented in Figure 6 for LGS subjects only. Overall, in all subjects and in LGS subjects only the exposure to rufinamide appear to be lower with concomitant phenytoin or carbamazepine and higher in the presence of valproate compared to the that in subjects not receiving any of these concomitant AEDs. As illustrated in the boxplots there is substantial overlap in exposure with and without these concomitant AEDs. According to the MAH, concomitant administration of rufinamide with the two inducing AEDs phenytoin and carbamazepine and the inhibiting AED valproate does not warrant rufinamide dose adjustment for any of these AEDs.

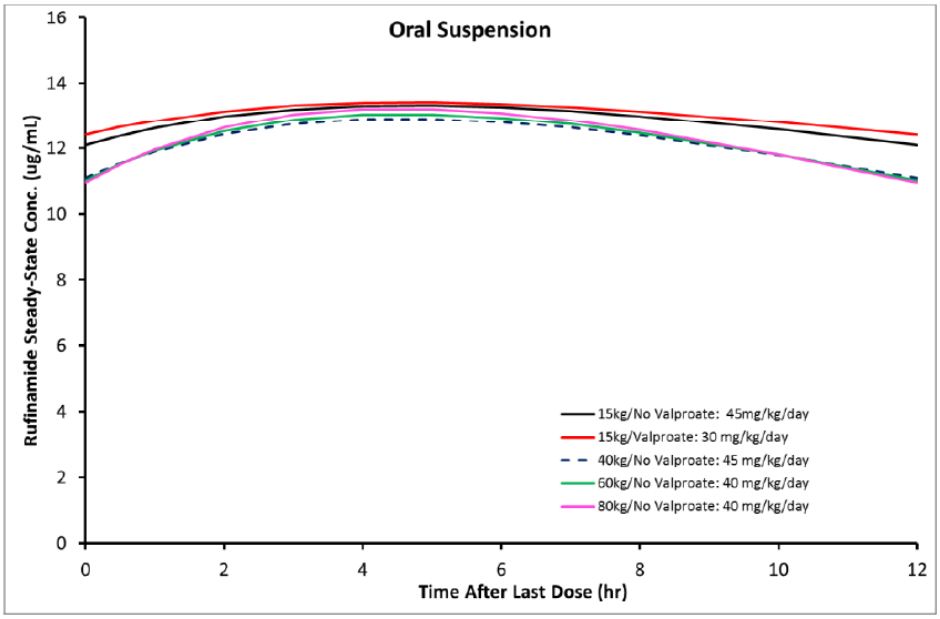
Figure 6 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State by Concomitant AED Medication in LGS Patient Only (N=154)



To assess the clinical implications of covariates which had statistically significant effect on rufinamide exposure with relevance to current labelling guidelines (body weight, formulation and AED co-administration), a series of PK simulations were performed using parameter estimates from the final PK model, rufinamide steady state concentration-time profiles.

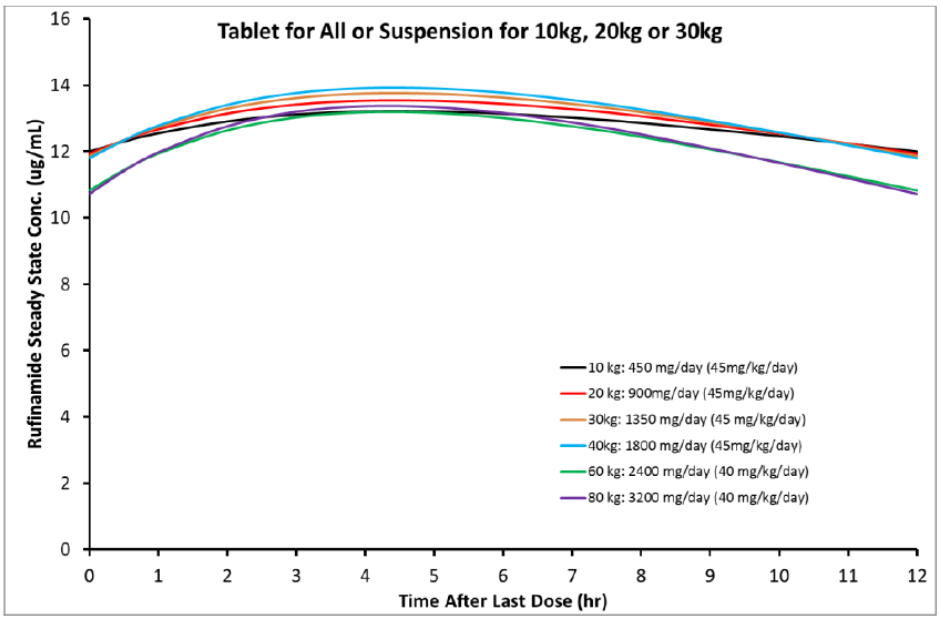
To assess the effect of dosing by body weight and valproate co-administration on rufinamide exposure following administration of the oral suspension formulation, simulations were performed for children of 15 kg titrated to a maximum rufinamide dose of 30 and 45 mg/kg/day (maximum 800 and 1000 mg/day, respectively, twice daily) in the presence and absence of valproate, respectively, and in adolescent and adult subjects of body weight of 40, 60 and 80 kg titrated to a maximum rufinamide dose of 40 mg/kg/day rufinamide (maximum 1800 and 2400 and 3200 mg/day, respectively, split twice daily.) without concomitant valproate. The simulations presented in **Figure 7** show a considerable overlap in typical steady state rufinamide concentrations over a dosing interval in 15 kg subjects titrated to a maximum rufinamide dose of 30 and 45 mg/kg/day in the presence and absence of valproate, respectively. In addition rufinamide concentrations at steady state in 40, 60 and 80 kg body weight subjects titrated to a maximum dose of 40 mg/kg/day rufinamide in the absence of valproate show considerable overlap. This applies equally to the two bioequivalent marketed formations (Stud E2080-044-003).

Figure 7 Model Predicted Rufinamide Concentration-time profile following 30 & 45 mg/kg/day Oral Suspension in 15kg Children in presence/absence of Valproate and following 40mg/kg/day Oral Suspension in 45, 60 & 80kg Subjects in absence of Valproate



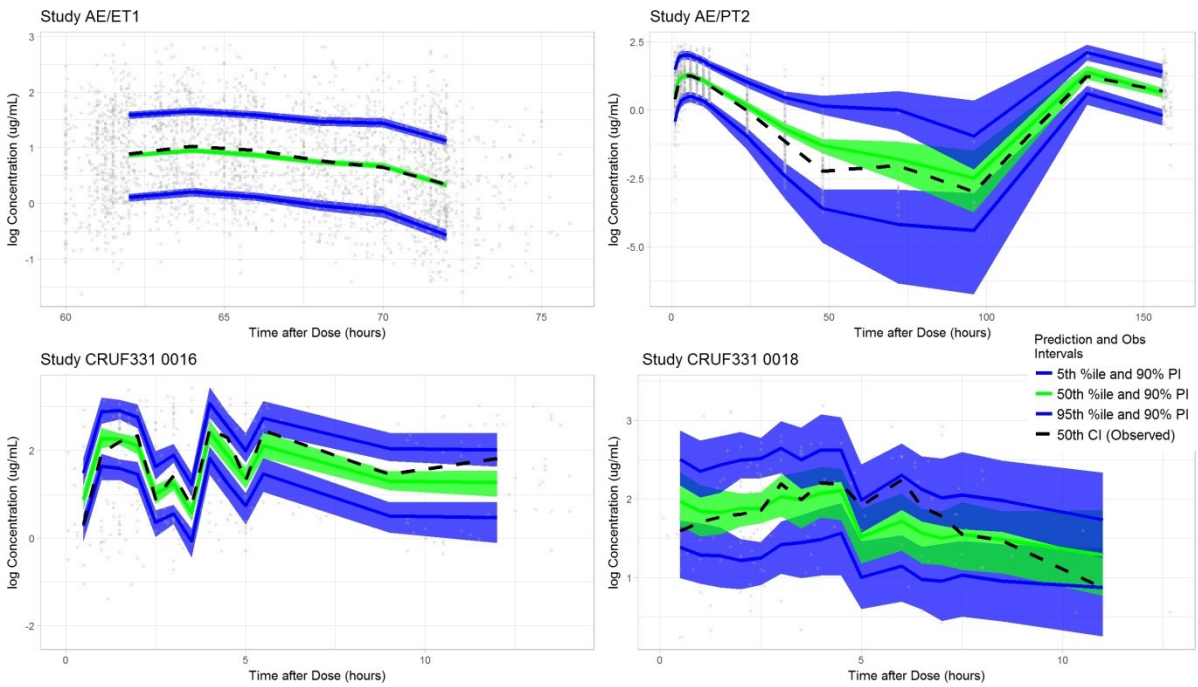
To further assess the effect of dosing by body weight on rufinamide exposure following tablet (all subjects) or oral suspension formulation (for younger children of 10 and 20 kg), simulations were performed for children of body weight 10, 20 and 30kg kg titrated to a maximum dose of 45 mg/kg/day tablet or suspension formulation (maximum 450, 900 and 1350mg/day, respectively, split twice daily) and 40, 60 and 80 kg adolescents/adults titrated to a maximum dose of 45, 40 and 40 mg/kg/day, respectively, tablet formulation (maximum 1800, 2400 and 3600 mg/day, respectively, split twice daily) in the absence of any other AEDs. The simulations presented in **Figure 8** show an overlap in typical steady state rufinamide concentrations over a dosing interval in 10, 20 and 30 kg young children administered tablet or suspension formulation titrated to a maximum dose of 45 mg/kg/day with 40, 60 and 80 kg subjects administered tablet formulation titrated to a maximum dose of either 40 or 45 mg/kg/day.

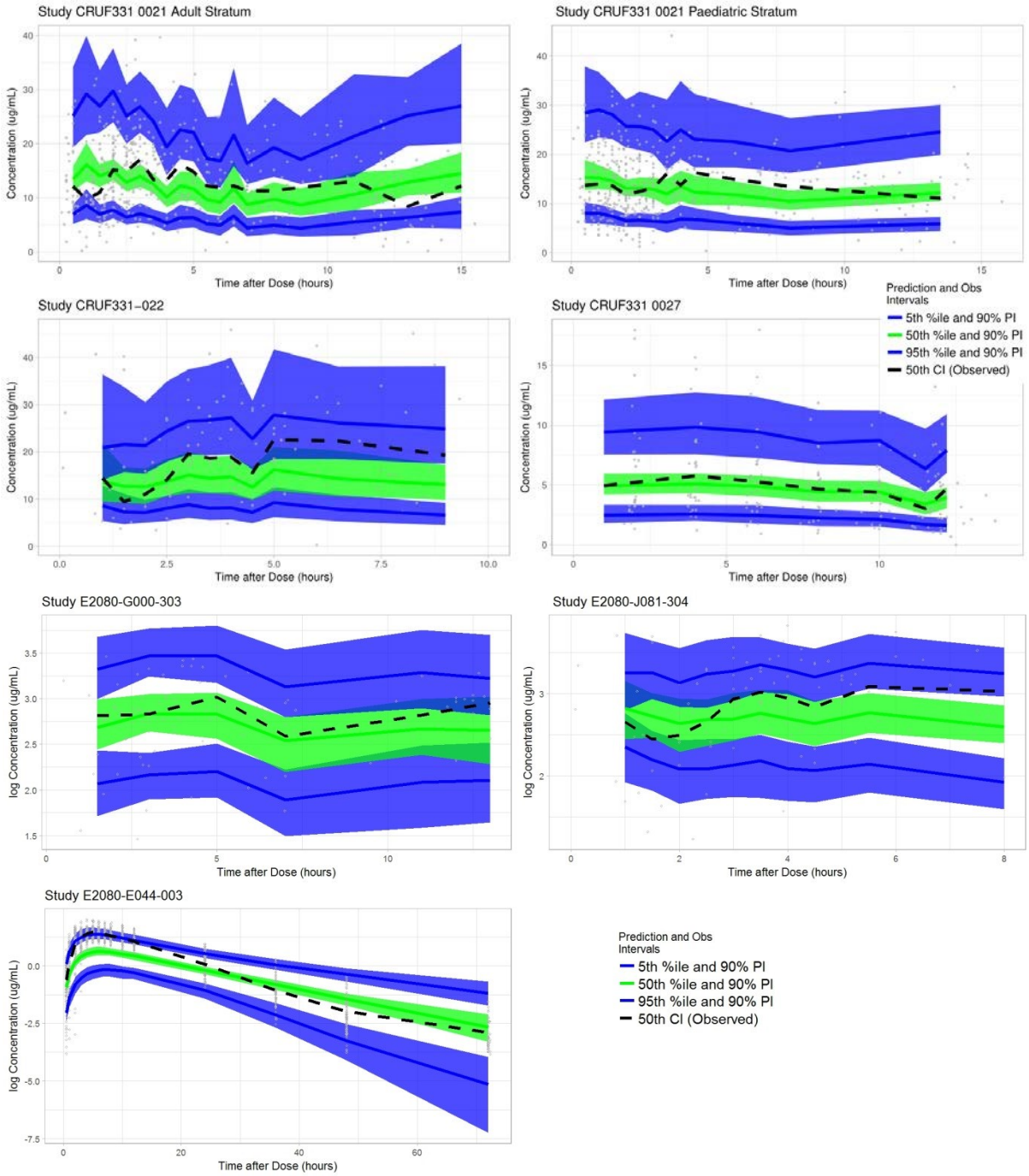
Figure 8 Model Predicted Rufinamide Concentration-time profile following 40 & 45 mg/kg/day Tablet or Oral Suspension Rufinamide Alone in 10-60 kg Subjects



The predictive performance of the final PK model for rufinamide was evaluated using the prediction corrected visual predictive check plots (pcVPCs) by study and non-parametric bootstrap methods and the results are presented below:

Figure 9 Prediction Corrected Visual Predictive Check Plots for Rufinamide PK Model Evaluation by Study



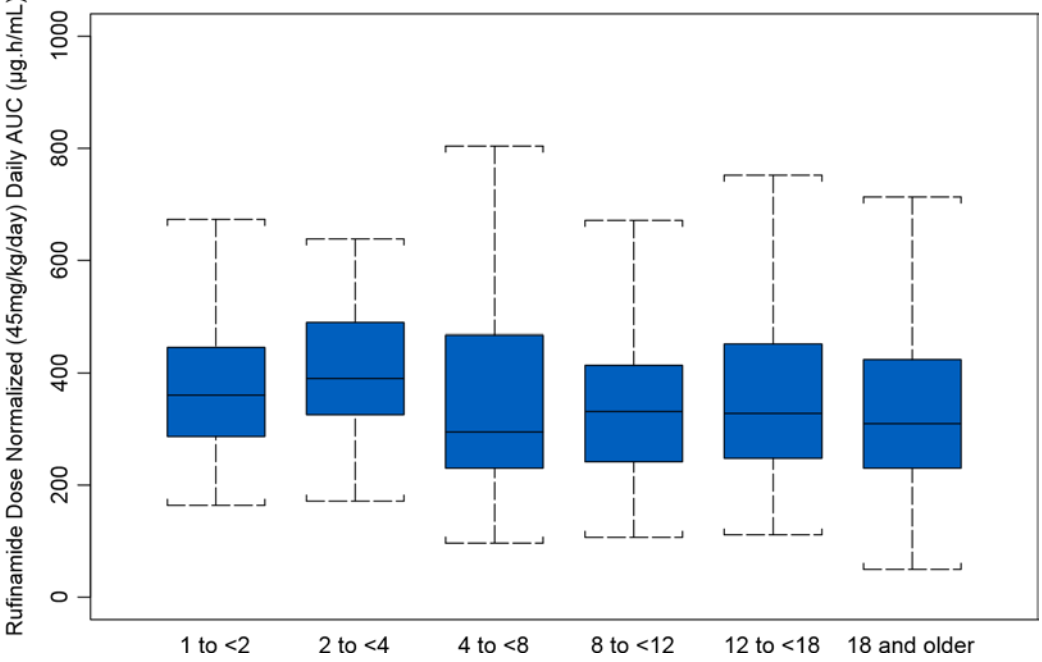


Prediction of exposure to rufinamide in young children (under 4 years) and comparison to other group of patients:

Boxplots of dose-normalized (45 mg/kg) steady-state daily AUC by age category are presented in **Figure 10** for all subjects and in **Figure 11** for LGS subjects only. In general, dosenormalized (45 mg/kg) steady-state daily AUC was comparable across all age groups at approximately 380 µg·h/mL in all subjects and for LGS-only subjects.

Figure 1.

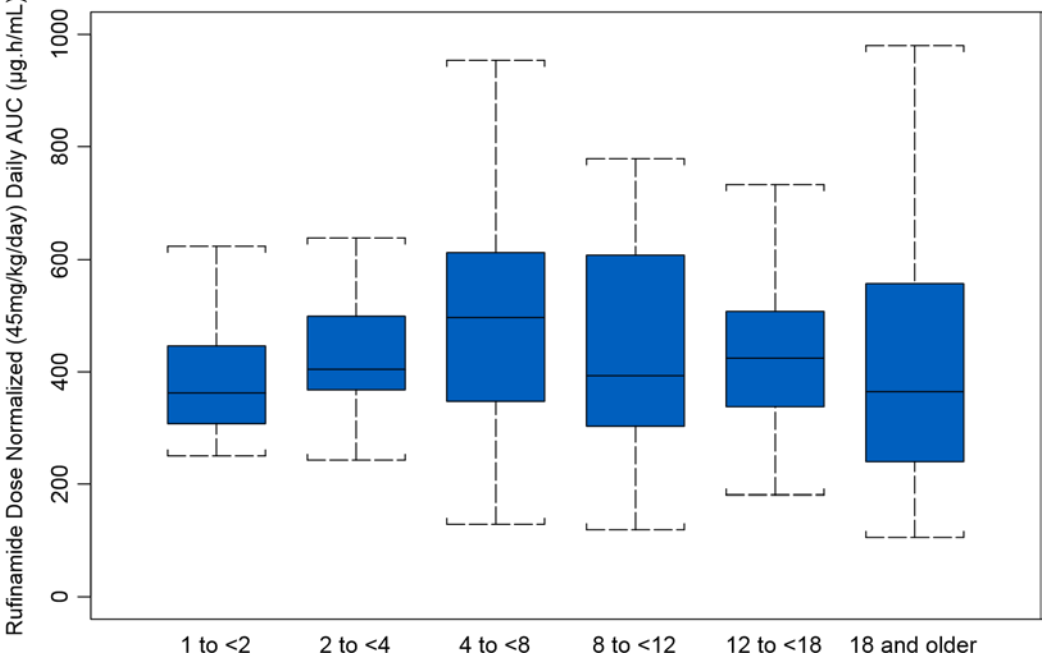
Figure 10 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State Across Different Age Groups in All Subjects, Including LGS (N=1158)



AUC = area under the concentration-time curve, LGS = Lennox-Gastaut syndrome.

Rufinamide Dose Normalized (45mg/kg/day) Daily AUC (µg.h/mL) vs. Age Category: All Visits/LGS Patients

Figure 11 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State



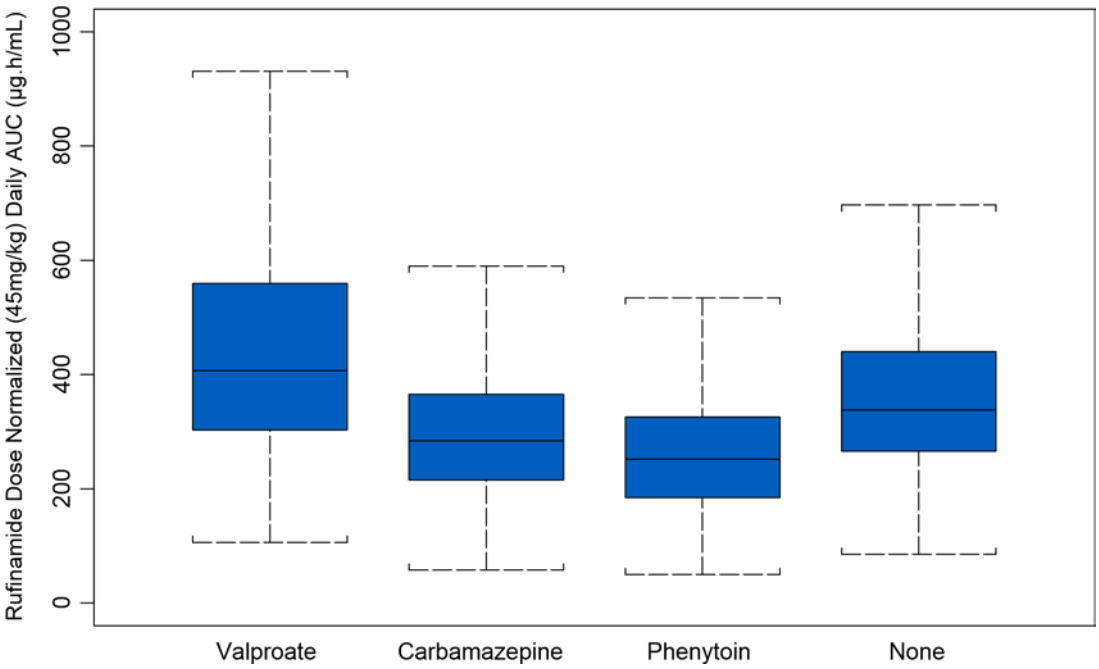
Across Different Age Groups in LGS Subjects Only (N=154)

AUC = area under the concentration-time curve, LGS = Lennox-Gastaut syndrome.

Prediction of extrinsic factors (co-administred drugs) effect on exposure to rufinamide in young children (under 4 years) and comparison to other group of patients:

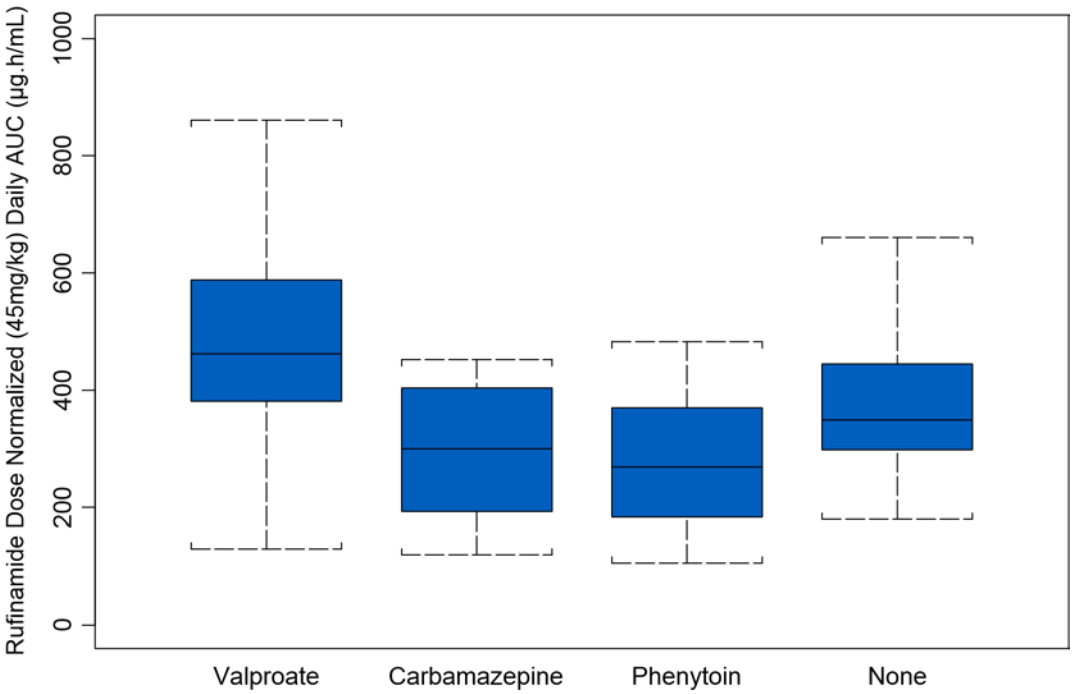
Boxplots of dose-normalized (45 mg/kg) steady-state daily AUC by concomitant medication are presented in **Figure 12** for all subjects and in **Figure 13** for LGS subjects only. Overall, in all subjects and in LGS subjects only the exposure to rufinamide appear to be lower with concomitant phenytoin or carbamazepine and higher in the presence of valproate compared to the that in subjects not receiving any of these concomitant AEDs. However, as illustrated in the boxplots there is substantial overlap in exposure with and without these concomitant AEDs. Hence, concomitant administration of rufinamide with the two inducing AEDs phenytoin and carbamazepine and the inhibiting AED valproate does not warrant rufinamide dose adjustment for any of these AEDs and rufinamide could be titrated to a maximum dose based on tolerability and efficacy.

Figure 12 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State by Concomitant AED Medication in All Subjects, Including LGS (N=1158)



AED = antiepileptic drug, AUC = area under the concentration-time curve, LGS = Lennox-Gastaut syndrome.
Rufinamide Dose Normalized (45mg/kg) Daily AUC (µg.h/mL) vs. Concomitant AED: All Visits/LGS Patients

Figure 13 Figure 9 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State by Concomitant AED Medication in LGS Subjects Only (N=154)



AED = antiepileptic drug, AUC = area under the concentration-time curve, LGS = Lennox-Gastaut syndrome.

- **Updated Model**

At the CHMP's request to improve the feasibility of the modelling exercise (see discussion section), the aplicant conducted a new population PK analysis on pooled data from 3 selected Phase 3 studies in LGS patients (Studies 022, 303 and 304) and 1 single-dose study in healthy subjects (Study E2080- E044-003). Both fixed and estimated allometric scaling for body weight effect on clearance and volume of distribution were evaluated during model development and the objective function with estimated allometric exponents (df=2) was only 3.4 points lower compared to that with fixed exponents (Report CPMS-E2080-004R-v1). A fixed allometric scaling exponent was chosen for the final PK model, which adequately captured rufinamide PK from all 4 studies. This model was fully qualified and validated and was used to predict exposure in children < 4 years to guide dosing recommendations in children 1 to < 4 years old, with maximum doses of 30 mg/kg/day and 45 mg/kg/day with and without concomitant valproate, respectively. The parameter estimates of the final PK model are presented in **Table 9**, goodness-of-fit-plots are presented in **Figure** 14 and prediction-corrected visual predictive checks (pcVPC) are presented in **Figure 15** (Report CPMS-E2080-004R-v1).

Table 9 Final Population Pharmacokinetic Parameter Estimates of Rufinamide

	NONMEM Estimate		
Parameter	**Point Estimate**	**%RSE**	**95% CI**
Apparent clearance: CL/F=θ_1*(WGT/36)$^{0.75}$* θ_8^{VAL}			
Basal CL/F (Θ_1; L/h)	4.27	6.25	3.75 – 4.79
Effect of VAL on CL/F (Θ_8)	0.742	6.74	0.644 – 0.840
Apparent volume of distribution: V/F= θ_2*(WGT/36)			
Basal V/F (Θ_2; L)	44.3	3.48	41.3 – 47.3
Ka			
Ka for suspension (Θ_3; 1/hour)	0.372	8.44	0.310 – 0.434
Ka for WP tablet (Θ_4; 1/hour)	0.632	13.0	0.471 – 0.793
D1			
D1 for suspension (Θ_5; hour)	0.607	27.5	0.280 – 0.934
D1 for WP tablet (Θ_6; hour)	1.79	19.4	1.11 – 2.47
Relative bioavailability			
F1= 1+θ_7*(LOG(DDOS/1000))			
Effect of daily dose (DDOS) on F1 (Θ_7)	–0.290	6.74	–0.367 to –0.213
Inter-individual variability(%CV)			
CL/F	31.5	14.4	—
V/F	6.33	67.6	—
Ka for suspension	30.5	49.0	—
Ka for WP tablet	37.4	67.9	—
D1 for suspension	87.5	42.7	—
D1 for WP tablet	95.2	47.3	—
Inter-occasion variability (%CV)			
Ka for suspension	25.9	41.5	—
D1 for suspension	70.6	34.3	—
Residual variability (%CV)			
Proportional	18.6	2.67	—

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, CL/F = apparent clearance, V/F = apparent volume of distribution, Ka = first-order absorption rate constant, D1 = duration of zero-order absorption, WGT = body weight, DDOS = daily dose, WP = wet granulation/predensification tablet formulation, VAL = valproate, CI = confidence interval, %CV = square root of variance *100.

Figure 14 Goodness-of-fit Plot for Final Rufinamide PK model: Studies 022, 303, 304 and 003

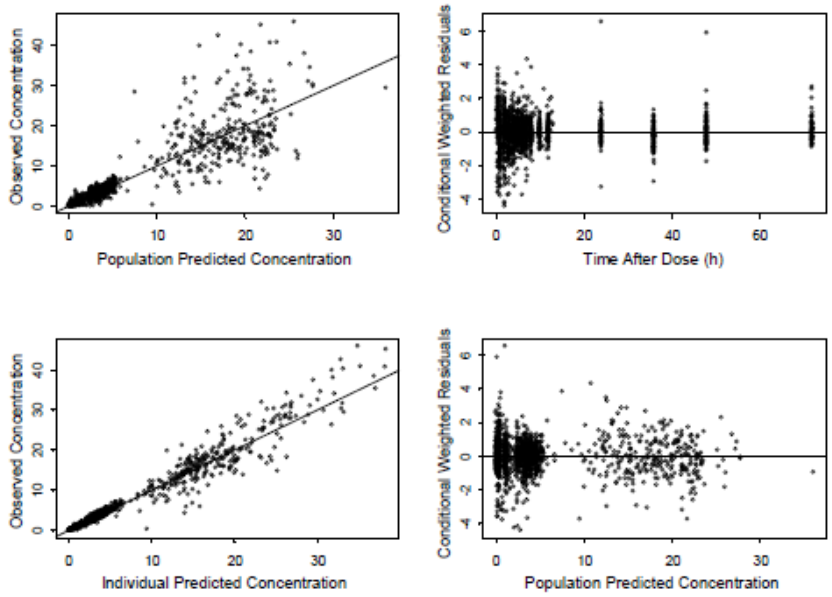


Figure 15 Prediction Corrected Visual Predictive Check Plots for Rufinamide PK Model Evaluation (linear and Log scale) by Study

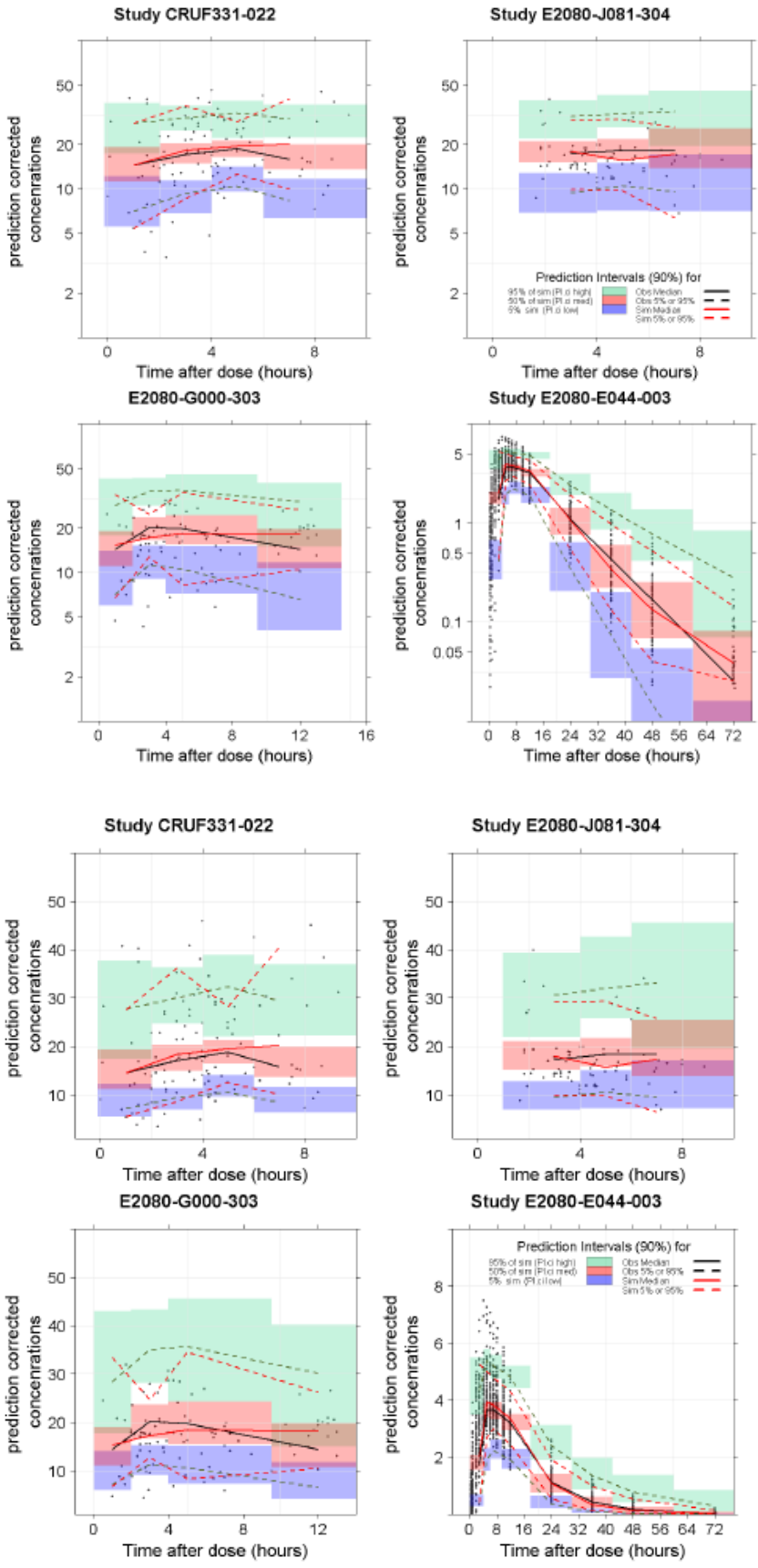


Figure 2 **Prediction Corrected Visual Predictive Check Plots for Rufinamide PK Model Evaluation (Linear & Log scale) – By Study**

The population basal estimates from the new analysis of 4.27 L/h for CL/F and 44.3 L for V/F are comparable with published data by Perucca, et al. (2008) (CL/F=3.00 – 5.55L/h and V/F=52.7 – 81.6 L).

Overall, the outcome of this new modelling is in close agreement with the previous modelling. We acknowledge that the profiles from Study E2080-E044-003 in the previous model are not well captured by the model based on pcVPC only; however, the profiles from all remaining 10 studies in that modelling, including AE/PT2 and 3 studies in LGS subjects (022, 303 and 304), are well captured. Hence, overall, based on composite criteria for model evaluation including Goodness-of-Fit (GOF) plots, pcVPCs, and bootstrap findings, the model is well qualified to describe the data. Additionally, the model was shown to predict well the observed rufinamide exposure in children under 4 years old. Thus, the slight bias in the pcVPC for one single-dose study, which represents only 2% in the PK dataset, does not meaningfully impact the key conclusions and applications of the model.

Model-derived exposure predictions

Graphs of dose-normalised exposure indicate that exposure is similar across the full patient population and different concomitant anti-epileptic drugs.

Figure 16 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State Across Different Age Groups in LGS Subjects

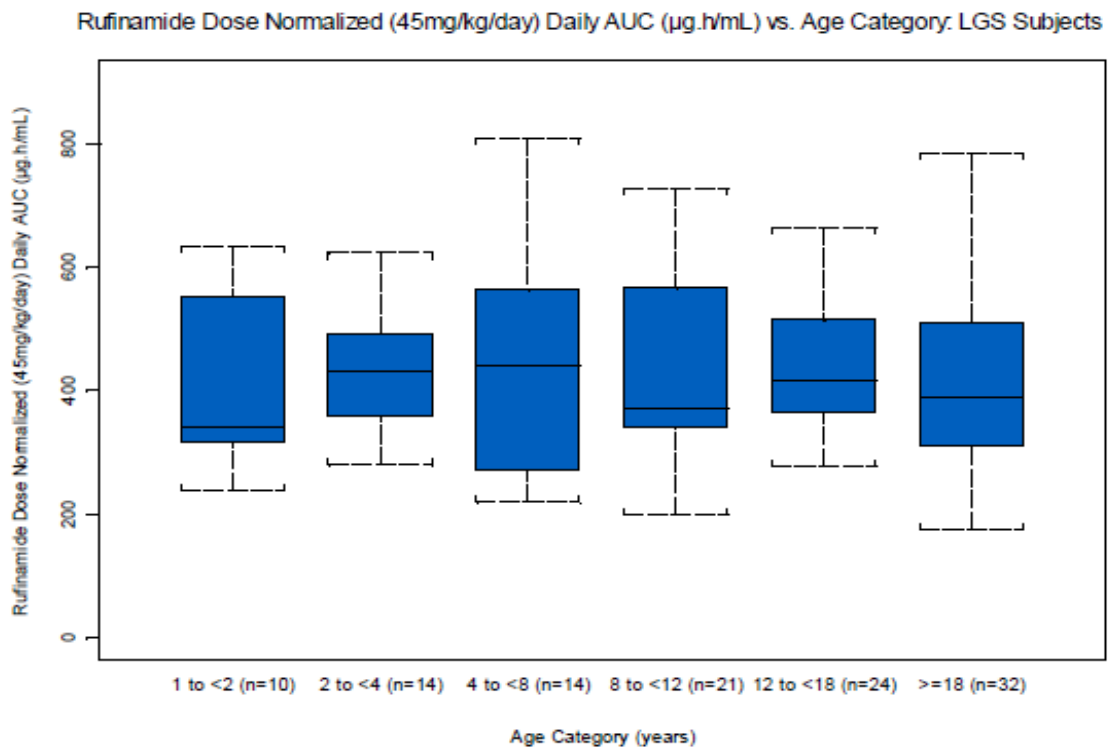
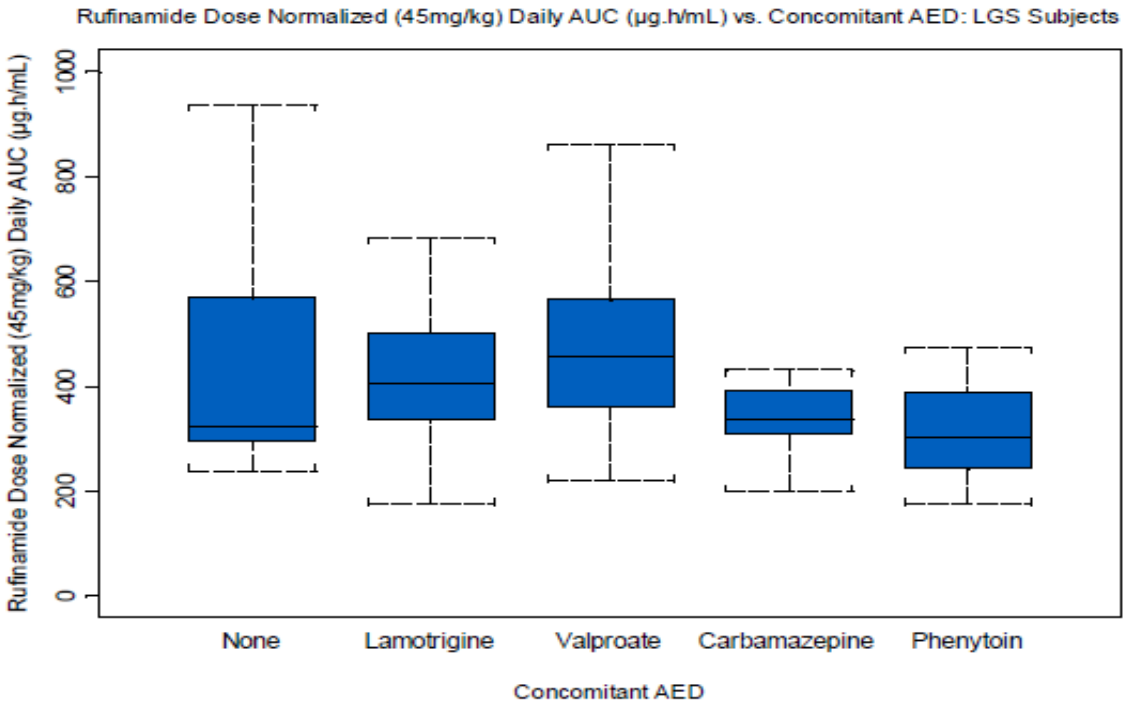


Figure 17 Boxplot Comparing Model-Predicted Rufinamide Dose Normalized (45 mg/kg) Daily AUC at Steady State by Concomitant AED Medication in LGS Subjects

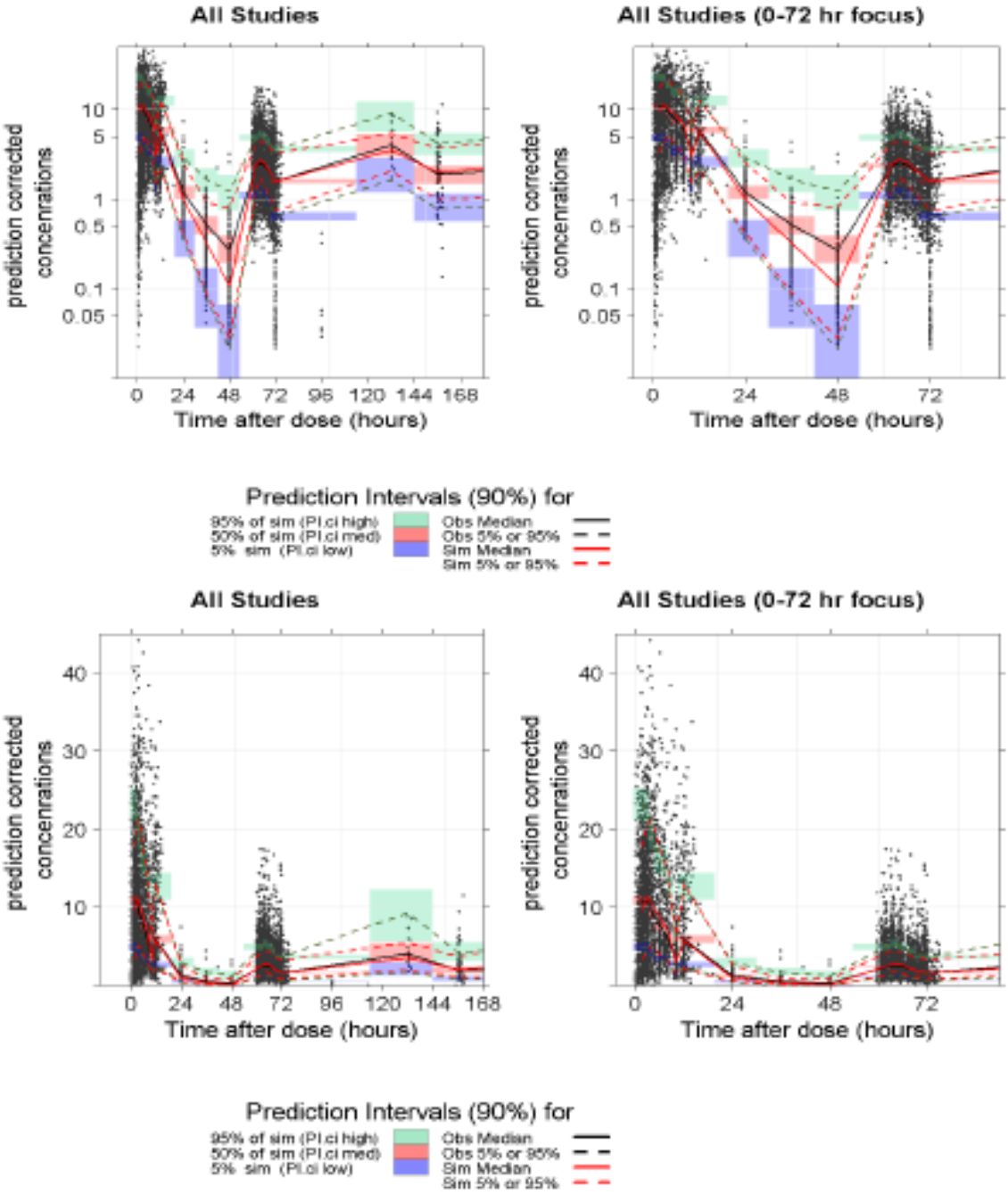


- **Additional data analyses / presentations requested by CHMP for initial model (003R)**

At the CHMP request (see discussions section) pcVPCs stratified by study, age, and weight, with the observed median and corresponding 5th and 95th percentiles, were provided both on normal and log scale. The plots further illustrate the ability of the initial model to describe the data across studies and in particular across the range of body weights and ages present in this dataset used to inform the model.

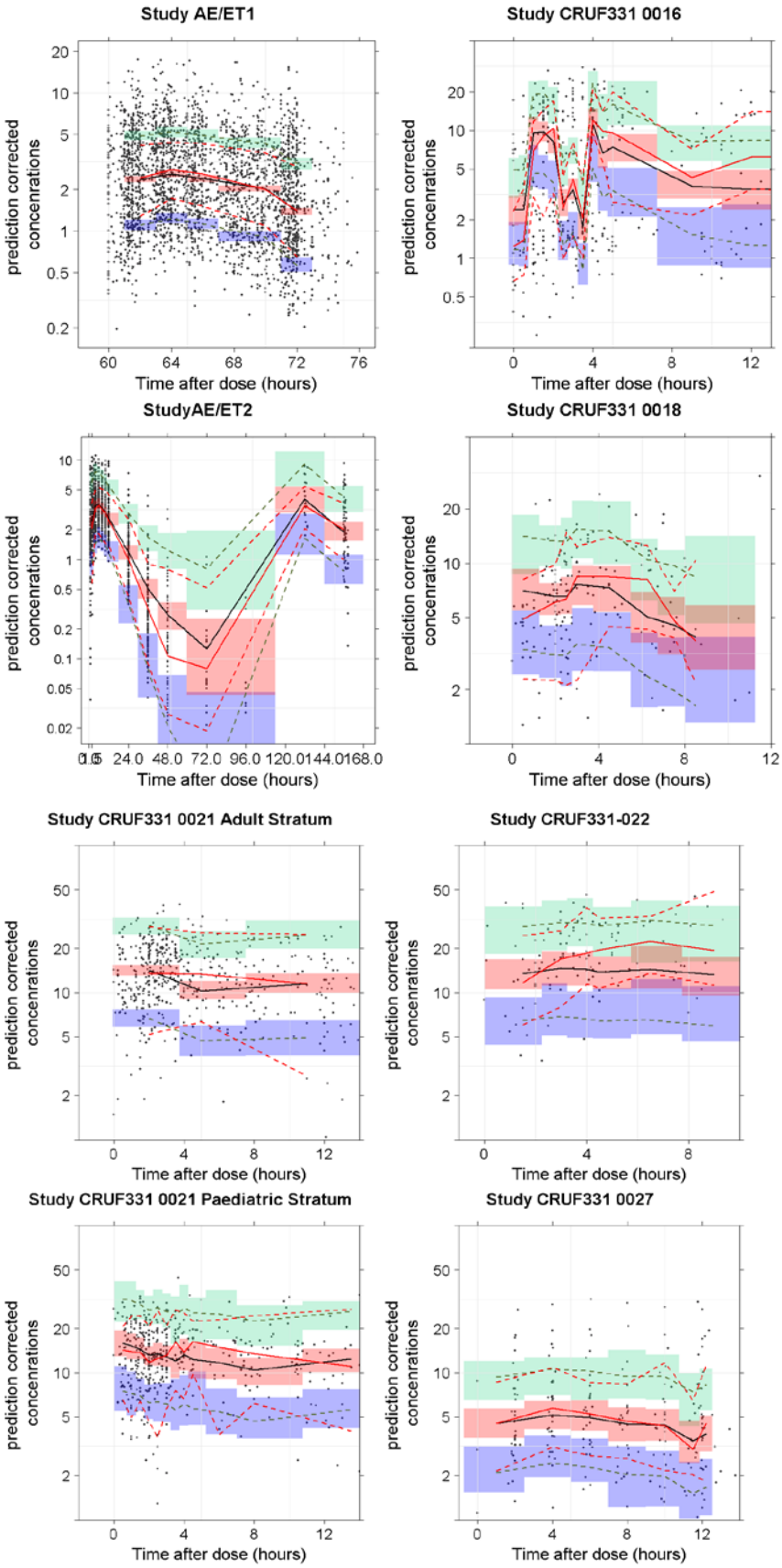
The pcVPCs with log-transformed and normal y-scale for all studies, including observed median for the 5% and 95% percentiles, are presented in **Figure 18** below. A right hand plot provides an early time focus.

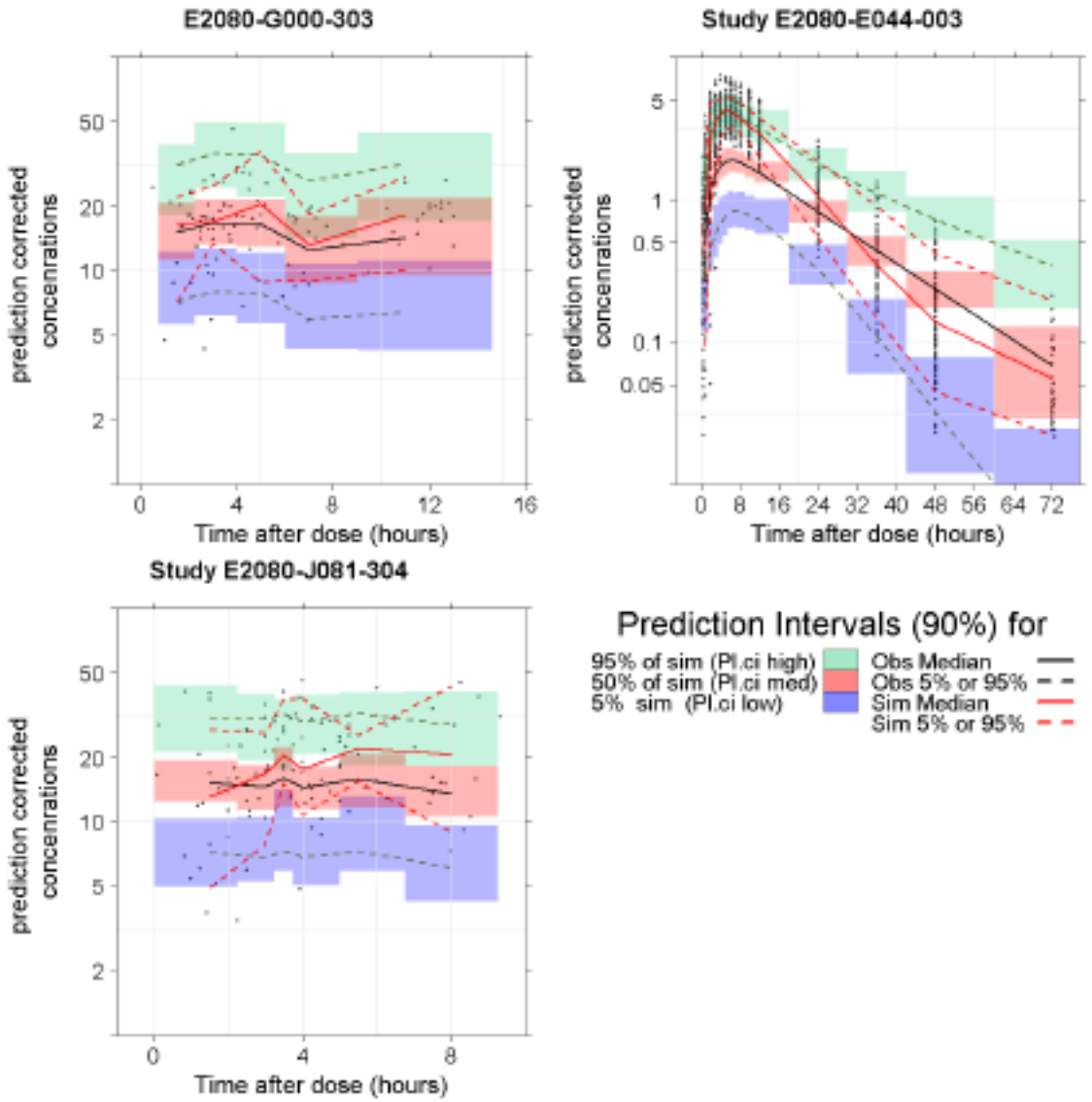
Figure 18 Log-Linear and Linear-Linear pc VPCs for all studies



The pcVPCs with log-transformed y-scale stratified by study are presented below in **Figure 19**. This is a repeated set of pcVPCs from Report CPMS-E2080-003R-v2 with the observed and simulated 5th and 95th quantiles and the 90% prediction interval associated with the corresponding quantile.

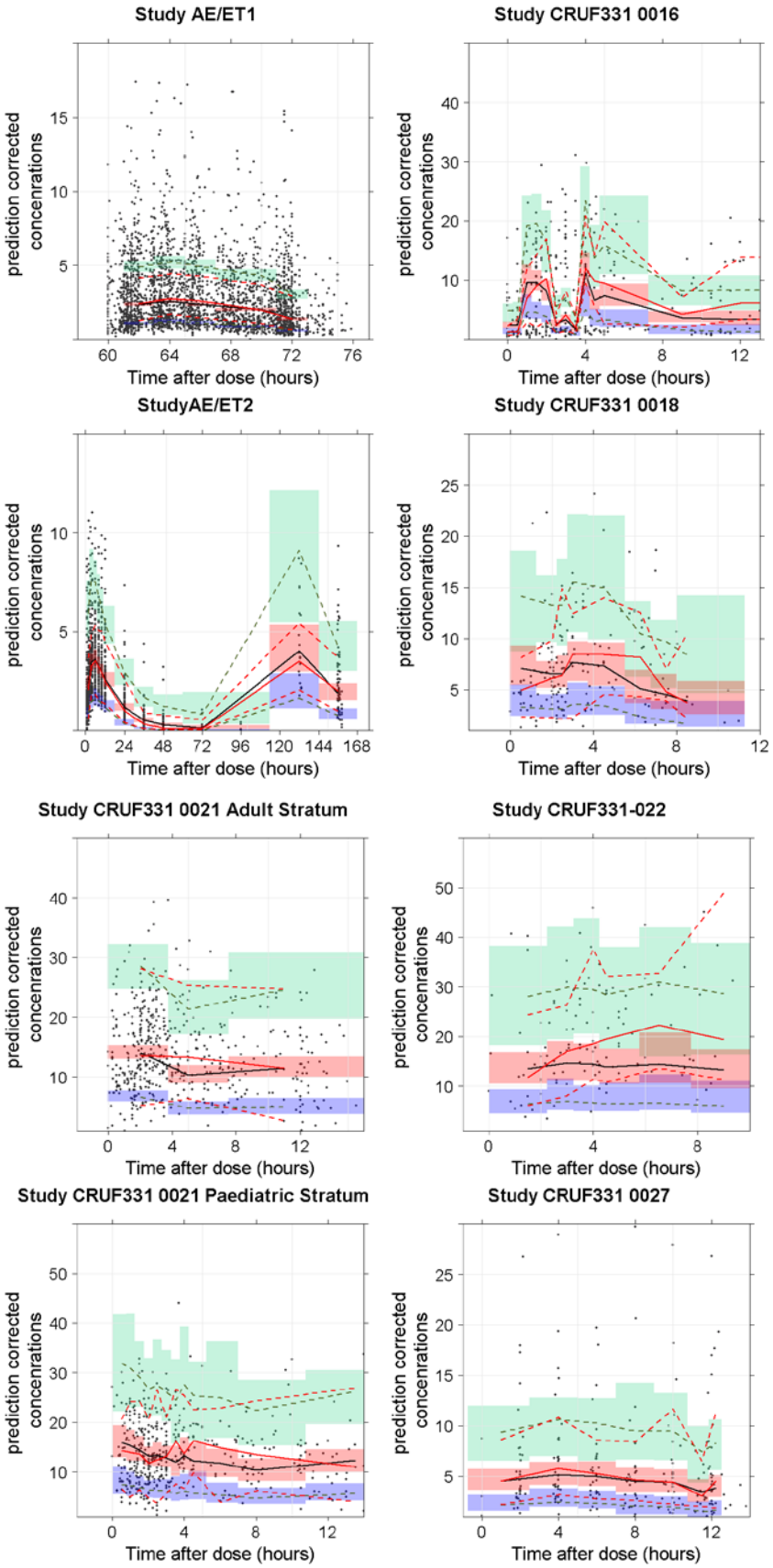
Figure 19 Log-Linear pcVPCs by Study

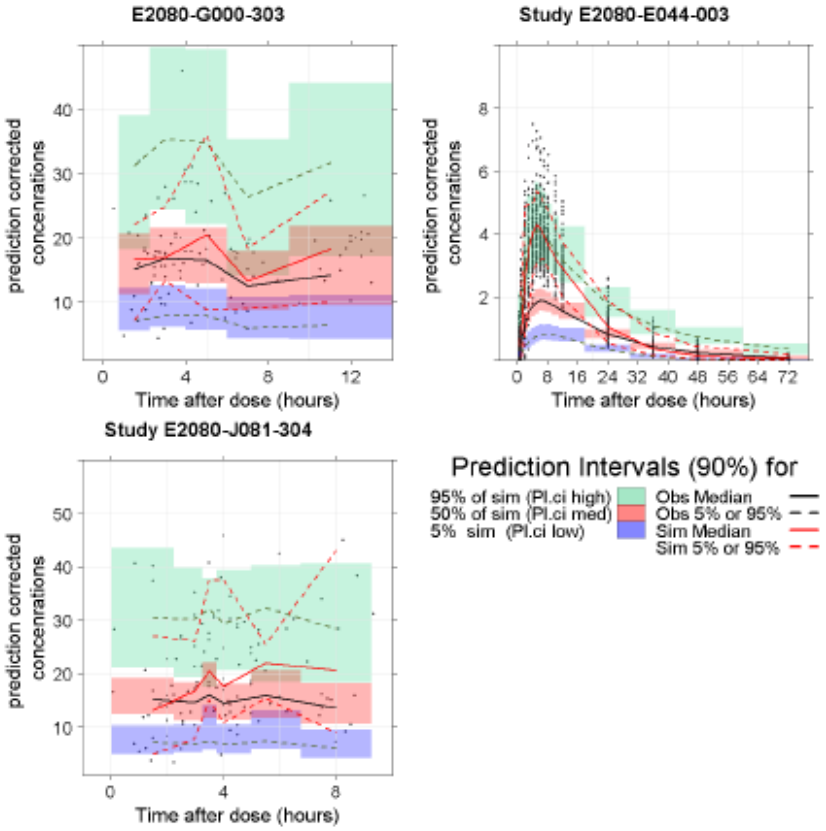




The pcVPCs with untransformed y-scale stratified by study, including observed median for the 5% and 95% percentiles, are presented in **Figure 20** below.

Figure 20 Linear-Linear pcVPCs by Study

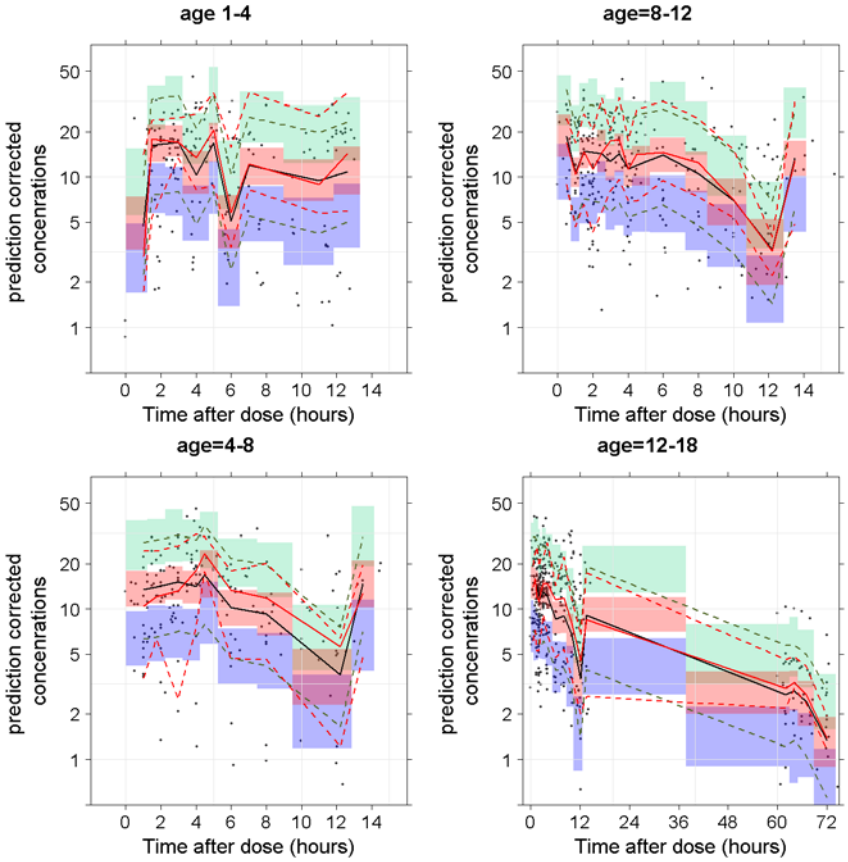


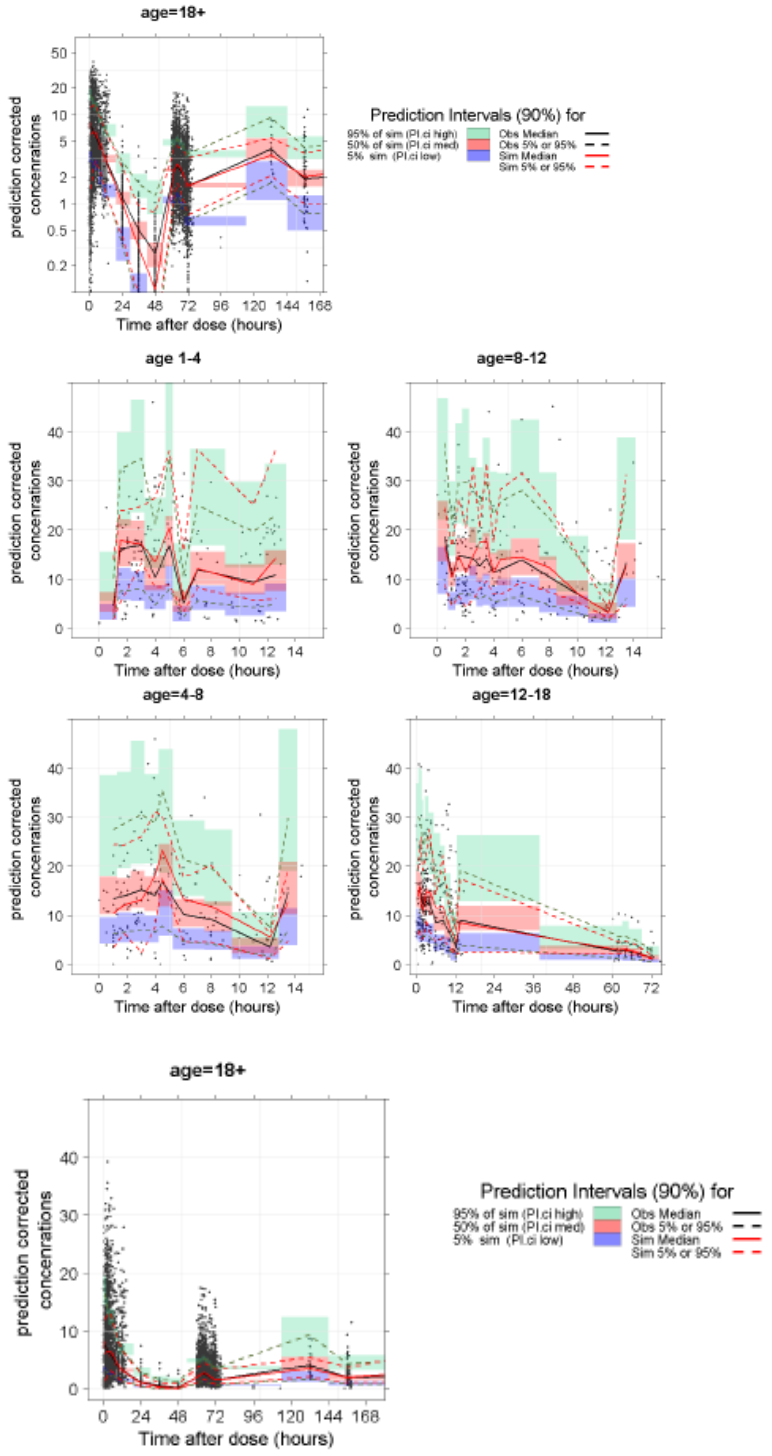


Overall, the pcVPCs indicate no systematic deviations of observed data and simulations based on the final model; the PIs contain the observed median, 5% or 95% percentiles of the data across time and support the predictive use of the rufinamide model for extrapolation to LGS patients aged 1 to < 4 years.

Stratification using 5 bins of age (1 to < 4 years, 4 to < 8 years, 8 to < 12 years, 12 to < 18 years and ≥ 18 years) for the log-transformed concentration and natural scale pcVPCs are presented in **Figure 21** below.

Figure 21 Log- Linear and Linear-Linear pcVPCs by Age category





Stratification using 5 bins of body weight (< 20 kg, 20 to < 30kg, 30 to < 40 kg, 40 to <60 kg, 60 to < 80 kg and ≥ 80 kg) for the log-transformed concentration and natural scale pcVPCs are presented respectively in **Figure 22** and **Figure 23** below.

Figure 22 Log-Linear pcVPCs by Body Weight category

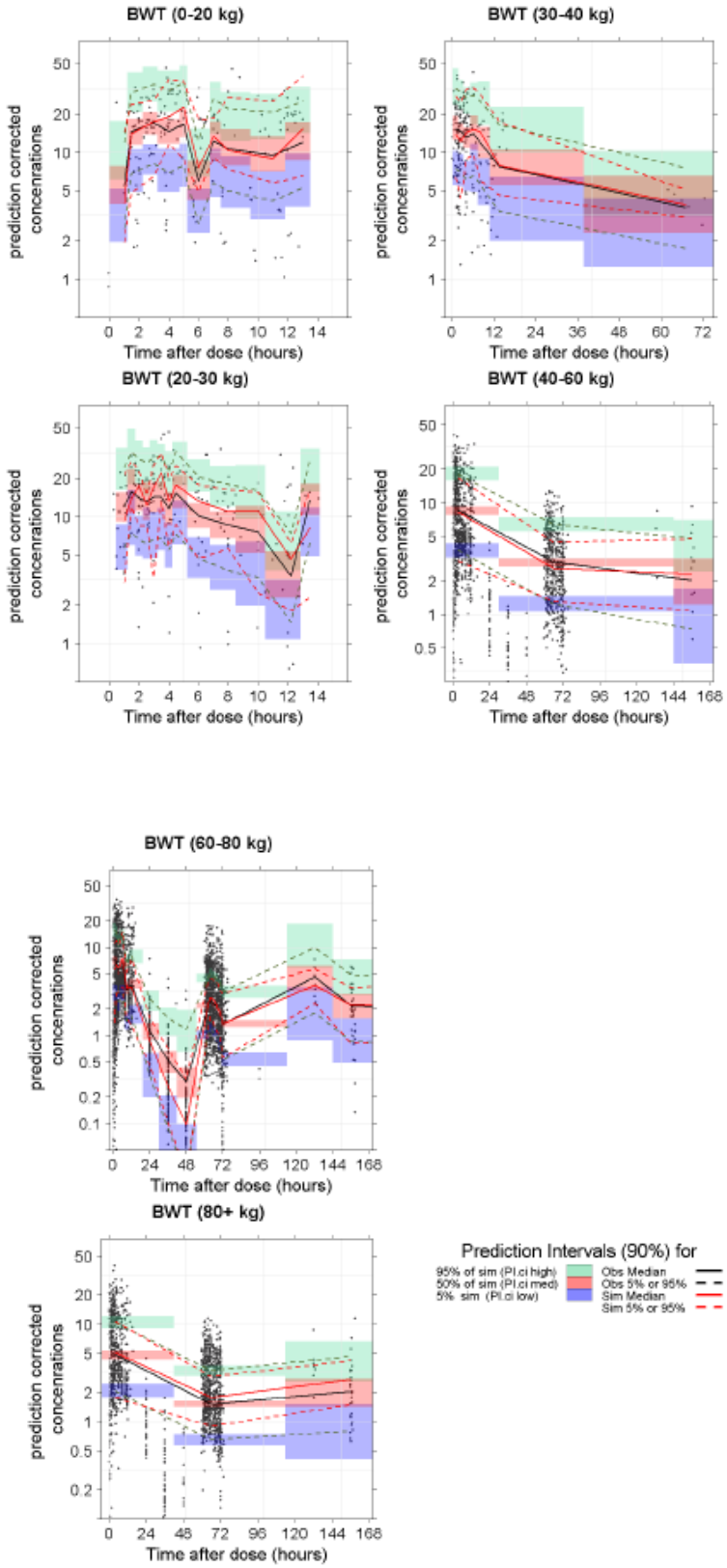


Figure 23 Linear-Linear pcVPCs by Body Weight category

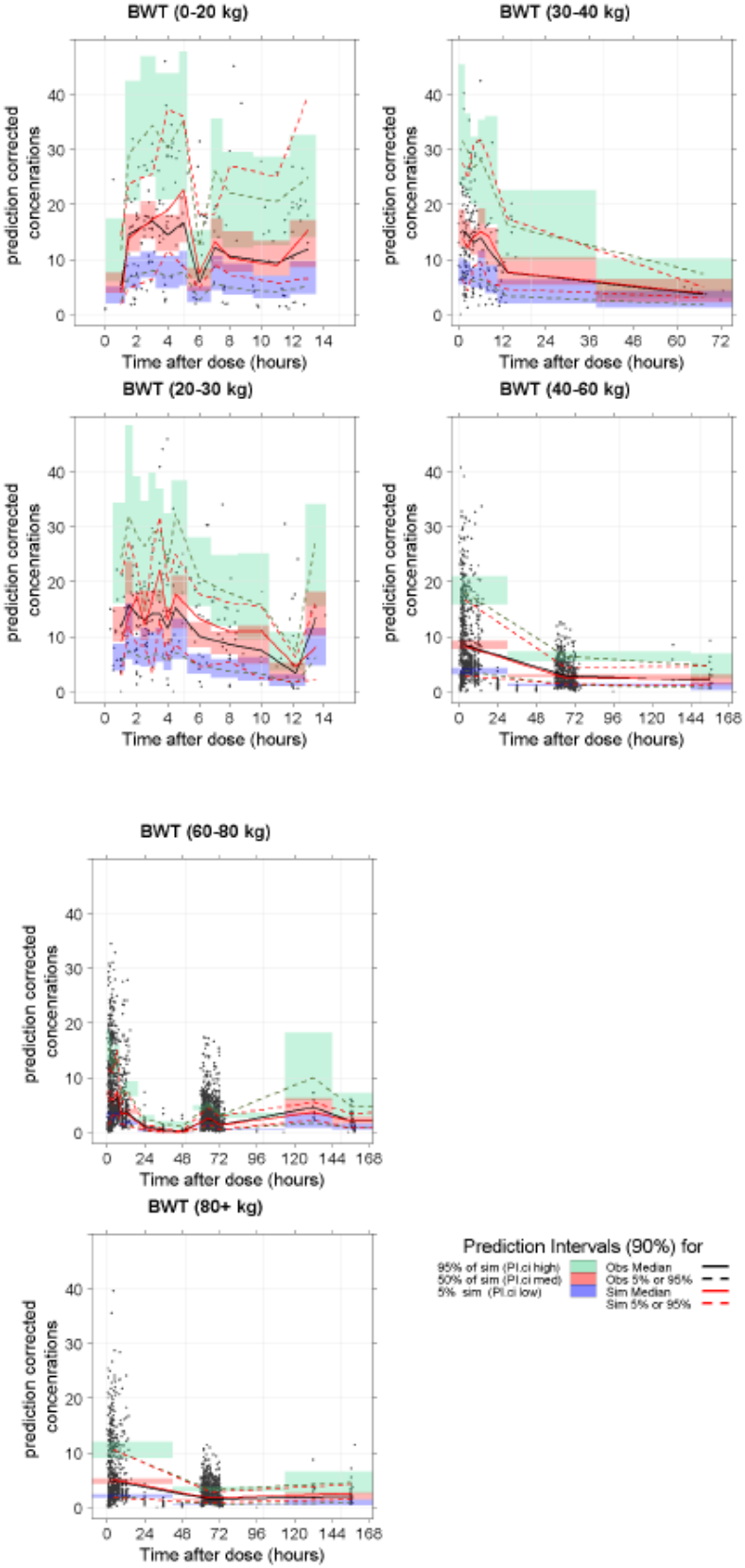


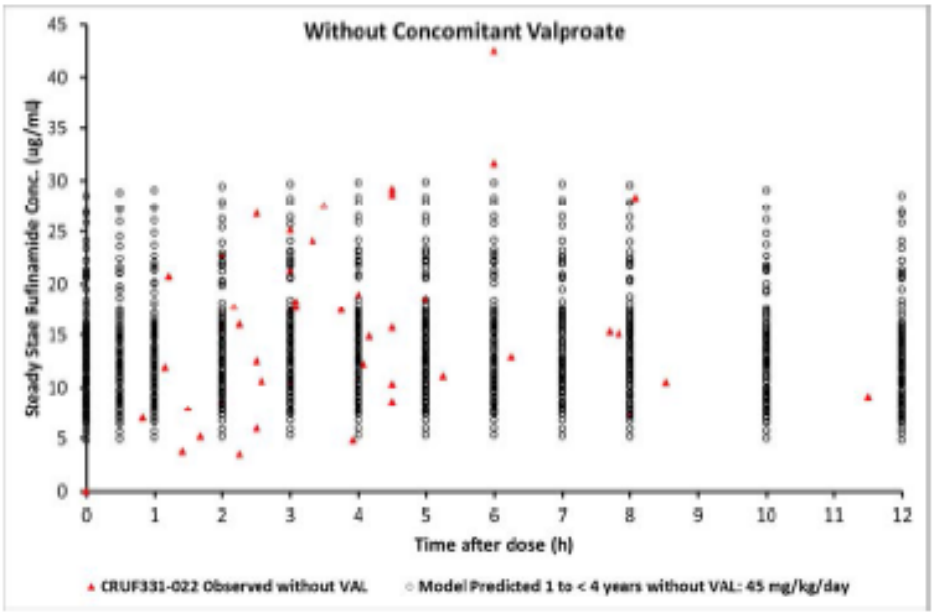
Figure 9 Linear-Linear pcVPCs by Body Weight Category

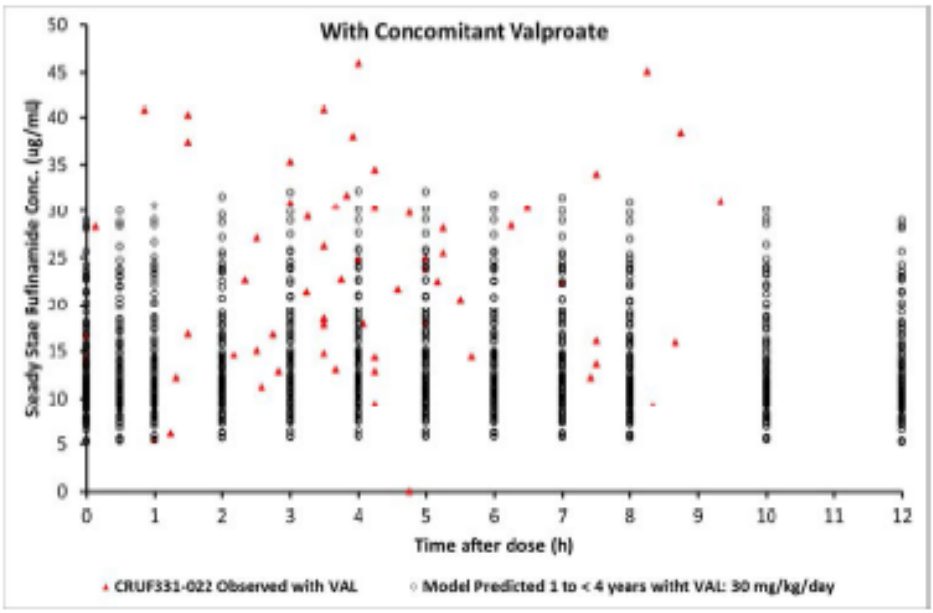
Overall, the pcVPCs indicate no systematic deviations of observed data and simulations based on the final model; the PIs contain the observed median, 5% or 95% percentiles of the data across time and support the predictive use of the rufinamide model for extrapolation to LGS patients aged 1 to < 4 years.

- Weigh based dosing recommendations for LGS subjects aged 1 to < 4 years

Using the final PK model rufinamide concentrations at steady state were predicted following 45 mg/kg/day alone and following 30 mg/kg/day in the presence of valproate in subjects aged 1 to < 4 (for 50 subjects with median body weight of 11.1 kg for subjects aged 1 to < 2 years and for 50 subjects with median body weight of 15.4 kg for subjects aged 2 to < 4 years. Model-predicted individual concentrations were overlaid with observed steady state concentrations from subjects aged 4 to 36 years in Study 022, which was the core study used to obtain Market Authorization approval in the EU, both in the presence and absence of valproate. As depicted in **Figure 24**, based on the proposed dosing of 45 mg/kg/day alone or 30 mg/kg/day in the presence of valproate in subjects aged 1 to < 4 years, model predicted steady state concentrations in subjects aged 1 to < 4 years were comparable. This is demonstrated by the large overlap with concentrations observed in Study 022 in subjects aged ≥ 4 years dosed as per the approved SmPC.

Figure 24 Plot of observed Rufinamide Concentrations from Studies 303 and CRUF331 0022





For the patient population aged 1 to less than 4 years, a weight based dosing is recomended. For both tablet and oral suspension formulations, treatment should be initiated at a dose of 10 mg/kg/day (0.25 mL/kg/day). As described in the SmPC, each daily dose should be administered in 2 equally divided doses separated by approximately 12 hours.

For the patient population aged 1 to less than 4 years, each dose of the oral suspension should be rounded off to the nearest 0.5 mL. The suitability for accurate dosing using the oral syringe with 0.5 mL increments is demonstrated in Module 3.2.P.2.4 (Suitability of Dosing Devices for Rufinamide Oral Suspension) of the EU dossier. The grading accuracy of the syringe and compliance with Ph. Eur. 2.9.27 both demonstrate the dosing accuracy of the 20 mL oral syringe.

This syringe is also CE marked and complies with the requirements of Directive 93/42/EEC. The smallest volume increment of 0.5 mL that can accurately be measured using this syringe corresponds to 20 mg of rufinamide.

For the tablets, daily dose should be rounded off to the nearest 100 mg. Rufinamide tablets comply with the requirement on subdivision of tablets according to the Ph. Eur., hence consistency in drug substance content of half dosage units is assured. This has been confirmed for all strengths (100 mg, 200 mg and 400 mg) of rufinamide tablets following the conduct of the test for subdivision of tablets as per the Ph. Eur. Monograph. Ease of tablet breaking was demonstrated by the fact that no tablet was rejected during testing due to difficulty in breaking. A 100 mg tablet subdivided into 2 halves may be used to administer 50 mg to patients in the lower range of weight. As indicated in the SmPC, if the patient has difficulty with swallowing, tablets can be crushed and administered in half a glass of water.

2.3.3. Discussion on clinical pharmacology

The main purpose with the population PK analysis is to provide evidence that the proposed dosing regimen in children 1-4 years of age provides similar exposure levels as for the previously approved population. In order to predict adequate individual exposure values and derive a correct posology it is important that CL/F is well described. It is acknowledged that due to the individual titration based dosing, non-normalised exposure can be misleading as different dosing regimens are allowed. The aim of the exposure similarity comparison is to assure that the exposure given a maximum dose is similar across body sizes (and ages). Hence, it is more informative to evaluate dose-normalized exposure as well as simulated exposure given the maximum dose. The graphs of dose-normalised exposure indicate that exposure is similar across the full patient population and different concomitant anti-epileptic drugs,

The PK analysis for the initial model (003R) was conducted using 7272 rufinamide plasma concentration observations from a total of 1182 subjects. For Studies 303, 304, and 022 in LGS subjects, 340 rufinamide plasma concentrations from 154 LGS subjects were available. Other studies contributed 6932 observations from 1028 subjects. 110 plasma concentrations collected in 24 LGS patients aged 1 to 4 years were included in the modeling work. This represents merely 1.5% of the total dataset for the initial model (003R). The data collected in the target group of patients aged 1 to < 4 years represent approximately 2% in the PK dataset corresponding to the updated model (004R) – see discussion below, Although the PK data in children 1 to <4 years is limited, the model diagnostics of the updated PK model (004R) indicate that the model describes rufinamide PK in children 1 to <4 years sufficiently well. The updated PK model is considered adequate for prediction of plasma concentrations for all body sizes (and subsequently all ages).

The MAH has provided a pooled population PK analysis to describe the PK of rufinamide in small children, including body size relations on CL and V. The general approach is endorsed, however the CHMP raised some concerns regarding the model fit to data. The provided visual predictive checks indicate that the clearance and volume are not well captured for the single dose data (Study E2080-E044-003 and AE/PT2) which are the data that would contain most information regarding volume of distribution. Additionally, the parameter estimate of volume of distribution deviates substantially from previously reported values for rufinamide (Perucca et al, 2008) which warrants further investigation. During the procedure the Applicant was advised to consider using fixed allometric exponents as it appears that the population parameters of clearance and volume are insensitive to the value of the exponent which could be an indication of an over parameterized model. Alternatively, different exponents for the paediatric and adult population can be considered since the relation between body size and drug disposition in the adult population is not necessarily quantitatively similar to the relation in children. According to the principle of parsimony, estimation of fewer parameters could facilitate more accurate estimation of the remaining parameters. During the procedure the MAH has provided an updated population PK model which describes the rufinamide PK data well. The new population PK analysis was performed on pooled data from 3 selected Phase 3 studies in LGS patients (Studies 022, 303 and 304) and 1 single-dose study in healthy subjects (Study E2080- E044-003). Both fixed and estimated allometric scaling for body weight effect on clearance and volume of distribution were evaluated during model development and the objective function with estimated allometric exponents (df=2) was only 3.4 points lower compared to that with fixed exponents (Report CPMS-E2080-004R-v1). A fixed allometric scaling exponent was chosen for the final PK model, which adequately captured rufinamide PK from all 4 studies. The goodness-of-fit plots and visual predictive checks all indicate an adequate model fit to data. Furthermore, the model parameters are in line with previously reported PK parameters for rufinamide. The model is deemed adequate for exposure predictions for all body weights (and subsequently all ages) and hence the exposure predictions can be used in the evaluation of exposure similarity between age groups and to support the proposed posology for Inovelon in LGS patients 1 to <4 years.

Based on GOF plots and bootstrap findings, the initial model (003R) appeared to be qualified to describe already well the data. However, a clear tendency of under estimation of the individual predicted plasma concentrations over 20 ng/mL was observed. The predictive performances of the initial model (003R) showed clear mis-specifications on the basis of the produced graphs. However these concerns have been addressed by the applicant by developing the updated PK model (004R) which describes the rufinamide PK data sufficiently well and displays no major model misspecification for any of the included studies.

The MAH has provided simulations of steady-state concentrations to support the proposed weight based dosing. The simulation method is considered adequate. It is agreed that the predicted steady-state concentration in LGS patients 1 to < 4 years largely overlap the observed concentrations in study CRUF331-022, with a slight tendency towards the lower range of observed concentrations. The proposed dosing regimen in combination with valproate is considered acceptable as the predicted exposure in patients 1 to <4 years of age does not fall outside of the observed exposure range.

The Applicant has provided clear description on how weight based dosing will be handled in clinical practice when using the oral suspension and the tablet formulation. Dose administration instructions included in the SmPC section 4.2 are considered accurate and detailed enough by the CHMP. For each strength of the tablet formulation compliance with the requirement on subdivision of tablets according to the Ph Eur has been shown. The dose accuracy of the 20 ml oral syringe to be co-packed with the suspension has been satisfactorily demonstrated down to the lowest proposed dose volume of 1 ml.

In line with the Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2 the feasibility of administration through a feeding tube should be addressed. The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be

considered. Dose recovery after extrusion needs to be demonstrated using feeding tubes and rinse volumes relevant to the target age group(s). The applicant is recommended to evaluate post approval the feasibility of administrating the rufinamide oral suspension via an enteral feeding tube; as reflected in their letter of recommendation.

2.3.4. Conclusions on clinical pharmacology

A population PK model based on an enlarged data set from patients with LGS (including 24 patients 1-4 years old), other forms of epilepsy and from healthy subjects was presented by the applicant. In order to address the CHMP concerns related to the shortcoming of this initial PK model the MAH has provided an updated population PK model which describes the rufinamide PK data well. The new population PK analysis was performed on pooled data from 3 selected Phase 3 studies in LGS patients (Studies 022, 303 and 304) and 1 single-dose study in healthy subjects (Study E2080- E044-003). Both fixed and estimated allometric scaling for body weight effect on clearance and volume of distribution were evaluated during model development and the objective function with estimated allometric exponents (df=2) was only 3.4 points lower compared to that with fixed exponents (Report CPMS-E2080-004R-v1). A fixed allometric scaling exponent was chosen for the final PK model, which adequately captured rufinamide PK from all 4 studies. The goodness-of-fit plots and visual predictive checks all indicate an adequate model fit to data. Furthermore, the model parameters are in line with previously reported PK parameters for rufinamide. The model is deemed adequate for exposure predictions for all body weights (and subsequently all ages) and hence the exposure predictions can be used in the evaluation of exposure similarity between age groups and to support the proposed posology for Inovelon in LGS patients 1 to <4 years.

The proposed dosing regimen in combination with valproate as reflected in the SmPC section 4.2 is considered acceptable as the predicted exposure in patients 1 to <4 years of age does not fall outside of the observed exposure range. Dose administration instructions are considered accurate and detailed enough by the CHMP.

In addition, the applicant is recommended to evaluate post approval the feasibility of administrating the rufinamide oral suspension via an enteral feeding tube.

2.4. 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.

As discussed in section “2 Scientific discussion” above, an overview of the efficacy of rufinamide for the proposed paediatric population has been extensively discussed in the initial application EMEA/H/C/000660/II/0037. No new data was submitted for the current Application.

From the initial discussions, 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 acceptable. However,

although the efficacy extrapolation strategy was considered acceptable, use of rufinamid in the targeted population is conditioned by the assessment and establishment of an adequate dose (*see comments below in section 2.4.3*).

2.4.1. Dose response study(ies)

No dose-response studies were conducted which was considered acceptable by the CHMP.

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).

2.4.2. Main study(ies)

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.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 below also Figure 6):

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.

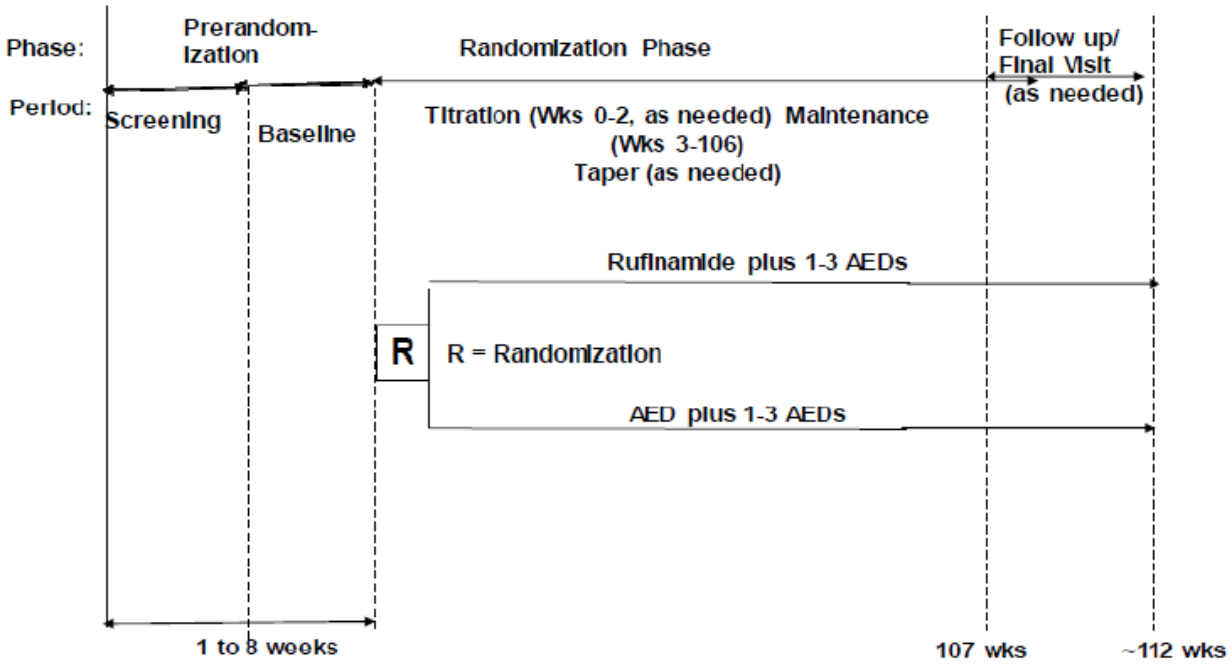


Figure 6 – Study 303 Diagram

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

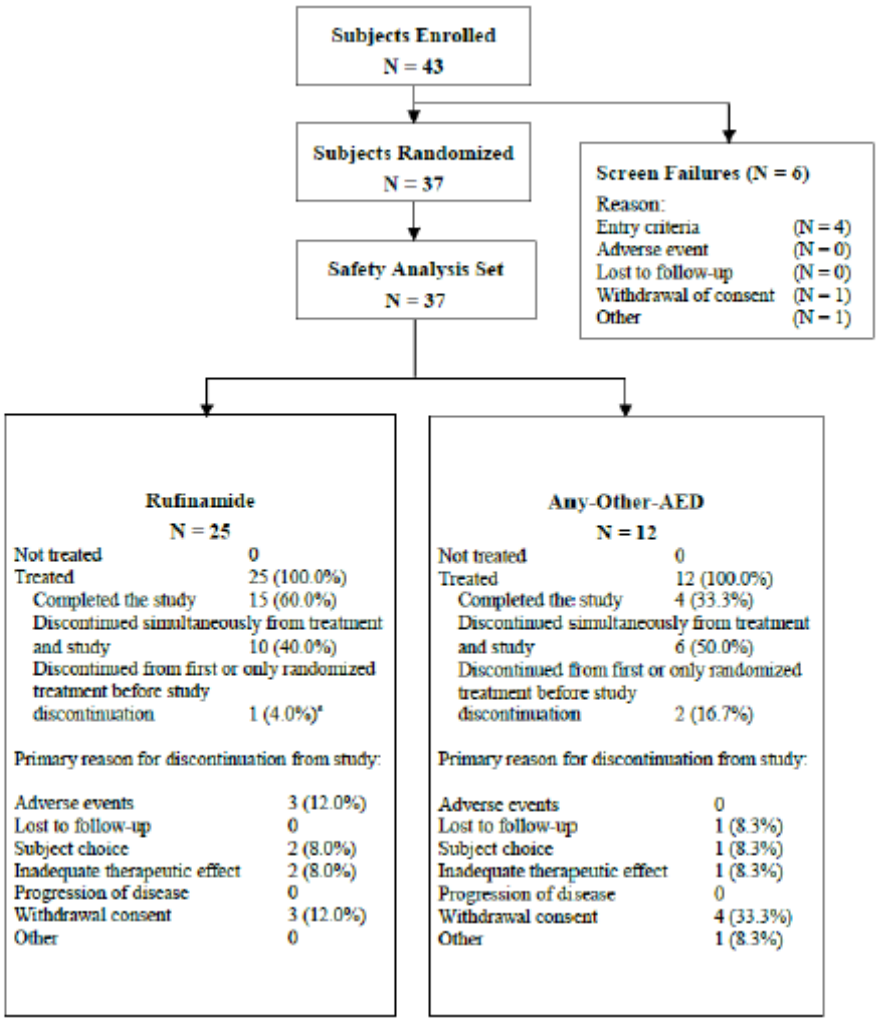
Evaluation of safety was performed on the Safety Population. Treatment-emergent adverse events (TEAEs) were summarized by presenting, for each treatment group, the incidence of AEs. Descriptive summary statistics (mean plus standard deviation, median, minimum, and maximum) of the laboratory, and vital 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.

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 10 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
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.

Table 11 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 12**. 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 13.

Table 12 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 13 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 14**).

Table 14 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 15 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	
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)
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				
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

<u>LDS Average Phrase Length</u>

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(ies)

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

Table 16 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.	

2.4.3. 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.

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.

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.

Dose recommendations

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.

Indeed, in study 303, rufinamide was not administered as per the current EU approved dosing recommendations for patients <30 kg where a daily dose of 200 mg is recommended for treatment initiation. Rather rufinamide was dosed in line the FDA US labelling. This schedule was similar to the one used in study 022 (pivotal trial for the initial MAA of Inovelon), which formed the basis for the current EU posology in patients aged 4 years and older. However, as highlighted in the initial application, patients in study 303 weight substantially less (mean weight: 12.78 kg, Min, Max: 7.0, 19.0) than in study 022 (mean weight: 42.3 kg, Min, Max: 15.5, 138.5). Maximum weight based doses in study 303 were thus always below the doses that would be achieved when applying the approved EU posology. Even if similar exposure in the younger children (1-4 years) compared to the older ones can be shown, the current EU approved dosing scheme is not optimal.

Thus, the weight based dosing regimen for the younger children as applied in the studies 303 and 022 and mentioned in the FDA US labelling (either dose/kg) would be appropriate. The proposed wording in the Product information is in line with the proposed weight based dosing regimen.

As stated in the adopted PIP, the dose regimen of rufinamide used in this study was shown to be well-tolerated and effective in subjects ≥ 4 years of age, and is approved at these doses in the tablet form in the EU and US, on the basis of results from Study CRUF331 0022 (efficacy and safety of rufinamide as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS). Study CRUF331 0022 was the primary basis for approval of rufinamide, using this dosing regimen (45 mg/kg/day for 28 days during the 3 year extension) and patient population (LGS). The oral suspension (OS) was demonstrated to be bioequivalent to the tablet and well tolerated in studies comparing tablet and suspension formulations.

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) behaviour 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 paediatric 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.

2.4.4. Conclusions on the clinical efficacy

Rufinamide film-coated tablets were first approved in the EU via the Centralised Procedure in 2007 for use as adjunctive therapy in the treatment of seizures associated with LGS in patients 4 years of age and older. In support of the sought broadening of the indication to include pediatric patients from 1 year to less than 4 the MAH has submitted the results of an open label safety study (Study E2080-G000-303; [Study 303]). All results should be interpreted with caution because of the small sample sizes and methodological limitations of the clinical design.

As discussed above in section *2.4 Clinical efficacy*, no new efficacy data have been submitted within this new application. Efficacy part is based on the previous submitted data and discussions. Thus, as concluded by the CHMP at the time of the first submission, 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.

The weight based dosing regimen for the younger children as applied in the studies 303 and 022 and mentioned in the FDA US labelling (either dose/kg) would be appropriate provided that the newly proposed PK data analysis support a posology yielding similar exposure as in adults, where clinical efficacy was directly studied. Indeed, an update of the population-PK modelling including paediatric data (1-4 years) and other data collected in older children, adolescent and adults with LGS are also provided.

2.5. Clinical safety

Introduction

As discussed above in section *2.4 Clinical efficacy*, no new safety data have been submitted within this new application

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 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 1 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 report section. 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 section 2.4.2 in this report.

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 17 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)
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

Study 303

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 experiencing 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).

Study 303

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

Study 303

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 (OS) has been approved for marketing in 34 countries. Rufinamide is sold under the trade names Inovelon and Banzel.

The use of rufinamide in children aged 1 year and over was approved by the FDA in February 2015.

As highlighted above, no new safety/efficacy data was submitted as part of this application, even with respect to post-marketing experience. From the initial application, a search based on the global rufinamide adverse event report database for Spontaneous Serious and Non-serious and Solicited SADR Reports of Events in Paediatric Age (<4 Years of Age), when an age was provided by the reporter for the period 08 Jan 2015 through 31 August 2016, was provided.
The search revealed 8 reports (5 serious) describing 18 adverse events received in this age group. According to the applicant, the review of these reports is consistent with the underlying disease of this patient population and with the safety profile of rufinamide described in the product information for children aged ≥ 4 years of age.

Table 18 Database for Spontaneous Serious and Non-serious events

Age/ Gender	Event PT Name	Total Daily Dose/ Action taken with drug	Time to onset	Event Outcome	Con Meds	Comment
3.5y/Female	Rash	Inovelon 50 mg/kg Inovelon therapy reduced to 45mg/kg	19 days	Improved	Clobazam	Health professional report (physician). Nonserious case. Inovelon (suspension) prescribed for the treatment of Lennox-Gastaut syndrome Following week of receiving the lower dose of Inovelon 45 mg/kg the dose was increased to 50 mg/kg and a rash reappeared on hands, abdomen and face. Dose reduced again to 45 mg/kg. Two days later, that patient was seen by a dermatologist, and what was left of the rash was not toxicodermia.
3y/Male	Decreased appetite Transaminases increased	Inovelon 250 mg daily dose Inovelon therapy continued	Days	Complete recovery	Depakine	Consumer report Nonserious case. Inovelon prescribed for the treatment of Lennox-Gastaut syndrome. Patient experienced loss of appetite and transaminases doubling from normal values the transaminases. Inovelon continued and depakine dose was reduced and the event abated.
3y/Male	Somnolence	Inovelon titrated up to 250 mg daily dose Inovelon continued.	Months	Complete recovery	Valproate sodium Levetiracetam Clobazam Topiramate	Health professional report (physician) and literature report (Experience Of Using Rufinamide For Intractable Epileptic Patients With Severe Motor And Intellectual Disabilities" by Satoshi Kidowaki, et al,) Nonserious case. Inovelon (tablets) prescribed for the treatment of Lennox-Gastaut syndrome Patient experienced somnolence on the Inovelon 250 mg daily dose. Inovelon continued and sodium valproate was decreased because of the somnolence and the event abated.
3y/Male	Pyrexia Rhabdomyolysis	Inovelon 200 mg daily dose Inovelon therapy discontinued.	5 days	Improved	Carbocisteine Phenobarbital Zonisamide Valproate sodium Trihexyphenidyl HCl Levocarnitine HCl Lamotrigine Diazepam Budesonide Ambroxol HCl Pranlukast Famotidine	Health professional report (physician)Solicited report from the Post-Marketing Surveillance of Long-Term Administration of Inovelon Tablets in Patients with Lennox-Gastaut Syndrome Serious case. Patient was hospitalized and diagnosed with rhabdomyolysis. Inovelon was discontinued and the events improved. The investigator classified the event as "Possibly related" to the Inovelon therapy and commented: "Inovelon was increased; on the following day,

						the patient had continuous strong muscle tightness with high fever of 42º C. CK was 4000 U/L. The symptoms included an element of symptomatic myotonia of concomitant disease which worsened temporarily. Inovelon was discontinued. Patient was medically treated and symptoms improved. Alternate causes other than Inovelon for pyrexia: Concomitant disease. Rhabdomyolysis: Aggravation of epileptic seizure was not noted. Pyrexia: Pyrexia was suspected to be caused as a result of hypertonia."
2y/Male	Condition aggravated Diarrhoea Metabolic acidosis Nausea Seizure Vomiting Weight decreased	Banzel®: 300 mg daily dose Banzel® discontinued	Days	Complete Recovery	Sodium bicarbonate Calcium Cyproheptadine HCl Lansoprazole Colecalciferol	Health Authority report Serious case (hospitalization). Banzel® prescribed for the treatment of generalized convulsive epilepsy. Banzel® discontinued and events abated
3Y/Male	Rash	Inovelon dosage and frequency not provided Inovelon was discontinued	2 weeks	Continued	Valproate sodium	Health professional report (nurse) Serious case (hospitalization). Inovelon prescribed for an unknown indication. Following 2 weeks of Inovelon therapy the patient experienced rash. The patient was hospitalized. Inovelon was discontinued and the rash continued.
1Y/Male	Seizure	Inovelon dosage not provided Co suspect medications: Ciprofloxacin (dose and frequency not provided) Vigabatrin (dose and frequency not provided) Vigabatrin therapy continues Ciprofloxacin and rufinamide therapy action is unknown	Days	Unknown	Corticotropin Clobazam	Consumer report Serious case: Considered medically important by the company. Banzel® prescribed for an unknown indication. Patient began co-suspect medications vigabatrin for the treatment of infantile spasm and ciprofloxacin for UTI and rufinamide and soon after starting rufinamide (dates not provided) the patient experienced an increase in seizure activity. Vigabatrin therapy continues therapy with ciprofloxacin and rufinamide is unknown. Outcome of the event is unknown.
3y/Male	Coordination abnormal	Inovelon 600 mg daily dose/ Inovelon	Unknown	Continued Continued Complete	Oxcarbazepam Ergenyl chrono Diazepam	Health Authority Serious case Inovelon prescribed for the treatment of tuberous sclerosis

	Status epilepticus Balance disorder	therapy increased to 1000 mg daily dose and then discontinued		recovery		and epilepsy. Following an unknown latency period but on the same day the dose was increased to 300 mg twice daily the patient experienced balance difficulty and coordination disturbance requiring hospitalization. A few days later the dose of Inovelon was increased to 500 mg twice daily. The patient experienced focal status epilepticus which prolonged the hospitalization. Inovelon was discontinued.

Moreover, data on cumulatively events was provided by the reporter from the IBD January 2007 through 31 August 2016 (see Table 19 below). According to this database, it seems that there have been 36 reports in this age group, 19 of which were serious.

Review of these cases indicates that events in the SOCs of Nervous System Disorders and Skin and subcutaneous tissue disorders appear to have the highest reporting rate in those younger than 4 years of age, consistent with the underlying disease of this patient population and with the safety profile of rufinamide described in the product information for children aged ≥ 4 years of age.

Table 19 Cumulative Summary of Spontaneous Serious and Non-serious and Solicited SADR Reports of Events in Paediatric Age (<4 Years of Age) Received from the IBD through 31 Aug 2016

Total Reports	***36***
Report Seriousness	
Non-serious	***17***
Serious	***19***
Total Events	***72***

Events (PTs)*	**Non-serious**	**Serious**
Seizure	0	8
Rash	5	2
Decreased appetite	4	0
Vomiting	2	1
Balance disorder	0	2
Diarrhoea	0	2
Nausea	1	1
Off label use	1	1
Pyrexia	0	2
Somnolence	2	0
Status epilepticus	0	2
Abnormal behaviour	1	0
Acute hepatic failure	0	1
Aggression	1	0
Agitation	0	1
Atonic seizures	0	1
Blood creatinine increased	1	0
Bradycardia	1	0
Cholestasis	0	1
Complex partial seizures	0	1

Condition aggravated	0	1
Coordination abnormal	0	1
Dehydration	0	1
Dysphagia	1	0
Dysphemia	1	0
Ear infection	0	1
Gamma-glutamyltransferase increased	1	0
Hepatitis fulminant	0	1
Hyperaemia	0	1
Hyperhidrosis	0	1
Hypertonia	0	1
Insomnia	1	0
Metabolic acidosis	0	1
Muscle rigidity	0	1
Nephrotic syndrome	0	1
Pain	0	1
Pneumonia aspiration	0	1
Pruritus	0	1
Rash maculo-papular	1	0
Restlessness	1	0
Rhabdomyolysis	0	1
Screaming	1	0
Tachycardia	0	1
Transaminases increased	1	0
Tremor	1	0
Urine abnormality	1	0
Weight decreased	0	1

Age	
Range	4 months to 3.5 years
Gender	
Males	20
Females	14
Not provided	2
Latency	
Range	1 day to 14 months
Country (≥ 3 reports)	
US	12
Italy	4
Japan	4
Germany	3
Dechallenge	
Negative	3
Not Applicable	9
Positive	17
Unknown	13
Outcome	

Complete Recovery	19
Continued	7
Improved	7
Unknown	10
*The number of events exceeds the number of reports because frequently more than 1 sign or symptom is reported.	

AT the CHMP's request rufinamide post-marketing safety data (for Spontaneous Serious and Non-serious and Solicited SADR reports) contaning reports received from a data lock point (DLP) of 31 Aug 2016 through 13 Nov 2017 was submitted.

During the reporting period of 31 Aug 2016 through 13 Nov 2017 there have been a total of 4 reports (all non-serious) associated with use in a child less than 4 years of age; 3 of the 4 reports were from a single literature article. Review of these cases indicates that events in those younger than 4 years of age continue to be consistent with the underlying disease of this patient population and with the safety profile of rufinamide described in the product information for children aged ≥ 4 years of age. These 4 cases are summarized in **Table 20**.

Table 20 Cumulative Summary of Initial Spontaneus Serious and Non-serious and Solicited SADR Reports in Paediatric Age (<4 years of age) received from Safety DLP of last Company Response (31 August 2016) through 13 Nov 2017

Age/ Gender	Event PT Name	Total Daily Dose/ Action taken with drug	Time to onset	Event Outcome	Medical history	Con Meds	Comment
3 years/ Unknown	Epilepsy	Inovelon 53.3 mg/kg daily dose Inovelon therapy discontinued	Unknown	Complete recovery	Not provided	None Provided	Health professional report (Physician) and literature report by Sasaki S., et al. Nonserious case. Inovelon prescribed for the treatment of Dravet Syndrome. Patient experienced epilepsy aggravated. Inovelon discontinued and the event abated.
3 years/ Unknown	Heart rate increased Mood altered Agitation	Inovelon 54.5 mg/kg daily dose Inovelon discontinued	Unknown	Complete recovery	Concomitant perinatal disorder	Not provided	Health professional (Physician) and literature report Sasaki S., et al. Nonserious case. Inovelon prescribed for the treatment of West's Syndrome Patient experienced increased heart rate (100 bpm to 140 bpm) and bad mood on the Inovelon 54.5 mg/kg daily dose. Inovelon

							discontinued and the events abated.
3 years/ Unknown	Decreased appetite	Inovelon 36.4 mg/kg daily dose Inovelon therapy continued.	Unknown	Complete recovery	Brain malformation	Not provided	Health professional report (Physician) and literature report; Sasaki S., et.al. Nonserious case. Inovelon prescribed for the treatment of West's Syndrome. Patient experienced decreased appetite on the Inovelon 36.4 mg/kg daily dose. Inovelon continued and the event abated.
2 years/ Female	Gamma-glutamyltransferase increased	Inovelon 380 mg total daily dose Inovelon continued	212 Days	Unknown	None Provided	Phenobarbital Zonisamide	Health professional report (Physician) nonserious case Inovelon prescribed for the treatment of LGS. Patient experienced increase in gamma-GT to 700 (units unspecified). No action was taken for abnormal laboratory test. While increase and drop in gamma-GT had repeated since before administration of Inovelon, marked elevation was noted. Inovelon continued and event outcome unknown.

Children 4 to Less than 17 Years of Age

At the time of the initial application, 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

At the time of the initial application, 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 initial 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.

Serious adverse events / other significant events

A cumulative summary table of serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources that have been reported from marketing approval (IBD) to 13 Nov 2017, is presented below. Cumulatively there have been 19 serious reports describing 43 serious events in children less than 4 years of age, with ages ranging from 4 months to < 4 years of age. More than half of the patients were male. Latency ranged between hours to just over 1 year. None had fatal outcomes and the majority had outcomes of complete recovery or improvement. Of the 19 reports, 18 reported concomitant medications, mostly other anti-epileptics; in 4 of these 18 cases another medication was considered co-suspect. One of the 19 reports (nephrotic syndrome) was considered to be 'Not Related' by the reporter.

As would be expected for this indication, the SOC of nervous system disorder has the highest reporting rate of serious adverse reactions in those younger than 4 years of age. The most commonly reported serious adverse events in the nervous system disorders SOC was seizure (8 events). Serious adverse events reported in more than 1 patient included 2 reports each of balance disorder, status epilepticus, pyrexia, diarrhea and rash. Review of the serious cases indicates that most of the events occurred in one patient.

An additional search of the global rufinamide adverse event report database was performed for all reports with an event coded to the SOCs of hepatobiliary disorders and renal and urinary disorders since the IBD through 13 Nov 2017 in children younger than 4 years of age. The search yielded 2 post marketing reports where one patient experienced an event of nephrotic syndrome and another patient experienced events of acute hepatic failure, cholestasis, hepatitis fulminant and ear infection. These 2 reports are summarized below.

The report of fulminant hepatitis, and acute liver failure is a health authority report that describes a 2 year old female who received Inovelon for convulsions and was also treated with co-suspect anti-epileptic agent, phenobarbital (Gardenal), and an antibiotic, amoxicillin/clavulanic acid (Augmentin). The patient received Inovelon 100 mg twice daily. Days later following a diagnosis of bilateral otitis requiring hospitalization and antibiotic treatment the patient experienced fulminant hepatitis, acute liver failure and hepatic cholestasis. All suspect and concomitant medications were discontinued and the events abated. Concomitant medications included: levocarnitine, clonazepam, amitriptyline hydrochloride, trihexyphenidyl hydrochloride, and esomeprazole magnesium. Medical history consisted of Crisponi syndrome.

The report of nephrotic syndrome is a physician and consumer report that describes a 3 year old female who received rufinamide (known as Banzel in the US) for the treatment of epilepsy. The patient received Banzel 120 mg daily which was titrated up to 320 mg/daily. The patient experienced a urinary tract infection and was diagnosed with nephrotic syndrome associated with proteinuria (urinary protein 4+) and hypoalbuminemia albumin (3.3 gm/dl), following a 4 months latency period. The event of nephrotic syndrome was considered medically important by the company. Banzel therapy continued. The nephrotic syndrome continues and the patient is being treated with prednisone for the event. The reporting physician considered the event of nephrotic syndrome to be not related to the Banzel therapy. Concomitant medications included: clobazam, levetiracetam, and vigabatrin. Medical history consisted of congenital brain malformation/microcephaly.

The SADRs observed in children younger than 4 years of age are consistent with the underlying disease in this patient population and with the safety profile of rufinamide described in the product information for children aged ≥ 4 years of age. There is no single adverse event or grouping of adverse events that appears to be occurring at a higher than expected rate for this population or that indicates a new safety signal.

Table 21 Cumulative summary table of Serious Spontaneous and Solicited SADR Reports of Events in Paediatric (<4 Years of Age) received from the IBD through 13Nov 2017

Total Serious Reports	19
Total Events	43
Events (PTs) reported in ≥ 2 patients	**Serious**
Seizure	8
Rash	2
Decreased appetite	0
Vomiting	1
Balance disorder	2
Diarrhoea	2
Gamma-glutamyltransferase increased	0
Nausea	1
Pyrexia	2
Somnolence	0
Status epilepticus	2
Age	
Range	4 months to ~ 3.5 years
Gender	
Males	13
Females	6
Latency	
Range	Hours to 14 months
Country (≥ 1 reports)	
US	7
Canada	2
Italy	2
Japan	2
Dechallenge	
Negative	3
Not Applicable	3
Positive	29
Unknown	8
Outcome	
Complete Recovery	27
Continued	6
Improved	4
Unknown	6

2.5.1. 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.

Of the 19 serious adverse events (SAE)cases reported post marketing (43 serious events), 18 cases were considered as related to rufinamide by the reporter. No signal was raised based on these SAE. All SAE are known with rufinamide and mentioned in the current SmPC.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.

The MAH provided the 2 requested Cioms forms:

- One case of **fulminant hepatitis** and **acute liver failure** reported in a 2 year old female patient also treated with amoxicilline/clavulanic acid. Hepatitis is a known ADR with amoxicillin. No further investigation is required.
- One case of **nephrotic syndrome** is reported in a 3 year old female who presented urinary tract infection 4 months after rufinamide treatment initiation. This infection could induce nephrotic syndrome. According to the reporter, diabetes could also be suspected. Some infection are known ADR with rufinamide (pneumonia, ear infection, sinusitis, and rhinitis). No further investigation is required at this stage. Renal disorders should be followed as part of routine pharmacovigilance until further available data on this risk.

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). In addition, the applicant provided a scientific rational based on literature and published data to discuss the metabolic differences and capacity of children (especially children less than 4 years of age) compared to adults. Based on these data, it appears that the main enzyme system responsible for metabolism/hydrolysis of parabens esters are the carboxylesterases in humans (hCE1 and hCE2 [human carboxylesterase]). Although there is some uncertainty around the nature and maturity of the metabolic routes of parabens in very young children, with a large variability among different age groups (less than 1 year of age, children [1-10 years old], and adults, evidence suggests that hCEs activity is approximately 50% of adult levels of activity by the age of 3 months. These data provides some reassurance on the capacity of young children to hydrolyze propylparaben via hCE in particular with regard to the proposed maximum dose of rufinamide. The CHMP considers that the content of propylparaben has been satisfactorily justified and no safety concerns in the proposed age group are foreseen.

2.5.2. 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.

2.5.3. PSUR cycle

In order to closely monitor this newly added population of children less than 4 years of age the PSUR cycle for the medicinal product should follow a yearly cycle until otherwise agreed by the CHMP.

Based on the above considerations, the CHMP is of the opinion that the already existing entry in the EURD

list for rufinamide needs to be amended as follows: the PSUR cycle for the medicinal product should follow a 1 year cycle. This new frequency will take effect after the next data lock point currently published in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC. The next PSUR, which will still maintain the previous frequency, should cover the period to 15/01/2020 and be submitted within 90 days of the data lock point in accordance with the updated EURD list. Taking into account the new frequency, the data lock point for the following PSUR will be 15/01/2021.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 10.1 (dated 20 March 2018) is acceptable.

The CHMP endorsed the RMP version with the following contents.

Safety concerns

Table - Summary of Safety Concerns

Important identified risks	• Rash and Hypersensitivity including DRESS and SJS • Decreased Appetite and Weight Loss • Coordination Abnormal (Ataxia) • Somnolence • Dizziness
Important potential risks	• Status Epilepticus • Shortened QT interval on ECG • Suicidality
Important missing information	• Pregnancy • Hepatic Impairment • Children Younger than 1 Year of Age

DRESS = Drug Reaction with Eosinophilia and Systemic Symptoms, ECG = electrocardiogram, QT = time interval from the onset of the QRS complex to the end of the T wave on an ECG tracing, SJS = Stevens-Johnson syndrome.

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Rash and Hypersensitivity including DRESS and SJS	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities

Decreased Appetite and Weight Loss	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4	Routine PV activities
Coordination Abnormal (Ataxia)	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Somnolence	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Dizziness	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Important Potential Risks		
Status Epilepticus	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Sections 2 and 4	Routine PV activities
Shortened QT interval on ECG	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2	Routine PV activities
Suicidality	Routine risk minimisation measures: • SmPC Section 4.4 • PL Sections 2 and 4	Routine PV activities
Missing Information		
Pregnancy	Routine risk minimisation measures: • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.6 • PL Section 2	Routine PV activities, and: Pregnancy registry will be maintained by EURAP
Hepatic Impairment	Routine risk minimisation measures: • SmPC Section 4.2 • SmPC Section 5.2 • PL Section 2, Section 4	Routine PV activities
DRESS = Drug Reaction with Eosinophilia and Systemic Symptom, EURAP = European and International Registry of Anti-epileptic drugs in Pregnancy, PL = Package Leaflet, PV = Pharmacovigilance, QT = time interval from the onset of the QRS complex to the end of the T wave on an ECG tracing, SJS = Stevens-Johnson syndrome, SmPC = Summary of Product Characteristics.		

2.7. Update of the Product information

As a consequence of the new indication related to include the treatment of seizures associated with Lennox Gastaut syndrome in patients 1 year of age and older as adjunctive therapy, sections 4.1, 4.2, 4.5, 5.1, 5.2 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Belgium and Luxemburg.

The changes pertaining to SmPC sections 4.1, 4.2, 4.5, 5.1 and 5.2 are indicated below (new text in bold, deleted text double strikethrough). The remaining SmPC changes are highlighted in the attached Product Information (PI) document.

4.1 Therapeutic indications

Inovelon is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients~~4~~ **1** year~~s~~ of age and older.

4.2 Posology and method of administration

[…]

Posology

Use in children from one year to less than four years of age

Patients not receiving valproate:

Treatment should be initiated at a dose of 10 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. According to clinical response and tolerability, the dose may be increased by up to 10 mg/kg/day every third day to a target dose of 45 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. For this patient population, the maximum recommended dose is 45 mg/kg/day.

Patients receiving valproate:

As valproate significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon is recommended for patients being co-administered valproate. Treatment should be initiated at a dose of 10 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. According to clinical response and tolerability, the dose may be increased by up to 10 mg/kg/day every third day to a target dose of 30 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. For this patient population, the maximum recommended dose is 30 mg/kg/day.

If the recommended calculated dose of Inovelon is not achievable, the dose should be given to the nearest whole 100 mg tablet.

Use in children four years of age or older and less than 30 kg

Patients <30 kg not receiving valproate:

Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every ~~two~~ **third** day~~s~~, up to a maximum recommended dose of 1000 mg/day.

Doses of up to 3600 mg/day have been studied in a limited number of patients.

Patients <30 kg also receiving valproate:

As valproate significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon is recommended for patients <30 kg being co-administered valproate. Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, after a minimum of 2 days the dose may be increased by 200 mg/day, to the maximum recommended dose of 600 mg/day.

Use in adults, adolescents and children four years of age or older of 30 kg or over

Patients >30 kg not receiving valproate:

Treatment 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, as frequently as every ~~two~~ **other** day~~s~~, up to a maximum recommended dose as indicated in the table below.

Weight range	30.0 – 50.0 kg	50.1 – 70.0 kg	≥70.1 kg
Maximum recommended dose	1,800 mg/day	2,400 mg/day	3,200 mg/day

Doses of up to 4,000 mg/day (in the 30 -50 kg range) or 4,800 mg/day (in the over 50 kg) have been studied in a limited number of patients.

Patients >30 kg also receiving valproate:

Treatment 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, as frequently as every other day, up to a maximum recommended dose as indicated in the table below.

Weight range	**30.0 – 50.0 kg**	**50.1 – 70.0 kg**	**≥70.1 kg**
Maximum recommended dose	**1,200 mg/day**	**1,600 mg/day**	**2,200 mg/day**

[…]

*Discontinuation of ~~treatment~~ **rufinamide***

When rufinamide treatment is to be discontinued, it should be withdrawn gradually. In clinical trials rufinamide discontinuation was achieved by reducing the dose by approximately 25% every two days (see section 4.4).

[…]

Paediatric population

The **safety and** efficacy of rufinamide in ~~children~~ **new-born infants or infants and toddlers** aged ~~4 years and~~ less ~~has~~ **than 1 year** have not ~~yet~~ been established. ~~Currently~~ **No data are** available ~~data are described in~~ **(see** section ~~4.8 and~~ 5.2~~1 but no recommendation on a posology can be made~~**)**.

Method of administration

Rufinamide is for oral use. ~~It~~**The tablet** should be taken twice daily with water in the morning and in the evening, in two equally divided doses. ~~As a food effect was observed,~~ Inovelon should be administered with food (see section 5.2). If the patient has difficulty with swallowing, tablets can be crushed and administered in half a glass of water. **Alternatively, use the score line to break the tablet into two equal halves.**

[…]

4.5 Interaction with other medicinal products and other forms of interaction

For patients on Inovelon treatment who have administration of valproate initiated, significant increases in rufinamide plasma concentrations may occur. ~~The most pronounced increases were observed in patients of low body weight (<30 kg).~~Therefore, consideration should be given to a dose reduction of Inovelon in patients who ~~<30kg~~ are initiated on valproate therapy (see section 4.2).

[…]

5.1 Pharmacodynamic properties

[…]

The Least Square mean change of the Child Behaviour Checklist (CBCL) Total Problems score 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~~**p**=0.6928), and the difference between treatments was -2.776 (95% CI: -13.3, 7.8, ~~P~~**p**=0.5939). ~~However, due to the limitations of the available data the study was inconclusive in respect of efficacy.~~

[…]

5.2 Pharmacokinetic properties

[…]

Children (1-12 years)

Children generally have lower clearance of rufinamide than adults, and this difference is related to body size **with rufinamide clearance increasing with body weight**.

A recent population PK analysis of rufinamide on data pooled from 139 subjects (115 LGS patients and 24 healthy subjects), including 83 paediatric LGS patients (10 patients aged 1 to < 2 years, 14 patients aged 2 to < 4 years, 14 patients aged 4 to < 8 years, 21 patients aged 8 to < 12 years and 24 patients aged 12 to < 18 years) indicated that when rufinamide is dosed on a mg/kg/day basis in LGS subjects aged 1 to < 4 years, comparable exposure to that in LGS patients aged ≥ 4 years, in which efficacy has been demostrated, is achieved.

5.3 Preclinical safety data

[…]

Environmental Risk Assessment (ERA):

Environmental risk assessment studies have shown that rufinamide is persistent in the environment (see section 6.6).

[…]

6.6 Special precautions for disposal and other handling

[…]

This medicinal product could have potential risk for the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 5.3)

[…]

2.7.1. User consultation

User consultation of Inovelon PL had been submitted for the initial Market Authorisation Application (treatment of seizures associated with Lennox-Gastaut Syndrome in paediatric patients 4 year of age and older). 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.

3. Benefit-Risk Balance

3.1. Favourable effects

Rufinamide is authorized for the adjunctive treatment of LGS seizures in patients 4 years of age or older based on the results 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.

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.

With the present application, results from study 303, a 2-year multicenter, randomized, controlled, open-label study for 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.

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. Rufinamide was administered orally as 100, 200, or 400 mg tablets twice daily. Dosing started at approximately 10 mg/kg/day, and was titrated to approximately 45 mg/kg/day over a 1- to 2-week period. Superiority of rufinamide over placebo in all primary efficacy variables was demonstrated as percentage change in total seizure frequency; percentage change in tonic-atonic seizure frequency; and the seizure severity rating. Subjects in the rufinamide-treatment group experienced a 32.7% median reduction in the total seizure frequency per 28 days relative to baseline compared to an 11.7% median reduction for the placebo-treatment group (P=0.0015). An improvement in seizure severity was observed in 53.4% of rufinamide-treated subjects versus 30.6% of placebo-treated subjects (P=0.0041). The median percentage change in tonic-atonic seizure frequency per 28 days was significantly higher for rufinamide-treated subjects (42.5) than for placebo-treated subjects (1.4) (P<0.0001).

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.

During the procedure the MAH has provided an updated population PK model which describes the rufinamide PK data well. The goodness-of-fit plots and visual predictive checks all indicate an adequate model fit to data. Furthermore, the model parameters are in line with previously reported PK parameters for rufinamide. The model is deemed adequate for exposure predictions for all body weights (and subsequently all ages) and hence the exposure predictions can be used in the evaluation of exposure similarity between age groups and to support the proposed posology for Inovelon in LGS patients 1 to <4 years.

3.2. Uncertainties and limitations about favourable effects

For the study 303, 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 favour 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.

3.3. 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 rufinamide 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.

3.4. Uncertainties and limitations about 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.

3.5. Effects Table

Table 22 Effects Table for rufinamide in children aged 1 to 4 years old.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint	CBCL Total problems score and change from baseline at the end of the 2-year treatment period	LS mean (SE)	55.454 (2.469)	58.230 (4.561)	Treatment difference -2.776 95% CI (p value) -13.3, 7.8 (p=0.5939) The mean change at the end of the 2-year treatment was -0.3 for rufinamide and -6.7 in the control group; clinical relevance?	CSR-E2080-G000-303
Primary endpoint	Total seizure frequency per 28 days	Median % change	-32.7	-11.7	p 0.0015	Study 022 EPAR Inovelon
Primary endpoint	Tonic-atonic seizure frequency per	Median % change	-42.5	1.4	p <0.0001	Study 022 EPAR Inovelon

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	28 days					
Primary endpoint	Seizure severity subscale of global evaluation	% Improvement	53.4	30.6		Study 022 EPAR Inovelon
Secondary endpoint	Response to treatment	Responder rate (50%)	42.5	16.7	p 0.0020	Study 022 EPAR Inovelon
Secondary endpoint	Change in other seizures per 28 days	Median % change	-44.8 (*)	-21.0 (*)	p 0.0125	Study 022
			-50.6 (*)	-29.8 (*)	p 0.0222	EPAR Inovelon
Secondary endopint	Global Evaluation composite score	Median	1	0	P 0.342	Study 022 EPAR Inovelon
Unfavourable Effects						
Vomiting	Incidence	%	28.0	8.3	(**)	CSR-E2080-G000-303
Pneumonia	Incidence	%	20.0	0	(**)	CSR-E2080-G000-303

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Somnolence	Incidence	%	20.0	0	(**)	CSR-E2080-G000-303
Nasal congestion	Incidence	%	12.0	0	(**)	CSR-E2080-G000-303
Rash	Incidence	%	12.0	8.3	(**)	CSR-E2080-G000-303
Decrease appetite	Incidence	%	12.0	8.3	(**)	CSR-E2080-G000-303
Bronchitis	Incidence	%	12.0	8.3	(**)	CSR-E2080-G000-303
Constipation	Incidence	%	12.0	8.3	(**)	CSR-E2080-G000-303
Weight loss	Incidence	%	8.0	0	(**)	CSR-E2080-G000-303

3.6. Benefit-risk assessment and discussion

3.6.1. 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. Nevertheless, at the time of initial application (EMEA/H/C/000660/II/0037), the proposed models 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. In response, an update of the population-PK modelling including paediatric data (1-4 years) and other data collected in older children, adolescent and adults with LGS was provided (CPMS-E2080-004R-v1). The updated population PK model describes the rufinamide PK data well. The goodness-of-fit plots and visual predictive checks all indicate an adequate model fit to data. Furthermore, the model parameters are in line with previously reported PK parameters for rufinamide. The model is deemed adequate for exposure predictions for all body weights (and subsequently all ages) and hence the exposure predictions can be used in the evaluation of exposure similarity between age groups and to support the proposed posology for Inovelon in LGS patients 1 to <4 years.

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.

3.6.2. Balance of benefits and risks

As concluded by the CHMP at the time of the first submission, 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, it is agreed that the expression of LGS is 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, the result of efficacy trial performed in children > 4 years affected by LGS could be extrapolated in population <4 years old provided the dose is established.

A pooled PK model has been provided (CPMS-E2080-004R-v1) which is describes the rufinamide PK data well. The model is deemed adequate for exposure predictions for all body weights (and subsequently all ages) and hence the exposure predictions can be used in the evaluation of exposure similarity between age groups and to support the proposed posology for Inovelon in LGS patients 1 to <4 years. The results from study 303 after 2 years of exposure, demonstrated that rufinamide was well tolerated in subjects 1 to less than 4 years of age. The safety profile of the younger paediatric subjects revealed no new safety signals. No new or unexpected risks were identified compared to older paediatric patients.

The benefit-risk balance of Inovelon for the applied extension of indication in patients from 1 years of age to 4 years with LGS is currently considered positive.

3.7. Conclusions

The overall B/R of Inovelon is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, 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

Extension of indication to include the treatment of seizures associated with Lennox Gastaut syndrome in patients 1 year of age and older as adjunctive therapy; as a consequence sections 4.1, 4.2, 4.5, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet and the RMP (version 10.1) are updated accordingly. In addition the Marketing Authorisation Holder (MAH) took the opportunity to make small corrections with the Product Information and to update the name and contact details of the local representative in Belgium and Luxembourg. Furthermore, the Product Information is brought in line with the latest QRD template version 10.

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Obligation to conduct post-authorisation measures

Not applicable

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 Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the treatment of seizures associated with Lennox Gastaut syndrome in patients 1 year of age and older as adjunctive therapy; as a consequence sections 4.1, 4.2, 4.5, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet and the RMP (version 10.0) are updated accordingly. In addition the Marketing Authorisation Holder (MAH) took the opportunity to make small corrections with the Product Information and to update the name and contact details of the local representative in Belgium and Luxembourg. Furthermore, the Product Information is brought in line with the latest QRD template version 10.

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

Summary

For further details please refer to the Scientific Discussion Inovelon EMEA/H/C/000660/II/0045.