

Reviewer's Comments

Sponsor's QT Analysis

Because the baseline (Day -1) QTc was higher than those during the study (Day 9, 12, 15, and 18), the use of the Day 18 measurement to baseline adjust moxifloxacin overestimated the moxifloxacin effect on the QTc interval. Thus, the reviewer recalculated the baseline adjusted moxifloxacin data using Day -1 QTc. All figures/tables in the review show the reviewer's analysis unless otherwise noted. The moxifloxacin effects based on the reviewer's analysis are similar to previous reports.

The sponsor's primary QT analysis is an appropriate way to analyze the data. This method of analysis is a simultaneous analysis that accounts for the correlation from one QT to the next due to time. The linear mixed analysis treats time as a categorical variable. It uses an unstructured covariance structure for residual variance-covariance matrix, which assumes different variances at each ECG time and different covariances between all pairs of ECG times.

QTc Shortening

Although it is not clear how to interpret the QTc shortening, a look at the data shows the following:

The shortest baseline QTcF was 340 msec. The shortest QTcF on rufinamide was 334 msec. A "negative" QTcF outlier analysis is shown in Table 9. Another patient had a decrease of 82 msec (Subject 258, baseline was 394 msec), however this was on Day 20 and the QTc before and after it were very different.

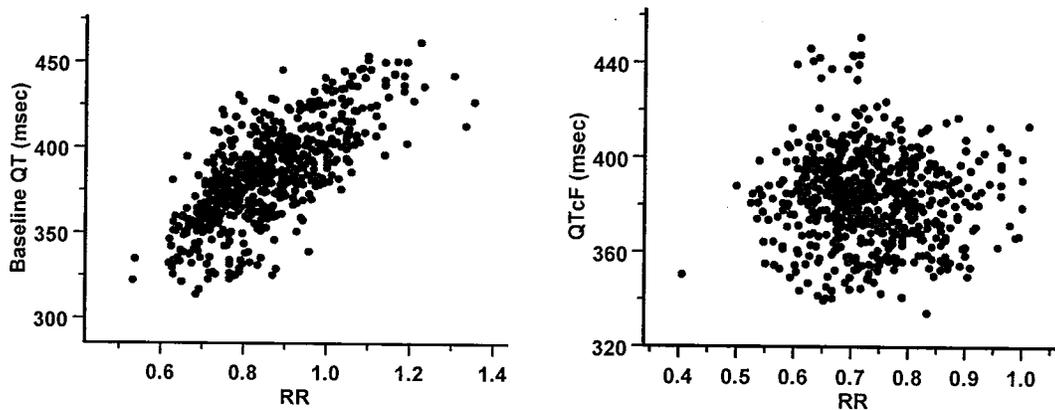
Table 14. "Negative" Categorical Analysis

Category	Number of subjects
-60 msec \leq ddQTcF < -30 msec	60
ddQTcF \leq -60 msec	2

While there were short QTc intervals in these healthy subjects, they are not as short as that seen in patients with the Short QT syndrome (usually a QTc < 320 msec). This may partially explain the lack of serious adverse events, despite the large number of subjects with large decreases in the QTc interval.

It seems that the HR correction made QTc independent of HR (See Figure 11). The individual correction factor (0.341) was similar to Fridericia's correction (0.33). (Thus, because of the similarity in correction factor and because QTcF was the primary endpoint, the reviewer chose to show QTcF for most of the review.)

Figure 15. Rufinamide 3600 mg QT(c) vs. RR

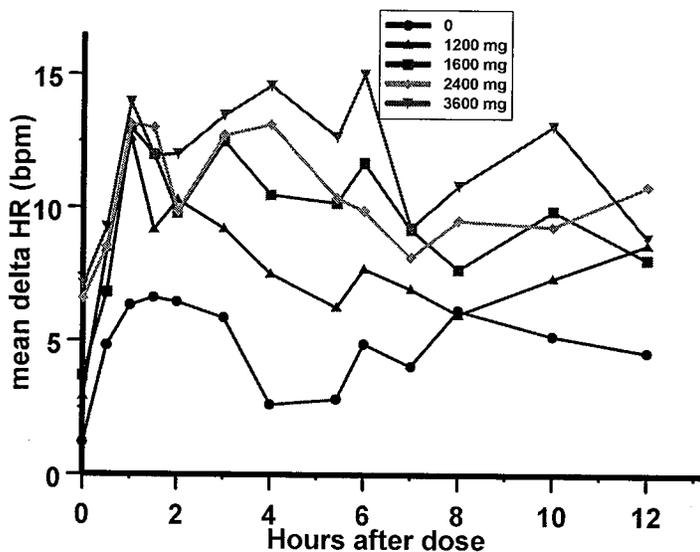


Safety

No serious AE were reported during the study. There were no deaths or syncopes. Dizziness and headache were reported by greater than 5% of subjects. Two subjects experienced thrombocytopenia (with one very severe (206 down to 44 thousand/uL).

Rufinamide increased heart rate (See Figure 12). The mean differences from placebo ranged from 4.4 to 10.4 beats per minute between 2 and 8 hours after the highest dose. Change in HR (compared to predose) was notably larger on rufinamide on Days 15 through 18 compared to placebo (17.52 to 20.92 bpm increase versus 11.30 to 13.83 bpm increase). The largest mean change from time-matched baseline in HR (with the 3600 mg bid dose) was 10 bpm (95% UB 14 bpm).

Figure 16. Change in HR with Dose



Palpitations were reported in six subjects, of which two were taking rufinamide. An ECG collected in one subject taking rufinamide was within normal limits. Two subjects reported chest pain, however both of these subjects received placebo.

Lack of a Clear Dose Response

The two lowest and the two highest doses are very similar in QTc response (Figure 5, Figure 6). This can be partially explained by the less than dose proportional concentration increase with dose increase, and the fact that at the lowest dose, concentrations are well above the EC50 of 6.61 ug/mL. It may have been possible to tease out a dose response as concentrations declined after 12 hours, however these data were only available for the highest dose of 3600 mg po q 12 hours (Figure 3). The effect on QTcF diminishes after 12 hours.

The sponsor found in a trend in dose response because their analysis grouped the two lowest doses and the two highest doses together and simply tested if the two higher doses were different from the two lower doses.

Overall Conclusions

Rufinamide 3600 mg given every 12 hours decreases the QTcF interval by a mean of 20.2 msec according to the ICH E14 statistical analysis. The sophisticated concentration QTcF analysis confirms the results of the statistical analysis (Emax of -27.8 msec and EC50 of 6.61 ug/mL). The clinical implications of the shortening of QTc interval are not known. The reviewer recommends that the QTcF shortening be described in the label.

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Appendices

Proposed Package Insert Section with respect to QT



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Rufinamide Final PK Parameters

Parameters	Estimate	SEE	95% CI	Variability (% CV)
Fixed Effects				
<i>Disposition parameters</i>				
CL= θ_1				
θ_1 : intercept (L/h)	7.68	0.752	[6.21; 9.15]	
V= θ_2				
θ_2 : (L)	161	15.0	[132; 190]	
<i>Absorption</i>				
Ka = Ke + θ_3				
θ_3 : (h^{-1})	0.157	0.00981	[0.138; 0.176]	
<i>Relative bioavailability</i>				
F1=1+(θ_4 *(DDKG-15.58))/(θ_5 +DDKG-15.58)				
θ_4 : Emax effect of dose	-1.47	0.313	[-2.08; -0.86]	
θ_5 : DDKG for 50% Emax	97.9	38.8	[21.9; 173.9]	
Lag time = ALAG1				
θ_6 : (h^{-1})	0.808	0.0619	[0.687; 0.929]	
θ_7 AGE on F1	0.215	0.0874	[0.044; 0.386]	
θ_8 SEX on F1	0.127	0.0536	[0.022; 0.232]	
θ_9 HISP on V	-29.7	9.76	[-48.8; -10.6]	
Random effects				
<i>Between-subject variance / Exponential model</i>				
ω^2 of CL	0.0837	0.0219	[0.041; 0.127]	28.9
ω^2 of V	0.147	0.0322	[0.084; 0.210]	38.3
ω^2 of ka	2.87	0.479	[1.93; 3.81]	169.4
ω^2 of ALAG	2.39	0.71	[1.00; 3.78]	154.6
ω^2 of F1	0.0642	0.0208	[0.023; 0.105]	25.3
<i>Proportional residual error</i>				
σ^2	8.10E-03	9.24E-04	[0.006; 0.010]	9.0

Source: Supporting Table 2

DDKG: daily dose per kg (mg/kg)

ke = CL/V (h^{-1})

Derivation of Rufinamide PK Parameters

Parameters	Estimate	SEE	95% CI	Variability (% CV)
Fixed Effects				
<i>Disposition parameters</i>				
CL= θ_1				
θ_1 : intercept (L/h)	7.68	0.752	[6.21; 9.15]	
V= θ_2				
θ_2 : (L)	161	15.0	[132; 190]	
<i>Absorption</i>				
Ka = Ke + θ_3				
θ_3 : (h^{-1})	0.157	0.00981	[0.138; 0.176]	
<i>Relative bioavailability</i>				
F1=1+(θ_4 *(DDKG-15.58))/(θ_5 +DDKG-15.58)				
θ_4 : Emax effect of dose	-1.47	0.313	[-2.08; -0.86]	
θ_5 : DDKG for 50% Emax	97.9	38.8	[21.9; 173.9]	
Lag time = ALAG1				
θ_6 : (h^{-1})	0.808	0.0619	[0.687; 0.929]	
θ_7 AGE on F1	0.215	0.0874	[0.044; 0.386]	
θ_8 SEX on F1	0.127	0.0536	[0.022; 0.232]	
θ_9 HISP on V	-29.7	9.76	[-48.8; -10.6]	
Random effects				
<i>Between-subject variance / Exponential model</i>				
ω^2 of CL	0.0837	0.0219	[0.041; 0.127]	28.9
ω^2 of V	0.147	0.0322	[0.084; 0.210]	38.3
ω^2 of ka	2.87	0.479	[1.93; 3.81]	169.4
ω^2 of ALAG	2.39	0.71	[1.00; 3.78]	154.6
ω^2 of F1	0.0642	0.0208	[0.023; 0.105]	25.3
<i>Proportional residual error</i>				
σ^2	8.10E-03	9.24E-04	[0.006; 0.010]	9.0

Source: Supporting Table 2
DDKG: daily dose per kg (mg/kg)
ke = CL/V (h^{-1})

		Total daily Dose (mg)	
		Day 9 2400 mg	Day 18 7200 mg
Relative bioavailability	$F1=1-1.47*(DDKG-15.6)/(97.9+DDKG-15.6)$	0.77	0.32
Apparent clearance	$CL/F1 (L/h) 7.68/F1$	9.92	24.04
Apparent volume	$V/F1 (L): (161-29.7*HISP) /F1(L)$	208	504

DDKG= total daily dose/BW for median BW=72 kg, HISP:Hispanic

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Moxifloxacin Final PK Parameters

Parameters	Estimate	SEE	95% CI	Variability (% CV)
Fixed Effects				
<i>Disposition parameters</i>				
CL = θ_1				
θ_1 : intercept (L/h)	14.4	1.05	[12.3; 16.5]	
V = θ_2				
θ_2 : (L)	182	11.7	[159; 205]	
<i>Absorption</i>				
Ka = θ_3				
θ_3 : (h^{-1})	1.37	0.118	[1.14; 1.60]	
Lag time = ALAG1				
θ_4 : (h^{-1})	0.364	0.136	[0.097; 0.631]	
Random effects				
<i>Between-subject variance /Exponential model</i>				
ω^2 of CL	0.143	0.0375	[0.070; 0.217]	37.8
ω^2 of V	0.145	0.0329	[0.081; 0.209]	38.1
ω^2 of ka	2.23	0.622	[1.01; 3.45]	149.3
ω^2 of ALAG1	3.03	3.63	[-4.09; 10.15]	174.1
<i>Residual error</i>				
σ^2 prop	0.0261	0.00946	[0.008; 0.045]	16.2
σ^2 add	2.41E-9	0.024	[-0.047; 0.047]	5E-5

Source: Supporting Table 3

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PKPD Analysis Final Parameter Estimates for QTcF Model

Parameters and models	Estimate	SEE	95% CI	SD
Population PKPD model				
Rhythm adjusted baseline	RYT = THETA(1)			
Diurnal variation 1	B = AMP1*COS(3.141*DTIM/24-SHIF1)			
Diurnal variation 2	C = AMP2*COS(3.141*DTIM/12-SHIF2)			
Baseline	BAS= RYT*(1+B+C) +ETA(1)			
Effect of Time in the study	TIM = (THETA(2)+ETA(2))*TIME/(THETA(3)+TIME)			
Effect of rufinamide concentrations	ERUF=(THETA(4)+ETA(3))*CRUF/(THETA(5)+CRUF)			
Effect of sex on rhythm adjusted baseline	BASP = RYT*(1+B+C)+ THETA(11)+ETA(1)			
Effect of moxifloxacin treatment concentrations>0	EMOX = THETA(6)*MOX with MOX=1 if concentrations>0			
Final QTcF model	QTcF = BAS+TIM+ERUF+EMOX +EPS(1)			
θ_1 : Rhythm adjusted baseline QT (ms)	391	2.62	[386; 396]	
θ_2 : Maximum effect of placebo/time (ms)	-4.46	1.76	[-7.91; -1.01]	
θ_3 : Time for 1/2 maximum decrease (h)	584	333	[-69; 1237]	
θ_4 : Maximum effect of rufinamide (ms)	-27.8	1.86	[-31.4; -24.2]	
θ_5 : Rufinamide conc for 1/2 max decrease	6.61	1.33	[4.00; 9.22]	
θ_6 : Effect of moxifloxacin treatment	7.83	0.693	[6.47; 9.19]	
θ_7 : Amplitude of 1 st diurnal variation function	0.0313	0.00709	[0.0174; 0.0452]	
θ_8 : Phase shift of 1 st diurnal variation function	20.2	0.0444	[20.1; 20.3]	
θ_9 : Amplitude of 2 nd diurnal variation function	0.0186	0.00283	[0.0131; 0.0241]	
θ_{10} : Phase shift of 2 nd diurnal variation function	-25.1	0.0595	[-25.2; -25.0]	
θ_{11} : SEX effect of baseline	13.5	2.96	[7.7; 19.3]	
<i>Between subjects: additive error</i>				
$\omega^2 \eta_1$ on baseline	245	35.3	[1768; 314]	15.7
$\omega^2 \eta_2$ on max time effect	238	145	[-46.2; 522]	15.4
$\omega^2 \eta_3$ on max rufinamide effect	137	34.9	[69; 205]	11.7
<i>Additive residual error</i>				
σ^2	58.9	2.0	[55.0; 63.0]	7.7

Source: Supporting Table 7

TIME: time in hours from 1st ECG, CONC rufinamide predicted concentration in µg/mL, for females: SEX=2; for males: SEX=1; MOX=0, 1

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PKPD Analysis Final Parameter Estimates for Final Model (QTcI)

Parameters and models	Estimate	SEE	95% CI	SD
Population PKPD model				
Rhythm adjusted baseline	RYT = THETA(1)			
Diurnal variation 1	B = AMP1*COS(3.141*DTIM/24-SHIF1)			
Diurnal variation 2	C = AMP2*COS(3.141*DTIM/12-SHIF2)			
Baseline	BAS= RYT*(1+B+C) +ETA(1)			
RR correction	CORR = (RR/1000)**(THETA(2)+ETA(2))			
Effect of Time in the study	TIM = (THETA(3)+ETA(3))*TIME/(THETA(4)+TIME)			
Effect of rufinamide concentrations	ERUF=(THETA(5)+ETA(4))*CRUF/(THETA(6)+CRUF)			
Effect of sex on adjusted baseline	BAS = RYT*(1+B+C)+ THETA(12)*(SEX-1)+ETA(1)			
Effect of moxifloxacin treatment concentrations>0	EMOX = THETA(7)*MOX with MOX=1 if			
Final QT model	QT=BAS*CORR+TIM+ERUF+EMOX +EPS(1)			
θ_1 : Rhythm adjusted baseline QT (ms)	390	2.71	[385; 395]	
θ_2 : Population RR correction exponent	0.341	0.00569	[0.330; 0.352]	
θ_3 : Maximum effect of placebo/time (ms)	-3.68	1.36	[-6.35; -1.01]	
θ_4 : Time for 1/2 maximum decrease (h)	439	265	[-80.4; 958]	
θ_5 : Maximum effect of rufinamide (ms)	-25.0	1.82	[-28.6; -21.4]	
θ_6 : Rufinamide conc for 1/2 max decrease	6.68	1.46	[3.82; 9.54]	
θ_7 : Effect of moxifloxacin treatment	7.04	0.628	[5.81; 8.27]	
θ_8 : Amplitude of 1 st diurnal variation function	0.0313	0.00681	[0.0180; 0.0446]	
θ_9 : Phase shift of 1 st diurnal variation function	-4.91	0.0443	[-5.00; -4.82]	
θ_{10} : Amplitude of 2 nd diurnal variation function	0.0186	0.00273	[0.0132; 0.0240]	
θ_{11} : Phase shift of 2 nd diurnal variation function	-6.23	0.059	[-6.35; -6.11]	
θ_{12} : SEX effect of baseline	16.6	3.25	[10.2; 23.0]	
<i>Between subjects: additive error</i>				
$\omega^2 \eta_1$	290	44.6	[203; 377]	17.0
$\omega^2 \eta_2$	0.00259	0.000462	[0.00168; 0.00350]	0.0509
$\omega^2 \eta_3$	142	80.5	[-15.8; 299.8]	11.9
$\omega^2 \eta_4$	129	35.7	[59; 199]	11.4
<i>Additive residual error</i>				
σ^2	46.1	1.46	[43.2; 49.0]	6.8

Source: Supporting Table 5

TIME: time in hours from 1st ECG, CONC rufinamide predicted concentration in µg/mL, for females: SEX=2; for males: SEX=1; MOX=0, 1

Office of Clinical Pharmacology Pharmacometrics

Drug	Rufinamide
NDA	21911
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram
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Background

The primary goal of this review is to answer the question of whether there is adequate evidence of rufinamide's effectiveness or not.

Specifically, the aim is to explore the exposure-response relationship for rufinamide in patients with partial seizures and Lennox Gastaut Syndrome

To address the issue of exposure-response relationship, data from the following clinical trials were analyzed.

Clinical Trials

Study AE/ETI

Objective: To assess the efficacy, safety, tolerability and pharmacokinetics of each dose of rufinamide (200, 400, 800, 1600 mg/day) relative to placebo in a patient population with inadequately controlled partial seizures who were receiving one to three concomitant AEDs.

Design: Multicentre, multinational, double-blind, randomized, placebo-controlled, parallel group study. The study consisted of three periods: baseline (3 months), double-blind (3 months), and long-term extension.

Number of patients: 647 patients were randomized: 127 to 200 mg/day rufinamide, 125 to 400 mg/day rufinamide, 129 to 800 mg/day rufinamide, 133 to 1600 mg/day rufinamide, and 133 to placebo.

Study CRUF331-022

Objective: To evaluate the safety and efficacy of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with Lennox-Gastaut syndrome.

Design: Multicentre, double-blind, placebo-controlled, randomized, parallel group study. The study consisted of three periods: baseline (28 days), double-blind (84 days: 14 days of titration followed by 70 days of maintenance) and long-term extension.

Number of patients: 139 paediatric and adult patients were randomised: 75 to rufinamide and 64 to placebo.

Exposure-Response Analysis

SAS (Version 8) was used in the data analysis. Various linear and nonlinear models were used to describe the relationship between dose/concentrations and primary endpoint. The following are the primary endpoints used for exposure-response analysis (For greater details please refer to the review by Dr Ohidul Siddiqui, Biometrics):

Study AE/ET1

The primary effectiveness variable in Study AE/ET1 was the seizure frequency per 28 days in the Double-blind Phase. Rufinamide was considered effective if linear trend of the dose-response relationship for seizure frequency per 28 days in the double-blind phase demonstrated a statistically significant decrease as the dose increased from placebo.

Study CRUF331-022

Variable 1- The percentage change (PCH) in total seizure frequency per 28 days in the Double-blind Phase relative to the Baseline Phase. The percentage change was calculated as $PCH=100*(T-B)/B$, where T is the total seizure frequency per 28 days during the Double-blind Phase and B is the total seizure frequency per 28 days during the Baseline Phase.

Variable 2- The percentage change in tonic-atonic (the sum of tonic and atonic seizures) seizure frequency per 28 days in the Double-blind Phase relative to the Baseline Phase. The percentage change was calculated as: $PCH=100*(T-B)/B$, where T is the tonic-atonic seizure frequency per 28 days during the Double-blind Phase and B is the tonic-atonic seizure frequency per 28 days during the Baseline Phase.

Study 21A

The primary efficacy variable in Study 21A was the percent change in partial seizure frequency during the Double-blind Phase relative to the Baseline Phase, and it was defined as: (the number of partial seizures per 28 days during the Double-blind Phase minus the number of partial seizures per 28 days during the Baseline Phase multiplied by 100) divided by the number of partial seizures per 28 days during the Baseline Phase.

Partial Seizure

1. Is there is evidence of effectiveness?

Yes, there is evidence of effectiveness as supported by the following:

Dose-Response Relationship

1. Seizure frequency per 28 days in active treatment groups of 400, 800 and 1600 mg are significantly different from placebo (p=0.0172), during the double-blind phase. Seizure frequency per 28 days in active treatment groups of 400, 800 and 1600 mg are significantly different from placebo (p=0.0172). Further, doses beyond 800 mg do not show any additional benefit (Table 1).

Table 1. Statistical Analysis of Dose-Response as performed by Sponsor

Comparison	p-value
All doses	0.0039
Placebo vs 400, 800, 1600	0.0172
Placebo vs 200	0.660
Placebo vs 400	0.114
Placebo vs 800	0.014
Placebo vs 1600	0.074

2. Figure 1 shows the relationship between % change in total seizure frequency (Median), during double-blind phase, from baseline versus dose in study AE/ET1.

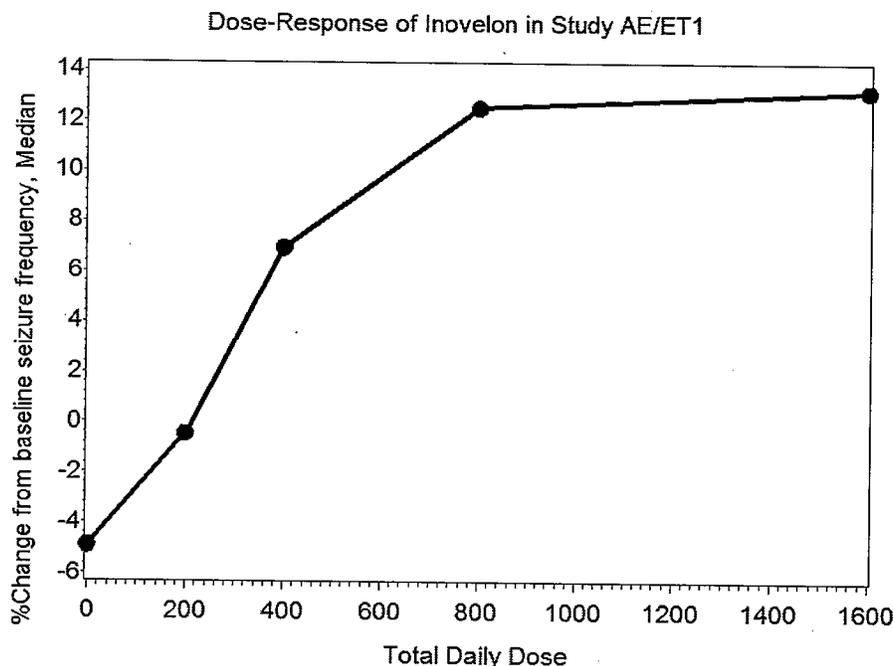


Figure 1. Relationship between change from baseline total seizure frequency and rufinamide total daily dose in study AE/ET1

3. The sponsor's primary analyses treated doses as non-continuous data. That is, doses of 200, 400, 800 and 1600 mg were treated as 1, 2, 3 and 4. The interpretation of such dose-response slope is not obvious. Further, the ratio of lowest to highest doses is distorted (sponsor's 1:4 versus 1:8). **This transformation results in a steeper dose-response curve.** The reviewer performed dose-response relationship using the dose as

continuous variable (linear and nonlinear) with and without covariates such as sex, treatment centers. Table 2 shows the statistical analysis results based on various models with only dose as covariate using linear and nonlinear models. **Overall there is a statistically significant dose-response relationship ($p < 0.05$)**

Table 2. Statistical Analysis of Dose-Response Relationship

Model with dose as	-2LL difference from model with only intercept	p-value
Categorical (0, 1, 2, 3, 4)	861	0.0040**
Continuous (0, 200, 400, 800, 1600) • Linear	845	0.0157**
Continuous (0, 200, 400, 800, 1600)* • Nonlinear	13	~0.001***

* Note that in this model, the baseline subtracted seizure frequencies are being analyzed while in other two, baseline seizure frequency was included as a covariate. One should conclude from this table that there is an overall statistical significance favoring the drug over placebo.

** The null hypothesis is that the dose-response slope is zero.

*** The p-value here refers to whether there is a statistical significance based on LLR (Log likelihood ratio) test after including parameters for nonlinear model.

Figure 2 shows the observed (Mean, Median) and model fitted (linear, nonlinear) dose response relationship (Note: Ratio of Log of treatment vs baseline is shown here). **A clear evidence of dose-response is evident irrespective of the metric used for both observed and model predicted data.**

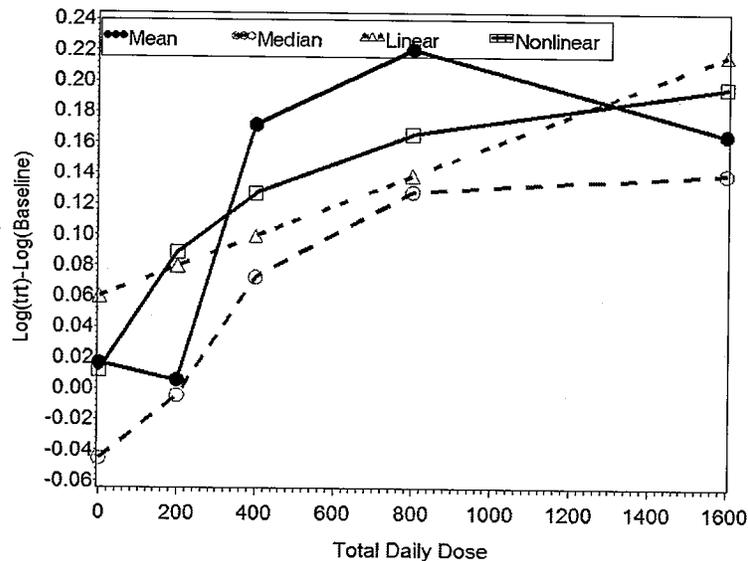


Figure 2. Log ratio of seizure frequency per 28 days versus total daily dose in study AE/ET1. Shown are observed mean, observed median, model predicted mean based on linear model, model predicted mean based on nonlinear model.

There was also an evidence of center effect in the dose-response analysis. Figure 3 shows the % change in total seizure frequency versus dose in Spain vs other centers combined. The number of patients contributing to the overall sample size is 32 out of 641. **Inspite, of a center effect there is still evidence of dose-response relationship.** Table 3 below shows the estimates of dose-response analysis after removing Spain from the dataset.

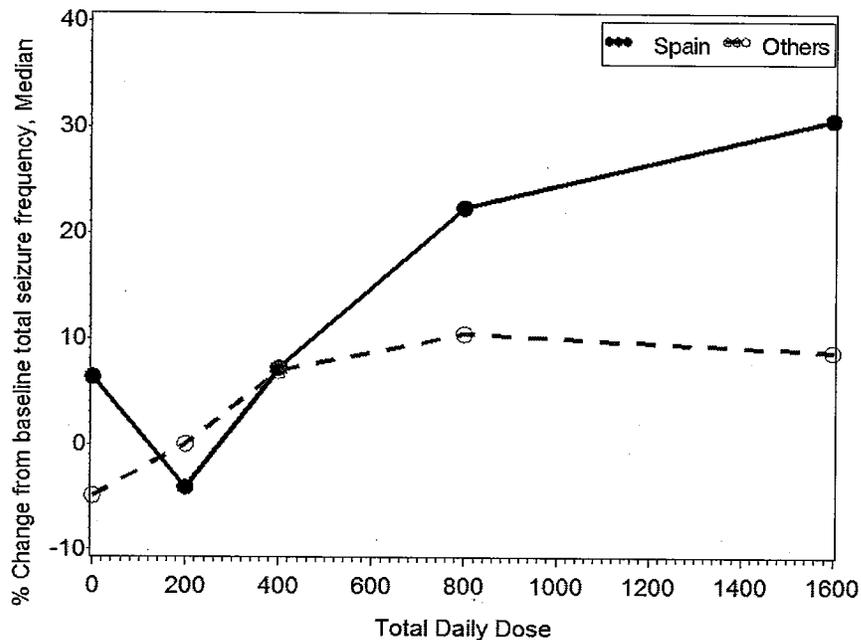


Figure 3. Relationship between change from baseline total seizure frequency and (A) rufinamide total daily dose in Spain and other centers

Table 3. Statistical Analysis of Dose-Response Relationship after removing Spain as center

Model with dose as	-2LL difference from model with only intercept	p-value
Categorical (0, 1, 2, 3, 4)	914	0.0066**
Continuous (0, 200, 400, 800, 1600) • Linear	900	0.0234**
Continuous (0, 200, 400, 800, 1600)* • Nonlinear	13	~0.001***

* Note that in this model, the baseline subtracted seizure frequencies are being analyzed while in other two, baseline seizure frequency was included as a covariate. One should conclude from this table that there is an overall statistical significance favoring the drug over placebo.

** The null hypothesis is that the dose-response slope is zero.

*** The p-value here refers to whether there is a statistical significance based on LLR (Log likelihood ratio) after including parameters for nonlinear model.

Concentration-Response Relationship

Figure 4 show the relationship between % change in total seizure frequency (Median), during double-blind phase, from baseline versus midpoints of the four quartiles of average model predicted rufinamide concentrations in study AE/ET1. The slight differences in the shape of dose-response and concentration-response is due to overlap in concentrations at 800 and 1600 mg dose groups in few individuals. However, one should note that the overall trend is similar to that of dose-response.

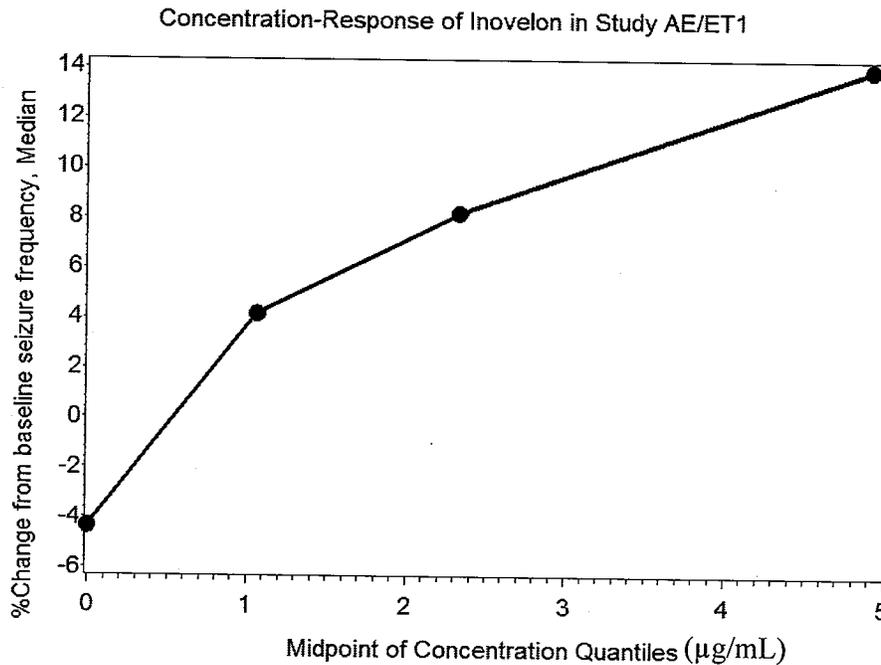


Figure 4. Relationship between change from baseline total seizure frequency and midpoint of average rufinamide concentration quartiles (0, 1.06, 2.33, 4.92 ug/mL) in study AE/ET1 (Data from 38 individuals of 641 was not included as there were no concentrations post-baseline. This is approximately 5% of the entire study population.)

Sponsor's utilized population pharmacokinetic modeling approach to estimate primary pharmacokinetic parameters such as Clearance (CL), Volume of distribution (V) etc. Figure 5 below shows the goodness of fit of the population pharmacokinetic model. Based on the individual estimates of CL, sponsor calculated individual average steady state (C_{av}) concentrations of rufinamide. The formula used to calculate the C_{av} is shown below:

$$AUC_{24ss} = \frac{\text{Total daily dose}}{CL / \text{relF}}$$

$$C_{avss} = \frac{AUC_{24ss}}{24}$$

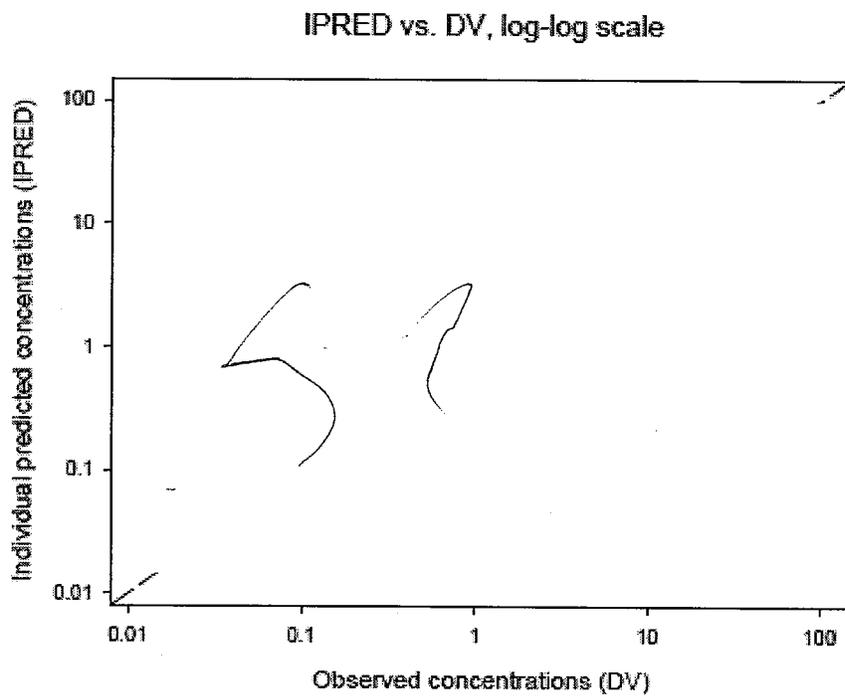
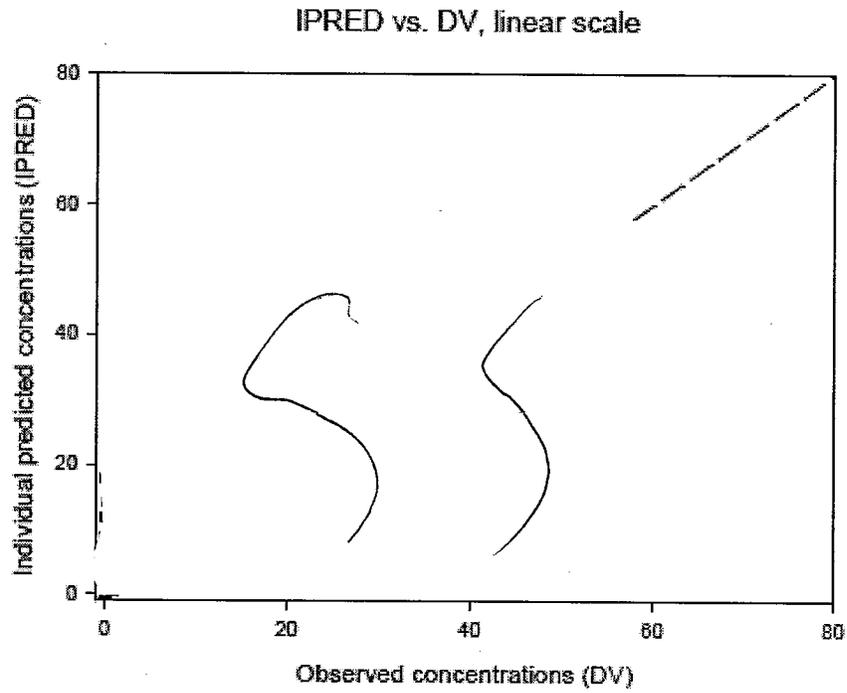


Figure 5. Goodness-of-fit of rufinamide PK final model (n= 5937 observations)

Table 4 shows the statistical analysis results based on various models with only Cav as covariate using linear and nonlinear models. **Overall there is a statistically significant concentration-response relationship ($p < 0.05$)**

Table 4. Statistical Analysis of Concentration-Response Relationship

Model with concentrations as	-2LL difference from model with only intercept	p-value
• Linear*	832	0.0023**
• Linear	2	>0.05***
• Nonlinear	17	<0.001***

* Note that in this model, the baseline subtracted seizure frequencies are being analyzed while in other two, baseline seizure frequency was included as a covariate. One should conclude from this table that there is an overall statistical significance favoring the drug over placebo.

** The null hypothesis is that the concentration-response slope is zero.

*** The p-value here refers to whether there is a statistical significance based on LLR (Log likelihood ratio) test after including parameters for linear and nonlinear model.

Figure 6 shows the observed (Mean, Median) and model fitted (linear, nonlinear) concentration response relationship (Note: Ratio of Log of treatment vs baseline is shown here). **A clear evidence of concentration-response is evident irrespective of the metric used for both observed and model predicted data.**

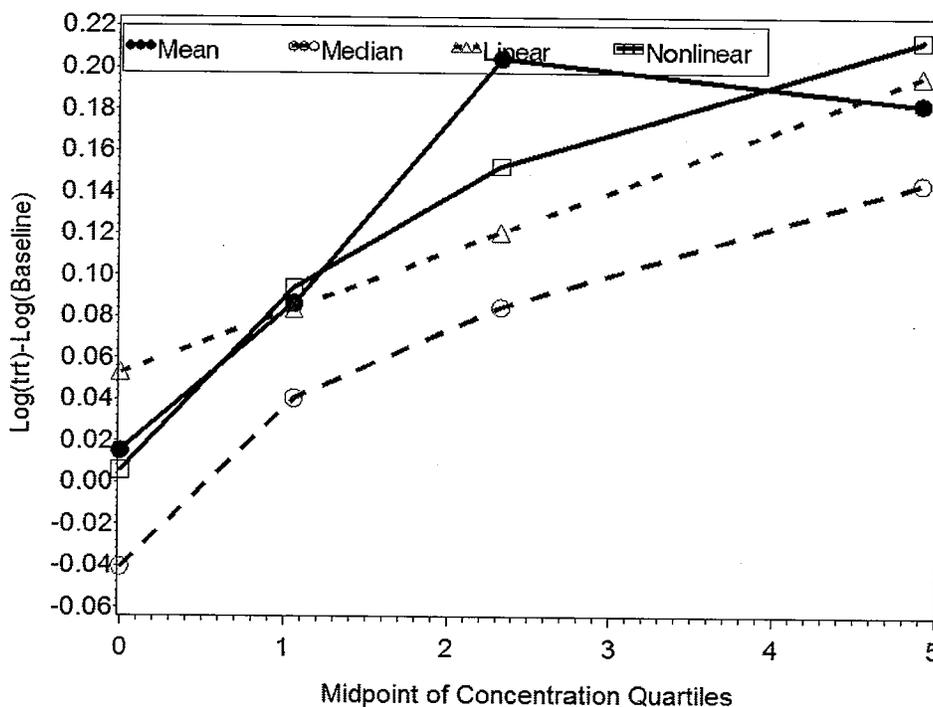


Figure 6. Log ratio of seizure frequency per 28 days versus midpoint of concentration quartiles. Shown are observed mean, observed median, model predicted mean based on linear model, model predicted mean based on nonlinear model.

There was also an evidence of center effect in the concentration-response analysis. Figure 7 shows the % change in total seizure frequency versus midpoint of concentration quartiles in Spain vs other centers combined. The number of patients contributing to the overall sample size is 32 out of 641. **Inspite, of a center effect there is still evidence of concentration-response relationship.** Table 5 below shows the estimates of concentration-response analysis after removing Spain from the dataset.

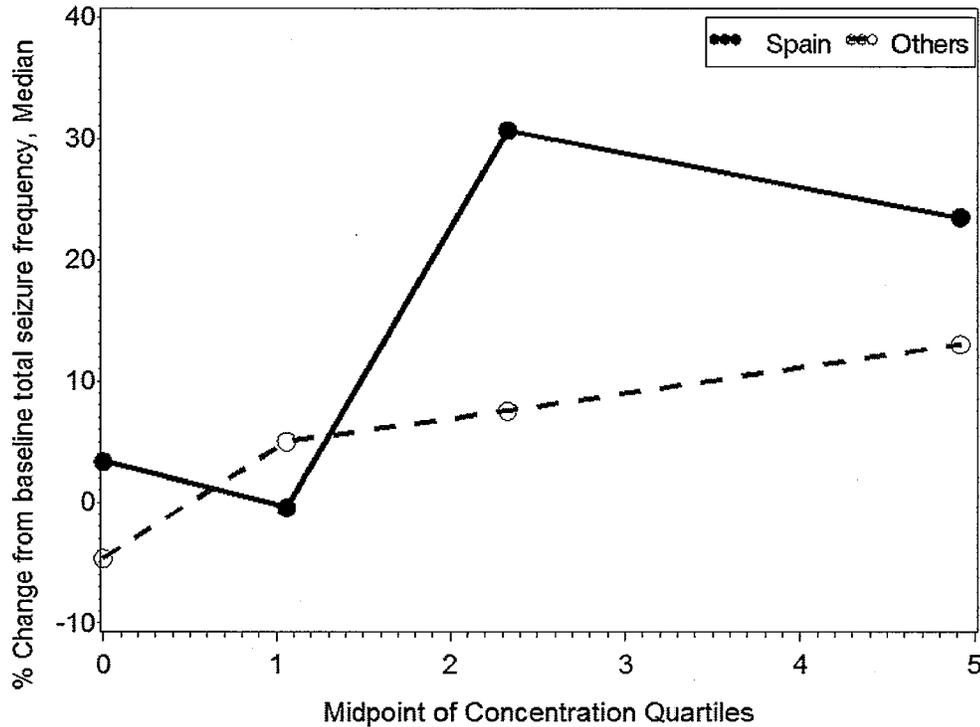


Figure 7. Relationship between % change from baseline, Median, seizure frequency per 28 days and midpoint of concentration quartiles in Spain and other centers.

Table 5 Statistical Analysis of Concentration-Response Relationship after removing Spain as center

Model with concentrations as	-2LL difference from model with only intercept	p-value
• Linear*	900	0.0046**
• Linear	1	>0.05***
• Nonlinear	17	<0.001***

* Note that in this model, the baseline subtracted seizure frequencies are being analyzed while in other two, baseline seizure frequency was included as a covariate. One should conclude from this table that there is an overall statistical significance favoring the drug over placebo.

** The null hypothesis is that the concentration-response slope is zero.

*** The p-value here refers to whether there is a statistical significance based on LLR (Log likelihood ratio) test after including parameters for linear and nonlinear model.

Responder Analysis

Figure 8 shows the percentage of responders at various cutoffs for % change from baseline ($\geq 0\%$, $\geq 10\%$, $\geq 25\%$, $\geq 50\%$, $\geq 75\%$) in 0, 200, 400, 800 and 1600 mg dose groups. As can be seen in the figure doses above 800 mg do not offer much additional benefit.

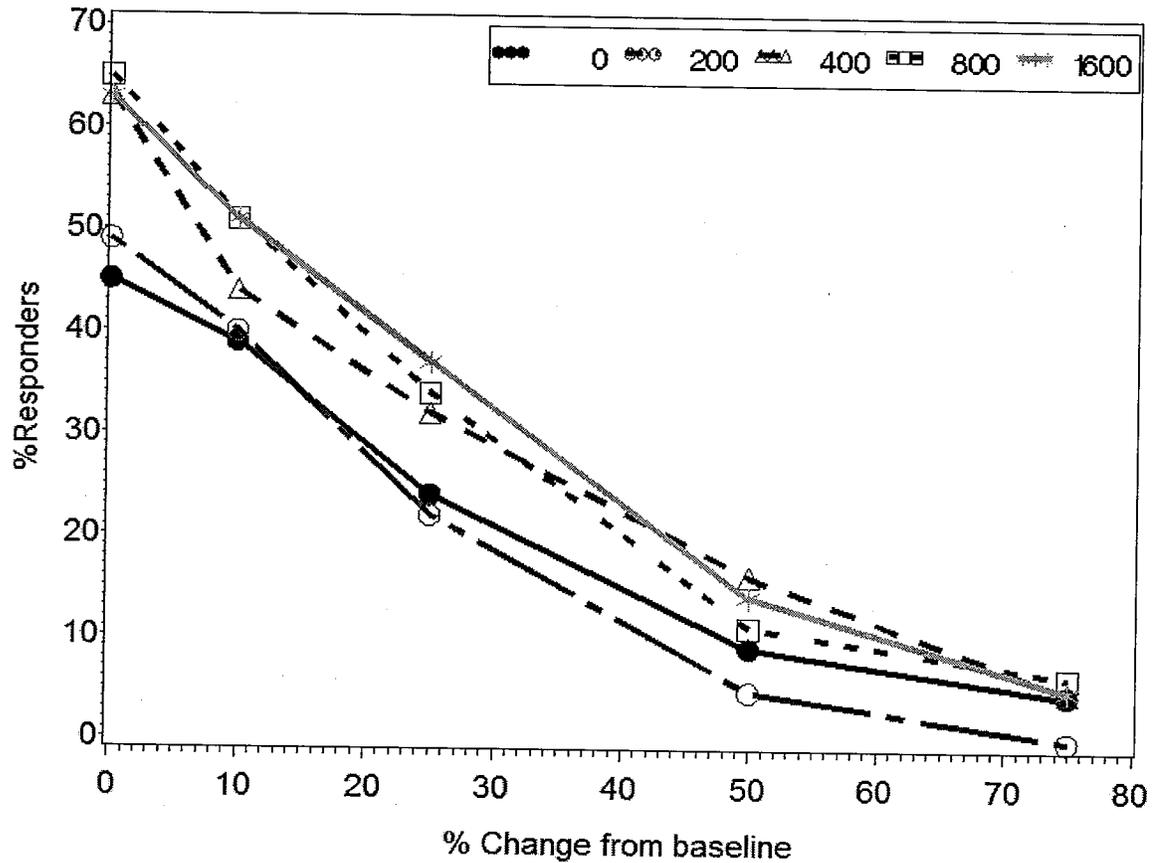


Figure 8. % responders vs various cutoffs for % change from baseline total seizure frequency in various dose groups (Placebo, 200, 400, 800 and 1600 mg)

Conclusions

↳

↳

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Lennox Gastaut syndrome

1. Is there is evidence of effectiveness?

Yes, there is evidence of effectiveness.

Primary efficacy variable percent change in total seizure frequency per 28 days showed a significant difference between the 2 treatment groups in favor of rufinamide ($p=0.0015$). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency (see Figure 9). Primary efficacy variable percent change in tonic-atonic seizure frequency per 28 days showed a significant difference between the 2 treatment groups in favor of rufinamide ($p<0.0001$). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 Days (see Figure 9).

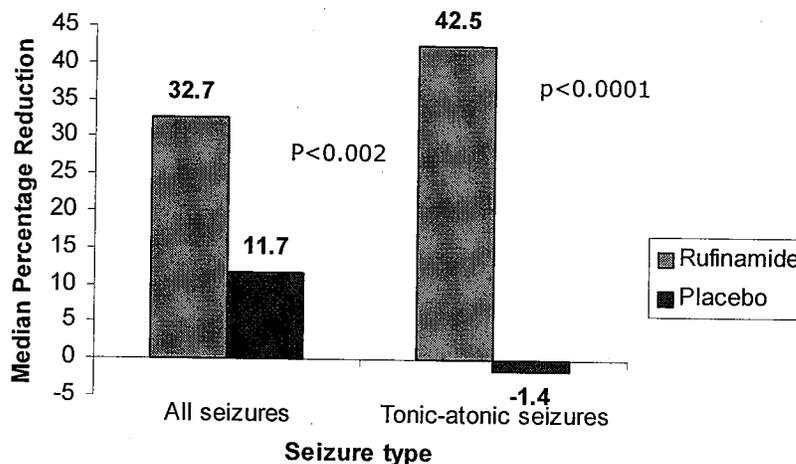


Figure 9. Median percentage reduction in total and tonic-atonic seizures frequency per 28 days for rufinamide and placebo groups.

Dose-Response Relationship

The sponsor used a body weight based dosing guidelines. This did not allow for evaluation for dose-response.

Concentration-Response Relationship

Sponsor also analyzed the relationship between log total seizure frequency, tonic-atonic seizure and rufinamide concentrations (Figure 10) in Study CRUF331-022. There was a significant relationship between total seizure frequency and rufinamide average concentrations.

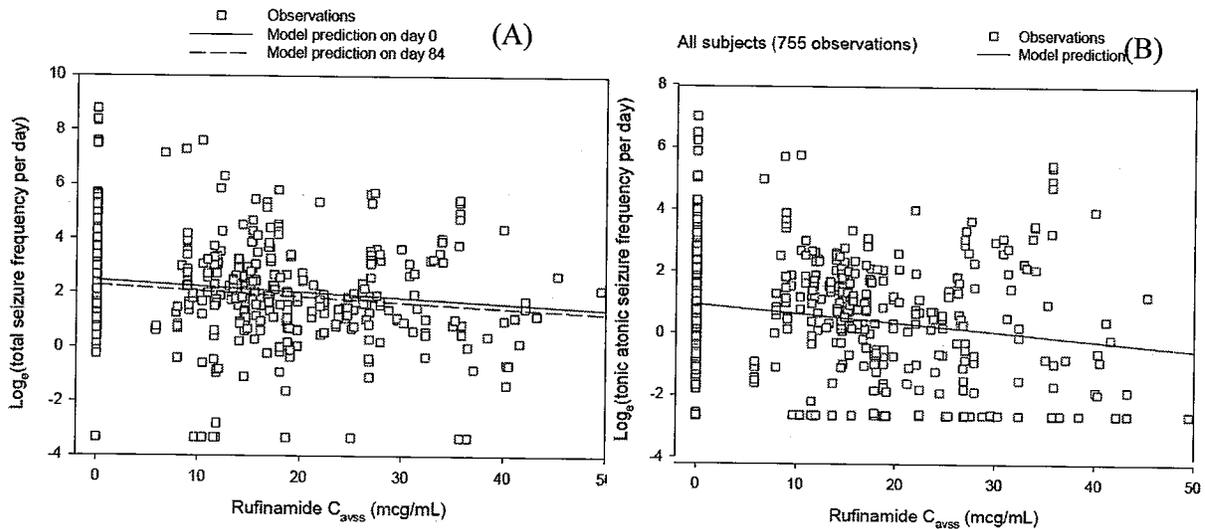


Figure 10 (A) Total seizure frequency (B) Tonic-atonic seizure frequency data (log-transformed) and model predictions vs rufinamide average concentrations

Conclusion

Rufinamide is superior to placebo as per protocol stated primary analysis.

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Overall Dose-Response Relationship

Figure 11 below shows the overall dose-response relationship for partial seizures based on data from Study AE/ET1 (Dose-response study; ;Placebo, 200, 400, 800, 1600 mg)) and Study 21A (Placebo, 3200 mg). As can be seen, the dose-response is essentially flat and one could conclude that doses above 800 mg would not offer any substantial benefit.

NOTE: In Study 21A, the sponsor used the 'to be marketed' formulation which has a higher relative bioavailability (21% higher AUC, 34% higher Cmax). In Study AE/ET1 the sponsor used the formulation which had lower bioavailability. This difference is not of a concern as higher exposures would not result in lower effectiveness. If the exposure-safety relationship is not very steep, the slight changes in AUC should not be of a concern).

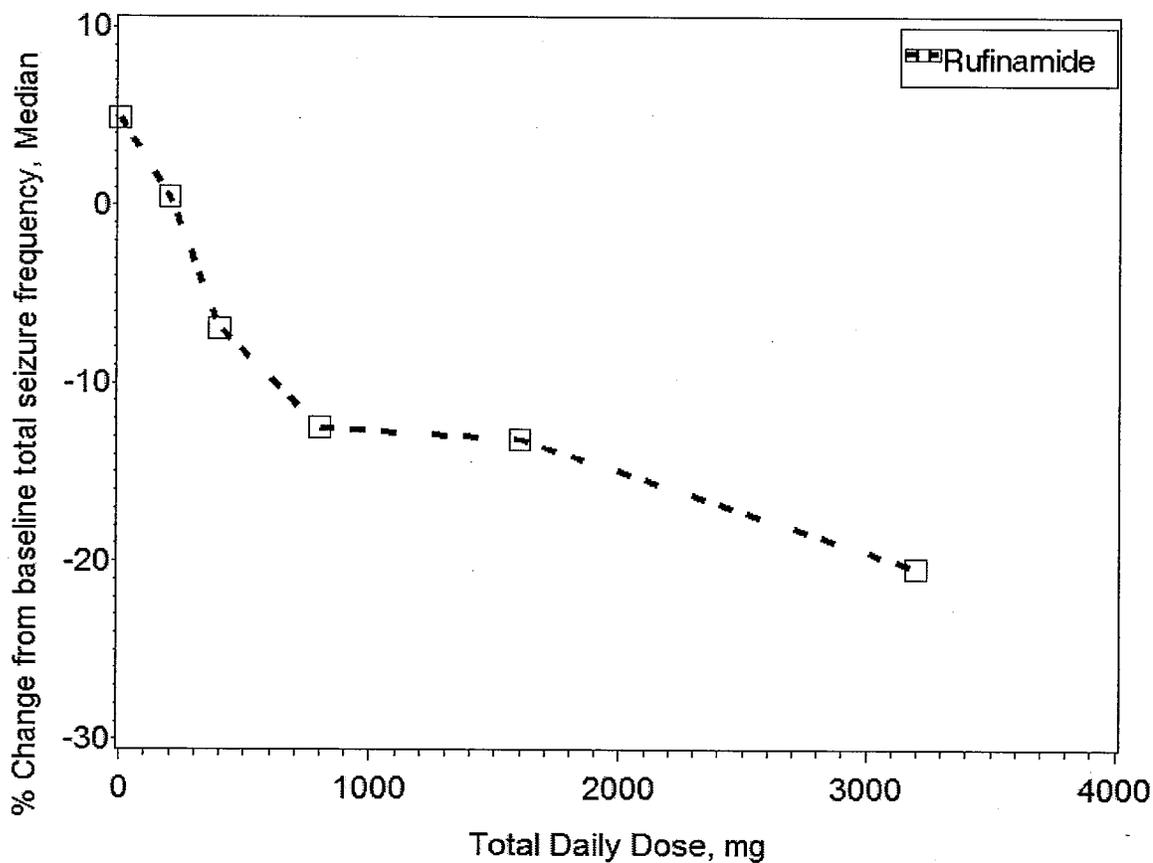


Figure 11. Relationship between % change from baseline total seizure frequency, Median versus total daily dose, mg of rufinamide.

Rufinamide vs Other Antiepileptic Drugs

Figure 12 below shows the comparison of rufinamide versus other approved antiepileptic drugs such as Pregabalin, Keppra, Trileptal. The % change from baseline total seizure frequency information was obtained from approved drug labels and are shown against the doses. As can be seen in the graph, all other approved treatments have much higher reduction in seizure frequency when compared to rufinamide. This needs to be weighed along with the shortening of QT interval observed in the thorough QTc study (Please refer to the review by Dr Nhi Beasley on the effects of rufinamide on QT prolongation).

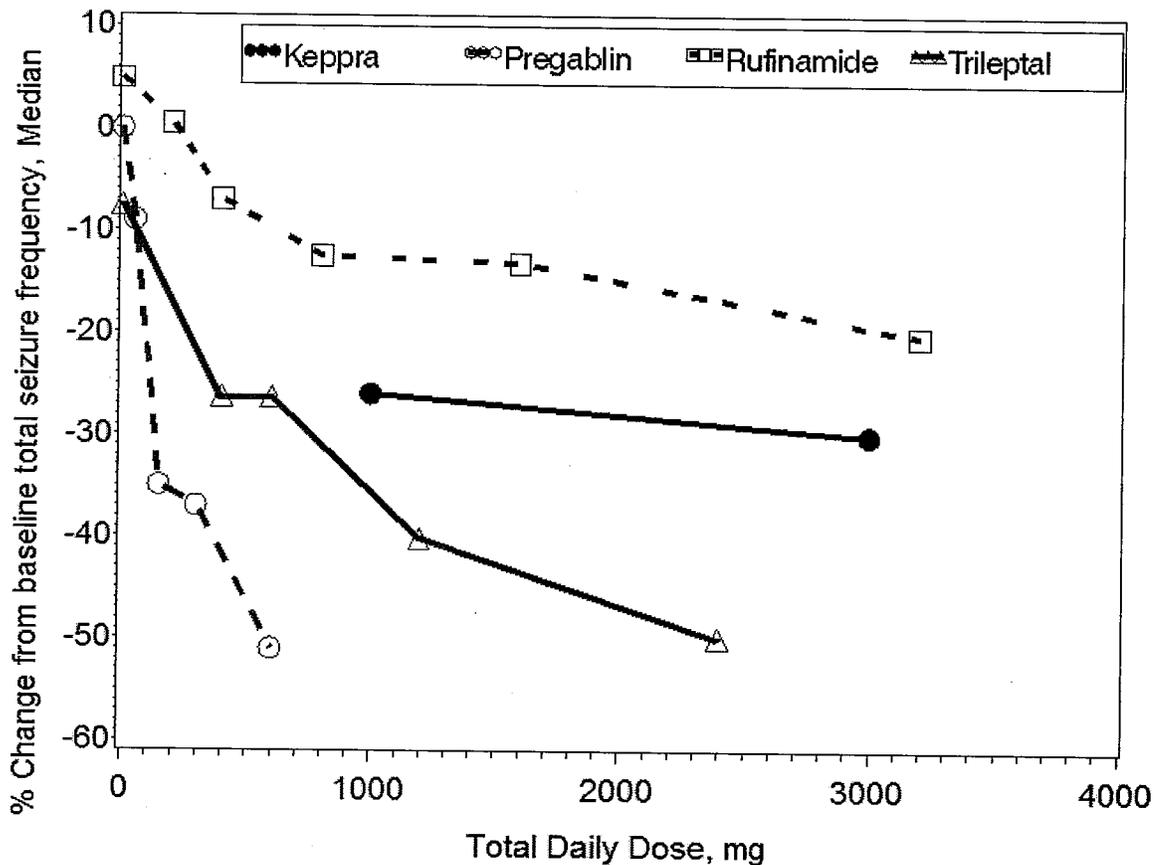


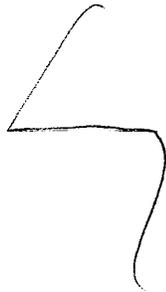
Figure 12. Relationship between % change from baseline total seizure frequency, Median versus total daily dose, mg of rufinamide, pregabalin, keppra, trileptal.

Sponsor Proposed Dosing Regimen

The proposed dosing regimen by the sponsor for the two indications is shown below. Based on the evidence from the studies,

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Based on the submitted information for LGS, it is not possible to comment on the appropriateness of the proposed dosing regimen. It is possible to better understand the dosing guidelines for LGS if the sponsor were to conduct a dose-response study in patients with LGS.



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Adjunctive therapy in pediatric (4 - 17 years) and adult patients with Lennox-Gastaut syndrome.

Children: Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a maximum of 45 mg/kg/day or 3200 mg/day whichever is less, administered in two equally divided doses.

Adults: Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg/day every 2 days until a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached.

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Overall Conclusions

Based on the dose/concentration-response analysis, the following conclusions are derived:

1. There is clear evidence of dose-response relationship.
2. There is clear evidence of concentration-response relationship.
3. _____
4. Sponsor should conduct a dose-response study (Similar to AE/ET1) in patients with LGS.
5. The overall effect size is smaller when compared to other approved treatments and should be considered when approving rufinamide along with the risk of QT shortening.

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Veneeta Tandon
9/11/2006 12:53:30 PM
BIOPHARMACEUTICS

Atul Bhattaram
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Nhi Beasley
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Mehul Mehta
9/11/2006 03:01:57 PM
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N21-911	Brand Name	Inovelon
OCPB Division (I, II, III)	DPE-I	Generic Name	Rufinamide
Medical Division	HFD-120	Drug Class	Antiepileptic
OCPB Reviewer	John Duan	Indication(s)	Adjunctive treatment of 1. seizure for 12 yr & older; 2. seizure associated with Lennox Gastaut Syndrome for 4 yr & older.
OCPB Team Leader	Ramana Uppoor	Dosage Form	Tablets 100, 200, 400mg
		Dosing Regimen	Dose titration bid. Adults: start: 400-800mg/day; increment: 400-800mg/day q2d; max: 3200mg/day. Children: start: 10mg/kg/day; increment: 10mg/kg/day q2d; max: 45mg/kg/day 3200mg/day
Date of Submission	9/8/05	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/8/06	Sponsor	Eisai Medical Research, Inc.
PDUFA Due Date	7/8/06	Priority Classification	Standard
Division Due Date	6/8/06		

Clin. Pharm. and Biopharm. Information

Summary: The overall clinical pharmacology program of rufinamide consists of 24 studies, including 495 subjects (469 healthy subjects and 25 patients), treated either with rufinamide or placebo or both. Twenty-three (23) studies were conducted with healthy subjects (one study including also patients with renal impairment). One study was conducted in pediatric patients with epilepsy. Additionally, clinical efficacy and safety studies with pharmacokinetic information contributed to the PK database and provided doses and formulations, drug-drug interactions and exposure-response information. These studies have been analyzed using population PK/PD modeling, separately or as part of a large pooled database. Together with eight double blind, controlled studies evaluating the safety and efficacy of rufinamide in epilepsy related indications, the applicant tries to provide information of the onset of the effect, confirm that the effects seen in adjunctive studies are related to rufinamide and not to interaction with other concomitant antiepileptic drugs, and confirm the dose-response relationship.

The formulations used in the studies include _____, referred to as the Clinical Service Form (CSF): _____

referred to as the Final Market Image (FMI). While the suspension was shown to be bioequivalent to the tablets at 400mg dose, the 200 mg FMI and CSF tablets (200 or 400mg) in fed conditions are not bioequivalent. Two of three clinical studies supporting the adjunctive indication did not use FMI. This will be a review issue regarding the studies using CSF formulations.

Various dissolution test methods were explored. Both the clinical service formulation tablet and the final market image tablet were studied for *in vivo/in vitro* correlations (IVIVC) and _____

Eight bioanalytical methods have been validated for the assay of rufinamide (and its main metabolite CGP47292) in different human matrices (plasma and urine). Cross validation was conducted between two methods.

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The effect of renal impairment was evaluated by study 029 and using population modeling (EMFFR2004/014/00). The influence of liver function markers was investigated in the pooled data analyses, showing no relationship with serum bilirubin or AST and ALT.

There is no evidence of oxidative metabolism by cytochrome P450 enzymes, or of conjugation with glutathione. Less than 2% of the dose is excreted unchanged in the urine. Rufinamide is extensively metabolised by hydrolysis of the carboxamide group to the carboxylic acid derivative CGP 47292. This metabolite, which is pharmacologically inactive, is mainly cleared by renal excretion. At pharmacologically relevant concentrations, rufinamide has essentially no capacity to function as an inhibitor of the major P450 enzymes in human liver microsomes (Study DMET 96012). Rufinamide demonstrated no significant capacity to inhibit any of 8 major human CYP isozymes. The K_i values for each of the P450s assayed were $\geq 1350 \mu\text{mol/L}$ ($\geq 450 \mu\text{mol/L}$ for CYP2E1). Definite DDI study showed CYP3A induction potential.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	11		
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	1		
Blood/plasma ratio:	-	-		
Plasma protein binding:	-	-		
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	4	-	
multiple dose:	X	5	-	
<i>Patients-</i>				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	-	-		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	1		
In-vivo effects of primary drug:	X	4		
In-vitro:	-	-		
Subpopulation studies -				
ethnicity:	-	-		
gender:	-	-		
pediatrics:	X	1		
geriatrics:	X	1		
Renal impairment:	X	1		
Hepatic impairment:	-	-		
PD:	X	1		

Phase 2:	-	-		
Phase 3:	-	-		
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-		
Phase 3 clinical trial:	X	3		
Population Analyses -				
Data rich:	X	1		
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability:	-	-		
Relative bioavailability -	X	6 (2 also food)		
solution as reference:	-	-		
alternate formulation as reference:	-	-		
Bioequivalence studies -				
traditional design; single / multi dose:	X	4		
replicate design; single / multi dose:	X	1		
Food-drug interaction studies:	X	3 (2 also rel bio)		
Dissolution:	X	1		
(IVIVC):	X	1		
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies	QTc	2		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		40		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X	Yes from OCPB point of view, but No from Pharm/Tox.		
Comments sent to firm?	X	Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1. Although it is stated that no plasma protein binding study was conducted in the CTD table of contents, there is a statement regarding the binding (34%). Please provide an explanation. 2. Eight assay methods have been used. Only one comparison between two sites was found. Please direct us to find the cross-validation data among these methods.		
QBR questions (key issues to be considered)		1. Is it confirmed that the effects seen in adjunctive studies are related to rufinamide and not to interaction with other concomitant antiepileptic drugs? 2. What are the dose-response and concentration-response relationships? 3. What is the implication of the dose-response and concentration-response relationship? 4. What are the consequences of two of three studies supporting adjunctive indication that used clinical formulation which is not bioequivalent to the to-be-marketed formulation?		
Other comments or information not included above		1. The drug interaction studies used dose of 800 mg/day whereas the maximum proposed dose is 3200 mg/day. 2. Mass balance study used only three subjects 3. Two of the three clinical studies to support adjunctive therapy did not use the to-be-marketed formulation. BE studies between these two formulations failed.		
Primary reviewer Signature and Date	John Duan			
Secondary reviewer Signature and Date	Ramana Uppoor			

CC: NDA 21-898, HFD-850 (Electronic Entry), HFD-120 (Wheelous), HFD-860 (V. Tandon, R. Uppoor, A. Rahman, M. Mehta)

Attachment. Study summary

Mass balance study of disposition, metabolism and excretion route in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
HPH9213		Mass balance, disposition, excretion and metabolism	Open label, single centre study, fed	600 mg ¹⁴ C-rufinamide 200 mg gelatine capsule, oral, 6.1 kBq/mg	3 HS (3M)	<p>-The absorption of 600 mg of ¹⁴C-labelled rufinamide with food was at least 85%. 81% of radioactivity in plasma was associated with parent drug. Blood and plasma concentrations of total radioactivity were similar.</p> <p>-The predominant clearance mechanism of rufinamide was metabolism, by hydrolysis of the carboxamide group to the carboxylic acid derivative CGP 47292, mainly cleared by renal excretion.</p> <p>-Some minor metabolites (P3 and P4) were identified as acyl-glucuronide metabolites of CGP 4792. There was no evidence of oxidative metabolism by cytochrome P450 enzymes, or of conjugation with glutathione.</p> <p>-¹⁴C-labelled rufinamide was well tolerated. Clinical laboratory values showed marginal deviations from the normal range.</p>

Single dose pharmacokinetic studies in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
A 184		Tolerability, safety, PK	Randomised, double-blind, placebo-controlled, 4-period cross-over	1, 2, 5, 10, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, and 600 mg and placebo SD, 1 & 10mg DC 50, 100 & 200 mg tablets	28 HS (28 M) Age: 22-34	<p>-The rate and extent of absorption decreased with increasing dose, as shown by increased t_{max} and decreased dose normalized C_{max} and AUC</p> <p>$-t_{1/2}$ 8 to 9 hours, irrespective of dose</p> <p>-No SAEs or deaths were reported during the study. Minor and non-specific adverse events were reported in all treatment groups. Two subjects reported mild or moderate dizziness: one subject treated with 600 mg rufinamide, the other with placebo. There were no clinically significant changes in the subject's vital signs, ECGs, EEGs, self-rating VAS scale, quality of sleep and laboratory parameters. Single oral doses of rufinamide were well tolerated up to 600 mg in healthy male subjects.</p>
A 233		Tolerability, safety, PK	Randomised, double-blind, placebo-controlled, 4-period cross-over	600, 800, 1000, 1200, 1500, 1800, 2100 mg and placebo SD 100 & 200 tablets	11 HS (11M) Age:20 to 31	<p>The rate and extent of absorption decreased with increasing dose, as shown by increased t_{max} and decreased dose normalized C_{max} and AUC</p> <p>$-t_{1/2}$: 7 to 11 h at all doses.</p> <p>-Less than 1% of the dose is excreted in urine as rufinamide and 23-35% of the dose is excreted in urine as metabolite CGP 47292.</p> <p>-No SAEs or deaths were reported during the study. There were no clinically significant changes in the subject's vital signs, ECGs, EEGs, self-rating VAS scale, quality of sleep, and laboratory parameters. Single oral doses of rufinamide up to 2100 mg were well tolerated in healthy male subjects.</p>

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
EPI-001		Safety and PK in plasma and urines	Open label, cross-over	100, 200, 400 and 800 mg 50 & 200 mg JPN tablet	12 HS Japanese (12 M) Age: 20 to 34	<p>$-t_{max}$ 4 to 8 hours post-dose.</p> <p>$-C_{max}$ and AUC_{0-96} values increased with dose but less than proportionally.</p> <p>$-t_{1/2}$ constant: 9-11 hours independently of dose.</p> <p>-Less than 1% of the dose was excreted unchanged in the urine over 96 hours and the urinary excretion of CGP 47292 in 96 hours was 50% of the dose.</p> <p>-All adverse events were mild in severity and transient. There was no effect on vital signs, EEG, ECG, Kraepelin tests and laboratory safety parameters.</p>

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Single dose pharmacokinetic studies in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results															
04		Dose proportionality	Open-label, randomised 4x4 Latin-square, crossover trial	200, 400, 800, 1200 mg SD 200 mg tablet	19 HS (19 M/0 F) 20 to 38 years	<p>- No dose-proportionality in the dose range of 200 to 1200 mg in healthy male subjects. There was less than dose-proportional increase in C_{max} and AUC with increasing dose.</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="3">90% CI of difference between the dose and reference</th> </tr> <tr> <th>400 mg vs. 200 mg</th> <th>800 mg vs. 200 mg</th> <th>1200 mg vs. 200 mg</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>-13.6%; 1.6%</td> <td>-38.1%; -22.8%</td> <td>-44.1%; -28.9%</td> </tr> <tr> <td>AUC₀₋₄₈</td> <td>-7.6%; 7.7%</td> <td>-23.4%; -8.0%</td> <td>-35.0%; -19.6%</td> </tr> </tbody> </table> <p>- Dose normalised C_{max} and AUC₀₋₄₈ at dose 200 mg and 400 mg were not statistically different. The differences between 800 and 200 mg, and between 1200 and 200 mg were all statistically significant whatever the PK parameter considered. There were no statistically significant differences in t_{max} and $t_{1/2}$.</p> <p>- No SAEs or deaths were reported during the study. No subject discontinued due to AEs or abnormal laboratory values. There were no clinically significant changes in the subject's vital signs, ECG and laboratory parameters. Rufinamide was well tolerated at single 200, 400, 800, and 1200 mg oral doses in healthy male subjects.</p>	Parameter	90% CI of difference between the dose and reference			400 mg vs. 200 mg	800 mg vs. 200 mg	1200 mg vs. 200 mg	C_{max}	-13.6%; 1.6%	-38.1%; -22.8%	-44.1%; -28.9%	AUC ₀₋₄₈	-7.6%; 7.7%	-23.4%; -8.0%	-35.0%; -19.6%
Parameter	90% CI of difference between the dose and reference																				
	400 mg vs. 200 mg	800 mg vs. 200 mg	1200 mg vs. 200 mg																		
C_{max}	-13.6%; 1.6%	-38.1%; -22.8%	-44.1%; -28.9%																		
AUC ₀₋₄₈	-7.6%; 7.7%	-23.4%; -8.0%	-35.0%; -19.6%																		

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Multiple doses pharmacokinetic studies in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
A 202		Tolerability, safety, pharmacokinetics of multiple doses	Randomised, placebo-controlled, double-blind cross-over	200 mg SD Day 0 Day 7 to 35: Multiple rising: 50/100/150/200 mg b.i.d. 50, 100, 200 mg / tablet	7 HS 7 M Age: 26-43	<p>-No change after multiple dose treatment: the AUC_{0-inf} on day 0 was comparable to AUC₀₋₁₂ at steady state on day 28.</p> <p>-On day 35, concentrations were almost three times greater than the concentrations observed on the first day.</p> <p>-There were no clinically significant changes in vital signs, ECGs, EEGs, self-rating VAS scale, quality of sleep, and laboratory parameters. No SAEs or deaths were reported during the study. No relationship of frequency or intensity of any AE to the dose level was detected. One subject discontinued treatment (200 mg bid) due to adverse events (headache, dizziness, difficulty to concentrate) on day 23.</p>
AEMD2		Tolerability, safety, pharmacokinetics of multiple doses	Double-blind, crossover, placebo-controlled	600 mg SD on day 0 4-week rising multiple dose 150/300/450/600 mg b.i.d. or placebo 50, 100, 200 mg / tablet	18 HS 18M Age: 18-45	<p>-No change after multiple dose treatment: the AUC_{0-inf} on day 0 was comparable to AUC₀₋₁₂ at steady state on day 28.</p> <p>-After treatment bid during 28 days, concentrations were approximately three times greater than the concentrations observed on the first day.</p> <p>-Rufinamide was well tolerated; adverse events, which were mild to moderate, resolved spontaneously at the end of the study. There was no evidence of mood change, sleep quality and duration change. Subject 1 who experienced feeling nervous and depressed during 8 days, disoriented during 4 hours, was withdrawn from the study on day 21 due to these adverse events. There were no clinically significant changes in the subject's vital signs, ECG, EEG and laboratory parameters. No SAEs or deaths were reported during the study.</p>

Multiple doses pharmacokinetic studies in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
EPI-002		Safety, pharmacokinetics of multiple doses	Open-label study	200 mg SD on day 1 and 10; 200 mg b.i.d. day 3 - 9 200 mg Japanese tablet	6 HS Japanese male Age: 21-27	-Pharmacokinetics on day 10 was comparable with day 1. -After b.i.d administration over 10 days, exposure to rufinamide was increased by 171%. -Trough levels show that steady state was reached after 2 days of multiple dosing. - $t_{1/2}$ was 9.1 h, the lag time was close to 1h and the rate constant of absorption was 0.52 h^{-1} -Only one metabolite: CGP 47292 was quantifiable in plasma and did not accumulate more than predicted upon repeated dosing. -The urinary recovery of rufinamide was <1% of the dose and CGP 47292 urinary excretion after 48 to 96 h represented approximately 60% of the dose. -No clinically significant subjective or objective symptoms were observed. Laboratory tests found no clinically significant abnormal changes
E2080-A001-001		MTD and pharmacokinetics after multiple doses	Double-blind, randomised, multiple rising dose	800/ 1600/ 2400/ 3200/ 4800/ 7200 mg per day, 3 days 400 mg F1, tablet, Oral	20 HS 10M, 10F Age: 19-43	-The absorption is slow: $K_a = 0.18 \text{ h}^{-1}$ and rate limiting. — $t_{1/2}$: 7.7 h. -The maximum effect of the dose on the bioavailability was E_{max} : -1.18 and the total daily dose at half maximum D_{50} 101 mg/kg. -CL/F varies with BSA: in a typical subject with population median BSA, CL/F at 800 mg/d is 3.41 L/h. -Rufinamide decreases the QT intervals, after correction for the RR interval using subject's specific correction, QTc Fridericia correction or uncorrected QT. The decrease of QT was approx. 7.5ms at a typical concentration of 15µg/mL.
Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
E2080-A001-002		MTD and pharmacokinetics after multiple doses	Double-blind, randomised, multiple rufinamide rising dose, single moxifloxacin dose	Rufinamide: 800/ 1600/ 2400/ 3200/ 4800/ 7200 mg per day, 3 days 400 mg F1, tablet, Oral Moxifloxacin: 400 mg oral tablet	20 HS 10M, 10F Age: 19-43	-The absorption of rufinamide is slow: $K_a = 0.20 \text{ h}^{-1}$ with lag time 0.8 h -The maximum effect of the dose on the bioavailability was E_{max} : -1.47 and the total daily dose at half maximum D_{50} 97.9 mg/kg. -In a typical subject with body weight 72 kg, CL/F at 2400 mg/d is 9.92 L/h. -Rufinamide decreases the QT intervals, after correction for the RR interval using subject's specific correction, QTc Fridericia correction or uncorrected QT. The decrease of QT was approx. 17 msec at a typical concentration of 15µg/mL.

b(4)

b(4)

Pharmacokinetic studies in patients with epilepsy (rich sampling PK)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results																																																						
AE/PT2		PK, safety, tolerability, safety and potential efficacy in patients with epilepsy.	Multicentre, double blind randomised, placebo-controlled, 2-armed parallel weekly rising dose	Day 1 and 35: 800 mg single dose. Day 8 to 34: 400/ 800/ 1200/ 1600 mg b.i.d. or placebo 200 mg tablet Oral	50 patients (M/F) Age 18-60,	<p>-The pharmacokinetics of rufinamide was not modified in time. -Rufinamide trough levels increase less than proportionally to the dose. -Rufinamide AUC was lower in patients treated with phenytoin or carbamazepine than in patients treated with valproate.</p> <p>Influence of valproate co administration on rufinamide PK</p> <table border="1"> <thead> <tr> <th>Parameters</th> <th colspan="2">All 50 patients, day 1</th> </tr> <tr> <th>Geom. Mean (95% CI)</th> <th>With valproate</th> <th>Without valproate</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>16</td> <td>34*</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>4.15 (3.44; 5.02)</td> <td>3.17 (2.80; 3.58)</td> </tr> <tr> <td>AUC_{0-∞} (h.µg/mL)</td> <td>88.37 (66.91; 116.71)</td> <td>51.85 (46.45; 57.87)</td> </tr> <tr> <td>t_{1/2} (h)*</td> <td>8.55 (7.32; 10.00)</td> <td>6.42* (6.04; 6.82)</td> </tr> </tbody> </table> <p>*33 subjects only for t_{1/2}</p> <p>Influence of carbamazepine co administration on rufinamide PK</p> <table border="1"> <thead> <tr> <th>Parameters</th> <th colspan="2">All 50 patients, day 1</th> </tr> <tr> <th>Geom. Mean (95% CI)</th> <th>With carbamazepine</th> <th>Without carbamazepine</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>35*</td> <td>15</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>3.40 (3.01; 3.85)</td> <td>3.57 (2.84; 4.50)</td> </tr> <tr> <td>AUC_{0-∞} (h.µg/mL)</td> <td>60.15 (53.14; 68.07)</td> <td>64.75 (45.09; 92.98)</td> </tr> <tr> <td>t_{1/2} (h)*</td> <td>6.69 (6.30; 7.09)</td> <td>7.95 (6.50; 9.73)</td> </tr> </tbody> </table> <p>*Only 34 subjects for t_{1/2}</p> <p>Influence of phenytoin co administration on rufinamide PK</p> <table border="1"> <thead> <tr> <th>Parameters</th> <th colspan="2">All 50 patients, day 1</th> </tr> <tr> <th>Geom. Mean (95% CI)</th> <th>With phenytoin</th> <th>Without phenytoin</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>18</td> <td>32*</td> </tr> <tr> <td>C_{max} (µg/mL)</td> <td>3.21 (2.74; 3.75)</td> <td>3.60 (3.11; 4.16)</td> </tr> <tr> <td>AUC_{0-∞} (h.µg/mL)</td> <td>47.67 (41.39; 54.90)</td> <td>70.97 (59.61; 84.49)</td> </tr> <tr> <td>t_{1/2} (h)*</td> <td>6.51 (5.87; 7.21)</td> <td>7.38 (6.69; 8.16)</td> </tr> </tbody> </table> <p>*Only 31 subjects for t_{1/2}</p> <p>The median seizure frequency decreased by 41% in patients treated with rufinamide and increased by 52% in patients treated with placebo (significant difference: p=0.0397). -No deaths occurred. Three patients experienced SAEs, two of whom discontinued prematurely. There was no change in vital signs or laboratory parameters. -There is no evidence that dose adjustment is necessary when rufinamide is co administered with valproate, carbamazepine or phenytoin.</p>	Parameters	All 50 patients, day 1		Geom. Mean (95% CI)	With valproate	Without valproate	N	16	34*	C _{max} (µg/mL)	4.15 (3.44; 5.02)	3.17 (2.80; 3.58)	AUC _{0-∞} (h.µg/mL)	88.37 (66.91; 116.71)	51.85 (46.45; 57.87)	t _{1/2} (h)*	8.55 (7.32; 10.00)	6.42* (6.04; 6.82)	Parameters	All 50 patients, day 1		Geom. Mean (95% CI)	With carbamazepine	Without carbamazepine	N	35*	15	C _{max} (µg/mL)	3.40 (3.01; 3.85)	3.57 (2.84; 4.50)	AUC _{0-∞} (h.µg/mL)	60.15 (53.14; 68.07)	64.75 (45.09; 92.98)	t _{1/2} (h)*	6.69 (6.30; 7.09)	7.95 (6.50; 9.73)	Parameters	All 50 patients, day 1		Geom. Mean (95% CI)	With phenytoin	Without phenytoin	N	18	32*	C _{max} (µg/mL)	3.21 (2.74; 3.75)	3.60 (3.11; 4.16)	AUC _{0-∞} (h.µg/mL)	47.67 (41.39; 54.90)	70.97 (59.61; 84.49)	t _{1/2} (h)*	6.51 (5.87; 7.21)	7.38 (6.69; 8.16)
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b(4)

Pharmacokinetic / pharmacodynamic studies in patients with epilepsy (sparse sampling PK)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
22		Safety, efficacy, PK in patients with Lennox-Gastaut syndrome (LGS).	Multicentre, double-blind, placebo-controlled, randomized, parallel-group	Titration from 10 mg/kg/day, to 45 mg/kg/day <1-2 weeks or placebo 100, 200, or 400 mg FMI tablets b.i.d. Oral	138 paediatric patients with LGS (79M, 50F) Age: 59 age 2-11 40 age 12-17 30 age 18+	<p>-C_{1/2} proportionally to BSA; -Bioavailability decreases with increasing total daily dose per kg BW; -Co administration of valproate is associated with a moderate decrease of clearance. -Significant difference between rufinamide and placebo groups in change from baseline for total seizure frequency (p = 0.0015) and tonic-atonic seizure frequency (p < 0.0001). -Significant improvement in seizure severity (p = 0.0041). -The decrease of the Log_e(total seizure frequency) and Log_e(tonic-atonic seizure frequency) and rufinamide exposure was proportional to rufinamide concentrations at steady-state C_{avg,ss}. None of the concomitant AEDs affects this relationship. -Seizure severity rating improvement was proportional to the logarithm of rufinamide concentrations; this relationship was not affected by concomitant AEDs. -Subjects who experienced vomiting, diarrhoea, pyrexia or somnolence did not have higher rufinamide exposure than subjects who did not.</p>

Pharmacokinetic / pharmacodynamic studies in patients with epilepsy (rich PK sampling)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
27		Safety, tolerability and PK in paediatric patients with inadequately controlled seizures.	Multicentre, open label, weekly-ascending dose design	10 mg/kg/day (Week 1) and 30 mg/kg/day (Week 2). 100, 200 mg tablets Oral	16 patients 8M, 8F Age: 1-16	-No statistically significant difference in PK parameters between age groups. -No proportionality with the dose from 10 to 30mg/kg -No death was reported. One SAE, felt to be related to the condition under study and not to rufinamide treatment, was reported: the patient had an episode of increased seizures, which required hospitalisation for 1 day. No clinically relevant effects of rufinamide were observed in other vital signs, physical examination findings or routine laboratory analyses. Rufinamide was safe and well tolerated by all patients at 10 mg/kg/day and 30 mg/kg/day.

b(4)

Pharmacokinetic / pharmacodynamic studies in patients with epilepsy (sparse PK sampling)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
EMFFR20 04/014/00 Pooled studies: 0016, 0018, 0021, 0022, 0027, AE/ET1 and AE/PT2		Pooled population PK, PKPD analysis	Double-blind, randomised, placebo controlled multiple dose	200-3200 mg /d adults 10-45mg/kg /d paediatric Tablets 100 mg F2, 200 mg F1 100 mg F3, 400 mg F1, 200 mg F2	PK: 1072 (534F; 538M) PKPD: 1725 (842F; 883M) Patients with epilepsy Age: 2-77	-PK was described by a one-compartment model, with first order absorption: $K_a=0.624h^{-1}$ for the tablet. No absorption for the FMI tablet. -Relative bioavailability between CSF and FMI tablets is 0.54. -The bioavailability and K_a decrease with increasing dose -CL/F and V/F increase with BSA. CL/F is not affected by age, renal or liver function. Lamotrigine or topiramate do not affect rufinamide PK. Concomitant valproate decreases CL, increases Cavss: by 55 to 70% in children, less in adolescent and adults. Concomitant phenytoin, phenobarbital or primidone increase CL, decrease Cavss by 43-46% in children, 30-32% in adolescent and 25-26% in adults. Concomitant carbamazepine or vigabatrin increase CL, decrease Cavss by <30%. -The inter subject variability is CL: 46.3%; V: 49.8% (moderate). Predicted Cavss was not different between White and Black populations. -The PKPD model of $\log_e(\text{total seizure frequency})$ is the sum of an intercept ("baseline"), a decrease due to placebo/time in the study and a decrease proportional to Cavss. The rufinamide effect on seizure frequency is not affected by concomitant AED, age and sex of the patients, different types of epilepsy: inadequately controlled primarily generalised tonic-clonic, simple partial, complex partial ± secondarily generalised, LGS. -The PKPD model for the logit of the probability of response is a linear function of an intercept (chance change), a disease model of placebo time effects (the probability of response decreasing according to a second degree polynomial) and an increase proportional to predicted rufinamide concentrations. -Rufinamide effect on response probability is not affected by concomitant AED, and does not differ between the populations studied.

b(4)

Pharmacokinetic study in healthy elderly subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
31		Pharmacokinetics in elderly	Open-label, parallel group	SD 400 mg day 1 and 8, MD 400 mg b.i.d day 4 to 7 200 mg tablet	7 Healthy younger subjects (4M, 3F) Age: 18-40 8 healthy elderly (4M, 4F) Age: 66-77	- C_{max} and AUC similar between young and elderly subjects after single or multiple doses. -Rufinamide was extensively metabolised: <2% of the dose unchanged and 60% of the dose as CGP 47292 recovered in urine after SD and MD. -There was no significant difference in urinary excretion of rufinamide and CGP 47292 between young and elderly subjects. One healthy elderly subject discontinued after the single dose administration due to adverse events. No SAEs or deaths were reported during the study.

Pharmacokinetic studies in the patients with severe renal impairment

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
29		Pharmacokinetics, safety, tolerability in severe renal failure	Open-label, two-part study: HS vs. renal patients before and after dialysis	400 mg 400 mg F1 / tablet	9 HS (2M, 7F) 9 chronic renal failure (2M, 7F) Age: 29 to 63	-There were no difference between healthy subjects and subjects with chronic renal failure. -Haemodialysis reduced AUC_{0-12h} and C_{max} by 30% and 16%, respectively. -Rufinamide was extensively metabolised in both renal patients and healthy subjects, with <1% of the dose recovered unchanged in the urine -Rufinamide 400 mg was safe and well tolerated in subjects with chronic and severe renal failure and in healthy matched control subjects. No SAEs or deaths were reported during the study. The frequency and severity of AEs were comparable between healthy subjects and subjects with chronic renal failure.

Pharmacodynamic study in healthy subjects

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
237		PD study: Acoustically evoked potential N100; contingent negative variation (CNV); hyperventilation related EEG-changes	Randomised, placebo-controlled, double-blind, cross-over	SD 800 mg 200 mg F1 tablet	24 HS (24M) Age: 18-35	- Rufinamide increased the N100 amplitude (attentional and orienting processes), which suggests an intensified attentional focusing on target stimuli. - There was no change of CNV (anticipation and behavioural control) and mean reaction time. Rufinamide had no influence on the spontaneous-EEG parameters α -power and centre frequency (cortical excitability). Rufinamide did not change hyperventilation-related negative DC-shift suggesting the lack of general depressant effects of rufinamide. - No SAEs or deaths were reported during the study. There were no clinically significant changes in the subject's ECGs, self-rating VAS scale, quality of sleep, and laboratory parameters.

b(4)

Pharmacokinetic drug interaction studies in healthy subjects (rich PK sampling)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results
14		Effect of rufinamide on PK of oral contraceptive Ortho Novum 1/35*	Open-label, crossover trial	Ortho Novum 1/35* days 1-56 ethinyl estradiol: 35µg; norethindrone 1mg Days 22 to 35: 800 mg b.i.d. Rufinamide 200 mg F1 tablet	25 HS (25F) Age: 19 - 44	-Rufinamide decreased exposure: of ethinyl estradiol by 22% on AUC_{0-24} , 31% on C_{max} , of norethindrone by 14% on AUC_{0-24} , 18% on C_{max} . It is unknown if such changes can affect prevention of ovulation. -No SAEs or deaths were reported during the study. No subjects were withdrawn from the study because of an AE or a laboratory abnormality. There were no clinically significant changes in the subject's vital signs, ECGs, and laboratory parameters. The majority of AEs were of mild severity.
104		Effect of rufinamide on PK of triazolam, a cytochrome P450 3A4 substrate (induction potential)	Open-label, three period study.	SD 0.25 mg of triazolam on day 1&15. MD 400 mg bid rufinamide day 4 -14, SD 400 mg day 15. Rufinamide: 400 mg FMI tablet Oral	21 HS (1F, 20M) Age: 19- 43	- Concomitant rufinamide decreases triazolam AUC by 36%, C_{max} by 24% - Rufinamide was safe and well tolerated. No SAEs or deaths were reported during the study. No subject discontinued due to AEs or abnormal laboratory values. All events were mild in severity and suspected to be related to study medication. There were no clinically significant changes in the subject's vital signs, ECGs, and laboratory parameters.
105		Effect of rufinamide on PK olanzapine, a cytochrome 1A2 substrate	Open-label, three period study	SD 5mg olanzapine, day 1&22. MD 400 mg bid day 11 to day 21, SD 400 mg on day 22 rufinamide. 400 mg FMI tablet	19 HS (19M) Age: 18 -44	- Co administration of rufinamide had no effect on olanzapine exposure - Rufinamide was safe and well tolerated with and without single 5 mg olanzapine dose. No SAEs or deaths were reported during the study. No subject discontinued due to AEs. The AEs were considered not likely to be related to rufinamide. There were no clinically significant changes in the subject's vital signs, ECGs and laboratory parameters.

Pharmacokinetic drug interaction in patients with epilepsy (Sparse PK sampling)

Study	Report Location	Objective	Study Design	Treatments Dose Dosage Form	Number & type of subjects (M/F) Age range	Results																								
EMFFR2004/0019/00		Population PK analysis: Effect of rufinamide on PK of AEDs: carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate and valproate.	Double-blind, randomised, placebo controlled multiple dose	AED at constant dose from screening Rufinamide: 200-3200 mg/d for adults, 10-45mg/kg/d for paediatric, oral	Carbamazepine: 903 (408F; 495M) Lamotrigine: 200(106F; 94M) Phenobarbital: 149(62F; 87M), Phenytoin: 299(137F; 162M) Topiramate: 69(39 F; 30M) Valproate: 488 (225F; 263M) Patients with epilepsy Age: 3-72	<p>- Rufinamide did not modify the clearance of topiramate and valproate. - Rufinamide increased the clearance of carbamazepine and lamotrigine - Rufinamide decreased the clearance of phenobarbital and phenytoin. - The effects of rufinamide on clearance of carbamazepine, lamotrigine, phenobarbital and phenytoin do not differ with age. - The percentage changes of AED clearance induced by a typical concentration of rufinamide (15 µg/mL) by age class were less than 18% of the value without rufinamide:</p> <table border="1"> <thead> <tr> <th colspan="4">% Change of AED clearance with rufinamide concentrations of 15 µg/mL.</th> </tr> <tr> <th>AED</th> <th>Children</th> <th>Adolescents</th> <th>Adults</th> </tr> </thead> <tbody> <tr> <td>Carbamazepine</td> <td>+ 15.4%</td> <td>+ 8.7%</td> <td>+ 7.9%</td> </tr> <tr> <td>Lamotrigine</td> <td>+ 15.6%</td> <td>+ 10.6%</td> <td>+ 7.7%</td> </tr> <tr> <td>Phenobarbital</td> <td>- 11.7%</td> <td>- 8.7%</td> <td>- 7.1%</td> </tr> <tr> <td>Phenytoin</td> <td>- 17.5%</td> <td>- 9.1%</td> <td>- 6.5%</td> </tr> </tbody> </table> <p>None of these clearance changes would result in changes of steady-state AED concentration greater than 21 % in typical subjects, which are unlikely of clinical significance.</p>	% Change of AED clearance with rufinamide concentrations of 15 µg/mL.				AED	Children	Adolescents	Adults	Carbamazepine	+ 15.4%	+ 8.7%	+ 7.9%	Lamotrigine	+ 15.6%	+ 10.6%	+ 7.7%	Phenobarbital	- 11.7%	- 8.7%	- 7.1%	Phenytoin	- 17.5%	- 9.1%	- 6.5%
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Bioavailability studies

Study	Report Location	Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Number of subjects (M/F) Type Age mean (range)	Results															
03		Comparative bioavailability of tablet and suspension	Single dose, open, randomised, 4 way cross-over, wash-out	Dose: 400 mg Tablet 200 mg and Suspension (40 mg/mL)	16 HS 16 M/0 F Age: 21-50	Tablet and suspension are bioequivalent (both C _{max} and AUC) Intra and inter subject variability for suspension is larger than for tablet No change in laboratory values, ECG and vital signs No death or serious adverse event															
015		Bioequivalence between 2 formulations	Single dose, open, randomised, 2 way cross-over, wash-out	Dose 600 mg Tablet 200 mg, Tablet 200 mg	12 HS 12 M/0 F Age: 23-32	<p>Tablets are bioequivalent with regard to AUC. Ratio of C_{max} indicates that _____ tablet has higher bioavailability than the _____</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>1.2944 (1.2038; 1.3917)</td> </tr> <tr> <td>AUC_{0-∞}</td> <td>1.1815 (1.1393; 1.2254)</td> </tr> </tbody> </table> <p>No change in laboratory values, ECG and vital signs. No death or serious adverse event. Both formulations were well tolerated.</p>	Parameter	Ratio Estimate (90% CI)	C _{max}	1.2944 (1.2038; 1.3917)	AUC _{0-∞}	1.1815 (1.1393; 1.2254)									
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036		Bioequivalence of _____ tablets from low, medium and high bulk density	Single dose, open label, randomised, cross-over, wash-out, 3 treatments A: low density tablet B: medium density tablet C: high bulk density tablet	Dose 400 mg Tablets 400 mg from 3 different bulk density substance	24 HS 24 M/0 F Age 20-35	<p>The extent of absorption increases when bulk density decreases, up to 19% on C_{max} between high and low bulk density. Formulations are equivalent with regard to AUC. 90% CI C_{max} ratio is outside the bioequivalence limits when comparing the high to low bulk density formulations.</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="3">Ratio Estimate (90% CI)</th> </tr> <tr> <th>Medium / Low</th> <th>High / Low</th> <th>High / Medium</th> </tr> </thead> <tbody> <tr> <td>C_{max}</td> <td>0.9525 (0.9278; 0.9778)</td> <td>0.8146 (0.7935; 0.8363)</td> <td>0.8553 (0.8331; 0.8780)</td> </tr> <tr> <td>AUC_{0-∞}</td> <td>0.9475 (0.9316; 0.9636)</td> <td>0.8717 (0.8570; 0.8865)</td> <td>0.9200 (0.9045; 0.9357)</td> </tr> </tbody> </table> <p>All formulations were well tolerated. No SAEs or deaths were reported during the study. There were no clinically significant changes in the subjects' vital signs, ECG and laboratory parameters.</p>	Parameter	Ratio Estimate (90% CI)			Medium / Low	High / Low	High / Medium	C _{max}	0.9525 (0.9278; 0.9778)	0.8146 (0.7935; 0.8363)	0.8553 (0.8331; 0.8780)	AUC _{0-∞}	0.9475 (0.9316; 0.9636)	0.8717 (0.8570; 0.8865)	0.9200 (0.9045; 0.9357)
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Study	Report Location	Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Number of subjects (M/F) Type Age mean (range)	Results																
037		Bioequivalence between final market image (FMI) and clinical service formulation (CSF) Effect of food on FMI tablet bioavailability	Single dose, open label, randomised, cross-over, wash-out, 3 treatments	400 mg; Tablets 400 mg (FMI fed) 200 mg (CSF fed)	24 HS 22 M/ 2 F Age: 18-45	CSF and FMI are not bioequivalent: none of the 90% confidence intervals of the ratio for C_{max} , AUC_{0-12h} falls within the pre-specified bioequivalence limits (0.80; 1.25). <table border="1"> <thead> <tr> <th>Parameter</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">FMI-fed versus CSF-fed</td> </tr> <tr> <td>C_{max}</td> <td>1.3378 (1.2738; 1.4049)</td> </tr> <tr> <td>AUC_{0-12h}</td> <td>1.2105 (1.1618; 1.2624)</td> </tr> </tbody> </table> Food increases exposure after administration of FMI by 56% for C_{max} and 36% for AUC_{0-12h} ; none of the 90% confidence intervals of the ratio for C_{max} , AUC_{0-12h} fall within the bioequivalence limits. <table border="1"> <thead> <tr> <th>Parameter</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">FMI-fed versus FMI-fasted</td> </tr> <tr> <td>C_{max}</td> <td>1.5606 (1.4859; 1.6389)</td> </tr> <tr> <td>AUC_{0-12h}</td> <td>1.3431 (1.2892; 1.3993)</td> </tr> </tbody> </table> Safety: No SAEs or deaths were reported during the study. No subject discontinued due to AEs or abnormal laboratory values. There were no clinically significant changes in the subjects' vital signs, ECGs and laboratory parameters.	Parameter	Ratio Estimate (90% CI)	FMI-fed versus CSF-fed		C_{max}	1.3378 (1.2738; 1.4049)	AUC_{0-12h}	1.2105 (1.1618; 1.2624)	Parameter	Ratio Estimate (90% CI)	FMI-fed versus FMI-fasted		C_{max}	1.5606 (1.4859; 1.6389)	AUC_{0-12h}	1.3431 (1.2892; 1.3993)
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102		Relative bioavailability of tablet (fed) and oral suspension (fed and fasting condition)	Single dose, open label, randomised, cross-over, wash-out, 3 treatments	400 mg 400 mg (FMI) tablet in fed condition 40 mg/mL suspension Fed and fasting conditions	24 HS 17 M/7 F Age: 19-44	FMI tablet and suspension are bioequivalent: the 90% confidence intervals of C_{max} , AUC_{0-12h} ratio is within (0.80; 1.25) limits. <table border="1"> <thead> <tr> <th>Parameters</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">FMI-fed versus Oral suspension-fed</td> </tr> <tr> <td>C_{max}</td> <td>0.9311 (0.8813; 0.9837)</td> </tr> <tr> <td>AUC_{0-12h}</td> <td>1.0170 (0.9847; 1.0505)</td> </tr> </tbody> </table> Food increases exposure to rufinamide after administration of the suspension, by 36% on C_{max} and 31% on AUC_{0-12h} . <table border="1"> <thead> <tr> <th>Parameters</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">Oral suspension fed versus fasted</td> </tr> <tr> <td>C_{max}</td> <td>1.3630 (1.2901; 1.4400)</td> </tr> <tr> <td>AUC_{0-12h}</td> <td>1.3053 (1.2637; 1.3482)</td> </tr> </tbody> </table> Safety: No SAEs or deaths were reported during the study. There were two AE-related discontinuations. Both AEs were of moderate intensity. Higher incidence of AEs was noted when rufinamide was administered under fed compared to fasted conditions. There were no clinically significant changes in the subjects' vital signs, ECGs and laboratory parameters. Rufinamide was safe and well tolerated when administered at a 400 mg dose with FMI tablet (400F1) or with 40 mg/mL suspension.	Parameters	Ratio Estimate (90% CI)	FMI-fed versus Oral suspension-fed		C_{max}	0.9311 (0.8813; 0.9837)	AUC_{0-12h}	1.0170 (0.9847; 1.0505)	Parameters	Ratio Estimate (90% CI)	Oral suspension fed versus fasted		C_{max}	1.3630 (1.2901; 1.4400)	AUC_{0-12h}	1.3053 (1.2637; 1.3482)
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EPI-006		Bioequivalence between final market image (FMI) and Japanese tablet formulation	Cross-over, open, Fed	400 mg 200 mg JPN tablet 200 mg FMI tablet	16 HS 16 M/0 F Japanese subjects Age 20-28	The two formulations were not equivalent: both C_{max} and AUC_{0-96} of rufinamide were increased with FMI tablets compared to Japanese Clinical Formulation, by 42% for C_{max} and 23% for AUC_{0-96} . <table border="1"> <thead> <tr> <th>Parameters</th> <th>Ratio Estimate (90% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="2">FMI versus JPN</td> </tr> <tr> <td>C_{max}</td> <td>1.420 (1.356; 1.484)</td> </tr> <tr> <td>AUC_{0-96}</td> <td>1.227 (1.184; 1.270)</td> </tr> </tbody> </table> The 90% confidence intervals of the ratio for C_{max} and AUC_{0-96} did not contain unity. In addition, the 90% confidence interval of the ratio for C_{max} and AUC_{0-96} were outside the bioequivalence limits (0.80; 1.25). No clinically relevant subjective or objective symptoms or physiological examination and laboratory test findings were found. The investigational drug was well tolerated in this clinical study.	Parameters	Ratio Estimate (90% CI)	FMI versus JPN		C_{max}	1.420 (1.356; 1.484)	AUC_{0-96}	1.227 (1.184; 1.270)								
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HPH9029		Food effect	Open, randomised, 2 periods, wash-out	600 mg 200 mg tablet	12 HS 10 M/ 2 F Age 21-56	Food increased rufinamide exposure: C_{max} and AUC_{0-96} increased by 95 and 37% respectively when rufinamide was administered with food. Safety: No SAEs or deaths were reported during the study. There were no clinically significant changes in safety measures during the study.																

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/s/

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