CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-911

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology

NDA	21911
Drug	Rufinamide
Indication	• Adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older. • Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in children 4 years and older and adults.
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Introduction

Esiai Medical Research Inc. (Will be referred in this review as Sponsor) is seeking approval for Rufinamide for the following indications:

- Adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older.
- Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in children 4 years and older and adults.

The current submission is in response to the "Approvable" letter sent by the Agency on September 15th, 2005. At the end-of-review meeting on December 18th, 2006 it was discussed if PK/PD modeling can provide more insights to the data collected. The aim of this review is to address the following issue based on PK/PD modeling:

- Is there a evidence of exposure dependent reduction in seizure frequency in adults and pediatrics?

Data

The PK/PD analysis included data from

Pediatric population: 269 children and adolescents in Study protocol 21P (age 4 to 16 years, weight 15.8 to 121.2 kg) with partial seizures, treated at doses of 100 to 2400 mg/day with formulation to be marketed or placebo.

Adults population: 665 adults (age 15 to 72 y, weight 35.4 to 128.2 kg) treated for partial seizures at doses of 200 to 1600 mg/day of clinical development formulation in study protocols AE/ET1, AE/PT2 or placebo and in study protocol 21A at doses 800 to 3200 mg/day with formulation to be marketed or placebo.

Methodology

The sponsor developed a longitudinal model that describes

- Time course of log-transformed seizure frequency per day in placebo group.
- Concentration dependent changes in log-transformed seizure frequency per day.

The model is shown below:

$$\mathrm{Log_e}(TotalSeizureFrequency) = \theta_1 + \theta_2 \bullet (nday > 0) + \theta_3 \bullet (Cavss)$$

nday is the number of treatment days

Cavss is the individual predicted rufinamide concentration on the visit day
θ1 is the population intercept
θ2 is the population placebo/time effect

Sponsor's Findings

The PK/PD model included (A) Constant placebo effect (B) Linear relationship between plasma concentrations of rufinamide and reduction in log-transformed seizure frequency (response). Figure 1 shows the relationship between median change in seizure frequency per 28 days and midpoint of Cav (Average concentrations) quantiles in adults (Study AE/ET1). There is a concentration-dependent decrease in the seizure frequency in adults.

Figure 1. Relationship between median change in seizure frequency per 28 days and midpoint of Cav (Average concentration) quantiles.

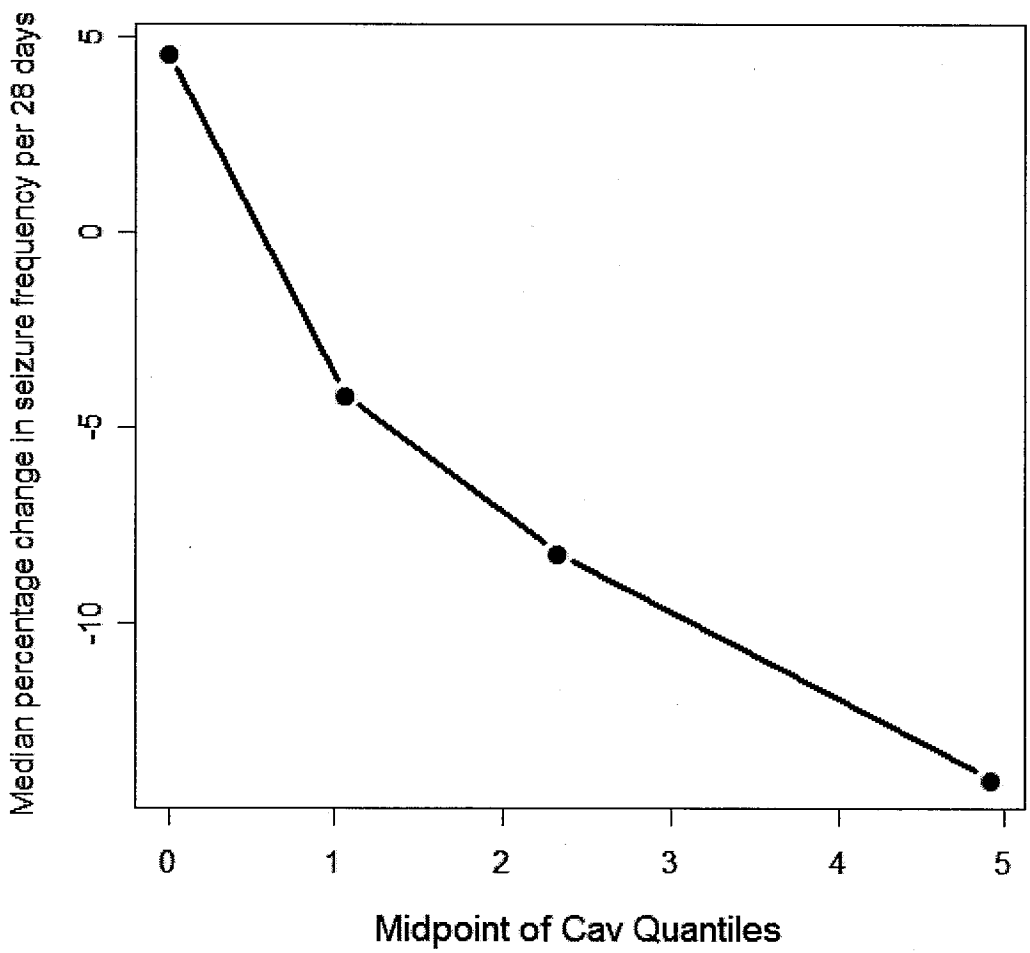

Table 1 shows the slope of the concentration-response relationship in adults and pediatric population.

Table 1. Estimate of the slope of the relationship between rufinamide concentrations and log-transformed seizure frequency (response).

Patient Group	Slope of concentration-response	95% Confidence Interval
Adults	-0.0233	-0.0128, -0.0338
Pediatrics	-0.0114	-0.0001, -0.0227

The slope of the concentration-response relationship in pediatrics is shallower than adults.

Based on the PK/PD model, the predicted baseline, placebo subtracted changes in seizure frequency in adults and pediatric population are shown in Figure 2. The observed average steady state concentrations calculated using equations shown in Table 2 in adults is about 13 ng/mL (Table 3) in children, adolescents after a dose of about 3200 mg (45 mg/kg) rufinamide.

Table 2. Equations used to derive average steady state concentrations (Cavss) under assumption of one-compartment pharmacokinetics.

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

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

Where

relF	is the relative bioavailability (fraction of the bioavailability at the smallest total daily dose per kg body weight),
CL	is the rufinamide clearance,
V	is the volume of central compartment,

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Table 3. Observed average steady state concentrations (Cavss) in children, adolescents and adults.

Parameter	Age class	Daily Dose (mg/kg BW)	N	Geometric Mean
Cavss (mcg/mL)	>2;<12	21-30	29	8.57
		31-40	64	11.36
		41-50	177	12.63
		51-60	63	16.34
		>60	4	7.99
		11-20	2	4.23
	>=12;<18	<5	1	1.06
		11-20	25	6.82
		21-30	29	9.69
		31-40	80	12.11
		41-50	108	13.23
		51-60	19	18.94
		>60	6	18.56
	>=18	<5	155	1.86
		6-10	56	4.78
		11-20	152	5.85
		21-30	100	10.09
		31-40	154	11.34
		41-50	212	12.68
		51-60	96	13.11
		>60	63	14.32

About 11-13% reduction in seizure frequency is predicted at average steady state concentrations of 13 ng/mL after a dose of 45 mg/kg in adults, children and adolescents.

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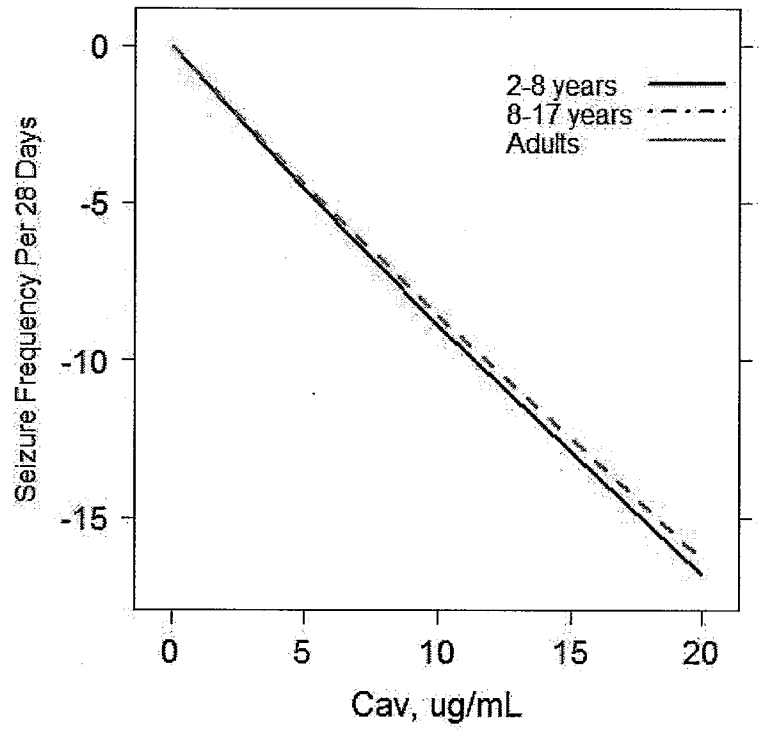
Figure 2. Predicted changes in baseline, placebo corrected seizure frequency per 28 days in adults, children (2-8 years) and adolescents (8-17 years) versus Cav (Average steady state concentrations of Rufinamide).



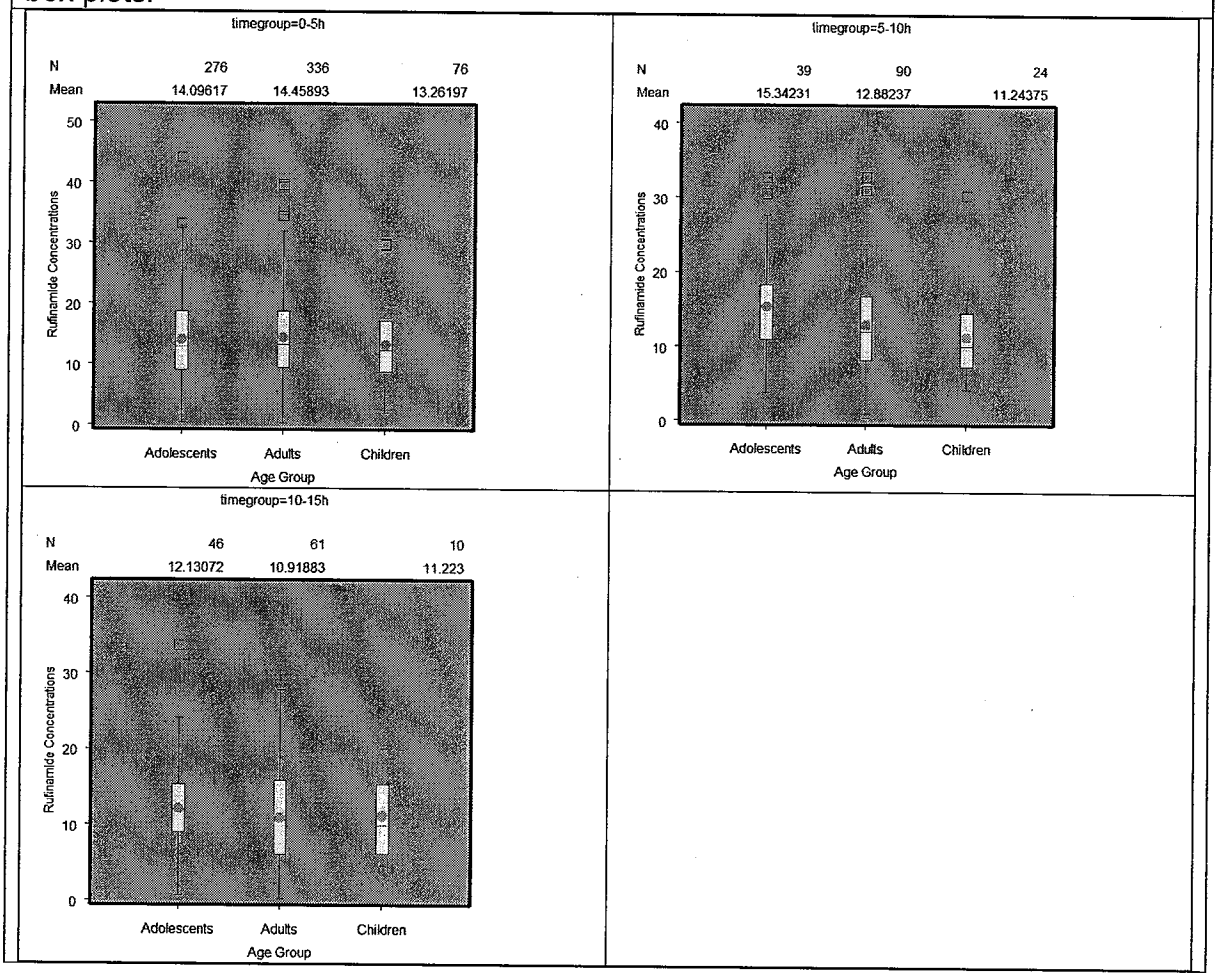
Reviewer's Findings

The reviewer analyzed the data as submitted by the sponsor and was able to confirm the sponsor's findings. Of interest was to understand the lack of evidence of effectiveness in Study 21P in which children and adolescents were enrolled. The intent-to-treat analysis showed that patients in the rufinamide group experienced a 7.0% median reduction in the partial seizure frequency per 28 days, compared to a 12.8% median reduction for patients in the placebo group.

Two factors could have potentially contributed to the lack of effectiveness in Study 21P.
1. Rufinamide concentrations are not similar in children, adolescents and adults.
2. Effects of placebo administration are different in children, adolescents and adults.

Figure 3 shows that observed plasma concentrations of rufinamide between 0-5 h, 5-10 h and 10-15 h in children, adolescents and adults in Study 21A and 21P are similar.

Figure 3. Comparison of plasma concentrations of rufinamide in children (21P), adolescents (21P) and adults (21A) between 0-5 h, 5-10 h and 10-15 h. Shown are the box plots.



The effects after placebo administration (Study 21A, 21P) are different in children, adolescents and adults as shown in Figure 4. This could contribute to the lack of strong evidence of effectiveness in Study 21P.

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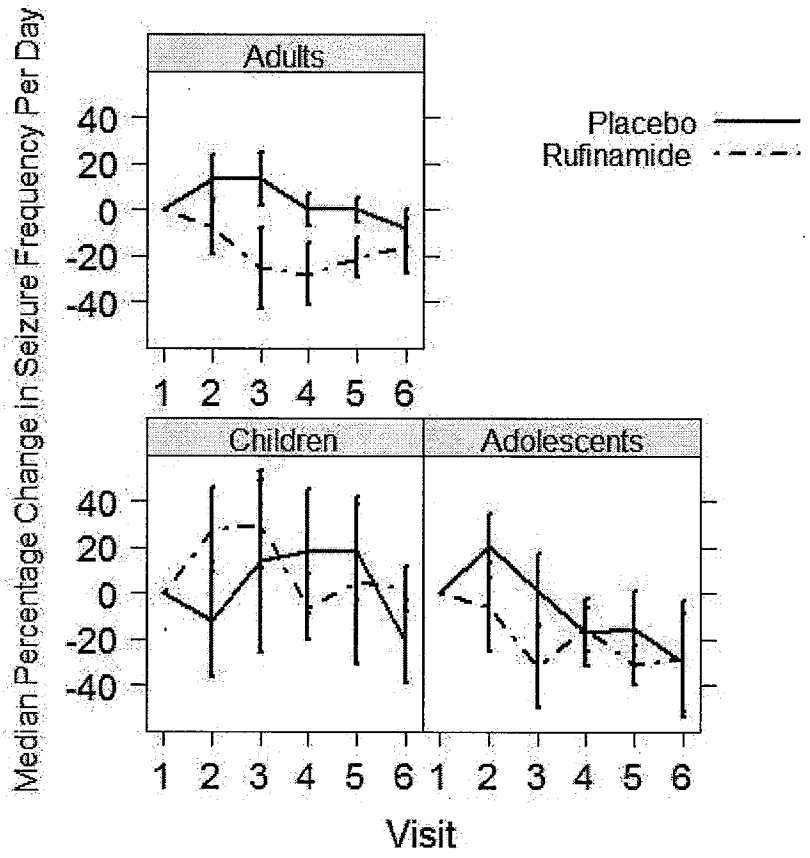
Figure 4. Time course of median percentage change in seizure frequency per day in adults (21A) and children (21P), adolescents (21P).



The sponsor's PK/PD analysis assumes a constant placebo effect post-baseline visit, which is not supported by Figure 4. The reviewer did not conduct any analysis further as empirical evidence clearly showed that effects in placebo and rufinamide group are not in the correct direction. In addition, sponsor also conducted a study (CRUF331 0038) in which the primary objective of this study was to evaluate the safety and efficacy of rufinamide versus placebo as monotherapy in patients with refractory partial seizures (which include the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures) who had completed an inpatient evaluation for epilepsy surgery. Patients were randomized in a 1:1 ratio to either rufinamide 3200 mg/day (with a 1-day titration beginning at 2400 mg/day on Day 1) or placebo. The primary efficacy variable was the time to meeting one or more of four exit criteria: (1) four partial seizures, with or without partial seizures evolving to secondarily generalized seizures, which were measured from the first dose on Day 2; (2) two partial seizures evolving to secondarily generalized seizures, if none were present during the 1-year prior to randomization, which were measured from the first dose on Day 1 if the seizures

began on Day 1; (3) serial seizures requiring investigator intervention, which were measured from the first dose on Day 1, and (4) status epilepticus, which was measured from the first dose on Day 1.

The analysis of the primary efficacy variable demonstrated a significantly longer time to meeting one of the exit criteria in the rufinamide group than in the placebo group. The median number of days for patients in the rufinamide and placebo groups was 4.8 and 2.4 days, respectively ($p = 0.0499$), based on the Kaplan-Meier estimates of the survival curves. For greater details of the study please refer to the review by Dr Norman Herskowitz, Division of Neurology Drug Products.

Conclusions

Adults
Overall, there is clear evidence of effectiveness based on concentration-response analysis in adults.

Pediatfrics
The effectiveness of rufinamide in children and adolescents based on reduction in seizure frequency is not clearly demonstrated.

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7/29/2008 11:21:20 AM
BIOPHARMACEUTICS

Jogarao Gobburu
8/4/2008 01:55:58 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Rufinamide
NDA:	21-911
PRODUCT (Brand Name):	INOVELON
DOSAGE FORM:	Film coated tablets
DOSAGE STRENGTHS:	100, 200, and 400 mg
INDICATION:	Adjunctive treatment of partial seizure for ≥12 years Adjunctive treatment of seizure associated with Lennox Gastaut syndrome for ≥4years
NDA TYPE:	1S
SUBMISSION DATES:	11/17/2005, 3/13/2006, 3/17/2006, 5/23/2006
SPONSOR:	Eisai Medical Research
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1.0 EXECUTIVE SUMMARY

Rufinamide is a triazole derivative indicated for (i) Adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older; (ii) Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. Sponsor's proposed dosing regimen for adults in [redacted] indication [redacted]is that treatment should be initiated with a daily dose of 400-800 mg/day, as twice-daily dosing. Additional dosing increments may be given (400-800 mg/day every 2 days in two equally divided doses) to a maximum recommended daily dose of 3200 mg. For 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.

Rufinamide (INOVELON®) will be marketed as 100, 200 and 400 mg film coated tablets.

The clinical pharmacology of rufinamide has been evaluated in 24 studies in 495 subjects. The clinical efficacy and safety was evaluated from 7 completed double blind controlled studies. Safety and efficacy data was also obtained from 3 open label extension studies.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 21-911. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Agency's labeling recommendations and the Phase IV commitment.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review on page 59 should be conveyed to the sponsor.

Comment to the Medical Officer:

The medical officer should consider the need for a dose-response study in LGS patients to gain better understanding of effectiveness across all doses in this population.

PHASE IV COMMITMENT

The sponsor should evaluate the in vitro P-gp inhibition potential of rufinamide.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Evidence of Effectiveness:
Sponsor conducted two pivotal trials (Studies AE/ET1, 21A) for adjunct therapy in patients with partial seizures and one trial in Lennox Gastaut syndrome patients. For partial seizures, the significant dose/exposure-change in seizure frequency relationship provides evidence for the effectiveness of rufinamide. For Lennox Gastaut syndrome rufinamide is superior to placebo for both total and tonic-atonic seizures.

Dose Selection:
For partial seizure, [redacted] The proposed dosing for LGS is reasonable. Adverse events such as nausea, vomiting, dizziness and somnolence were exposure dependent. b(4)

Exposure-Response for Safety: Most of the adverse events increased as the dose increased, except for fatigue, which was not dose related. Side effects like Nausea, Vomiting, dizziness and somnolence were related to increased exposure, but side effects like Fatigue, headache, nasopharyngitis and upper respiratory tract infection were not exposure related.
Headache, dizziness, fatigue and nausea occurred at lowest rates in the youngest group. Somnolence decreased with the increase in age. The number of subjects in the elderly population (> 65 years) was low (n=27), therefore the results in this age group may not be conclusive. Headache, dizziness, nausea, and upper respiratory tract infection occurred in higher percentages of female patients than male patients. The remaining very common adverse events occurred in similar percentages of female and male patients.

Effect of Rufinamide on QTc interval:
Rufinamide shortens the QTc interval when analyzed by both the maximum-mean approach and a PK/PD analysis. The maximum mean effect at the clinical and supratherapeutic dose is shown in the following Table:

Dosing Regimen	ddQTcF (msec)	90% CI (msec)
1200 mg po q 12 h (clinical dose)	-16.7	-20.2, -13.1
3600 mg po q 12 h (supratherapeutic dose)	-20.2	-24.3, -16.1
Moxi 400 mg (reviewer calculated)	11.5	8.7, 14.4

The QTcF shortening should be described in the label.

General Pharmacokinetics (ADME characteristics) of Rufinamide:
Absorption: Plasma rufinamide concentrations peaked within 4-6 hours postdose. Based on urinary data from a radiolabeled study, the extent of absorption was at least 85% following administration of a 600 mg dose of rufinamide.
Distribution: About 34% of rufinamide is bound to human serum proteins. The Vd increases (38-82 L) with the dose of rufinamide.
Metabolism: It is highly metabolized by carboxylesterases to CGP 47292 and not by CYP 450s.
Elimination: It is eliminated through renal excretion of metabolites. Traces of parent are found in urine and feces. The elimination t1/2 is 7-11 hours. The apparent clearance varied with body surface area (4.4-6.1 L/hr)

Single dose and multiple dose pharmacokinetics: Multiple dose pharmacokinetics of rufinamide are predicted from single dose pharmacokinetics. The accumulation factor upon multiple dosing is 2-3, which is consistent with the half-life of the drug. There was no significant accumulation of the metabolite either.

Dose proportionality: The pharmacokinetics of rufinamide are less than dose proportional.

Pharmacokinetics in patients: The pharmacokinetics of rufinamide are similar between patients and healthy subjects.

Intrinsic Factors:
Renal Impairment: Severe renal impaired subjects dosed 2 hours prior to dialysis had an approximately 10% decrease in all AUCs and a 4% increase in Cmax when compared with matched healthy subjects. Therefore, no dosage adjustment is needed for severe renal impaired subjects (CrCl <30 ml/min). When dialysis occurred post dosing (3 hours after dosing); the AUC and Cmax was reduced by 29% and 16%. For dialysis-dependent renal subjects who require treatment with rufinamide for seizure disorder, adjusting the rufinamide dose to compensate for loss of drug during the dialysis process should be considered, when dialysis and rufinamide absorption coincide.
Hepatic Impairment: Study in hepatic impaired patients has not been conducted. Given that rufinamide is metabolized by carboxylesterases, which are present extensively in liver and extrahepatic tissues and blood, therefore a study in hepatic impaired subjects will not be necessary.
Age:
Elderly: There are no differences in the pharmacokinetics between the elderly and the young.
Pediatrics: There are no differences in the pharmacokinetics between the pediatrics and the adults when dosed according to body weight.
Gender: No clinically significant gender related differences in the pharmacokinetics of rufinamide were observed.
Race: No clinically significant race related differences in the pharmacokinetics of rufinamide, although in the pharmacokinetic studies there were 58% White, 4% Black and 33% unknown. Since there was a large number of subjects for whom race of

unknown, the results should be interpreted with caution. Although, no mechanistic basis for the differences are expected.

Extrinsic Factors:
In vitro studies: Studies have shown that rufinamide is an inhibitor of CYP 2E1 at pharmacologically relevant concentrations of rufinamide. It is also a weak inducer of CYP 3A4. Rufinamide is not a substrate of P-gp, but its metabolite CGP 47292 is. Rufinamide's ability to inhibit P-gp is not known.

Drug-drug Interactions:
Effect of rufinamide on pharmacokinetics of other drugs:

- Rufinamide decreased the AUC and Cmax of ethinyl estradiol by 22% and 31%, respectively and that of norethindrone by 14% and 18%, respectively.
- Rufinamide decreased the AUC of Triazolam by 36%.
- Rufinamide had no effect on olanzapine
- For the Concomitant AEDs: rufinamide increased the plasma levels of phenytoin by 21%, but due to non linearity in the pharmacokinetics of phenytoin, this increase may be more than predicted. For other AEDs (carbamazepine and lamotrigine: decreased concentrations, Phenobarbital: increased concentrations), the change in plasma concentrations were less than 13%. There was no effect of rufinamide on topiramate and valproate.
- The influence of rufinamide on the AEDs was greater in children, compared to adolescents and adults.

Effect of other drugs on rufinamide pharmacokinetics:

- Valproate increases rufinamide concentrations by 16-70%, dependent on concentration of valproate.
- Phenobarbital, phenytoin and primidone decrease rufinamide concentration by 25-46%, independent of conentrations of these drugs.
- Carbamazepine and vigabatrin decrease rufinamide concentration by <30%.
- Lamotrigine, topiramate and benzodiazapines had no effect on rufinamide pharmacokinetics
- Effects were more pronounced in children.

Biopharmaceutics:

BCS Class: Rufinamide has low solubility and high intrinsic permeability. Likely to be BCS Class II drug, although not classified by the sponsor.
Bioequivalence: The proposed to-be-marketed formulation is NOT bioequivalent (greater bioavailability) to the formulation used in some pharmacokinetic and clinical efficacy studies under FED conditions. But all strengths of the proposed to-be-marketed formulation have been used in pivotal clinical efficacy studies (Study 21 and 22 and open label studies)
Food Effect: High fat food increases AUC by 34% and Cmax by 56%. In pivotal clinical efficacy studies dosing was administered with food.

Dissolution:

Apparatus	Flow-through cell open system (Apparatus 4
Cell diameter	22.6mm
Flow	Laminar, glass beads in the cone
Number of tablets per cell	1 tablet lying on glass beads
Temperature	37°C
Flow rate	16ml/minute, pulsating

Specifications (Q):

Dosage Strength (mg)	Time Point (minutes)	Acceptance Criteria (% of stated content)	
100	240	NLT	
	600	NLT	
200	300	NLT	
	720	NLT	
400	360	NLT	
	960	NLT	

NLT = Not Less Than

b(4)

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2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: 100, 200 and 400 mg film coated tablets

Indication: INOVELON® (rufinamide) is indicated as:

1. Adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older.
2. Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults.

Dosage and administration (Sponsor's Proposed):

For Indication 1 (see above):

b(4)

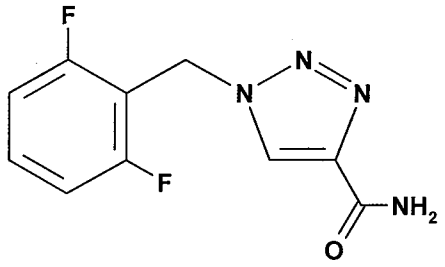
For indication 2:

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. b(4)

Pharmacologic Class: Rufinamide is a triazole derivative

Chemical Name: Rufinamide has the chemical name 7 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 8 carboxamide. It has an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.2.



Physical Characteristics: The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile.

Mechanism of action: The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. *In vitro* studies have shown that the principal mechanism of action of rufinamide is considered to be the modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel.

Formulation: Quantitative formula for all the dose strengths

Ingredient	Dosage Strength			Function
Core	100 mg	200 mg	400 mg	
[redacted]				
Rufinamide				drug substance
Microcrystalline cellulose[a]				filler
Lactose monohydrate[b]				filler
Corn starch				filler, disintegrant
Hypromellose[c]				binder
Sodium laurylsulfate				surfactant
Water, [redacted]				granulating liquid

b(4)

Core Weight				
Film Coat				
Opadry				coating and coloring agent
Water	q.s.	q.s.	q.s.	aqueous solvent
Film Coat Weight				
Total Weight				
a:				
b:				
c:				
d:				

q.s. = a sufficient quantity

b(4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

The dosing claims are:
1) as adjunctive therapy in adults and adolescents with refractory partial seizures,
2) as adjunctive therapy in patients with Lennox-Gastaut syndrome (LGS).

Eight double-blind, controlled studies were initiated to evaluate the safety and efficacy of rufinamide in these epilepsy-related indications. Seven studies were completed, and 1 (Study 039) was terminated early due to lack of enrollment after 22 months of attempted enrollment.

For adjunctive therapy in refractory partial seizures (ages 12 and older):
Two studies (Study 21A and AE/ET1) were considered pivotal for the first indication. Study AE/PT2 was supportive.

Three double-blind, placebo-controlled studies (Study 21A, AE/ET1 and AE/PT2) provide data supporting the efficacy of adjunctive therapy with rufinamide in adults with inadequately controlled partial seizures. In the 3 studies, a total of 695 patients received rufinamide and 315 patients received placebo for treatment periods of up to approximately 3 months. All patients also received fixed doses of 1 to 3 licensed AEDs.

Key features of these studies are given in the following Table:

Study ID	Design	Study & control drugs: dose, route, regimen	No. subjects by arm entered/ completed	Duration of treatment	No. M/F Mean age (range)	Diagnosis and main inclusion criteria	Primary endpoint(s)
AE/ET1	Randomized, DB, placebo-controlled, parallel group	RUF: 200 mg/day 400 mg/day 800 mg/day 1600 mg/day b.i.d. PLA	 127/111 125/105 129/110 133/112 133/116	3 months	347/ 300 36.1 (14-68)	Adults with inadequately controlled partial seizures who were using 1 to 3 fixed-dose AEDs	Linear trend in dose response for Total seizure frequency per 28 days
021A	Randomized, DB, placebo-controlled, parallel group	RUF: 3200 mg/day b.i.d. PLA	156/120 157/137	91 days Titration: 14 days Maintenance: 77 days	139/ 174 36.9 (16-72)	Adults with inadequately controlled partial seizures who were using 1 or 2 fixed-dose AEDs	Percentage change in partial seizure frequency per 28 days, relative to baseline
AE/PT2	Randomized, DB, placebo-controlled,	RUF: 400 mg/day at Week 1, rising Weekly to 1600 mg/day at Week 4 b.i.d PLA	25/23 25/25	28 days	34/16 34 (20-60)	Adults with partial seizures who were using no more than 2 fixed dose AEDS	Seizure frequency ratio (ratio of seizure frequency during DB Phase to seizure frequency during 3-month retrospective baseline phase)
021P*	Randomized, DB, placebo-controlled, parallel group	RUF: 45 mg/kg/day b.i.d. PLA	137/117 132/122	91 days Titration: 14 days Maintenance: 77 days	156/ 112 10.5 (3-17)	Children (4 to <16 years) with inadequately controlled partial seizures who were using 1 or 2 fixed-dose AEDs	Percentage change in partial seizure frequency per 28 days, relative to baseline

*In pediatrics

For Lennox-Gastaut Syndrome (ages 4 and older):

One double-blind, placebo-controlled study provided data demonstrating the effectiveness of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with LGS. The design features of this study are shown in the following Table:

Study ID	Design	Study & control drugs: dose, route, regimen	No. subjects by arm entered/ completed	Duration of treatment	No. M/F Mean age (range)	Diagnosis and main inclusion criteria	Primary endpoint(s)

022*	Randomized, DB, placebo-controlled, parallel group	RUF: 45 mg/kg/day b.i.d. PLA	75/64 64/59	84 days Titration: 14 days Maintenance: 70 days	86/52 14.1 (4-37)	Children or adults with inadequately controlled seizures associated with LGS and using 1 to 3 fixed-dose AEDs	1) Percentage change in total seizure frequency per 28 days, relative to baseline 2) Percentage change in tonic-atonic seizure frequency per 28 days, relative to baseline 3) Seizure severity rating

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

The following variables were used in the evaluation of effectiveness. Although the variables were similar across studies, every study did not evaluate each variable, because of the specific study design, patient population, etc.

i) Percentage change in seizure frequency per 28 days

Seizure frequency was expressed as the rate per 28 days in all studies that used this efficacy variable.

The percentage change in frequency during the Double-blind Phase relative to the Baseline Phase was calculated using the following formula:

$$\text{Percentage change} = 100*(T-B)/B$$

where T was the seizure frequency per 28 days during the Double-blind Phase and B was the seizure frequency per 28 days during the Baseline Phase.

The analysis plan for each study that used this variable specified whether the percentage change was in total seizure frequency or in the frequency of specific seizures subtypes.

ii) Seizure frequency

In most adjunctive therapy studies, seizure frequency was expressed as the median number of seizures per 28 days during the Baseline and Double-blind Phases.

iii) Response to treatment

Response to treatment was defined as experiencing at least a 25%, 50%, or 75% reduction in seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase. The analysis plan for each study specified the level of reduction (i.e percent of patients with a reduction in seizure frequency over 50%).

iv) Seizure frequency ratio

The seizure frequency ratio for each patient was the number of seizures that occurred during the Double-blind Phase divided by the number of seizures that occurred during the Baseline Phase.
This was expressed per 28-day intervals.

v) Global assessments

Study AE/ET1 used a Global Assessment of Therapeutic Effect (GATE), which was completed by the investigator at the end of double-blind treatment. The GATE was a 4-point categorical scale, ranging from "very good" to "none," for rating the effect of study treatment.

Study 022 included a Global Evaluation of the patient's condition performed by the parent/guardian at the end of the Double-Blind Phase. Five parameters (level of alertness, level of interaction with the environment, responsiveness to verbal requests, ability to perform activities of daily living, and seizure severity) were each assessed on a 7-point scale ranging from -3 (very much worse) to +3 (very much improved). The results reported were either the seizure severity rating alone or the composite score, which was the sum of five 7-point assessments.

vi) Time to seizure

A secondary efficacy variable in Study 038 was the onset of therapeutic effect, defined as the cumulative time to the occurrence of the first, second, third, and fourth partial seizure for each patient.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

Three double-blind, placebo-controlled studies (AE/ET1, 21A and AE/PT2) provide data supporting the efficacy of adjunctive therapy with rufinamide in adolescents (ages 14 and older) and adults with inadequately controlled partial seizures. In the 3 studies, a total of 695 patients received rufinamide and 315 patients received placebo for treatment periods of up to approximately 3 months. All patients also received fixed doses of 1 to 3 licensed AEDs.

Study AE/ET1 was the only study in which the subjects were randomized to 1 of the 5 treatments (dose response study: all the doses evaluated: 200, 400, 800 and 1600 mg/day given as BID). Study 21 A had a 2 week titration phase that was followed by a 77 day maintenance phase. Study AE/PT2 was a weekly dose rising study in 25 patients on rufinamide.

In Study AE/ET1 (partial seizures) 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. The primary efficacy variable in Study AE/ET1 was the linear trend in dose response for seizure frequency per 28 days in the double-blind Phase. One of the secondary efficacy variables was: Seizure frequency ratio, based

on total seizure frequency per 28 days. Data from this study were employed for assessing dose/exposure-response relationships.

One double-blind, placebo-controlled study (Study 22) provided data demonstrating the effectiveness of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with LGS. In this study, 74 patients received rufinamide and 64 patients received placebo for a treatment period of up to 84 days, including a 14-day Titration Period and a 70-day Maintenance Period. During the Titration Period, the dose was increased from 200-800 mg/day (approximately 10 mg/kg/day) to 1000-3200 mg/day (approximately 45 mg/kg/day), given on a b.i.d. schedule. All patients also received fixed doses of 1 to 3 licensed AEDs.

Dose in milligrams depended on patient's body weight:

18.0 to 29.0 kg:	dose increased from 200 mg/day at beginning of Titration Phase to 1000 mg/day at end.
29.1 to 50.0 kg:	dose increased from 400 mg/day at beginning of Titration Phase to 1800 mg/day at end.
50.1 to 70.0 kg:	dose increased from 600 mg/day at beginning of Titration Phase to 2400 mg/day at end.
70.1 kg:	dose increased from 800 mg/day at beginning of Titration Phase to 3200 mg/day at end.

Primary effectiveness variable was percent change in total seizure frequency per 28 days. Data from this study were also employed for assessing dose/exposure-response relationships.

Sponsor combined studies AE/ET1 and 22, along with other studies, to conduct the exposure-response relationship.

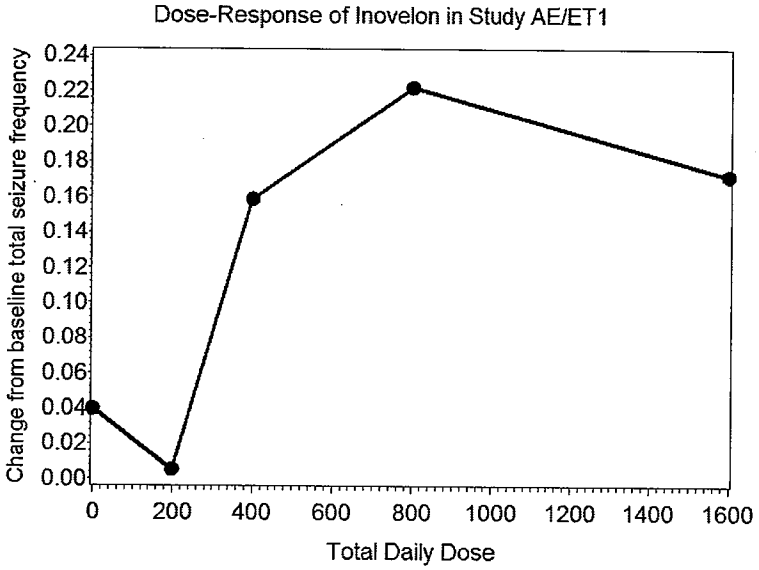
There is adequate evidence that rufinamide is effective to treat partial seizures based on the dose/exposure-response assessment. Substantiation for this inference is provided below:

Partial Seizure

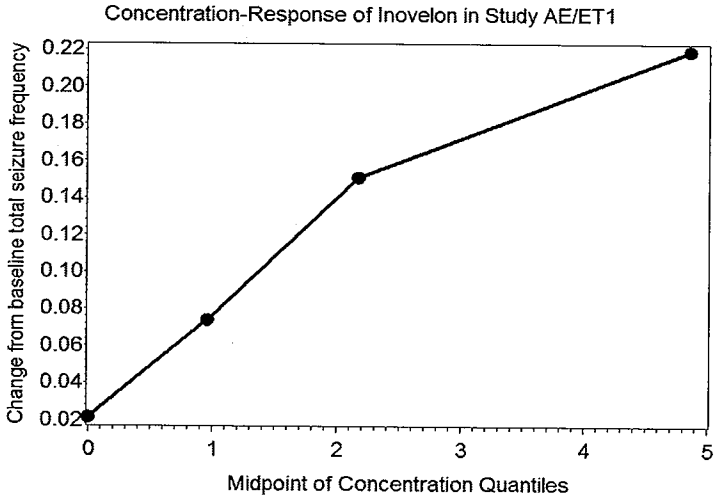
1. There is a clear and significant dose and concentration response relationship. Higher doses/concentrations lead to higher effects. Figure 1 (A) and (B) show the relationship between mean change in total seizure frequency, during double-blind phase, from baseline (log transformed differences) versus dose and midpoints of the four quartiles of average rufinamide concentrations in study AE/ET1. Both linear and Emax models were tested to describe the observed total seizure frequency data and average rufinamide concentrations in study AE/ET1. **The inclusion of drug effect was statistically significant ($p<0.05$).**

2. 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. Based on Figure 1A, 200 mg is not included in the analysis as it is not different from placebo. Further, doses beyond 800 mg do not show any additional benefit.

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 (while baseless in the first place) results in a steeper dose-response curve.



(A)



(B)

Figure 1. Relationship between change from baseline total seizure frequency and (A) rufinamide dose (B) midpoint of average rufinamide concentration quartiles in study AE/ET1.

For overall dose response relationship including a 3200 mg dose from Study 21A, please refer to page 277 of the review.

Lennox Gastaut syndrome

1. 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 2). 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 2).

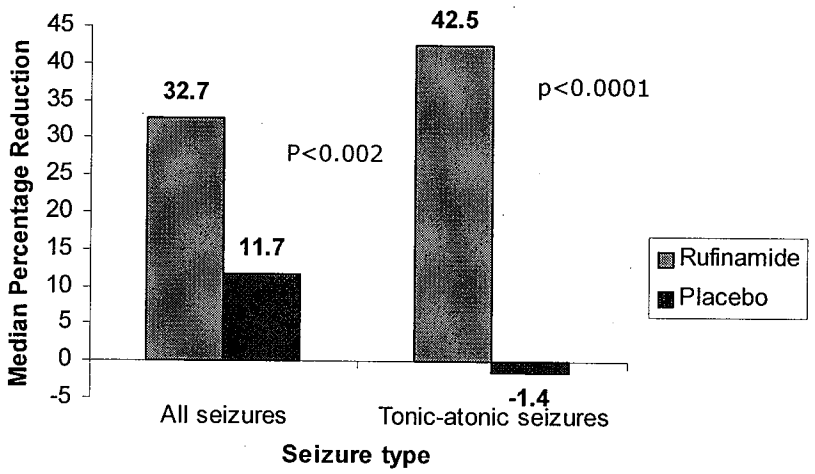


Figure 2. Median percentage reduction in total and tonic-atonic seizures frequency per 28 days for rufinamide and placebo groups.

2. The relationship between concentration and the responders (defined as achieving at least 50% reduction in seizure frequency, (tonic and atonic) relative to baseline during the double-blind phase) in Study 22 was explored using logistic regression. The percentage of patients who experienced atleast 50% reduction in seizure frequency relative to baseline is significant in comparison to placebo (p<0.01). Based on the model, the Figures 3 and 4 shows the probability of achieving 50% reduction in total seizure and (tonic and atonic) frequency relative to baseline at various average rufinamide drug concentrations. Sponsor analyzed the relationship between log total seizure frequency, tonic-atonic seizure and rufinamide concentrations (Figure 5). This analysis was conducted using data pooled from both these and other studies. There was a significant relationship between total seizure frequency and rufinamide average concentrations.

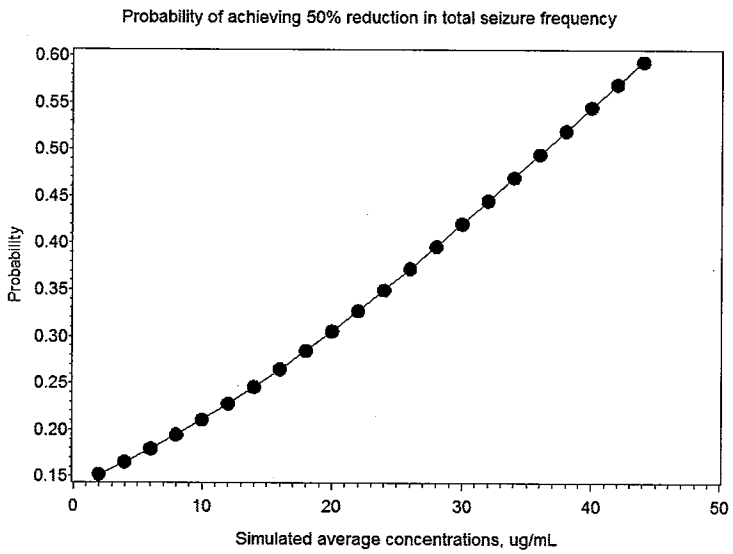


Figure 3. Probability of achieving 50% reduction in total seizure frequency vs simulated average rufinamide concentrations at steady state. (Note the average concentrations at steady state in study CRUF331-022 are in the range of 15-17 ug/ml).

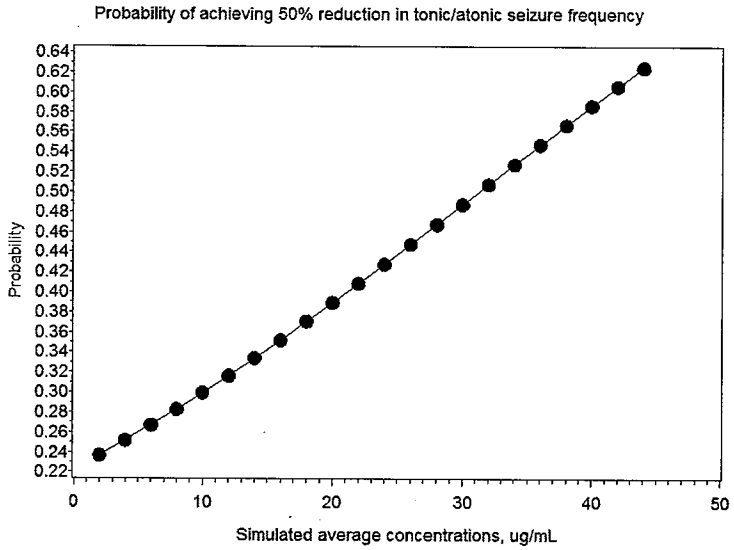
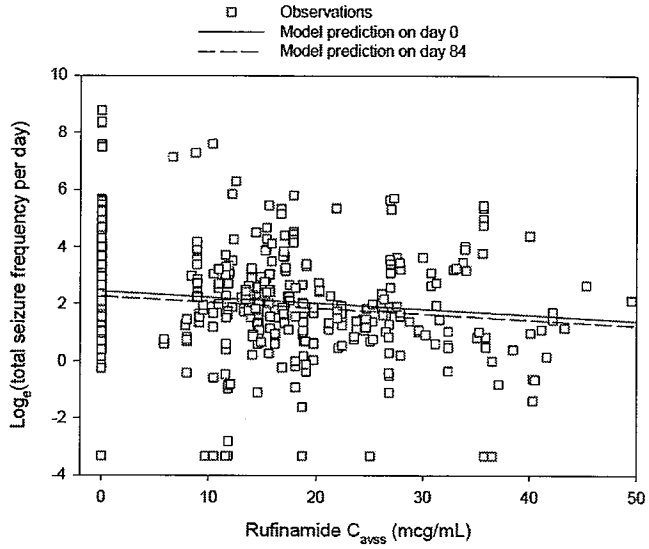
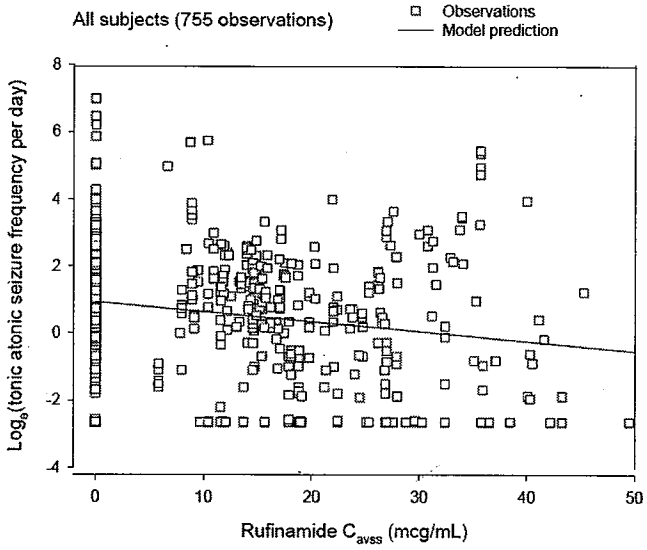


Figure 4. Probability of achieving 50% reduction in tonic, atonic seizure frequency vs simulated average rufinamide concentrations at steady state. (Note the average concentrations at steady state in study CRUF331-022 are in the range of 15-17 ug/ml).



(A)



(B)

Figure 5 (A) Total seizure frequency (B) Tonic-atonic seizure frequency data (log-transformed) and model predictions vs rufinamide average concentrations. Both the relationships are statistically significant.

Overall there is a clear evidence of effectiveness of rufinamide in study AE/ET1 and in study CRUF331-022.

2.2.4 What are the characteristics of exposure-safety relationships?

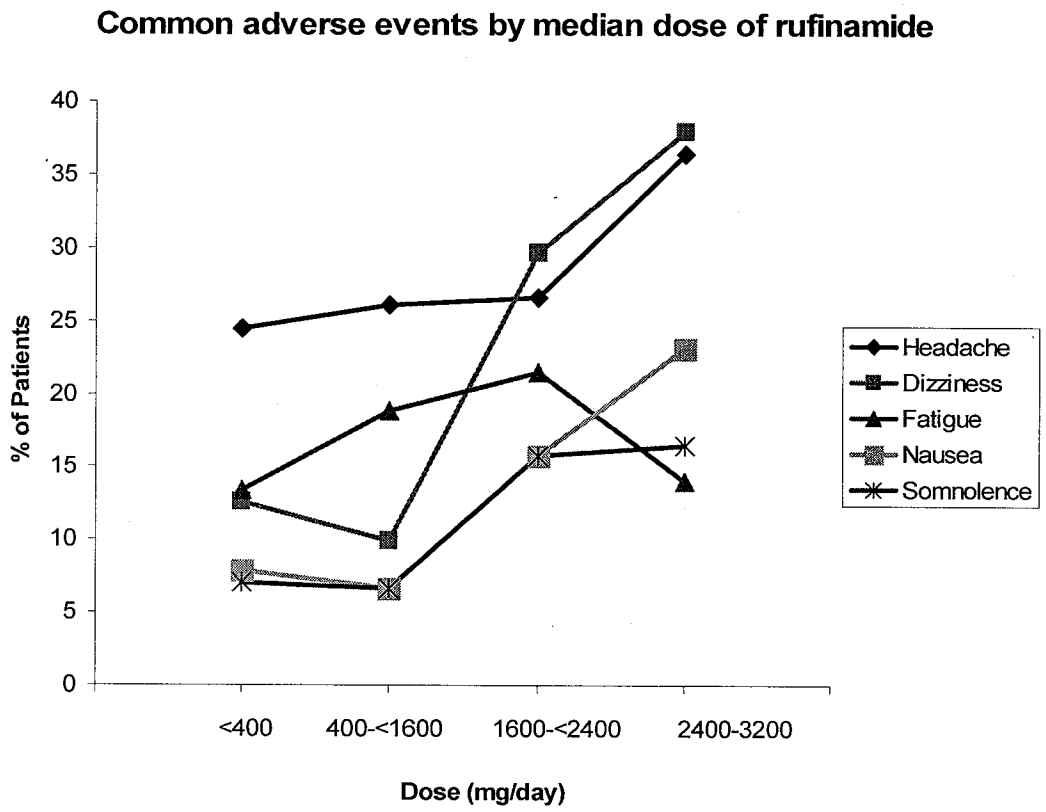
The following Table shows the number of patients with the significant adverse events (10% or greater). These are the most common adverse events that were greater in the rufinamide group compared to the placebo group.

Table: Number (%) of patients with adverse events (10% or greater for either treatment group) by severity (Double-blind, adjunctive therapy studies in adults with partial seizures)

	Rufinamide		Placebo	
	n	(%)	n	(%)
Total number of patients studied	720		290	
Total number of patients with an adverse event	580	(80.6)	236	(81.4)
Mild	215	(29.9)	110	(37.9)
Moderate	274	(38.1)	96	(33.1)
Severe	91	(12.6)	30	(10.3)
Headache - Total	199	(27.6)	76	(26.2)
Mild	113	(15.7)	48	(16.6)
Moderate	70	(9.7)	21	(7.2)
Severe	16	(2.2)	7	(2.4)
Dizziness - Total	140	(19.4)	33	(11.4)
Mild	77	(10.7)	25	(8.6)
Moderate	56	(7.8)	7	(2.4)
Severe	7	(1.0)	1	(0.3)
Fatigue - Total	127	(17.6)	34	(11.7)
Mild	71	(9.9)	24	(8.3)
Moderate	46	(6.4)	6	(2.1)
Severe	10	(1.4)	4	(1.4)
Nausea - Total	84	(11.7)	29	(10.0)
Mild	50	(6.9)	21	(7.2)
Moderate	31	(4.3)	8	(2.8)
Severe	3	(0.4)	0	
Somnolence - Total	75	(10.4)	21	(7.2)
Mild	51	(7.1)	15	(5.2)
Moderate	23	(3.2)	5	(1.7)
Severe	1	(0.1)	1	(0.3)

The rates of any adverse event and of each of the most frequently occurring adverse events were generally higher in the 2 highest dose groups. Interpretation of the results for the lower median dose ranges is confounded by the inclusion of a relatively large number of patients who were enrolled in studies (primarily Studies AE/ET1 and AE/PT2) that evaluated lower doses and that used the older Clinical Service Form of rufinamide tablets, which is known to have lower bioavailability than the newer Final Market Image formulation.

The following figure shows the % of patients with adverse events (10% or greater for either treatment group) by median dose of rufinamide in mg/day



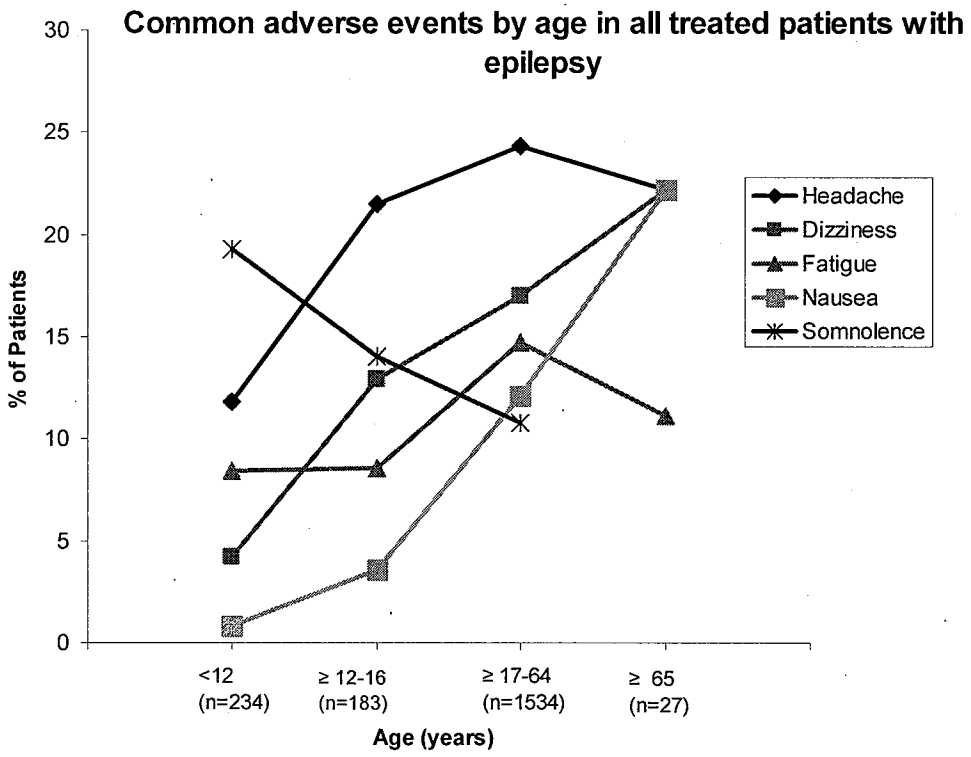
Except for fatigue, all other adverse events increase as the dose increases.

The following common side effects were related to higher exposures: Nausea, Vomitting, dizziness and somnolence.

The following common side effects did not have a correlation with exposure: Fatigue, headache, nasopharyngitis and upper respiratory tract infection. Although, headache seemed to increase at the highest dose.

Adverse events by special population:

Age:
The following figure shows the % of patients with adverse events (10% or greater for either treatment group) in all epilepsy treated patients by age (years)



Headache, dizziness, fatigue and nausea occurred at lowest rates in the youngest group. Somnolence decreased with the increase of age. The number of subjects in the elderly population (> 65 years) was low, therefore the results in this age group may not be conclusive (see number of subjects in each age group in the Figure above).

For the double blind studies similar trends were seen in the placebo group, except for dizziness.

Gender:
Headache, dizziness, nausea, and upper respiratory tract infection occurred in higher percentages of female patients than male patients. The remaining very common adverse events occurred in similar percentages of female and male patients.

2.2.5 Are the proposed dosage regimens for partial seizures and LGS indications adequately supported by the clinical trial and consistent with the dose-response relationship?

For partial seizure, there is little additional benefit beyond 800 mg daily dose. The proposed dosing for LGS is reasonable, given the study design. A dose response study in LGS patients will be helpful in this regard.

2.2.6 Does rufinamide prolong QT or QTc interval?

The following questions describe the effect of rufinamide on QT interval:

i) What background information was considered to determine the adequacy of the TQT?

Rufinamide tablets dosed twice daily are intended for adjunctive treatment of partial seizures (ages 12 years and older) and seizures associated with Lennox-Gastaut Syndrome (ages 4 years and older). Seizure control was found with doses ranging from 400 mg/day to 3200 mg/day, given twice daily.

Rufinamide is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AED). In vitro, rufinamide prolongs the inactive state of the sodium channel.

Metabolism

The metabolism of rufinamide is independent of cytochrome P450. The drug is primarily eliminated by metabolism. The primary metabolite is formed by enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid.

Pharmacokinetics

The time to peak concentration is between 4 to 6 hours after fed or fasted conditions. Peak Cmax and AUC increase less than proportionally with doses greater than 400 mg (probably due to limited solubility). Between subject variability in clearance is approximately 28.9 %. Elimination half-life ranges between 6-10 hours in healthy subjects and in epileptic patients. Steady state concentrations were three times the concentration after single dose.

ii) Are the doses used in the TQT study acceptable?

Yes. The TQT dose of 7200 mg/day is more than double the maximum dose used in clinical trials in patients with epilepsy. The rufinamide dosing regimen is 1200 mg by mouth every 12 hours. In clinical trials, rufinamide was titrated over 1 to 2 weeks (for tolerability) up to a maximum dose of 1600 mg by mouth every 12 hours. The TQT study titrated over 18 days up to 3600 mg by mouth every 12 hours. This is the maximum tolerated dose in healthy volunteers. b(4)

Even after considering factors that may increase rufinamide concentration, the dose used in the TQT is acceptable. Drugs that are inhibitors of carboxylesterases may decrease rufinamide metabolism. The largest increase in rufinamide concentration from other AEDs was caused by valproate, a reported concentration increase of up to 70% in children. Neither gender nor age affects the steady state PK. Pharmacokinetics in

children ages 2-17 years old are similar to adults. Food increases the extent of absorption by 34% and peak exposure by 56%.

iii) Does rufinamide prolong the QTc interval?

Rufinamide does not prolong the QTc interval, corrected by any correction formula (Bazett's, Fridericia or individual correction).

iv) Does rufinamide shorten the QTcF interval?

Yes. Table 1 and Figure 1 show the effect (baseline and placebo adjusted) of rufinamide on QTcF for each dose.

Table 1. Maximum Mean Effect by Dose

Dose	ddQTcF (msec)	90 % CI (msec)	Time post dose (h)
1200 mg po q 12 h	-16.7	-20.2, -13.1	4
1600 mg po q 12 h	-16.1	-20.0, -12.2	4
2400 mg po q 12 h	-20.2	-24.1, -16.2	4
3600 mg po q 12 h	-20.2	-24.3, -16.1	4
Moxi 400 mg (sponsor)	18.7	14.9, 22.5	3
Moxi 400 mg (reviewer)	11.5	8.7, 14.4	3

Sponsor – used Day 18 for baseline correction
Reviewer – used Day -1 for baseline correction

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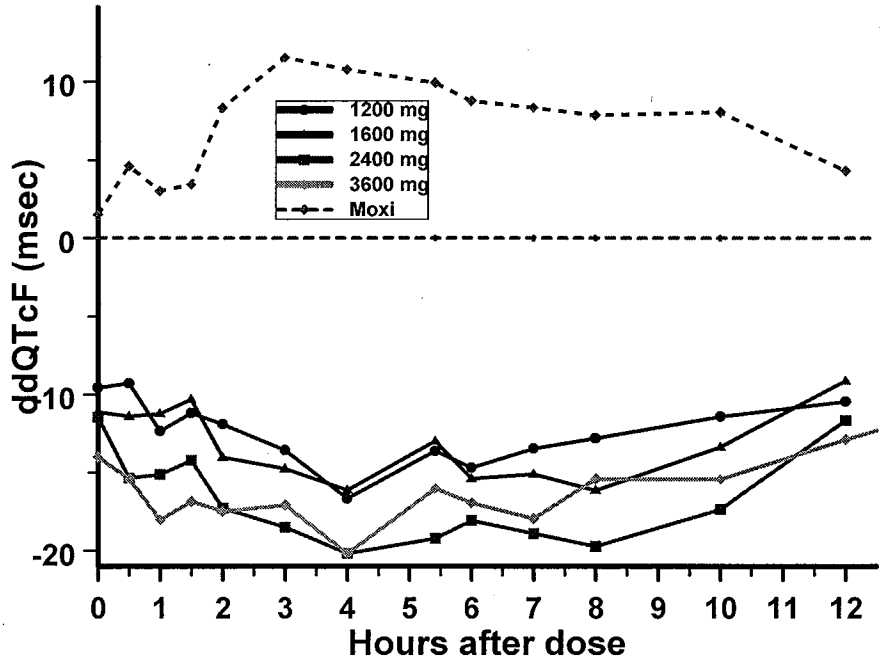
Figure 1. Mean ddQTcF for All Doses



v) What is the concentration QTc relationship?

The concentration QTc model confirmed the results of the statistical analysis. The population average maximum QTcF effect of rufinamide was -27.8 msec (90% CI: -30.9, -24.7) with a SD of 11.7 msec and 42% CV. Half this effect (EC50) was observed at a concentration of 6.61 ug/mL (90% CI: 4.42, 8.80). Between subject variability was not estimated for EC50. The mean Cmin for the lowest dose is 10.6 ug/mL; therefore, concentrations are well above the EC50 during most of the 1200 mg q 12 hour dosing period. The high concentrations in the TQT study may partially explain the lack of or small dose response over the 12-h dosing interval.

vi) Is QTc shortening detrimental?

Information on QTc shortening is scarcer than that on QTc prolongation. The short QT syndrome was first described in 2000 and is a congenital disorder. It is associated with sudden death, atrial fibrillation and ventricular fibrillation. The limited numbers of patients described in the literature have QTc intervals ranging from 248 to 320 ms. Non-clinical data with QTc shortening has been associated with ventricular fibrillation.

vii) What information is available from the safety database with respect to deaths that may be cardiovascular?

Twenty-two patients (18 on rufinamide) from the pooled safety database died during the clinical studies or within 30 days after receiving the last dose of study drug.

Out of 1978 treated patients, 8 (6 females, 2 males) deaths among rufinamide treated patients, all during open-label treatment, and four deaths among placebo treated patients were considered sudden deaths. Sudden death occurred at a rate of 0.31 per 100 patient years of exposure to rufinamide. Overall, these values are similar to rates described in a population of patients with refractory seizures (Reference: Lathers and Schrader, 2002). It is difficult to discern if the eight sudden deaths were related to QTc shortening since ECG recordings were unavailable. The narrative reports suggest that most of the deaths were possibly due to seizures.

Serious adverse events were related to epilepsy (convulsions and seizures).

The TQT study in 117 healthy subjects had no evidence of syncope, arrhythmias or deaths.

2.2.7 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

The assay validation for rufinamide and its metabolite CGP47 292 is acceptable. Different analytical methods for the measurement in biological samples of rufinamide were developed and validated throughout the human clinical development of rufinamide. Methods developed to assay rufinamide in biological fluids (plasma and urine) evolved with the doses and concentrations used in clinical studies over time. Initial method utilized HPLC with UV detection with different limits of quantitation. The newest method was LC/MS/MS. The LLOQ for rufinamide ranged from 0.20- 1.00 μg/mL in plasma and 0.125-5.00 μg/mL in urine.

A summary of all methods used is given in the analytical section of this review.

2.2.8 What are the general ADME characterstics of rufinamide?

The key ADME characteristics of rufinamide are summarized below:

Absorption:

- Following single and multiple-dose administration under fasting conditions in healthy young subjects, plasma rufinamide concentrations peaked within 4-6 hours postdose.
- Plasma Cmax and AUC increase less than proportionally with the increase of doses both after single and multiple doses.
- The absolute bioavailability of rufinamide is not known. Based on urinary data from a radiolabeled study, the extent of absorption was at least 85% following administration of a 600 mg dose of rufinamide.
- The absorption of rufinamide involves active transport process in addition to the possible passive diffusion. Rufinamide is unlikely to be a P-gp substrate.

Distribution:

- *In vitro* studies indicate that about 34% of rufinamide is bound to human serum proteins.
- The apparent volume of distribution is dependent on dose and varies with body surface area. The apparent volume of distribution was 38.0 L, 52.7 L and 81.6 L at 800 mg/day, 3200 mg/day, and 7200 mg/day, respectively.

Metabolism:

- Rufinamide was extensively metabolized. The essential biotransformation pathway was hydrolysis of the carboxylamide group to the acid derivative CGP 47292 and mediated by carboxylesterase(s). No other metabolite could be detected in the plasma.
- A few minor additional metabolites were detected in urine, which appeared to be acyl glucuronides of CGP 47292. Otherwise, no other metabolites were detected in urine and feces.
- There is no indication for involvement of oxidizing cytochrome P450 enzymes or glutathione in the biotransformation process.

Elimination:

- Rufinamide is eliminated from the systemic circulation predominantly through renal excretion of drug related material (84.7%). Based on a radiolabeled mass balance study only traces (2%) of unchanged drug were found in urine and feces. About 66% of dose was excreted in the urine and 8% in feces as CGP 47292.
- The elimination half-life of rufinamide is 7-11 hours.
- The apparent clearance varied with body surface area (BSA): in a typical subject with population median BSA (1.79 m^2), CL/F at 800 mg/d was 4.41 L/h. Likewise, at doses of 3200mg/day and 7200 mg/day CL/F was 6.12 and 9.47 L/h, respectively.

2.2.9 What are the basic pharmacokinetic parameters of rufinamide after single and multiple doses?

Single Dose Pharmacokinetics:

Three studies were conducted with single rising doses in fasting healthy subjects, with the clinical service formulation, with [redacted] (1 and 10 mg strength) or [redacted] (50, 100 and 200 mg) in studies A184 and A233, and with a Japanese tablet in Japanese healthy subjects (study EPI-001). The pharmacokinetics of rufinamide after single oral doses of 50-1800 mg are shown in the following Table:

Table: Rufinamide pharmacokinetic parameters after single dose

Study	Dose (mg)	Cmax (µg/mL)	tmax (h)	AUC0-inf (h.µg/mL)	t1/2 (h)
A184 N=28 Males	50	0.59 (0.51; 0.68)	1.50 (1.0; 3.0)	8.92 (7.89; 10.10)	9.03 (8.25; 9.89)
	100	0.97 (0.73; 1.29)	3.00 (1.5; 4.0)	14.09 (11.28; 17.60)	7.52 (5.61; 10.08)
	200	1.49 (1.13; 1.96)	6.00 (3.0; 12.0)	29.58 (24.79; 35.30)	8.97 (6.48; 12.41)
	400	1.92 (1.24; 2.98)	5.00 (3.0; 12.0)	48.10 (28.27; 81.85)	8.02 (4.83; 13.31)
A233 N=11 Males	800	2.99 (2.29; 3.92)	10.00 (8.0; 12.0)	75.99 (56.96; 101.38)	8.70 (5.29; 14.29)
	1200	3.45 (1.80; 6.63)	3.00 (3.0; 12.0)	94.91 (66.30; 135.86)	7.20 (2.36; 22.01)
	1800	4.05 (2.89; 5.66)	6.00 (3.0; 24.0)	141.32 (69.11; 288.98)	10.25 (7.65; 13.73)
EPI-001 N=12 males	100	0.74 (0.59; 0.92)	4.00 (3.0; 6.0)	13.8 (11.9; 16.0)	9.39 (8.21; 10.74)
	200	1.01 (0.85; 1.20)	6.00 (4.0; 8.0)	23.2 (19.2; 28.0)	9.05 (8.20; 9.99)
	400	1.49 (1.19; 1.85)	6.00 (4.0; 12.0)	41.3 (34.8; 49.0)	9.96 (9.28; 10.70)
	800	2.09 (1.71; 2.54)	8.00 (8.0; 24.0)	63.5 (47.6; 84. 7)	11.08 (7.57; 16.22)

For Study EPI 001 value is for AUC(0-96)

Plasma pharmacokinetics after single dose:

For rufinamide these studies show that:

- the exposure increases less than proportionally when the dose increases, i.e. that the apparent clearance increases with the dose
- Peak plasma concentrations were reached at 4-8 hours post dose
- the elimination half-life remains constant at between 7 and 11 hours
- the number of subjects in each dose group is very small (4 to 6), the confidence interval of parameters is narrow indicating low between subject variability.
- Results are similar across studies at similar doses

For metabolites these studies show that:

- With respect to metabolites found in plasma (CGP 47291 and CGP 47292), the principal metabolite was CGP 47292 at all dose levels, and CGP 47291 was almost always at concentrations below the lower limit of quantification. AUC values of CGP 47292 represented 11 to 15% of those of CGP 33101, and an almost linear relationship was found between dose and AUC.

Urinary excretion after single dose:

- Cumulative urinary CGP 33101 excretion levels increased in a dose-dependent manner, but the cumulative urinary excretion rates during the first 96 hours were less than 1% at all dose levels.
- With respect to metabolites possibly found in urine (CGP 47291 and CGP 47292),

CGP 47292 was found as a metabolite at all dose levels, while CGP 47291 was not detected at any dose level. The cumulative urinary CGP 47292 excretion rates at 96 hours post-dose were 34 to 50% of the administered dose.

- The urinary excretions of CGP 47292 as well as parent drug were slightly lower at the 1000 mg than at 800 mg dose level, thereby suggesting a slight saturation of the absorption when the dose is increased.
- The urinary half-life of CGP 47292 and parent were similar (8-12 hrs)

Multiple Dose Pharmacokinetics:

Multiple dose studies with rufinamide were conducted with tablets made by [redacted] (Study A 202, AE/MD2), Japanese Tablets (Study EPI-002) at doses up to 600 mg BID as well as the final marketing image using [redacted] (Study E2080-A001-001: MTD and Study E2080-A001-002: QTc) at doses 400-3600 mg given BID. In most of these studies multiple rising doses were used and the same dose levels have been given up to 8 days. b(4)

Plasma pharmacokinetics after multiple doses:

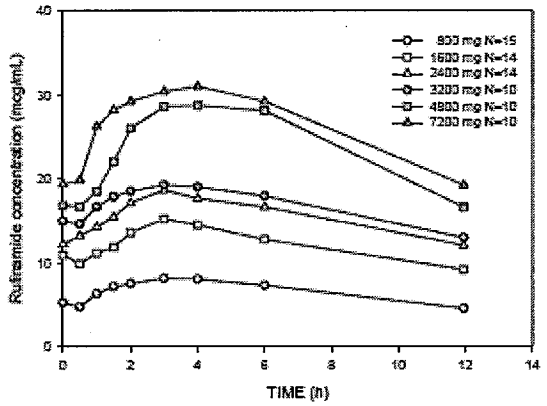
Multiple dose pharmacokinetic parameters are given in the following Table:

Table: PK parameters following multiple dosing of 200 mg BID for 8 days:

Dose	Cmax (ng/ml)	Tmax (h)	AUC0-inf (ng.h/ml)	T1/2(24-48) (h)
200 mg SD	1957.5±131.2	5	35582.3±6473.8	8.9±1.2
200 mg BID for 8 days	3324.8±591.6	4	59342.9±15223.6	8.8±1.2

The following figure shows the median rufinamide concentrations following multiple dosing of the final marketing image at doses up to 3600 mg BID, in which doses were increased every 3 days, PK profiles collected immediately before a new increase, on the third treatment day at each dose.

Figure: Median rufinamide concentration time profile after multiple doses in healthy subjects (FMI tablet, study E2080-A001-001)



Urinary excretion after multiple dosing:

- repeat-dose administration has no effect on urinary excretion rate of the unchanged drug.
- With respect to metabolites possibly found in urine (CGP 47291 and CGP 47292), CGP 47292 was found as a metabolite while CGP 47291 was not detected. The cumulative urinary CGP 47292 excretion rates at 48 hours following the Single Post-Meal Dose Administration and at 96 hours following the Repeat-Dose Administration were both about 60% of the administered dose.

2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing?

Single dose pharmacokinetics can predict multiple dose pharmacokinetics of rufinamide.

For rufinamide, multiple dose studies show that (see Table above in the previous question):

- The t1/2 of rufinamide does not change upon multiple dosing.
- The mean AUCinf at steady state was about 2-3 times higher than the single dose. The accumulation ratio was about 2-3, which is in accordance with the t1/2 of about 11 hours for rufinamide (see Tables below)

Table: Accumulation ratios from multiple dose studies

Study	Dose (mg) on	Dose (mg) on	Accumulation ratio:
	day 1 & N	day N-1	AUC0-12 dayN/day1
202 (N=7)	200	200 BID	2.59 (1.48; 4.56)
AE/MD2 (N=18)	600	600 BID	3.11 (2.71; 3.57)
EPI-002 (N=6)	200	200 BID	1.71 (1.49; 1.97)

- the exposure increases less than proportionally when the dose increases as seen with single dose studies

For metabolites, the multiple dose studies show that:

- With regards to the major metabolite CGP 47292 in plasma, no significant accumulation was found on repeat dosing. CGP 47291 was always below the limit of quantitation.

2.2.11 What is the variability in the PK data?

The intersubject variability is low for rufinamide. Based on a population analysis of a multiple dose study, the % CV on CL and Ka was about 19%.

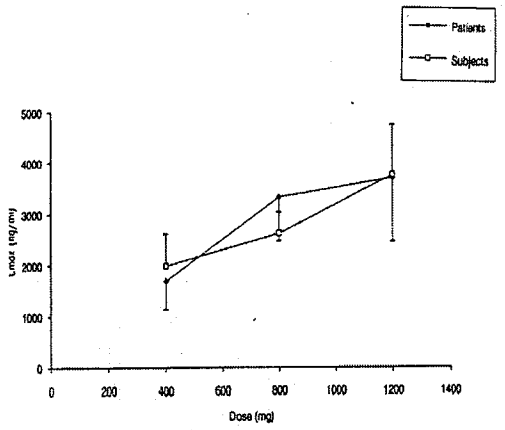
2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in epilepsy patients?

Pharmacokinetics of rufinamide were similar between patients and healthy subjects. This was evaluated in a single dose PK study with parallel groups (Study 92064) and efficacy studies AE/PT2 and Study 27 (see Tables below)

Table: Rufinamide pharmacokinetic parameters in patients and healthy subjects

Study	Dose (mg)	Cmax (µg/mL)	tmax (h)	AUC0-120 (h.µg/mL)	t1/2 (h)
92064 N=16 patients	400	1.70	5.3	26.45	6.7
	800	3.32	4.7	55.25	6.9
	1200	3.70	3.7	72.37	8.7
92064 N=3 healthy	400	1.98	5.3	43.14	10.8
	800	2.62	6.0	61.04	9.0
	1200	3.75	4.0	90.17	9.0

Other pharmacokinetic studies in healthy subjects also showed that the pharmacokinetics of rufinamide were similar in patients and healthy subjects.



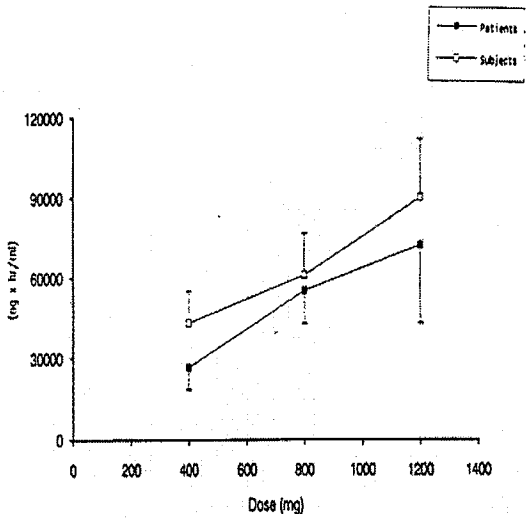


Figure: Cmax versus Dose AUC versus dose

Table: Rufinamide pharmacokinetic parameters from clinical studies

Study		Cmax (µg/mL)	tmax (h)	AUC0-inf (h.µg/mL)	t1/2 (h)
AE/PT2 Patients	Day 1 800 mg placebo	3.60 (3.10; 4.17)	6.00 (3.0; 12.0)	65.69 (54.09;79.79)	7.22 (6.40; 8.15)
	Day 35 800 mg placebo	3.82 (3.24; 4.50)	4.00 (3.0; 10.0)	69.35 (55.57; 86.55)	7.46 (6.61; 8.42)
	Day 1 800 mg rufinamide	3.31 (2.82; 3.89)	4.00 (2.0; 10.0)	57.56 (47.76; 69.38)	6.89 (6.28; 7.56)
	Day 35 800 mg rufinamide	5.72 (4.78; 6.85)	3.00 (1.0; 10.0)	103.16 (82.15; 129.55)	6.98 (6.31; 7.71)
27 Patients	10 mg/kg age ≤6	6.38 (6.26)	NA	61.7 (65.3)	NA
	30 mg/kg age ≤6	12.50 (10.39)	NA	130.9 (119.1)	NA
	10 mg/kg, age 7-12	3.82 (0.93)	NA	36.1 (10.4)	NA
	30 mg/kg age 7-12	7.65 (1.70)	NA	82.8 (12.3)*	NA
	10 mg/kg age 13-17	3.92 (0.45)	NA	37.7 (5.50)	NA
	30 mg/kg age 13-17	8.65 (3.04)	NA	86.4 (30.7)	NA

The urinary excretion in healthy volunteers and patients is given in the following Table:

Subjects	Dose		
	400 mg	800 mg	1200 mg
Healthy volunteers (n = 3)	33 ± 5	32 ± 12	33 ± 11
Patients* (n = 7)	31 ± 8	34 ± 10	29 ± 8

* : Only those patients whose excretion was complete for the three dose levels were considered.

These data show that

- The relationship of AUC and Cmax with the increase of dose was not different between patients and healthy subjects.
- Tmax and T1/2 was also similar between patients and healthy subjects
- The urinary excretion was similar in patients and healthy volunteers.

2.2.13 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The pharmacokinetics of rufinamide was not dose-proportional in the dose range of 200 to 1200 mg in healthy male subjects (table below from study cpd 93056 or 04). There was less than dose-proportional increase in C_{max} and AUC with increasing dose. But T1/2 does not change. This suggests saturation in the absorption process.

The differences between 400 and 200 mg were not statistically significant for dose normalized C_{max} and AUC_{0-48}. 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 $t_{1/2}$.

Table: Pharmacokinetics of rufinamide after single oral dose (200 to 1200mg): PK parameters normalized to a 200 mg dose (protocol 04)

Dose (mg)	Cmax (µg/mL)	tmax (h)	AUC0-inf (h.µg/mL)	t1/2 (h)
200	1.47 (1.35; 1.60)	6.00 (4.0; 12.0)	26.87 (23.56; 30.66)	9.61 (8.42; 10.97)
400	1.36 (1.22; 1.52)	6.00 (4.0; 8.0)	25.68 (22.21; 29.70)	9.80 (8.60; 11.16)
800	1.00 (0.90; 1.11)	7.00 (4.0; 12.0)	22.42 (19.92; 25.22)	11.49 (10.05; 13.14)
1200	0.90 (0.80; 1.00)	6.00 (2.0; 8.0)	19.67 (16.74; 23.12)	11.28 (10.11; 12.60)

*Median (min-max) for tmax

The exposure to rufinamide did not increase proportionally to the dose administered at single dose or at multiple doses, for both the clinical service formulation tablet

b(4)

and for the final market image tablet ( ), under fed or fasting state (see figures below). b(4)

The following figures show effect of dose on Cmax and AUC:

Figure: Effect of dose on Cmax and AUC0-inf after single administration of tablets

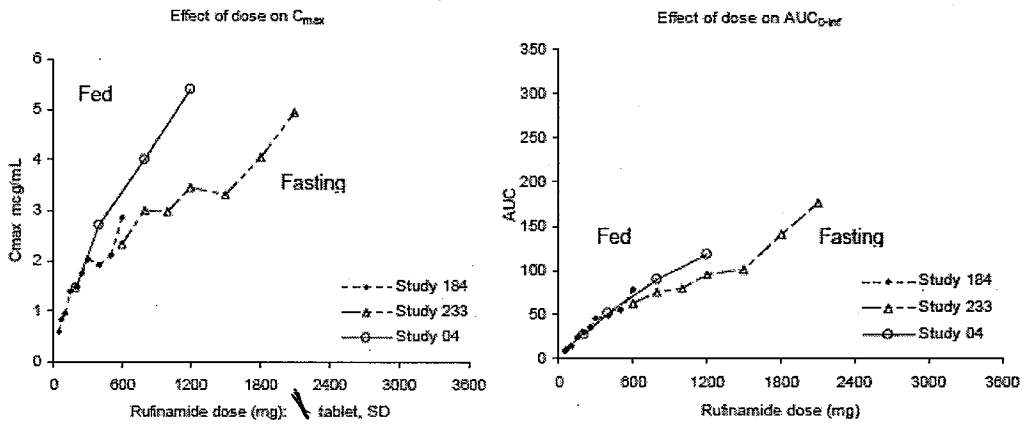


Figure: Effect of dose on Cmax and AUC0-12 after multiple dose administration of FMI tablets

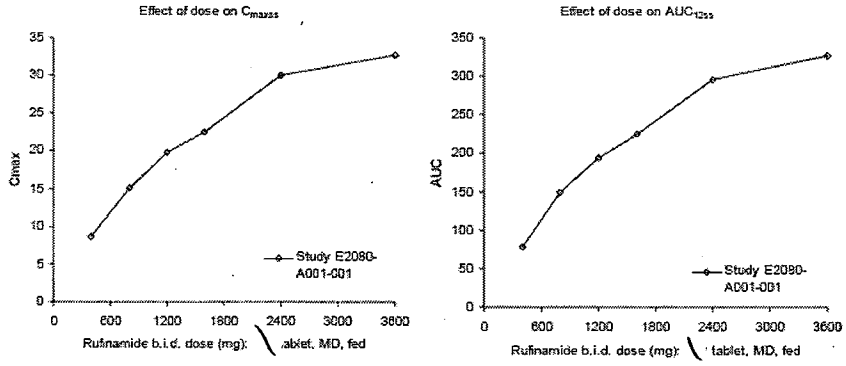
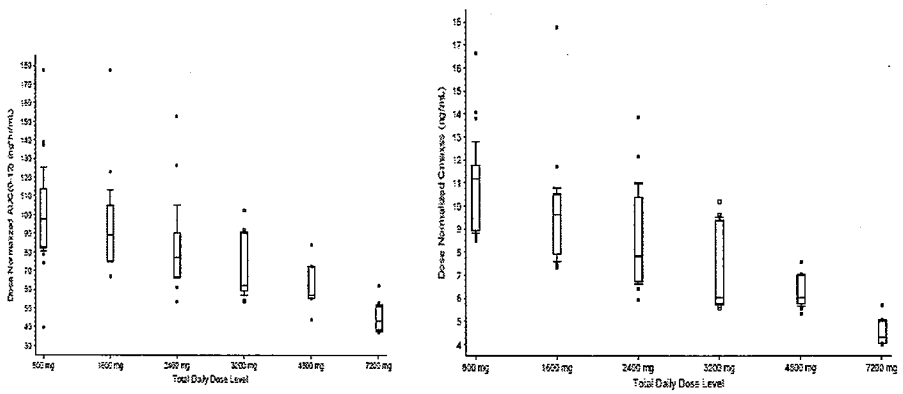


Figure: Dose normalized AUC and Cmax on multiple dosing (FMI Tablets)



Dose normalized AUC

Dose normalized Cmax

These figures show that there is a less than dose proportional increase in AUC and Cmax with the increase of rufinamide doses. The statistical results from the dose proportionality assessment also indicate that exposure to rufinamide did not increase proportionately as the doses increased. The 95% CI for the comparison of the dose-normalized ln-transformed Cmaxss and AUC(0-12) did not include the value of 0 as indicated for the conclusion of dose proportionality. In addition, the slopes of the lines for these parameters were below the value of 0 with the differences being statistically significant (p-values < 0.05).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 Effect of Renal Impairment:

A single dose study was conducted in patients with severe renal impairment in comparison to healthy subjects using the final marketing image (Study 029).
Severe renal impaired subjects dosed 2 hours prior to dialysis had an approximately 10% decrease in all AUCs and a 4% increase in Cmax when compared with matched healthy subjects (Part I of Study). These magnitudes of changes were not statistically significant as shown in the Table below:

Parameter	Group	N	Mean (±SD)	P-value	Estimated ratio of means	90% CI for ratio of means
$AUC_{(0-\infty)}$ (µg*hr/mL)	Renal Healthy	4 9	60.75 (±10.11) 76.30 (±20.88)	0.617	0.90	(0.57, 1.42)
$AUC_{(0-60\ h)}$ (µg*hr/mL)	Renal Healthy	9 9	68.82 (±26.50) 74.54 (±19.44)	0.414	0.91	(0.74, 1.12)
C_{max} (µg/mL)	Renal healthy	9 9	4.79 (±0.96) 4.63 (±0.90)	0.516	1.04	(0.94, 1.14)
t_{max} (hr) *	Renal Healthy	9 9	4.00 3.00			
$t_{1/2}$ (hr)	Renal Healthy	4 9	8.98 (±3.80) 10.14 (±2.38)			

* Instead of Mean (±SD), the Median value was reported for t_{max}.

When dialysis occurred post dosing (3 hours after dosing); the AUC and Cmax was reduced by 29% and 16%, respectively, as shown in the Table below:

Parameter	Part**	N	Mean (±SD)	P-value	Estimated ratio of means	90% CI for ratio of means
$AUC_{(0-60\ h)}$ (µg*hr/mL)	II	7	50.27 (±12.36)	0.001	0.71	(0.63, 0.79)
	I	9	68.82 (±26.50)			
C_{max} (µg/mL)	II	7	4.23 (±1.21)	0.162	0.84	(0.68, 1.04)
	I	9	4.79 (±0.96)			
t_{max} (hr) *	II	7	4.00			
	I	9	4.00			
$t_{1/2}$ (hr)	II	2	15.78 (±12.48)			
	I	9	8.98 (±3.80)			

* Instead of Mean (±SD), the Median value was reported for t_{max}.

**Part I: includes renal subjects who underwent dialysis prior to rufinamide dosing; Part II: includes renal subjects who underwent dialysis 3 hours after rufinamide dosing

The observed ~30% decrease in the bioavailability of rufinamide noted in the renal subjects may be considered the maximal amount of drug removal occurring with dialysis, given that the dialysis was timed to coincide with the expected time of maximum plasma concentration levels (tmax).

Dosage adjustment:

- Severe renal impaired subjects (CrCl <30 ml/min) do not need dosage adjustment
- For dialysis-dependent renal subjects who require treatment with rufinamide for seizure disorder, adjusting the rufinamide dose to compensate for loss of drug during the dialysis process should be considered, when dialysis and rufinamide absorption coincide.

Use in Overdose:

Hemodialysis might be one of the effective means of drug removal in the event of a rufinamide overdose.

2.3.1. 2 Effect of Hepatic Impairment:

Pharmacokinetic studies in hepatic impaired patients have not been conducted. A study in this population will not be necessary because carboxylesterases are ubiquitous; hence hepatic impairment is unlikely to alter the pharmacokinetics of rufinamide.

2.3.1. 3 Effect of age:

Elderly:

There is no significant difference in the pharmacokinetics of rufinamide and its metabolite CGP 47 292 in the elderly subjects when compared to the younger subjects both after single as well as multiple doses.

This was established from a parallel group study (Study 031) with a 400 mg SD and 400 mg BID dosing for 4 days in 8 elderly (65-80 years) and 7 young (18-45 years) subjects.

After single dose:

	C_{max} (µg/mL)	t_{max} (median) (hr)	$AUC_{(0-12)}$ (µg·hr/mL)	$AUC_{(0-last)}$ (µg·hr/mL)	$AUC_{(0-\infty)}$ (µg·hr/mL)	$t_{1/2}$ (hr)
Elderly	4.6±1.1	6.0±2.1 (6.0)	38.9±10.0	82.7±23.2	84.5±23.5	8.5±1.3
Young	4.2±0.7	6.6±1.9 (8.0)	34.0±6.9	78.6±17.2	81.0±18.8	10.8±3.2

After multiple doses:

	C_{max} (µg/mL)	t_{max} (median) (hr)	$AUC_{(0-12)}$ (µg·hr/mL)	$AUC_{(0-last)}$ (µg·hr/mL)	$AUC_{(0-\infty)}$ (µg·hr/mL)	$t_{1/2}$ (hr)
Elderly	7.6±1.5	3.9±2.4 (3.0)	66.2±10.3	124.1±22.0	126.4±22.7	8.3±1.1
Young	7.5±1.1	4.6±1.5 (4.0)	72.3±14.1	139.2±38.0	141.3±38.2	10.2±2.4

Statistical analysis comparing the young and the elderly for single dose and multiple dose is given in the following Table:

PK variable	Dose	P value	Ratio of means (elderly/young)	90% CI
AUC0-inf	single	0.7721	1.04	0.83-1.29
	multiple	0.4913	0.91	0.72-1.15
Cmax	single	0.5274	1.07	0.89-1.28
	multiple	0.8811	1.02	0.85-1.21
T1/2	single	0.0746	0.80	0.58-0.98
	multiple	0.0698	0.83	0.64-0.98

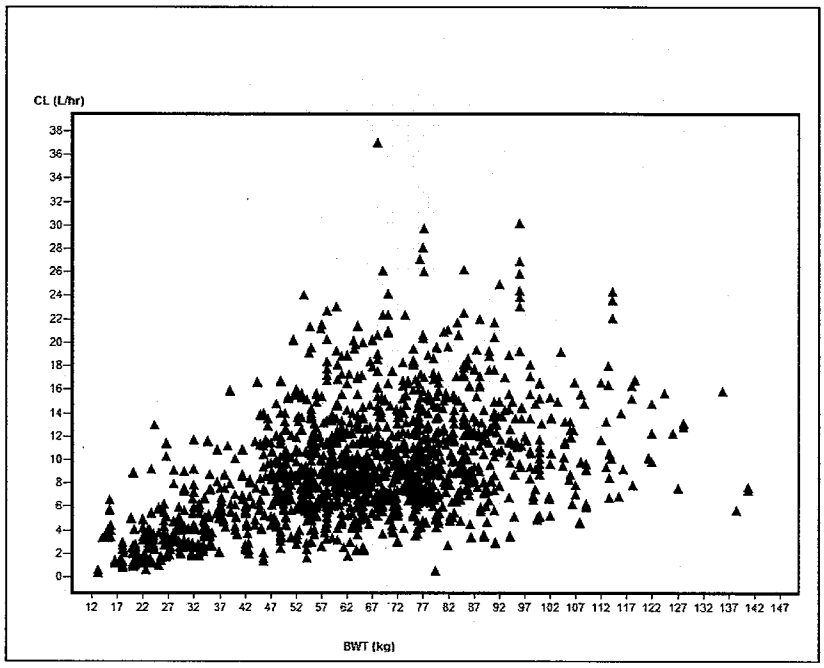
The urinary excretion of the metabolite CGP 47 292 was also similar in the two populations.

Dosage adjustment:
No dosage adjustment is necessary.

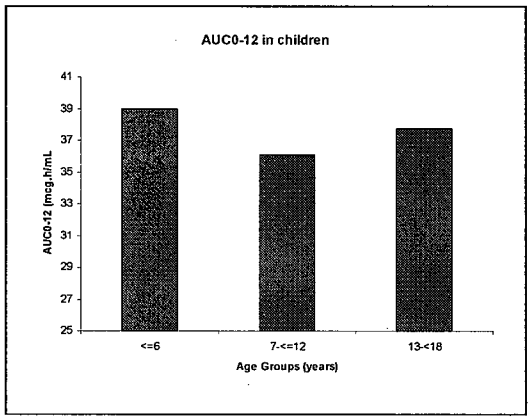
Pediatrics:

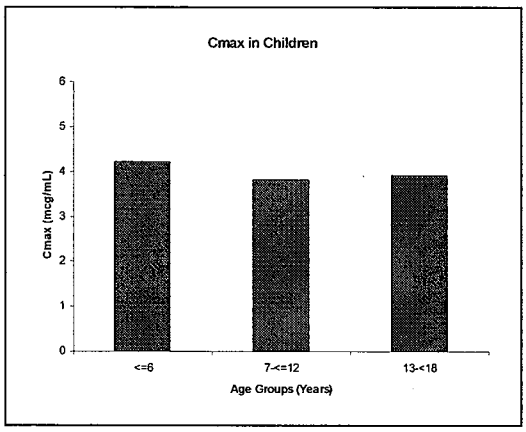
There was no difference in the pharmacokinetics of rufinamide in children (ages 2-17 years) as a function of age when corrected for body weight differences.

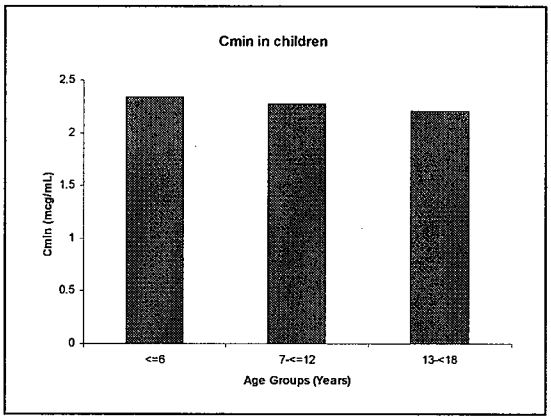
The following figure shows that as body weight increases the clearance also increases:



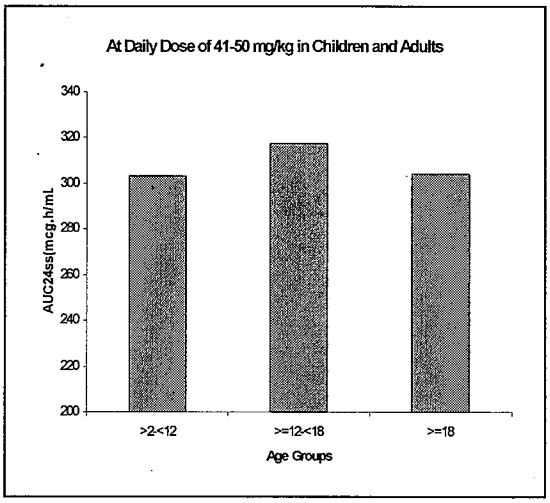
The pharmacokinetics was evaluated in an open label study in children on weekly rising doses of 10 mg/kg/day and 30 mg/kg/day given as a BID regimen (see figures below for parameters AUC0-12, Cmax and Cmin). There were no statistical differences (p values >0.482) in the pharmacokinetic parameters in the age groups (≤6, 7-12, 13-≤18 years)

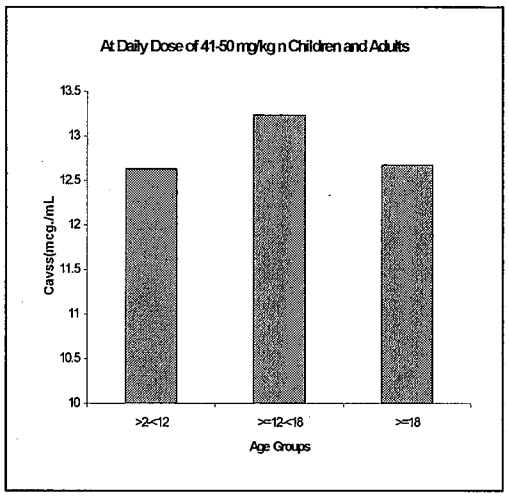


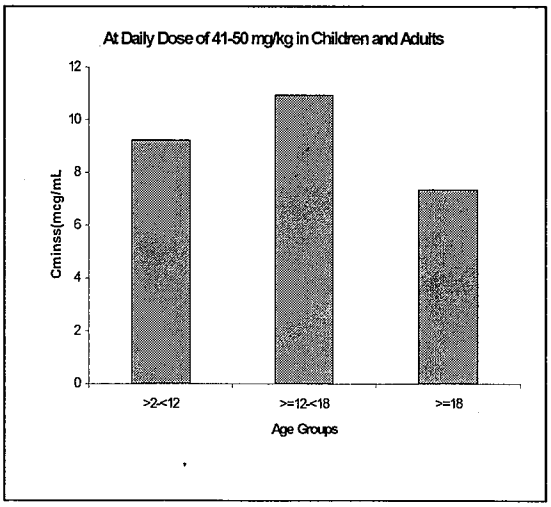




Based on population analysis the pharmacokinetics in children (N=119 for age 2-11 years and N=99 for age 12-17 years) was also found to be similar to adults when dosed according to body weight (i.e at similar body weight adjusted doses). The following figures show the pharmacokinetic parameters (AUC24ss, Cmaxss, Cminss) at a daily dose of 41-50 mg/kg (maximum number of subjects at this dose). Similar trends were also seen at doses 11-20 mg/kg, 21-30 mg/kg, 31-40 mg/kg, 51-60 mg/kg.







Dosing Adjustment:
Dosing should be administered in the pediatric population according to the body weight.

2.3.1.4 Effect of Gender:

Based on population analysis, the Clearance of rufinamide is slightly less in female than in male patients, irrespective of body size: -0.267 L/h in children, adolescents as well as adults. This difference is not likely to be clinically significant.

	CL (L/h)	C_{avss} (µg/mL)
Male children	3.47	14.2
Female children	3.00	16.4
Male Adolescents	5.55	14.0
Female Adolescents	5.12	15.2
Male adults	5.19	7.3
Female adults	4.88	7.8

There were no differences in efficacy and safety based on gender.

Dosage adjustment:
No dosage adjustment is necessary.

2.3.1.5 Effect of Race:

About 58% of the patients in the all-treated population were white, 4% were black, 0.3% were oriental, and 5% were of other races. The remaining 33% did not have race reported, primarily because they were enrolled in studies that did not require collecting that information.

Based on population analysis only the Black and White population were sufficiently represented for a population analysis. The predicted exposure was no different between the Black and White populations.

For the analysis of adverse events by race, the patients were categorized into three race subgroups: White, Black, and other. "Other" includes the patients for whom race was not recorded. The results by race must therefore be interpreted with caution. The analysis showed that adverse events were similar across all races.

Dosage adjustment:
No dosage adjustment is necessary.

2.3.1.6 Effect of pregnancy or lactation:

There are no adequate data on the use of rufinamide in pregnant women.
The protocols for the rufinamide clinical studies required that female participants of childbearing potential be using an acceptable method of contraception upon study entry and continue to use acceptable contraception throughout the course of the study. Oral contraceptives/ hormonal contraceptive techniques were not considered acceptable methods of contraception. Study treatment was to be discontinued immediately if a woman became pregnant.

Thirteen pregnancies occurred during the clinical studies in patients who were receiving rufinamide. Ten of the pregnancies occurred during open-label extensions, 1 occurred during the open-label, compassionate use study (Study 2301), and 2 occurred in patients who were receiving rufinamide during double-blind studies. The duration of rufinamide treatment in these 13 patients ranged from 3 days to 5.6 years.

Six of the 13 pregnancies were known to have resulted in the birth of 6 healthy babies. One pregnancy was ended by a spontaneous abortion, and 3 by elective abortions. No information was provided to the sponsor about the outcome of the remaining 3 pregnancies.

Studies in animals have shown embryo-fetal toxicity at doses associated with maternal toxicity. Therefore, rufinamide should not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the fetus. If rufinamide is prescribed, careful pre-natal monitoring is recommended.

It is not known if rufinamide is excreted in human breast milk; however, studies in rats and rabbits suggest that it is likely to be excreted into milk. Therefore, breast-feeding is not recommended during treatment with rufinamide.

2.4 EXTRINSIC FACTORS

2.4.1 Is rufinamide a substrate, inhibitor or inducer of CYP enzymes?

Substrate:
Rufinamide is not a substrate of CYP 450 isoenzymes.

In vitro studies indicate that carboxylesterase is predominantly involved in metabolism of rufinamide to form metabolite CGP 47 292 in human liver microsomes in vitro. The formation of metabolite CGP 47 292 from rufinamide was also inhibited by bis(4-nitrophenyl) phosphoric acid (BNPP), a specific inhibitor of carboxylesterase, in a concentration dependent manner and inhibition potency on the formation of CGP 47 292 was about 50 – 60% at 1 μmol/L of BNPP.

Inhibitor:
Rufinamide is an inhibitor of CYP 2E1 isozymes at pharmacologically relevant concentrations (mean Cmax 22.75 µg/mL or 96 µM) . The Ki values for each of the P450s assayed were 1350 µM, except for CYP2E1 450 µM). The I/Ki for CYP 2E1 is 0.213 at this concentration.

The highest plasma concentration of rufinamide found in clinical study (Study 22) was approximately 282 µM (67 µg/mL) during repeated dosing at approximately 45 mg/kg per day, which was less than half of the lowest estimated Ki. The I/Ki at this concentration was 0.202 for other CYP isoenzymes. Thus, rufinamide is expected to inhibit the other CYP isoenzymes at very high concentrations, but not at average concentrations.

Inducer:
Rufinamide was shown to be a very weak inducer of CYP3A4 in human hepatocytes with potency at 100 µM being only 10 % of that observed with 10 µM rifampicin, the positive control. No clear induction was found for CYP1A1/2, carboxylesterase (CES) and UDPGT. However, positive control data for the CES and UDPGT assays were insufficient to validate the experiment, so conclusions regarding these enzymes are preliminary.
CES is the enzyme responsible for metabolism of rufinamide to its major metabolite (Study B05015). Human PK data suggest very strongly that autoinduction does not occur and so significant induction of CES in man is unlikely. Thus, clearance of other drugs metabolized by CES is not likely to be affected by rufinamide co-administration.

2.4.2 Is rufinamide a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

Rufinamide is not a substrate of P-gp, but its metabolite CGP 47 292 is. Rufinamide's ability to inhibit P-gp is not known.

2.4.3 Is there an in vitro basis to suspect drug-drug interaction?

- In vitro studies have shown that rufinamide is not metabolized by CYP 450 isoenzymes. It is metabolized by carboxylesterases. Therefore drugs that are inhibitors and inducers of carboxylesterases may alter the pharmacokinetics of rufinamide
- Rufinamide is likely to inhibit CYP 2E1, but unlikely to inhibit the other isoenzymes at the mean Cmax values (22.75 µg/ml) observed from clinical

studies. Drugs that are substrates of CYP 2E1 (chlorzoxazone) may have increased plasma levels in the presence of rufinamide

- Rufinamide is a weak inducer of CYP 3A4. Substrates of CYP 3A4 may have lower concentrations in the presence of rufinamide
- Rufinamide has low protein binding (34%), therefore, drug-drug interaction due to protein displacement are unlikely.

2.4.4 What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of extrinsic factors like herbal products and smoking have not been conducted. Rufinamide is not metabolized by any of the CYP enzymes.

2.4.5 Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

2.4.5.1 Influence of rufinamide on other drugs:

Influence of rufinamide on the pharmacokinetics of concomitant drugs is summarized in the following Table:

Concomitant Medication	Concomitant medication dose	Rufinamide doses evaluated	Cmax Ratio (90% CI) w/wo rufinamide % change	AUC Ratio (90%CI) w/wo rufinamide	Dosage Adjustment
Ethinyl Estradiol (Ortho-Novum 1/35)	Ortho-Novum 1/35 3 cycles	800 mg BID for 14 days	0.6850 (0.6308;0.7438) 31 % ↓	0.7768 (0.7368; 0.8189) 22% ↓	Caution (Effect of this not known)
Norethindrone (Ortho-Novum 1/35)	Ortho-Novum 1/35 3 cycles	800 mg BID for 14 days	0.8241 (0.7419; 0.9155) 18 % ↓	0.8608 (0.8167; 0.9074) 14 % ↓	Caution (Effect of this not known)
Triazolam	0.25 mg SD day 1 and end of study	400 mg BID for 10 days	0.7621 (0.6638; 0.8750) 24 % ↓	0.6441 (0.6002; 0.6913) 36 % ↓	none
Olanzapine	5 mg SD day one and	400 mg BID for 10 days	0.9853 (0.9275; 1.0465)	0.9970 (0.9495; 1.0052)	none

	end of study				

All these studies were done with lower doses, therefore a 3200 mg/day may have a greater effect than seen in these studies.

2.4.5.2 Influence of rufinamide on concomitant AEDs

The following Table shows the % change in concomitant AED clearance with a typical concentration of rufinamide (15 µg/ml) in children, adolescents and adults.

The value of 15 µg/mL was selected as a typical value for the Cavss for rufinamide at the highest doses administered to patients (45 mg/kg/day for children and 3200 mg/day for adults). From the population PK analysis of pooled studies (report EMFFR2004/014/00) the median Cavss obtained in studies using the WP tablets at the doses indicated were 13 µg/mL for study 21 (both adult and pediatric strata) and 17 µg/mL for study 22. A value of 15 µg/mL was selected to represent the typical value of exposure in these studies, and for patients treated at high doses.

Table: % change in concomitant AED Clearance (and Cavss) with typical concentration of rufinamide (15 µg/mL)

AED	N (males and females)	Children	Adolescents	Adults
carbamazepine	903 495M, 408F	15.4% (-13%)	8.7% (-8%)	7.9% (-7%)
lamotrigine	200 94M,106F	15.6% (-13%)	10.6% (-10%)	7.7% (-7%)
phenobarbital	149 87M, 62F	-11.7% (13%)	-8.7% (10%)	-7.1% (8%)
phenytoin	299 162M, 137F	-17.5% (21%)	-9.1% (10%)	-6.5% (7%)
topiramate	69 30M, 39F	No effect	No effect	No effect
valproate	488 263M, 225F	No effect	No effect	No effect

The highest percentage changes in clearance of these AEDs due to rufinamide at any given concentration are observed in children. All of these changes in clearance would result in only moderate change in the average concentration at steady state of the respective AEDs.

For the individual AEDs, the following Tables show the clearance values with the increase in age and rufinamide concentration (median, maximum and typical

concentrations). Except for phenytoin and phenobarbital, the clearance of the AED increases with its total daily dose.

Carbamazepine:

Table: Population carbamazepine clearance in males by age with and without rufinamide concentration

Age (yr)	Dose (mg)	CL (L/h) without RUF	CL (L/h) and % of change with RUF (10.10 µg/mL)	CL (L/h) and % of change with RUF (58.67 µg/mL)	CL (L/h) and % of change with RUF (15 µg/mL)
5	400	2.55	2.88; 13.2%	3.14; 23.2%	2.94; 15.4%
15	900	4.51	4.84; 7.4%	5.10; 13.1%	4.90; 8.7%
30	1000	4.96	5.30; 6.8%	5.55; 11.9%	5.35; 7.9%

The carbamazepine clearance increased with rufinamide concentrations, dose and age. Carbamazepine clearance is 5.54% higher in female than in male patients.
To put this in perspective, it is increased by 10.4% when valproate is co administered, by 34.6% when phenytoin is co administered, and by 23.1% when phenobarbital is co administered.

Lamotrigine:

Table: Population lamotrigine clearance by weight with and without rufinamide concentration

Age (yr)	Weight (kg)	Median dose (mg)	CL (L/h) without RUF	CL (L/h) and % of change with RUF (14.28 µg/mL)	CL (L/h) and % of change with RUF (45.90 µg/mL)	CL (L/h) and % of change with RUF (15 µg/mL)
5	20	100	1.10	1.27; 14.9%	1.63; 47.8%	1.28; 15.6%
15	50	200	1.62	1.79; 10.1%	2.15; 32.5%	1.80; 10.6%
30	75	400	2.23	2.39; 7.4%	2.75; 23.7%	2.40; 7.7%

The lamotrigine clearance increases with rufinamide concentrations, dose and weight. Lamotrigine clearance is increased by 121% when phenytoin is co administered, is increased by 47.1% when carbamazepine is co administered, and decreased by 46.1% when valproate is co administered.

Phenobarbital:

Table : Population phenobarbital clearance by weight with and without rufinamide concentration

Age (yr)	Weight (kg)	Median dose (mg)	CL (L/h) without RUF	CL (L/h) and % of change with RUF (9.66 µg/mL)	CL (L/h) and % of change with RUF (32.6 µg/mL)	CL (L/h) and % of change with RUF (15 µg/mL)
5	20	100	0.154	0.142; -7.5%	0.115; -25.4%	0.136; -11.7%

15	50	100	0.208	0.196; -5.6%	0.169; -18.8%	0.190; -8.7%
30	75	100	0.253	0.241; -4.6%	0.214; -15.5%	0.235; -7.1%

The co administration of rufinamide decreases the clearance of phenobarbital.
The phenobarbital clearance increases with dose and weight.
Phenobarbital clearance is decreased by 22.7% when valproate is co administered.

Phenytoin:

Table: Population phenytoin clearance by weight with and without rufinamide concentration

Age (yr)	Weight (kg)	CL (L/h) without RUF	CL (L/h) and % of change with RUF (8.46 µg/mL)	CL (L/h) and % of change with RUF (28.7 µg/mL)	CL (L/h) and % of change with RUF (15 µg/mL)
5	20	0.41	0.37; -9.9%	0.27; -33.6%	0.34; -17.5%
15	50	0.79	0.75; -5.1%	0.65; -17.4%	0.72; -9.1%
30	75	1.11	1.07; -3.7%	0.97; -12.4%	1.04; -6.5%

The co administration of rufinamide decreases the clearance of phenytoin.
The phenytoin clearance increases with weight.

Topiramate:

The topiramate clearance increases with dose and age and is not modified by the coadministration of rufinamide.
Topiramate clearance increases by 125% when phenytoin is co administered and by 59.6% when carbamazepine is co administered.

Valproate:

The valproate clearance linearly increases with age for young patients up to 18 years old, and is constant for patients over 18. It increases with dose and is not modified by the coadministration of rufinamide.
Valproate clearance is increased by 38.1% when phenytoin is co administered, by 27.4% when carbamazepine is co administered, and by 38.7% when phenobarbital is co administered.

Overall Conclusions:

- 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.

With the maximum concentrations of rufinamide, the maximal changes in C_{avss} predicted by the models are:

- Carbamazepine (23.2% increase in CL at 58.7 µg/mL rufinamide) corresponds to a decrease in C_{avss} of 19%.
- Phenobarbital (25.4% decrease in CL at 32.6 µg/mL rufinamide) corresponds to an

increase in C_{avss} of 34%.

- Phenytoin (33.6% decrease in CL at 28.7 µg/mL rufinamide) corresponds to an increase in C_{avss} of 51%.
- Lamotrigine (47.8% increase in CL at 45.9 µg/mL rufinamide) corresponds to a decrease in C_{avss} of 32%

Carbamazepine, phenytoin and valproate have non linear pharmacokinetics (due to autoinduction for carbamazepine, to saturation of metabolism for phenytoin and saturation of plasma protein binding for valproate), hence the population predictions have shown an over prediction at the lower concentrations and an underprediction at the higher concentrations of these AEDs as compared to the observed values. Therefore, it is possible that the exposure of these AEDs will be greater than the model predicted.

2.4.5.3 Influence of AEDs on rufinamide:

Valproate

The following Table shows that rufinamide concentrations increase by 55 to 70% in children, 23 to 26% in adolescents and 15 to 16% in adults treated with valproate based on a population analysis.

Table: Effect of interacting valproate* on model predicted apparent CL and Cavss in typical subjects
:ablet)

	Without valproate		Valproate conc.(µg/mL)	With valproate	
	CL (L/h)	C_{avss} (µg/mL)		CL (L/h)	C_{avss} (µg/mL)
Male children	3.47	14.2	100	2.24	22.0
Female children	3.00	16.4		1.77	27.9
Male Adolescents	5.55	14.0	88	4.50	17.3
Female Adolescents	5.12	15.2		4.07	19.2
Male adults	5.19	7.3	71	4.54	8.4
Female adults	4.88	7.8		4.23	9.0

*In patients treated with valproate

In study AE/PT2, rich pharmacokinetic profiles had been collected on the first day of the study, when all 50 patients included received a single dose rufinamide 800 mg. Rufinamide concentrations had been analysed by non-compartmental method.

Phenobarbital, phenytoin and primidone:

With co administration of phenobarbital, phenytoin or primidone, rufinamide C_{avss} decrease by approximately 42-46% in children, 30-32% in adolescents and 25-26% in adults (Table below):

Table: Effect of interacting phenobarbital, phenytoin or primidone(PHEN) on model predicted apparent CL and Cavssin typical subjects (tablet)

	Without PHEN		With PHEN	
	CL (L/h)	C_{avss} (µg/mL)	CL (L/h)	C_{avss} (µg/mL)
Male children	3.47	14.2	6.04	8.2
Female children	3.00	16.4	5.57	8.8
Male Adolescents	5.55	14.0	7.93	9.8
Female Adolescents	5.12	15.2	7.50	10.4
Male adults	5.19	7.3	6.89	5.5
Female adults	4.88	7.8	6.58	5.8

Carbamazepine:

Rufinamide concentrations in subjects treated concomitantly with carbamazepine would decrease by approximately 23-26% in children, 19-20% in adolescents and 21-22% in adults (Table below):

Table: Effect of interacting carbamazepine* on model predicted apparent CL and Cavssin typical subjects tablet)

	Without carbamazepine			With carbamazepine	
	CL (L/h)	C_{avss} (µg/mL)	Carbamazepine dose (mg/d)	CL (L/h)	C_{avss} (µg/mL)
Male children	3.47	14.2	600	4.53	10.9
Female children	3.00	16.4		4.06	12.2
Male Adolescents	5.55	14.0	800	6.86	11.4
Female Adolescents	5.12	15.2		6.42	12.1
Male adults	5.19	7.3	1200	6.59	5.8
Female adults	4.88	7.8		6.28	6.1

Vigabatrin:
Vigabatrin is associated with rufinamide C_{avss} decreases of approximately 27-30% in children, 18-19% in adolescents, and 14-15% in adults (Table below):

Table: Effect of interacting vigabatrin on model predicted apparent CL and Cavssin typical subjects (b) (4) tablet)

	Without vigabatrin		With vigabatrin	
	CL (L/h)	C_{avss} (µg/mL)	CL (L/h)	C_{avss} (µg/mL)
Male children	3.47	14.2	4.74	10.4
Female children	3.00	16.4	4.27	11.5
Male Adolescents	5.55	14.0	6.73	11.6
Female Adolescents	5.12	15.2	6.30	12.4
Male adults	5.19	7.3	6.03	6.3
Female adults	4.88	7.8	5.72	6.6

Lamotrigine, topiramate and benzodiazepines:

These had no effect on rufinamide concentrations.
There are no in vitro basis for these interactions with other AEDs. These drug interactions might be ascribed to some heteroinduction of the metabolism of rufinamide, mainly by phenytoin, and to a lesser extent by carbamazepine, as commonly found between AEDs.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on the BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The BCS classification of rufinamide has not been characterized by the sponsor, although rufinamide is practically insoluble in water (b) (4) Based on Caco-2 cell studies, rufinamide has high intrinsic permeability (b) (4). An absolute bioavailability study has not been conducted with rufinamide tablets. Based on these information rufinamide is likely to be BCS Class II drug.

2.5.2 Is the proposed to-be-marketed formulation of rufinamide bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

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3.0 DETAILED LABELING RECOMMENDATION

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4.0 APPENDIX

4.1 APPENDIX I

INDIVIDUAL STUDY REVIEW

SINGLE DOSE PHARMACOKINETIC STUDIES

Study 91076 or EP 001: Safety and Pharmacokinetics Study on Single Administration of CGP 33101 in Healthy Subjects.

A brief overview of some essential components of the study design is given below:

Study Design	Open-label, single-dose
Study Population	N=12 (6 in each dose group) Age: 20-35 years (mean 23 years) Gender: 12 males Weight: 51-71 kg (mean 63 kg) Race: Japanese
Treatment Group	Two groups
Dosage and Administration	The initial dose was: 100 mg (Step 1), followed by dose escalation to 200 mg (Step 2), 400 mg (Step 3), and 800 mg (Step 4) Escalation to the next higher dose was allowed based on safety confirmation by fully considering the subject's general condition. Same subjects (N=6) used for step 1 and 3 and 2 and 4 (N=6) Lot no: 50 mg tablet 150/72/2 200 mg tablet 150/15/2 Diet: During the study, lunch and dinner were provided at 13:30 and 18:30, respectively. Breakfast was provided at 9:30 on and after Day 2. Subjects were fasted from 10 hours pre-dose to 4 hours post-dose. Caffeine-containing and alcoholic beverages were prohibited from 23 hours pre-dose to 96 hours post-dose. Smoking was prohibited from 10 hours pre-dose to 4 hours post-dose. No drugs allowed 23 hrs pre-dose till end of study
Sampling: Blood	At pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours post-dose.
Urine	pre-dose (at any time) and post-dose (during 0-2, 2-4, 4-6, 6-12, 12-24, 24-36, 36-48, 48-72 and 72-96 hours).
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma / Urine Rufinamide 25 ng/mL / 50 ng/ml CGP 47291 50 µg/mL / 2 ng/ml

	CGP 47292 50 ng/ml 2 ng/ml Rufinamide: Linear range : 25-1000 ng/mL in plasma, 50-2500 ng/ml in urine CGP 47,291: Linear range : 50-500 ng/mL in plasma, 2-100 µg/ml in urine CGP 47,292: Linear range : 50-1000 ng/mL in plasma, 2-200 µg/ml in urine No additional assay information provided.
PK Assessment	AUC0-96, Cmax, Tmax, T1/2, urinary excretion parameters
Safety Assessment	blood pressure, pulse rate, body temperature and weight, ECGs, Laboratory tests etc
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in plasma:

CGP 33101 **(**Rufinamide) plasma concentrations are shown in the following table:

Dose (mg)	C_{max} (ng/mL)	C_{max}/dose (ng/mL/mg)	T_{max} (hr)	AUC $_{(0-96)}$ (ng hr/mL)	AUC $_{(0-96)}$/dose (ng hr/mL/mg)	Ke $_{(24-48)}$ (L/hr)	$T_{1/2\ (24-48)}$ (hr)
100	750.6 ± 144	7.5 ± 1.4	4	13901.4 ± 1906	139.0 ± 19	0.07428 ± 0.0098	9.5 ±1.2
200	1026 ±164	5.1 ±0.8	6	23532 ±3993	118 ±20	0.07681 ± 0.00732	9.1 ±20
400	1515 ±314	3.8 ±0.8	6	41713 ±6113	104 ±15.3	0.06959 ±0.00478	10 ±0.7
800	2117 ±397	2.6 ±0.5	8	65517 ±18367	81.9 ±23	0.06557 ±0.01858	11.8 ±5.4

Mean concentration-time plot for the 4 different doses is shown in the following figure:

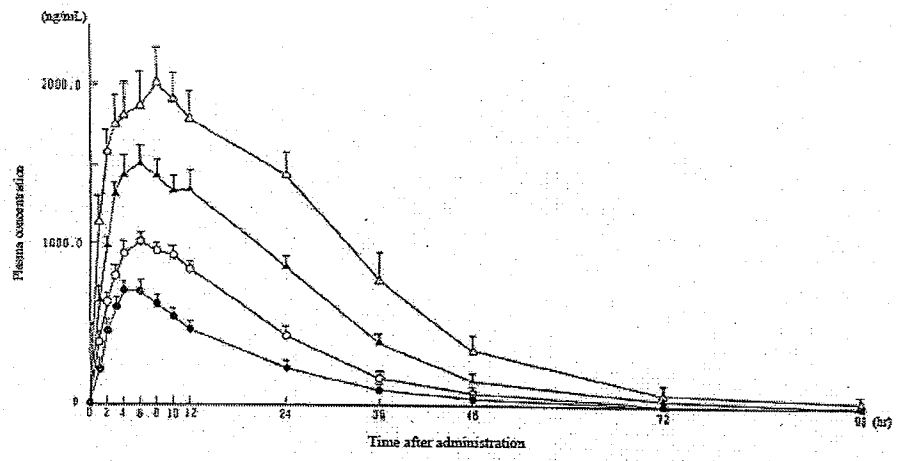
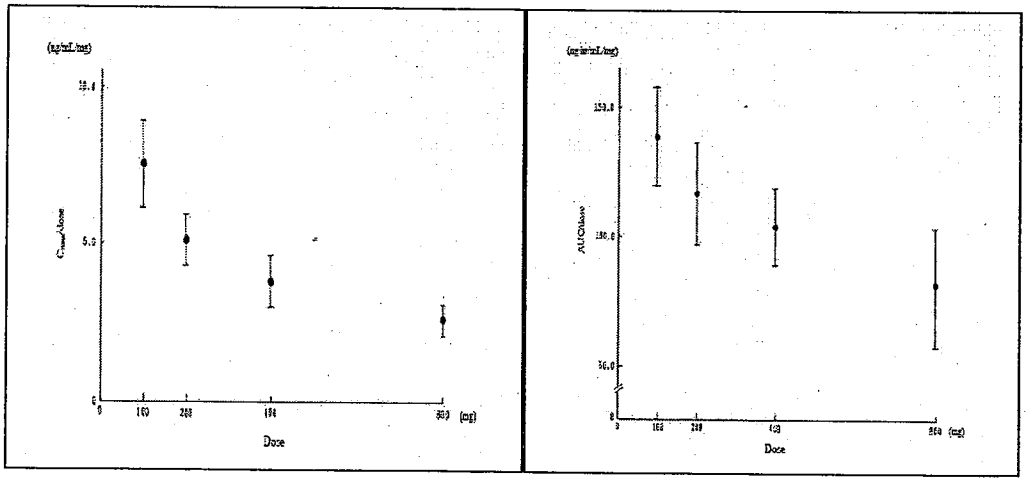


Figure 3 Change in CGP 33101 concentrations in plasma after single oral administration of CGP 33101, for each dose (Mean ± S.E., n=6)

•: 100 mg ○: 200 mg ▲: 400 mg △: 800mg

- Cmax following administration of 100, 200, 400 and 800 mg showed a dose-dependent increase, but a less than proportional increase. Cmax/dose values decreased with increased dose and had a non-linear relationship to dose (Figure a).
- The median values of time to maximum plasma CGP 33101 concentration (Tmax) following these doses, although accompanied by a large variability due to the fact that plasma CGP 33101 levels remained at or near maximum concentrations for several hours.
- The area under the plasma concentration-time curve (AUC(0-96 hr)) also showed a dose-dependent increase, but AUC(0-96 hr)/dose values decreased with increased dose and had a non-linear relationship to dose (Figure b).
- Elimination half-life remained constant irrespective of dose level.



(a) (b)

Metabolites in plasma (CGP 47291 and CGP 47292):

At any post-dose time, mean CGP 47291 levels in plasma were below the lower limit of quantification.
Mean CGP 47292 levels in plasma are shown in the following Table:

Dose (mg)	T_{max} (hr)	C_{max} (ng/mL)	AUC $_{(0\text{-}96\ hr)}$ (ng.hr/mL)
100	4	91.6±24.0	772.0±360.1
200	7	143.8±30.9	2550.5±629.3
400	4	209.3±47.1	4788.5±1346.4
800	3	363.8±74.1	10041.5±1241.3[2]

- With respect to CGP 47292 in plasma, Tmax values were not correlated with increased doses and ranged between 3 and 7 hours, which were similar to the corresponding values of CGP 33101 in plasma.
- The Cmax values of CGP 47292 tended to increase in somewhat smaller increments compared to the dose increments and represented 12 to 17% of the Cmax values of CGP 33101 at each dose.
- The AUC(0-96 hr) values of CGP 47292 tended to increase in somewhat larger increments compared to the dose increments, but actual AUC(0-96 hr) values following a 100 mg dose seem to have been considerably underestimated in relation to the lower limit of quantification in the measurement of concentrations, and at and above 200 mg doses a linear relationship was found between doses and AUC(0-96 hr) values. It was shown that at 200 mg and all higher doses, the AUC(0-96 hr) values of CGP 47292 represented 11 to 15% of the corresponding values of CGP 33101.

Rufinamide in Urine:

Cumulative CGP 33101 excretion rates for the respective doses seen in the 100, 200, 400 and 800 mg dose groups were 0.67 ± 0.07, 0.68 ± 0.07, 0.47 ± 0.05 and 0.59 ± 0.07%, respectively, at 48 hours post-dose, and 0.67 ± 0.07, 0.69 ± 0.06, 0.50 ± 0.06 and 0.63 ± 0.09%, respectively, at 96 hours post-dose. This means that for each dose level the urinary CGP 33101 excretion during the first 48 hours post-dose represented more than 90% of that during the first 96 hours post-dose.

Metabolites in urine (CGP 47291 and CGP 47292):

- No peak was observed for CGP 47291 in any urine samples.

- Cumulative urinary CGP 47292 excretion rates following administration of 100, 200, 400 and 800 mg up to 48 hours post-dose were 48.1 ± 5.0, 48.2 ± 8.5, 32.4 ± 2.4 and 31.4 ± 2.8%, respectively, and those up to 96 hours post-dose were 48.1 ± 5.0, 50.2 ± 8.7, 34.5 ± 2.6 and 34.3 ± 2.8%, respectively. The cumulative urinary CGP 47292 excretion rates at 48 hours following these doses represented 100, 96, 94 and 92% of the corresponding rates at 96 hours post-dose, excretion of metabolites in urine seemed to have almost been completed by 48 hours post-dose irrespective of dose. Cumulative urinary CGP 47292 excretion rates during the first 96 hours post-dose showed a tendency to decrease with increased doses. This tendency is similar to the tendency of AUC(0-96 hr)/dose values of CGP 33101 in plasma to decrease with increased doses, suggesting that absorption becomes saturated with increased doses.

Conclusions:

- With respect to CGP 33101 in plasma, at all dose levels plasma concentrations almost reached maximum levels in 4 to 8 hours post-dose and remained at or near the maximum levels for 2 to 8 hours before decrease. Cmax and AUC(0-96 hr) values increased in a dose-dependent manner but showed a non-linear relationship to dose. T1/2(24-48 hr) values remained constant at about 10 hours independently of dose.
- With respect to metabolites found in plasma (CGP 47291 and CGP 47292), the principal metabolite was CGP 47292 at all dose levels, and CGP 47291 was almost always at concentrations below the lower limit of quantification. AUC values of CGP 47292 represented 11 to 15% of those of CGP 33101, and an almost linear relationship was found between dose and AUC.
- Cumulative urinary CGP 33101 excretion levels increased in a dose-dependent manner, but the cumulative urinary excretion rates during the first 96 hours were less than 1% at all dose levels.
- With respect to metabolites possibly found in urine (CGP 47291 and CGP 47292), CGP 47292 was found as a metabolite at all dose levels, while CGP 47291 was not detected at any dose level. The cumulative urinary CGP 47292 excretion rates at 96 hours post-dose were 34 to 50% of the administered dose.

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Study t-03-1990: Pharmacokinetics of unchanged CGP 33101 in plasma of healthy volunteers after single oral doses (50-600 mg)
and

Study A184: Acute study on tolerability and kinetics of CGP 33101 in Healthy Subjects.

(two separate reports for different sections of the same study)

A brief overview of some essential components of the study design is given below:

Study Design	Randomized, single rising dose, placebo controlled, cross-over
Study Population	N=28 Age: 23-34 years (mean 27 years) Gender: 28 males Weight: 63-86 kg (mean 73 kg) Race: Japanese
Treatment Group	Five groups: each subject received two doses
Dosage and Administration	Doses evaluated were 50-600 mg and placebo given in random order. Each subject received two doses with 200 ml water with a wash out phase of 1 week between doses. Lot no: 1 mg 13/922/1 10 mg 13/923/1 50 mg 13/924/1 100 mg 13/925/1 200 mg 13/926/1 Diet: Doses administered after 12 hour fast, breakfast given 2 hours after drug intake. Two weeks before and after no medication allowed, no alcohol during the study
Sampling: Blood	At pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose.
Urine	At 0-6, 6-12, 12-24, 24-48, 48-2, 72-96 hours after dosing
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma / Urine Rufinamide: 210 nmol/L (50 ng/ml) / none

	Rufinamide (from analytical report crb-r66-1987): Intra-day Precision (%CV for Quality Controls) : ≤4.4% Intra-day Accuracy: 99-107% Inter-day Precision (%CV for Quality Controls) : ≤11.3% Inter-day Accuray: 94-122%
PK Assessment	AUC0-inf, Cmax, Tmax, T1/2
Safety Assessment	blood pressure, pulse rate, body temperature and weight, ECGs, Laboratory tests etc
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in plasma:
Rufinamide was absorbed quicker at doses up to 150 mg. With each increase of dose beyond 150 mg the Tmax become longer. At doses 500-600 mg, the high plasma concentration remained at plateau level for several hours. The dose corrected Cmax decreased with the increase in dose. This suggests that at higher doses the rate of absorption and/or distribution slows down. The dose corrected AUC remained constant with the increase in dose after doses greater than 75 mg. The half-life did not change with the increase in doses. This suggests that the extent of absorption does not change at doses 50-600 mg.

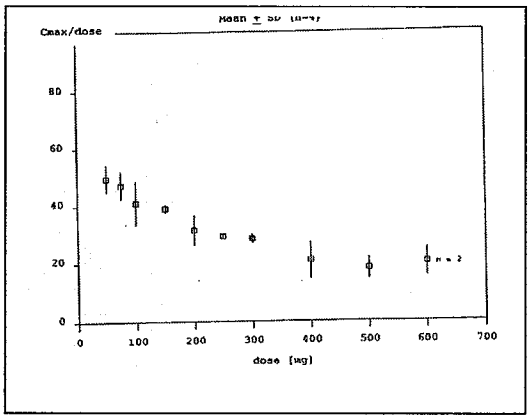
The pharmacokinetic parameters at the various doses are shown in the Table below:

Pharmacokinetic data (mean ± SD) of CGP 33 101 in plasma after single doses of CGP 33 101 given orally

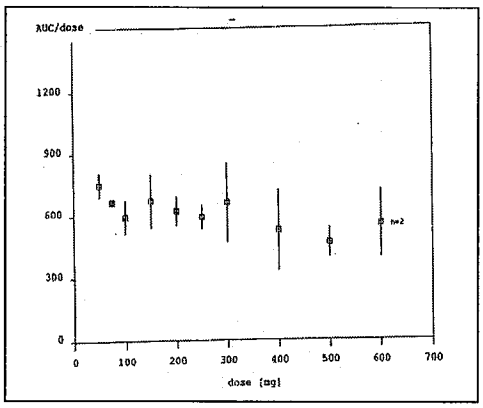
Dose [mg]	Vol. n	C_{max}/dose [nmol/(L*mg)]	t_{max}@ [h]	$AUC_{(0-\infty)}$/dose [nmol*h/(L*mg)]	$t_{1/2}$ [h]
50	4	49.6 ± 4.6	1.5	751.0 ± 56.9	9.0 ± 0.5
75	4	47.2 ± 4.7	2.0	667.7 ± 179.5	8.5 ± 1.9
100	4	41.1 ± 7.6	3.0	595.8 ± 80.8	7.6 ± 1.4
150	4	39.0 ± 1.3	3.0	673.0 ± 129.6	8.9 ± 1.8
200	4	31.5 ± 5.1	6.0	623.8 ± 70.1	9.1 ± 1.8
250	4	29.3 ± 0.7	5.1	592.9 ± 56.6	8.3 ± 2.1
300	4	28.4 ± 1.5	4.5	663.2 ± 190.0	8.0 ± 2.1
400	4	20.8 ± 6.3	5.0	527.9 ± 194.0	8.3 ± 2.6
500	4	18.1 ± 3.6	12.0*	466.4 ± 71.2	8.8 ± 2.4
600	2	20.2 ± 4.7	10.0*	554.8 ± 162.4	9.3 ± 1.4

* arbitrary (plateau for several hours)
@ - median

The dose proportionality assessment is shown in the following figures, showing a decrease in Cmax with the increase of dose, but AUC did not change much with the increase of dose although high variability was seen at the higher doses:



(a) Dose corrected Cmax vs dose



(b) Dose corrected AUC vs dose

Safety:

Dizziness was reported at doses greater than 500 mg.

Conclusions:

At higher doses the rate of absorption becomes slower (decreased Cmax and prolonged Tmax). This is also supported by a plateau for several hours at the higher doses.

Reviewer's Comment:

- *Urine samples were collected but no data was provided in the study report.*
- *Reference is made to Assay validation report crb-r66-1987, but the LOQs reported in the report crb-r66-1987 are different from that reported in this study report.*
- *In Study 91076, there was a decrease in AUC with the increase of doses up to 800 mg along with the decrease of Cmax and prolongation of Tmax. In this study this observation was not true for AUC.*

Study A 233: Single rising dose (600-2100 mg) on tolerability, pharmacodynamics and Pharmacokinetics of unchanged CGP 33101 in Healthy volunteers.

And

Study T07-1990: Pharmacokinetics of unchanged CGP 33101 in Healthy Subjects after Single Oral Doses (600-2100 mg) –two separate reports for different sections of the same study

And

Study crb-r29-1991: Urinary excretion of CGP 33101 and its two acid metabolites CGP 47292 and CGP47291 in healthy volunteers following single oral doses of 600-1000 mg

A brief overview of some essential components of the study design is given below:

Study Design	Randomized, single-dose, placebo controlled, cross-over
Study Population	N=11 Age: 22-31 years (mean 27 years) Gender: 11 males Weight: 61-98 kg (mean 79 kg) Race: NA
Treatment Group	Single group
Dosage and Administration	Doses evaluated were 600-2100 mg and placebo given in random order. Each subject received two doses with 200 ml water with a wash out phase of 1 week between doses. Lot no: 100 mg tablet 13/925/1 200 mg tablet 13/926/1 Diet: Doses administered after 12 hour fast, breakfast given 2 hours after drug intake. Two weeks before and after no medication allowed, no alcohol during the study
Sampling: Blood	At pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose.
Urine	Not in the protocol but collected from 4 subjects on 600, 800 and 1000 mg at 0-6, 6-12, 12-24, 24-48 and 48-72 hour after dosing
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma / Urine Rufinamide 200 nmol/L (47.64 ng/ml) / 1.05 µmol/L(0.25 µg/ml)

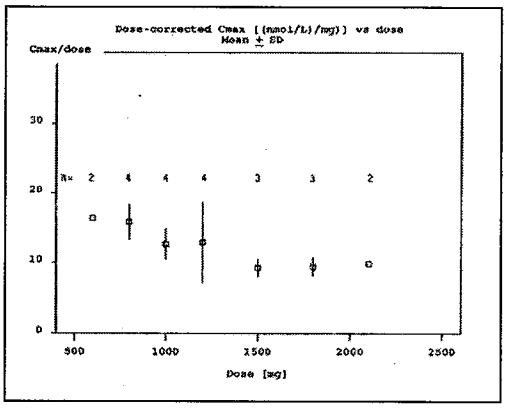
	CGP 47292 20 µg/ml CGP 47291 20 µg/ml Rufinamide (from analytical report crb-r66-1987): Intra-day Precision (%CV for Quality Controls) : ≤ 4% Intra-day Accuracy: 99-107% Inter-day Precision (%CV for Quality Controls) : ≤ 11% Inter-day Accuracy: 95-120% CGP 47292: not reported CGP 47291: not reported
PK Assessment	AUC0-72, AUC0-inf, Cmax, Tmax, T1/2
Safety Assessment	blood pressure, pulse rate, body temperature and weight, ECGs, Laboratory tests etc
PD Assessment	None

Pharmacokinetic Results:

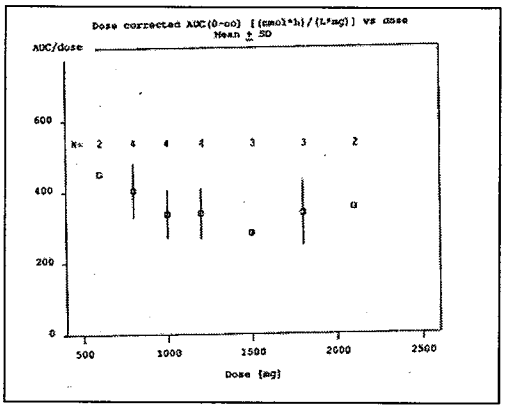
Rufinamide in plasma:
Thirty minutes after administration, the drug levels reached 45% of the peak values. The concentration remained high, close to peak value for several hours (plateau like shape, Tmax ranging from 3-11 hours). There was large interindividual variability of drug concentration. Profiles with two peaks were frequently observed. There was no dose proportionality for Cmax or AUC for individual subjects. The dose corrected Cmax and AUC decreased with the increase of dose suggesting saturation in the absorption process.The elimination half-life did not change with dose (~10 hours). The sponsor makes a note here that the in vitro dissolution rates of tablets decreased with increasing doses.
The following Table shows the pharmacokinetic parameters:

Dose [mg]	n	C_{max} [µmol/L]	$t_{1/2}$ [h]	$AUC_{(0-\infty)}$ [(µmol*h)/L]
600	2	9.8	9.6	270.0
800	4	12.7 ± 2.0	9.0 ± 2.8	323.1 ± 60.7
1000	4	12.7 ± 2.2	8.0 ± 1.6	336.9 ± 68.4
1200	4	15.5 ± 6.9	10.4 ± 4.8	405.7 ± 85.0
1500	3	14.0 ± 1.8	11.2 ± 0.8	422.8 ± 13.6
1800	3	17.1 ± 2.3	10.3 ± 1.2	609.2 ± 163.8
2100	2	20.7	10.9	742.4

The dose proportionality assessment is shown in the following figures:



(a) Dose corrected Cmax vs dose



(b) Dose corrected AUC vs dose

Rufinamide and metabolites in urine:

The urinary excretion of unchanged CGP 33101 and CGP 47292 over 72 hours (% of dose) is shown in the following Table:

Compound	Subject	Dose		
		600 mg	800 mg	1000 mg
CGP 33 101	02	0.71	0.73	
	03		0.38	0.24
	04		0.28	0.19
	05			0.19*
CGP 47 292	02	27.2	34.8	
	03		28.5	22.9
	04		30.0	22.9
	05			17.9*

* : over 24 h.

- CGP 33101 was extensively metabolized. It's urinary excretion was less than 1 % of dose.
- CGP 47 292 was excreted to the extent of 23-35% of the dose.
- Metabolite CGP 47 291 was not detected in the urine (less than 1.5% of dose-based on LOQ and urine volume).
- The urinary excretions of CGP 33101 and CGP 47292 were slightly lower at the 1000 mg than at 800 mg dose level, thereby suggesting a slight saturation of the absorption when the dose is increased.
- The urinary half-life of CGP 33101 and CGP 47292 were similar (8-12 hrs)

Safety:
Adverse events reported were headache, tiredness, drowsiness, difficulties to concentrate, slurred speech- no relationship to dose was observed and also observed with placebo. No clinically relevant changes in laboratory parameters.

Conclusions:

- Dose corrected AUC and Cmax decreased with the increase of dose.
- Half-life was not changed with the increase of dose, suggesting saturation of the absorption process alone.

Reviewer's Comment:

- *Reference is made to Assay validation report crb-r66-1987, but the LOQs reported in the report crb-r66-1987 are different from that reported in this study report.*

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Study crb-r39-1991: Absorption kinetics of CGP 33101 after oral administration of single doses in the range 50-2100 mg. Evaluation of data from tolerability studies in healthy volunteers.

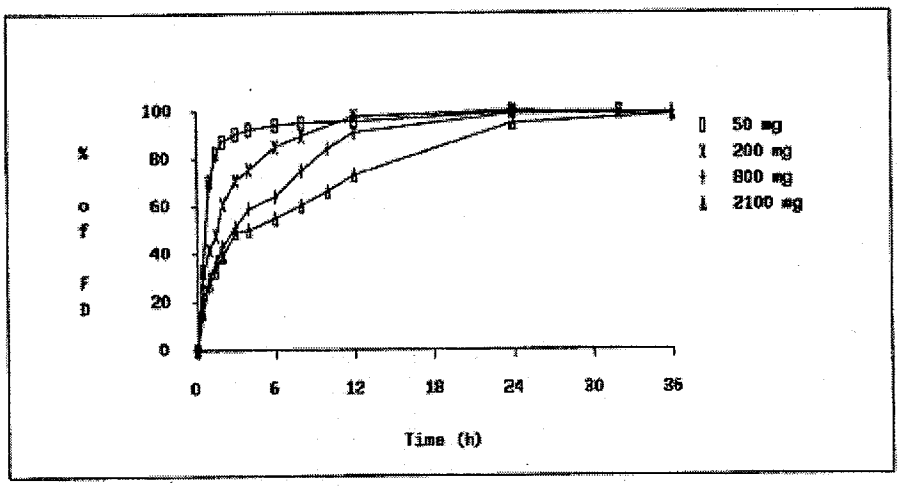
This study report is a combined report for studies A233 and A184 previously reviewed to assess linearity in pharmacokinetics at doses 50-2100 mg, to evaluate absorption kinetics and to assess any in vitro- in vivo correlation.

The results showed that the increase in Cmax and AUC was not dose proportional at doses higher than 300 mg.

The absorption rate was faster for doses up to 250 mg, after which it slowed down.

As observed in vivo, the in vitro dissolution rate decreased as the dose increased. This was evaluated only at strengths 50, 100 and 200 mg because all the doses used multiple tablets to add up to the dose.

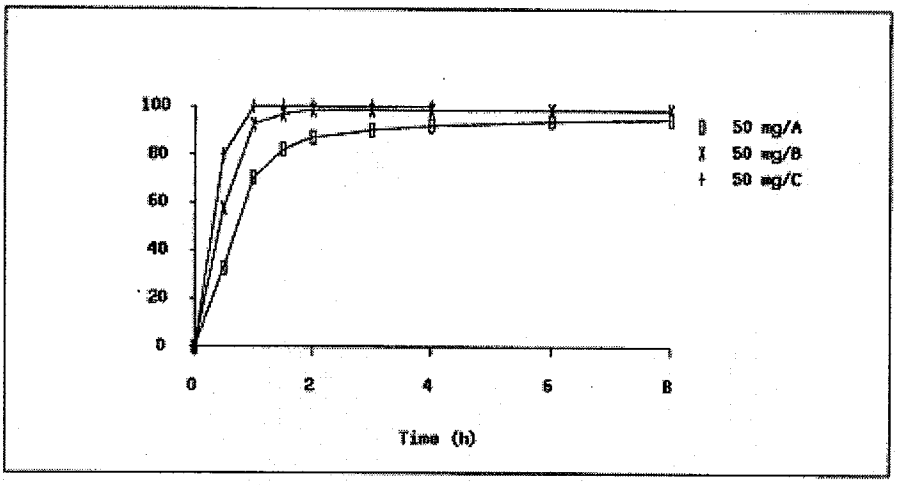
Comparative mean absorption profiles for few doses in the range of 50-2100 mg are shown in the following figure, showing that the absorption rate and the amount absorbed decreased with the increase of doses:

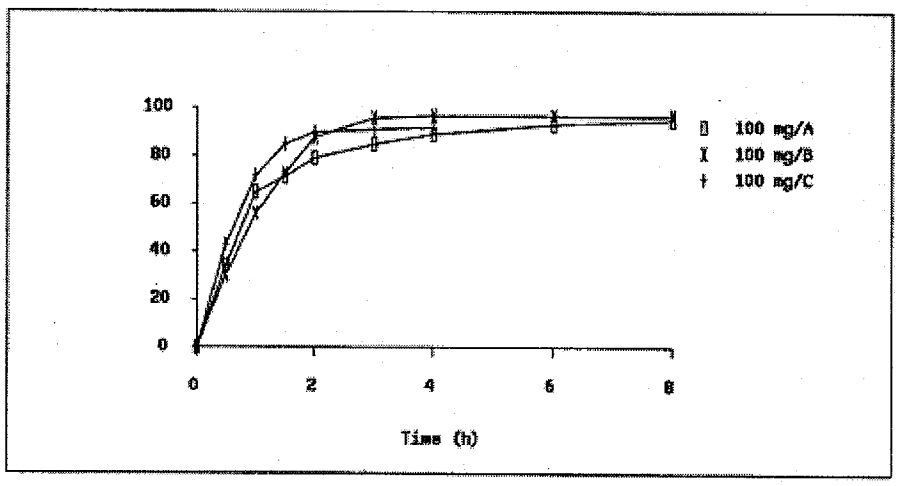


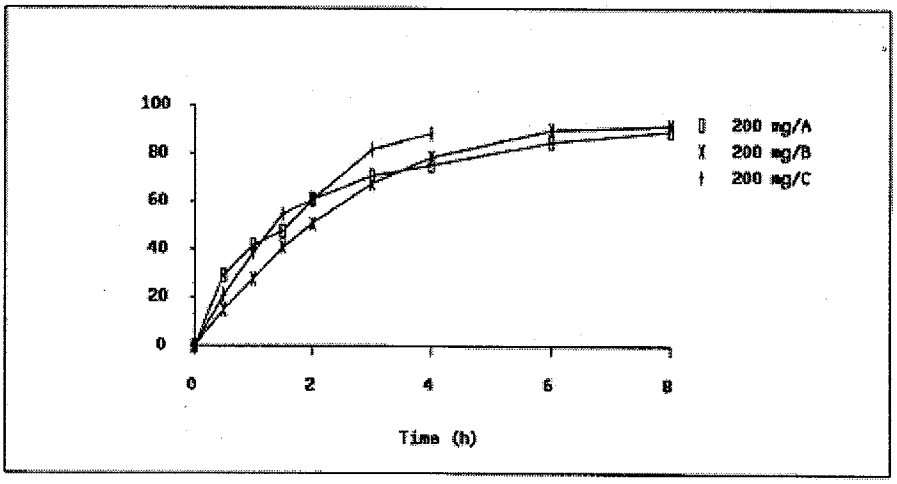
Comparison of in vitro dissolution and in vivo absorption of 50,100 and 200 mg tablets is shown in the following figures, showing that the invitro dissolution slows down with the increase of doses:

Figures where A: in vivo absorption
B: in vitro dissolution (flow rate 16 ml/min)
C: in vitro dissolution (flow rate 25 ml/min)

In vitro dissolution was done using flow cell method with laminar flow.


100
80
60
40
20
0
0
2
4
6
8
Time (h)
50 mg/A
50 mg/B
50 mg/C


100
80
60
40
20
0
0
2
4
6
8
Time (h)
100 mg/A
100 mg/B
100 mg/C


100
80
60
40
20
0
0
2
4
6
8
Time (h)
200 mg/A
200 mg/B
200 mg/C

Conclusion:

This shows that the in vitro dissolution rate decreased when the dose strength increased. The same phenomenon was observed in vivo: the absorption rate and the absorbed amount decreased when the dose increased.

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SINGLE DOSE RADIOLABELED STUDY

Study hph9213: Pharmacokinetics, disposition and biotransformation of rufinamide in healthy volunteers after single oral dose of 600 mg ^{14}C-radiolabeled preparation administered with food.

A brief overview of some essential components of the study design is given below:

Study Design	single-dose, open label
Study Population	and N=3 healthy subjects (1 pilot), subjects 1 and 3 were extensive metabolizers of debrisoquin and subject 2 was a poor metabolizer Age: 20-60 years (mean 33.5 years) Gender: males Weight: 57-101 kg (mean 84 kg) Race: NA
Treatment Group	Single group
Dosage and Administration	Single dose of 600 mg (3.65 MBq) Lot no: Microcrystalline powder in gelatin capsules Diet: Doses administered orally after high fat breakfast
Sampling: Blood	At 0-168 hours post-dose.
Urine	At 0-168 hours post-dose.
Feces	At 0-168 hours post-dose.
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma / Urine / Feces Radioactivity: 0.062 µg/ml / 0.048 µg/ml / 0.12-2.4 µg/ml Rufinamide: 0.026 µg/ml / 2.5 µg/ml CGP 47292: 0.12 µg/ml / 5 µg/ml CGP 47291: 4 µg/ml
PK Assessment	AUC0-t, Cmax, Tmax, T1/2
Safety Assessment	Blood pressure, routine laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

The pharmacokinetic data is shown in the following Tables:

Table 1:

Parameter		Radioactivity in Blood	Radioactivity in Plasma	rufinamide in Plasma	CGP 47292 in Plasma
t_{max} (median)	[h]	5	5	5	5
C_{max}	[µmol/L]	29.0 ± 2.0	30.1 ± 2.0	25.5 ± 2.5	5.1 ± 1.8
$t_{½}$ [a]	[h]	8.8 ± 3.7	9.1 ± 3.2	9.0 ± 2.8	8.0 ± 3.3
$AUC_{(0-t)}$	[(µmol/L)·h]	508.8 ± 186.2	513.0 ± 159.0	430.3 ± 167.1	66.2 ± 3.3
t	[h]	48 - 96	48 - 72	48 - 96	24 - 32
AUC	[(µmol/L)·h]	514.5 ± 185.5	524.0 ± 163.6	432.4 ± 167.2	74.0 ± 5.8

[a] typical time period: 10 - 48 h

Table 2:

Time Interval [h]	Excretion of Radioactivity [% of dose]		
	Urine	Faeces	Total
0 - 48	81.7 ± 6.4	12.6 ± 3.1	94.2 ± 4.2
0 - 168	84.7 ± 3.9	13.7 ± 3.5	98.4 ± 1.0

Table 3:

HPLC peak / Compound / Metabolite	Excretion (0-48 h) [% of dose]		
	Urine	Faeces	Total
rufinamide (P1)	2 ± 0	2 ± 2	4 ± 2
CGP 47292 (P2)	66 ± 5	8 ± 3	74 ± 5
P3	5 ± 1	not detected	5 ± 1
P4	5 ± 1	not detected	5 ± 1
P5	1 ± 0.5	not detected	1 ± 0.5
Total of P1 - P5	79 ± 6	11 ± 3	89 ± 4
Other unidentified [a]	3 ± 1	2 ± 1	5 ± 1
Total ^{14}C-excretion (0-48 h)	81.7 ± 6.4	12.6 ± 3.1	94.2 ± 4.2

[a] trace peaks and minor loss of radioactivity during sample processing and HPLC analysis

- About 85% of the dose was absorbed after oral dosing (assuming the drug is stable in the GI tract).
- About 98% of the total radioactivity was accounted for at the end of 168 hours including the parent (P1), major (P2) and minor metabolites (P3-P5). See Tables 2 and 3.
- Predominantly unchanged rufinamide (81% of radioactivity) was present in the plasma at the Tmax of 5 hours and there were low concentrations of the metabolite.
- Rufinamide is extensively metabolized with only traces of unchanged drug found in urine and feces.
- There was little rufinamide and large proportions of metabolite 47292 in the urine and feces. At 0-48 hours there was ~66% of the dose excreted as the main metabolite CGP 47292 and ~1% as rufinmaide.
- Excretion was complete by 7 days mainly via renal route (~85%). The biliary/fecal elimination was low (~14%)
- The main metabolite identified was CGP 47292 (carboxylic acid derivative of rufinamide-P2) formed by the hydrolysis of the carboxamide group of rufinamide by esterases/amidases of the liver.
- Minor metabolites were acyl conjugates of CGP47292 (P3 and P4).

- Subject 2 who was a poor metabolizer of CYP 2D6 did not show any different plasma or metabolite concentrations as compared to other two subjects.

Figure 1: mean plasma concentrations of radioactivity, rufinamide and CGP 47292 (n=3, ± SD

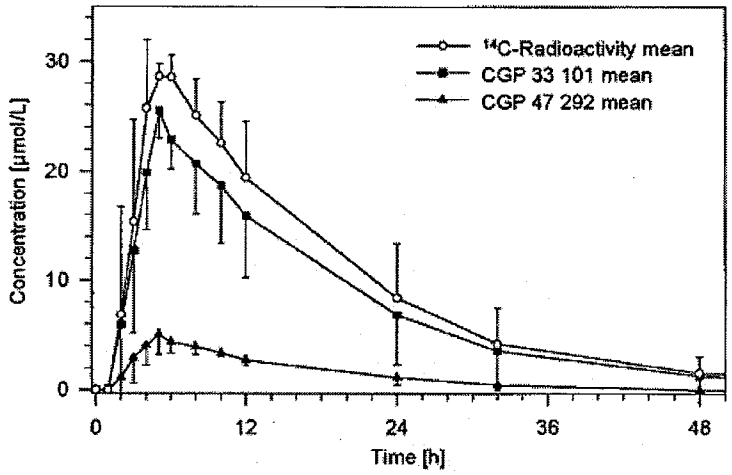
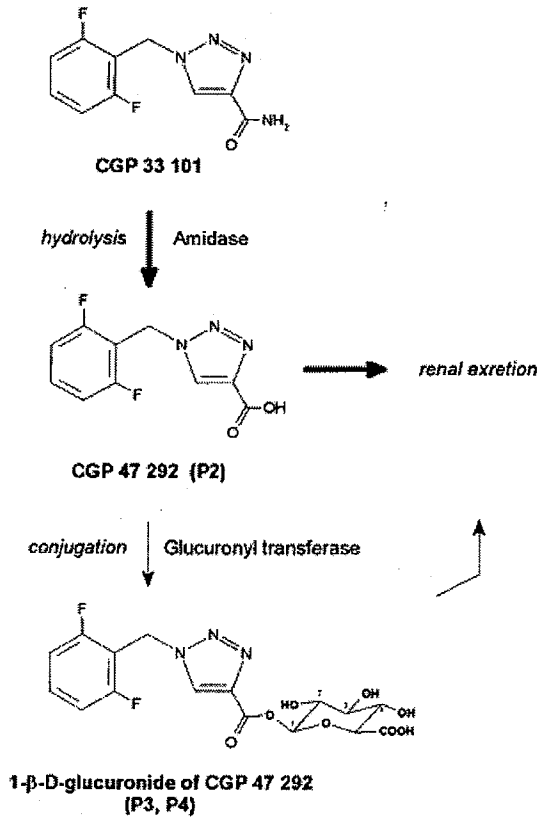


Figure 2: Scheme of biotransformation and elimination processes



Conclusions:

- Absorption of rufinamide with food was 85%.
- Rufinamide was extensively metabolized with minimal amounts of unchanged rufinamide was excreted in the urine.
- CGP 47 292 was the major metabolite.
- Excretion was complete by 7 days mainly via renal route (~85%). The biliary/fecal elimination was low (~14%).
- The predominant clearance mechanism of rufinamide was biotransformation by hydrolysis of the carboxamide group to the carboxylic acid derivative CGP 47292, followed by renal excretion. No evidence of oxidative biotransformation by CYP 450 nor of conjugation by glutathione.

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SINGLE DOSE: DOSE PROPORTIONALITY STUDY

Study 04 or cpd 93056: Dose proportionality of CHP 33 101 after administration of single 200, 400, 800 and 1200 mg oral doses to healthy volunteers

A brief overview of some essential components of the study design is given below:

Study Design	single-dose, open label, randomized, four by four crossover
Study Population	N=16 healthy subjects Age: 20-38 years (mean 27 years) Gender: males Weight: 65-92.5 kg (mean 79.6 kg) Race: 10 white, 5 Black and 1 oriental
Treatment Group	4 groups with 4 subjects each, dosing with 200 mg tablets only A: 200 mg B: 400 mg C: 800 mg D: 1200 mg
Dosage and Administration	1 week washout between groups 200 mg tablets Lot no: E-14867, H-3371 Diet: Subjects fasted overnight. Doses administered orally after a standardized breakfast. Dosing taken with 200 ml water
Sampling: Blood	At 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.
Urine	none
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma Rufinamide 50 ng/ml Rufinamide (from analytical report 91046) Linear range : 50-4000 ng/ml Intra-day Precision (%CV for Quality Controls) : ≤ 8% Inter-day Precision (%CV for Quality Controls) : ≤ 15.3%
PK Assessment	AUC0-t, Cmax, Tmax, T1/2
Safety Assessment	Blood pressure, routine laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

The pharmacokinetic parameters are shown in the following Table:

	Cmax (ng/ml)	Tmax (hr)	AUC(0-48) (ng•hr/ml)	AUC(0-∞) (ng•hr/ml)	T½ (hr)
200 mg dose					
Mean	1488		25661	26862	9.9
S.D.	253		5704	6658	2.4
C.V.(%)	17.0		22.2	24.8	24.6
Median (Range)	---	6(4-12)	---	---	---
N	16	16	16	16	15
400 mg dose					
Mean	2776		50433	52889	10.1
S.D.	566		11656	13247	2.8
C.V.(%)	20.4		23.1	25.0	27.8
Median (Range)	---	6(4-8)	---	---	---
N	16	16	16	14	14
800 mg dose					
Mean	4070		84656	89949	11.9
S.D.	738		17661	20380	3.5
C.V.(%)	18.1		20.9	22.7	29.8
Median (Range)	---	7(4-12)	---	---	---
N	16	16	16	16	15
1200 mg dose					
Mean	5502		110814	122232	11.5
S.D.	1131		26292	32498	2.3
C.V.(%)	20.6		23.7	26.6	19.9
Median (Range)	---	6(2-8)	---	---	---
N	16	16	16	14	14

Mean dose normalized (to 200 mg) pharmacokinetic parameters are listed in the following Table:

Dose		Cmax (ng/ml)	AUC(0-48) (ng•hr/ml)	AUC(0-∞) (ng•hr/ml)
200 mg	Mean	1488	25661	26862
	S.D.	253	5704	6658
	C.V.(%)	17.0	22.2	24.8
	Median (Range)	—	—	—
	N	16	16	16
400 mg	Mean	1388	25216	26445
	S.D.	283	5828	6623
	C.V.(%)	20.4	23.1	25.0
	Median (Range)	—	—	—
	N	16	16	14
800 mg	Mean	1017	21164	22487
	S.D.	184	4415	5095
	C.V.(%)	18.1	20.9	22.7
	Median (Range)	—	—	—
	N	16	16	16
1200 mg	Mean	917	18469	20372
	S.D.	189	4382	5416
	C.V.(%)	20.6	23.7	26.6
	Median (Range)	—	—	—
	N	16	16	14

The summary of statistical test for between-dose comparison of pharmacokinetic parameters is shown in the following Table:

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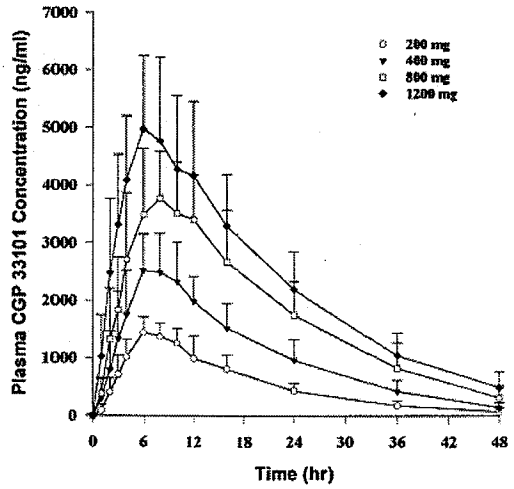
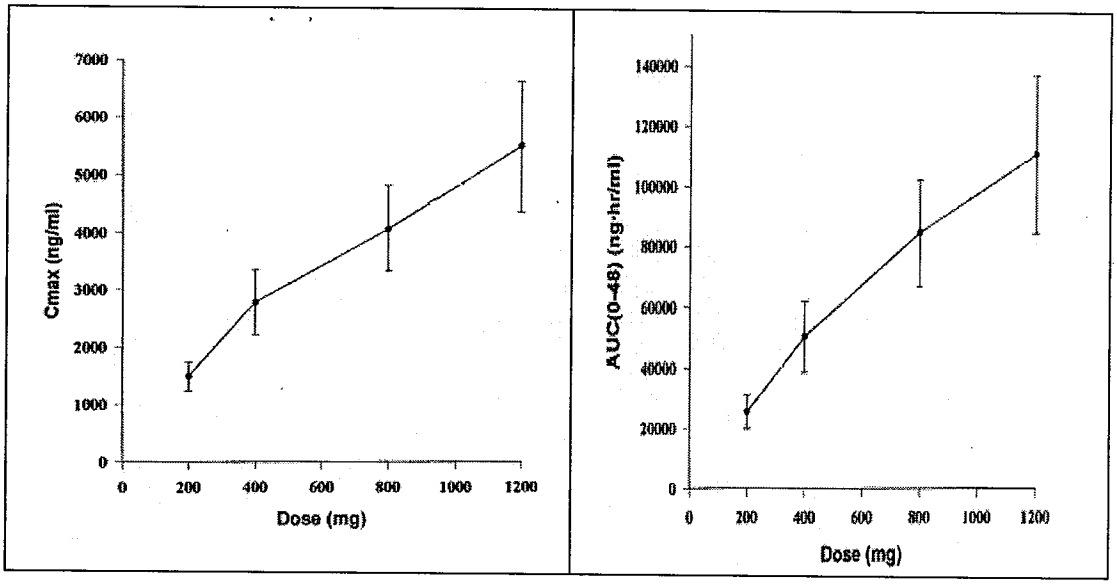
	90% Confidence Interval	ANOVA P-Value	Wilcoxon Signed-Rank Test P-Value
Cmax (normalized to 200-mg dose)			
400 mg vs. 200 mg	-13.6%, 1.6%	0.193	—
800 mg vs. 200 mg	-38.1%, -22.8%	< 0.001	—
1200 mg vs. 200 mg	-44.1%, -28.9%	< 0.001	—
AUC(0-48) (normalized to 200-mg dose)			
400 mg vs. 200 mg	-7.6%, 7.7%	0.993	—
800 mg vs. 200 mg	-23.4%, -8.0%	0.001	—
1200 mg vs. 200 mg	-35.0%, -19.6%	< 0.001	—
AUC(0-∞) (normalized to 200-mg does)			
400 mg vs. 200 mg	-9.8%, 6.4%	0.723	—
800 mg vs. 200 mg	-22.3%, -6.7%	0.003	—
1200 mg vs. 200 mg	-33.2%, -16.9%	< 0.001	—
T½			
400 mg vs. 200 mg	-16.4%, 7.8%	0.549	—
800 mg vs. 200 mg	-4.4%, 19.5%	0.295	—
1200 mg vs. 200 mg	-5.7%, 18.7%	0.372	—
Tmax			
400 mg vs. 200 mg	-14.5%, 19.8%	—	0.796
800 mg vs. 200 mg	-7.6%, 26.7%	—	0.353
1200 mg vs. 200 mg	-28.6%, 5.7%	—	0.267

The mean plasma concentration-time curve is shown in the following figure:



The mean Cmax and AUC0-48 are shown in the following figure showing a curvilinear relationship:



Conclusions:

- CGP 33101, after single oral doses of the drug administered as 200 mg tablets was not dose proportional in the dose range of 200-1200 mg in healthy subjects. There were less than dose proportional increases in Cmax and AUC values with increasing doses.
- There were no statistically significant differences in Tmax and T1/2 between the four dose groups, suggesting non-linearity is not due to disposition or the absorption rate, but likely due to extent of absorption.
- CGP 33101 has a low solubility in aqueous solution. The solubility of CGP 33101 in simulated intestinal fluid was 59 mg/L. Limited solubility of CGP 33101 in intestinal fluid could be the reason for the decreasing Cmax and AUC values at higher doses.

MULTIPLE DOSE STUDIES

Study Reprot t-15-1990: Pharmacokinetics of unchanged CGP 33101 in plasma after multiple oral doses in healthy volunteers

and

Study Report A202: Multiple dose study on tolerability, pharmacodynamics and pharmacokinetics of CGP 33 101 in healthy volunteers (100-400 mg

A brief overview of some essential components of the study design is given below:

Study Design	multiple-dose, double-blind, weekly rising doses, cross over
Study Population	N=6 healthy subjects Age: 26-43 years (mean 30 years) Gender: males Weight: 61-88 kg (mean 76 kg) Race: NA
Treatment Group	A: placebo for 28 days B: 200 mg SD: Day 0, followed by: 50 mg BID: Days 1-7 100 mg BID: Days 8-14 150 mg BID: Days 15-21 200 mg BID: Days: 22-27 200 mg SD: Day 28
Dosage and Administration	50 mg tablets Lot no: 14/477/1 100 mg tablets Lot no: 14/478/1 200 mg tablets Lot no: 14/479/1 Diet: Subjects fasted overnight for the first 200 mg dose. Two hours after dosing subjects received a standardized breakfast. Dosing taken with 200 ml water. For the rising dose part no special instruction in relation to meals was given.
Sampling: Blood	At 0, 0.5, 1, 1.5, 3, 4.5, 6, 9, 12, 24, 36 and 48 and 72 hours post-dose on day 28.
Urine	none
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation Plasma Rufinamide 48 ng/ml (200 nmol/L)

	Rufinamide (from analytical crb r66/1987 report) Intra-day Precision (%CV for Quality Controls) and accuracy : ≤ 4.4% 99-107% Inter-day Precision (%CV for Quality Controls) and accuracy : ≤ 11.3% 94-122%
PK Assessment	AUC0-72, AUC0-inf, Cmax, Tmax, T1/2, accumulation factor
Safety Assessment	Blood pressure, routine laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in plasma:

The pharmacokinetics parameters [mean(sd)] of rufinamide after the 200 mg dose are given in the following Table:

	C_{max} [µmol/L]	t_{max}[a] [h]	$AUC_{(0-\infty)}$ [µmol*h/L]	$t_{1/2}$ [h]	n
d0	4.2 ± 0.9	5.3	106.9 ± 33.7	10.9 ± 2.1	6
d28	11.3 ± 4.2	1.5	247.4 ± 144.1	10.8 ± 2.7	5

- The t1/2 did not change with multiple dosing.
- The mean AUC0-inf at steady state was two times higher than that after a single dose. The accumulation factor was 2.8±1.1 which is in accordance with the half-life of 11 hours.
- The mean morning plasma levels increased proportionally with the dose as seen in the following figure:

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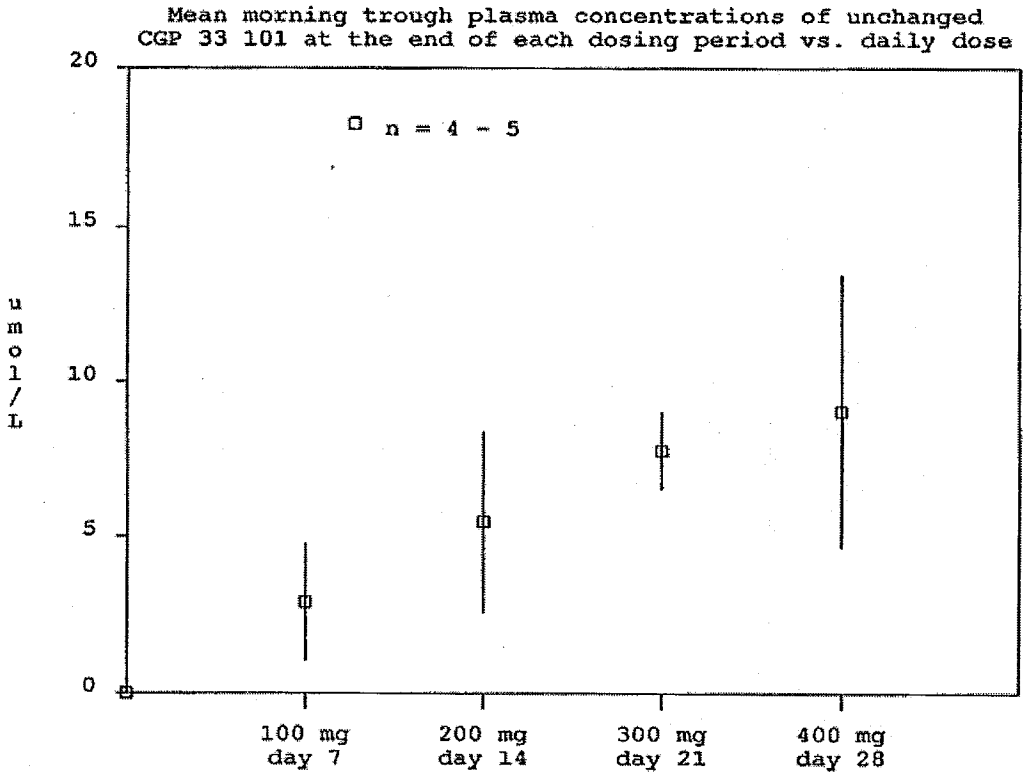

Safety:

Headache, dizziness, difficulties to concentrate and speak, lack of spontaneity, palpitations, nausea and watery bowel movements. No relation to frequency or intensity with dose level detected.

Conclusions:

Pharmacokinetics of rufinamide did not change upon multiple dosing. The accumulation (2.8 times) was in accordance with the half-life of the drug.

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Study Reprot 91077: Safety and Pharmacokinetics of repeated administration of CGP 33101 in healthy volunteers

A brief overview of some essential components of the study design is given below:

Study Design	multiple-dose
Study Population	N=6 healthy subjects Age: 21-27 years (mean 24 years) Gender: males Weight: 56.4-60.8 kg (mean 59.3 kg) Race: Japanese
Treatment Group	200 mg BID for 8 days A single dose of 200 mg was also administered after a meal. The repeat dose was started 48 hours after this dose, extending the total duration to 10 days
Dosage and Administration	200 mg tablets Lot no: 150/15/2 Diet: standardized breakfast provided on Days 1 and 10. Dosing taken with 200 ml water.
Sampling: Blood	Day 1: At 0, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 hours post-dose. Day 3: before morning dose Day 4-9: before and 6 h after morning dose Day 10: At 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96 hours after the last dose
Urine	Day 1: Before and during 0-24 hours after initial dose Day 2: During 24-48 hours after initial dose (immediately before morning dose on Day 3) Days 3 to 9: During 0 (after morning dose) to 24 hours (immediately before morning dose) Day 10: During 0-24, 24-48 , 48-72, 72-96 hours after final dose
Feces	none
Analysis	Method HPLC-UV Lower Limits of Quantitation and range Plasma / Urine CGP 33101: 25-1000 ng/mL / 50-2500 ng/mL CGP 47291: 50-500 ng/mL / 2-100 µg/mL CGP 47292: 50-1000 ng/mL / 2-200 µg/mL Cross-link to analytical validation report and QC % CVs not given with this report
PK Assessment	AUC0-72, AUC0-inf, Cmax, Tmax, T1/2, accumulation factor
Safety Assessment	Blood pressure, routine laboratory tests at baseline and 6, 12, 24 h post dose on Day 1; before and at 6, 12 h after morning dose on Days 3-10 and on mornings of Days 11-14 and adverse events ECGs on days 1,3, 5, 7, 9, and 10 before morning dose and on

	mornings of days 12 and 14
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in plasma:

Pharmacokinetic parameters after single and multiple dose administration is shown in the following Table:

Dose	Cmax (ng/ml)	Tmax (h)	AUC(0-48h) (ng.h/ml)	T1/2(24-48) (h)
200 mg SD	1957.5±131.2	5	34360.2±5859.7	8.9±1.2
200 mg BID for 8 days	3324.8±591.6	4	59342.9±15223.6	8.8±1.2

Both AUC(0-48 hr) and Cmax values following the final dose of the Repeat-Dose Administration increased to about 170% of the values following the Single Post-Meal Dose Administration, but the Tmax and T1/2(24-48 hr) values were similar.

Plasma CGP 33101 concentrations reached a steady state on day 2 following start of the Repeat-Dose Administration. The ratio of AUC(0-12hr) following the final dose of the Repeat-Dose Administration to AUC(0-∞) following the Single Post-Meal Dose Administration was 0.91, showing no unexpected accumulation after the 8-day Repeat-Dose Administration.

CGP 33101 Average plasma concentration profile after single post-meal dose administration and last repeat-dose administration of CGP 33101 is shown in the following figure:

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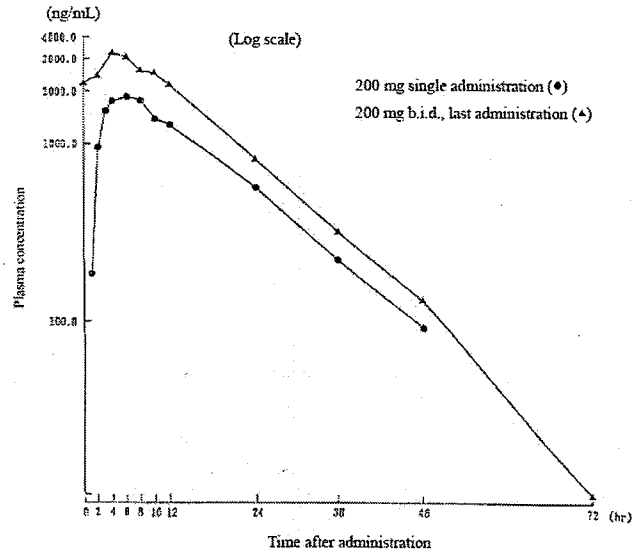

Metabolites in plasma:

At any post-dose time, average plasma CGP 47291 concentrations were below the lower limit of quantification.

Mean pharmacokinetic parameters of metabolite CGP 47292 are shown in the following Table:

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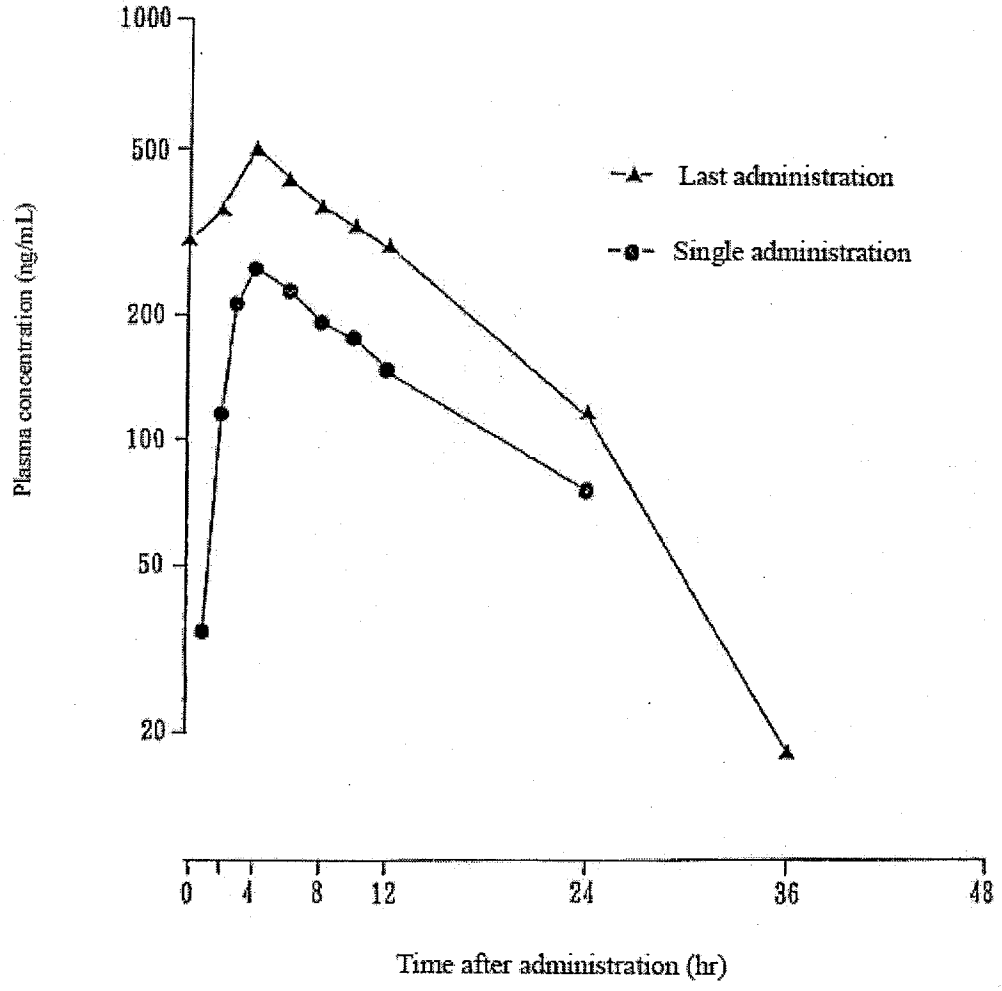
Table 29 Pharmacokinetic parameters of plasma CGP 47292 calculated from CGP 47292 after single post-meal dose administration (1) and final dose of repeat-dose administration (2) of CGP 33101

	Vol. No.	T_{max} (hr)	C_{max} (ng/mL)	AUC[1)] (ng·hr/mL)	$T_{1/2}$[2)] (hr)
(1) Single administration	21	4	267.1	4107.4	11.1
	22	4	198.8	3636.8	14.0
	23	4	283.8	4129.2	9.3
	24	4	220.4	3013.5	10.7
	25	4	275.4	3858.3	11.5
	26	4	331.9	4468.6	11.2
		4[3)]	262.9±47.5[4)]	3869.0±504.0[4)]	11.3±1.5[4)]
(2) Last administration	21	4	535.4	4823.8	10.5
	22	4	405.6	3754.7	10.0
	23	4	559.5	4553.6	9.0
	24	4	285.4	2842.4	-[5)]
	25	4	527.0	5049.8	14.9
	26	4	697.3	6138.1	8.5
		4[3)]	501.7±141.0[4)]	4527.1±1130.7[4)]	10.6±2.6[4)]
(2)/(1)	21			1.17	
	22			1.03	
	23			1.10	
	24			0.94	
	25			1.31	
	26			1.37	
				1.15±0.16[4)]	

1) (1): 0-48 hr, (2): 0-12 hr
2) 4-24 hr
3) median
4) mean±S.D.
5) not obtained

The accumulation factor estimated as the ratio of AUC(0-12hr) following final dose of the Repeat-Dose Administration to AUC(0-48hr) following the Single Post-Meal Dose Administration was 1.5 ± 0.16 (mean ± S.D.).

CGP 47 292 average plasma concentration profile after single post-meal dose administration and last repeat-dose administration of CGP 33101 is shown in the following figure:



Pharmacokinetic parameters under fasting (from previous study) and fed conditions (this study) from a 200 mg dose is given in the following Table:

Table 44 Pharmacokinetic parameters of plasma CGP 33101 after single fasting (1) and non-fasting (2) dose administration of CGP 33101 200 mg

Administration condition	T_{max} (hr)	$T_{1/2}$ (24-48 hr) (hr)	C_{max} (ng/mL)	AUC (0-48 hr) (ng·hr/mL)
(1) Fasting*	6	9.1 ± 0.8	1025.6 ± 164.0	22669.5 ± 3681.8
(2) Non-fasting	5	8.9 ± 1.2	1957.5 ± 131.2	34360.2 ± 5859.7
(2)/(1)			1.9	1.5

Each value represents the mean ± S.D. (n=6)
T_{max}: median

*: Chiba Geigy Japan, Report R.38/1991

Pharmacokinetics of rufinamide following single fasting administration and single post-meal administration of 200 mg investigational drug showed increased bioavailability following post-meal administration. The $AUC_{(0-48hr)}$ and C_{max} values following the Single Post-Meal Dose Administration increased to about 150% and 190%, respectively, of the corresponding values measured following the single fasting dose administration.
This seems to mean that absorption by the body of CGP 33101 is increased by the effects of a meal.

Pharmacokinetic parameters of plasma CGP 47292 calculated from CGP 47292 after fasting (1) and non-fasting (2) single dose administration of 200 mg CGP 33101

	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-48\,hr)}$ (ng·hr/mL)
(1) Fasting	7	143.8 ± 30.9	2550.5 ± 629.3
(2) Non-fasting	4	262.9 ± 47.5	3869.0 ± 504.0
(2)/(1)		1.83	1.52

Each value represents the mean ± S.D. (n=6)
T_{max}: median

With respect to plasma CGP 47292 concentrations following administration of single fasting and post-meal doses of 200 mg CGP 33101, Cmax and AUC(0-48hr) values following the post-meal dose administration showed increases to 183% and 152%, respectively, of the values measured following fasting dose administration.
The rate of increase in AUC by a meal effect was similar to the corresponding rate for the unchanged form.

Rufinamide in urine:

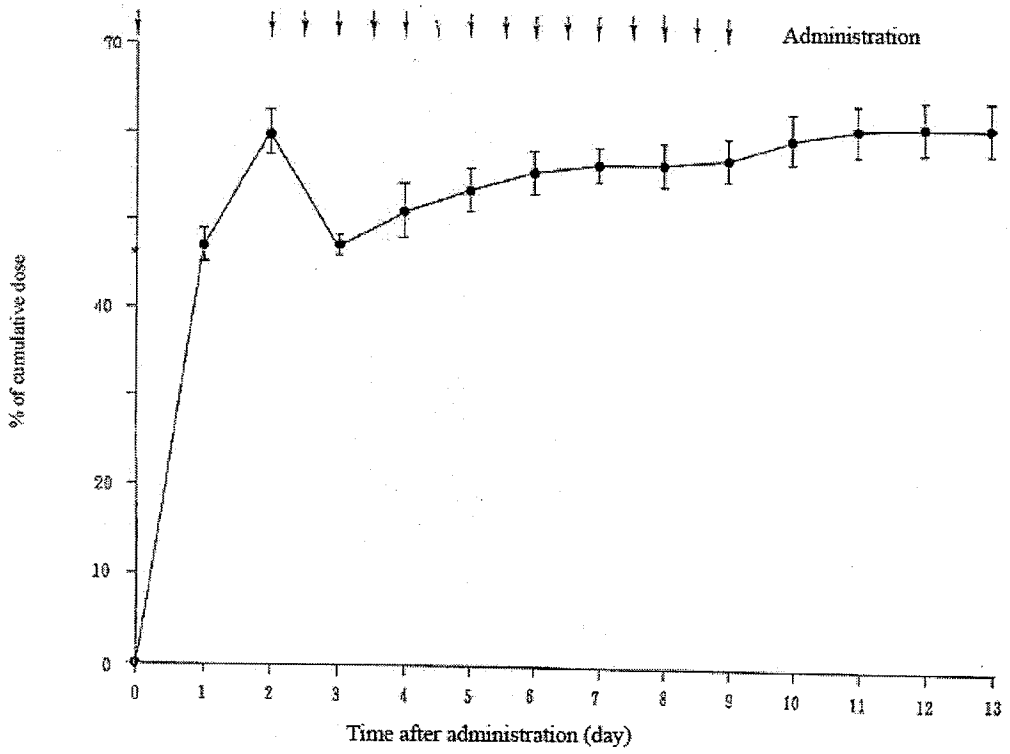
The cumulative urinary CGP 33101 excretion rate following the single post-dose administration up to 96 hours following completion of the Repeat-Dose Administration was 1.03 ± 0.11%.

Metabolites in Urine:

No peak was observed for CGP 47291 in any urine samples following the Single Post-Meal Dose and the Repeat-Dose Administrations of 200 mg CGP 33101.

Cumulative urinary CGP 47292 excretion rates following start of the Single Post-Meal Dose Administration up to 48 and 96 hours following completion of the Repeat-Dose Administration were 60.6 ± 2.9% and 60.8 ± 2.9%, respectively.

Cumulative urinary CGP 47292 excretion rates for respective doses of single post-meal dose administration and during repeat-dose administration of CGP33101 (Mean ± Standard Deviation, n=6) is shown in the following figure:



Conclusions:

- With respect to CGP 33101 in plasma, although AUC(0-48hr) and Cmax values following multiple dose increased to about 170% of corresponding values following the single post-meal dose administration, the Tmax and T1/2(24-48hr) values were similar. No unexpected accumulation was observed.
  Plasma CGP 33101 concentrations reached a steady state on day 2 following start of the repeat-dose administration.
  Bioavailability is increased in the presence of food.
- With respect to metabolites found in plasma (CGP 47291 and CGP 47292), the principal metabolite was CGP 47292, and CGP 47291 was almost always at concentrations below the lower limit of quantification. With respect to plasma CGP 47292 concentrations, no significant accumulation was found following the Repeat-Dose Administration, and the rate of increase in AUC by a meal effect was similar to the corresponding rate for the unchanged form.
- With respect to CGP 33101 in urine, an increase in cumulative excretion rate was seen following the single post-meal administration compared to following the single fasting dose administration, which seems to have resulted from increased bioavailability caused by meal. Cumulative urinary CGP 33101 excretion rates during the first 48 hours following the Single Post-Meal Dose Administration and during the first 96 hours following final dose of the Repeat-Dose Administration were both about 1% of the administered dose, which seems to mean that repeat-dose administration has no effect on urinary excretion rate of the unchanged drug.

- With respect to metabolites possibly found in urine (CGP 47291 and CGP 47292), CGP 47292 was found as a metabolite while CGP 47291 was not detected. The cumulative urinary CGP 47292 excretion rates at 48 hours following the Single Post-Meal Dose Administration and at 96 hours following the Repeat-Dose Administration were both about 60% of the administered dose.

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Study Report cct-90-026 or AE/MD2: Double blind, crossover, placebo-controlled, weekly rising dose, multiple application study on tolerability and Pharmacokinetics in healthy volunteers

and

Study Report crb-r-40-1992: Urinary excretion of CGP 33 101 and 2 metabolites, CGP 47 292 and CGP 47 291, in healthy volunteers following repeated BID application of weekly rising doses (300, 600, 900, 1200 mg/day)

and

Study Report crb r24/1991: Plasma kinetics of unchanged CGP33101 in healthy volunteers following BID application of rising doses (300, 600, 900, 1200 mg/day)

A brief overview of some essential components of the study design is given below:

Study Design	multiple-dose, double-blind, crossover
Study Population	N=18 healthy subjects, out of these 2 received single dose only Age: 18-45 years Gender: males Weight: 55-102 kg Race: Japanese
Treatment Group	A: 600 mg SD in the morning for at least 4 days prior to MD B: Weekly rising doses (300, 600, 900, 1200 mg/d given in divided BID doses) for 7 days each, except for last day of last week Week 1: 150 mg BID Week 2: 300 mg BID Week 3: 450 mg BID Week 4: 600 mg BID There were two multiple dose series (crossover placebo or drug) with a 7 day wash out between the two series (drug and placebo treatment) C: last day 28: 600 mg SD for both dose series
Dosage and Administration	200 mg tablets Lot no: 14/479/1 100 mg tablets Lot no: 14/478/1 50 mg tablets Lot no: 14/477/1 Diet: The single and last dose were taken under fasting conditions. 4 hrs after these doses a light lunch was given. Dosing taken with 100 ml water. During the multiple dose regimen, the morning dose was taken before breakfast.
Sampling: Blood	Day 0-3 and 28-30: At 0, 0.5, 1, 1.5 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose. Days 6, 7, 8, 13,14, 15, 20, 21, 22, 26, 27, 28: before morning dose

Urine	Day 1 and 28: During 0-6, 6-12, 12-24, 24-48 , 48-72, hours after dose
Feces	none
Analysis	Method (report crb r6-1993 for urine, crb r66-1987 in plasma) HPLC-UV Lower Limits of Quantitation Plasma / Urine CGP 33101: 0.105 µmol/L(25ng/ml) / 11 µmol/L CGP 47291: 25 µmol/L CGP 47292: 25 µmol/L Cross-link to analytical validation report and QC % CVs not given with this report
PK Assessment	AUC0-72, AUC0-inf, Cmax, Tmax, T1/2, accumulation factor
Safety Assessment	Blood pressure, routine laboratory tests, ECGs
PD Assessment	None

Pharmacokinetic Results:

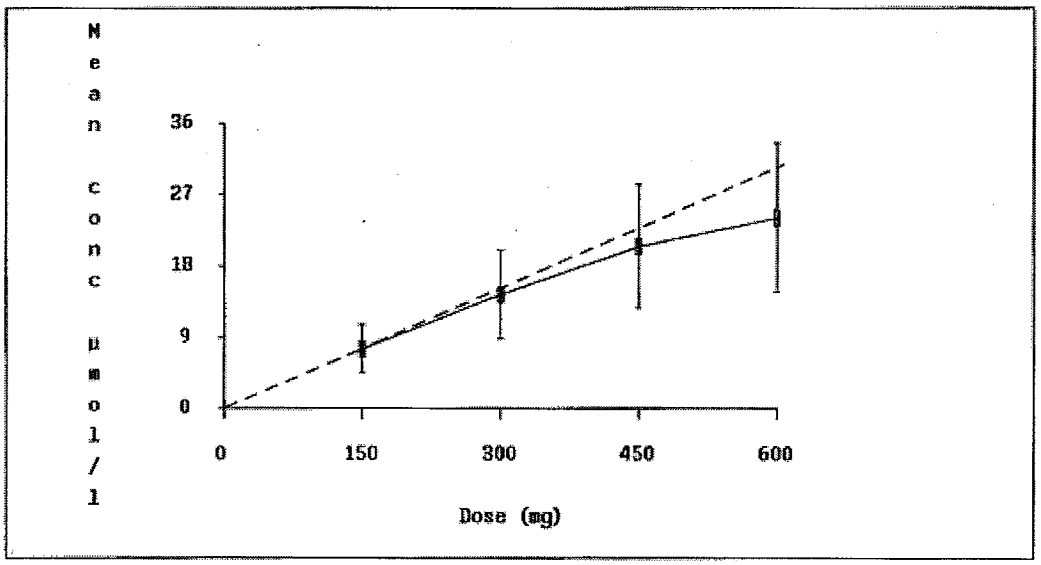
Rufinamide in Plasma:

The mean pharmacokinetic parameters after the 600 mg single and multiple dose is given in the following Table:

DOSE	Cmax (µmol/l)	Median Tmax (h)	AUC(0-72 h) (µmol.h/l)	T1/2 (h)
SINGLE DOSE	8.7* ± 2.6	8	257* ± 94	11 ± 2
LAST DOSE	28* ± 10	2	582* ± 275	11 ± 2

* : n = 14 (several doses were not taken by two subjects).

- The AUC after single and repeat dosing were determined to be not statistically different.
- The cmax at steady state was 2-5 times higher than that obtained after single dose.
- The mean accumulation factor was 3.2 ± 0.9 (based on calculation of AUC0-12)
- The trough plasma concentrations during the weekly rising phase showed high intra-individual variability for several subjects and decreased with the higher doses (450 and 600 mg) as shown in the figure below, suggesting saturation of absorption.



Rufinamide in Urine:

Only trace amounts of rufinamide were found in the urine after single dosing, corresponding to recovery less than 1% of dose over 24 hours. This suggests that rufinamide was extensively metabolized. For the multiple dosing the data could not be analyzed due to some interference.

Metabolites in Urine:

Metabolite CGP 47 291 was not detected.

The mean t1/2 determined from urinary data for CGP 47 292 after single dose was 12±3 h, and similar to that found from plasma data. The t1/2 of this metabolite was not modified upon repeated administration.

The mean±SD renal excretion of this metabolite was 40±7% of the dose over 72 hours after single dose and was 48±7% over 12 hour on Day 28. The sponsor speculates that this increase after multiple doses could be due the food taken on the rest of the days, because food is known to increase the bioavailability of unchanged rufinamide by 40%. After correction for this effect and normalizing poor renal excretion up to 12 hours, the sponsor estimates the renal excretion of multiple dose to be 38.2% of the dose and suggests that the kinetics of CGP 47 292 is not modified upon repeat dosing.

Study Report MTD or E2080-A001-001: A Double blind, crossover, placebo-controlled, multiple dose study to evaluate safety, tolerability and Pharmacokinetics in healthy subjects

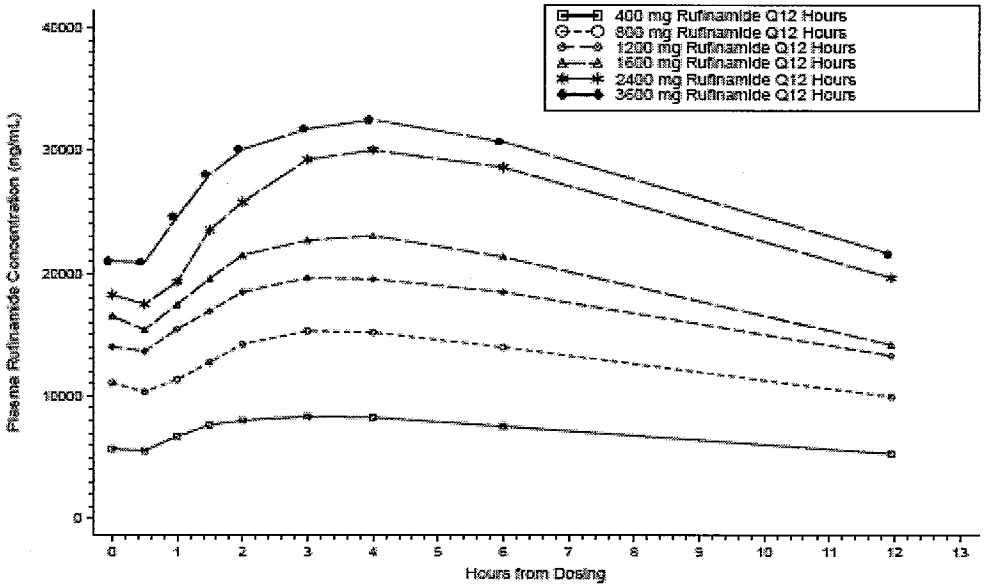
The first aim of this study was to determine the maximum tolerated dose of rufinamide and secondly to evaluate the pharmacokinetics of rufinamide after multiple ascending doses. A brief overview of some essential components of the study design is given below:

Study Design	multiple-dose, double-blind, crossover
Study Population	N=20 healthy subjects, out of these 15 received stepwise escalating doses of rufinamide and 5 received placebo Age: 18-44 years (mean 29.1 years) Gender: 10 M & 10 F (mean 70.5 kg) Weight: 55.3-92.8 kg Race: 3 White, 10 Black and 7 Hispanic
Treatment Group	A: 15 subjects on drug B: 5 subjects on placebo Days 1-3: 400 mg BID (800 mg/day) Days 4-6: 800 mg BID (1600 mg/day) Days 7-9: 1200 mg BID (2400 mf/day) Days 10-12: 1600 mg BID (3200 mg/day) Days 13-15: 2400 mg BID (4800 mg/day) Days 16-18: 3600 mg BID (7200 mg/day)
Dosage and Administration	400 mg tablets FMI: Lot no: X1840900 Diet: Doses taken 15 minutes after consumption of a standardized breakfast
Sampling: Blood	PK was done at each dose level after 3 days of dosing Days 3, 6, 9, 12, 15 and 18: At 0, 0.5, 1, 1.5, 2, 3, 4, 6, 12 hours post-dose.
Urine	none
Feces	none
Analysis	Method HPLC-MS/MS Linear Range: 20-20000 ng/ml Lower Limits of Quantitation Plasma / Urine Rufinamide 20 ng/ml Intra-day precision and accuracy: % CV <1.9%, 95.4-99.4% Inter-day precision and accuracy: % CV <5.1%, 99.6-101.9%
PK Assessment	AUC0-12, Cmax, Cmin, Tmax
Safety Assessment	Blood pressure, routine laboratory tests, ECGs, vital signs, adverse events
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in Plasma:

Mean plasma concentration time plot for each dose is shown in the following figure:



Geometric mean pharmacokinetic parameters at each dose level is given in the following Table:

	Cmaxss (ng/mL)		Cminss (ng/mL)		tmax (hr)		AUC(0-12) (ng*hr/mL)	
Dose Level	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI
Dose Level 1	8761.113	(7800.471,9840.060)	4960.877	(4148.210,5932.750)	3.01	(2.44,3.71)	82400	(71500,95000)
Dose Level 2	15133.434	(13194.237,17357.641)	9380.079	(7881.182,11164.047)	3.50	(3.10,3.95)	148000	(127000,172000)
Dose Level 3	19750.439	(17005.179,22938.885)	12142.785	(10016.334,14720.679)	3.78	(3.09,4.63)	193000	(164000,228000)
Dose Level 4	22519.104	(18826.523,26935.938)	13400.937	(11271.987,15931.985)	3.57	(3.21,3.98)	223000	(188000,265000)
Dose Level 5	30014.830	(27673.192,32554.611)	16382.730	(13533.562,19831.721)	3.78	(3.10,4.61)	294000	(257000,336000)
Dose Level 6	32750.632	(29963.786,35796.674)	18878.277	(15425.636,23103.705)	3.82	(3.03,4.82)	325000	(286000,369000)

Dose Level 1 = 400 mg Rufinamide Q12 Hours
Dose Level 2 = 800 mg Rufinamide Q12 Hours
Dose Level 3 = 1200 mg Rufinamide Q12 Hours
Dose Level 4 = 1600 mg Rufinamide Q12 Hours
Dose Level 5 = 2400 mg Rufinamide Q12 Hours
Dose Level 6 = 3600 mg Rufinamide Q12 Hours

- Less than proportional increases in rufinamide peak concentrations (C_{maxss}) and exposure [$AUC_{(0-12)}$] were observed with increasing rufinamide dose.
- Mean rufinamide concentrations and C_{maxss}, C_{minss}, and $AUC_{(0-12)}$ parameter values increased with increasing rufinamide dose.
- Median rufinamide tmax was comparable between the rufinamide dose levels.

Dose proportionality assessment following 800-3600 mg oral doses of rufinamide is given in the following Table:

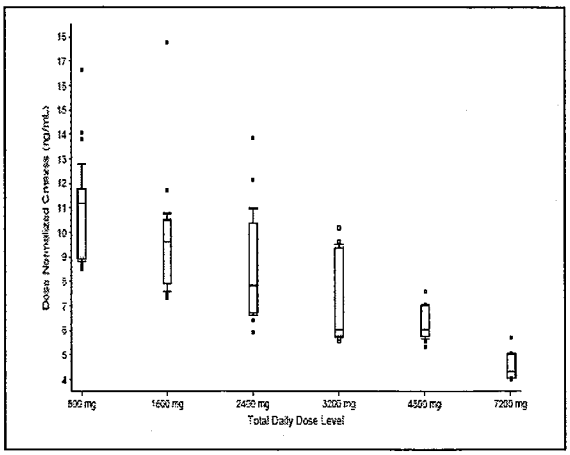
Pharmacokinetic Parameter	Intercept	Slope	95% CI for Slope	P-Value for Slope=0
AUC(0-12)	6.8792	-0.3251	(-0.3617,-0.2884)	<.0001
Cmaxss	4.7826	-0.3484	(-0.3860,-0.3108)	<.0001

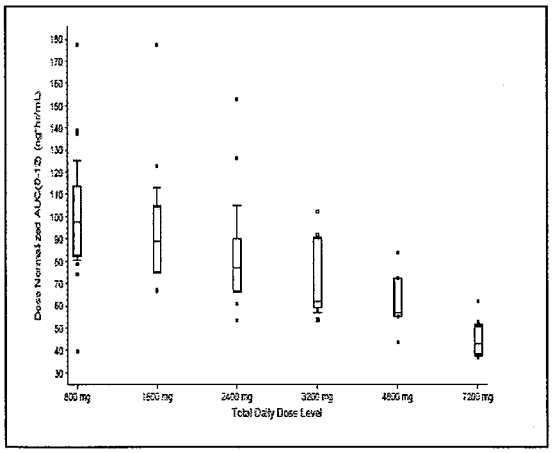
The statistical analyses were performed using the SAS Mixed Procedure.
A linear regression model with ln-transformed dose normalized parameter and ln-transformed dose was used.
Dose proportionality was not rejected if the 95% CI for the slope includes the value of 0.

The geometric mean Cmaxss and AUC(0-12) values showed dose related increases between dose levels, and the percent differences for each parameter (divided by dose) were similar between dose levels. The % differences between dose levels were 13.7%, 12.7%, 14.5%, 11.3%, and 27.2% for Cmax (ratios of 1.7, 2.3, 2.6, 3.4, and 3.7), while the % differences between dose levels were 10.2%, 13.1%, 13.3%, 12.1%, and 26.3% for AUC(0-12) (ratios of 1.8, 2.3, 2.7, 3.6, and 3.9).

However, the statistical results from the dose proportionality assessment indicate that exposure to rufinamide did not increase proportionately as the doses increased. The 95% CI for the comparison of the dose-normalized ln-transformed Cmaxss and AUC(0-12) did not include the value of 0 as indicated for the conclusion of dose proportionality. In addition, the slopes of the lines for these parameters were below the value of 0 with the differences being statistically significant (p-values < 0.05).

Box plots showing the dose normalized Cmax and AUC versus dose at each dose levels are given in the following figures:





Population PK modeling of the data demonstrated the following:

- The rate of absorption was slow: Ka= 0.21 h^{-1} and rate limiting. The half-life of absorption was 3.4 h.
- The half-life of elimination was 6.0 h and the rate constant of elimination was 0.12 h^{-1}.
- The maximum decrease in bioavailability (Emax) was –1.18 and the total daily dose at half maximum (D_{50}) was 101 mg/kg.
- The apparent clearance varied with body surface area (BSA): in a typical subject with population median BSA (1.79 m^2), CL/F at 800 mg/d was 4.41 L/h. Likewise, at doses of 3200mg/day and 7200 mg/day CL/F was 6.12 and 9.47 L/h, respectively.
- The apparent volume of distribution was 38.0 L, 52.7 L and 81.6 L at 800 mg/day, 3200 mg/day, and 7200 mg/day, respectively.

Adverse Events:

The percentage of subjects experiencing AEs was similar for the active (67%) and placebo (60%) treatment groups. Overall, the percentage of subjects reporting AEs did not increase with rufinamide dose level. Of the 44 AEs experienced, 37 were mild in severity and 7 were moderate.
Headache was the most common AE in the active treatments (8 of 15 subjects, 53%) and placebo treatment, (2 of 5 subjects, 40%).
Other side effects were dizziness, upper abdominal pain, decreased appetite, visual disturbance etc.

Mean ECG parameters (PR, QRS, QT, QTc, and heart rate) remained within normal limits at all assessed time points for active and placebo treated subjects following drug administration. There were no mean QTc increases from baseline ≥ 30 msec. On the contrary, it was associated with a small increase in heart rate and small decrease in QTcSS, as determined by population PK/PD modeling. For each 1 μg/mL, the rufinamide effect on QTcSS was to cause a decrease of 0.5 ms, which equates to a decrease of 7.5 ms at a typical concentration in patients (15 μg/mL).

Conclusions:

- Mean rufinamide concentrations and C_{maxss}, C_{minss}, and $AUC_{(0-12)}$ parameter values increased with increasing rufinamide dose; however, C_{maxss} and exposure [$AUC_{(0-12)}$] were less than proportional due to absorption limitations.
- Rufinamide did not appear to cause prolongation of the QTc interval, on the contrary, it was associated with a small increase in heart rate and small decrease in QTcSS, as determined by population PK/PD modeling.