

PATIENT PHARMACOKINETICS

Study cpd 92064(AE/PT1): Plasma concentrations of CGP 33101 in Epileptic Patients and Healthy Subjects after Ascending Single Oral Dosing with 400-1200 mg of the Drug

And

Study crb-r16-1993: Excretion of CGP 33101 and its main metabolite CGP 47292 in Epileptic Patients and Healthy Subjects after Ascending Single Oral Dosing with 400-1200 mg of the Drug

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

Study Design	Randomized, single-dose, placebo controlled, parallel group									
Study Population	N=16 patients (12 on drug and 4 on placebo) and N=3 healthy subjects <u>Age:</u> 18-50 years (mean 33.5 years) of patients 20-38 years (mean 31.7 years) of healthy <u>Gender:</u> males <u>Weight:</u> 57-101 kg (mean 84 kg) of patients; 83-102 kg (mean 85.2 kg) of healthy <u>Race:</u> 18 White, 1 Black									
Treatment Group	Single group									
Dosage and Administration	Doses evaluated were 400, 800 and 1200 mg and placebo given in random order. A 5 day washout between doses. All patients were on stabilized doses of other anticonvulsants Lot no: 200 mg tablet E14495; H3371, H3372 <u>Diet:</u> Doses administered after 12 hour fast, breakfast given 1 hour after drug intake.									
Sampling: Blood	At pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96 (for 400 mg dose) and 120 (only for 800 and 1200 mg doses) hours post-dose.									
Urine	At 0-24, 24-48, 48-72, 72-96, 96-120 hours post dose									
Feces	none									
Analysis	<u>Method (from analytical report 91046 and crb-r6-1993)</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table style="width: 100%; border: none;"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> <td style="text-align: center;"><u>Urine</u></td> </tr> <tr> <td>Rufinamide</td> <td style="text-align: center;">50 ng/ml</td> <td style="text-align: center;">2.5 µg/ml</td> </tr> <tr> <td>CGP 47292</td> <td></td> <td style="text-align: center;">5 µg/ml</td> </tr> </table> <u>Rufinamide in plasma</u>		<u>Plasma</u>	<u>Urine</u>	Rufinamide	50 ng/ml	2.5 µg/ml	CGP 47292		5 µg/ml
	<u>Plasma</u>	<u>Urine</u>								
Rufinamide	50 ng/ml	2.5 µg/ml								
CGP 47292		5 µg/ml								

	Linear range : 50-4000 ng/ml Intra-day Precision (%CV for Quality Controls) : ≤ 11.3% Inter-day Precision (%CV for Quality Controls) : ≤ 7.7% <u>CGP 47,292 in urine:</u> Intra-day Precision (%CV for Quality Controls) : ≤ 5% Inter-day Precision (%CV for Quality Controls) : ≤ 16%
PK Assessment	AUC0-t, Cmax, Tmax, T1/2
Safety Assessment	none
PD Assessment	None

Pharmacokinetic Results:

Rufinamide in plasma:

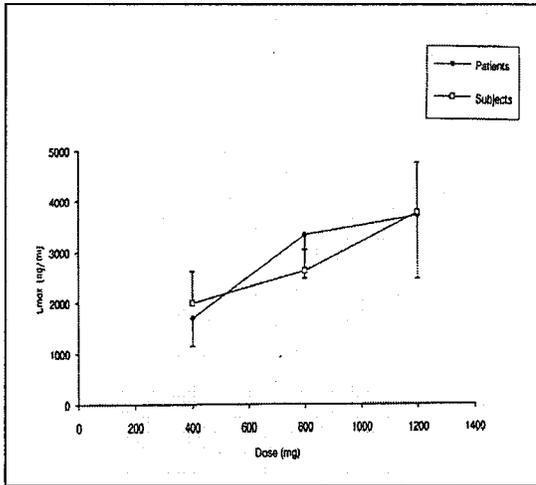
The mean plasma concentrations in healthy subjects and patients were similar. The mean plasma concentrations were below the limit of quantitation in all subjects by 72 hours. The Cmax and AUC increased roughly dose proportionally with the increase in doses. The relationship between Cmax and AUC and the administered doses did not change for patients or healthy subjects when corrections were made for dose and body weight. The half-life was somewhat higher in healthy subjects. Subject 511 was excluded from the analysis as his plasma levels were 2-8 times the levels of other subjects. Reason for this could not be determined.

The mean pharmacokinetic parameters are summarized in the following Table:

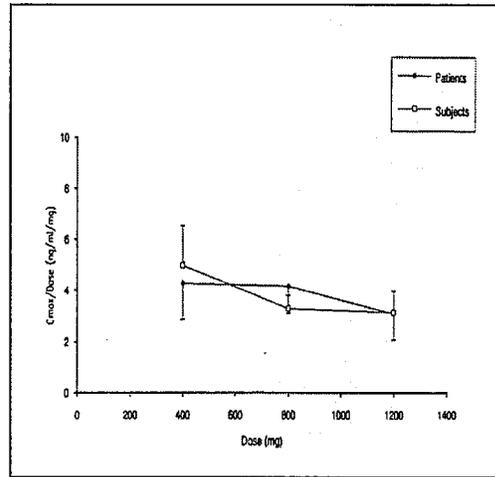
Mean* CGP 33101 Pharmacokinetic Parameters					
	Dose (mg)	Tmax (hr)	Cmax (ng/ml)	AUC (0-120) (ng · hr/ml)	T½ (hr)
Patients (N=10-11)	400	5.3	1700	26453	6.7
	800	4.7	3323	55254	6.9
	1200	3.7	3701	72373	8.7
Subjects (N=3)	400	5.3	1988	43145	10.8
	800	6.0	2618	61042	9.0
	1200	4.0	3756	90176	9.0

* Patient 511 excluded from calculations because he was an outlier.

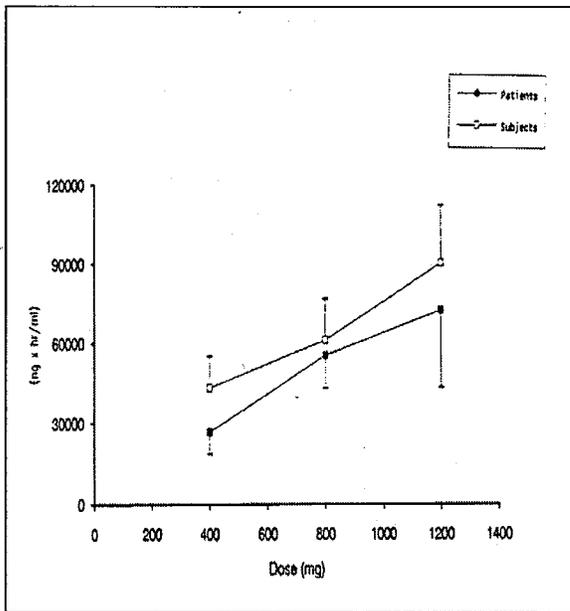
The mean C_{max} and AUC and dose corrected C_{max} and AUC at the various doses in patients and healthy subjects is shown in the following figure:



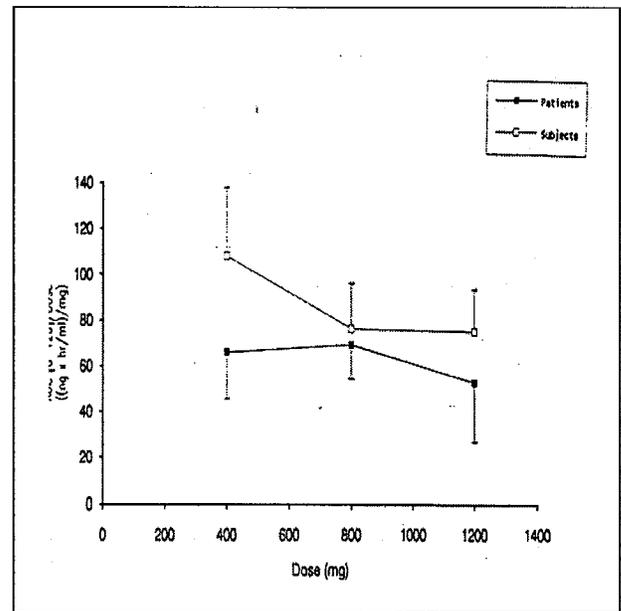
C_{max} vs dose



Dose corrected C_{max} vs dose



AUC vs dose



Dose corrected AUC vs dose

Rufinamide and Metabolites in Urine:

Unchanged rufinamide was not detected in the urine of 3 healthy subjects and 4 patients. Traces were found in two patients. Interference prevented from determining it from other patients.

The mean (SD) urinary excretion of CGP 47292 (% of dose) over 120 hours is shown 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.

The urinary excretion was similar in patients and healthy volunteers. There was no influence of the dose of the drug on the excretion of the major metabolite CGP 47292.

Conclusions:

- The relationship of AUC and Cmax with the increase of dose was not different between patients and healthy subjects.
- Tmax was also similar between patients and healthy subjects
- Half-life was shorter in patients as compared to healthy subjects was independent of dose
- The urinary excretion was similar in patients and healthy volunteers.

Therefore, pharmacokinetics of rufinamide were in general similar between patients and healthy subjects.

Reviewer's Comment:

In this study Cmax and AUC increased in a somewhat dose proportional manner in both patients and healthy subjects, although difficult to conclude without statistical evaluations. This was not observed in most other studies conducted.

INTRINSIC FACTORS

Study 031: A pharmacokinetic evaluation of rufinamide in an elderly subject population

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

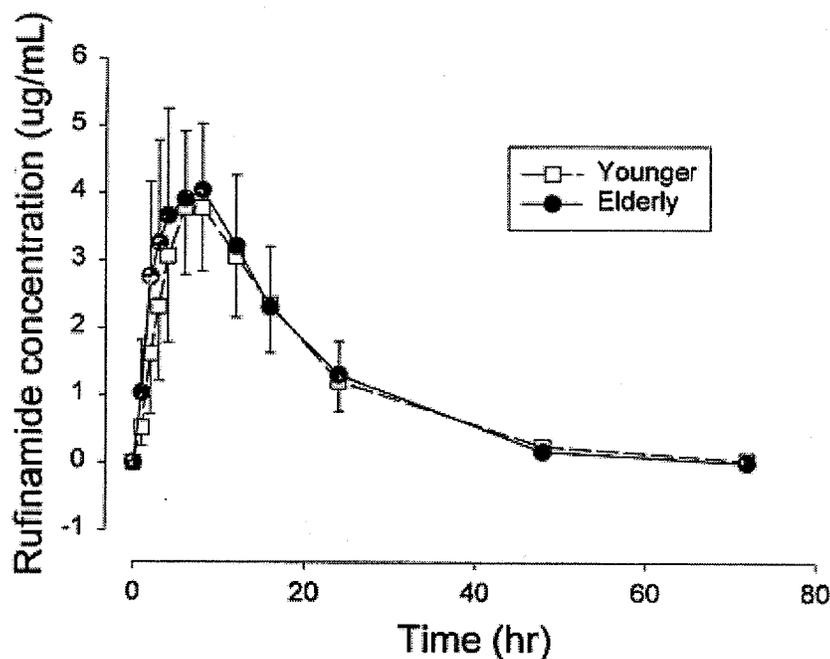
Study Design	single and multiple doses, open label, parallel group									
Study Population	N=15 healthy subjects (8 healthy elderly and 7 healthy younger subjects); 14 completed the study <u>Age:</u> 65-80 years (mean 72.9 years) of elderly; 18-45 years (mean 32.7 years) of young subjects <u>Gender:</u> 7 young (4M & 3F), 8 elderly (4M & 4F) <u>Weight:</u> 61-92 kg (mean 77.6 kg) of elderly; 64-92 kg (mean 79.9 kg) of young <u>Race:</u> 13 White, 1 Other									
Treatment Group	Young and elderly									
Dosage and Administration	Single dose 400 mg on Day 1 Multiple dose 400 mg BID (800 mg/day) on Days 4-7 Single dose 400 mg on Day 8 Doses given with 240 ml water. Lot no: 200 mg tablet E-15764, H-3982 <u>Diet:</u> Doses administered after 12 hour fast, lunch given 4 hours after drug intake. No fruit juices, caffeine or alcohol was allowed									
Sampling: Blood	Days 1, 5-7 and 8: At pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 hours post-dose.									
Urine	At 0-2, 2-4, 4-8, 8-16, 16-24, 24-32, 32-40, 40-48, 48-60, 60-72 hours post dose									
Feces	none									
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table style="width: 100%; border: none;"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> <td style="text-align: center;"><u>Urine</u></td> </tr> <tr> <td>Rufinamide</td> <td style="text-align: center;">50 ng/ml</td> <td></td> </tr> <tr> <td>CGP 47292</td> <td style="text-align: center;">2.5 µg/ml</td> <td style="text-align: center;">5 µg/ml</td> </tr> </table> Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 50-4000 ng/ml for rufinamide in plasma 2.5-200 µg/ml for rufinamide in urine 5-200 µg/ml for CGP 47 292 in urine <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.5%		<u>Plasma</u>	<u>Urine</u>	Rufinamide	50 ng/ml		CGP 47292	2.5 µg/ml	5 µg/ml
	<u>Plasma</u>	<u>Urine</u>								
Rufinamide	50 ng/ml									
CGP 47292	2.5 µg/ml	5 µg/ml								

	<p>Inter-day accuracy: 93.7-100.2%</p> <p><u>Rufinamide in urine:</u> Inter-day Precision (%CV for Quality Controls) : $\leq 10.6\%$ Inter-day accuracy: 96.2-108.2%</p> <p><u>CGP 47 292:</u> Inter-day Precision (%CV for Quality Controls) : $\leq 10.7\%$ Inter-day accuracy: 99-106.8%</p>
PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , C _{min} , T _{max} , T _{1/2} , total amount of metabolite excreted.
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

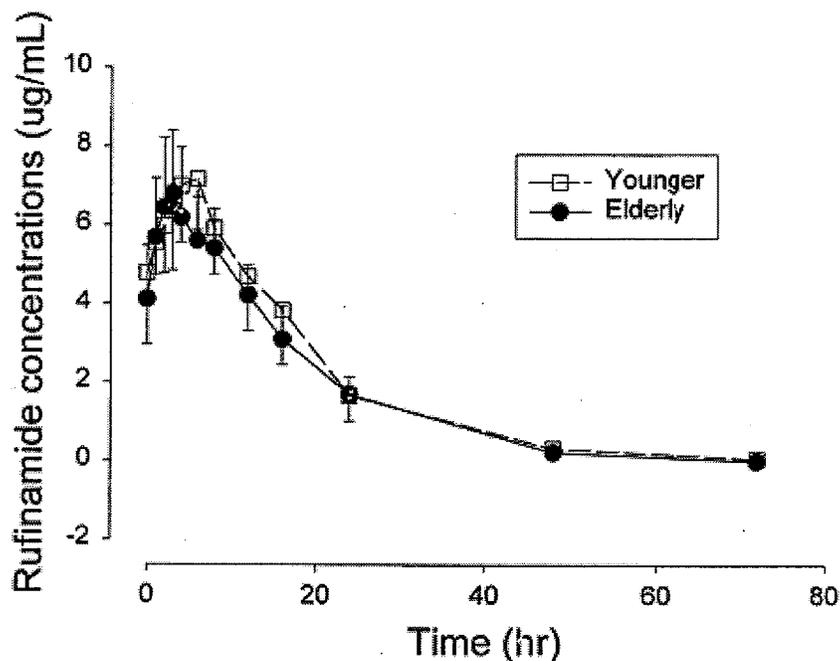
Pharmacokinetic Results:

Rufinamide in plasma:

Mean concentration time profile after single oral dose of 400 mg rufinamide is shown in the following figure:



Mean concentration time profile after multiple oral dose of 400 mg rufinamide is shown in the following figure:



Pharmacokinetic parameters after single (8 elderly and 7 young) and multiple dose (7 elderly and young each) in the elderly and young population is given in the following Tables:

After single dose:

	C_{max} ($\mu\text{g}/\text{mL}$)	t_{max} (median) (hr)	$AUC_{(0-12)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$AUC_{(0-last)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$AUC_{(0-\infty)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$t_{1/2}$ (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} ($\mu\text{g}/\text{mL}$)	t_{max} (median) (hr)	$AUC_{(0-12)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$AUC_{(0-last)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$AUC_{(0-\infty)}$ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	$t_{1/2}$ (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

Trough plasma concentrations did not rise from Day 6 to Day 8, confirming attainment of steady state as shown in the following Table:

C_{min} ($\mu\text{g/mL}$)	Day 5	Day 6	Day 7	Day 8, a.m.	Day 8, p.m.
Elderly	3.7 \pm 0.4*	4.5 \pm 1.0*	4.7 \pm 1.7	4.1 \pm 1.4	4.2 \pm 0.8
Young	4.0 \pm 0.7	5.0 \pm 1.1	5.0 \pm 1.6	4.8 \pm 1.8	4.7 \pm 1.4

*N=8; data included Subject 011 who dropped out after day 6.

These tables show that the pharmacokinetics (rate and extent of absorption) were not different between the elderly and the young population.

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
AUC _{0-inf}	single	0.7721	1.04	0.83-1.29
	multiple	0.4913	0.91	0.72-1.15
C _{max}	single	0.5274	1.07	0.89-1.28
	multiple	0.8811	1.02	0.85-1.21
T _{1/2}	single	0.0746	0.80	0.58-0.98
	multiple	0.0698	0.83	0.64-0.98

Drug accumulation ratio was examined by comparison of multiple dose versus single dose values of AUC₀₋₁₂. The estimated accumulation ratio and its 90% CI for the elderly were 1.79 (1.49, 2.16) respectively. The corresponding accumulation ratio and its 90% CI for the young were 2.13 (1.77, 2.56) respectively. These were not significantly different from each other.

There were no significant differences in C_{min} values either.

Rufinamide and CGP 47 292 in urine:

Urinary excretion (0-72 hours) after single and multiple doses is given in the following Tables:

After single dose:

	Rufinamide (mg)	CGP 47292 (mg)	% of dose in urine		
			Rufinamide	CGP 47292*	Rufinamide + CGP 47292*
Elderly	6.3 \pm 2.2	232.4 \pm 57.5	1.6 \pm 0.6	57.9 \pm 14.3	59.5 \pm 14.6
Young	6.6 \pm 5.9	247.6 \pm 52.4	1.7 \pm 1.5	61.6 \pm 13.0	63.3 \pm 12.2

* % rufinamide equivalent = [% of rufinamide equivalent excreted as CGP 47292/dose]

After multiple doses:

At 0-12 hours

	Rufinamide (mg)	CGP 47292 (mg)	% of dose in urine		
			Rufinamide	CGP 47292*	Rufinamide + CGP 47292*
Elderly	6.2±2.2	262.6±41.7	1.5±0.6	65.4±10.4	66.9±10.7
Young	8.1±4.8	227.8±54.1	2.0±1.2	56.7±13.5	58.7±13.7

* % rufinamide equivalent = [% of rufinamide equivalent excreted as CGP 47292/dose]

At 0-72 hours:

	Rufinamide (mg)	CGP 47292 (mg)	% of dose in urine		
			Rufinamide	CGP 47292*	Rufinamide + CGP 47292*
Elderly	8.1±3.6	513.7±103.5	2.0±0.9	127.9±25.8	129.9±25.8
Young	13.7±14.5	518.4±123.2	3.4±3.6	129.1±30.7	132.5±33.1

* % Rufinamide equivalent = [% of rufinamide equivalent excreted as CGP 47292/dose]

These tables show that the urinary excretion was similar between the elderly and the young.

Rufinamide was extensively metabolized with less than 2% of the dose being recovered unchanged in urine after single dose between the dosing interval 0-12 hours at steady state. CGP 47 292 accounted for about 60% of the total dose in urine.

Conclusions:

The pharmacokinetics are similar between patients and healthy volunteers. No dosage adjustment is necessary in the elderly population.

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Study 027: An open label, multicenter, add-on safety and tolerability study of weekly ascending doses of CGP 33101 in pediatric patients with in adequately controlled seizures

This study was presented in the clinical section, but contained PK information in pediatrics, hence reviewed. A brief overview of some essential components of the study design is given below:

Study Design	open label, weekly ascending dose						
Study Population	N=18 patients; 16 completed the study <u>Age:</u> 1-18 years <u>Gender:</u> 8M & 8F <u>Weight:</u> <u>Race:</u> 14 White, 2 Other						
Treatment Group	Group I: ≤ 6 years Group II: 7-12 years Group III: 13-≤18 years						
Dosage and Administration	Week 1: 10 mg/kg/day given as BID Week 2: 30 mg/kg/day given as BID Patients were on 1 or 2 AEDs Tablet 100 : lot E 15750 and 200 mg: lot E 15702 ****It is not clear how tablets were administered to 1 year olds. No information provided.						
Sampling: Blood	Days 7 and 15: At pre-dose and 0.5, 2, 4, 6, 8, 10 and 12 hours post-dose for rufinamide concentrations						
Urine	none						
Feces	none						
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table style="width: 100%; border: none;"><tr><td></td><td style="text-align: center;"><u>Plasma</u></td><td style="text-align: right;"><u>Urine</u></td></tr><tr><td>Rufinamide</td><td style="text-align: center;">50 ng/ml</td><td></td></tr></table> Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 50-4000 ng/ml for rufinamide in plasma <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.4% Inter-day accuracy: 101.8-109.9%		<u>Plasma</u>	<u>Urine</u>	Rufinamide	50 ng/ml	
	<u>Plasma</u>	<u>Urine</u>					
Rufinamide	50 ng/ml						
PK Assessment	AUC ₀₋₁₂ , C _{max} , C _{min} , T _{max} of rufinamide						
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events						
PD Assessment	None						

Pharmacokinetic Results:

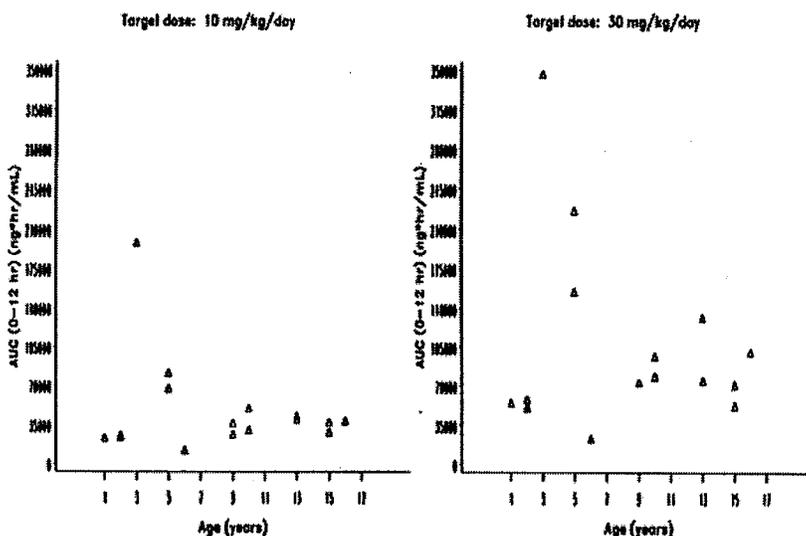
Rufinamide in plasma:

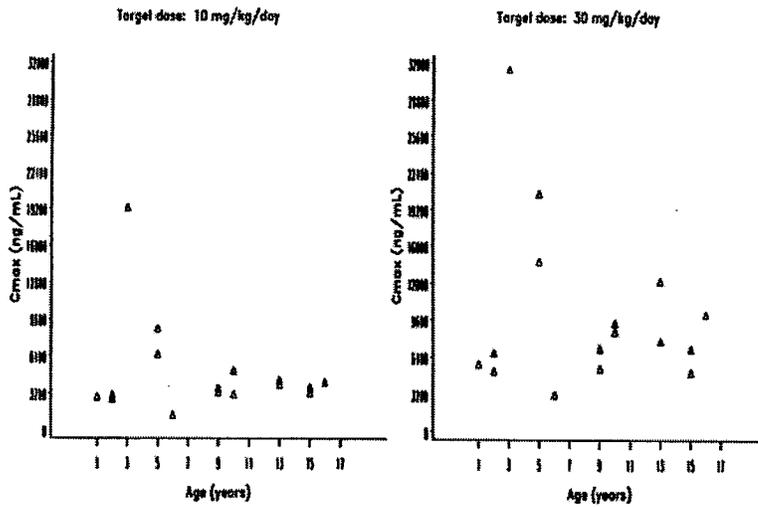
Summary statistics of the pharmacokinetics in different age groups is given in the following Table, and individual data in the following figures:

Table 9-4. Summary statistics for the pharmacokinetic parameters of rufinamide by age group and target dose (all 16 completed patients)

Age group	N	Target dose	Mean (S.D.)			
			AUC _{0-12h} (ng h/mL)	C _{max} ^{ss} (ng/mL)	C _{min} ^{ss} (ng/mL)	t _{max} (h)
≤ 6 yrs	7	10 mg/kg/day	61732 (65345)	6381 (6255)	4096 (5001)	3.0 (1.8)
		30 mg/kg/day	130862 (119124)	12549 (10391)	8917 (9734)	5.6 (2.6)
7-12 yrs	4	10 mg/kg/day	36125 (10422)	3816 (931)	2273 (975)	4.5 (2.0)
		30 mg/kg/day	82808 (12253)*	7649 (1704)	4448 (1807)	4.5 (1.9)
13 - <18 yrs	5	10 mg/kg/day	37738 (5490)	3915 (446)	2209 (527)	3.1 (1.7)
		30 mg/kg/day	86392 (30684)	8645 (3036)	5425 (1897)	2.8 (1.1)

* The summary statistics of AUC_{0-12h} for the target dose of 30 mg/kg/day were based on three patients in the 7-12 y age group.





Two patients (1 and 2 year olds) were on lamotrigine, which was later found to interfere with the analysis. Using different chromatographic columns the two peaks were separated.

One patient (6 year old) had levels that were 4-5 fold higher than the other subjects. This subject was on valproic acid as well. Based on population analysis conducted later, valproate was known to alter the PK of rufinamide up to 70% and this increase was more pronounced in the younger children.

Summary statistics without this subject is given in the following Tables for the two doses:

Summary statistics for pharmacokinetic parameters of Rufinamide
by age group for each target dose
(all completed patients, except M0385V/110, with evaluable PK parameters)

Target dose: 10 mg/kg/day

	Age group			Total
	Group I (5-6 yrs)	Group II (7-12 yrs)	Group III (13-18 yrs)	
AUC (0-12 hr)				
(ng·hr/mL)				
N	6	4	5	15
Mean	18984.9	36125.2	37737.6	17007.4
SD	27890.8	10422.0	5490.2	17643.8
Min	12477.3	26616.3	20605.9	12477.3
Median	24951.4	33768.7	38955.9	17090.5
Max	88941.4	50346.9	43359.0	88941.4
Cmax (ng/mL)				
N	6	4	5	15
Mean	4225.9	3816.0	5915.2	4013.0
SD	2816.2	930.8	445.4	1763.2
Min	1336.5	2124.8	3235.0	1336.5
Median	2490.4	3485.9	4011.3	3482.3
Max	8776.3	5167.3	6378.4	8776.3
Cmin (ng/mL)				
N	6	4	5	15
Mean	2343.2	2273.0	2209.4	2279.8
SD	2048.4	975.3	516.7	1336.2
Min	683.5	1513.3	1363.9	683.5
Median	1291.8	1991.1	2278.1	2233.8
Max	5031.2	3396.9	2834.4	5031.2
Tmax (hr)				
N	6	4	5	15
Mean	3.4	4.5	3.1	3.7
SD	1.4	2.0	1.7	1.6
Min	1.9	1.8	2.0	1.8
Median	3.3	5.1	2.0	3.9
Max	5.5	6.2	5.8	6.2

TABLE 4

Summary statistics for pharmacokinetic parameters of Rufinamide
by age group for each target dose
(all completed patients, except N0585V/110, with evaluable PK parameters)

Target dose: 30 mg/kg/day

	Age Group			Total
	Group I (4-6 yrs)	Group II (7-12 yrs)	Group III (13-18 yrs)	
AUC (0-12 hr) (ng/hr/ml.)				
N	4	3	8	15
Mean	9499.9	8208.1	8439.6	8927.6
SD	7887.8	1225.1	5048.7	5294.7
Min	2353.9	7331.2	5284.8	2353.9
Median	5678.9	7847.5	7483.8	7487.1
Max	22605.9	9663.5	13193.8	22605.9
C_{max} (ng/ml.)				
N	4	4	5	13
Mean	939.5	768.6	865.2	867.6
SD	4747.8	1784.8	3035.9	4484.7
Min	329.9	542.3	514.7	329.9
Median	432.6	788.8	776.8	7169.8
Max	28604.6	9352.1	13837.8	28604.6
C_{min} (ng/ml.)				
N	4	4	5	13
Mean	594.6	444.1	542.3	537.2
SD	4290.6	1807.1	1896.9	4830.8
Min	120.3	306.8	382.4	120.3
Median	2634.6	3830.9	4869.1	4192.6
Max	14972.2	7866.8	8415.8	14972.2
T_{max} (hr)				
N	6	4	5	15
Mean	3.5	4.5	2.8	4.3
SD	2.8	1.9	1.1	2.3
Min	2.0	2.8	2.0	2.0
Median	4.9	4.9	2.0	4.0
Max	9.5	6.0	4.2	9.5

The PK was less than dose proportional. With the increase in dose 3 times, the exposure was increased only twice.

Conclusions:

The pharmacokinetics of rufinamide in the 3 age groups seem to be similar. The p-values in group comparisons ranged from 0.4842 to 0.9997 suggesting no statistical differences in the PK parameters between the 3 groups.

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Study 029: *An open label, parallel-group study to evaluate the pharmacokinetics of rufinamide in subjects with chronic renal failure in comparison with healthy controls*

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

Study Design	Single dose, open label, parallel group
Study Population	<p>N= healthy subjects and subjects with severe chronic renal failure <u>Age:</u> 32-61 years (mean 44.8 years) of renal; 29-63 years (mean 42.9 years) of healthy <u>Gender:</u> 14M & 4F <u>Weight:</u> 51-100 kg (mean 80 kg) of renal; 60.4-119 kg (mean 83.8 kg) of healthy <u>Race:</u> 8 White, 9 Black, 1 Indian/Asian</p>
Treatment Group	<p>Group I: subjects with severe chronic renal failure requiring hemodialysis (CLCR <30 ml/min) Group II: Healthy subjects (CLCR >80 ml/min)</p>
Dosage and Administration	<p><u>Part I (N=18, 9+9): dialysis prior to dosing:</u> The treatment period was initiated after an overnight fast of at least 10 hours. On the morning of dosing, a standardized breakfast was served to both groups (I and II) of subjects. The renal failure subjects then underwent their usual dialysis protocol, lasting approximately 4 hours. Healthy subjects remained resting during this period. Approximately 2 hours following the completion of dialysis in Group I, and upon completion of a standardized lunch (within 30 minutes of commencing the meal), all subjects (Groups I and II) received a single oral dose of 400 mg of rufinamide. Subjects remained domiciled for 60 hours post-dose for the remaining PK and safety evaluation.</p> <p>Wash out of 1 week, followed by Part II.</p> <p><u>Part II (N=7): dialysis subsequent to dosing:</u> seven of the nine subjects with severe chronic renal failure returned to the study site for a second treatment phase. Baseline evaluations were conducted 24 hours prior to dosing, and subjects again observed an overnight fast of at least 10 hours. A standardized breakfast, matched in content to the lunch served in Part I, was served to the subjects, who had to consume the entire contents of the meal within 30 minutes. Subjects were then dosed with 400 mg rufinamide. Plasma sampling for pharmacokinetic and safety evaluations was then conducted in the same manner as in Part I of the study. Three hours after dosing, the subjects underwent hemodialysis, during which additional pharmacokinetic sampling was performed on dialysate fluid for up to 4 hours following the initiation of dialysis. All subjects remained domiciled for 60 hours post-dose for the remaining PK and safety evaluation.</p> <p>Doses given with 200 ml water.</p>

	<p>Lot no: 400 mg tablet , Lot 17/366/1</p> <p><u>Diet:</u> Doses administered after 10 hour fast, dosed after standardized lunch. No fruit juices, caffeine or alcohol was allowed</p>									
Sampling: Blood	<p>Part I: At pre-dose and 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60 hours post-dose.</p> <p>Part II: Dialysis was to take place at 3 hours after the subjects had been dosed, and sampling was done at the following intervals: prior to the start of dialysis, then at 0.5, 1, 1.5, 2, 3 and 4 hours after the initiation of dialysis (equivalent to 3.5, 4, 4.5, 5, 6 and 7 hours post-dose).</p> <p>Also extent of drug removed by hemodialysis was evaluated by sampling dialysate fluid</p>									
Urine	At 0-12, 12-24, 24-48, 48-60 hours post dose									
Feces	none									
Analysis	<p><u>Method</u></p> <p>HPLC-UV</p> <p><u>Lower Limits of Quantitation</u></p> <table border="0"> <thead> <tr> <th></th> <th><u>Plasma</u></th> <th><u>Urine</u></th> </tr> </thead> <tbody> <tr> <td>Rufinamide</td> <td>0.025 µg/ml</td> <td>2.5 µg/ml</td> </tr> <tr> <td>CGP 47292</td> <td></td> <td>5 µg/ml</td> </tr> </tbody> </table> <p>Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 0.025-60 µg/ml for rufinamide in plasma 2.5-200 µg/ml for rufinamide in urine 5-200 µg/ml for CGP 47 292 in urine</p> <p><u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 8% Inter-day accuracy: -1.3 to 1.6%</p> <p><u>Rufinamide in urine:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.2% Inter-day accuracy: -6.5 to -1.8%</p> <p><u>CGP 47 292:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 10% Inter-day accuracy: -5.9 to -1.9</p> <p><u>Rufinamide in dialysate:</u> Precision %CV ≤ 3.2%, accuracy -3.4 to 0.8%</p>		<u>Plasma</u>	<u>Urine</u>	Rufinamide	0.025 µg/ml	2.5 µg/ml	CGP 47292		5 µg/ml
	<u>Plasma</u>	<u>Urine</u>								
Rufinamide	0.025 µg/ml	2.5 µg/ml								
CGP 47292		5 µg/ml								
PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , A _{e0-t}									
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events									
PD Assessment	None									

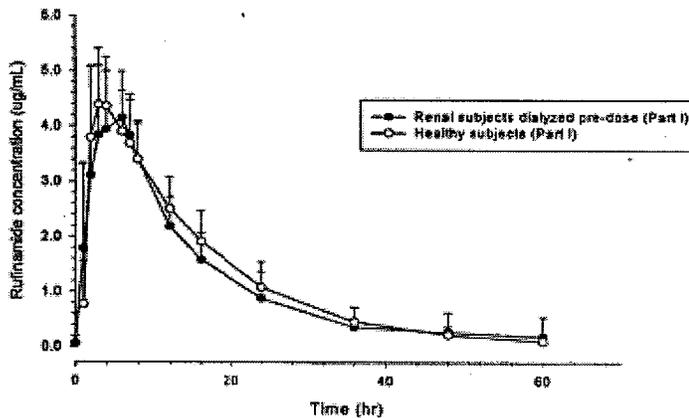
Pharmacokinetic Results:

Rufinamide in plasma:

Dosing prior to dialysis:

In Part I of the study, during which renal subjects underwent dialysis prior to rufinamide dosing, the extent of absorption (AUC) and the absorption rate (C_{max}) were similar between renal subjects and healthy subjects (Figure below).

Mean plasma concentration time profile in the healthy subjects and the renally impaired subjects after a single 400 mg dose of rufinamide is shown in the following figure:



Comparisons between matched groups were made for pharmacokinetic parameters AUC (0-last), AUC (0-48), AUC (0-60), AUC_{0-inf}, and C_{max}. All nine matched pairs were included in the analysis except when there were non-evaluable PK parameters. There were five renal subjects having non-evaluable data for AUC_{0-inf}. Therefore, only data from four matched pairs were included in the analysis of AUC_{0-inf}.

Analyses indicated that renal subjects, compared with matched healthy subjects, had an approximately 10% decrease in all AUCs and a 4% increase in C_{max}. These magnitudes of changes were not statistically significant. Summary for the analysis results of AUC (0-60), AUC_{0-inf}, and C_{max} are presented in the following Table.

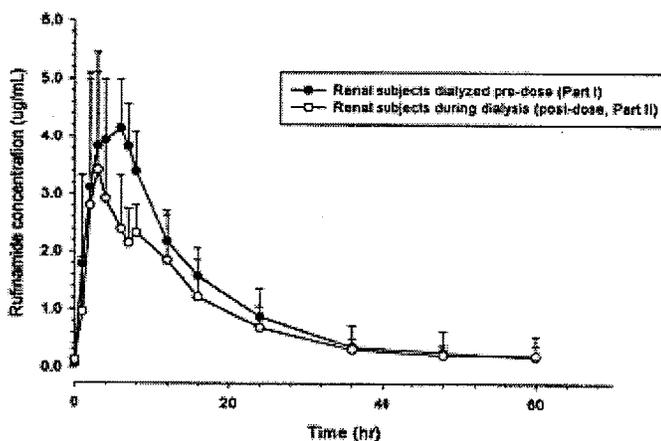
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Parameter	Group	N	Mean (\pm SD)	P-value	Estimated ratio of means	90% CI for ratio of means
AUC _(0-∞) ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	Renal	4	60.75 (\pm 10.11)	0.617	0.90	(0.57, 1.42)
	Healthy	9	76.30 (\pm 20.88)			
AUC _(0-60 h) ($\mu\text{g}\cdot\text{hr}/\text{mL}$)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

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

Dosing post dialysis:

However, during Part II of the study, in which dialysis occurred subsequent to rufinamide dosing, decreases in rufinamide AUC and C_{max} values were noted on an intrasubject basis, relative to the values seen in Part I. This suggests that hemodialysis can affect the level of drug exposure in subjects with chronic and severe renal failure; as shown in the Figure below:



The extent of drug removal by hemodialysis was analyzed by PK data from renal failure subjects who had gone through Part II of the study. All seven subjects who continued through Part II were included in the comparisons between Parts I and II for the analysis of AUC (0-last), AUC (0-48), AUC (0-60), AUC_{0-inf}, and C_{max}.

The results indicate that hemodialysis significantly reduced AUC and C_{max} by 29% and 16%, respectively. Summary results of AUC (0-60) and C_{max} are presented in the following Table.

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 (t_{max}).

Rufinamide and metabolite in urine:

Urine samples were available from all healthy subjects. However, due to the nature of renal disease and the severity of the condition, urine samples were not available from all renal subjects. As such, urine samples were obtained from only six renal subjects in Part I and from four renal subjects in Part II. In addition, sample volume was significantly less than that obtained from the healthy subjects in the study. Therefore, it is not possible to make conclusive statements based upon the data collected in this study.

From the limited data collected in this study, rufinamide was found to be extensively metabolized in both renal and healthy subjects, with only a trace amount (<1% of the dose) being recovered unchanged in urine after a single dose. The inactive metabolite (CGP 47292) was also found in urine, and accounted for approximately 10% to 60% of the total dose in renal and healthy subjects.

The urine concentration levels from the healthy subjects (Part I only) and from the renal subjects, pre-and-post-dialysis (Parts I and II), were similar, but due to the small volume of urine available from renal subjects, a lesser amount of CGP 47292 was recovered from these subjects.

Rufinamide in dialysate:

Dialysate samples were collected from renal subjects in Part II of the study. The presence of rufinamide in the dialysate was confirmed; however, the amount present was not calculated, due to the unknown total volume of the dialysate, per subject. This also confirmed that the disappearance of the drug from plasma is reflected in dialysate.

However, the mass balance of all three components (plasma, dialysate and urine), could not be performed due to the inadequate volume of urine available for analysis, as well as the unknown total volume of dialysate collected from each renal subject.

Conclusions:

- When renal subjects underwent dialysis prior to rufinamide dosing, the extent and rate of absorption (AUC and C_{max}) were similar between renal subjects (n=9) and healthy subjects (n=9). Therefore, it appears that subjects with severe and chronic renal disease who are not dialysis-dependent, would not require any special dose adjustments when taking rufinamide.
- Applying hemodialysis during the absorption phase will remove approximately 30% of rufinamide from the blood stream. Therefore, 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. Based upon these findings, hemodialysis might also then provide an effective means of drug removal in the event of a rufinamide overdose.

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EXTRINSIC FACTORS

Study r34: *Plasma kinetics of CGP 33 101 in patients on up to 2 concomitant antiepileptic drugs following a single 800 mg dose and repeated BID applications of weekly rising doses of CGP 33 101 (400, 800, 1200 and 1600 mg/day)*

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

Study Design	single and multiple doses, multi-center, double-blind, randomized to placebo or drug						
Study Population	N=50 patients treated with one or two other antiepileptic drugs <u>Age:</u> 20-64 years <u>Gender:</u> 35 M & 15F <u>Weight:</u> 50-106 kg <u>Race:</u> White						
Treatment Group	none						
Dosage and Administration	Day 1: 800 mg rufinamide SD Day 8-34: weekly rising doses of 200, 400, 600 and 800 mg BID rufinamide to half the patients and placebo to the other half (for 1 week each) Day 35: 800 mg rufinamide SD Doses given with 240 ml water. Lot no: 200 mg tablet 14/279/1 and 15/487/1 Daily dose of other antiepileptic drugs remained constant through out the study. <u>Diet:</u> Doses given with breakfast except for 6 patients on Day 1. No fruit juices, caffeine or alcohol was allowed						
Sampling: Blood	Days 1 and 35: At 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96 hours post-dose.						
Urine	none						
Feces	none						
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%;"></td> <td style="text-align: center;"><u>Plasma</u></td> <td style="text-align: center;"><u>Urine</u></td> </tr> <tr> <td>Rufinamide</td> <td style="text-align: center;">24 ng/ml</td> <td style="text-align: center;">NA</td> </tr> </table>		<u>Plasma</u>	<u>Urine</u>	Rufinamide	24 ng/ml	NA
	<u>Plasma</u>	<u>Urine</u>					
Rufinamide	24 ng/ml	NA					
PK Assessment	AUC ₀₋₉₆ , AUC _{0-inf} , C _{max} , C _{min} , T _{1/2}						
Safety Assessment	none						
PD Assessment	None						

Pharmacokinetic Results:

Influence of concomitant AEDs on rufinamide kinetics on Day 1:

Patients on phenytoin (N=3) and phenytol (N=13) were grouped in one as they have similar structure.

Patients on Phenobarbital (n=4) and primidone (N=1) were grouped in one since Phenobarbital is predominant active metabolite of primidone.

Patients on single AED:

The AUC_{0-inf} of rufinamide on Day 1 in patients who received a single AED appeared to be higher in patients treated with valproic acid than the other AEDs. One patient has markedly higher concentrations (more than twice the highest value) with valproic acid. Mean AUCs were calculated with and without this subject. There was decrease in rufinamide levels with phenytoin and carbamazepine. Historical data shows that AUC₀₋₉₆ in healthy subjects with food (600 mg single oral dose) was $343 \pm 93 \mu\text{mol.h/l}$.

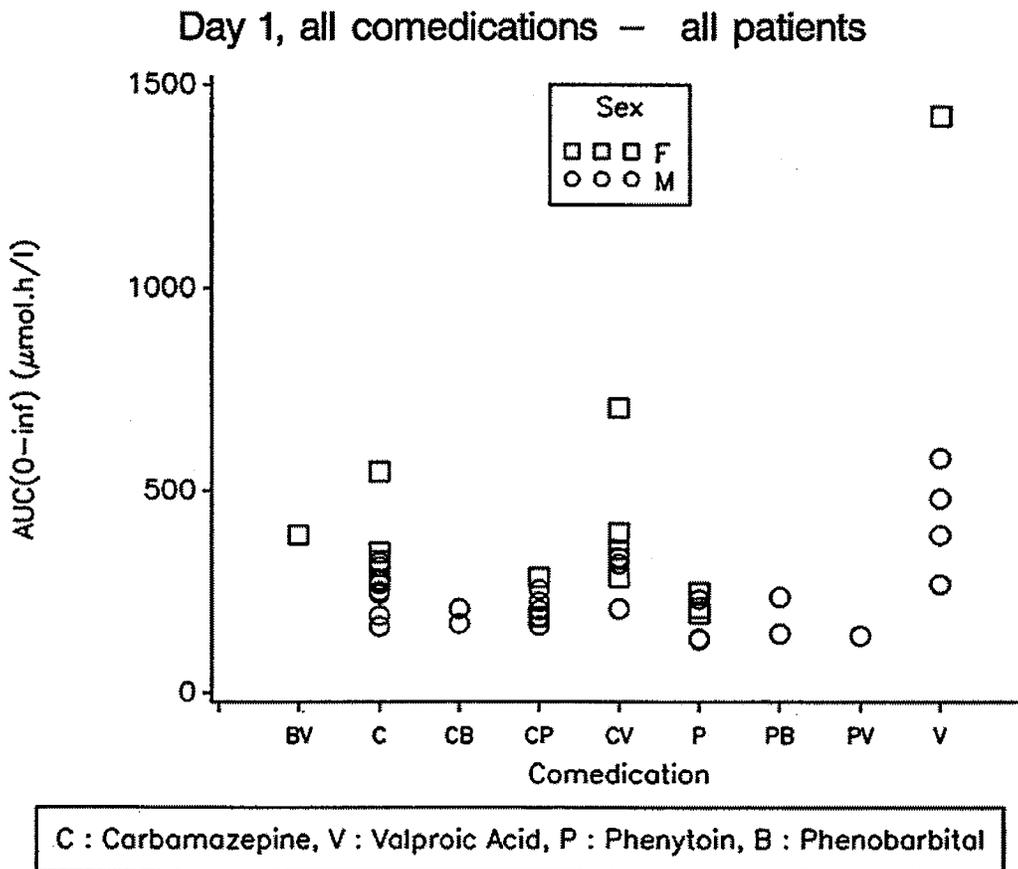
The mean \pm SD values of AUC(0-inf) on day 1 were :

Associated AED :	{	valproic acid (n = 4) :	$430 \pm 133 \mu\text{mol.h/l}$
		(n = 5) :	$628 \pm 459 \mu\text{mol.h/l}$
		phenytoin (n = 6) :	$192 \pm 49 \mu\text{mol.h/l}$
		carbamazepine (n = 12) :	$294 \pm 96 \mu\text{mol.h/l}$

without and with patient 16 for the valproic acid group.

The difference between gender was also significant. The AUC in women had a tendency to be higher than in men, although no relation appeared with weight and age. Therefore the gender differences may be due to biological functions rather than weight differences.

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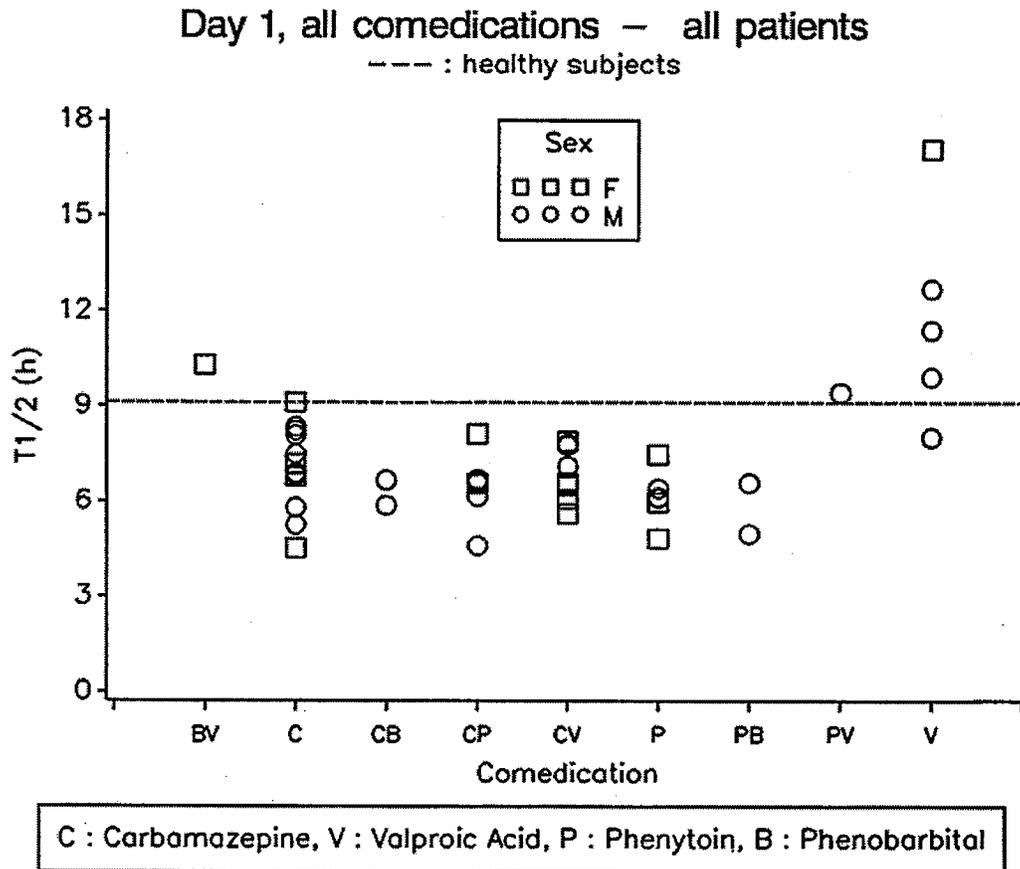
The influence of AED on rufinamide $t_{1/2}$ values was highly significant.

The mean \pm SD values of $T_{1/2}$ were :

Associated AED : { valproic acid (n = 4) : 10.5 ± 2.0 h
 phenytoin (n = 5) : 11.8 ± 3.4 h
 carbamazepine (n = 12) : 7.0 ± 1.3 h

without and with patient 16 for the valproic acid group.

No gender differences in $t_{1/2}$ was detected. Historical data shows that the $t_{1/2}$ in healthy subjects (600 mg SD) was 9.1 ± 2.1 h.



Patients on one or two AEDs:

One patient with both phenytoin and valproic acid showed higher AUC than healthy subjects.

Influence of repeated administration of rufinamide on its kinetics:

The mean (SD) accumulation factor based on AUC values was 1.9 ± 0.5 . The mean ratio of C_{max} values were similar. Rufinamide kinetics were not modified upon repeat administration. The ratio of steady state to single dose AUCs was 0.94 ± 0.2 .

Conclusions:

- Patients on valproic acid had higher rufinamide concentration and patients on phenytoin had lower rufinamide concentrations on Day 1.

Study bpkf-1995-032: Plasma concentrations of CGP 33 101 and dose dependency in patients with partial seizures on up to 3 concomitant antiepileptic drugs (200, 400, 800, and 1600 mg/day)

This international multicenter, double-blind, double-dummy, randomized, placebo controlled, 5-arm, parallel-group trial was designed to investigate the efficacy and tolerability, as well as kinetics in patients (in- or out-patients) with epilepsy on up to 3 concomitant antiepileptic drugs, over a 3-month administration of one of 4 different dosages or placebo. The patients were randomized in blocks of 5 patients, 1 patient for each of the 4 dosages, and 1 patient on placebo.

Patients, aged 14-65 included in the trial were randomly allocated to one of 5 treatment groups after a 3-month Prospective Baseline Period:

1. 200 mg of CGP 33 101 daily, i.e. 100 mg b.i.d.
2. 400 mg of CGP 33 101 daily, i.e. 200 mg b.i.d.
3. 800 mg of CGP 33 101 daily, i.e. 400 mg b.i.d.
4. 1600 mg of CGP 33 101 daily, i.e. 800 mg b.i.d.
5. matching placebo

The patients were asked to take the trial medication orally with about 100 mL of water, and with food, at approximately 8:00 in the morning and 8:00 in the evening.

Formulations (different sizes): CGP 33 101 tablets of 200 mg, and matching placebo
CGP 33 101 tablets of 100 mg, and matching placebo

Batch numbers for CGP 33 101: 16/055/2 (100 mg), 16/054/1 (200 mg), 16/091/1 (200 mg). Batch numbers for placebo: 16/040/6 (matching 100 mg), 16/145/2 (matching 200 mg).

There was a 12-week baseline period to ensure steady state trough levels of all AEDs followed by a 12 week dosing period.

Patients were categorized into 3 groups:

- Group 1: Patients treated with carbamazepine which did not significantly decrease the plasma clearance of CGP 33 101, but showed however a tendency to increase it. Patients treated with AEDs which significantly modified CGP 33 101 kinetics were excluded from this group, i.e. phenytoin, primidone, phenobarbital, valproate and clonazepam.
- Group 2: Patients treated with AEDs which significantly increased the plasma clearance of CGP 33 101, i.e. phenytoin, primidone and phenobarbital. Patients treated with valproate and clonazepam were excluded. Patients treated

concomitantly with carbamazepine were included since the greater part of the patients of this trial was treated with this AED.

- Group 3: Patients treated with valproate which significantly decreased the plasma clearance of CGP 33 101. Patients treated with phenytoin, primidone, phenobarbital and clonazepam were excluded. Patients treated concomitantly with carbamazepine were included.

In each group, patients could be concomitantly treated with AEDs (oxcarbazepine, vigabatrin and clonazepam) which were shown not to significantly modify CGP 33 101 kinetics. The number of patients from groups 1, 2 and 3 and the total number of patients are different because a few patients were treated with AEDs different from those selected to define the three patient groups.

Results:

Trough concentration/dose values were slightly dependent on the dose and more markedly on the concomitant AED, as seen in the following Table:

Group of patients*	100 mg b.i.d.	200 mg b.i.d.	400 mg b.i.d.	800 mg b.i.d.
	Mean conc./dose \pm SD [$(\mu\text{mol/L})/(\mu\text{mol})$] x 1000			
All patients	6.88 \pm 3.85 (n = 838)	6.39 \pm 3.60 (n = 810)	6.34 \pm 4.29 (n = 811)	5.66 \pm 2.97 (n = 856)
Group 1	6.36 \pm 2.39 (n = 311)	5.59 \pm 2.39 (n = 309)	5.79 \pm 2.18 (n = 283)	5.01 \pm 1.82 (n = 265)
Group 2	5.43 \pm 2.39 (n = 256)	5.06 \pm 2.14 (n = 222)	4.62 \pm 2.26 (n = 252)	4.50 \pm 1.68 (n = 276)
Group 3	10.0 \pm 6.2 (n = 160)	11.5 \pm 5.1 (n = 109)	11.1 \pm 8.0 (n = 121)	8.89 \pm 3.69 (n = 164)

*: See paragraph 2.2.4

It was between 1.8 and 2.4 times higher in patients from group 3 (main AED: valproate) than in patients from group 2 (main AEDs: phenytoin, primidone and phenobarbital).

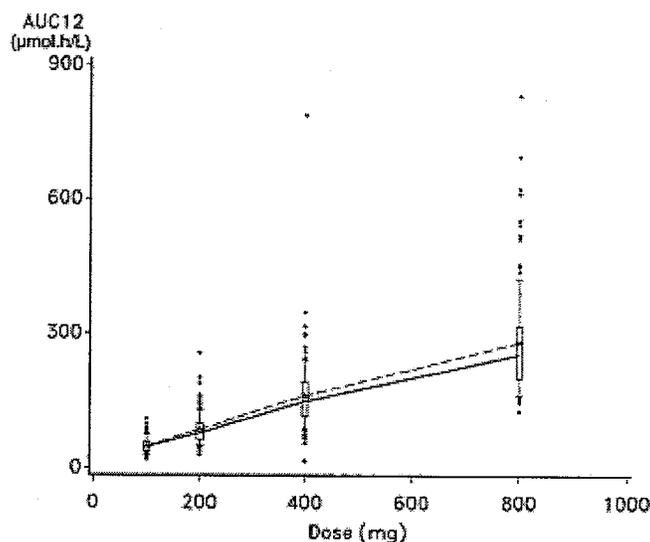
Pharmacokinetic parameters at steady state:

The value of mean AUC₀₋₁₂/dose was 28% lower at the 800 than at the 100 mg dose level. It was between 1.5 and 2.1 times higher in patients from group 3 than in patients from group 2, as seen in the following Table.

Group of patients*	100 mg b.i.d.	200 mg b.i.d.	400 mg b.i.d.	800 mg b.i.d.
	Mean AUC ₁₂ /dose ± SD [(µmol.h/L)/(µmol)] × 1000			
All patients	117 ± 41 (n = 114)	102 ± 43 (n = 114)	96 ± 49 (n = 118)	84 ± 36 (n = 117)
Group 1	112 ± 29 (n = 45)	95 ± 27 (n = 42)	89 ± 23 (n = 41)	75 ± 18 (n = 37)
Group 2	99 ± 33 (n = 32)	79 ± 22 (n = 32)	74 ± 32 (n = 34)	66 ± 21 (n = 35)
Group 3	151 ± 57 (n = 23)	163 ± 62 (n = 15)	144 ± 86 (n = 20)	122 ± 40 (n = 22)

Dose dependency:

The box plot of AUC12 values versus dose (all patients included) is shown in the following figure. The characteristics of the regression line Log(AUC12) versus Log(dose) are given in the following Table. The slope of the regression line was significantly different from unity, except for patients from group 3. It amounted to about 0.82 in patients from groups 1 and 2, and was slightly higher (0.90) in patients from group 3.



◊: Data point outside 90% limit.
Boxes: 25 and 75 percentiles.
Whiskers: 10 and 90 percentiles.

- - - -: Mean values.
—: Median values.

Group of patients*	N	Slope ± SE	Test: slope different from 1	Intercept ± SE
All patients	463	0.8363 ± 0.0230	p = 0.0001	- 0.0292 ± 0.1312
Group 1	165	0.8186 ± 0.0260	p = 0.0001	0.0383 ± 0.1466
Group 2	133	0.8163 ± 0.0399	p = 0.0001	- 0.1272 ± 0.2285
Group 3	80	0.9030 ± 0.0535	p = 0.0735	- 0.0382 ± 0.3053

This shows that there was a less than dose proportional increase with the increase of doses. By increasing the dose by a factor 2, the mean AUC₁₂ increased by 1.89 between 200 and 400 mg b.i.d. and by 1.73 between 400 and 800 mg. A similar dose dependency of CGP 33 101 plasma levels has been reported in 16 healthy volunteers following a single dose of CGP 33 101 taken with food: mean AUC(0-inf) increased by 1.97 between 200 and 400 mg b.i.d. and by 1.70 between 400 and 800 mg. The extent of dose dependency seemed to be also influenced by the concomitant AED.

Metabolism autoinduction:

No autoinduction of CGP 33 101 metabolism occurred since the mean morning trough concentrations of CGP 33 101 did not display a tendency to decrease from visit 5 to visit 13.

Inter-patient rufinamide concentration variability:

Variability in comparison to another study is shown in the following Table:

Subjects	Patients: Steady-state mean AUC ₁₂ ± SD (µmol.h/L)		Healthy: mean AUC(0-inf) ± SD (µmol.h/L)
	This study 800 mg b.i.d.	Ref. 6** 800 mg b.i.d.	Ref. 4 800 mg single dose
All patients/healthy	281 ± 120 (n = 17)	260 ± 109 (n = 21)	378 ± 86 (n = 16)
Group 1*	251 ± 61 (n = 37)	294 ± 96 (n = 12)	
Group 2*	223 ± 71 (n = 35)	192 ± 49 (n = 6)	
Group 3*	411 ± 133 (n = 22)	430 ± 133 (n = 4)	

*: See paragraph 3.3.4.

** Patients treated with a single AED: carbamazepine for group 1, phenytoin for group 2, valproate for group 3.

**Ref 6: Study r34

Ref 4: Study cpd93056

CGP 33 101 plasma levels were influenced by the concomitant AED, the patients from group 2 (main AEDs: phenytoin, primidone and phenobarbital) and group 3 (main AED: valproate) giving rise to the prominent differences in plasma levels. The mean trough plasma concentration in patients from group 3 was about twice that in patients from group 2, whatever the dose level.

The mean AUC₁₂ in patients from group 2 at the 800 mg b.i.d. dose level was markedly lower than the mean AUC(0-inf) in healthy volunteers, when they should have been equal since CGP 33 101 kinetics are not modified upon repeated dosing. This supports that phenytoin, primidone and phenobarbital increased CGP 33 101 clearance.

The mean AUC₁₂ in patients from group 1 (main AED: carbamazepine) ranged between those in patients from groups 2 and 3, but was distinctly closer to that in patients from

group 2. Therefore, carbamazepine might also increase CGP 33 101 clearance, but to a lesser extent than phenytoin, primidone and phenobarbital.

Phenytoin, carbamazepine, phenobarbital, and primidone induce hepatic monooxygenase and, to a lesser extent, conjugating enzymes, while valproate acts as an enzyme inhibitor. Such opposite effects on enzymes are in agreement with the differences between CGP 33 101 AUC values determined in groups 1, 2 and 3. However, despite the fact that CGP 33 101 is extensively biotransformed, no oxidative biotransformation pathway of CGP 33 101 in man could be detected. The main biotransformation pathway of CGP 33 101, carboxylamide hydrolysis, is catalysed by esterases/amidases, for which there is no published evidence that these enzymes are inducible by drugs. Therefore, the nature of CGP 33 101 interactions is unclear with the actual knowledge of the compound.

Intra-patient rufinamide concentration variability:

The mean + SD fluctuation index (FI) at the 800 mg dose level, $0.61 + 0.22$, is similar to that ($0.57 + 0.16$) previously determined in epileptic patients who took also b.i.d doses of 800 mg of CGP 33 101 and concomitant AEDs.

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Study 014: *Single center, open label, pharmacokinetic trial investigating the interaction between rufinamide and an oral contraceptive [Ortho-Novum 1/35] in healthy female volunteers*

This study was designed to evaluate the potential induction of oral contraceptive clearance by rufinamide. A brief overview of some essential components of the study design is given below:

Study Design	Single center, open label, cross over								
Study Population	N=25 healthy female subjects enrolled, 23 completed <u>Age:</u> 19-44 years (mean 28.7 years) <u>Gender:</u> females <u>Weight:</u> 49.8-90.8 kg (mean 77.6 kg) <u>Race:</u> 22 White, 1 Black								
Treatment Group	one								
Dosage and Administration	Baseline: Subjects maintained on Ortho-Novum for two pill cycles before baseline and Days 1-21: Ortho-Novum Days 29-49: Ortho-Novum Days 22-35: rufinamide 800 mg BID (1600 mg/day) within 15 minutes of Ortho-Novum dosing Doses given with 240 ml water.								
Sampling: Blood	<u>Ethinyl estradiol (EE) and non ethinndrone (NED) concentrations:</u> Day 7 and 35: At pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours post-dose. <u>Rufinamide trough concentrations:</u> Days 34, 35 and 36 in the morning								
Urine	none								
Feces	none								
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table border="0"> <tr> <td></td> <td style="text-align: center;"><u>Plasma</u></td> </tr> <tr> <td>Rufinamide</td> <td style="text-align: center;">50 ng/ml</td> </tr> <tr> <td>EE</td> <td style="text-align: center;">2 pg/ml</td> </tr> <tr> <td>NED</td> <td style="text-align: center;">0.05 ng/ml</td> </tr> </table> Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 50-4000 ng/ml for rufinamide in plasma 2-1000 pg/ml EE in plasma 0.05-25 ng/ml for NED in plasma <u>EE in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 5.77% Inter-day accuracy: 99.5-103%		<u>Plasma</u>	Rufinamide	50 ng/ml	EE	2 pg/ml	NED	0.05 ng/ml
	<u>Plasma</u>								
Rufinamide	50 ng/ml								
EE	2 pg/ml								
NED	0.05 ng/ml								

	<p><u>NED in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.5% Inter-day accuracy: 100-106%%</p> <p><u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 5.6% Inter-day accuracy: 97.7-108.8%</p>
PK Assessment	AUC0-24, Cmax, Tmax of EE and NED
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Ethinyl estradiol in plasma:

The pharmacokinetic parameters with and without rufinamide are shown in the following Table:

Mean ± SD, % coefficient of variation; Tmax given as median and range; N=23

Treatment	Tmax (hr)	Cmax (pg/mL)	AUC(0-24hr) (pg-hr/mL)
Ortho-Novum® without Rufinamide	1.0 (median) 1.0 to 3.0	138.9 ± 43.5 31 %CV	1232.3 ± 318.2 26 %CV
Ortho-Novum® with Rufinamide	1.5 (median) 0.5 to 6.0	94.7 ± 25.7 27 %CV	953.7 ± 217.3 23 %CV

The 90% CI for the parameters for EE are given in the following Table:

Parameter	Point estimate of the ratio	90% CI for the ratio
AUC0-24	0.777	0.737, 0.819
Cmax	0.685	0.631, 0.744

The point estimate for the ratio of 0.777 for AUC0-24 indicates an approximately 22% decrease in the AUC0-24 of EE when Ortho-Novum 1/35 was coadministered with rufinamide. The 90% confidence limits of (0.737, 0.819) correspond to a reduction of 18% to 26%.

The point estimate for the ratio of 0.685 indicates an approximately 31% decrease in the C_{max} of EE when Ortho-Novum 1/35 was coadministered with rufinamide. The 90% confidence limits of (0.631, 0.744) correspond to a reduction of 26% to 37%.

The median T_{max} of EE was longer with coadministration of rufinamide (1.5 hr) than without (1.0 hr). The difference between treatment was detected to be statistically significant (p=.004).

Norethindrone in plasma:

The pharmacokinetic parameters with and without rufinamide are shown in the following Table:

Mean ± SD, % coefficient of variation; T_{max} given as median and range; N=23

Treatment	T _{max} (hr)	C _{max} (ng/mL)	AUC(0-24hr) (ng-hr/mL)
Ortho-Novum® without Rufinamide	1.0 (median) 1.0 to 3.0	20.6 ± 6.3 31 %CV	144.4 ± 61.2 42 %CV
Ortho-Novum® with Rufinamide	1.0 (median) 0.5 to 4.0	16.5 ± 3.6 22 %CV	120.2 ± 39.9 33 %CV

The 90% CI for the parameters for NED are given in the following Table:

Parameter	Point estimate of the ratio	90% CI for the ratio
AUC0-24	0.861	0.817, 0.907
C _{max}	0.824	0.742, 0.915

The point estimate for the ratio of 0.861 indicates an approximately 14% decrease in the AUC₀₋₂₄ of NED when Ortho-Novum 1/35 was coadministered with rufinamide. The 90% confidence limits of (0.817, 0.907) correspond to a reduction of 9% to 18%.

The point estimate for the ratio of 0.824 indicates an approximately 18% decrease in the C_{max} of NED when Ortho-Novum 1/35 was coadministered with rufinamide. The 90% confidence limits of (0.742, 0.915) correspond to a reduction of 8% to 26%.

The median T_{max} was same for both treatment cycles.

Plasma rufinamide trough levels:

Plasma rufinamide concentrations did not appear to be rising from Day 34 to Day 36, confirming the attainment of steady state of rufinamide at the time of the second blood sampling for EE and NED.

C_{min} (ng/mL)	Day 34	Day 35	Day 36
Mean	5593.5	6159.1	5588.3
S. D.	1346.3	1238.6	1580.0
Min	3410.0	3280.0	2190.0
Median	5380.0	6290.0	5960.0
Max	9140.0	8170.0	9160.0

Conclusions:

- Co-administration of rufinamide (800 mg bid) with Ortho-Novum 1/35 resulted in estimated 22% and 31% decreases in AUC and C_{max}, respectively, of EE.
- Co-administration of rufinamide (800 mg bid) with Ortho-Novum 1/35 also resulted in estimated 14% and 18% decreases in AUC and C_{max}, respectively, of NED.
- It is not known whether the decreased levels of EE and NED are sufficient to prevent ovulation. This finding should be mentioned in the labeling for rufinamide.

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Study 104: *An open label, three period trial investigating the interaction effect of rufinamide on the pharmacokinetic profile of triazolam, a CYP 3A4 substrate*

This study was conducted to determine the induction potential of rufinamide by evaluating the pharmacokinetic profile of triazolam. A brief overview of some essential components of the study design is given below:

Study Design	open label, 3-period						
Study Population	N=21 healthy subjects enrolled, 18 completed <u>Age:</u> 19-43 years (mean 32.1 years) <u>Gender:</u> 20M & 1F <u>Weight:</u> 56-94.6 kg (mean 78.5 kg) <u>Race:</u> 12 White, 8 Black, 1 other						
Treatment Group	one						
Dosage and Administration	Period 1: 0.25 mg triazolam SD immediately after breakfast on Day 1 Period 2: 400 mg BID (800 mg/day) rufinamide on Days 4-15 following breakfast and dinner Period 3: 400 mg rufinamide and 0.25 mg triazolam on Day 15 following breakfast Doses given with 240 ml water. Rufinamide 400 mg FMI tablets Lot B980118 Triazolam: 0.25 mg lot 97 BXU						
Sampling: Blood	<u>Triazolam concentrations:</u> Day 1 and 15: At pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 hours post-dose. <u>Rufinamide trough concentrations:</u> Days 14 and 15 in the morning						
Urine	none						
Feces	none						
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <table style="margin-left: 40px;"><tr><td></td><td style="text-align: center;"><u>Plasma</u></td></tr><tr><td>Rufinamide</td><td style="text-align: center;">50 ng/ml</td></tr><tr><td>Triazolam</td><td style="text-align: center;">0.05 ng/ml</td></tr></table> Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 50-4000 ng/ml for rufinamide in plasma 0.05-50 ng/ml for triazolam in plasma <u>Triazolam in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 11.7% Inter-day accuracy: 98.9-103%		<u>Plasma</u>	Rufinamide	50 ng/ml	Triazolam	0.05 ng/ml
	<u>Plasma</u>						
Rufinamide	50 ng/ml						
Triazolam	0.05 ng/ml						

	Rufinamide in plasma: Inter-day Precision (%CV for Quality Controls) : $\leq 5.76\%$ Inter-day accuracy: 92.3-95.7%
PK Assessment	AUC _{0-last} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2} of triazolam
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

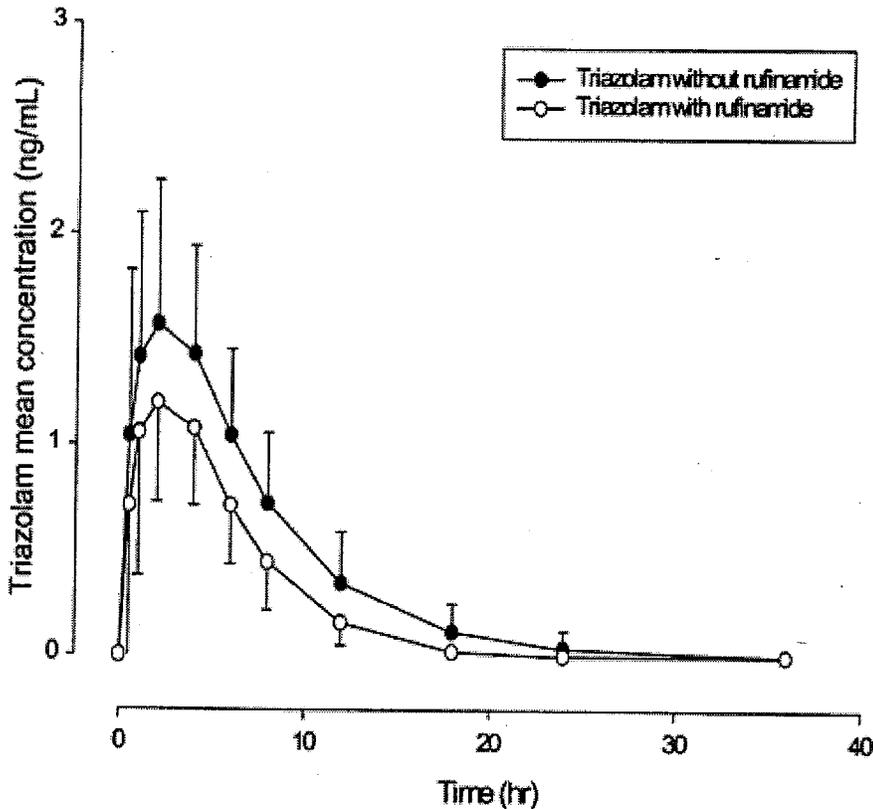
Triazolam in plasma:

Summary pharmacokinetic parameters of triazolam with and without rufinamide is given in the following Table:

Parameter	<u>triazolam alone</u>	<u>triazolam + rufinamide</u>	P-value	<u>Least squares mean ratio</u>	
	Mean(\pm SD)**	Mean(\pm SD)**		Estimate	90% C. I.***
AUC _(0-last) (ng*hr/mL)	13.31(\pm 5.99)	8.40(\pm 3.47)	0.0001*	0.64	(0.59, 0.69)
AUC _(0-∞) (ng*hr/mL)	14.06(\pm 6.42)	8.90(\pm 3.50)	0.0001*	0.64	(0.60, 0.69)
C _{max} (ng/mL)	1.86(\pm 0.63)	1.44(\pm 0.62)	0.0033*	0.76	(0.66, 0.88)
V/F (L)	104.63(\pm 26.02)	121.04(\pm 35.17)	0.0016*	1.15	(1.08, 1.22)
CL/F (L/hr)	20.90(\pm 8.10)	32.07(\pm 11.69)	0.0001*	1.55	(1.45, 1.67)
t _{1/2} (hr)	3.76(\pm 1.07)	2.73(\pm 0.53)	0.0001*	0.73	(0.65, 0.80)
t _{max} (hr)	2.00	2.00	--	--	--

Triazolam concentration time profile is shown in the following figure:

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Results indicated that coadministration of triazolam reduced the AUC and Cmax of triazolam significantly by 37% and 23% respectively.

Rufinamide trough concentrations:

Rufinamide trough concentrations did not change on Days 14 and 15, confirming attainment of steady state.

Conclusions:

- Pretreatment of rufinamide (800-mg/day, administered b.i.d.) resulted in 37% decrease in AUC_{0-inf} with 90% confidence intervals of 60% to 69% and a 23% decrease in Cmax of triazolam with 90% C.I. of 66% to 88% for the ratio of means of triazolam with rufinamide vs. triazolam alone.
- Rufinamide may induce metabolism of other drugs metabolized by 3A4; the magnitude and clinical relevance of such induction will depend on the degree to which other metabolic pathways are involved in elimination of such drugs.

Study 105: *An open label, three period trial investigating the interaction effect of rufinamide on the pharmacokinetic profile of olanzapine, a CYP 1A2 substrate*

This study was conducted to determine the induction potential of rufinamide by evaluating the pharmacokinetic profile of olanzapine. A brief overview of some essential components of the study design is given below:

Study Design	open label, 3-period
Study Population	N=19 healthy subjects enrolled, 18 completed <u>Age:</u> 18-44 years (mean 31.7 years) <u>Gender:</u> 19M <u>Weight:</u> 58-110 kg (mean 82.2 kg) <u>Race:</u> 14 White, 5 Black
Treatment Group	one
Dosage and Administration	Period 1: 5 mg olanzapine SD immediately after breakfast on Day 1 Period 2: 400 mg BID (800 mg/day) rufinamide on Days 11-22 following breakfast and dinner Period 3: 400 mg rufinamide and 5 mg olanzapine on Day 22 following breakfast Doses given with 240 ml water. Rufinamide 400 mg FMI tablets Lot B980118 Olanzapine: 5 mg lot 97 2AM16B
Sampling: Blood	<u>Olanzapine concentrations:</u> Day 1 and 15: At pre-dose and 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 hours post-dose. <u>Rufinamide trough concentrations:</u> Days 21 in the evening and 22 in the morning and evening
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 50 ng/ml Olanzapine 0.25 ng/ml N-desmethyl olanzapine 0.25 ng/ml Rufinamide in plasma (from analytical report crb-r6-1993) Linear range : 50-4000 ng/ml for rufinamide in plasma 0.25-50 ng/ml for olanzapine in plasma

	0.25-50 ng/ml for N-desmethyl olanzapine in plasma <u>Olanzapine in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.81% Inter-day accuracy: 97.8-104% <u>N-desmethyl Olanzapine in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 8.26% Inter-day accuracy: 94.4-106% <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 4.48% Inter-day accuracy: 90.8-93.5%
PK Assessment	AUC _{0-last} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2} of olanzapine
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Olanzapine in plasma:

Summary pharmacokinetic parameters of Olanzapine with and without rufinamide are given in the following Table:

Parameter	<u>Olanzapine</u>	<u>Olanzapine +</u>	P-value	<u>Least squares mean</u>	
	<u>alone</u>	<u>Rufinamide</u>		<u>ratio</u>	<u>95% C. I.</u>
	Mean(±SD)*	Mean(±SD)*		Estimate	
AUC _(0-last) (ng*hr/mL)	241.2(± 49.2)	236.4(± 52.4)	0.1678	0.98	(0.94, 1.01)
AUC _(0-∞) (ng*hr/mL)	260.4(± 54.7)	254.7(± 55.1)	0.1729	0.98	(0.94, 1.01)
C _{max} (ng/mL)	6.47(± 1.97)	6.42(± 1.98)	0.6730	0.99	(0.92, 1.06)
V/F (L)	968.5(± 283.4)	948.7(± 284.4)	0.4924	0.98	(0.91, 1.05)
CL/F (L/hr)	19.9(± 3.9)	20.4(± 4.0)	0.1905	1.02	(0.99, 1.06)
T _{1/2} (hr)	34.4(± 11.2)	31.8(± 7.6)	--	--	--
T _{max} (hr)	6.0	7.0	--	--	--

The results indicated that the coadministration of rufinamide would not change the PK of olanzapine. For AUC and C_{max}, the estimated least squares mean ratios (for rufinamide + olanzapine vs. olanzapine alone) were both close to one and yielded tight confidence intervals.

N-desmethyl olanzapine in plasma:

Only four subjects had measurable concentrations of N-desmethyl olanzapine in this study. Due to the small number of measurable samples, the pharmacokinetic parameters of N-desmethyl olanzapine could not be calculated. However, the plasma concentration-

time profiles of the measurable N-desmethyl olanzapine are similar, following administration of olanzapine with or without 11-day pre-treatment and concomitant administration of rufinamide.

Rufinamide trough concentrations:

Rufinamide trough concentrations did not change on Days 21 and 22, confirming attainment of steady state.

Conclusions:

- Co-administration and pre-treatment with rufinamide (800 mg/day, administered b.i.d.) resulted in no change in AUC and Cmax of olanzapine.
- Rufinamide did not alter the CYP1A2 mediated metabolism of olanzapine, suggesting rufinamide to not be an inducer of CYP 1A2.
- Rufinamide is not likely to affect the pharmacokinetics of other concomitant medications that are primarily metabolized via CYP1A2 pathway (some other CNS active drugs such as amitriptyline, clomipramine, imipramine, thioridazine, and clozapine are metabolized through the CYP1A2 pathway)

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BIOPHARMACEUTICS

Study 93029: Intra- and inter-subject variabilities in bioavailability of CGP 33101 after 400 mg single oral doses of suspension and 200 mg tablets

This was a single-center, single dose, open label, four sequence, randomized crossover trial evaluating the the intra- and inter-subject variabilities in bioavailability of CGP 33101 after oral administration. The drug, either as two 200-mg tablets (Treatment A) or as 400 mg powder suspended in water (Treatment B), was administered immediately after a standardized breakfast. Sixteen healthy subjects were randomly assigned to four groups and received each of these two treatments twice according to one of the four treatment sequences (AABB, BBAA, ABBA, BAAB,). There was a 1-week wash out between drug administration. Serial blood samples were collected up to 48 hours post dose after each administration. The LOQ for rufinamide was 50 ng/ml (linear range 50-4000 ng/ml)

Results:

The mean (SD) pharmacokinetics parameters are listed in the following Table:

		C _{max} (ng/ml)	T _{max} (hr)	AUC(0-48) (ng•hr/ml)	T _{1/2} (hr)
Tablet	Mean	3025	6.56	49380	8.80
	S.D.	680	1.70	11070	3.02
	C.V.(%)	22.5	25.9	22.4	34.3
	Median(Range)	---	6(4-10)	---	---
	N	32	32	32	27
Suspension	Mean	3324	7.22	57026	9.08
	S.D.	816	2.77	14706	1.63
	C.V.(%)	24.5	38.3	25.8	18.0
	Median(Range)	---	6(3-16)	---	---
	N	32	32	32	31

Summary statistics for assessing intra-subject variability is given in the following Table:

	AUC(0-48)	Cmax
Intra-subject variance (MSE from two-way ANOVA)		
<ul style="list-style-type: none"> ● Tablet ● Suspension 	47035612 74798024	146584 229426
Ratio of Intra-subject variance (Tablet/Suspension)	0.63	0.64
F-test P-value	0.414	0.430

Summary statistics for assessing inter-subject variability is given in the following Table:

	AUC(0-48)	Cmax
Inter-subject variance from Pitman-Morgan Test		
<ul style="list-style-type: none"> ● Tablet ● Suspension 	118102048 203411703	380047 679871
Ratio of Inter-subject variance (Tablet/Suspension)	0.58	0.56
Pitman-Morgan test P-value	0.168	0.207

There was a larger inter and intra- subject variability for the suspension as compared to the tablet, but these differences were not statistically significant.

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Study 102: *A randomized, open label, three-way crossover trial to compare the relative bioavailability of rufinamide oral suspension and tablets in healthy subjects under fed conditions.*

This study gives the relative bioavailability of a tablet and suspension formulation of rufinamide. In addition, this evaluates the food effect of a suspension, since rufinamide will be given to a large pediatric population (Note: suspension formulation was NOT used in any of the clinical trials in the pediatric population). Food effect studies have been conducted with the clinical service tablets (Study crb-r 33) and the final marketing image tablets (FMI) as well (Study 0037).

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

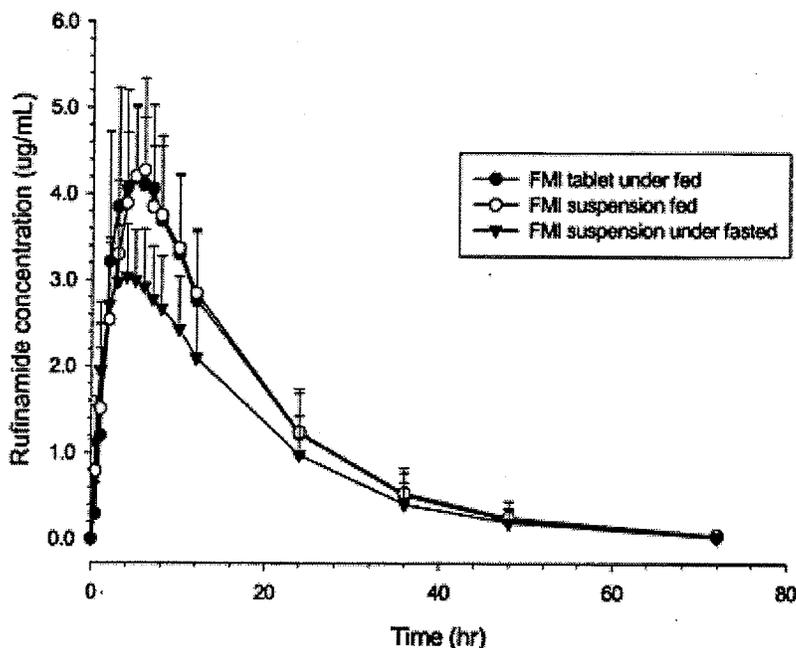
Study Design	Randomized, open label, 3-period
Study Population	N=26 healthy subjects enrolled, 24 completed. One subject discontinued at the baseline for period 3, prior to dosing, due to tremors and shakiness, suspected to be related to study medication by the investigator. One other subject was discontinued after dosing for period 3 due to severe abdominal pains suspected to be causally related to study medication. <u>Age:</u> 19-44 years (mean 29.5 years) <u>Gender:</u> 18M & 8F <u>Weight:</u> 50.1-99.7 kg (mean 77.9 kg) <u>Race:</u> 13 White, 11 Black, 2 Other
Treatment Group	A: 400 mg rufinamide FMI tablet SD under fed conditions B: 400 mg rufinamide suspension SD under fed conditions C: 400 mg rufinamide suspension SD under fasted conditions A 7-Day washout between treatments
Dosage and Administration	For the fed arm the doses were administered with 5 minutes of completion of a standardized FDA breakfast (total 1000 calories) For the fasted arm subjects were required to fast for ~5 hours post-dose as well Doses given with 240 ml water. No caffeine and alcohol allowed from 72 hours prior study initiation Rufinamide 400 mg FMI tablets manufactured by _____ ; Lot US 051 0797 Rufinamide 400 mg suspension; lot U006 0499
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 72 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u>

b(4)

	<p style="text-align: center;"><u>Plasma</u></p> <p>Rufinamide 0.025 µg/ml</p> <p>Rufinamide in plasma (from analytical report r99-1704) Linear range : 0.025-6.0 µg/ml for rufinamide in plasma</p> <p><u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 12.6% Inter-day accuracy: 98.8-101.4%</p>
PK Assessment	AUC _{0-last} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2}
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Mean (SD) plasma rufinamide concentration-time profiles after single oral dose of 400 mg rufinamide as tablets and suspension is shown in the following figure:



Relative Bioavailability:

The pharmacokinetic profiles were bioequivalent following the administration of FMI tablet and FMI suspension with food. The mean of AUC ratios of suspension-fed versus tablet-fed was 1.02. The mean of C_{max} ratios of suspension-fed versus tablet-fed was 0.94, as seen in the following Table:

Parameter	<u>Single 400-mg tablet under fed conditions</u>	<u>Single 400-mg oral suspension under fed conditions</u>	<u>Ratio of least squares means (suspension/tablet)</u>	
	Mean(±SD)	Mean(±SD)	Estimate	90% C. I.
AUC _(0-∞) (ng*hr/mL)	82.4(±22.7)	83.8(±23.2)	1.02	(0.98, 1.05)
AUC _(0-last) (ng*hr/mL)	81.1(±22.3)	82.6(±22.5)	1.02	(0.99, 1.05)
C _{max} (ng/mL)	4.72(±0.95)	4.41(±1.06)	0.93	(0.88, 0.98)
t _{1/2} (hr)	9.8(±1.9)	10.4(±2.2)**	--	--
t _{max} (hr)*	4.0	5.1	--	--

- * Median is reported for t_{max}
- ** Mean and SD of t_{1/2} under oral suspension fed conditions was based on n=23 since subject 16 has non-evaluable t_{1/2} value

Food Effect:

Comparisons of the rufinamide bioavailability following the administration of a single dose of 400-mg oral suspension with and without food indicated that food increased the rufinamide AUC and C_{max} by 31% and 36%, respectively. Administration of suspension without food seemed to decrease the extent of absorption of rufinamide with no effect on the elimination rate of rufinamide as indicated by t_{1/2}. The mean of AUC ratios of suspension-fed versus suspension- fasted was 1.31. The mean of C_{max} ratios of suspension-fed versus suspension-fasted was 1.38.

Parameter	<u>Single 400-mg oral suspension under fasted conditions</u>	<u>Single 400-mg oral suspension under fed conditions</u>	<u>Ratio of least squares means (fed/fasted)</u>	
	Mean(±SD)	Mean(±SD)	Estimate	90% C. I.
AUC _(0-∞) (ng*hr/mL)	64.4(±19.4)	83.8(±23.2)	1.31	(1.26, 1.35)
AUC _(0-last) (ng*hr/mL)	63.1(±18.9)	82.6(±22.5)	1.31	(1.27, 1.36)
C _{max} (ng/mL)	3.24(±0.72)	4.41(±1.06)	1.36	(1.29, 1.44)
t _{1/2} (hr)	9.8(±1.8)	10.4(±2.2)**	--	--
t _{max} (hr)*	4.0	5.1	--	--

- * Median is reported for t_{max}
- ** Mean and SD of t_{1/2} under oral suspension fed conditions was based on n=23 since subject 16 has non-evaluable t_{1/2} value

Adverse Events:

Higher incidence of adverse events was noted when rufinamide was administered under the fed state as compared to fasted state in this study. This finding confirms the observations noted in a previous bioequivalence study conducted with FMI tablets and CSF in healthy subjects. The higher incidence of adverse events may be related to the overall higher systemic exposure (AUC) achieved by rufinamide when administered under fed conditions.

Conclusions:

- The rufinamide suspension administered with food is bioequivalent to the rufinamide FMI tablet administered with food.
- Food significantly increases the systemic exposure (AUC) and C_{max} of rufinamide suspension by 31% and 36%, respectively.
- Adverse events were greater under fed conditions.

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Study crb-r33: *Study of a possible influence of food on the pharmacokinetics of CGP 33 101 after single oral administration of a 600 mg dose to healthy volunteers*

And

Study hph9029: *Influence of food intake on the kinetics of a single 600 mg dose: tolerability*

This study has been conducted with the CSF (tablets manufactured by _____ method). A brief overview of some essential components of the study design is given below:

b(4)

Study Design	Randomized, open label, 2-period
Study Population	N=12 healthy subjects enrolled, <u>Age:</u> 21-53 years <u>Gender:</u> 10M & 2F <u>Weight:</u> 55.8-94 kg <u>Race:</u> NA
Treatment Group	A: 3x200 (600 mg) rufinamide tablet SD under fasted conditions B: 3x200 (600 mg) mg rufinamide tablet SD under fed conditions A 7-Day washout between treatments
Dosage and Administration	For the fed arm the doses were administered with 5 minutes of completion of a standardized non FDA breakfast (total 730 kcalories) For the fasted arm subjects were required to fast for ~2 hours post-dose as well Doses given with 100 ml water. Rufinamide 200 mg film coated tablets (CSF- _____ method) Lot 14/479/1
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 96 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 0.25 ng/ml Rufinamide in plasma (from analytical report r66-1987) Linear range : 0.025-6.0 µg/ml for rufinamide in plasma <u>Rufinamide in plasma:</u>

b(4)

	Inter-day Precision (%CV for Quality Controls) : $\leq 12.6\%$ Inter-day accuracy: 98.8-101.4%
PK Assessment	AUC0-last, AUC0-inf, Cmax, Tmax, t1/2
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

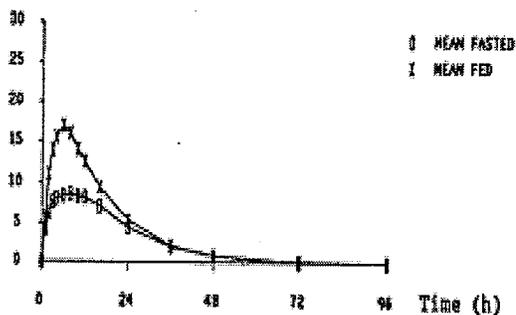
The drug appeared more rapidly in the systemic circulation and its concentration was higher after food intake than under fasting conditions. Under fasting conditions, a plateau of concentrations was observed for almost all subjects from 2 to 16 h postdosing. Beyond 24 h after the administration, the concentrations became similar for the two treatments.

The mean pharmacokinetic parameters are given in the following Table:

Parameter	Administration conditions	
	Fasting	Postprandial
AUC(0-96h) ($\mu\text{mol}\cdot\text{h}/\text{l}$)	240 \pm 67	343 \pm 93
Cmax ($\mu\text{mol}/\text{l}$)	9.2 \pm 1.8	18.0 \pm 3.7
Tmax (h), median	8	6
TI/2 (h)	9.4 \pm 2.3	9.1 \pm 2.1

- As a mean, the AUC were increased by 44 \pm 16 % after food intake. This increase was statistically significant.
- The Cmax was about doubled, again the increase was statistically significant.
- The Cmax occurred slightly more rapidly after food intake, not statistically significant though.
- The terminal elimination TI/2 was the same for the two treatments.

Mean pharmacokinetic profile under fed and fasted conditions is shown in the following figure:



Safety Assessment:

Under fed conditions there was a higher incidence (twice) of headache and low blood pressure. The low blood pressure could probably be attributed to the post prandial state of treatment

Conclusions:

- The extent of absorption was increased by 44%.
- And the rate is more rapid under fed conditions.

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Study 036: A randomized, open label, three-way crossover trial to evaluate the definitive bioequivalence of 400 mg rufinamide tablets manufactured by [redacted] with low, medium and high bulk densities, in healthy fed subjects after a single oral dose of 400 mg of rufinamide.

The tablets used in this study used the commercial process of [redacted] (used in pivotal studies).

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

Study Design	Single Center, Randomized, open label, 3-period, crossover
Study Population	N=24 healthy subjects Age: 20-35 years (mean 26.7 years) Gender: 24M Weight: 59.7-89.4 kg (mean 76.2 kg) Race: 22 White, 2 Other
Treatment Group	A: 400 mg rufinamide tablet SD manufactured by [redacted] with [redacted] (low bulk density) under fed conditions B: 400 mg rufinamide tablet SD manufactured by [redacted] (medium bulk density) under fed conditions C: 400 mg rufinamide tablet SD manufactured by [redacted] (high bulk density) under fed conditions A 7-Day washout between treatments
Dosage and Administration	After an overnight fast, the doses were administered with 5 minutes of completion of a standardized FDA breakfast Doses given with 240 ml water. No caffeine and alcohol allowed from 72 hours prior study initiation Rufinamide 400 mg tablets manufactured by [redacted] (low bulk density) [redacted], Lot 17/367/1 Rufinamide 400 mg tablets manufactured by [redacted] (medium bulk density) [redacted]; Lot B 97-0055 Rufinamide 400 mg tablets manufactured by [redacted] (high bulk density) [redacted]; Lot B 97-0092
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 72 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 0.025 µg/ml Rufinamide in plasma

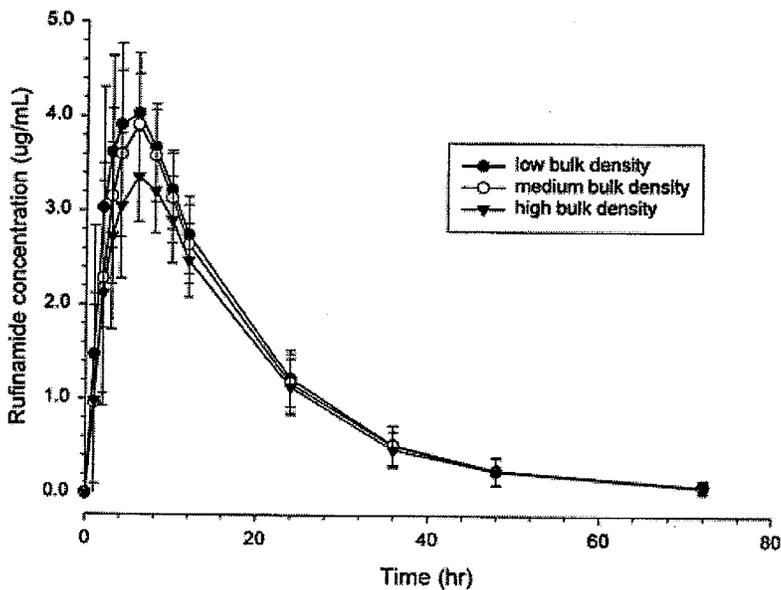
b(4)

b(4)

	Linear range : 0.025-6.0 µg/ml for rufinamide in plasma <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 7.5% Inter-day accuracy: -3.31 to +3.08%
PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2}
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Mean pharmacokinetic profiles of the three treatments (low, medium and high bulk density) is shown in the following figure:



The summary of pharmacokinetic parameters for the different bulk densities is shown in the following Table:

Treatment (rufinamide 400-mg tablet)	C _{max} (µg/mL)	t _{max} (median) (hr)	AUC _(0-t) (µg·hr/mL)	AUC _(0-∞) (µg·hr/mL)	t _{1/2} (hr)
low density	4.41±0.46	4.79±1.77 (5.00)	79.87±13.85	81.86±14.53	10.40±2.15
medium density	4.21±0.50	4.88±1.81 (4.01)	75.73±13.26	77.57±13.93	10.45±2.24
high density	3.59±0.38	5.50±2.50 (6.00)	69.56±13.50	71.54±13.85	10.45±2.15*

*n=23

90% CI for the ratio of the means for the different bulk densities is shown in the following Table:

	90% confidence interval for ratio of means		
	medium vs low bulk density	high vs low bulk density	high vs medium bulk density
AUC _(0-∞) (μg•hr/mL)	(0.932, 0.964)	(0.857, 0.887)	(0.905, 0.936)
AUC _(0-t) (μg•hr/mL)	(0.930, 0.966)	(0.852, 0.884)	(0.898, 0.933)
C _{max} (μg/mL)	(0.928, 0.978)	(0.794, 0.836)	(0.833, 0.878)

The absorption of rufinamide was reduced as the bulk density increased, but the change in the mean values between were within 20% for all of these parameters assessed.

Medium bulk density versus low bulk density: The mean values of AUC_{0-inf}, AUC_{0-t}, and C_{max} for the medium bulk density tablets were lower than those from the low bulk density by 5.2%, 5.2%, and 4.6% respectively. The **bioequivalence criterion was met** for comparison between the two bulk density levels on all three pharmacokinetic parameters.

High bulk density versus low bulk density: The mean values of AUC_{0-inf}, AUC_{0-t}, and C_{max} for the high bulk density tablets were lower than those from the low bulk density by 12.6%, 12.9%, and 18.5%, respectively. The bioequivalence criterion was met for comparison between the two bulk density levels on all pharmacokinetic parameters, **except for C_{max} which had a 90% confidence interval of (0.794, 0.836)**. The ratio of mean C_{max} in this comparison is 0.81.

According to the sponsor, in a previous clinical trial (AE/ET1: n=514 rufinamide treated patients), rufinamide presented a good tolerability profile, and its therapeutic window was shown to be wide (efficacious from doses 200 mg bid to 800 mg bid). It was also recognized that C_{max} does not characterize the rate of absorption particularly well but is an important parameter for safety. Therefore, even with a small deviation from bioequivalence criterion at the lower end after single dose treatment, the comparison between high bulk density versus low bulk density tablets shall be considered as bioequivalent in the clinical setting.

High bulk density versus medium bulk density: In addition to the objectives of the study, a comparison of high versus medium bulk density was performed to verify known information. The mean values of AUC_{0-inf}, AUC_{0-t}, and C_{max} for the high bulk density tablets were lower than those from the medium bulk density by 7.8%, 8.2%, and 14.6% respectively. The **bioequivalence criterion was met** for comparison between the two bulk density levels on all three pharmacokinetic parameters.

Conclusions:

All three tablets containing different bulk densities (low, medium and high) were found bioequivalent, although the C_{max} for the high bulk density tablets was marginally lower

than that of the low bulk density tablets. However, the higher the bulk density of rufinamide, the lower the level of absorption in terms of AUC and Cmax.

Note: the proposed specification for the bulk density for the drug substance is:

Bulk density	Acceptance criteria	USP <616> Bulk density
Mean value (n = 3)		3.2.S.4.2.2
Individual values		

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Study 015: Bioequivalence of two 200 mg tablets of rufinamide after single administration of a 600 mg dose to healthy male volunteers

This study compares 200 mg tablets prepared by _____ (used in some open extension studies) (FMI) to 200 mg tablets prepared by _____ (previously studied).

b(4)

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

Study Design	open label, 2-period, crossover
Study Population	N=12 healthy subjects Age: 23-32 years (mean 26 years) Gender: 12 M Weight: 63.8-99.3 kg (mean 78.5 kg) Race: 12 White
Treatment Group	A: 3 x 200 mg rufinamide tablet SD manufactured by _____ (FMI) under fed conditions B: 3 x 200 mg rufinamide tablet SD manufactured by _____ (CSF) under fed conditions A 14-Day washout between treatments
Dosage and Administration	After an overnight fast, the doses were administered within 5 minutes of completion of a standardized FDA breakfast Doses given with 240 ml water. No caffeine and alcohol allowed from 72 hours prior study initiation Rufinamide 200 mg tablets _____ (FMI); Lot 17/068/2 Rufinamide 200 mg _____, Lot 17/101/1
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 96 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method (crb r66/1987)</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 0.025 µg/ml Rufinamide in plasma Linear range : 0.025-6.0 µg/ml for rufinamide in plasma <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 11% Inter-day accuracy: -3.31 to +3.08%
PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2}
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events

b(4)

b(4)

PD Assessment	None
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Pharmacokinetic Results:

The mean pharmacokinetic parameters from the _____ tablets are shown in the following Table:

b(4)

Treatment	C _{max} (μmol/L)	t _{max} * (h)	t _{1/2} (h)	AUC (μmol.h/L)
_____ (FMI)	25.8 ± 3.6	6	9.93 ± 2.56	488 ± 129
_____ tablets	19.9 ± 2.8	6	10.61 ± 2.60	414 ± 118

*. Median

The mean AUC after administration of the _____ tablets was 18% higher than that after administration of the _____ tablets. The mean C_{max} was 30% higher. The mean apparent elimination half-life was around 10 h for both tablets.

b(4)

The 90% CIs are shown in the following Table:

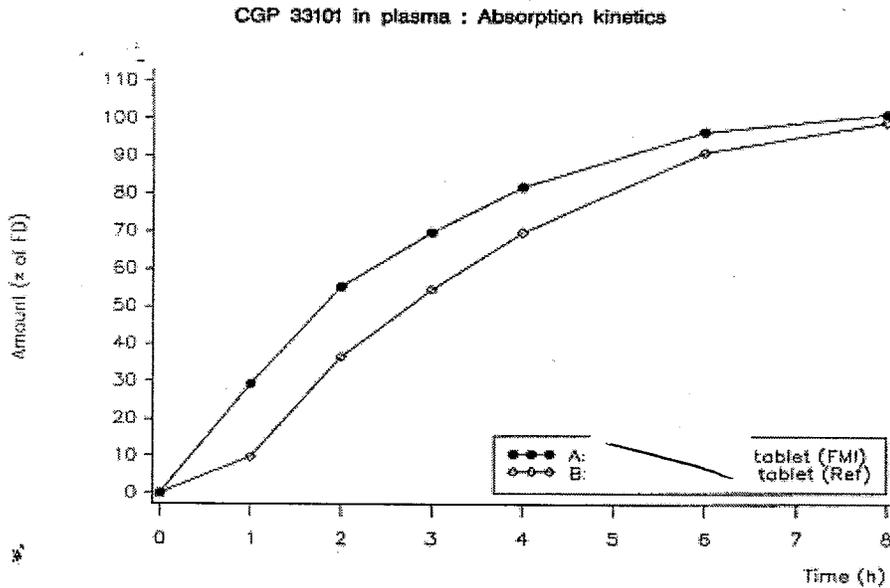
Parameter	Ratio	90% confidence interval of ratio
AUC	1.18	[1.14, 1.23]
C _{max}	1.29	[1.20, 1.39]

The _____ tablet can be considered as bioequivalent with regard to the extent of absorption, as based on the 90% confidence interval of ratio for AUC [1.14, 1.23] which lies within the limits [0.80-1.25] accepted to establish bioequivalence.

The 90% confidence interval of C_{max} ratio [1.20-1.39] does not lie within the limits [0.80-1.25] accepted to establish bioequivalence.

The median value of t_{max} was the same for both tablets. But T_{max} could not precisely characterize the absorption rate because the concentration peak was broad in most subjects. Therefore, the individual times to absorb 10%, 50% and 90% of the total amount absorbed and the mean absorption profiles were determined by the Wagner-Nelson method. The mean absorption plasma profiles (Figure below) suggested a slightly more rapid absorption from the _____ tablets.

b(4)



b(4)

The mean time to absorb 10%, 50% and 90% of the total amount absorbed from the [redacted] tablets was 34, 22 and 18% lower, respectively. The difference between the two treatments was significant ($p = 0.0302$) for the time 10%, not significant ($p = 0.0911$) for the time 50%, and marginal ($p = 0.0566$) for the time 90%. Therefore, CGP 33101 was slightly more rapidly absorbed/dissolved from the [redacted] tablet than from the [redacted] tablet.

b(4)

Conclusions:

As based on mean AUC and Cmax the amount of CGP 33101 absorbed from the [redacted] tablet (FMI) was slightly higher than that from the [redacted] tablet and the absorption rate slightly more rapid.

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Study 037: *A randomized, open label, three-way crossover trial to compare the bioavailability of single 400 mg doses of rufinamide administered as the Final Market Image (FMI) and as the Clinical Service Formulation (CSF) in healthy subjects under fed conditions*

The primary objective of this study was to evaluate the bioequivalence of the pharmacokinetic profile of a single 400 mg dose of the rufinamide FMI tablet (manufactured by _____ used in pivotal studies) and CSF tablet (manufactured by _____ under fed conditions). The secondary objective was to evaluate the effect of food on the bioavailability of rufinamide FMI tablets. b(4)

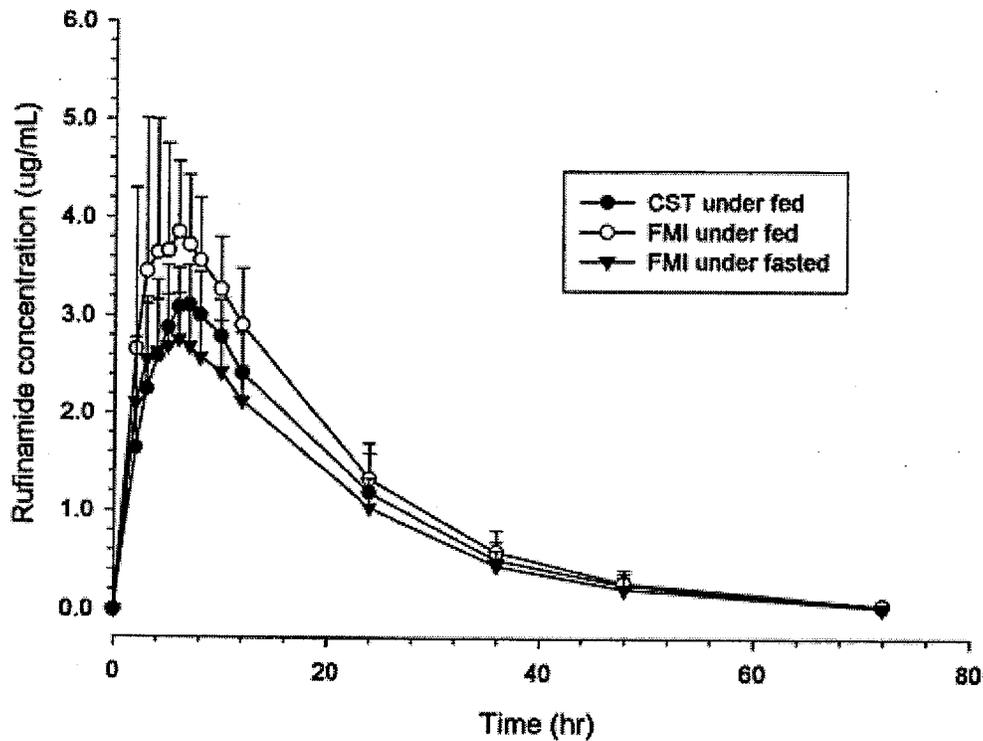
A brief overview of some essential components of the study design is given below:

Study Design	Single Center, Randomized, open label, 3-period, crossover
Study Population	N=25 healthy subjects enrolled, 24 completed, One subject was disqualified after completing the first treatment period due to a positive drug test at the baseline for period 2. <u>Age:</u> 18-45 years (mean 29.84 years) <u>Gender:</u> 23M and 2F <u>Weight:</u> 62-90 kg (mean 76.41 kg) <u>Race:</u> 9 White, 15 Black, 1 Other
Treatment Group	A: 400 mg rufinamide FMI tablet SD under fed conditions B: 400 mg rufinamide FMI tablet SD under fasted conditions C: 400 mg rufinamide CSF tablet SD under fed conditions A 7-Day washout between treatments
Dosage and Administration	After an overnight fast, the doses were administered with 5 minutes of completion of a standardized FDA breakfast (~1000 cal) Doses given with 240 ml water. No caffeine and alcohol allowed from 72 hours prior study initiation Rufinamide 400 mg FMI tablets; Lot B970055 Rufinamide 200 mg CSF tablets; Lot 17/101/1
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 72 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 0.025 µg/ml Rufinamide in plasma Linear range : 0.025-6.0 µg/ml for rufinamide in plasma

	<u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : $\leq 8.2\%$ Inter-day accuracy: -4.0 to +4.0%
PK Assessment	AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , t _{1/2}
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

Mean pharmacokinetic profiles of the three treatments is shown in the following figure:



The mean pharmacokinetic parameters for the three treatments are given below:

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	2x200-mg tablet CSF-fed (mean ± SD)	400-mg tablet FMI-fed (mean ± SD)	400-mg tablet FMI-fasted (mean ± SD)
AUC_(0-∞) (µg*hr/mL)	69.85 ± 13.35	84.33 ± 13.84	63.25 ± 14.61
AUC_(0-last) (µg*hr/mL)	68.63 ± 13.16	83.10 ± 13.33	61.78 ± 14.34
C_{max} (µg/mL)	3.30 ± 0.37	4.42 ± 0.57	2.85 ± 0.52
t_{1/2} (hr)	10.71 ± 1.64	10.63 ± 1.88	10.75 ± 2.03
t_{max} (hr) *	6.00	4.00	6.00

* Median values are provided for t_{max}.

Extent of absorption was assessed in terms of AUCinf. The mean AUC ratios of FMI-fed versus CSF-fed, FMI-fed versus FMI-fasted, and FMI-fasted versus CSF-fed were 1.21, 1.32, and 0.93, respectively.

The rate of absorption was assessed in terms of C_{max} and t_{max}. The mean C_{max} ratios of FMI-fed versus CSF-fed, FMI-fed versus FMI-fasted, and FMI-fasted versus CSF-fed were 1.33, 1.56, and 0.87, respectively. The median t_{max} values ranged from 4.00 to 6.00 hr.

The 90% CI for ratio of means of AUC and C_{max} are given in the following Table:

	90% confidence interval for ratio of means		
	FMI-fed vs. CSF-fed	FMI-fed vs. FMI-fasted	FMI-fasted vs. CSF-fed
AUC_(0-∞) (µg*hr/mL)	(1.16, 1.26)	(1.29, 1.40)	(0.87, 0.94)
AUC_(0-last) (µg*hr/mL)	(1.16, 1.27)	(1.30, 1.42)	(0.86, 0.94)
C_{max} (µg/mL)	(1.27, 1.41)	(1.49, 1.64)	(0.82, 0.90)

FMI-fed versus CSF-fed indicated AUC(0-inf) and AUC(0-last) failed to meet the regulatory bioequivalence criterion of 0.80 to 1.25 by a small margin, 1.16 to 1.26 and 1.16 to 1.27, respectively. The mean values of AUC(0-inf), AUC(0-last) and C_{max} for FMI were higher than those for CSF by 21%, 22%, and 34%, respectively. The bioequivalence criterion was not met for C_{max}.

FMI-fed versus FMI-fasted indicated all three parameters were outside the 0.8 to 1.25 range, indicating that food has a statistically significant increase in the absorption of the FMI tablet. The mean values of AUC(0-inf), AUC(0-last) and C_{max} for FMI under the fed condition were higher than those under fasted condition by 34%, 36%, and 56%, respectively.

FMI-fasted versus CSF-fed indicated the regulatory bioequivalence criteria were met for all three parameters. The mean values of AUC(0-inf), AUC(0-last) and Cmax for the 400-mg FMI tablet under fasted condition were lower than those for the 2x200-mg CSF tablets under fed conditions by 10%, and 14%, respectively.

Adverse Events:

Adverse events were reported by 11 of 25 subjects. Only 3 of the subjects reported more than one adverse experience during the study. The most common adverse events were headache (7 episodes in 6 subjects) and drowsiness (4 episodes in 3 subjects). Single occurrences of the following adverse events also were reported: right side pain, dizziness, nausea, and diarrhea. All events were classified as mild to moderate in severity.

Conclusions:

- FMI tablets _____ are more bioavailable than the CSF tablets under fed conditions (21% increase in AUC and 34% increase in Cmax). According to the sponsor, clinical trials show that rufinamide has a wide therapeutic index, with dosing recommendation between 400-3200 mg. Therefore, this increase in exposure is unlikely to affect the safety profile of rufinamide.
- Food significantly increases the bioavailability of the FMI tablets by 34% increase in AUC(0-inf) and 56% increase in Cmax.

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Study epi 006: Biological equivalence study of CGP 33101: Comparison between Japanese clinical formulation and FMI

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

Study Design	Single Center, Randomized, open label, 3-period, crossover
Study Population	N=16 healthy subjects enrolled, 24 completed, One subject was disqualified after completing the first treatment period due to a positive drug test at the baseline for period 2. <u>Age:</u> 20-28 years (mean 23 years) <u>Gender:</u> 16M <u>Weight:</u> 57-70 kg (mean 62 kg) <u>Race:</u> 16 Japanese
Treatment Group	A: 200 mg rufinamide Japanese tablet SD under fed conditions B: 200 mg rufinamide FMI tablet SD under fasted conditions A 14-Day washout between treatments
Dosage and Administration	After an overnight fast, the doses were administered after breakfast Doses given with 150 ml water. No caffeine and alcohol allowed from 72 hours prior to study initiation Rufinamide 200 mg FMI tablets; Lot 17/068/2 Rufinamide 200 mg Japanese tablets; Lot 015
Sampling: Blood	<u>Rufinamide concentrations:</u> Up to 96 hours post-dose.
Urine	none
Feces	none
Analysis	<u>Method</u> HPLC-UV <u>Lower Limits of Quantitation</u> <u>Plasma</u> Rufinamide 0.025 µg/ml <u>Rufinamide in plasma:</u> Inter-day Precision (%CV for Quality Controls) : ≤ 5.6% Inter-day accuracy: 94.3-101.2%
PK Assessment	AUC0-t, AUC0-inf, Cmax, Tmax, t1/2
Safety Assessment	Medical history, vital signs, ECGs, laboratory tests and adverse events
PD Assessment	None

Pharmacokinetic Results:

The mean pharmacokinetic parameters are shown in the following Table:

Parameter	Japanese Tablets	FMI	Ratio FMI vs JPN	90% CI
Cmax (ng/ml)	2037.5	2893.9	1.42	1.356-1.484
AUC0-96 (ng.h/ml)	37081.1	45484.3	1.23	1.184-1.27
Tmax (h)	4	3.5	-	-
T1/2 (h)	9.1	9.0	-	-

Conclusions:

The two formulations were not bioequivalent for both Cmax and AUC0-96. The Cmax and AUC were 42% and 23% higher respectively.

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X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Proposed Dissolution Method Specifications

Apparatus Flow-through cell open system (Apparatus 4) in accordance with USP <724>, "Drug Release".

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

Filter _____ in the filter insert, then a _____ filter and a _____, or equivalent filter. For the testing of 400 mg tablet, additional _____ is used to fill the open tube above the sieve.

b(4)

Two-point specifications (Q) with the acceptance criteria shown in the following Table are proposed for the marketed product.

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)

Dissolution of _____ tablets and _____ tablets using flow cell method:

The flow through cell method was used to assess release from the clinical service formulations (CSF tablets produced by _____) and the final market image tablet.

b(4)

The *in vitro* dissolution tests were conducted on the **CSF formulation**: 50, 100 and 200 mg tablet (batches 13/924/1, 13/925/1 and 13/926/1 respectively) using the flow cell with laminar flow. The flow rates were 16 and 25 mL/min were used. In all cases, tablets were exposed to HCl, pH 1 for one hour. Thereafter, phosphate buffer pH 6.8 was used as a dissolution medium.

The discriminatory power of the method was further supported on **FMI formulations** with study 036 by investigating the influence of various bulk densities on the dissolution rate of the drug substance.

Figure 1 Dissolution results of  tablets 50 mg, 100 mg and 200 mg used in studies A184 and A233

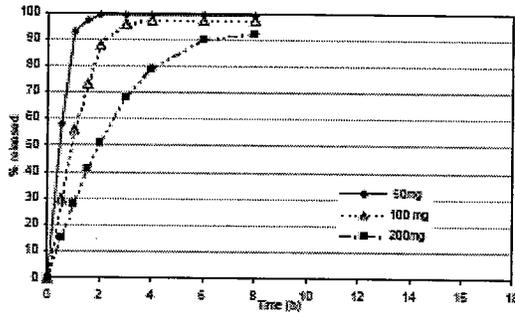
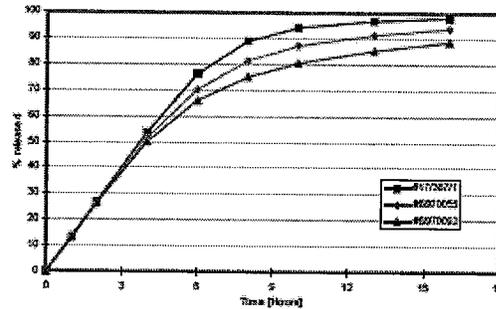


Figure 2 Dissolution results of  tablets 400 mg used in study 36



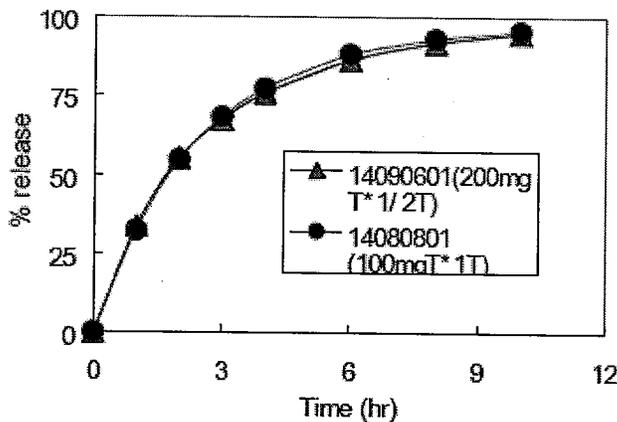
b(4)

The dissolution test results indicate that the release rate decreases with increasing strength of the tablet, from 50 to 200 mg with the  tablet and further to 400 mg with the final market image:  tablet (Figure 1 and Figure 2).

Comparison of Divided and Intact  Tablets:

b(4)

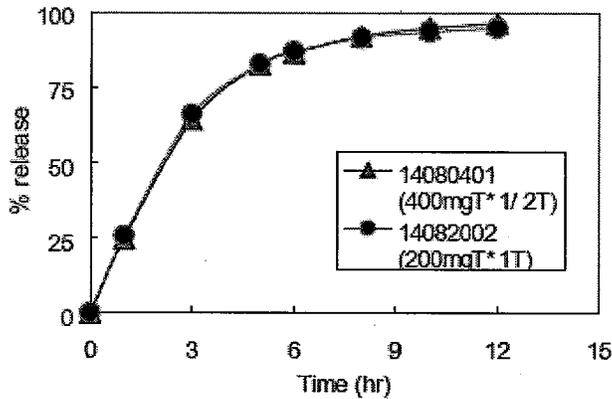
200 mg x 1/2 tablet vs. 100 mg x 1 tablet:



Since the f2 values were over 50 for all batches evaluated, the data demonstrate that dissolution of the split 200 mg tablets was equivalent to the intact 100 mg tablets.

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400 x 1/2 tablets vs. 200 mg x 1 Tablet:



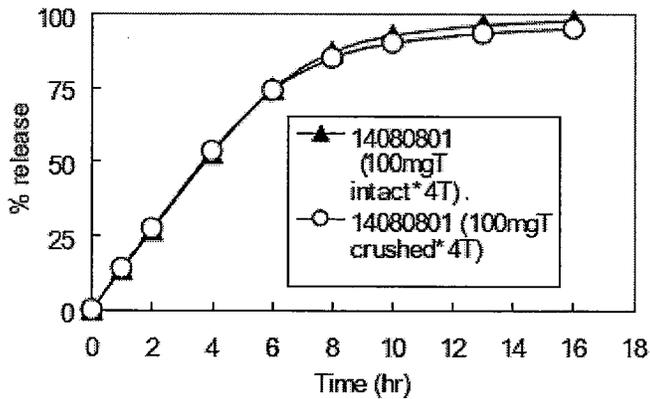
Since the f2 values were over 50 for all batches evaluated, the data demonstrate that dissolution of the split 400 mg tablets was equivalent to the intact 200 mg tablets.

Comparison of Crushed versus intact tablet:

b(4)

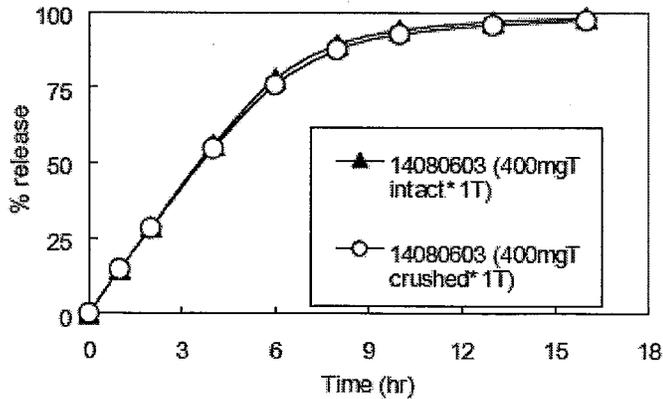
Tablets were crushed in a mortar and pestle to about 2 mm diameter particles.

100 mg intact x 4 tablets vs 100 mg crushed x 4 tablets:



The f2 values were over 50, the data demonstrate that dissolution of the crushed 100 mg tablets was equivalent to the intact 100 mg tablets.

400 mg intact x 1 tablets vs 400 mg crushed x 1 tablets:



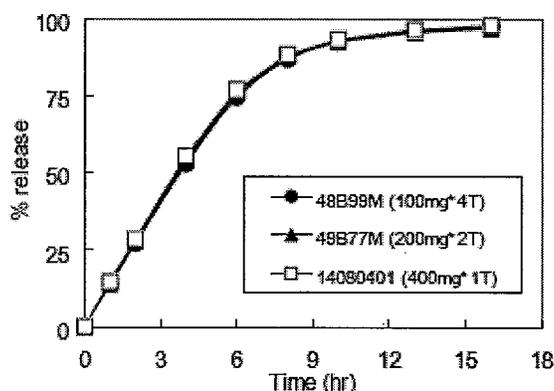
The f2 values were over 50, the data demonstrate that dissolution of the crushed 400 mg tablets was equivalent to the intact 400 mg tablets.

Comparison of Single and Multiple Strengths:

The above data also demonstrates the equivalency of multiple and single tablets at the same total amount/dose. For example, four 100 mg tablets and one 400 mg tablet were both equivalent to crushed tablets of 400 mg strength. This equivalency shows that either four 100 mg tablets or one 400 mg tablet could be used. Similar results were obtained for two 200 mg tablets.

b(4)

The following figure shows dissolution comparison of single and multiple strengths of the the \ tablets:



Overall, the release of rufinamide in dissolution tests suggest that the dissolution may be rate limiting for the absorption of the drug *in vivo*, doses of 400 mg releasing only approximately 50% in 4 hours.

Technical Transfer from Novartis to Eisai and Process Optimization

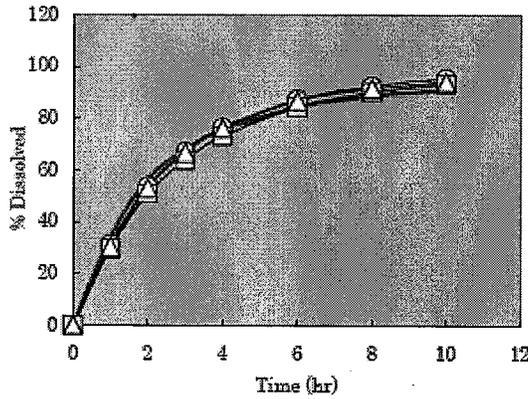
The manufacturing process at Eisai is essentially the same as that at Novartis. Components and compositions are common to all dosage strengths, and the formulations are the same as those of Novartis. Pivotal clinical trials were done with the Novartis batches.

A difference in the processes is that Opadry[®] _____, a pigment blend, is used in the filmcoating process at Eisai. Opadry[®] _____ contains hypromellose, _____, titanium dioxide, _____ and ferric oxide (red). At Novartis, small amounts of _____

b(4)

The dissolution profiles of Rufinamide Film-coated Tablets manufactured at Eisai Misato

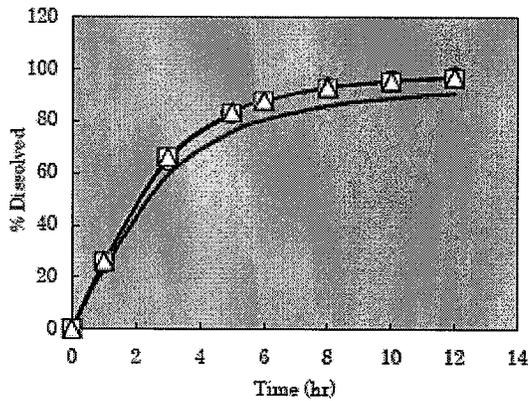
(three batches each of the three strengths) were compared with those of the Novartis process validation batches.



The f2 values were over 50 (70.86), the data demonstrate that dissolution of the crushed 100 mg Eisai tablets was equivalent to the Novartis 100 mg tablets.

- Eisai Misato Batch 14080801
- Eisai Misato Batch 14081102
- △ Eisai Misato Batch 14081703
- Novartis Batch 980112

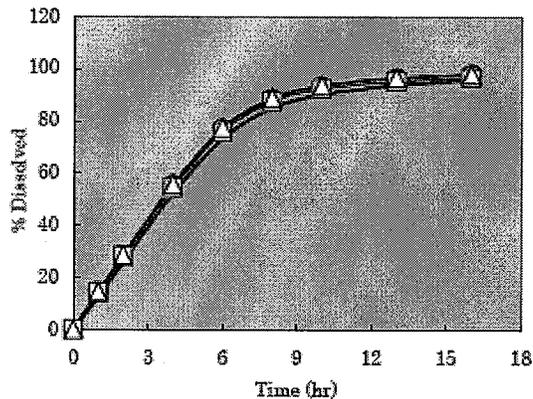
Figure: Dissolution of 100 mg Tablets



The f2 values were over 50 (58.52), the data demonstrate that dissolution of the crushed 200 mg Eisai tablets was equivalent to the Novartis 200 mg tablets.

- Eisai Misato Batch 14090601
- Eisai Misato Batch 14082002
- △ Eisai Misato Batch 14082303
- Novartis Batch 980114

Figure: Dissolution of 200 mg Tablets



The f2 values were over 50 (72.52), the data demonstrate that dissolution of the crushed 400 mg Eisai tablets was equivalent to the Novartis 400 mg tablets.

- Eisai Misato Batch 14080401 — Novartis Batch 980116
- Eisai Misato Batch 14080502
- △ Eisai Misato Batch 14080603

Figure: Dissolution of 400 mg Tablets

This shows that the batches made at Eisai, are similar to the batches made at Novartis.

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BIOANALYTICAL METHODS

Report crb-r66-1987: Determination of CGP 33101 in human plasma and urine by HPLC

Method: HPLC with UV detection

LLOQ: 0.025 µg/ml in plasma and 0.125 µg/ml in urine

Intra-day Precision and accuracy: mean recovery % $\geq 98.4\%$, %CV $\leq 5.7\%$ in plasma

Intra-day Precision and accuracy: mean recovery % $\geq 99.3\%$, %CV $\leq 4.6\%$ in urine

Inter-day Precision and accuracy: mean recovery % $\geq 101\%$, %CV $\leq 3.8\%$ in plasma

Inter-day Precision and accuracy: mean recovery % $\geq 98\%$, %CV $\leq 1.6\%$ in urine

Freeze-thaw cycles: 5

Storage Conditions: 72 days at -20°C

Report cpd-91042: A quantitative analytical method for the determination of CGP 33101 in human plasma by HPLC

Method: HPLC with UV detection

Linear Range: 50-4000 ng/ml

LLOQ: 50 ng/ml in plasma

Intra-day Precision and accuracy: mean recovery % 92.8-111.1%, %CV $\leq 4.1\%$ in plasma

Inter-day Precision and accuracy: mean recovery % 96.7-100.8%, %CV $\leq 6.0\%$ in plasma

Recovery: $\geq 88.3\%$

Stability: 6 hours at room temperature

Freeze-thaw cycles: 3

Storage Conditions: 4 weeks at -20°C

Report cpd-91046: An automated analytical method for the determination of CGP 33101 in human plasma by HPLC

This method was developed to automate the preparation and analysis of human plasma samples for CGP 33101 concentrations using a laboratory robotic system that aliquots

biological samples, adds the internal standard and buffer, extracts the compound into the organic phase and concentrates the extract for HPLC analysis.

Method: HPLC with UV detection

Linear Range: 50-4000 ng/ml

LLOQ: 50 ng/ml in plasma

Intra-day Precision and accuracy: mean recovery % 90.4-114.1%, %CV \leq 11.3% in plasma

Inter-day Precision and accuracy: mean recovery % 95.4-110.8%, %CV \leq 7.7% in plasma

Report crb-r27-191: Automated method for the determination of CGP 33101 in human plasma by HPLC using either the _____ or the _____

b(4)

Method: HPLC with UV detection

Good agreement between the two systems with correlation coefficient of 0.99

Linear Range: 50-20,000 ng/ml

LLOQ: 50 ng/ml in plasma

Intra-day Precision and accuracy: mean recovery % 95-107%, %CV \leq 7% in plasma for both systems

Inter-day Precision and accuracy: mean recovery % 93-104%, %CV \leq 11% in plasma

Mean Recovery: 98 \pm 4%

Stability: plasma samples 11 hours at room temperature; extract 65 hours at room temperature

Report crb-r37-1992: Cross-comparison of CGP 33101 concentration values measured in spiked plasma samples with methods used at CIBA-GEIGY, Ardsley, USA and CRB, France

Method: HPLC with UV detection

Several QC samples were compared for the USA and France methods. For the two methods, the mean recoveries (%) were 104.1% for the USA method and 95.9 % for the France method. The individual recoveries were in the range of _____

Good agreement between the two systems with correlation coefficient of 0.99, suggesting two results can be reliably compared.

b(4)

Report crb-r6-1993: Automated determination of CGP 33101 and its metabolite CGP 47 292 and detection of CGP 47 291 in human urine by HPLC.

Method: HPLC with UV detection

Linear Range: 2.5-50 µg/ml for CGP 33 101 in urine
5-200 µg/ml for CGP 47 292 in urine
LLOQ: 2.5µg/ml (10 µmol/l) for CGP 33 101 in urine
5µg/ml (20 µmol/l) CGP 47 292 in urine

Intra-day Precision and accuracy: mean recovery % 97-98%, %CV ≤ 7% for CGP 33 101 in urine

Intra-day Precision and accuracy: mean recovery % 100-107%, %CV ≤ 5% for CGP 47 292 in urine

Inter-day Precision and accuracy: mean recovery % 93-101%, %CV ≤ 6.0% for CGP 33 101 in urine

Inter-day Precision and accuracy: mean recovery % 87-103%, %CV ≤ 16% for CGP 47 292 in urine

Report bpkf-1995-021: Quantitative determination of CGP 33101 in small human plasma aliquots by HPLC and UV detection

Method: HPLC with UV detection

Linear Range: 0.025-100 µg/ml
LLOQ: 0.025 µg/ml in plasma

Intra-day Precision and accuracy: mean recovery % 92.8-102.3%, %CV ≤ 5.7% in plasma

Inter-day Precision and accuracy: mean recovery % 98.9-103.7%, %CV ≤ 15% in plasma

Recovery: ≥ 79%

Report crb-r23-1993: Stability of CGP 33 101 and its main metabolite CGP 47 292 in biological fluids and in solution

Method: HPLC with UV detection

The main objective in this study was to evaluate stability of the samples. This is an extension of reports crb-r66/1987 and crb-r 27/1991 and crb-r6-1993. The following conclusions were made:

CGP 33 101 in plasma:

Stability: 11 hours at room temperature
Freeze-thaw cycles: 2
Storage Conditions: 20 months at -20°C, 2h at 5 °C

CGP 47 292 in urine:

Stability: 20 hours at room temperature
Freeze-thaw cycles: 3
Storage Conditions: 9 months at -20°C, 2h at 5 °C

Report r00-1862: Quantitative determination of RUF 331 (rufinamide) in human plasma by LC/MS (2001)

Method: LC/MS

Specificity: The method is specific for RUF331 in human plasma; the
Interference at the LLOQ is less than 20% of mean
peak area.
Extraction recovery: 71.0% (range)

b(4)

Linear range: 50 to 4000 ng/mL
LLOQ: 50 ng/ml

Intra-day accuracy and precision: At LLOQ: accuracy 99.6% to 102%,
Precision % CV: 2.98% to 4.53%.
Above LLOQ: accuracy 89.6% to 104%,
Precision % CV: 1.24% to 3.22%.

Inter-day accuracy and precision: At LLOQ: accuracy 101%,
Precision % CV: 3.76%.
Above LLOQ: accuracy 91.8% to 102%,
Precision % CV: 2.04% to 3.51%.

Report r99-046: 96-well disk plate solid phase extraction and parallel column chromatography coupled with UV detection for the quantitative determination of RUF331 in plasma in presence of concomitant anti-epileptic drugs: Method description and validation

Method: HPLC with UV detection

Specificity No significant interference from different plasma batches of healthy human not given any medication and from plasma of patients given phenytoin, valproic acid, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin or gabapentin. With phenobarbital, a peak interfered with that of the internal standard.

Extraction recovery: 66% for RUF331

Linear range 0.05-20 µg/mL

LLOQ 0.05 µg/mL

Intra-day validation: The mean accuracy (96-101% for the upper 3 QCs and 107% at the LLOQ) and the precision (2-10% for the upper 3 QCs and 9% at the LLOQ) were within the tolerance range

Inter-day validation: The mean accuracy (99-102% for the upper 3 QCs and 104% at the LLOQ) and the precision (3-9% for the upper 3 QCs and 7% at the LLOQ) were within the tolerance range

Stability: Sample on the autosampler: 38 h at 4C

Report AM-034-R40:

Method: LC/MS/MS (used for study MTD)

Specificity No significant interference with and without internal standard.

Extraction recovery: 91.1 for RUF331

Linear range 20-20000 ng/mL

LLOQ 20 ng/mL

Intra-day validation: precision: %CV \leq 1.9% in plasma, accuracy >98.1%

Inter-day validation: %CV \leq 5.3% in plasma, accuracy >99.6%

Dilution: % CV 0.7%

Stability: At room temperature for 6 hrs

Freeze-thaw cycles : 3

Processed samples: 41 hours

Long term stability for 34 days at -20C

Stock solution: 7days at 4C, 24 hours at room temperature

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IN VITRO STUDIES

In Vitro Inhibition potential of rufinamide:

Study DMET 96012: Evaluation of CGP 33101 as an inhibitor of human CYP 450 enzymes:

CGP 33101 was tested for inhibition of several of the major human P450s in vitro. Whenever possible, known competitive or mechanism-based inhibitors of P450 activity were included as positive controls.

CGP 33101, was evaluated for its ability to inhibit the following human P450 enzymes:

CYP1A2	7-Ethoxyresorufin O-dealkylation
CYP2A6	Coumarin 7-hydroxylation
CYP2C9	Tolbutamide methyl-hydroxylation
CYP2C19	S-Mephenytoin 4'-hydroxylation
CYP2D6	Dextromethorphan & demethylation
CYP2E1	Chlorzoxazone 6-hydroxylation
CYP3A4/5	Testosterone 6 β -hydroxylation
CYP4A9/11	Lauric acid 12-hydroxylation

To evaluate CGP 33101 as a competitive inhibitor of P450 activity, human liver microsomes were incubated with marker substrates at K_m and $4 \times K_m$ in the presence or absence of CGP 33101 at concentrations ranging from 10 to 300 μM . The highest concentration of 300 μM is approximately 30 times plasma trough levels (11 μM) in humans. The data were analyzed by Dixon plots to determine the type of inhibition (competitive or non-competitive) and the inhibitory constant (K_i). For each P450 enzyme assay, a positive control (known competitive inhibitor) was included, as indicated below:

CYP1A2	α -Naphthoflavone
CYP2A6	Nicotine
CYP2C9	Sulfaphenazole
CYP2C19	Hexobarbital
CYP2D6	Quinidine
CYP2E1	4-Methylpyrazole
CYP3A4/5	Ketoconazole
CYP4A9/11	No competitive inhibitor is available for this enzyme

To evaluate CGP 33101 as a mechanism-based inhibitor of P450 activity, human liver microsomes were incubated for 0 or 10 min with CGP 33101 prior to the addition of the marker substrate at K_m . The concentration of CGP 33101 selected for this experiment

corresponded to the highest concentration of CGP 33101 that caused less than 20% competitive inhibition of P450 activity at a substrate concentration equal to K_m .

A mechanism-based inhibitor has not been identified for each P450 enzyme. However, the following mechanism-based inhibitor served as positive controls.

CYP1A2	Furafylline
CYP2A6	8-Methoxypsoralen
CYP2E1	3-Amino-1,2,4-triazole
CYP3A4/5	Troleandomycin

According to the sponsor, the results of this study suggest that, under the experimental conditions examined, CGP 33101 has little or no capacity to function as a competitive or mechanism-based inhibitor of the major P450 enzymes expressed in human liver microsomes, including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11 as seen in the following Table:

P450 Enzyme	P450 Activity	Competitive Inhibitor		Mechanism-based inhibitor
		Ki (μM)	[Plasma]/Ki ^a	
CYP1A2	7-Ethoxyresorufin O-dealkylase	> 1350 ^b	< 0.0081	None observed
CYP2A6	Coumarin 7-hydroxylase	> 1350	< 0.0081	None observed
CYP2C9	Tolbutamide methyl-hydroxylase	> 1350	< 0.0081	None observed
CYP2C19	S-Mephenytoin 4'-hydroxylase	> 1350	< 0.0081	None observed
CYP2D6	Dextromethorphan O-demethylase	> 1350	< 0.0081	None observed
CYP2E1	Chlorzoxazone 6-hydroxylase	> 450	< 0.0244	None observed
CYP3A4/5	Testosterone 6 β -hydroxylase	> 1350	< 0.0081	None observed
CYP4A9/11	Lauric Acid 12-hydroxylase	> 1350	< 0.0081	None observed

a: plasma trough level is 11 μM

Reviewer's Comment:

The reviewer disagrees with the sponsor's conclusion that rufinamide has no capacity to inhibit any of the CYP 450 isoenzymes, because the plasma concentration that the sponsor has used is a trough level of 11 μM . This does not represent the highest concentrations observed at the highest dose of rufinamide in a clinical study. The Cavss based on the population analysis was 12 $\mu\text{g/ml}$ (50 μM). The mean C_{max} based on the MTD study with the highest proposed dose 3200 mg was 22.75 $\mu\text{g/ml}$ (96 μM) (range 19.67-26.69 $\mu\text{g/ml}$). Some subjects, mainly children have concentrations that were higher than 26 $\mu\text{g/ml}$ in the efficacy studies (eg. 46.9 and 67.05 $\mu\text{g/M}$, i.e 197 μM and 281 μM , respectively in two subjects). Given these higher concentrations the following Table shows the I/Ki values at these higher concentrations

Rufinamide Concentration $\mu\text{g/ml}$ (μM)	I/Ki	
	For Ki=1350	For Ki-450
12 (50)	0.03	0.11
26 (96)	0.07	0.213
47(197)	0.146	0.437
67(282)	0.202	0.626

The K_i values for each of the P450s assayed were $> 1350 \mu\text{M}$ ($>450 \mu\text{M}$ for CYP2E1). Since the I/Ki values based on the higher exposures as seen in clinical studies are greater than 0.1, it is possible that drug interactions may take place with these isoenzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11), with I/Ki being greater for CYP 2E1 as compared to the other isoenzymes, although, even with an C_{avss} of $26 \mu\text{g/ml}$ ($96 \mu\text{M}$), the I/Ki is 0.08 for most of the CYP 450, suggesting borderline possibility of an interaction and a higher potential drug-drug interaction with CYP 2E1 substrates..

The sponsor states that “the highest plasma concentration of rufinamide found in clinical study (Study 22) was approximately $200 \mu\text{mol/L}$ ($45.9 \mu\text{g/mL}$) during repeated dosing at approximately 45 mg/kg per day, which was less than half of the lowest estimated K_i . Thus, rufinamide is not expected to inhibit the CYP dependent metabolism of concomitant medications”. The highest concentration from study 22 was $46.9 \mu\text{g/mL}$ and may have been a typographical error, although this concentration being less than half the lowest estimated K_i is not satisfactory. The I/Ki should be 1/10 th the estimated K_i to rule out any in vivo drug interactions.

Inhibition potential of CYP 2B6 has not been evaluated.

Study B05012: Induction potency of E2080 for CYP 450, UDP-Glucuronosyl transferase and carboxylesterase in human hepatocytes

To evaluate the induction potency of E2080 (rufinamide) on cytochrome P450 (CYP), UDP-glucuronosyl transferase (UDPGT) and carboxylesterase (CES), the effect on mRNA levels of CYP1A1, CYP1A2, CYP3A4, CES1 and CES2, and on enzyme activities of CYP3A4, UDPGT and CES by E2080 were studied using 3 lots of fresh human hepatocytes and 2 lots of cryopreserved human hepatocytes.

Rifampicin (RIF), β -naphthoflavone (BNF), clofibrate (CLO) and Phenobarbital (PB) were used as positive controls and their concentrations were set to 10, 10, 30 $\mu\text{mol/L}$ and 2 mmol/L, respectively. RIF is one of the most potent enzyme inducers in humans and induces several CYP isoforms and specific isoforms of UDPGT. PB, which is also known to induce several metabolizing enzymes including CYP3A4 and some transporters, was used as a reference compound. Since some isoforms of UDPGT are reported to be target

genes of the nuclear receptor peroxisome proliferator-activated receptor (PPAR), the effect of CLO, a PPAR agonist, was concomitantly evaluated.

The enzyme activities of CYP3A4, UDPGT and CES were evaluated by midazolam 1'-hydroxylation, 4-methylumbelliferone (4-MU) glucuronidation and p-nitrophenylacetate (PNPA) hydrolase activity, respectively.

The responses to compounds used were qualitatively similar between fresh and cryopreserved hepatocytes, and thus the mean induction ratios with the standard deviation of all of 5 lots used are tabulated as follows.

Summary Table 1 Induction ratio of mRNA level compared with vehicle control in 5 lots of human hepatocytes

Sample	IA1	IA2	3A4	CES1	CES2
Control ^{a)} 0.1% DMSO	1.00 ± 1.10	1.00 ± 0.67	1.00 ± 0.94	1.00 ± 0.85	1.00 ± 0.47
E2080 2 µmol/L	1.17 ± 0.09	1.07 ± 0.12	1.12 ± 0.49	1.15 ± 0.16	0.86 ± 0.09
E2080 10 µmol/L	1.21 ± 0.17	1.21 ± 0.19	1.29 ± 0.41	1.22 ± 0.15	0.90 ± 0.12
E2080 20 µmol/L	1.99 ± 0.81	1.55 ± 0.78	2.02 ± 1.03	1.52 ± 0.66	1.10 ± 0.44
E2080 50 µmol/L ^{b)}	0.95 ± 0.09	0.94 ± 0.23	1.88 ± 0.74	0.88 ± 0.10	0.77 ± 0.08
E2080 100 µmol/L	1.12 ± 0.22	1.20 ± 0.44	3.76 ± 2.22	0.90 ± 0.08	0.77 ± 0.07
Rifampicin 10 µmol/L	1.79 ± 0.57	0.71 ± 0.12	98.00 ± 107.64	1.04 ± 0.19	0.58 ± 0.10
β-Naphthoflavone 10 µmol/L	333.51 ± 219.00	26.69 ± 12.84	0.30 ± 0.17	1.09 ± 0.39	0.65 ± 0.27
Clofibrate 30 µmol/L	1.03 ± 0.17	1.09 ± 0.26	1.06 ± 0.17	1.08 ± 0.30	0.89 ± 0.17
Phenobarbital 2 mmol/L	3.22 ± 1.45	1.09 ± 0.26	84.17 ± 75.99	1.52 ± 0.67	0.75 ± 0.21

Each value represents the mean ± S.D. (n=5). a): For control samples, the mean and the standard deviation of mRNA ratios of CYP or CES/GAPDH were calculated, and the values divided by the mean were shown. b): n=4

Summary Table 2 Induction ratio of enzyme activity compared with vehicle control in 5 lots of human hepatocytes

Sample	Midazolam 1'-hydroxylation	4-MU glucuronidation	PNPA hydrolase activity
Control ^{a)} 0.1% DMSO	1.00 ± 0.49 (2.71 ± 1.32)	1.00 ± 0.15 (0.898 ± 0.133)	1.00 ± 0.38 (0.313 ± 0.119)
E2080 2 µmol/L	1.06 ± 0.17	1.08 ± 0.12	1.00 ± 0.08
E2080 10 µmol/L	1.10 ± 0.10	0.98 ± 0.13	1.03 ± 0.11
E2080 20 µmol/L	1.25 ± 0.22	1.09 ± 0.18	0.97 ± 0.11
E2080 50 µmol/L ^{b)}	1.56 ± 0.44	1.04 ± 0.21	0.97 ± 0.06
E2080 100 µmol/L	2.60 ± 0.64	1.10 ± 0.29	0.97 ± 0.10
Rifampicin 10 µmol/L	29.37 ± 9.26	1.18 ± 0.21	1.06 ± 0.12
β-Naphthoflavone 10 µmol/L	0.80 ± 0.16	1.11 ± 0.29	1.05 ± 0.12
Clofibrate 30 µmol/L	1.11 ± 0.28	0.93 ± 0.12	0.96 ± 0.16
Phenobarbital 2 mmol/L	27.07 ± 12.62	1.11 ± 0.20	1.05 ± 0.16

Each value represents the mean ± S.D. (n=5). The value in a parenthesis expresses enzyme activity (pmol/min/mg, nmol/min/mg, µmol/min/mg) a): For control samples, the mean and the standard deviation of activity were calculated, and the values divided by the mean were shown. b): n=4

The mRNA levels of CYP1A1 and 1A2 were augmented markedly after the treatment of BNF. However, after the treatment with 2 to 100 µmol/L of E2080, the mean induction ratios of mRNA of CYP1A1 and CYP1A2 ranged from 0.95 to 1.99 and from 0.94 to 1.55, respectively, and did not show concentration-dependent increase. Thus the induction potency of E2080 on CYP1A1 and CYP1A2 is thought to be minimal, if any.

RIF and PB showed more than ten fold increases of both mRNA and activity of CYP3A4. E2080 showed weak induction potency and the mean induction ratios of CYP3A4 mRNA and midazolam 1'-hydroxylation activity at 100 µmol/L E2080 were 3.76 and 2.60, respectively, which were 10 % or less of those of 10 µmol/L RIF (table 2).

No compound showed clear induction of mRNA (CES1 or CES2), or hydrolase activity (PNPA).

Concerning the induction of UDPGT, E2080 did not show any clear induction of 4-MU glucuronidation activity (table 2) . Since even RIF and PB showed only weak induction ratios for UDPGT (on average less than 1.2), it is very difficult to draw the definitive conclusions on the UDPGT induction potential of E2080.

Conclusions:

Based upon the results of this in vitro human hepatocytes study, rufinamide is a weak CYP3A4 inducer and its induction potency at 100 µmol/L is less than 10% of 10 µmol/L RIF. In addition, the induction of CYP1A1 and CYP1A2 would be minimal, if any, and that of CES would be unlikely. On the UPGGT, no clear induction of rufinamide was observed in the in vitro human hepatocyte study, although its relevance to in vivo is still unclear.

Study B05015: Identification of enzyme responsible for rufinamide hydrolysis in human liver microsomes

p-nitrophenylacetate (PNPA) hydrolase activity, a typical reaction of CES was inhibited by bis(4-nitrophenyl) phosphoric acid (BNPP), which is the specific inhibitor of CES, in concentration dependent manner. The inhibition potency on PNPA hydrolysis was about 60% at 1 µmol/L of BNPP. The formation of metabolite CGP 47 292 (named Ditrice in this study) from E2080 was also inhibited by BNPP 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. These results suggest that CES is responsible for E2080 hydrolase activity (see Tables below).

Table 5 Relative activity for the Formation of *p*-Nitrophenol in Presence of BNPP in Human Liver Microsomes

BNPP ($\mu\text{mol/L}$)	Enzyme Activity ($\mu\text{mol/min/mg}$)			Relative Activity (%)
	1	2	Mean	
0	3.120	2.967	3.044	100
0.1	2.180	2.134	2.157	70.9
1	1.218	1.212	1.215	39.9
10	0.575	0.598	0.587	19.3
100	0.098	0.098	0.098	3.2

Table 4 Inhibitory Effect of BNPP on Ditraca Production

BNPP conc. ($\mu\text{mol/L}$)	E2080 conc. ($\mu\text{mol/L}$)							
	10				100			
	Ditraca conc. ($\mu\text{mol/L}$)			Relative Activity (%)	Ditraca conc. ($\mu\text{mol/L}$)			Relative Activity (%)
1	2	Mean	1		2	Mean		
0	0.245	0.249	0.247	100	3.191	3.164	3.178	100
0.1	0.249	0.237	0.243	98.4	2.476	2.618	2.547	80.1
1	0.130	0.113	0.122	49.4	1.367	1.160	1.264	39.8
10	B.Q.L.	B.Q.L.	N.C.	N.C.	0.090	0.119	0.105	3.3
100	B.Q.L.	B.Q.L.	N.C.	N.C.	0.076	0.067	0.072	2.3

B.Q.L. : Below the quantification limit
N.C. : Not calculated

Conclusions:

The results obtained in this study indicate that carboxylesterase is predominantly involved in metabolism of E2080 to form Ditraca (metabolite CGP 47 292) in human liver microsomes in vitro.

Study crb r24/1993: In vitro binding of CGP 33 101 to human serum proteins, human erythrocytes and serum proteins from rat, dog, baboon and marmoset

The in vitro binding of CGP 33 101 to serum proteins from man, rat, dog, baboon and marmoset was determined at 37°C using equilibrium dialysis. The binding to erythrocytes was determined using incubation at 37°C. ¹⁴C-labelled compound was used.

The equilibrium with human serum was reached after 3 h of dialysis.

The bound fraction in human serum amounted to 34.0 % for CGP 33 101 concentrations ranging from 0.25 to 1.96 µg/ml.

The binding of CGP 33 101 to human serum albumin (HSA, 40 g/l) amounted to 27.3%. There was no effect of CGP 33 101 concentration on its binding to HSA in the range 0.196-1.96 µg/ml. The binding was comparable with three different references of albumin. Albumin mainly contributed to the binding of CGP 33 101 in serum.

The bound fraction to alpha-1-acid glycoprotein (1 g/l) and to gamma globulins was less than 4 % for CGP 33 101 concentrations ranging from 0.196 to 1.96 µg/ml.

The partition between erythrocytes and plasma was similar : the fraction bound to erythrocytes was 51.0 : and 57.2 % with CGP 33 101 concentrations in blood of 0.098 and 0.49 µg/ml, respectively.

Table 3 : Effect of CGP 33 101 concentration on its binding to human serum proteins.

Dialysis at 37°C for 3 h with serum 4.

CGP 33 101 concentration (µg/ml)			Bound (%)	Free (%)	Recovery* (%)
in buffer before dialysis (% ethanol)	after dialysis				
	in dialysate (Cf)	in serum (Ct)			
0.25**(0.25)	0.096	0.148	34.8	65.2	98
0.98 (0.25)	0.383	0.573	33.3	66.7	98
0.98**(0.25)	0.379	0.578	34.4	65.6	98
1.96 (0.50)	0.765	1.15	33.4	66.6	98
Mean SD			34.0 0.7	66.0 0.7	98
4.90 (1.25)	1.93	2.82	31.7	68.3	97
9.80 (2.50)	3.96	5.58	29.0	71.0	97
10.0 (10.00)	4.38	5.56	21.2	78.8	99
14.7 (3.75)	6.04	8.25	26.7	73.3	97
19.6 (5.00)	8.27	11.2	26.2	73.8	99

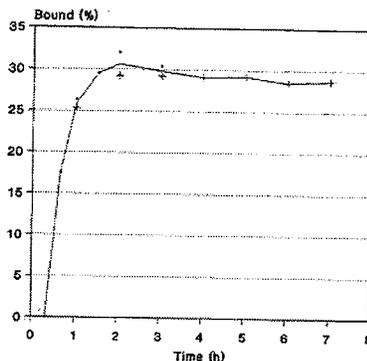


Figure showing time dependent binding:

Table 6 : Binding of CGP 33 101 to three different references of HSA (40 g/l).

Dialysis at 37°C for 3 h, CGP 33 101 concentration before dialysis : 1.96 µg/ml (with 0.5 % ethanol).

HSA Ref*	CGP 33 101 concentration (µg/ml)		Bound (%)	Free (%)	Recovery** (%)
	after dialysis				
	in dialysate (Cf)	in HSA solution (Ct)			
HSA S1	0.796	1.09	27.1	72.9	96
HSA S2	0.781	1.10	28.8	71.2	96
HSA S3	0.785	1.10	28.5	71.5	96
	Mean		28.1	71.9	96
	SD		0.9	0.9	

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Table 9 : Binding of CGP 33 101 to alpha-1-acid glycoprotein (AAG, 1 g/l) and to gamma globulins (GG, 12 g/l).

Dialysis at 37°C for 3 h.

Protein	CGP 33 101 concentration (µg/ml)			Bound (%)	Free (%)	Recovery* (%)
	before dialysis (% ethanol)	after dialysis				
		in dialysate (Cf)	in protein solution (Ct)			
AAG	0.196 (0.05)	0.093	0.097	3.9	96.1	97
	0.980 (0.25)	0.478	0.473	0	101	97
	1.96 (0.50)	0.943	0.961	1.9	98.1	97
GG	0.196 (0.05)	0.092	0.092	0	100	94
	0.980 (0.25)	0.468	0.474	1.3	98.7	96
	1.96 (0.50)	0.962	0.975	1.3	98.7	99

Conclusions:

Binding to human serum proteins is 34% for CGP 33 101 concentrations ranging from 0.25 to 1.96 µg/mL

Report DMPK (CH) R99-1620: Mechanistic transport studies across Caco-2 cell monolayers

Bidirectional drug transport

RUF 331 transport through the Caco-2 cells is clearly dependent on the transport direction. From Table 1 it can be seen that for 0.2 µM RUF 331 a very high apical to basolateral transport was detected (~490 10⁻⁵ cm/min). The determined permeability value is about 3-fold higher than that of Propranolol. The corresponding basolateral to apical RUF 331 transport was about 2-fold lower. The Caco-2 data suggests that RUF 331 is submitted to active transport system (Carrier).

Concentration dependency of drug transport

Using 50 µM RUF 331 a significant decrease of apical to basolateral transport was observed (about 1.3-fold). Basolateral to apical transport on the other hand did not change significantly. However, the permeability values in both transport directions did not converge completely at 50 µM concentrations, indicating that 100% saturation of transporter system was not achieved at the RUF 331 concentrations used.

RUF 331 transport in the presence of different AED's

From Table 1 it can be seen that for 0.2 µM RUF 331 in the presence of Valproic Acid and Phenytoin, respectively, a significant decrease of apical to basolateral transport could be determined (about 1.3-fold for Valproic acid and about 1.5-fold for Phenytoin). All these data suggest that both AED compounds may act as inhibitors on the carrier system involved in RUF 331 transport, with Phenytoin being the stronger inhibitor than Valproic acid.

Table 1: Permeability coefficients P_e of RUF 331 at pH 7.4 across Caco-2 cell monolayers.

Compound	Conc. [µM]	Caco-2 P_e [10^{-3} cm/min]			
		AP-to-BL		BL-to-AP	
RUF 331	0.2	491 ± 19	(10)	246 ± 34	(100)
RUF 331	50	371 ± 68	(10)	262 ± 42	(102)
RUF 331 + Valproic acid	0.2/100	369 ± 30	(10)	-	
RUF 331 + Phenytoin	0.2/100	337 ± 13	(10)	-	
Mannitol		5.2 ± 0.86	(10)	-	
Propranolol		161 ± 15	(54)	-	

() = recovery values in %

Conclusions:

The absorption of rufinamide involves active transport process in addition to the possible passive diffusion and this absorptive process may be interfered in the presence phenytoin and valproic acid. Based on the results of this study, rufinamide is unlikely to be a P-gp substrate.

Report DMPK(CH) R99-2040: Stability studies across Caco-2 cell monolayers:

The aim of this study was to determine the metabolic stability of RUF331 during the permeation process through Caco-2 cell monolayers (cleavage to the corresponding free acid CGP 47292) and to determine the transport mechanistics of this metabolite.

The methodology included the determination of RUF331 [10 µM] and CGP 47292 [10 µM] transport in apical (AP) to basolateral (BL) and basolateral to apical directions of Caco-2 cells.

During the permeation process of RUF331 no parallel appearance of CGP47292 could be detected, indicating a high metabolic stability of RUF331 during its transport through the

Caco-2 cell monolayers. A hydrolyzation to the corresponding free acid is therefore also very unlikely to occur during the absorption process in humans. However, different isoenzymes expressed in human tissues (intestinal mucosa, kidneys, etc.) but not in Caco-2 cells may still promote such a cleavage.

No apical to basolateral transport could be determined for 10 μ M CGP 47292. Basolateral to apical transport on the other side was with a permeability value of about 1 10^{-5} cm/min significantly different from apical to basolateral permeability data.

CGP47292 transport through Caco-2 cells is clearly dependent on the transport direction, suggesting CGP47292 to be submitted to a prominent efflux system like Pgp or MRP. Even at a 10 μ M concentration the determined basolateral to apical permeability values for CGP47292 did not completely converge with the corresponding apical to basolateral transport data, indicating that 100% transporter saturation was not achieved at the CGP47292 concentration used. Saturation therefore needs CGP47292 concentrations higher than 10 μ M, suggesting this compound to have a medium or low transporter affinity (K value > 1 μ M).

Table 1: Permeability coefficients P_a of RUF331 and CGP47292 across Caco-2 cell monolayers

Compound	Conc. [μ M]	Caco-2 P_a [10^{-5} cm/min]	
		AP-to-BL	BL-to-AP
RUF331	10		
- appearance of RUF331		319 \pm 47 (98)	380 \pm 78 (138)
- appearance of CGP47292		n.d.	n.d.
- appearance of RUF331 and CGP47292		319 \pm 47 (98)	380 \pm 78 (138)
CGP 74292	10	n.d.	1.21 \pm 0.27 (83)
Mannitol		3.59 \pm 0.5 (101)	-
Propranolol		125 \pm 19 (80)	-

Conclusions:

Rufinamide was not metabolized during the apical to basolateral transport. The intrinsic permeability of the metabolite, CGP 47 292 is low and it is substrate for the efflux pump, therefore probably not reabsorbed in the gut.

4.2 APPENDIX II

QTC CONSULT

Appears This Way
On Original

Clinical Pharmacology Review of Thorough QT Study

NDA:	21-911
Type	Original
Applicant:	Novartis
Submission dates:	November 17, 2005 March 17, 2006
Brand name:	Inovelon®
Generic name:	rufinamide (RUF331, E2080)
Dosage form and strengths:	100, 200, 400 mg tablets
Indication:	epilepsy
OCP Division:	Pharmaceutical Evaluation I
ORM Division:	Neurological Drug Products
Primary Reviewer:	B. Nhi Beasley, Pharm.D.
Secondary Reviewer:	Christine Garnett, Pharm.D.

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Abbreviations

AUC	Area under the curve
bid	twice daily
bpm	Beats per minute
CI	Confidence interval
Cmax	Maximum concentration
Cmin	Minimum concentration
CV	Coefficient of variation
EC50	Concentration that produces half the maximal effect
ECG	electrocardiogram
E _{max}	Concentration that produces the maximum effect
fc	Film-coated
FMI	Final market image
h	Hour
HR	Heart rate
LB	Lower bound
mg	Milligram
msec	Millisecond
n	Number of subjects
PK	Pharmacokinetic
PKPD	Pharmacokinetic pharmacodynamic
po	By mouth
q	Every
QTc	Corrected QT interval
QTcB	Bazett Corrected QT interval
QTcF	Fridericia Corrected QT interval
QTcI	Individual Corrected QT interval
SD	Standard deviation
TQT	Thorough QT
UB	Upper bound
Ug/mL	Microgram/milliliter
uL	microliter

Executive Summary

The sponsor conducted a randomized, double-blind, placebo and active controlled, parallel study in 117 healthy volunteers to assess the effect of rufinamide on cardiac repolarization as measured by the QT interval. The study design and analysis of data are consistent with the recommendations proposed in the ICH E14 guidance document.

Rufinamide shortens the QTc interval when analyzed by both the maximum-mean approach (Table 1) and a PKPD analysis. The PKPD analysis, which used an Emax model to describe the relationship between concentrations and QTc, showed that rufinamide decreased the QTcF interval by a maximum of 27.8 msec (90% CI: -30.9, -24.7) and 42% between subject variability (BSV). Half this effect (EC50) was observed at a concentration of 6.61 ug/mL (90% CI: 4.42, 8.80), BSV not estimated.

Table 6. Maximum Mean Effect

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 most probable reasons for the lack of a clear dose-response using the max-mean approach can be explained by the nonlinearity in the concentration QT relationship as well as in the PK. At the lowest dose, most of the rufinamide concentrations are at or above the EC50. Therefore, increases in concentrations due to increased doses do not result in proportional decreases in the QTc interval. Additionally, there is a non-proportional increase in concentration with dose; a three-fold increase in dose results in a 1.8-fold increase in concentration.

Moxifloxacin produced a mean increase in ddQTcF of 11.5 msec (90% CI: 8.7, 14.4), which is consistent with prior reports.

There were no serious AEs in this population of 117 healthy volunteers. A review of the pooled safety database from all clinical trials shows 22 deaths (18 on rufinamide) during the study or within 30 days of taking the drug. Eight of these deaths were classified as sudden death. It is difficult to discern from the narratives if the patients died from a shortened QTc interval since ECGs were not recorded at the time of death.

1.1 Recommendation

The QTcF shortening should be described in the label.

Question Based Review

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 C_{max} 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.

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.

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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%.

Does rufinamide prolong the QTc interval?

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

Does rufinamide shorten the QTcF interval?

Yes. Table 2 and Figure 1 show the effect (baseline and placebo adjusted) of rufinamide on QTcF for each dose.

Table 7. Maximum Mean Effect by Dose

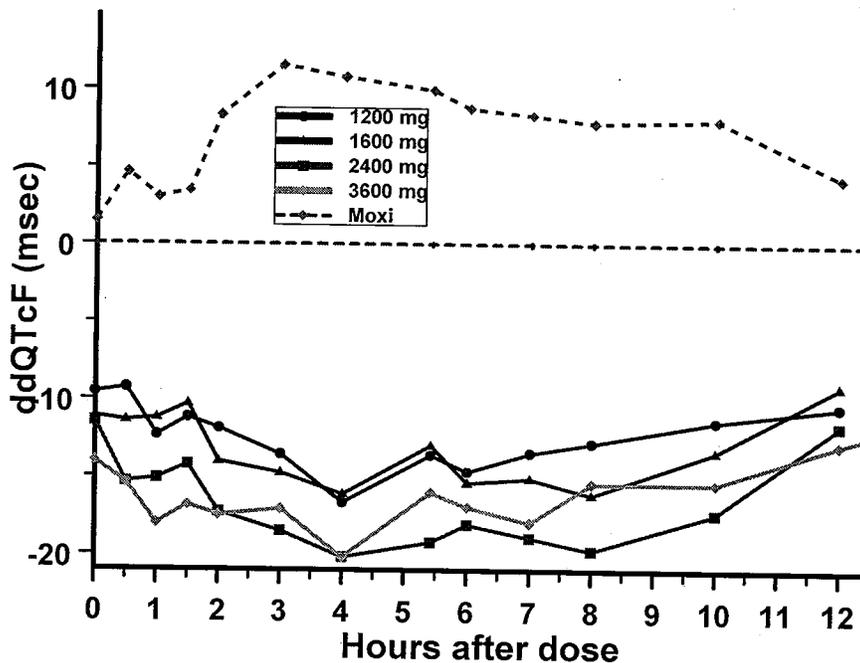
Dose	ddQTcF (msec)	90 % CI (msec)	Time post dose (h)
------	---------------	----------------	--------------------

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

Figure 5. Mean ddQTcF for All Doses



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.

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.

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

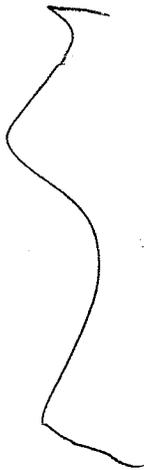
Twenty-two patients (18 on rufinamide) from the pooled safety database died during the clinical studies or within 30 days after receiving the last dose of study drug.

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.

Detailed Labeling Recommendations



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Individual Study Review

E2080-A001-002 - A double-blind, randomized, placebo-controlled, active comparator-controlled, parallel design trial of the electrocardiographic effects of rufinamide in healthy subjects: a definitive QTc study

INVESTIGATOR: _____

STUDY CENTERS: _____

STUDY PERIOD: January – May 2005

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Methods

This was a randomized, double-blind, placebo-controlled, active-controlled, parallel study. Subjects (n=117) were enrolled, stratified by gender, and randomized to one of two arms (rufinamide/placebo or placebo/moxifloxacin) (Table 3).

Dosing Information

Subjects took rufinamide five minutes after consuming a standardized meal, and the dose was escalated every 3 days as shown in Table 3. The test product was the final market image (FMI) rufinamide film-coated (fc) 400 mg tablet. Commercial moxifloxacin 400 mg was over-encapsulated and administered on Day 20.

Table 8. Dosing Scheme

Day	No. Subjects	Dose	No. Subjects	Dose	No. doses
1-3	58	400 mg po q 12 h	59	Placebo tablet	6
4-6	58	800 mg po q 12 h	59	Placebo tablet	6
7-9	58	1200 mg po q 12 h	59	Placebo tablet	6
10-12	58	1600 mg po q 12 h	59	Placebo tablet	6
13-15	58	2400 mg po q 12 h	59	Placebo tablet	6
16-18	58	3600 mg po q 12 h	59	Placebo tablet	5
19	58	No dose	59	No dose	0
20	58	Placebo capsule	59	Moxifloxacin 400 mg x 1	1

Bolded dose indicates PK estimated
n=number randomized

PK and ECG Sampling

Pharmacokinetic sampling and 12-lead continuous Holter ECG extraction coincided as shown in Table 4. Samples were collected after the fifth dose of each regimen with ECG

collection prior to PK sampling. The sponsor estimated PK parameters for oral rufinamide (1200 mg q 12 h and 3600 mg q 12 h) at steady state and for oral moxifloxacin (400 mg) after single dose. There were 18 possible coinciding samples per subject for analysis at the highest rufinamide dose. There were 13 samples per subject for the moxifloxacin analysis. PK samples collected on Day 12 and 15 were not analyzed. Individual ECGs from Lead II were extracted and evaluated by _____ in a blinded fashion. The mean of triplicate ECGs, approximately two minutes apart, was reported and corrected using Bazett's (QTcB), Fridericia's (QTcF), and Individual (QTcI) correction.

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Table 9. Plasma and ECG Sampling Times

Study Day	PK	ECG
Day -1		Baseline: Time matched to Day 18
Day 1	Pre-dose	
Day 9, 12, 15, 18, 20	pre-dose, 0.5, 1, 1.5, 2, 3, 4 hours, 5 hours and 25 minutes, 6, 7, 8, 10, and 12 hours after the first dose	pre-dose, 0.5, 1, 1.5, 2, 3, 4 hours, 5 hours and 25 minutes, 6, 7, 8, 10, and 12 hours after the first dose
Day 18	16, 20 hours and 24 hours and 25 minutes, 30 and 36 hours after the dose	16, 20 hours and 24 hours and 25 minutes, 30 and 36 hours after the dose

Analysis

PK

_____ computed PK parameters for rufinamide and moxifloxacin by _____ using WinNonlin, Version 4. Additionally, _____ performed PK and PKPD modeling using NONMEM (ver 5, level 1.1).

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QT

Baseline- and placebo-adjusted QT calculation

The delta QTc for baseline and for placebo was determined as follows:

- Rufinamide
 - Baseline (Group B) = QTc after 5th dose — QTc Day-1
 - Placebo (Group A) = QTc after 5th dose — QTc Day-1
- Moxifloxacin
 - Sponsor Baseline (Group A) = QTc Day 20 — QTc Day 18
 - Reviewer Baseline (Group A) = QTc Day 20 — QTc Day -1
 - Placebo (Group A) = QTc Day 9 — QTc Day-1

Since the time matched moxifloxacin baseline was not determined using Day -1 data, the reviewer recalculated the baseline-adjusted moxifloxacin QTc data. The double delta

(ddQTc), or time matched difference, was determined by subtracting the placebo-adjusted QTc from the baseline-adjusted QTc at each time.

If the null hypothesis was not rejected at the highest dose (3600 mg) and subsequent analyses of lower doses were necessary, then the baseline-adjusted QTc was calculated using the time matched ECG collected on the appropriate day for subsequent lower doses.

Primary QT analysis

The primary statistical analysis was what the sponsor called “the analysis of central tendency, which evaluated the largest time matched baseline corrected mean difference in QTcF between the rufinamide group and the placebo group over the collection period”. The sponsor states that this analysis is in accordance with the ICH E14 May 2005 document. The null hypothesis, that this difference is 10 msec, was tested by comparing the largest one-sided 95 % upper confidence bound on the highest dose on Day 18 with the corresponding time-matched baseline corrected placebo means on the same study day. If the largest upper confidence bound was less than 10 msec, then the null hypothesis was rejected. If the null hypothesis was not rejected, then testing was repeated for decremental doses until the null hypothesis was rejected. Thus, if there was a dose that prolonged the QTcF interval by more than 10 msec, the sponsor attempted to find the dose that did not result in QTcF prolongation greater than 10 msec. The repeated measures mixed effects analysis of variance was performed for each correction method and each study day using the SAS PROC MIXED code found in Section 4.2, with a modification for the correction method.

Categorical QT Analyses

Categorical analyses of specific QT changes were also conducted: number of subjects with QTc intervals > 450, > 480, and >500 msec and QTc interval increases from Day -1 baseline > 30 and > 60 msec at each dose.

Other QT Analysis

To assess the dose response among the four rufinamide dose levels, a post-hoc statistical test for trend was performed on the differences in baseline-subtracted QTcF means between rufinamide and placebo. The test assumed that the four doses were equally spaced. No test was applied to test the linearity of the relationship, only to test if there was a tendency of the differences to increase or decrease with increasing dose in some fashion.

The sponsor also tested if the QTc on Day 18 at each time, around the rufinamide median Tmax, was different between males and females.

QT Assay Sensitivity

To test assay sensitivity, dQTcF on moxifloxacin were compared to dQTc on placebo as discussed in Section 3.1.3.2.1. A paired t-test, including one-sided 95% lower confidence bound on the difference from the placebo (moxifloxacin minus placebo) was performed for each ECG time point. A significant p-value with > 5 msec difference or lower bound that exceeded zero at the time of maximum observed difference was used to indicate

assay sensitivity. No formal statistics were conducted between the moxifloxacin results and the rufinamide results.

PKPD Analysis

The sponsor conducted a PKPD analysis using mixed effects modeling to evaluate the effect of rufinamide and moxifloxacin on QTcI. QT intervals were rhythm adjusted for diurnal variation using two cosine functions. Concentrations of rufinamide and moxifloxacin were predicted for each ECG measurement using individual post-hoc PK parameters (Bayesian estimation). Between subject variability was estimated on the baseline, correction factor, the maximum rufinamide effect and on maximum time effect. The control stream can be found in Appendix 4.

For the rufinamide analysis, all subjects treated with rufinamide were included and likewise for the moxifloxacin analysis. This differs from the statistical analysis, which included only subjects treated according to the protocol. The following data were used:

- Rufinamide PK: 51 samples pre-treatment (baseline), 13 samples on Day 9 and 19 samples on Day 18/19 per subject.
- Moxifloxacin PK: 13 samples on Day 20 per subject
- ECG assessments: continuous ECG data were collected and up to three measurements were averaged by time point for the following periods: over a 24-hour period on Day -1 to Day 0 (baseline = 18 time points per subject), from one hour pre- to 12 hours post rufinamide dose on Days 9, 12, 15 (13 time points per subject), from one hour pre- to 24 hours post-rufinamide dose on Day 18 (18 time points per subject), and on Day 20 (moxifloxacin dose, 13 time points per subject).

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The population model employed four basic components: a structural PK or PKPD model, a covariate model, a between-subject variance component, and the residual error model components. Model selection for PK and residual error was based on the goodness of fit plots and on the difference in NONMEM objective function (-2 Log Likelihood) between hierarchical models. Model selection for the structural QT model and residual error was based on the distribution properties of the parameter and its relationship with the RR interval. The effect of rufinamide on heart rate was assessed and the best correction factor determined. Then placebo and drug effect were tested. Potential covariates were also tested with a p-value of 0.05 for retaining a covariate. Backward elimination was then performed, using a p-value of 0.005 to remain in the final model. Constant, linear, log-linear and Emax models were evaluated to describe the effects of time, of rufinamide and of moxifloxacin on QT.

Results

Subjects

The sponsor enrolled 117 subjects, 58 were randomized to rufinamide and 59 were randomized to placebo. Subject enrollment had been increased because 12 subjects were incorrectly dosed. One-hundred patients completed the study and 88 completed the study per protocol. All 117 subjects enrolled were analyzed for safety. The placebo and active

treatment groups were similar in terms of gender, race, age and ethnicity. The race was predominantly Hispanic, Black and White.

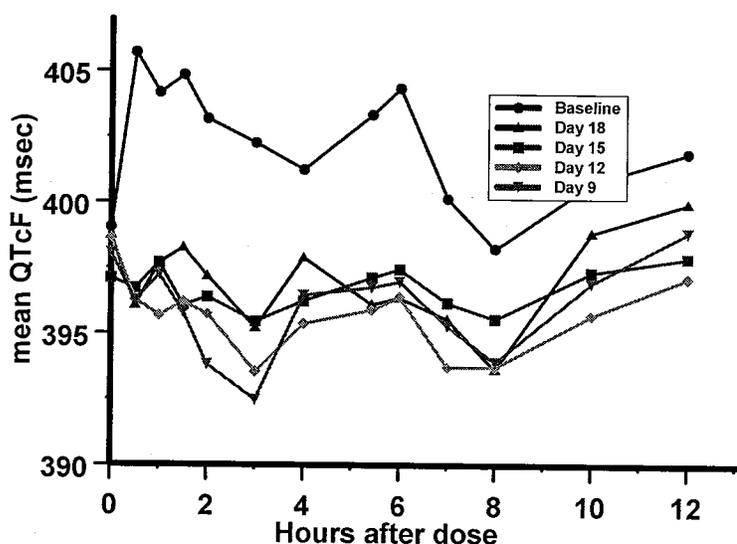
A total of 56 subjects (50% males) were included in the PK and QT analysis for rufinamide

The moxifloxacin PKPD analysis included 45 subjects that were correctly dosed. Six subjects in the rufinamide group were inadvertently given moxifloxacin on Day 20, instead of placebo, meaning that the placebo data will look worse. Thus, after corrections the drug will appear to have less QTc prolongation. These subjects were excluded from the Day 20 PK and QT analyses of moxifloxacin. All data prior to Day 20 were included in the analyses for these subjects.

Baseline and Placebo QTcF Data

Figure 2 shows that the baseline (Day -1) QTc was higher than the QTc during the study for subjects in the placebo group, despite ECG collection in the same patients and at the same time of day.

Figure 6. Placebo Group QTcF



Sponsor's Primary Analysis

Analysis of central tendency showed that the time-matched baseline-adjusted mean difference in QTcF between the rufinamide group and placebo group for the highest dose was -20.2 msec with a 95 % upper bound of -16.1 msec. Since the 95 % UB was less than 10 msec for the highest dose, the null hypothesis was rejected (see Figure 3). The 95% UB was less than 10 msec for all doses and for all correction methods (Figure 4, Table 5) (Data not shown for all correction methods). The sponsor's derived maximum mean effects for QTcF are shown in Table 5.

Table 10. 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

It is noted that the sponsor’s ddQTcF for moxifloxacin (Table 4) is much higher than previous literature reports (See Section 3.3.1 for further discussion).

Figure 7. Rufinamide ddQTcF Upper 95% Bound for the Largest Dose

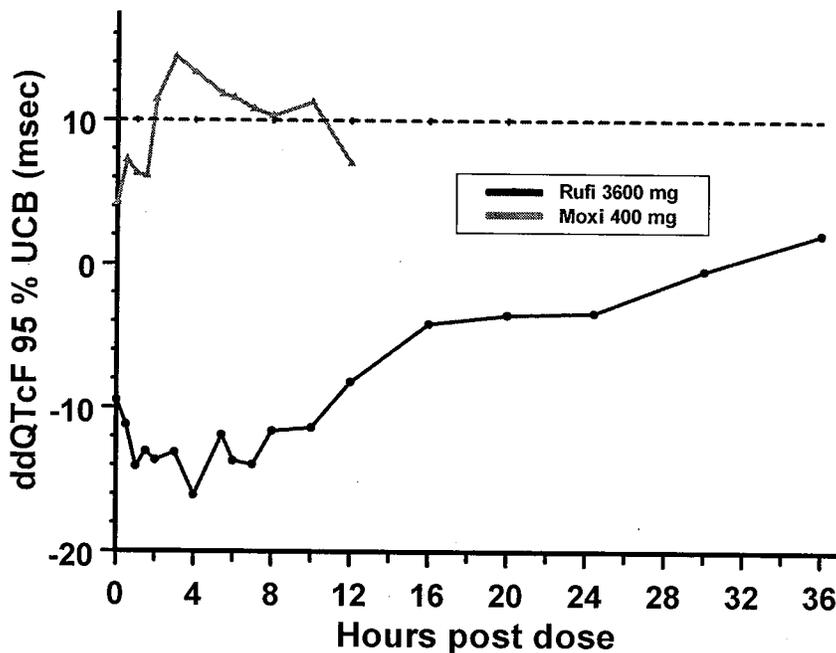


Figure 8. Rufinamide ddQTcF Upper 95% Bound for All Doses

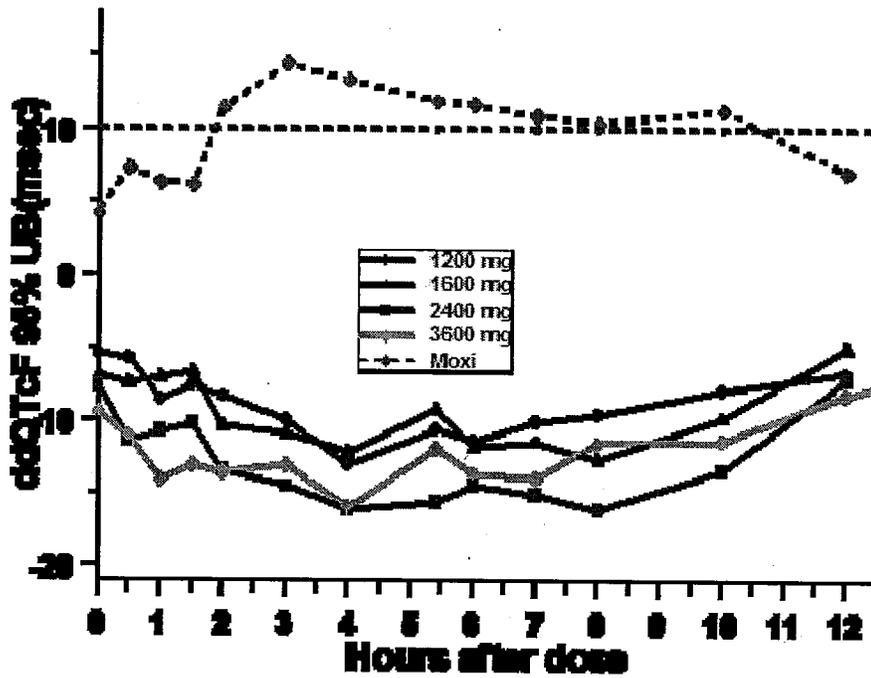


Figure 9. Mean ddQTcF for All Doses

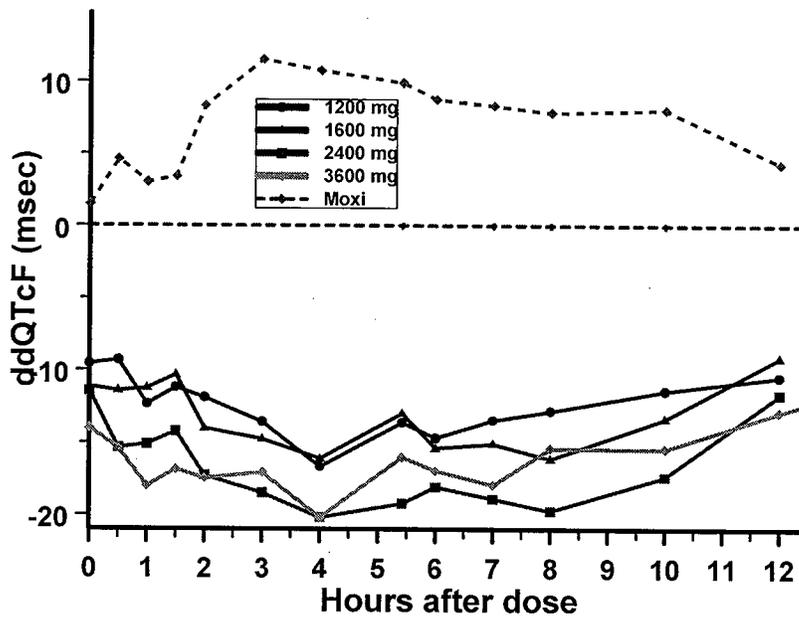
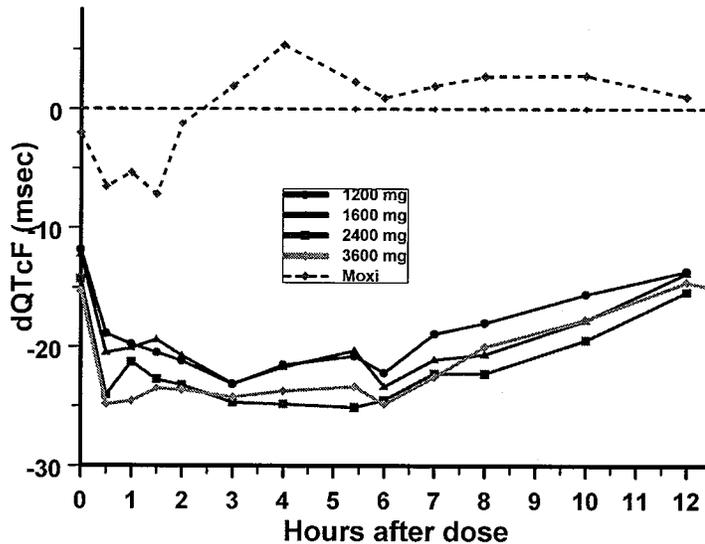


Figure 10. Mean dQTcF for All Doses



Sponsor’s Categorical Analysis

There were very few outliers (See Table 6).

Table 11. Categorical Analysis

Category	Number of subjects
QTc > 500 msec	0
QTc > 480 msec	2
At 1200 mg q 12 h	
QTcF > 450 msec	0
At 3600 mg q 12 h	
QTcF > 450 msec	4 on drug, 5 on placebo
QTc > 60	1 on placebo
QTc > 30	2 on drug, 2 on placebo

Sponsor’s Other QT Analysis

The sponsor found a decreasing trend in baseline-adjusted QTcF differences between rufinamide and placebo with increasing dose level, suggesting that the decreases in QTcF intervals are dose-related. At the following times postdose the test for trend achieved nominal statistical significance ($p < 0.05$): hour 0.5 ($p=0.005$), hour 1 ($p=0.010$), hour 1.5 ($p=0.005$), hour 2 ($p=0.009$), hour 3 ($p=0.030$), hour 4 ($p=0.026$), hour 6 ($p=0.048$), hour 7 ($p=0.011$), and hour 10 ($p=0.023$). While the post-hoc analysis showed a trend, this analysis grouped the two lower doses and the two higher doses together. Figure 5 suggests a lack of a clear dose response since there is overlap in dose response. See Section 3.3.4 for further discussion.

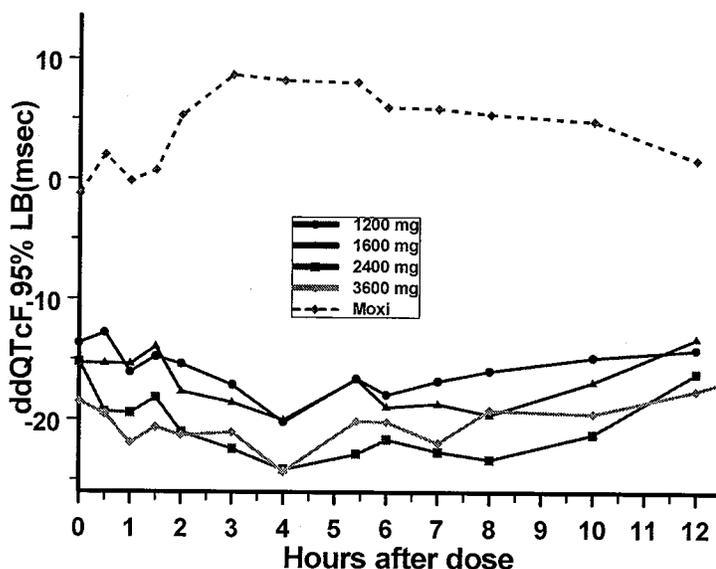
The greatest decrease in QTc was seen with the two higher doses and occurred between 4 and 8 hours post dose, around the times of maximum rufinamide concentrations.

The sponsor found no statistically significant difference between males and females in any QTc time-matched change from baseline from 2 to 8 hours after the highest rufinamide dose in subjects randomized to rufinamide versus placebo.

Assay Sensitivity Analysis

Moxifloxacin, used as a positive control, showed that the study had adequate assay sensitivity. Differences in time-matched mean changes from baseline for moxifloxacin (as calculated by the reviewer) was always greater than 10 msec between 2 and 8 hours post-dose. The lower 95 % confidence bounds were greater than 5 msec between 5 – 11 hours post dose (Figure 7). Maximum mean increase in QTcF was 18.7 msec (90% CI: 14.9, 22.5) by the sponsor’s analysis and 11.5 (90% CI: 8.7, 14.4) msec by the reviewer’s analysis. The differences between the two analyses are discussed in Section 3.3.1. Unless otherwise stated, all figures depicting moxifloxacin change from baseline show the reviewer’s analysis.

Figure 11. ddQTcF Lower 95% Bound for All Doses



PK Model

Rufinamide PK derived from non-compartmental analysis is summarized in Table 7. The increase in AUC and Cmax with dose is less than dose proportional (Table 7, Figure 8). Instead of concentrations increasing three-fold with a dose increase of 1200 mg to 3600 mg, concentrations increase about 1.8-fold.

Table 12. Rufinamide PK Parameters Derived by _____

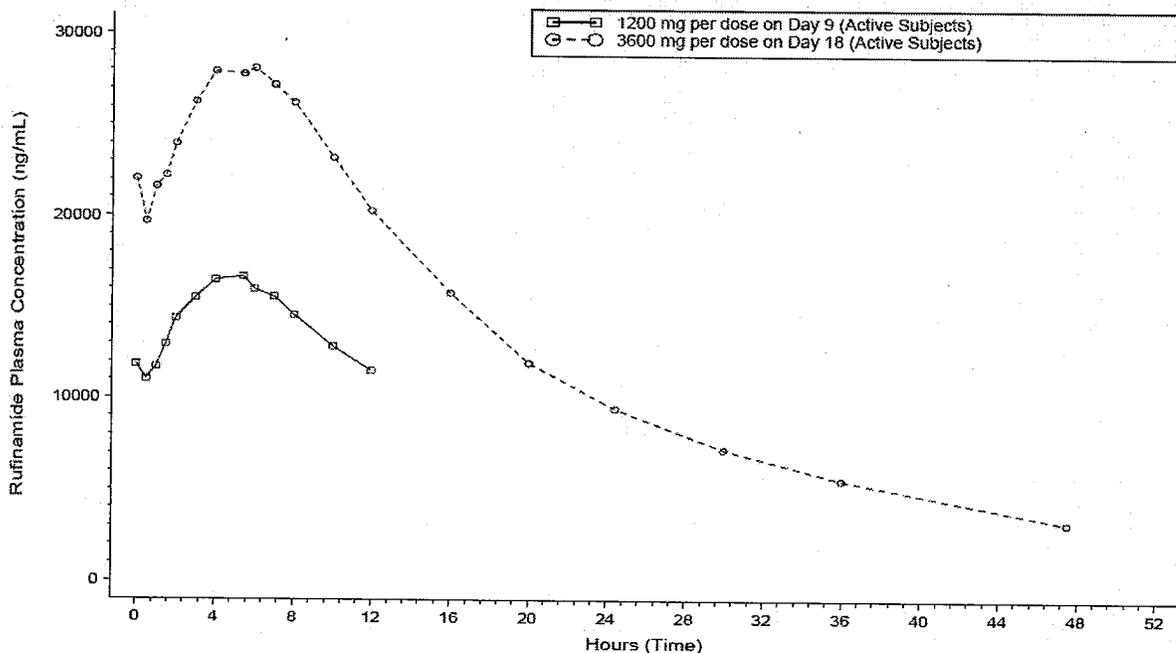
b(4)

PK Parameters	1200 mg bid on Day 9		3600 mg bid on Day 18	
	Geometric Mean	95% CI	Geometric Mean	95% CI
C_{maxss} ($\mu\text{g/mL}$)	17.3	(16.4, 18.3)	30.4	(28.9, 31.9)
C_{minss} ($\mu\text{g/mL}$)	10.6	(9.8, 11.5)	18.6	(17.3, 20.0)
t_{max} (hr) [#]	5.4	(2.0, 8.0)	5.4	(1.5, 8.0)
AUC_{0-12} ($\mu\text{g}\cdot\text{hr/mL}$)	170.7	(160.5, 181.5)	303.46	(287.4, 320.2)
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr/mL}$)	NA	NA	707.6	(641.7, 780.2)
$t_{1/2}$ (hr)	NA	NA	14.4	(12.8, 16.2)

Source: Table 14.2.7 and Table 11.4.1.2:1 Note: the PK parameter units were converted from ng/mL (Statistical Table 14.2.7) to $\mu\text{g/mL}$ in Table 11.4.1.2:1)
[#] For t_{max} , the median values with ranges (minimum, maximum) are presented
 The PK parameters were calculated using WinNonlin Version 4.0 and electronically transferred data from _____

b(4)

Figure 12. Median Rufinamide Concentrations Over Time



The sponsor's final PK model was a one-compartment model with first-order absorption and elimination, with an absorption lag time and decreasing relative bioavailability with increasing dose. Rufinamide final model parameters and derivation are shown in Appendix 4.3 and Appendix 4.4. Time/repeated dosing had no effect on rufinamide PK. The rate of absorption of rufinamide was slow ($K_a=0.205 \text{ h}^{-1}$). The absorption lag time was 0.808 h^{-1} for rufinamide. The sponsor attributes this to the fact that subjects were asked to remain in a supine position in order to facilitate the acquisition of continuous Holter ECG data.

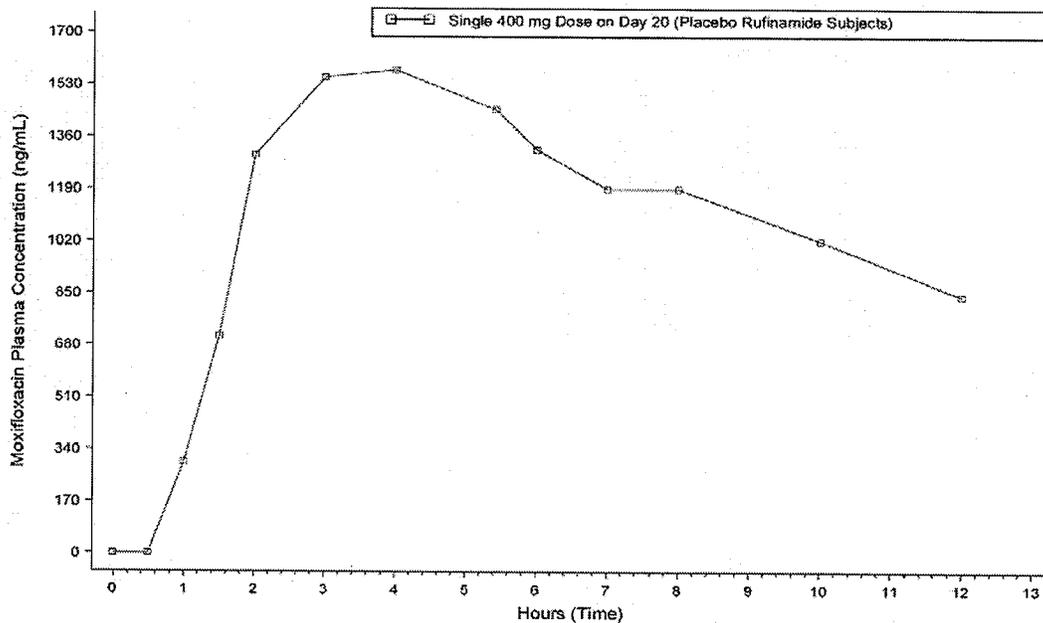
Moxifloxacin PK was also best described with a one compartment model with first order absorption and elimination and an absorption lag time. The final model parameters are shown in Appendix 4.6. Geometric mean PK parameters for moxifloxacin are shown in Table 8.

Table 13. Moxifloxacin PK Parameters

Parameter	Mean (90% CI)
Cmax (ug/mL)	2.0 (1.78, 2.1)□
Tmax (h)	3.02 (0.50, 6.00)
AUC0-12 (ug*h/mL)	14.8 (12.6, 15.5)□

Tmax is median (range)

Figure 13. Median Moxifloxacin Concentrations Over Time



PKPD Model

PKPD modeling results agreed with the statistical analysis. Rufinamide did not increase the QTc interval. Rufinamide effects on QTc were best estimated with a subject specific correction and an Emax model. The sponsor also had an Emax effect of time in the study and/or placebo effect. A total of 114 subjects contributed PK/PD information, with 9215 ECG observations. The parameter estimates for the QTcI model and the QTcF model were similar. Since the sponsor’s primary analysis was for QTcF, the PK QTcF model is discussed in the review, however the sponsor’s final model (QTcI) code and parameters can be found in Appendix 4.9 and 4.10, respectively.

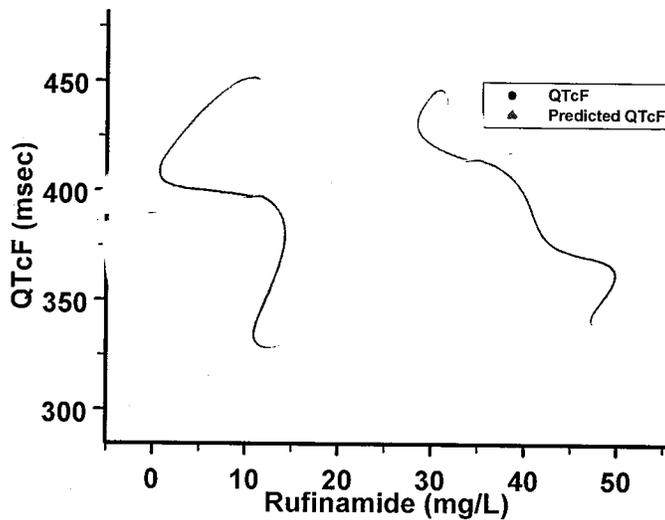
The population average maximum QTcF effect from rufinamide was -27.8 msec (90% CI: -30.9, -24.7) with a SD of 11.7 msec, 42% CV. Half this effect (EC50) was observed at a concentration of 6.61 ug/mL (90% CI: 4.42, 8.80). Between subject variability was not estimated for EC50. See also Appendix 4.7 and 4.8 for the QTcF code and parameter estimates. It is noted that the mean Cmin for the lowest dose is around 10.6 ug/mL; therefore, concentrations are well above the EC50 during most of the 1200 mg q 12 hour dosing period.

The population baseline rhythm adjusted QT in the study was 391 msec, with between subject variability (SD) of 15.7 msec. The within subject residual variability was 7.7 msec. In women, the baseline was greater by 13.5 msec (95% CI: 7.7, 19.3).

The effect of placebo/time in the study was a maximum decrease of -4.46 msec (SD=15.4), half this maximum being achieved in 584 (95% CI: -69, 1237) hours after the first ECG.

Figure 10 shows the model predicted QTcF (green symbols) and the observed QTcF (blue symbols). Women (top green points) had a higher baseline than men. The individual predictions are along the line of unity (data not shown).

Figure 14. Rufinamide Concentration-QTcF Relationship



By the PKPD analysis, moxifloxacin has a mean increase in QTcF of 7.8 msec (90% CI, 6.7, 9.0). The absorption lag time was 0.364 h⁻¹ for moxifloxacin. The sponsor attributes this to the fact that the subjects were asked to remain in a supine position in order to facilitate the acquisition of continuous Holter ECG data.

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