

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-911

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology
OND IO

NDA: 21-911

Submission date: 29-Feb-08 (response to Agency's approvable letter)

Drug: rufinamide

Sponsor: Eisai

Indication: epilepsy

Reviewing Division: Division of Neurology Products

Introductory Comments:

The first pharm/tox review of this NDA noted several significant deficiencies in the nonclinical data. As part of the first approvable letter, the applicant was informed that the rat carcinogenicity study was inadequate. The sponsor was told that that the study may not have adequately assessed the tumorigenic potential of rufinamide because of the excessive body weight effect (the only dose-limiting toxicity) at the mid and high doses. The original rat study was conducted by administering rufinamide in the diet. The sponsor was asked to address whether higher exposures could be achieved, without an excessive effect on body weight, by gavage administration of the drug.

Several other nonclinical studies were noted as inadequate and the sponsor was asked to repeat the following studies: in vivo micronucleus assay in rat, rat fertility study and rabbit embryo-fetal development study. The sponsor was also asked to expand the neurohistopathology and brain morphometry assessments in a juvenile rat study. Finally, a juvenile dog study was requested using animals of an age that corresponded to the clinical age range and incorporating bone and brain development endpoints.

Carcinogenicity:

The sponsor conducted a 3-month gavage study in rats which indicated that the dose limiting toxicity observed in the previous dietary carcinogenicity study could not be avoided by dosing via the gavage route. The pharmacology and toxicology reviewer and supervisor therefore concluded that an additional carcinogenicity study by the gavage route would not be necessary.

Genotoxicity:

The sponsor conducted another in vivo micronucleus assay in rats. This study was negative for micronucleus formation and was considered acceptable by the reviewer.

Reproductive and Developmental Toxicity:

Fertility:

The sponsor conducted another rat fertility study. This study showed impairment of fertility. A number of parameters were altered. A NOAEL was not established since some effects (e.g. increased preimplantation loss) were observed even at the lowest dose (20 mg/kg). Effects included decreased fertility index, conception rate and mating index;

decreased numbers of corpora lutea, implantations, and live embryos; increased preimplantation loss; and decreased sperm count and motility.

Embryo-fetal development:

The sponsor conducted another rabbit embryo-fetal toxicity study using doses of 30, 200 and 1000 mg/kg. This study showed maternal and fetal toxicity at the high dose of 1000 mg/kg. The original rabbit study showed increased embryofetal toxicity at doses of 200 mg/kg or greater. Effects included increased fetal death, decreased fetal body weight and increased incidences of fetal visceral and skeletal abnormalities. Considering both studies, the NOAEL appears to be 30 mg/kg which produced an AUC that was approximately 0.2 times the AUC in humans taking the maximum recommended human dose.

Neurohistopathology:

The following paragraph is taken from the primary pharm/tox review of this submission and refers to the expanded analysis of the juvenile rat study that was requested in the approvable letter:

Eisai conducted an expanded neuropathological evaluation on the brain sections from control and high dose animals with special stains for myelin phospholipids and axon fibers (Klüver Barrera and Holmes). There were no treatment-related neurohistopathological changes noted in this evaluation.

The sponsor has also agreed to conduct a juvenile dog study after approval. Conducting this study after approval was considered acceptable by the reviewer and supervisor because of the negative results found in the rat.

Conclusions:

The pharm/tox reviewer and supervisor concluded that the sponsor adequately addressed the nonclinical deficiencies outlined in the approvable letter of 9/15/06. The reviewer and supervisor provided wording for labeling in their reviews. I concur with the Division pharm/tox conclusion that this NDA can be approved and I concur with the wording for labeling as proposed in the supervisory review.

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/s/

Paul Brown
10/1/2008 04:47:07 PM
PHARMACOLOGIST

MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

Date: September 2, 2008

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-911 (Rufinamide), Complete response to Approvable letter (9/15/06),
received 2/29/08.

The Agency's Approvable letter (9/15/06) conveyed the following nonclinical comments:

1. We note that the rat carcinogenicity study is inadequate.

As you know, the high dose male and the mid- and high-dose female groups experienced excessive decreases in body weight relative to controls, resulting in reduced ability to detect potential carcinogenic effects. We believe that the body weight effect was likely exacerbated by unpalatability of the feed. Based on estimates of plasma AUCs, we note that the plasma exposures in the low dose females and the mid-dose males (the groups that did not suffer excessive weight loss) were not sufficiently greater than those achieved in humans to provide confidence that the tumorigenic potential of rufinamide has been adequately assessed at clinically relevant exposures. We further note evidence in your application suggesting that similar doses could be administered by gavage without the excessive body weight effects observed with dietary administration.

Were we convinced that rufinamide provides a significant clinical benefit, we might be persuaded that the rat study could be repeated in Phase 4. We do ask that you address the possibility that an adequate 2-year study in rats could be conducted using gavage dosing. The need for and the timing of the conduct of a repeat study will depend upon your response to this letter.

2. Several critical nonclinical studies do not conform to current standards and are, therefore, inadequate: a) the in vivo micronucleus assay in rat did not evaluate the recommended 2000 micronucleated polychromatic erythrocytes per animal, b) the rat fertility study evaluated too few male animals (12/group) and did not employ 1:1 mating, and c) the rabbit embryofetal development study did not evaluate a maternally toxic high dose. These studies need to be repeated (cf. OECD Guidelines for the Testing of Chemicals, Guideline 474; Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products ICH-S5A).
3. The finding of decreased whole and regional brain weights in the juvenile rat study should be further investigated, e.g., using expanded neurohistopathology and brain morphometry.
4. The developmental age range studied in juvenile dogs was inadequate. A dog study in which dosing is initiated at an earlier age (corresponding to the clinical age range) needs to be conducted, and bone growth and density and brain development (using expanded neurohistopathology) should

be evaluated in addition to the standard toxicity endpoints. There is particular concern regarding developmental effects on bone and brain based on the bone tumor findings in the mouse carcinogenicity study and the brain weight effects in the juvenile rat study. You are encouraged to submit a protocol for review and comment prior to initiation of the study.

These nonclinical issues were discussed in an End of Review meeting with the sponsor, held on 12/18/06. According to the Agency's final minutes of that meeting:

- The following nonclinical studies were considered necessary for approval: “a study comparing gavage and dietary administration in rat, a repeat in vivo micronucleus assay, a fertility and early embryonic development study in rat, an embryofetal development study in rabbit, and the expanded histopathology evaluation of juvenile rat brain.”
- “If the results of the expanded histopathology evaluation of brain in the juvenile rat study are negative, the juvenile dog study may be completed as a phase 4 commitment. If there is evidence of neurotoxicity in rat, the juvenile dog study would need to be completed prior to approval.”
- “If the results of the study comparing dietary and gavage administration indicate that the carcinogenicity study in rat needs to be repeated, it may be completed as a phase 4 commitment.”

The sponsor's Complete response (2/29/08) contained the following nonclinical studies:

- E2080: Transcellular study of E2080 using MDR1 expressing cells (Report No. W-20070606).
- E2080: A 13-week oral gavage dose range toxicity study in the albino rat (Study No. 802789).
- E2080: Rat micronucleus test (Study No. 961523).
- E2080: An oral gavage fertility and early embryonic development study in the rat (Study No. 901316).
- E2080: An oral embryo-fetal development study in the rabbit (Study No. 901317).
- E2080: A 10-week oral (gavage) toxicity study of RUF331 in neonatal albino rats. Final report amendment no. 2 (Study No. 96488).

All (but the in vitro study in MDR1 expressing cells) were reviewed by J. Edward Fisher, Ph.D. (Pharmacology/Toxicology Review and Evaluation of NDA 21-911, September 2, 2008). Based on his review, Dr. Fisher has concluded that the NDA is approvable from a pharmacology/toxicology standpoint.

According to Dr. Fisher's review:

- The data from the 13-week dose range finding oral gavage study in Sprague-Dawley rats indicate that the body weight effects observed with dietary administration were due to a drug-related effect on body weight and not an unpalatable drug-diet admixture. Therefore, body weight effects fairly similar to those observed in the 2-year dietary carcinogenicity study in rat cannot be avoided by use of gavage administration, indicating that a 2-year oral gavage

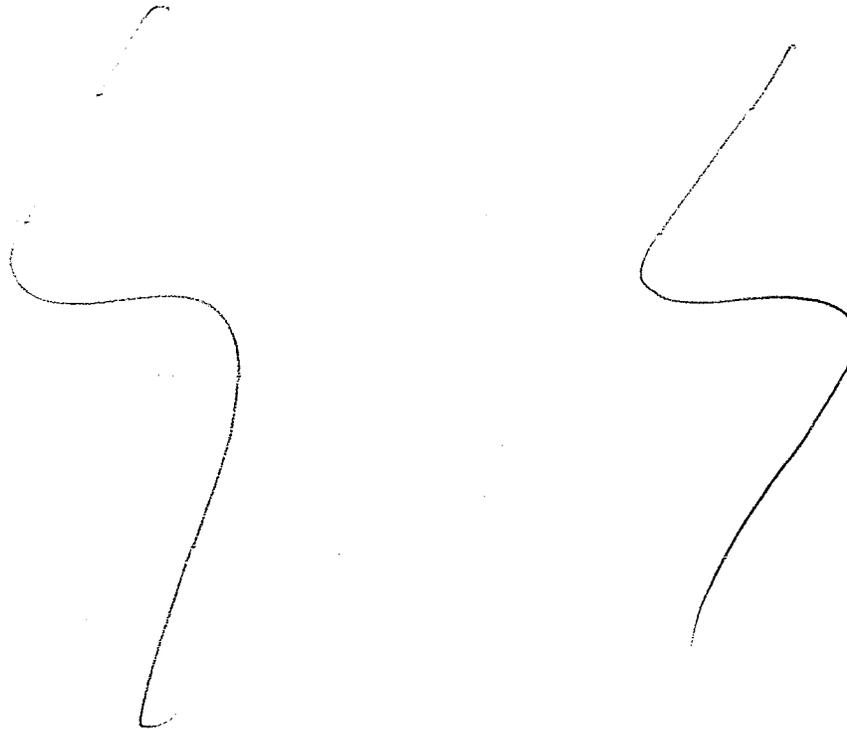
carcinogenicity study would not provide a better assessment of carcinogenic potential.

- The new genetic toxicology and reproductive toxicology studies (i.e., in vivo micronucleus in rat, fertility and early embryonic development in rat, embryo-fetal development study in rabbit) adequately address the deficiencies in the original studies.
- An expanded neurohistopathology evaluation conducted on brains from control and high-dose juvenile rats indicated no drug-related findings; therefore, the juvenile study in dog may be conducted phase 4.

Recommendations

I concur with Dr. Fisher's conclusions and recommendations. The sponsor needs to commit to a time line for submission of a study protocol and final study report for a juvenile study in dog.

Labeling recommendations (taking into account Dr. Fisher's suggested revisions to the sponsor's proposed labeling)



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 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Lois Freed
9/2/2008 06:35:19 PM
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-911
SUBMISSION:	Complete response to Approvable Letter
DATE RECEIVED BY CENTER:	2/29/08
PRODUCT:	rufinamide (CGP 33101)
INTENDED CLINICAL POPULATION:	epilepsy
SPONSOR:	Eisai
REVIEW DIVISION:	Division of Neurology Products (HFD-120)
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
DIVISION DIRECTOR:	Russell Katz
PROJECT MANAGER:	Susan Daugherty

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Note: Portions of this review were excerpted from the sponsor's submission

I. TOXICOLOGY

A. REPEAT-DOSE TOXICITY

1. E2080: A 13-Week Oral Gavage Dose Range Toxicity Study in the Albino Rat (Study Number: 802789; conducted by _____ Report dated 2/11/08; GLP)

b(4)

a. Methods

Rufinamide (Lot No. 86052401) was administered orally (by gavage) to rats (SD; 10/sex/group) at doses of 0, 200, 600, or 1000 mg/kg for 13 weeks. Additional rats (4/sex in Groups 2 to 4) were included for TK. The following were evaluated: mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, toxicokinetics, organ weights, and macroscopic and microscopic pathology.

b. Results

i. Mortality, Clinical signs, Body weight

There were no deaths. Decreased body weight gain and food consumption were observed at all doses in both sexes (**Table IA.1.1**). At the end of treatment, BW gain was -15, -27 and -31% below C in males and -18, -29 and -37% below C in females, at the LD, MD, and HD, respectively. Terminal BWs were -10, -19, and -20% lower in males and -8, -14, and -17% lower in females, at the respective doses. Decreased food consumption (up to 23% at termination) was also noted at all doses, and correlated with body weight changes. There were no treatment-related effects on clinical signs, hematology, biochemistry, urinalysis, or macroscopic pathology.

ii. Pathology

Liver-to-body weight ratios were increased all doses (SS in females; **Table IA.1.2**), and centrilobular hepatocellular hypertrophy was noted in the liver in all treatment groups (**Table IA.1.3**). The change was graded minimal to moderate in severity and correlated with the increased liver-to-body weight ratio observed. Vacuolation of the pituitary was noted in most males at the LD and MD, and in all males and in 3/10 females at the HD. This change did not progress with dose and was graded minimal in severity in affected females and minimal to moderate in males.

iii. Toxicokinetics (Table IA.1.4)

Rufinamide was slowly absorbed. Although C_{max} was observed as early as 2 hours post dose, it was also observed as late as 24 hours post dose. Absorption continued for the entire sampling period at all doses. C_{max} and AUC(0-tlast) did not increase appreciably with dose, indicating absorption limitation by the oral route. Although plasma levels were substantial 24 hours post dose, there was no accumulation with repeated dosing, further evidence of absorption limitation. No sex differences were observed.

c. Conclusions

Daily oral administration of rufinamide to rats at doses of 200, 600, or 1000 mg/kg for 13 weeks resulted in decreased body weight gain and histopathological changes associated with enzyme induction (centrilobular hepatocellular hypertrophy and vacuolation in the pituitary gland) at all doses. There was no increase in drug exposure with repeated administration or increasing dose levels.

Table IA.1.1

		Males					
		Group 1 - Vehicle control Group 2 - E2080 200 mg/kg		Group 3 - E2080 600 mg/kg Group 4 - E2080 1000 mg/kg			
Group	Summary Information	From: To:	Week			Abs Gain -1 to 13	% Gain -1 to 13
			10 11	11 12	12 13		
1	Mean		13.2	9.9	9.0	393.7	208.091
	SD		3.99	3.96	3.77	56.20	25.976
	N		10	10	10	10	10
2	Mean		4.6 D	14.1	10.5	333.8 A	175.255 B
	SD		8.71	4.23	5.06	34.58	15.612
	N		10	10	10	10	10
3	Mean		5.5 D	12.2	11.0	288.2 C	157.668 C
	SD		5.93	5.35	4.67	45.45	27.439
	N		10	10	10	10	10
4	Mean		4.7 D	13.7	6.8	270.8 C	141.035 C
	SD		3.13	6.43	5.35	38.76	21.907
	N		10	10	10	10	10

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

		Females					
		Group 1 - Vehicle control Group 2 - E2080 200 mg/kg		Group 3 - E2080 600 mg/kg Group 4 - E2080 1000 mg/kg			
Group	Summary Information	From: To:	Week			Abs Gain -1 to 13	% Gain -1 to 13
			10 11	11 12	12 13		
1	Mean		2.3	1.5	5.4	148.1	101.478
	SD		6.18	5.04	3.72	28.29	17.668
	N		10	10	10	10	10
2	Mean		-0.5	1.0	5.3	121.6	81.562
	SD		2.12	4.74	3.74	15.55	9.537
	N		10	10	10	10	10
3	Mean		-1.4	2.9	1.5	105.8 E	71.803 E
	SD		5.23	5.30	4.58	13.95	9.210
	N		10	10	10	10	10
4	Mean		0.9	2.1	3.0	92.9 F	62.092 F
	SD		3.87	6.31	4.67	8.99	5.694
	N		10	10	10	10	10

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table IA.1.2

Sex	Organ	Dose (mg/kg)	Males			Females		
			200	600	1000	200	600	1000
	Final Body		-9	-19	-19	-9	-15	-19
	Liver (Absolute)		-2	-13	-12	11	3	-2
	(Relative to body)		9	8	8	23	21	21

* Changes are the percent differences from means of concurrent controls. Values in bold are significantly different from control group; refer to the summary tables for actual significance level.

Table IA.1.3

Sex	Organ/Finding	Dose (mg/kg)	Males				Females			
			0	200	600	1000	0	200	600	1000
	No. of animals Examined.		10	10	10	10	10	10	10	10
	Liver									
	Hepatocellular hypertrophy		0	10	10	10	0	10	10	10
	Minimal		-	2	1	0	-	5	1	1
	Slight		0	8	8	9	-	5	9	9
	Moderate		-	-	1	1	-	-	-	-
	Pituitary									
	Vacuolation		1	9	7	10	0	0	0	3
	Minimal		1	4	2	2	-	-	-	3
	Slight		-	5	4	6	-	-	-	-
	Moderate		-	-	1	2	-	-	-	-

Table IA.1.4

		Day 1							
		Males				Females			
Group Number	Dose Level (mg/kg)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng·h/mL)	$C_{max}/Dose$	$AUC_{(0-24h)}/Dose$	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng·h/mL)	$C_{max}/Dose$	$AUC_{(0-24h)}/Dose$
2	200	52026	872844	260.1	4364.2	40949	762361	204.7	3811.8
3	600	46154	910242	76.9	1517.1	47134	1032299	78.6	1720.5
4	1000	50616	1067331	50.6	1067.3	51333	1114645	51.3	1114.6
Week 13 Males									
Group Number	Dose Level (mg/kg)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng·h/mL)	$C_{max}/Dose$	$AUC_{(0-24h)}/Dose$				
2	200	55373	1101916	276.9	5509.6				
3	600	43646	913223	72.7	1522.0				
4	1000	56953	1308814	57.0	1308.8				
Week 13 Females									
Group Number	Dose Level (mg/kg)	C_{max} (ng/mL)	$AUC_{(0-24h)}$ (ng·h/mL)	$C_{max}/Dose$	$AUC_{(0-24h)}/Dose$				
2	200	50640	914219	253.2	4571.1				
3	600	65204	1331871	108.7	2219.8				
4	1000	61370	1367081	61.4	1367.1				

B. GENETIC TOXICOLOGY

1. E2080: Rat Micronucleus Test (Study No. 961523, conducted by _____ dated 12/5/07, GLP)

b(4)

Rats were given a single dose of vehicle, cyclophosphamide, or rufinamide (500, 1000, or 2000 mg/kg [limit dose]) by oral gavage. Animals were euthanized 24 or 48 hours after treatment and bone marrow smears were fixed, stained with acridine orange, and examined by fluorescence microscopy. A total of 2000 immature erythrocytes per animal were examined for the presence of micronuclei. In addition, the proportion of immature erythrocytes was assessed for each animal as a measure of potential bone marrow toxicity

A dose-related reduction in group mean body weight gain was observed over the treatment period, with body weight gains of 11.0, 7.0, 0.2, and -0.7% for Groups 1 to 4, respectively. The results are summarized in **Table IB.1.1**. Animals treated with rufinamide did not show any statistically significant increases in the number of micronucleated immature erythrocytes at either sampling time. Individual and group mean values for animals treated with the vehicle control and test article all fell within the historical range for control animals. Cyclophosphamide caused large, highly significant increases in the frequency of micronucleated immature erythrocytes. Animals treated with rufinamide did not show any substantial increases in the incidence of micronucleated mature erythrocytes at either sampling time. The incidence of micronucleated mature erythrocytes for all groups was uniformly low, confirming the absence of micronucleus-like artifacts. Animals treated with rufinamide showed a significant decrease in the proportion of immature erythrocytes across dose levels at the 24 hour sampling time, indicative of bone marrow toxicity; however, no related decrease was seen at the 48-hour time point and all values were well within the historical control range. Cyclophosphamide also caused a statistically significant decrease in the proportion of immature erythrocytes.

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Table IB.1.1 Group Mean Micronucleus Results

Sampling Time - 24 Hours
Males

Group 1 - Vehicle control
Group 2 - E2080 500 mg/kg
Group 3 - E2080 1000 mg/kg

Group 4 - E2080 2000 mg/kg
Group 5 - Cyclophosphamide 20 mg/kg

Group	% IE/(IE+ME) [†] Δ	Incidence mie	Incidence nme
1	49.7	2.4	0.0
2	58.5	2.2	0.0
3	51.5	1.8	0.0
4	43.9	3.0	0.0
5	44.2 *	43.2 **	0.0

%IE/(IE+ME) Proportion of immature erythrocytes
mie Number of micronucleated cells observed per 2000 immature erythrocytes examined.
nme Number of micronucleated mature erythrocytes observed (mean value expressed per 2000 mature erythrocytes examined, see results for individual animals in appendices for actual numbers of cells examined).

Group 5 significantly different from control group (group 1) value: * - $P \leq 0.01$ ** - $P \leq 0.001$ (one-sided probabilities test)
Significant trend across dose levels (Groups 1 to 4): Δ - $P \leq 0.01$ $\Delta \Delta$ - $P \leq 0.001$ (one-sided probabilities test)
Significant trend across dose orders (Groups 1 to 4): Φ - $P \leq 0.01$ $\Phi \Phi$ - $P \leq 0.001$ (one-sided probabilities test)

† Occasional apparent errors of $\pm 1\%$ may occur due to rounding of values for presentation in the table.

Sampling Time - 48 Hours
Males

Group 1 - Vehicle control
Group 2 - E2080 500 mg/kg

Group 3 - E2080 1000 mg/kg
Group 4 - E2080 2000 mg/kg

Group	% IE/(IE+ME) [†]	Incidence mie	Incidence nme
1	47.7	3.6	0.0
2	43.6	1.6	0.8
3	43.3	1.6	0.0
4	44.8	2.2	0.8

%IE/(IE+ME) Proportion of immature erythrocytes
mie Number of micromucleated cells observed per 2000 immature erythrocytes examined.
nme Number of micronucleated mature erythrocytes observed (mean value expressed per 2000 mature erythrocytes examined, see results for individual animals in appendices for actual numbers of cells examined).

Significant trend across dose levels (Groups 1 to 4): Δ - $P \leq 0.01$ $\Delta \Delta$ - $P \leq 0.001$ (one-sided probabilities test)
Significant trend across dose orders (Groups 1 to 4): Φ - $P \leq 0.01$ $\Phi \Phi$ - $P \leq 0.001$ (one-sided probabilities test)

† Occasional apparent errors of $\pm 1\%$ may occur due to rounding of values for presentation in the table.

c. Conclusions

Administration of rufinamide by oral gavage to male SD rats (22/group) for 28 days prior to mating and during cohabitation and until necropsy and to female rats for 14 days prior to mating, during the mating period and until gestation Day 6, at doses of 0, 20, 60, 200, and 600 mg/kg produced clinical signs (dehydration and thinness) and decreased parental BW gain (males at ≥ 200 mg/kg and in females at ≥ 60 mg/kg); decreased fertility index (≥ 60 mg/kg), conception rate (≥ 60 mg/kg) and mating index (HD); decreased numbers of corpora lutea, implantations, and live embryos (≥ 200 mg/kg); increased preimplantation loss (all doses); and decreased sperm count and motility (≥ 200 mg/kg). Based on these findings, the LOAEL for fertility and early embryonic development is considered to be 20 mg/kg.

Figure 1 Group Mean Body Weights - Males

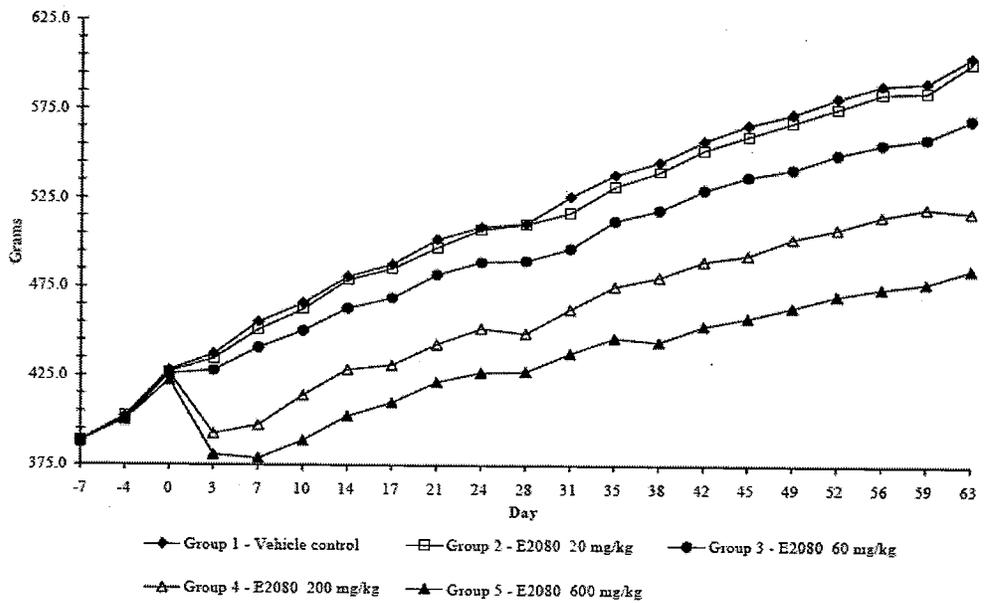


Figure 2 Group Mean Body Weights - Premating - Females

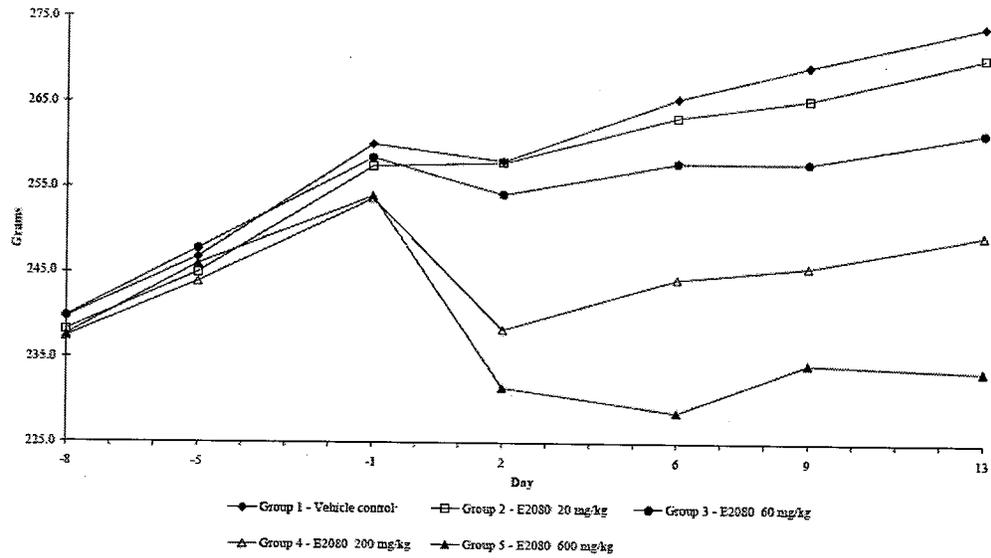


Figure 3 Group Mean Body Weights of Pregnant Females

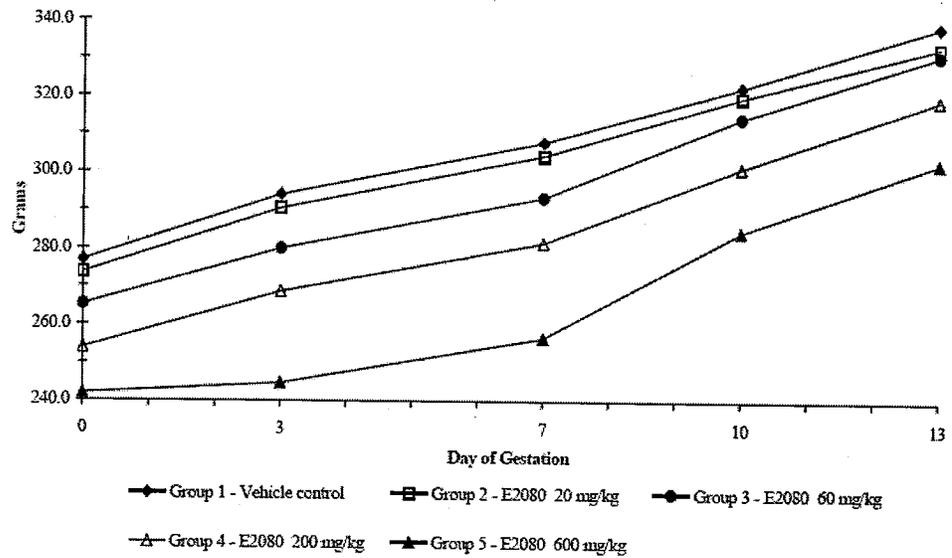


Table IC.1.1

Group 1 - Vehicle control
 Group 2 - E2080 20 mg/kg
 Group 3 - E2080 60 mg/kg

Group 4 - E2080 200 mg/kg
 Group 5 - E2080 600 mg/kg

Group	Number Placed for Mating		Number Mating	Mean (SD) Day to Mating	Number Females Pregnant	Mating Index (%)	Fertility Index (%)	Conception Rate (%)
	Males	Females						
1	22	22	21	2.6 (1.3) 21	20	95.5	90.9	95.2
2	22	22	21	2.8 (1.1) 21	21	95.5	95.5	100.0
3	22	22	22	2.9 (1.2) 22	19	100.0	86.4	86.4
4	22	22	21	2.9 (1.5) 21	19	95.5	86.4	90.5
5	22	22	20	2.9 (1.6) 20	18	90.9	81.8	90.0

Significantly different from control group (group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (Wilcoxon - day to mating only)

Significantly different from control group (group 1) value: * - $P \leq 0.05$ ** - $P \leq 0.01$ *** - $P \leq 0.001$ (Fisher's)

Table IC.1.2

Group	Summary Information	Total Number of Corpora Lutea	Total Number of Implantation Sites	Number of Live Embryos	Number of Dead Embryos
1	Mean	17.8	17.1	16.1	0.1
	SD	2.1	2.0	2.0	0.2
	N	20	20	20	20
2	Mean	18.8	16.7	15.4	0.0
	SD	2.7	3.3	3.6	0.0
	N	21	21	21	21
3	Mean	16.8	15.6	14.8	0.0
	SD	2.8	3.5	3.3	0.0
	N	19	19	19	19
4	Mean	16.3 a	14.8 b	13.6 b	0.1
	SD	2.4	2.2	2.4	0.3
	N	19	19	19	19
5	Mean	14.4 c	13.3 c	12.7 c	0.1
	SD	2.3	3.3	3.1	0.2
	N	18	18	18	18

Significantly different from control group (group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (Wilcoxon)

Table IC.1.3

Group	Summary Information	Number of Early Resorptions	Sum of Early Resorptions and Dead Embryos	Pre-Implantation Loss %	Post Implantation Loss %
1	Mean	1.0	1.0	3.86	5.82
	SD	1.0	1.0	3.15	5.80
	N	20	20	20	20
2	Mean	1.3	1.3	11.76 b	8.60
	SD	1.4	1.4	12.01	10.59
	N	21	21	21	21
3	Mean	0.8	0.8	7.61	5.19
	SD	1.0	1.0	12.98	5.69
	N	19	19	19	19
4	Mean	1.1	1.2	8.37 a	8.34
	SD	0.9	1.0	8.03	6.55
	N	19	19	19	19
5	Mean	0.6	0.6	8.29	4.41
	SD	0.7	0.8	16.49	5.41
	N	18	18	18	18

Significantly different from control group (group 1) value: a - $P \leq 0.05$ b - $P \leq 0.01$ c - $P \leq 0.001$ (Wilcoxon)

Table IC.1.4

Group	Summary Information	Cauda Epididymis Weight (g)	Spermatozoa Count Per Gram (Millions)	Percent Motility
1	Mean	0.3130	411.568	68.0
	SD	0.0374	81.709	11.5
	N	22	22	20
2	Mean	0.3263	395.793	70.7
	SD	0.0355	65.782	10.3
	N	22	22	22
3	Mean	0.3130	396.613	67.3
	SD	0.0303	71.020	12.2
	N	22	22	22
4	Mean	0.3136	373.535	64.7
	SD	0.0470	65.301	14.4
	N	22	22	22
5	Mean	0.3110	343.654 B	61.6
	SD	0.0352	74.680	16.6
	N	22	22	21

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunn)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

c. Conclusions

Oral (gavage) administration of rufinamide to time-mated female rabbits at doses of 30, 200 and 1000 mg/kg from GD 7 to 19 resulted maternal and developmental toxicity (abortion, death, clinical signs, and decreased maternal BW gain, decreased fetal BW, increased postimplantation loss, increased visceral and skeletal abnormalities) at the HD. Due to abortion and maternal mortality, the number of litters available for evaluation at the HD (13) was below the generally accepted minimum of 16. The NOAEL was 200 mg/kg in this study.

Figure IC.2.1

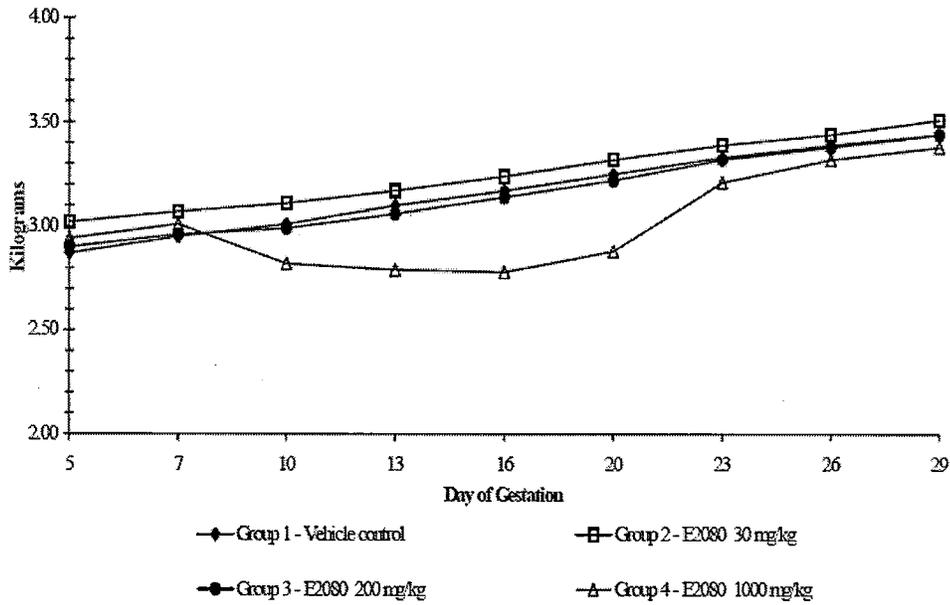


Table IC.2.1

		Group 1 - Vehicle control		Group 3 - E2080 200 mg/kg		Group 2 - E2080 30 mg/kg		Group 4 - E2080 1000 mg/kg			
Group	Summary Information	From: To:	Day of Gestation								
			5 7	7 10	10 13	13 16	16 20	20 23	23 26	26 29	7 16
1	Mean		0.08	0.06	0.09	0.07	0.08	0.08	0.06	0.05	0.22
	SD		0.038	0.030	0.047	0.046	0.063	0.055	0.070	0.062	0.088
	N		18	18	18	18	18	18	18	18	18
2	Mean		0.06	0.03	0.07	0.07	0.08	0.07	0.06	0.06	0.17
	SD		0.070	0.069	0.039	0.039	0.038	0.049	0.031	0.061	0.103
	N		18	18	18	18	18	18	18	18	18
3	Mean		0.06	0.02	0.07	0.08	0.08	0.10	0.06	0.06	0.18
	SD		0.061	0.083	0.039	0.039	0.044	0.071	0.071	0.061	0.109
	N		17	17	17	17	17	17	17	17	17
4	Mean		0.07	-0.19 F	-0.04 E	-0.01 D	0.07	0.11	0.04	0.05	-0.23 F
	SD		0.057	0.127	0.142	0.117	0.182	0.077	0.065	0.066	0.321
	N		20	20	20	20	19	14	13	13	20

Significantly different from control group (group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnst)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Table IC.2.2

Group 1 - Vehicle control Group 2 - E2080 30 mg/kg		Group 3 - E2080 200 mg/kg Group 4 - E2080 1000 mg/kg	
Group	Summary Information	Corrected Body Weights Day 29 of Gestation	Corrected Body Weight Gains Day 7-29 of Gestation
1	Mean	3.0206	0.0706
	SD	0.2004	0.1438
	N	18	18
2	Mean	3.0727	0.0005
	SD	0.2546	0.1949
	N	18	18
3	Mean	2.9733	0.0420
	SD	0.2027	0.1399
	N	16	16
4	Mean	2.9133	-0.0867
	SD	0.2558	0.1636
	N	13	13

Significantly different from control group (group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table IC.2.3

Group 1 - Vehicle control Group 2 - E2080 30 mg/kg	Group 3 - E2080 200 mg/kg Group 4 - E2080 1000 mg/kg							
	1		2		3		4	
	L/E	F/E	L/E	F/E	L/E	F/E	L/E	F/E
External (EXT)	18	124	18	132	17	130	13	104
Visceral (VIS)	18	124	18	132	17	130	13	104
Skeletal (SKE)	18	124	18	132	17	130	13	104
	L/A	F/A	L/A	F/A	L/A	F/A	L/A	F/A
Major Malformations (Total)	0	0	0	0	0	0	2	2
Face								
Upper jaw reduced (micrognathia)(EXT)	0	0	0	0	0	0	1	1
Nose: Single naris (EXT)	0	0	0	0	0	0	1	1
Mouth: Incisors absent (EXT)	0	0	0	0	0	0	1	1
Abdomen								
Intestines protruding at umbilicus (omphalocele) (EXT)	0	0	0	0	0	0	1	1
Skull								
Multiple fusions and anomalies in skull bones (SKE)	0	0	0	0	0	0	1	1

L/E = Litters examined L/A = Litters affected

F/E = Fetuses examined F/A = Fetuses affected

Significantly different from control group (group 1) value: * - $P \leq 0.05$ ** - $P \leq 0.01$ *** - $P \leq 0.001$ (Fisher's)

Table IC.2.4

	Group 1 - Vehicle control Group 2 - E2080 30 mg/kg		Group 3 - E2080 200 mg/kg Group 4 - E2080 1000 mg/kg		Group			
	1		2		3		4	
	L/E	F/E	L/E	F/E	L/E	F/E	L/E	F/E
External (EXT)	18	124	18	132	17	130	13	104
Visceral (VIS)	18	124	18	132	17	130	13	104
Skeletal (SKE)	18	124	18	132	17	130	13	104
Minor External and Visceral Anomalies (Cont'd)	L/A	F/A	L/A	F/A	L/A	F/A	L/A	F/A
Ureter(s)								
Ureter(s) retrocaval (VIS)	0	0	1	1	1	1	3	5*

L/E = Litters examined L/A = Litters affected
 F/E = Fetuses examined F/A = Fetuses affected
 Significantly different from control group (group 1) value: * - P ≤ 0.05 ** - P ≤ 0.01 *** - P ≤ 0.001 (Fisher's)

Table IC.2.5

	Group 1 - Vehicle control Group 2 - E2080 30 mg/kg		Group 3 - E2080 200 mg/kg Group 4 - E2080 1000 mg/kg		Affected Fetuses/Litters Mean % (SD)			
	1		2		3		4	
Common Skeletal Variants	11.19	12.83	12.85	13.31	18.78	25.60	6.81	9.23
Unilateral 13th rib (extra/rudimentary)	18	18	18	18	17	17	13	13
Bilateral 13th rib (extra/rudimentary/ ossification center)	33.22	35.48	43.35	34.19	29.77	29.42	65.12 a	28.08
	18	18	18	18	17	17	13	13
Ribs - total 13th (unilateral and bilateral) extra/rudimentary/ossification center	44.41	35.54	56.20	33.40	48.56	32.04	71.93	29.57
	18	18	18	18	17	17	13	13
Sternebrae (unossified/incomplete/semi-bipartite/ bipartite)	50.49	34.06	58.75	28.83	49.82	30.95	28.93	21.90
	18	18	18	18	17	17	13	13

Significantly different from control group (group 1) value: a - P ≤ 0.05 b - P ≤ 0.01 c - P ≤ 0.001 (Wilcoxon)

Table IC.2.6

Group Designation	*T _{max} (hr)	C _{max} (ng/mL)	AUC _(0-last) (hr*ng/mL)	AUC _(0-∞) (hr*ng/mL)	AUC _(last-∞) %	T _{1/2} (hr)	R ²
2	1	10950.91	72595.85	77228.91	7.16	2.66	0.986
3	4	31943.76	429598.68	434952.34	1.08	3.41	0.978
4	8	48297.76	933511.43	NR	NR	NR	NR

* T_{max} values represent the median rather than the mean.
 NR = Not Reported

II. SUMMARY AND EVALUATION

In the rat carcinogenicity study submitted with the original NDA, rufinamide was administered in the diet to S-D rats at approximate daily doses of 0, 20, 60 or 200 mg/kg for 97 (males) or 103 (females) weeks. (Due to low survival in controls, all remaining males were sacrificed during week 98. Surviving females were sacrificed as scheduled during week 104.) Effects consisted of decreased body weight gain (MD & HD; terminal BWs 10 & 29% below controls in males, 21 & 37% below controls in females); decreased mortality (MD & HD); and non-neoplastic microscopic changes in the liver and kidney. Plasma rufinamide concentrations were generally somewhat lower in females at the LD and MD but not at the HD. Based on TK from the 13-week dietary study, the AUC at the HD was approximately 4000 $\mu\text{mol}\cdot\text{hr/L}$ (human exposure at MRD = 1923 $\mu\text{mol}\cdot\text{hr/L}$). Neoplastic findings consisted of increased incidences of thyroid follicular (0/59, 1/60, 10/60, 4/60; statistically significant) and thyroid C-cell adenomas (1/59, 3/60, 6/60, 2/60; not significant) in males. The incidence of thyroid C-cell carcinoma was increased somewhat in MD males (1/59, 1/60, 3/60, 0/60; not significant). There was also a possible increase (not significant) in liver hepatocellular adenomas in MD males (3/59, 2/60, 7/60, 4/60) and HD females (2/60, 1/60, 1/60, 5/60).

The MD was considered the MTD based on decreases in body weight gain noted in both sexes by the end of the study. However, in view of the shortened duration and excessive BW effects, even at the MD in females (and the resulting reduced sensitivity to detect potential carcinogenic effects), the validity of the study was considered questionable (see original NDA pharm/tox and statistical reviews).

In addition to the problems with the rat carcinogenicity study, several critical studies did not conform to current standards: a) the in vivo micronucleus assay in rats did not evaluate the recommended 2000 micronucleated polychromatic erythrocytes per animal, b) the rat fertility study evaluated too few animals (12/group) and did not employ 1:1 mating, and c) the rabbit embryofetal development study did not evaluate a maternally toxic high dose. There was also some concern about a finding of decreased whole and regional brain weights in the juvenile rat study, and the developmental age range and endpoints studied in juvenile dogs were considered inadequate.

The following non-clinical comments were transmitted in the Approvable Letter (dated 9/15/06):

1. We note that the rat carcinogenicity is inadequate. As you know, the high dose male and the mid- and high-dose female groups experienced excessive decreases in body weight relative to controls, resulting in reduced ability to detect potential carcinogenic effects. We believe that the body weight effect was likely exacerbated by unpalatability of the feed. Based on estimates of plasma AUCs, we note that the plasma exposures in the low dose females and the mid-dose males (the groups that did not suffer excessive weight loss) were not sufficiently greater than those achieved in humans to provide confidence that the tumorigenic potential of rufinamide has been adequately assessed at clinically relevant exposures. We further note evidence in your application suggesting that similar doses could be administered by gavage without the excessive body weight effects observed with dietary administration. Were we convinced that rufinamide provides a significant clinical benefit, we might be persuaded that the rat study be repeated in Phase 4. We do ask that you address the possibility that an adequate 2-year study in rats could be conducted using gavage dosing. The need for and the timing of the conduct of a repeat study will depend upon your response to this letter.

2. Several critical non-clinical studies do not conform to current standards and are, therefore, inadequate: a) the in vivo micronucleus assay in rat did not evaluate the recommended 2000 micronucleated polychromatic erythrocytes per animal, b) the rat fertility study evaluated too few male animals (12/group) and did not employ 1:1 mating and, c) the rabbit embryofetal development study did not evaluate a maternally toxic high dose. These studies need to be

repeated (cf. OECD Guidelines for the Testing of Chemicals, Guideline 474; Guideline for Industry: Detection of Toxicity to Reproduction for Medicinal Products ICH-S5A).

3. The finding of decreased whole and regional brain weights in the juvenile rat study should be further investigated, e.g., using expanded neurohistopathology and brain morphometry.

4. The developmental age range studied in juvenile dogs was inadequate. A dog study in which dosing is initiated at an earlier age (corresponding to the clinical age range) needs to be conducted, and bone growth and density and brain development (using expanded neurohistopathology) should be evaluated in addition to the standard toxicity endpoints. There is particular concern regarding developmental effects on bone and brain based on the bone tumor findings in the mouse carcinogenicity study and the brain weight effects in the juvenile rat study. You are encouraged to submit a protocol for review and comment prior to initiation of the study.

Eisai Response:

1. Eisai submitted a recently completed 3-month rat oral gavage dose-ranging study (Study No. 802789) conducted in order to compare BW effects and exposure levels to those seen in the dietary studies. In this study, oral gavage administration of rufinamide (200, 600 or 1000 mg/kg) resulted in decreased body weight gains (-15, -27 and -31% below C in males and -18, -29 and -37% below C in females, at LD, MD and HD) and food consumption and changes associated with hepatic enzyme induction (increase in mean liver/body weight ratios, centrilobular hepatocellular hypertrophy, and vacuolation of the pituitary). TK showed exposure levels comparable to those seen with dietary administration at the LD but little or no increase in exposure with increasing doses (see Table II.1, below). In the 13-week dietary study (Study No. 92100) with doses of 200, 400, and 600 mg/kg, BW gains were decreased 31, 49, and 51% in males and 25, 28, and 32% in females compared to C at the respective doses. The results indicate that somewhat greater exposures were achieved with dietary administration at 200 mg/kg, which was the HD in the carcinogenicity study (doses of 20, 60, and 200 mg/kg in both sexes). The current data indicate that a gavage dose below 200 mg/kg would be necessary to avoid excessive BW effects, which would further reduce exposures. While the BW effect is diminished in the gavage study, the differences are not great in females, where the biggest effect was seen in the carcinogenicity study (terminal BWs 10 & 29% below C in males, 21 & 37% below C in females, at MD and HD). This suggests that palatability was not the primary cause of the BW effects seen in the dietary studies. Taken together, the data do not support the usefulness of repeating the rat carcinogenicity study.

2. In a repeat in-vivo micronucleus assay (Study No. 961523), which was conducted under current guidelines, male rats (SD; 5/dose/timepoint) were given 0, 500, 1000, or 2000 mg/kg of rufinamide by oral gavage and 2000 immature erythrocytes per animal were examined for micronuclei. The results were negative at all time points: animals treated with rufinamide did not show any statistically significant increase in the incidence of micronucleated immature erythrocytes and no significant differences in the proportion of immature erythrocytes were observed.

In a repeat rat fertility study (Study No. 901316, conducted under the current guidelines), rufinamide was given by oral gavage to male SD rats (22/group) for 28 days prior to mating and during cohabitation and until necropsy; and to female rats for 14 days prior to mating, during the mating period and until gestation Day 6, at doses of 0, 20, 60, 200, and 600 mg/kg. There was no T-R mortality. Clinical signs (dehydration and thinness) and decreased body weights were seen in males at ≥ 200 mg/kg and in females at ≥ 60 mg/kg (BW 20% below C in males [terminal] and 15 [premating] and 11% [gestational] below C in females, at HD). A number of effects on reproductive parameters were seen: decreased fertility index (≥ 60 mg/kg), conception rate (≥ 60 mg/kg) and mating index (HD); decreased numbers of corpora lutea, implantations, and live embryos (≥ 200 mg/kg); increased preimplantation loss (all doses); and decreased sperm count and motility (≥ 200 mg/kg). Based on these findings, the LOAEL for fertility and early embryonic

development is considered to be 20 mg/kg. This is close to the NOEL in the original Segment I study (oral doses of 15, 50, or 150 mg/kg given to males and females). In this study, BW was decreased slightly in HD males on days 28 (7% below C, SS) and 84 (6%, NS) of dosing and in MD and HD females at the end of the pre-mating period (6 and 7%, respectively, both SS) and in the HD females at the end of gestation (7% on GD20, SS). The percentage of mated females that were pregnant on either GD 13 or 21 was decreased at the HD and possibly the MD compared to C (83.3, 91.7, 79.2, and 70.8 in C, LD, MD, and HD, respectively). There were no effects on any examined reproductive parameter derived from females sacrificed on gestational day 13 (only 8-10 pregnant females evaluated). Thus, the new study revealed additional adverse effects on fertility.

In the repeated rabbit embryo-fetal study (Study No. 901317), rufinamide was administered by oral gavage to pregnant rabbits (NZW, 22/group) from GD 7 to 19 at doses of 30, 200 or 1000 mg/kg. Maternal/developmental toxicity (decreased food consumption, BW loss, abortion, and mortality) was excessive at the HD and resulted in a marginal number of evaluable litters (13) at this dose. Most of the maternal toxicity was associated with abortion. There was no increase in abortion in the original study (0, 30, 200, or 700 mg/kg in Chinchilla rabbits), but total resorption was increased somewhat (1 C, 1 LD, 3HD). It appears that the dose-response for this effect on the maintenance or progress of pregnancy is steep. As in the original study, increased resorption and decreased fetal weights were seen at the HD (in surviving litters). However, while abortion and total resorption were clearly increased, the effect on resorption rate in litters carried to term was limited, indicating that the embryoletality may not represent a selective effect on the conceptus. Malformations were only seen at the HD, where there were 2 malformed fetuses from 2 litters (1 with omphalocele and 1 with skull malformations). There were also increases in a minor visceral anomaly (retrocaval ureter) and a skeletal variation (13th rib) at the HD. Slight increases in skeletal malformations were seen at the MD and HD in the original study: 1 C, 2 MD, and 2 HD fetuses showed absent ossification of pubic bones; and 1 HD fetus had thoracic scoliosis. Thus, there is no clear evidence of teratogenicity in rabbits based on these 2 studies, although an effect could have been masked by embryoletality (total litter loss). Various skeletal minor anomalies were also very slightly increased at the MD (3 fetuses/3 litters) and HD (3/2) compared to C (2/2) and increases in skeletal variations were seen at these doses in the original study. The overall impression is of embryofetal toxicity in rabbits at ≥ 200 mg/kg.

3. Eisai conducted an expanded neuropathological evaluation on the brain sections from control and high dose animals with special stains for myelin phospholipids and axon fibers (Klüver Barrera and Holmes). There were no treatment-related neurohistopathological changes noted in this evaluation.

4. Eisai agreed to conduct an additional dog juvenile study as a post-marketing phase 4 commitment (see the February 7, 2007, signed minutes from the December 18, 2006 meeting).

Table II.1

Dose (mg/kg)	Sex	Male				Female			
		200	400	600	1000	200	400	600	1000
AUC($\mu\text{mol/hr/L}$)									
Gavage	Day 1	4626		3834	5494	3838		5591	5739
	Week 13	3664		3821	4481	3200		4334	4679
Diet	Week 2	3724	4442	4433		2918	4081	3724	
	Week 10	4320	5428	5655		3652	4706	5378	
Body weight (% difference from control)									
Gavage		-6		-17	-19	-7		-14	-17
Diet		-23	-38	-38		-15	-16	-19	

* gavage study: Study No. 802789 (dose level: 200, 600, 1000 mg/kg), diet study: Study No. 93027 (dose levels: 200, 400, 600 mg/kg)

III. RECOMMENDATIONS

The application can be approved from a pharm/tox standpoint. The sponsor has adequately addressed all of the preclinical deficiencies identified in the approvable letter. They should perform an adequate juvenile dog study Phase 4, as previously agreed. The new data indicate that repeating the rat carcinogenicity study would not be warranted. Labeling recommendations follow.

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Draft Labeling (b4)

Draft Labeling (b5)

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/s/

Edward Fisher
8/29/2008 11:20:29 AM
PHARMACOLOGIST

Lois Freed
9/2/2008 06:33:05 PM
PHARMACOLOGIST
Please see memo for concurrence.

MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN
SERVICES
Public Health
Service
Food and Drug Administration**

**Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research**

Date: September 29, 2006

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-911 (rufinamide)

Regarding the nonclinical safety data submitted in support of the NDA, a primary concern is the assessment of the carcinogenic potential of rufinamide. The dietary carcinogenicity studies and supportive data have been reviewed in detail by Ed Fisher, Ph.D. (Pharmacology/Toxicology Review and Evaluation, N21-911, 9/26/06). In addition, these data have been reviewed by the Executive CAC (meeting date: 8/1/06).

Mouse

Dr. Fisher concluded that the 2-year mouse study is adequate by design and conduct and was positive for carcinogenic potential. Neoplastic findings consisted of an increased incidence of osteomas and hepatocellular adenomas in males and females (increases in hepatocellular adenomas in high-dose males and females were not statistically significant).

TISSUE	FINDING	MALES				FEMALES			
		0	40	120	400*	0	40	120	400*
bone	osteoma	0/60	0/60	2/60	3/60 [#]	0/60	2/60	1/60	6/60 [#]
liver	hepatocellular adenoma	4/59	5/59	4/59	13/58 [#]	0/59	0/59	1/57	10/59 [#]
	hepatocellular carcinoma	8/59	7/59	8/59	14/58	1/59	0/59	1/57	4/59

* doses given in mg/kg/day; [#] statistically significant trend

The ExeCAC concurred with this interpretation.

Rat

Dr. Fisher concluded that the validity of the 2-year rat study (97 wks in males) is an issue. The study was positive for carcinogenic potential due to significant increases in thyroid follicular adenomas in males (0/59, 1/60, 10/60, 4/60 in C, LD, MD, and HD groups, respectively). (There was also a non-significant trend for thyroid C-cell adenomas in males (1/59, 3/60, 6/60, 2/60 in C, LD, MD, and HD groups, respectively).) However, adverse effects on body weight, the primary drug-related finding, were excessive in mid-dose females and high-dose males and females, resulting in reduced sensitivity to detect carcinogenic potential.

[The ExeCAC concurred that the study was positive for thyroid follicular adenomas (with a non-significant trend for thyroid C-cell adenomas) and noted that the rat study was “less than adequate” due to the body weight effects.]

It is Dr. Fisher’s opinion that doses similar to those used in the 2-yr dietary study could be administered by gavage to give similar plasma exposure without the excessive effect on body weight.

Table: summary of effects on final mean body weight (i.e., decreases relative to controls).

STUDY	MALES					FEMALES				
	20	60	200	400	600*	20	60	200	400	600*
2-yr dietary	2%	10%	29%			--	21%	37%		
3-mo dietary			23	38	38			16	16	19
26-wk/1-yr dietary [#]	--/9	4/10	22/25			--/--	7/8	21/32		
1-mo gavage [!]	9	8	12		18					
3-mo gavage		2	4		11		3	8		12

*doses expressed in mg/kg/day; [#]26-wk interim sacrifice in 1-yr study; [!]another 1-mo gavage study was conducted only in males at 0 and 600 mg/kg; mean body weight was reduced 14% compared to CM.

Table: summary of effects on overall mean body weight gain (estimated decreases relative to controls).

STUDY	MALES					FEMALES				
	20	60	200	400	600*	20	60	200	400	600*
2-yr dietary	2%	13%	38%			--	30%	53%		
3-mo dietary			31	49	51			25	28	32
26-wk/1-yr dietary [#]	2/2	4/5	30/31			4/4	15/18	33/41		
1-mo gavage [!]	19	24	33		49					
3-mo gavage		2	5		17		9	12		30

*doses expressed in mg/kg/day; [#]26-wk interim sacrifice in 1-yr study; [!]another 1-mo gavage study was conducted only in males at 0 and 600 mg/kg; mean body weight gain was reduced ≈40%.

Plasma AUC data were not available for the rat carcinogenicity study; however, estimates of AUC based on the plasma concentration data suggest that plasma exposure is similar with dietary and gavage administration at similar doses. Based on these estimates, it would appear that the mean plasma AUC in MDM in the carcinogenicity study is similar

to the anticipated human plasma AUC at the maximum recommended clinical dose (3200 mg/day); the plasma AUC in LD animals is ≈ 0.4 times the human plasma AUC. Therefore, there is no safety margin between the plasma exposure at doses not associated with excessive body weight effects and the anticipated human plasma exposure.

The data from the 3-month gavage study suggest that the 200-mg/kg dose could be used successfully in a 2-year study. If so, then the carcinogenic potential of rufinamide could potentially be adequately tested at plasma exposures (AUC) 2-3 times the anticipated human plasma AUC. However, the data from the 1-month gavage study demonstrate a greater body weight effect, and suggest that a high-dose of 200 mg/kg would result in excessive body weight effects.

Since the data suggest, but do not clearly indicate that a more adequate assessment of carcinogenic potential could be achieved using gavage dosing, the sponsor should be asked to address this issue. If a gavage study could provide a better assessment, then a decision as to whether study would need to be conducted prior to approval or Phase 4 would depend, at least in part, on the robustness of the clinical data.

Other nonclinical issues

In addition to concerns regarding the assessment of carcinogenic potential, Dr. Fisher noted several other nonclinical deficiencies:

- (1) the in vivo micronucleus assay in rat did not include an evaluation of the recommended number of polychromatic (immature) erythrocytes (PCEs); only 1000 PCEs/animal were examined rather than the recommended 2000 PCEs/animal.
- (2) the mating and fertility study in rat was conducted in an inadequate number of males/group (i.e., 12/group rather than the recommended 16-20/group) and employed 2:1 rather than the recommended 1:1 mating.
- (3) the embryofetal development study in rabbit was not conducted at sufficiently high doses. The high dose in that study was not associated with dose-limiting toxicity. In addition, no other data in rabbit were provided to establish that higher doses could not have been tolerated or achieved.
- (4) the study in juvenile dog did not cover the appropriate developmental age range; dosing was initiated at 4 months of age and continued for 13 weeks. Rufinamide is intended to treat Lennox-Gastaut and partial seizures in children and adults. Therefore, dosing should begin at as early an age as feasible and continue through sexual maturity.

Dr. Fisher has recommended that these nonclinical deficiencies be addressed by the sponsor. I concur, and recommend that the sponsor repeat these studies in a timely manner, preferably prior to approval.

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/s/

Lois Freed
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PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-911
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	11/17/05
PRODUCT:	rufinamide (CGP 33101)
INTENDED CLINICAL POPULATION:	epilepsy
SPONSOR:	Eisai
REVIEW DIVISION:	Division of Neurology Drug Products (HFD-120)
PHARM/TOX REVIEWER:	Ed Fisher
PHARM/TOX SUPERVISOR:	Lois Freed
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PROJECT MANAGER:	Courtney Calder

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Note: Portions of this review were excerpted from the sponsor's submission.

I. INTRODUCTION AND DRUG HISTORY

NDA number: 21-911

Date of submission: 11/17/05

Sponsor: Eisai Medical Research

Drug:

Trade name: Inovelon

Generic name: rufinamide

Code names: CGP 33101; RUF 331

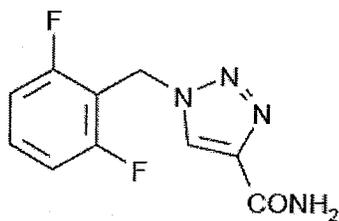
Chemical name: 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide

CAS registry number: 106308-44-5

Molecular formula: C₁₀H₈F₂N₄O

Molecular weight: 238.2

Structure:



Relevant IND: 35,534

Drug class: sodium channel modulator

Indication: epilepsy

Route of administration: oral (tablets)

II. PHARMACOLOGY

A. BRIEF SUMMARY

Rufinamide is a triazole derivative, intended for the treatment of partial seizures in adults and adolescents 12 years and older and seizures associated with Lennox-Gastaut syndrome in adults and children. In vitro studies indicate that rufinamide limits the frequency of firing of sodium-dependent action potentials in rat and mouse neurons. Rufinamide did not significantly interact with a number of neurotransmitter systems, including GABA, benzodiazepine, monoaminergic and cholinergic binding sites, NMDA, and other excitatory amino acid binding sites. In vivo oral rufinamide suppressed MES-induced tonic-clonic seizures in rodents. No development of tolerance occurred during a 5-day treatment period in mice and rats. Rufinamide was less potent in antagonizing clonic seizures induced by pentylenetetrazole and other chemoconvulsant agents. In Rhesus monkeys with chronically recurring partial seizures, rufinamide reduced seizure frequency. The PI and safety ratio of rufinamide were comparable to other AEDs.

B. SAFETY PHARMACOLOGY

In a preliminary hERG study in which only 2 cells were evaluated and 1 of those tested a single drug concentration (Study No. W-20040219), rufinamide (0.1, 1 and 10 $\mu\text{mol/L}$) inhibited hERG induced tail currents in 1 cell by 9.7%, 12.1% and 12.1%, respectively. In a second cell, 10 $\mu\text{mol/L}$ rufinamide inhibited tail currents by 6%. The positive control (300 nmol/L E-4031) inhibited tail currents by 80% in the second cell.

In the pivotal hERG study (Study No. DJNR1037), 100 μM rufinamide (15 min) produced a decrease in tail current of 35.9% (n=5 cells), but the study was invalid since the vehicle (1% DMSO) inhibited tail current by an average of 31.6% (n=4 cells). (A reasonable vehicle effect might be a few percent.) The positive control (100 nmol/L E-4031) decreased the tail current by 87% (n=4 cells). Thus, no definite conclusions can be drawn from these studies.

In an anesthetized dog study (Study No. 982069), 4 animals (male Beagles) were randomized to treatment and 2 served as controls. Dogs were anesthetized with sodium pentobarbital. Treated dogs were injected (iv) once at each escalating dose level (1, 3, and 10 mg/kg) with a 45 minute interval between each dose. The measurements taken included: arterial blood pressure (systolic, diastolic and mean); heart rate, electrocardiograms; arterial blood flow; and respiratory parameters (tidal volume, respiratory rate and minute volume). No clear differences in blood pressure were evident between control and rufinamide-treated animals. A slight decrease in heart rate (up to 10%) was observed with sequential administration of rufinamide (**Figure IIB.1**). HR was also decreased somewhat in C, so the effect was thought to be partly attributed to the vehicle (30% PEG 400 in saline). There were no apparent effects on blood flow in the femoral artery and on P-wave amplitude and duration, or PQ and QRS interval. The QT interval remained relatively constant throughout the experiment (**Table IIB.1**; QTc not calculated). Electrocardiography was also assessed in the chronic toxicity study in dogs (Study No. 89-6305). In this study, no notable treatment-related effects on heart parameters were observed following daily doses of up to 200 mg/kg for up to 52 weeks.

Figure IIB.1

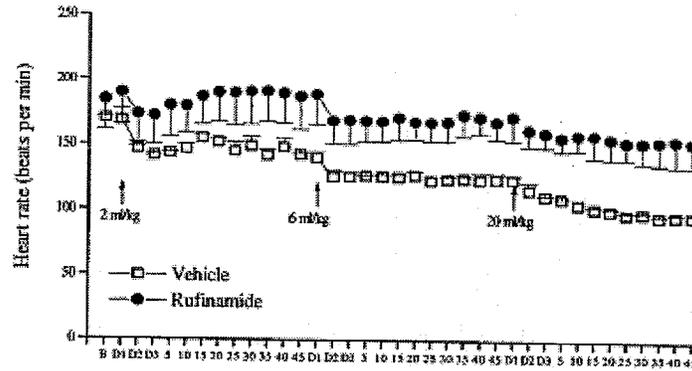


Figure 3. Effects of Rufinamide (1, 3 and 10 mg/kg, given as 2, 6 and 20 ml/kg, respectively) or vehicle (30 % PEG 400), on heart rate (beats per minute) following intravenous administration (at arrows) in the anaesthetised dog. B = before dosing; D1, D2, D3 = values measured during dosing; 5, 10, 15.....45 = minutes after dosing. Values are mean (+/- SD) of 2-4 observations.

Table IIB.1

ELECTROCARDIOGRAMS SUMMARY
Q-T Interval (msec)
MALES

		GROUP 2 1 MG/KG	GROUP 2 3 MG/KG	GROUP 2 10 MG/KG
TIME RELATIVE TO DOSING				
Before	MEAN	215.00	220.00	220.00
	ST.DEV.	12.91	18.26	23.09
	N	4	4	4
During 3	MEAN	217.50	227.50	230.00
	ST.DEV.	20.62	22.17	24.49
	N	4	4	4
15 min	MEAN	215.00	222.50	225.00
	ST.DEV.	12.91	20.62	19.15
	N	4	4	4
30 min	MEAN	217.50	222.50	225.00
	ST.DEV.	15.00	20.62	19.15
	N	4	4	4
45 min	MEAN	220.00	220.00	225.00
	ST.DEV.	18.26	23.09	19.15
	N	4	4	4

III. PHARMACOKINETICS

A. BRIEF SUMMARY

The disposition of rufinamide in animals after oral dosing was characterized by a low rate of absorption, relatively slow clearance, and little or no first pass metabolism. The extent of absorption was variable across the test species and generally decreased in proportion at high doses. This less than dose proportional increase in systemic exposure showed no pronounced sex difference. There was no unexpected accumulation on repeated administration of the same dose. Systemic exposure in young and mature dogs was similar for the same mg/kg dose. Radioactivity from labeled rufinamide was distributed throughout the body in rats, and there was no evidence of a peculiar or persistent affinity to specific organs and tissues. A marked and reversible transfer of rufinamide and/or metabolites to the embryo/fetal compartment was observed in rats and rabbits. Radiolabel was distinctly taken up into the mammary glands indicating the compound and/or metabolites could be excreted with the milk. Systemic exposure to metabolites was low. Based on urinary excretion data, the compound was cleared mainly by metabolism. The main metabolite in all species including humans was the carboxylic acid, designated CGP 47 292, formed by hydrolysis of the carboxylamide group, a reaction catalyzed by carboxylesterase(s). Oxidative metabolism was minor and apparently more pronounced in rodents than in dogs or primates. Rufinamide weakly induced drug-metabolizing enzymes in rat and mouse liver in a qualitatively similar manner to CBZ or PB. Rufinamide also weakly induced CYP3A4 in human hepatocytes. The effect was reversible in mice. In the cynomolgus monkey, crystals were found in the gallbladder following repeated dosing. These crystals were a metabolite of rufinamide derived from a glutathione adduct. A human radiotracer study showed that this metabolic pathway is not relevant to man. Serum protein binding of rufinamide in any species was low (23~35%). Rufinamide showed no significant or very weak capacity to inhibit the activity of the human P450 enzymes and carboxylesterase(s). Single dose PK parameters are shown in **Table IIIA.1** and TK data are shown in **Table IIIA.2** (conversion factor for ug.h/ml = 0.24). It should be noted that the clinical data underestimate human exposure, since they are based on AUC0-12h. Another comparison (**Table V.1**) estimates clinical exposure to parent at the MRD as 1923 umol.h/L.

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Table IIIA.1

Table 4 Mean pharmacokinetic parameters of rufinamide in plasma of mice, rats, dogs, baboons, Cynomolgus monkeys and humans following single i.v. or oral administration

Species/Route of administration (n)	Dose (mg/kg)	C _{max} (μmol/L)	t _{max} (hr)	AUC(0-∞) (μmol·hr/L)	t _{1/2} (hr)	Reference
Mouse						
i.v. (3)	5	17.4*	0.17* ^{a)}	73.5* ^{b)}	ND	DM 26/1993
p.o. (3)	5	12.0*	1*	71.1* ^{b)}	ND	
Rat						
i.v. (3)	5	23.5*	0.1* ^{a)}	265* ^{c)}	4-5* (8-24hrs)	BI13/1988
p.o. (4)	6	15.1	1.5	84.5 ^{d)}	5.4	CRB
p.o. (4)	30	56.2	3	361 ^{d)}	ND	R72/1988
Dog						
i.v. (2)	5	24.7 / 21.6	0.5 / 0.25	242 / 212 ^{d)}	9.6 / 6.4	CRB
p.o. (2)	5	1.7 / 3.7	24/2	26.7 / 44.9 ^{d)}	4.2 (n=1) ^{d)}	R63/1988
p.o. (1)	5	5.1*	24*	173* ^{e)}	h)	DMPK 1997/246
p.o. (1)	60	10.6	2	114 ^{e)}	5.6	CRB R63/1988
p.o. (1)	60	25.9*	4*	482* ^{e)}	8.6* (6-48hrs)	DMPK 1997/246
p.o. (1)	600	61.2	6	1160 ^{d)}	7.5	CRB R63/1988
Baboon						
i.v. (2)	3	14.1/13.3	0.5	215 / 248 ^{d)}	9.4 / 12.7	CRB R50/1990
p.o. (2)	5	4.3/5.8	8/12	130/185 ^{d)}	10.9 / 15.5	
p.o. (1)	275	247	24	14000 ^{d)}	16.2	
Cynomolgus monkey						
i.v. (2)	3	14.0 / 13.8*	0.08 ^{a)} / 0.25* ^{b)}	264 / 260* ^{b)}	14-16*	DMET 9/1996
p.o. (2)	3	10.9 / 9.3*	2 / 2*	259 / 211* ^{b)}	ND	
p.o. (2)	30	72.4 / 61.0*	8 / 6*	2019 / 1579* ^{b)}	ND	
p.o. (1m, 1f)	300	157 (m) 175 (f)	24 (m) 24 (f)	7040 (m) ^{d)} 8090 (f) ^{d)}	14.4 (m) 11.6 (f)	BPK 1995/038
Human						
p.o. (3)	600mg/ man	25.5	5	432.4 ^{d)}	9	HPH9213

Table IIIA.2

Daily Dose (mg/kg)	Mouse ^a		Rat ^a		Dog ^b		Baboon ^c		Monkey ^c		Guinea pig ^c	Human ^d
	M	F	M	F	M	F	M	F	M	F	M	
1					20.2 ^a	13.8 ^a						
					19.7 ^f	20.0 ^f						
5					55.3 ^a	63.0 ^a						
					58.3 ^f	105 ^f						
6					58.8 ^g	78.1 ^g						
20					734 ^h	352 ^h			1060 ^h	1010 ^h		626
30							1040	1190			340	814
35									1348 ^a	1096 ^a		
40												945
60	285 ^a	260 ^a			1890 ^f	2130 ^f			1690 ^h	2290 ^h		1243
100									2422 ^a	2196 ^a		1373
120												
200	1297 ^a	1306 ^a	4320 ^a	3632 ^a	3140 ^f	3370 ^f			3190 ^h	3060 ^h		
					991 ^h	3580 ^h						
					1640 ^a	1830 ^a						
					749 ^g	857 ^g						
300							2230	2330	3946 ^a	3312 ^a		
400			5428 ^a	4706 ^a								
600	3883 ^a	3195 ^a	5655 ^a	5378 ^a	4200 ^f	4660 ^f						
					1645 ^g	1865 ^g						

^a - in diet

^b - in capsules

^c - by gavage

^d - A001-001 Study (1600, 2400, 3200, 4800, and 7200 mg/day)

^e - 13-week toxicity study

^f - 13-week toxicity study in young dogs

^g - 3-month toxicity study

^h - 12-month toxicity study

ⁱ - 2-week toxicity study

B. METABOLISM

In animal studies, rufinamide was extensively metabolized, with less than 10% of the dose recovered unchanged in the urine in the animal species investigated: <3%, <2% and <4.4% in dogs, baboons, and cynomolgus monkeys, respectively. The major metabolite in all species investigated was CGP 47292. This metabolite is formed by hydrolysis of rufinamide, presumably by carboxylesterases, and is inactive. The comparison of AUC values for parent drug and total radioactivity in plasma of dogs and baboons given [¹⁴C] labeled rufinamide demonstrated a low systemic exposure to metabolites. Parent drug comprised 66-90% of the AUC of radioactive substances in the dog and 92-97% in the baboon. In cynomolgus monkeys given a single oral dose of rufinamide (300 mg/kg), the plasma AUC of CGP 47292 was 3-4% of the AUC of the parent compound. In rats, comparisons of the plasma concentration data from separate but comparable experiments with [¹⁴C]-labeled and unlabeled rufinamide suggests that in this species exposure to metabolites was also low. When plasma concentrations of rufinamide and CGP 47292, were determined after oral administration of a 270 mg/kg single dose of [¹⁴C] rufinamide to pregnant rats (strain Tif:RAIf), concentrations of CGP 47292 represented between 3% and 6% of those of rufinamide. The combined concentrations of rufinamide plus CGP 47292 were similar to those reported

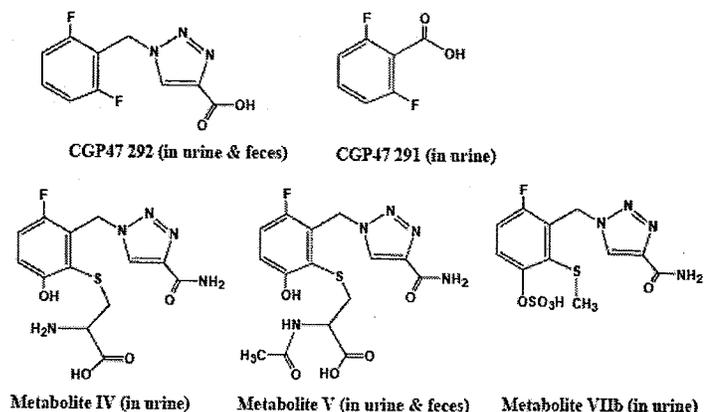
for total radioactivity. On the basis of its similarity with the rat in [14C] disposition, it seems plausible to assume the same behavior in the mouse. The plasma concentrations of CGP 47292 in two epileptic patients given CGP 33101 were 12-17% of parent levels.

Prominent in the urine of mouse and rat (10-40% of urinary radioactivity), but of minor importance in dogs, Cynomolgus monkeys and baboons ($\leq 5\%$ of urinary radioactivity), was 2,6-difluorobenzoic acid, CGP 47291, a metabolite formed by oxidative cleavage at the benzylic carbon atom. In a human radiotracer study this metabolite was found only in possible trace amounts in the urine. The 3-hydroxy-6-fluoro-2-S-cysteinyl conjugate of rufinamide (Metabolite IV) was one of the main metabolites in rat bile, dog bile and mouse urine. This conjugate was presumably formed by hepatic oxidation of the difluorophenyl ring followed by nucleophilic aromatic substitution of the 6-fluorine atom by glutathione and subsequent enzymatic degradation of the glutathione moiety in the bile. In human radiotracer study, there was no spectroscopic evidence for the presence of any similar or related glutathione-derived metabolites in urine and feces.

Comparison of the metabolism of rufinamide in mice (**Figure IIIB.1**) with that in other species indicates a common major pathway in all species and particular pathways in some species: 1) CGP 47292 was the main metabolite in urine of mouse, rat, dog, baboon, rabbit, and humans; 2) CGP 47291 was formed in substantial amounts in rats and mice only; and 3) cysteine-containing metabolites were observed in considerable amounts in the urine and feces of mice. Metabolite IV was observed as a major metabolite in the bile of cynomolgus monkey after chronic treatment. Based on studies in rats and mice, the mercapturic acid pathway is generally considered to occur as an interorgan process, with the liver as the primary site for glutathione (GSH) conjugation. The GSH conjugate is transported to the kidney, a secondary site of metabolism of GSH conjugates. The conjugate is degraded by p-glutamyltranspeptidase and cysteinyl-glycine-dipeptidase to metabolite IV. Metabolite IV may be excreted or further acetylated by the n-acetyltransferase to the mercapturic acid conjugate (metabolite V). Alternatively, the GSH conjugate may be excreted into the bile canaliculus, where essentially the same GSH conjugate degradation occurs, leading to biliary-fecal excretion of cysteine conjugates.

Figure IIIB.1

Figure 7 Metabolites identified in the mouse urine and feces



IV. TOXICOLOGY

A. SINGLE-DOSE TOXICITY

1. CGP 33101: Acute oral toxicity study in the rat (Test No. 87-6138; Ciba-Geigy, Basel, Switzerland; Report dated 10/13/87; GLP)

CGP 33101 (batch No. 800186) was given to rats (Tif:RAIf(SPF); 3/sex/grp) at single oral doses of 3000 and 5000 mg/kg and animals were observed for a 14-day period after administration. Mortality occurred at 5000 mg/kg in 1/6 rats, so the LD50 was estimated to be more than 5000 mg/kg. Animals of both sexes showed similar signs, including reduced spontaneous activity, ataxia, muscular hypotonia, irregular respiration, piloerection, cool body, salivation, recumbency, and unkempt fur. In the surviving animals, body weight gain over the 14-day observation period was not affected. Autopsies did not reveal any gross organ or tissue changes. It was concluded that "CGP 33 101 given orally is practically non-toxic in rats under these experimental conditions. The toxic reaction included signs of CNS inhibition."

2. CGP 33101: Acute exploratory oral toxicity study in beagle dogs (Test No. 87-6120; Ciba-Geigy, Basel, Switzerland; Report dated 8/20/87; GLP)

CGP 33101 (batch no. 800186) was given at single oral doses of 600 and 2000 mg/kg, each dose to a single female dog. 600 mg/kg led to slight trembling, 1/2 to 2 hours after administration. 2000 mg/kg caused emesis, about 3 1/2 hours after administration and at that time, feces contained amounts of non-absorbed compound. It was concluded that "600 mg/kg CGP 33 101 is expected to be a suitable high dose in the 10 day oral dose range finding study in dogs. Special attention must however be paid to the absorption of CGP 33 101 in the dog."

B. REPEAT-DOSE TOXICITY

1. CGP 33101: 13-week feeding study in mice (Test No. 92-6060; Ciba-Geigy, Summit, NJ; Report dated 12/28/93; GLP)

- a. Methods

CGP 33101 (Lot #800189) was administered orally via the feed to CD-1 mice (10/sex/group) at target doses of 0, 60, 200 or 600 mg/kg/day for 13 weeks. (The actual cumulative mean daily doses were 59.9, 198.3 and 592.0 mg/kg for males, and 60.3, 199.4 and 606.6 mg/kg for females, respectively.) Additional mice were placed on the same dosing regimen for 2 or 11 weeks for TK determinations. Standard clinical observations body weight, food consumption and organ weight determinations, and physical/auditory and gross pathological examinations were performed on all animals. Microscopic examinations were conducted on all gross lesions, on a standard list of tissues/organs from mice in the C and HD groups and from mice that died prior to scheduled sacrifice, and on livers and salivary glands from LD and MD mice.

b. Results

i. Mortality, clinical signs, body weight

There were no treatment-related mortalities or clinical signs. Body weight effects were inconsistent (**Table IVB.1.1**).

ii. Clinical Pathology

SGOT and SGPT were increased in HD males and MD and HD females, and alkaline phosphatase was increased at the HD in both sexes.

iii. Pathology

Increased liver weight was noted in MD and HD males and in HD females. Treatment-related microscopic lesions were found in the liver and salivary glands of treated mice in both sexes (**Table IVB.1.2**). The liver changes were seen in males at the MD or greater and in HD females and consisted of centrilobular hepatocellular hypertrophy, single cell necrosis, and periportal pigment. The latter was described as "pale, yellow-green pigment often in periportal areas within Kupffer's cells, occasional hepatocytes or extracellularly in canaliculi. The pigment was negative for bile and partially stained for iron and lipofuscin, and its exact nature was not evident." In dogs, intra- and extracellular pigment was identified as bile based on its positive staining for bile with Hall's method and its negative staining for iron with Perl's method.

Changes in the salivary glands of MD and HD males and HD females were described as atrophy of the acinar epithelium "characterized by the presence of decreased numbers of secretory granules and increased amounts of pale, basophilic cytoplasm that was occasionally vacuolated." The severity was minimal in both sexes. The pathogenesis of salivary gland atrophy and its significance was considered undetermined.

iv. Plasma levels (Table IVB.1.3)

Plasma analyses for rufinamide demonstrated near dose-proportional exposures that were generally somewhat higher in males than females.

c. Conclusions

Dietary administration of 60, 200, and 600 mg/kg to CD-1 mice for 13 weeks produced increased enzyme activities (SGOT, SGPT, ALK Phos) and microscopic changes in the liver and salivary glands, primarily at the MD and HD. These changes were characterized as centrilobular hepatocellular hypertrophy, single cell necrosis and periportal pigment and were generally more severe in the males than in the females. Atrophy of the submandibular salivary glands of males (MD and HD) and females (all doses) was considered treatment-related but of uncertain toxicological significance. The LD was considered to be a NOAEL.

Table IVB.1.1

CGP 33101: 13-WEEK FEEDING STUDY IN MICE (MIN 924183)

10.1. Mean body weight change during the dosing period*

Group Dose (mg/kg)	Males			Females		
	Body Weight (g)		Percent Change ^b	Body Weight (g)		Percent Change ^b
	Baseline	Week 13		Baseline	Week 13	
1 (0)	29.0	37.4	29.0	23.5	29.6	26.2
2 (60)	29.1	37.8	30.2 (3.6)	24.1	31.4	30.5 (19.7)
3 (200)	31.1	40.5	30.6 (11.9)	23.7	28.8	21.5 (-16.4)
4 (600)	29.7	36.5	23.5 (-19.0)	23.6	29.8	26.2 (1.6)

Table IVB.1.2

Salient Microscopic Changes of the Liver and Salivary Gland

Dose mg/kg	Male				Female			
	0	60	200	600	0	60	200	600
LIVER								
Hepatocellular hypertrophy	0/10	0/10	4/10	10/10	0/10	0/10	0/10	7/10
Single cell necrosis	1/10	0/10	1/10	9/10	0/10	0/10	0/10	5/10
Periportal pigment	0/10	0/10	0/10	8/10	0/10	0/10	0/10	8/10
SALIVARY GLAND								
Atrophy	1/10	0/10	2/10	5/10	0/10	3/10	4/10	6/10
Degeneration	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10

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Table IVB.1.3

Summary of AUC, Cmax, Tmax, Cmin and Tmin data^a for CGP 33101 in samples of plasma taken from mice on days 12 and 75 of a Toxicology 13-week feeding study (MIN 924183)

<u>Dose</u> <u>(mg/kg/day)</u>	<u>Sex</u>	<u>AUC^b</u> <u>(hr(ug/ml))</u>	<u>Cmax</u> <u>(ug/ml)</u>	<u>Tmax</u> <u>(hr)</u>	<u>Cmin</u> <u>(ug/ml)</u>	<u>Tmin</u> <u>(hr)</u>
<u>Day 12</u>						
60	M	92	6.1	19	1.2	10
	F	53	3.9	19	BQL ^c	7
200	M	358	18.9	19	8.3	7
	F	304	20.5	19	4.8	7
600	M	728	40.8	13	18.8	7
	F	584	34.8	16	13.4	7
<u>Day 75</u>						
60	M	68	4.5	16	BQL ^c	7
	F	62	4.1	16	0.8	10
200	M	309	15.7	16	9.3	7
	F	311	22.1	19	4.0	7
600	M	925	50.5	16	25.9	10
	F	761	40.8	19	22.6	7

^a Derived from the mean concentration data in Appendix, Tables 4 - 6.

^b Calculated for a 24-hour dosing interval by assuming that the concentration at 25 hr was equivalent to that at 1 hr.

^c Mean was below the quantification limit (0.5 ug/ml).

2. CGP 33101: 3-month oral toxicity study in rats (Test No. 87-6090; Ciba-Geigy, Basel; Report dated 4/25/89; GLP)

a. Methods

CGP 33101 (Batch No. 800185) was administered to rats (Tif:RAIf) by oral gavage at doses of 0, 60, 200, or 600 mg/kg. 10/sex/dose were treated for 3 months, and additional groups of 5/sex were treated with 0, 200, or 600 mg/kg for 3 months with a 1-month recovery period. No TK was conducted in this study.

b. Results

i. Mortality, Clinical signs, Body weight

There were no deaths. CNS clinical signs, including hyperemia, muscular hypotonia, decreased activity, and convulsions (described as short, lasting 30-60 sec, in 1 MD and 2 HD males), were observed at the MD and HD. White particles, presumed to be test material, were observed in the feces of all rufinamide-treated animals. All clinical signs were shown to be reversible in the recovery period. Reduced body weight gain and food consumption were observed in both sexes. At the end of treatment, BW gain was 2, 5 and 17% below C in M and 9, 12 and 30% below C in F, at the respective doses. BWs

were 2, 5 and 11% lower in M and 5, 7 and 15% lower in F, respectively. No T-R hearing or ophthalmologic effects were observed.

ii. Clinical Pathology

A decrease in leucocytes was seen at the HD. Clinical chemistry findings included increased urea at the MD and HD (**Table IVB.2.1**). Slight increases in creatinine levels were also observed in individual animals at these doses. There were no treatment-related urinalysis findings.

iii. Pathology

Thymus weights were reduced in both sexes and spleen weights were minimally reduced in the males at the 2 highest doses. T-R histopathological findings were observed in the liver and pituitary, but not in the thyroid. Pituitary effects were seen in males at all doses (**Tables IVB.2.2 and Table IVB.2.3**). Findings consisted of vacuolation and ballooning of TSH-secreting cells, which were to a lesser extent also positive for FSH and LH. Pituitary changes showed some reversibility in the recovery period. In the liver, minimal to slight centrilobular hypertrophy was seen in MD and HD rats, with males slightly more affected than females. These findings were reversible.

Pathology report: "Pituitary changes, consisting in vacuolization and ballooning of TSH-secreting cells (these cells were at a lesser degree also positive for FSH and LH, but negative for ACTH and prolactin) were observed in male rats only and at all three dose levels. This finding was present in all males at the end of treatment, showed a great variability of severity within the dose groups and no clear dose-dependency. Nevertheless, the mean grading of these findings per group indicated slightly more pronounced changes in the high and intermediate than in the low dose group; these pituitary changes showed a tendency towards reversibility after the follow-up period. Cellular vacuolization of minimal severity was also noted in the pituitary glands of most control male rats at the end of treatment and of the follow-up period. Due to the fact that no relevant pathological lesions and organ weight changes were evident in the thyroids of treated male rats when compared with controls, this vacuolization/ballooning was considered to be a treatment-related change of TSH-secreting cells without any perceptible influence on the thyroid morphology."

c. Conclusions

Oral (gavage) administration of rufinamide (0, 60, 200, or 600 mg/kg) to rats produced pituitary TSH-secreting cell vacuolation and ballooning at all doses in males, and convulsions, increased BUN and creatinine, and centrilobular hepatocellular hypertrophy in both sexes at the MD and HD.

Table IVB.2.1

Relative Incidence of Urea Values >8.00 mmol/l
(1.00 = all animals)

Dose	0 mg/kg	60 mg/kg	200 mg/kg	600 mg/kg
Pretest	0	0	0	0
Week 5	0.03	0.15	0.20	0.33
Week 9	0	0.05	0.23	0.57
Week 13	0.07	0.05	0.20	0.13
Week 18	0	-	0	0

Table IVB.2.2

PATHOLOGY REPORT -
SUMMARY TABLES

PAGE : 426
TEST NO. : 87-6090

TEST ARTICLE : CGP 33 101
TEST SYSTEM : RAT, 3 MONTHS, ORAL
SPONSOR : CIBA-GEIGY AG

PATHOL. NO.: 26090 MIC
DATE : 15-FEB-89

INCIDENCE AND GRADING TABLE OF NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KO
PITUITARY CHANGES IN MALE RATS

ORGAN/FINDING	SEX :					MALE		
	DOSE GROUP:	01	02	03	04	01	03	04
	NO. ANIMALS:	10	10	10	10			
PITUITARY GLAND	NO. EXAM.:	9	10	10	10			
- VACUOLIZATION, CYTOPL	:	7	10	10	10			
	PERCENT AFFECTED :	78	100	100	100			
	AVERAGE GRADING :	1.0	2.1	2.6	2.5			
- BALLOONING DEGENER.	:		7	8	8			
	PERCENT AFFECTED :		70	80	80			
	AVERAGE GRADING :		1.7	2.3	2.1			

b(4)

Table IVB.2.3

PATHOLOGY REPORT - SUMMARY TABLES	PAGE : 427 TEST NO. : 87-6090
TEST ARTICLE : CGP 33 101 TEST SYSTEM : RAT, 3 MONTHS, ORAL SPONSOR : CIBA-GEIGY AG	PATHOL. NO.: 26090 MIC DATE : 15-FEB-89

INCIDENCE AND GRADING TABLE OF NON-NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: R1
PITUITARY CHANGES IN MALE RATS

ORGAN/FINDING	SEX :							MALE		
	DOSE GROUP:	01	02	03	04	01	03	04		
	NO. ANIMALS:									
PITUITARY GLAND	NO. EXAM.:							5	5	5
- VACUOLIZATION, CYTOPL	:							4	3	5
	PERCENT AFFECTED :							80	60	100
	AVERAGE GRADING :							1.0	1.7	1.4
- BALLOONING DEGENER.	:								2	2
	PERCENT AFFECTED :								40	40
	AVERAGE GRADING :								1.0	1.0

b(4)

3. CGP 33101: Pilot 13-week feeding study in rats (Study No. 92100; Ciba-Geigy, Summit, NJ; Report dated 4/14/93; GLP)

a. Methods

Rufinamide (Lot #800589) was administered in the diet to S-D rats (20/sex/dose) at target doses of 0, 200, 400, or 600 mg/kg. Actual doses were on target. TK analyses were performed using samples taken at 3 hour intervals for a 24-hour period during Weeks 2 and 10 of dosing.

b. Results

i. Mortality, clinical signs, body weight

There were no treatment-related deaths during the study. There were D-R decreases in body weight and body weight gain (approximately 31 to 51% in males and 25 to 32% in females; **Table IVB.3.1**), with concomitant reductions in mean food consumption in both sexes at all dose levels. Polyuria was seen in males and females at all dose levels, and increased water consumption was observed at the HD in males and at MD and HD in females.

ii. Clinical Pathology

There were no treatment-related hematology findings. Clinical chemistry findings included minimal increases in serum creatinine values in both sexes at the HD, and minimal increases in BUN at the MD and HD (Table IVB.3.2). The increases observed were within the range of values of the concurrent control animals.

iii. Pathology

All organ weight changes were considered to be secondary to body weight reductions, and no treatment-related macroscopic findings were reported. There were histopathology findings in the liver and pituitary. In the liver, centrilobular hepatocellular hypertrophy was seen at all dose levels. Pituitary vacuolation was observed in all treated males at all dose levels (Table IVB.3.3). The vacuolation was said to be characterized by swollen cells containing numerous finely demarcated cytoplasmic vacuoles, with a severity ranging from minimal to moderate in a non-dose-related fashion. In females, the incidence of minimal to mild pituitary vacuolation was D-R (1/20, 5/20 and 7/20 at LD, MD, and HD, respectively). A D-R incidence of renal pelvic mineralization was observed in males (possible slight increase in HD F).

iv. Plasma levels (Table IVB.3.4)

Although the AUC increased somewhat (less than proportionally) between the LD and MD, there was no consistent difference between AUCs at the MD and HD. A similar dose-response profile was observed in C_{max} and C_{min} values. The plasma concentration versus time profiles were fairly flat at all dose levels and in both sexes, with C_{max} being generally less than 1.5 times C_{min}.

c. Conclusions

Dietary administration of rufinamide (0, 200, 400, or 600 mg/kg) to rats produced microscopic findings of centrilobular hepatocellular hypertrophy and vacuolation in the pituitary gland in both sexes, although more severe in males, and at all doses. There were increases in serum creatinine in both sexes at the HD and in BUN in males at the MD and HD. Although there were no associated histopathological changes in renal glomeruli or tubules, increased incidences of renal pelvic mineralization were seen in males. Based primarily on dose-related body weight decrements, the high dose for subsequent chronic feeding studies in rats recommended in the study report was 200 mg/kg.

Table IVB.3.1

CGP 33101: PILOT 13-WEEK FEEDING STUDY IN RATS (MIN 924109)

9.3. Mean body weight change during the dosing period^a

Group Dose (mg/kg)	Males			Females		
	Body Weight (g)	Percent ^b	Change	Body Weight (g)	Percent ^b	Change
	Baseline	Week 13		Baseline	Week 13	
1 (0)	147.8	606.6	312.6	123.5	306.1	149.6
2 (200)	149.0	466.9**	213.9** (-30.7)	121.1	258.1**	114.4** (-25.0)
3 (400)	143.1	379.0**	166.3** (-48.6)	124.8	257.1**	106.8** (-27.5)
4 (600)	152.0	377.5**	150.1** (-50.9)	124.3	247.7**	100.2** (-32.4)

^aThese data were taken directly from the statistical printout for all surviving animals, with the exception of values presented in parentheses.

^bValues in parentheses represent:

Percent gain relative to control =

$$\frac{\text{weight gain of group} - \text{weight gain of control}}{\text{weight gain of control}} \times 100$$

**Statistically significant relative to the control group at p < 0.01.

Table IVB.3.2

SUMMARY OF STATISTICAL ANALYSIS
BIOCHEMISTRY

		MALE					
GROUP NO.	DOSE	(N)	GLOBULIN (GM/DL)	CREAT (MG/DL)	BUN (MG/DL)		
			N MEAN±SE	N MEAN±SE	N MEAN±SE		
PERIOD:	DAY	89					
1	0 MG/KG	20	10 2.7±0.1	10 0.662±0.013	10 19.2±0.5		
2	200 MG/KG	20	10 2.7±0.1	10 0.679±0.023	10 19.6±1.0		
3	400 MG/KG	20	10 2.8±0.1	10 0.704±0.020	10 21.9±0.7**		
4	600 MG/KG	20	10 2.8±0.1	10 0.733±0.011**	10 22.1±0.5**		
TEST FOR TREND			P= NS	** P< 0.01	** P< 0.01		
		FEMALE					
GROUP NO.	DOSE	(N)	GLOBULIN (GM/DL)	CREAT (MG/DL)	BUN (MG/DL)		
			N MEAN±SE	N MEAN±SE	N MEAN±SE		
PERIOD:	DAY	89					
1	0 MG/KG	20	10 2.5±0.1	10 0.636±0.018	10 21.2±1.0		
2	200 MG/KG	20	10 2.4±0.1	10 0.644±0.012	10 20.6±1.3		
3	400 MG/KG	20	10 2.5±0.1	10 0.666±0.021	10 22.0±0.9		
4	600 MG/KG	20	10 2.5±0.1	10 0.702±0.018*	10 22.6±0.9		
TEST FOR TREND			P= NS	* P< 0.05	P< NS		

Table IVB.3.3

		Compound-related microscopic changes							
Dose (mg/kg)	Male				Female				
	0	200	400	600	0	200	400	600	
LIVER									
Hepatocellular hypertrophy	0/20	20/20	20/20	20/20	0/20	3/20	13/20	19/20	
PITUITARY									
Vacuolation	0/20	19/19	20/20	20/20	0/20	1/20	5/20	7/20	
KIDNEY									
Pelvic mineralization	0/20	3/20	9/20	7/20	1/20	1/20	0/20	2/20	

Table IVB.3.4

Dose (mg/kg)	Time (Week)	C _{max} (µmol/L)		AUC _(0-24 hr) (µmol·hr/L)		C _{min} (µmol/L)	
		Male	Female	Male	Female	Male	Female
200	2	182	149	3724	2918	128	99
400		223	205	4442	4081	154	143
600		210	174	4433	3724	154	144
200	10	223	223	4320	3652	121	89
400		256	254	5428	4706	183	160
600		262	258	5655	5378	204	175

4. CGP 33101: 26/52-week oral toxicity study (admixture with the diet) in rat (Study 90-6147; completed 10/14/92; GLP)

b(4)

a. Methods

Rufinamide (Batch no. 800389) was administered in the diet to S-D rats (42/sex/dose at LD and HD, 36/sex C and MD) at target doses of 0, 20, 60, or 200 mg/kg. (Actual doses were close to the target.) The first 10/sex/group were sacrificed at Week 26. Twenty six/sex/group (main study) were treated for 52 weeks. Six/sex/group (recovery) were maintained for 4 weeks. Six/sex in the LD and HD groups were used for blood level determinations on Day 1 and Weeks 13, 26 and 53 for assessment of absorption. Animals were observed for clinical signs, mortality, body weight and food consumption, ophthalmological examinations (pre-treatment and Weeks 25 and 51), and clinical pathology (pre-treatment, Weeks 13, 26, 39, 52 and 56). At 26 and 52 weeks and at the end of the recovery period, animals were sacrificed and organ weights and full macroscopic and histopathological investigations were performed. TK analyses were performed using samples taken at 3 hour intervals for a 24-hour period during Weeks 2 and 10 of dosing.

b. Results

i. Mortality, clinical signs, body weight

There were no treatment-related deaths or clinical signs. Decreased BW gain was seen primarily at the HD in both sexes (wk 50 BWs 0.3, 4, and 24% below C in M and 2, 11, 28% below C in F). Comparable reductions in food consumption were observed. Efficiency of food utilization was similar among groups. There were no treatment-related ophthalmological findings.

ii. Clinical Pathology

Hematological findings were not considered toxicologically significant, and there were no treatment-related urinalysis findings. The main clinical chemistry findings were associated with T4 and TSH. Total and free T4 were increased slightly to moderately in the MD and HD groups at Weeks 27 and 40 in a few animals, and at Week 53 in a few females. TSH levels were increased in some MD and HD males at Weeks 40 and 53, with partial to full reversibility observed.

iii. Pathology (Tables IVB.4.1-2)

There were no treatment-related macroscopic findings throughout the study. At Week 26, increased liver weights were observed in females at MD and HD and minimal to slight centrilobular hepatocellular hypertrophy was seen at the HD in both sexes. T-R increases in the severity of pituitary cell vacuolation was noted in males at the 2 highest doses. At Week 52, increased liver weights and centrilobular hepatocellular hypertrophy were seen in both sexes at the MD and HD. Pituitary vacuolation remained slightly more severe in males at the MD and HD. In the thyroids, slightly increased incidences and severity of follicular cell hypertrophy was noted in both sexes at the MD and HD.

iv. Plasma levels (Table IVB.4.3)

Steady-state concentrations of rufinamide did not change significantly during the study. Concentrations increased less than dose proportionately.

c. Conclusions

Dietary administration of rufinamide (at 20, 60 and 200 mg/kg/day) to rats for 52 weeks produced centrilobular liver cell hypertrophy and an increased severity of pituitary cell vacuolation (males), primarily at the MD and HD. The pituitary effect was thought to represent a treatment-related exacerbation of an existing species specific background condition. These changes were partially or completely reversible. The LD was considered to be a NOAEL.

Table IVB.4.1

PATHOLOGY REPORT
SUMMARY TABLES

PAGE 3
PROJECT: 6195 TCR

TEST ARTICLE : CGP 33 101
TEST SYSTEM : RAT, 26/52 WEEKS, DIET
SPONSOR : CIBA-GEIGY LTD/Proj.N*906147

PATHOL. NO.: 26195 VLG
DATE : 16-SEP-91

b(4)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: K1

ORGAN/FINDING	DOSE GROUP: SEX: NO. ANIMALS:	T		A		B		C	
		M	F	M	F	M	F	M	F
HEART	NO. EXAM.:	10	10					10	10
- MYOCARD. DEGEN/FIBR.		1							
MESENT. LYMPH NODE	NO. EXAM.:	10	10					10	10
- REACTIVE LYMPH NODE		10	10					9	10
- HISTIOCYTOSIS		9	6					6	7
- CEROID LAD. MACROPH.		4	5					6	7
- HEMOSID. LAD. MACROPH.		2	1					2	2
- PLASMOCYTOSIS			2					2	5
- EOSINOPH. INFILTRAT.			2						
- ERYTHROPHAGOCYTOSIS		1							
STOMACH	NO. EXAM.:	10	10		1			10	10
- SUP. NECR. GLAND. EPIT.					1				
LIVER	NO. EXAM.:	10	10	10	10	10	10	10	10
- PERICHOLANGITIS		2		1		2			
- CHOLANGIOFIBROSIS		1		1		1			
- BILE DUCT PROLIFER.				1					
- PERIVASCULITIS		3		1		1			
- MONONUCL. CEL. AGGREG.		2	4	2	1			2	1
- HEPATIC CYST(S)								1	
- FOC. HEPATOC. VACUOL.					1	1	2	1	2
- FOC. HEPAT. CEL. NECRO.				1	1	1			
- CENTRO. HEP. C. HYPERT.								7	6
- ALTERED CELL FOCUS							1		
MUZZLE	NO. EXAM.:	10	10					10	10
- EPITH. CEL. HYPERPLAS.		1							
- HYPERKERATOSIS		1							
- FOC. SUPPURAT. INFLAM.			1						
MANDIBUL. LYMPH NODE	NO. EXAM.:	10	10					10	10
- REACTIVE LYMPH NODE		10	10					10	10
- PLASMOCYTOSIS		9	10					10	10
- HISTIOCYTOSIS		2	3						3
- HAEMORRHAGE									2
- HEMOSID. LAD. MACROPH.									2

PITUITARY GLAND	NO. EXAM.:	10	10	10	9	10	10	10	10
- DEGRANUL. GONADOTROP.		10	3	10	2	10	3	10	4
- EXHAUSTED CELLS		9	7	8	7	9	7	10	7
- PROLACT. CEL. HYPERPL.			1						
.....									
LARYNX	NO. EXAM.:	10	9					10	10
- MONONUCL. CEL. AGGREG.			1						
.....									
ADRENAL GLANDS	NO. EXAM.:	10	10					10	10
- CEROID DEGENERATION			4						8
.....									
THYROID GLANDS	NO. EXAM.:	10	10					10	10
- DEVELOPMENT. CYST(S)		2	3					4	2
.....									
OVARIES	NO. EXAM.:		10		1				10
- PROOESTRUS			5						6
- OESTRUS			1						2
- METOESTRUS			4						2
- FOLLICULAR CYST(S)			1						
- LUTEAL CYST(S)			2						3
- PARA-OVARIAN CYST(S)					1				
.....									
UTERUS	NO. EXAM.:		10		2		2		10
- PROOESTRUS			5						6
- OESTRUS			1						2
- METOESTRUS			4						2
- DILATED HORNS			1		2		2		3
.....									
VAGINA	NO. EXAM.:		9						9
- PROOESTRUS			4						5
- OESTRUS			1						2
- METOESTRUS			4						2
.....									
PANCREAS	NO. EXAM.:	10	10					10	10
- FATTY INFILTRATION			2						
.....									
SPLEEN	NO. EXAM.:	10	10					10	10
- HEMOSIDEROSIS			7		10			4	10
.....									

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Table IVB.4.2

PATHOLOGY REPORT
SUMMARY TABLES

PAGE 2
PROJECT: 6195 TCR

TEST ARTICLE : CGP 33 101
TEST SYSTEM : RAT, 26/52 WEEKS, DIET
SPONSOR : CIBA-GEIGY LTD/Proj.N°906147
PATHOL. NO. : 26195 MAA
DATE : 14-NOV-91

b(4)

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
STATUS AT NECROPSY: KU, INCL. +
IN MG/KG/DAY: T=0; A=20; B=60; C=200

ORGAN/FINDING	DOSE GROUP: SEX: NO. ANIMALS:	T		A		B		C	
		M	F	M	F	M	F	M	F
HEART	NO. EXAM.:	20	20			1	1	20	20
- CARDIOMYOPATHY.		8	4					6	
- MYOCARD. DEGEN/FIBR.		5	1						
COLON	NO. EXAM.:	19	20			1	1	20	20
- ACUTE COLITIS.									1
MESENT. LYMPH NODE	NO. EXAM.:	19	20			1	1	20	19
- REACTIVE LYMPH NODE									1
- HISTIOCYTOSIS		12	15					14	16
- CEROID LAD. MACROPH.		17	13			1		16	11
- HAEMOSID. LAD. MACROP.		2	1						2
- PLASMOCYTOSIS		3	4						2
- MASTOCYTOSIS.		1						3	2
- FOCAL NECROSIS.		1							
- ERYTHROPHAGOCYTOSIS		6	1					4	
- HAEMORRHAGES.		1							
BRAIN	NO. EXAM.:	20	20			1	1	20	20
- VACUOLAT. WHITE MATT.			2			1			
STOMACH	NO. EXAM.:	20	20			1	1	20	20
- DILATED CRYPTS.		3	7					7	1
FORESTOMACH	NO. EXAM.:	20	20	1		1	1	20	20
- SUBMUCOSAL OEDEMA.						1			
- SUBMUC. INFL. CEL. AGG.			1			1			

LIVER	NO. EXAM.:	20	20	20	20	20	20	20	20
- PERICHOANGITIS			1	1					
- BILE DUCT PROLIFER.		1		2			2		1
- MONONUCL. CEL. AGGREG.		9	10	18	14	11	12	15	6
- HEPATOCELLULAR CYSTS						1		1	1
- FOC. HEPAT. CEL. NECRO.		2					1		1
- CENTRO. HEP. C. HYPERT.						14	10	18	17
- ALTERED CELL FOCI		3	1	2	3	2		1	
- STEATOSIS		2	4			1	1		
- FOC. TENSION LIPIDOS.		5	4	7	2	3	6	3	1
- EXTRAMEDUL. HAEMATOP.		3	4		3	3		1	1
- SINUSOIDAL ECTASIA		1					1		1
- MICROGRANULOMA(S)					2				
- MULTIF. HEP. CEL. NECR.									1
- INTRACEL. BR. YEL. PIG.									1
.....									
MAMMARY GLAND	NO. EXAM.:	20	20		3	1	3	19	20
- GALACTOCELE.					1				1
- DUCTAL ECTASIA.					2		2		
- FIBROADENOMA.					1				
- ADENOMA.									1
- ADENOFIBROMA.									1
.....									
SKIN	NO. EXAM.:	20	20			1	2	19	20
- HYPERKERATOSIS.						1			
- ACANTHOSIS.						1			
- ULCERATION.									1
- SUBACUTE CELLULITIS.									1
- PILOMATRICOMA.							1		
- BENIGN FIBR. HISTIOC.		1							
.....									
URINARY BLADDER	NO. EXAM.:	19	19			1	1	20	18
- FOLLICULAR CYSTITIS.			1						
.....									

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MANDIBUL. LYMPH NODE	NO. EXAM.:	20	20	1	2	2	1	20	20
- REACTIVE LYMPH NODE		11	15	1	2	2		16	7
- PLASMOCYTOSIS		16	18	1	2	2		17	16
- HISTIOCYTOSIS		2							4
- HAEMORRHAGE		1							1
- POST-REAC.ACID.INCL.		1							
- ERYTHROPHAGOCYTOSIS.		1	1						
- CEROID LADEN MACROP.		2							1
.....									
EXORBITAL LACR.GLDS.	NO. EXAM.:	20	20	2			7	19	20
- CHRONIC ADENITIS.							3	2	
- INTERST.MON.CEL.AGG.		5		2			2	5	
- ACINAR CELL DEGENER.		8		2			3	12	
- VACUOLAT.ACIN.EPITH.		2							
.....									
PITUITARY GLAND	NO. EXAM.:	20	20	19	20	20	20	20	19
- DEGRANUL.GONADOTROP.		17	9	10	4	16	5	17	7
- EXHAUSTED CELLS.		14	16	6	18	6	18	12	16
- PROLACT.CEL.HYPERPL.		2	4	3	3	2			4
- PROLACTIN CEL.ADENO.		3	3	4	3	4			
- IMMATURE CELL ADENO.			2	1	2	1			1
- DEVELOPMENTAL CYST			1			1	2		
- IMMATURE CEL.HYPERP.				1	1			1	1
- IMMAT./ACTH CEL.ADE.								1	
- INCREASE NO.TSH CEL.								2	
- ACTH CELL HYPERPLAS.									2
- ACTH CELL ADENOMA									1
.....									
ADRENAL GLANDS	NO. EXAM.:	20	20	1		1	3	20	20
- CEROID DEGENERATION			2				1		1
- CYSTDEGENERATION.			1		1		1		
- PELIOSIS.			2		1		2		1
.....									

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THYROID GLANDS		NO. EXAM.:	19	20	20	20	20	20	20	20	
- DEVELOPMENT. CYST(S)			1	3	2	2		20	3	3	2
- FOLLICUL. CEL. HYPERT.			3	3	1	3		11	6	6	8
- DECR. FOLLICUL. DIAMET			3	3	1	3		11	6	6	8
- INCRE. NUMB. FOLLICLES			3	3	1	3		11	6	6	8
- DECR. EOSINOP. COLLOID			3	3	1	3		11	6	6	8
- FOLLICULAR CYST			1								
- FOLLICUL. CEL. ADENOM.					1						
- INTERS. LYMPH. CEL. AG.								1			
- NODULAR HYPERPLASIA								1			
.....											
OVARIES		NO. EXAM.:	19		8			10		20	
- PROOESTRUS			1								
- OESTRUS								1		1	
- METOESTRUS										2	
- ATROPHY.			1					1		1	
- FOLLICULAR DEVELOPM.			16		6			8		12	
- FOLLICULAR ATRESIA.			17		6			8		16	
- FOLLICULAR CYST(S)			11		4			4		15	
- NO CORPORA LUTEA.			10		3			4		12	
- FEW CORPORA LUTEA.			8		3			5		4	
- MANY CORPORA LUTEA.										1	
- LUTEAL CYST(S)			2		1			2		2	
- PARA-OVARIAN CYST(S)			2		1			3		1	
- INTERST. CEROID. PIGM.								1			
.....											
UTERUS		NO. EXAM.:	20		2			5		20	
- PROOESTRUS			1								
- OESTRUS								1		1	
- METOESTRUS										2	
- DILATED LUMEN.			7		1			4		10	
- END. EPIT. CEL. HYPERT.			13		1			4		15	
- END. EPIT. CEL. HYPERP.								2			
- SQUAM. METAP., UT. HOR.			1								
- CONDENSAT. ENDM. STRO.			6								
- UTERINE ATROPHY.			2							2	
- ENDOMETR. STR. POLYP.								1			
.....											

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KIDNEYS		NO. EXAM.:							
- GLOMERULONEPHROPATHY		20	20	20	20	20	20	20	20
- CHRON. INTERS. NEPHRI.		2	1	1	1			2	2
- PERIGLOMERULAR FIBR.				2	1	1			
- PERITUBULAR FIBROSIS		1	1	2					
- CONTRACT. GLOMER. TUF.		2	2	3	1				
- DILATED PELVIS.			1						
- HYDRONEPHROSIS.				1		2		1	
- EOSINOPHIL. CAST(S)				1					
- RENAL CYST(S).		2	8	4	3	2	2	2	2
- MINERALIZATION					2				
- INTERST. MON. CEL. AGG.								2	
- TUBUL. DIL., PAPILLA.		5	1	5	5	5		6	
- FOCAL PAP. DEG./NECR.								1	
- CHRONIC PYELITIS.					1				
- LEUCOHISTIOC. PYELIT.		1	1	1	1	1	1	1	1
- CORT. TUB. DILATATION.		4	2	3	1	2		1	2
- TUBULAR BASOPHILIA		7	8	5	1	1	1	3	
- TUBULAR LIPOFUSCINO.		5	4	8	1	4			
- VACUOLAT. TUB. EPITHE.			1						
		1							
.....									
LUNGS		NO. EXAM.:							
- CHR. INTERST. PNEUMON.		20	20	20	20	18	20	20	20
- FOAM. ALVEOL. MACROPH.		4	3	11	7	8	1	6	2
- ALVEOLAR HAEMORRHAG.		1				2		5	
- CONGESTION.				1	1		1		
.....									
TESTES		NO. EXAM.:							
- DEGENER. SEMINIF. TUB.		20		1		2		20	
- INHIBIT. SPERMIOGENE.				1		1			
.....									
EYES		NO. EXAM.:							
- MYOSITIS.		20	20		1	1	1	20	20
- INFLAMM. CEL. INFILTR.								1	
- HAEMORRHAGE		2			1			1	1
.....									

Table IVB.4.3

Dose (mg/kg)	Time	Concentration ($\mu\text{mol/l}$)	
		Male	Female
20	Day 1	ND	ND
	Week 13	44.0 \pm 3.6	37.4 \pm 5.4
	Week 26	49.9 \pm 9.1	39.4 \pm 6.2
	Week 52	55.5 \pm 5.2	48.2 \pm 5.1
200	Day 1	ND	ND
	Week 13	256 \pm 10	257 \pm 37
	Week 26	255 \pm 8	265 \pm 30
	Week 52	257 \pm 18	255 \pm 33

ND = not detected

* : to convert into $\mu\text{g/ml}$, multiply the data by 0.238.

5. CGP 33101: 3 Month Oral (Capsule) Toxicity Study in Dogs (Study No. 87-6091; Ciba-Geigy, UK; report dated 6/21/88; GLP)

a. Methods

Beagle dogs (3/sex/dose) were orally dosed with rufinamide (batch 800187) in gelatine capsules at 0, 60, 200, or 600 mg/kg. There was an additional (1 month) recovery group of 3/sex at the HD. Observations included mortality, clinical signs, body weights and food consumption, clinical pathology (all dogs during the pretest period and weeks 5, 9 and 13, and on HD dogs during week 17), ophthalmic and hearing examinations, EKG (all dogs on 2 occasions during the pretest period and week 13, and HD dogs during week 17), and gross and microscopic pathology (all dogs). TK was performed at the end of the study.

b. Results

i. Mortality, Clinical Signs, Body Weight

Two HD females and 1 MD female had severe clinical signs over a few days, including lethargy, ataxia, pyrexia, stiff legged gait, reduced body weight, and food consumption. The 2 HD females had pallor, enlarged lymph nodes and abdomen, and prostration. One HD and 1 MD female were sacrificed. Since the clinical signs in the third animal began late in the study, the necropsy was completed as scheduled. Two HD females had infected scleral vessels and/or mucous membrane hyperemia during the study. Reduced body weights were observed in a few animals at all doses. Apart from the severely affected females, food consumption was reduced in 1 MD male. The appetite of this animal reportedly improved following cessation of dosing for 5 days.

ii. Clinical Pathology, EKG, Auditory, and Ophthalmology

Evidence of anemia was seen in MD and HD dogs of both sexes (**Table IVB.5.1**). Some reversibility was observed in the males. In 2 HD females with severe anemia, bone marrow evaluations showed increased levels of blasts, promyelocytes and early neutrophilic myelocytes, and reductions in mature neutrophils.

There was a progressive increase throughout the study in ALT in all treated groups and in alkaline phosphatase in the MD and HD groups (**Table IVB.5.2**). During the recovery period, increased ALP activities showed some reversibility, but ALT activities remained high. The 3 animals with severe signs had reduced albumin and increased globulin levels. Urinalysis showed no treatment-related effects.

There were no treatment-related ECG, auditory or ophthalmological findings.

iii. Pathology (Table IVB.5.3)

The 2 females (1 MD and 1 HD) killed early both showed a range of microscopic changes consisting of perivascular hypercellularity in both liver and kidneys. Additional liver changes included eosinophilic hepatocytes, sinusoidal cell

hypertrophy, and periacinar canalicular bile plugs. The femoral bone marrow showed increased cellularity (large cells, possibly monocytes). The HD female also showed splenic enlargement with decreased lymphocytes but generally increased cellularity (possibly monocytes).

Periacinar canalicular bile was seen in all treated groups, in both sexes, at the end of the main and recovery periods. In males kidney intracytoplasmic inclusions (said to be "suggestive of increased metabolism") were present in varying numbers at all dose levels.

According to the pathology report, "the pathological lesions, when associated with hematological data, suggested a possible drug-induced autoimmune reaction."

iv. Plasma levels (Table IVB.5.4)

There was a less than dose-proportional increase in exposures and only a slight sex difference (AUCs about 10% higher in females than in males).

c. Conclusions

Oral (capsule) administration of rufinamide (0, 60, 200, or 600 mg/kg) to dogs for 3 months produced clinical signs (MD and HD), anemia (MD and HD), increased liver enzyme activities (all doses), and pathological changes consisting of perivascular cellularity in the liver and kidney, intracytoplasmic inclusions in the kidney (males), eosinophilic hepatocytes, sinusoidal cell hypertrophy, periacinar canalicular bile (MD and HD). After recovery, alkaline phosphatase levels remained elevated and bile was still present in the canaliculi. There was no NOAEL.

Table IVB.5.1

GROUP MEANS HAEMATOTOLOGY BLOOD SAMPLE MALE WEEK 13										
DOSE			Hb	RBC	PCV	MCV	MCH	MCHC	Plate	Pro
mg/kg	Group									Time
CONTROL	1		14.4	6.17	0.401	65	23	36	267	7.4
60	2		14.8	6.26	0.402	64	24	37	260	7.4
200	3		14.7	6.11	0.402	66	24	37	234	8.1
600	4		13.4	5.53	0.368	67	24	36	335	7.3
600	5		15.3	6.28	0.411	65	24	37	301	8.7

GROUP MEANS HAEMATOTOLOGY BLOOD SAMPLE FEMALE WEEK 13										
DOSE			Hb	RBC	PCV	MCV	MCH	MCHC	Plate	Pro
mg/kg	Group									Time
CONTROL	1		15.3	6.40	0.409	64	24	37	302	8.1
60	2		14.4	5.95	0.400	67	24	36	278	8.0
200	3		16.3	6.81	0.449	66	24	36	331	8.0
600	4		14.5	6.08	0.401	66	24	36	299	8.8
600	5		10.2	4.37	0.285	66	23	35	193	6.8

Table IVB.5.2

GROUP MEANS CLINICAL CHEMISTRY BLOOD SAMPLE MALE WEEK 13									
DOSE mg/kg	Group	Na	K	Gluc	Urea	ASAT	ALAT	AP	Total Prot
CONTROL	1	140.7	4.07	5.66	6.42	26	43	123	63.7
60	2	141.0	3.93	4.92	6.01	35	76	157	66.3
200	3	142.3	3.96	5.59	5.83	29	50	261	63.6
600	4	141.1	3.99	5.92	7.11	39	72	299	64.4
600	5	143.2	3.98	5.19	7.50	23	74	336	63.6

GROUP MEANS CLINICAL CHEMISTRY BLOOD SAMPLE FEMALE WEEK 13									
DOSE mg/kg	Group	Na	K	Gluc	Urea	ASAT	ALAT	AP	Total Prot
CONTROL	1	142.6	4.45	5.27	8.42	48	51	162	62.9
60	2	142.4	4.25	5.67	7.64	38	91	207	62.3
200	3	144.3	4.24	4.66	8.53	40	75	218	67.1
600	4	141.7	4.01	5.43	8.21	34	51	403	59.8
600	5	144.2	4.06	5.00	6.17	26	72	544	66.4

Table IVB.5.3

Project Summary Table						
SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings						
PROJECT ID. NO:	FATES: Terminal Kill			SEX: MALE		
87004	DAYS: 1- 95					
GROUP:	Control	60MgK	200MgK	R 600	600MgK	
NUMBER OF ANIMALS:	3	3	3	0	3	
EPIDIDYMIS 2	#	#	#	#	#	
Interstitial Lymphocytosis	# Ex 3	3	3	0	3	
EYE 1	# Ex 3	3	3	0	3	
EYE 2	# Ex 3	3	3	0	3	
FEMUR/FEMORAL BONE MARROW	# Ex 3	3	3	0	3	
GALL BLADDER	# Ex 3	3	3	0	3	
HEART-Auricle	# Ex 3	3	3	0	3	
HEART-Ventricle (Coronary)	# Ex 3	3	3	0	3	
HEART-Ventricle (Papillary)	# Ex 3	3	3	0	3	
HEART-Ventricle (Septum)	# Ex 3	3	3	0	3	
ILEUM	# Ex 3	3	3	0	3	
JEJUNUM	# Ex 3	3	3	0	3	
KIDNEY 1	# Ex 3	3	3	0	3	
Sub-pelvic Lymphoid follicles	0	0	0	0	1	
Tubular Homogenous Cytoplasm	0	0	0	0	3	
Periarteriolar Cellularity	0	0	0	0	1	
Tubular cytoplasmic Inclusions	0	1	0	0	3	

	#	#	#	#	#	
KIDNEY 2	# Ex	3	3	3	0	3
Tubular Homogenous Cytoplasm		0	0	0	0	3
Tubular Cytoplasmic Inclusions		0	1	2	0	3
LACRIMAL GLAND 1	# Ex	3	3	3	0	3
LACRIMAL GLAND 2	# Ex	3	3	3	0	2
LIVER (2 areas)	# Ex	3	3	3	0	3
Periacinar Canalicular Bile		0	3	2	0	2

PROJECT ID: NO: B70004		FATES: Early Kill				
		DAYS: 1- BB			SEX: FEMALE	
GROUP:		Control	60MgKg	200MgKg	R 600	600MgKg
NUMBER OF ANIMALS:		0	0	1	0	1
EPIDIDYMS 2	# Ex	0	0	0	0	0
EYE 1	# Ex	0	0	1	0	1
EYE 2	# Ex	0	0	1	0	1
FEMUR/FEMORAL BONE MARROW	# Ex	0	0	1	0	1
Increased Cellularity		0	0	1	0	1
Monocyte (?) Increase		0	0	1	0	1
GALL BLADDER	# Ex	0	0	1	0	1
HEART-Auricle	# Ex	0	0	1	0	1
HEART-Ventricle (Coronary)	# Ex	0	0	1	0	1
HEART-Ventricle (Papillary)	# Ex	0	0	1	0	1
HEART-Ventricle (Septum)	# Ex	0	0	1	0	1
ILEUM	# Ex	0	0	1	0	1
JEJUNUM	# Ex	0	0	1	0	1
Mucosal Congestion		0	0	0	0	1
KIDNEY 1	# Ex	0	0	1	0	1
Glomerular Lipidosis		0	0	1	0	0
Periarteriolar Cellularity		0	0	1	0	1
Interstitial Haemorrhage		0	0	1	0	0

KIDNEY 2	#	#	#	#	#
# Ex	0	0	1	0	1
Periarteriolar Cellularity	0	0	1	0	1
Interstitial Haemorrhage	0	0	1	0	0
LACRIMAL GLAND 1	# Ex	0	0	1	0
LACRIMAL GLAND 2	# Ex	0	0	1	0
LIVER (2 areas)	# Ex	0	0	1	0
Eosinophilic Hepatocytes	0	0	1	0	1
Sinusoid-cell Hypertrophy	0	0	1	0	1
Periazular Conalicular Bile	0	0	1	0	1
Perivascular Hypercellularity	0	0	1	0	1
LUNGS-(2 areas)	# Ex	0	0	1	0
Fibrous inflammation	0	0	1	0	0
Focal Haemorrhage	0	0	1	0	0
Fibrino-purulent Pneumonia	0	0	0	0	1
LYMPHNODE-Axillary	# Ex	0	0	1	0
Lymphocyte Deficit / Oedema	0	0	1	0	1
LYMPHNODE-Mesenteric	# Ex	0	0	1	0
Lymphocyte Deficit / Oedema	0	0	1	0	1
LYMPHNODE-Retropharyngeal	# Ex	0	0	1	0
Sinus Erythroplasia	0	0	1	0	0
Lymphocyte Deficit / Oedema	0	0	1	0	1
MAMMARY AREA	# Ex	0	0	1	0

Table IVB.5.4 Plasma concentrations of CGP 33 101 at the end of 3-month oral dog study

Dose (mg/kg)	Dog number	C ₀ (µmol/l)	C _{max} (µmol/l)	T _{max} (h)	AUC (0-24 h) (µmol.h/l)
60	2004 (F)	28.7	161	4	2130
	2005 (M)	71.0	108	24	1890
200	3004 (F)	181	224	4	3370
	3005 (M)	178	186	4	3140
600	4004 (F)	141	244	6	4660
	4005 (M)	154	205	2	4200

6. CGP 33101: 26/52-Week Oral Repeat-Dose Toxicity in Dog (Study No. 89-6305; report dated 4/27/92; GLP)

a. Methods

Beagle dogs (8/sex/dose) were orally administered (capsule) rufinamide at doses of 0, 20, 60, or 200 mg/kg. Two/sex/dose were sacrificed at Week 26, 4/sex/dose were sacrificed at Week 52, and another 2/sex/dose were maintained for a 4-week recovery period. Endpoints included clinical signs, deaths, estimated food consumption, body weights, ECG, ophthalmoscopy, auditory evaluation, hematology, clinical chemistry, urinalysis, organ weights, full gross pathology and full histopathology (all animals). TK was performed on Day 1 and after 6 and 12 months using 2 males and 2 females from both the LD and HD groups (samples taken pre-dosing and over 24 hours).

b. Results

i. Mortality, Clinical Signs, Body Weight

There were no treatment-related clinical signs and no deaths throughout the study. Body weight gain of females was slightly reduced in the first 4 weeks at the HD. Food consumption was not affected by treatment.

ii. Clinical Pathology, EKG, Auditory, and Ophthalmology

There were no treatment-related effects in the ophthalmological and auditory tests or on ECG recordings. Hematology investigations revealed no significant findings. Clinical chemistry showed slight to moderate increases in ALP activities in a few HD animals throughout the treatment period. (This was considered possibly related to retardation of bile flow due to bile thrombi in these animals.) Reversibility was evident at the end of the 4-week recovery period. No T-R effects on total and free T4 and T3 were observed. There were no treatment-related urinalysis findings.

iii. Pathology (Table IVB.6.1 and Table IVB.6.2)

There were no T-R effects on organ weight and gross pathology. Histopathology showed a dose-related incidence and increase in severity of biliary thrombi in treated animals from all dose groups at Week 26. By Week 52, all treated animals showed bile thrombi, with severity increasing with dose. Partial reversibility (reduced severity) was noted after the 4-week recovery period. Dose-related brown/yellow pigment accumulation in hepatocytes and Kupffer cells was noted in all treated animals at the MD and HD and in 1 of 2 LD females at Week 26, and in some animals at all doses at Week 52. At the end of the recovery period, there was an increased incidence and severity at all doses. Using Hall's staining technique, the pigments were shown to be at least of partial biliary origin of all occasions throughout the study, and these deposits were seen in most treated animals. Using Perl's techniques, hemosiderin containing pigments were observed in hepatocytes and Kupffer cells of most animals at Week 52, with reductions and increases in incidences and severities in hepatocytes and Kupffer cells, respectively, at the end of the recovery phase. Liver inflammatory reactions and/or perivasculitis were found in higher incidence and/or severity in treated animals with biliary thrombi, compared to in the controls. This was considered to be due to the irritant effect of the biliary accumulation. Reversibility of the liver inflammatory cell infiltration was not observed at the end of the recovery phase at any dose level.

iv. Plasma levels (Table IVB.6.3)

There were no significant time or sex-related differences in TK parameters. At the HD, values in AUC and Cmax did not increase dose-proportionately. Values for the 2 female dogs were significantly greater than for the male dogs at the HD.

c. Conclusions

Oral (capsule) administration of rufinamide (0, 20, 60, or 200 mg/kg) to dogs for up to 1 year produced dose-related biliary thrombi, and accumulation of pigment of biliary origin or iron containing pigments in the hepatocytes and kupffer cells, associated with inflammatory cell infiltration and perivasculitis in all treated groups. Partial reversibility of biliary thrombi was noted after 4 weeks recovery. A slight to moderate increase in alkaline phosphatase activity was observed at the HD, possibly related to the retardation of bile flow. This change was found reversible after the 4-week recovery period.

Table IVB.6.1

PATHOLOGY REPORT		PAGE		11					
SUMMARY TABLES		PROJECT: 5927 TCC							
TEST ARTICLE : CGP 35 101 TEST N° 89-6305		PATHOL. NO. : 25927 VLG							
TEST SYSTEM : DOG, 25/52 Weeks + 4 Weeks, ORAL		DATE : 16-APR-91							
SPONSOR : CIBA-GEIGY									
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX STATUS AT NECROPSY: K0									
ORGAN/FINDING	DOSE GROUP: SEX: NO. ANIMALS:	T		A		B		C	
		M	F	M	F	M	F	M	F
AORTA	NO. EXAM.:	4	4	4	4	4	4	4	4
- CALCIFICATION		1		1	1	1	1		
- HAEMORRHAGE, ADVENT.			1			1	1		
BRAIN	NO. EXAM.:	4	4	4	4	4	4	4	4
- MONONUCL. CEL. AGGREG.						2	1		
- CAPILLAR. HAEMORRHAGE		1				1	1		1
- OEDEMA CHORO. PLEX.					1				1
- VASC. ECTA. CHORO. PLEX.					1				1
JEJUNUM	NO. EXAM.:	4	4	4	4	4	4	4	4
- CAPILLARY ECTASIA		1							
CAECUM	NO. EXAM.:	3	4	4	4	4	4	4	4
- HAEMORRHAGE MUCOSA									1
- INFLAMMATION					3				
RECTUM	NO. EXAM.:	4	4	4	4	4	4	4	4
- SUBMUCOS. HAEMORRHAGE			1						
- HAEMORRH. LYMPH. NOD.		1							
LIVER	NO. EXAM.:	4	4	4	4	4	4	4	4
- BILIARY THROMBI				4	4	4	4	4	4
- POSITIVE HALL REACT.				1	1	4	2	3	4
- POSITIVE PERLS' REACT.				2	4	3	2	4	4
- POSI. PERLS' REAC. KUP.			2	3	1		2	2	1
- NEGATIVE PERLS' REACT.		4	2	1		1	2		
- NEGATIVE HALL REACT.		4	4	4	3		2	1	
- BROWN/YEL. PIGN. ACCU.				2			4		
- PERIVASCULITIS		1		2	3	3	3	4	4
- INFLAM. CEL. INFILTR.				2	3	4	2	2	4
- MONONUCL. CEL. AGGREG.		2	2	2	2	1	2		
- FOC. HEPATOC. NECROS.						1	1		
- SINUSOID. DILATATION									1
- MICROGRANULOMA			1						
LACRIMAL GLANDS	NO. EXAM.:	3	3	3	3	3	3	3	3
- INTERS. MONO. CEL. INF.			1						1

b(4)

LUNGS	NO. EXAM.:	4	4	4	4	4	4	4	4
- CHROM. INTERST. PNEUM.							1		
- PERIBRONCHIOLITIS							1		
- ATELECTASIA		1							
- MONONUCL. CEL. AGGREG.			1		1	1			
- PERIVASCULITIS									1
- THICKENED PLEURA		1							
PROSTATE	NO. EXAM.:	4		4		4			4
- INTERS. MOMO. CEL. INF.									1
KIDNEYS	NO. EXAM.:	4	4	4	4	4	4	4	4
- BROWN PIGM. ACC. TUB.		2		3	1	1		3	1
- CALCIF. TUB. REN. PAP.		2	3	2		2	3	1	2
- CHR. TUB. INTER. NEPHR.				1					
- GRANULOMA							1		
- VACUOL. TUBUL. EPITH.			1		1		1		2
EPIDIDYMIDES	NO. EXAM.:	4		4		4			4
- OLIGOSPERMIA		1							2
- VASCULITIS						1			
THYROID + PARATH. GL.	NO. EXAM.:	4	4	4	4	4	4	4	4
- PARATHYROID MISSING		1	1		1		1	2	1
- INTERFOLL. ADENOMAT.		2	1	2	1	2	2	3	3
- DEVELOPMENTAL CYST		1	1			1	2		
- CYST, PARATHYROID GL.					2				1
- INTERS. MOMO. CEL. INF.									1
- CYSTIC FOLLICLE(S)			1						1
- LYMPHOID CELL AGGREG.				1					
- FATTY INFILTRATION,									1
TRACHEA	NO. EXAM.:	4	4	4	4	4	4	4	4
- MONONUCL. CEL. AGGREG.		1		1					
UTERUS	NO. EXAM.:	4		4		4			4
- PROOESTRUS				1					
- OESTRUS						1			1
- METOESTRUS		3		2		2			1
- ANOESTRUS		1		1		1			2

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Table IVB.6.2

PATHOLOGY REPORT		PAGE		10					
SUMMARY TABLES		PROJECT:		5927 TCC					
TEST ARTICLE :	CGP 33 101 TEST N° 99-6305	PATHOL. NO.:		35927 VLG					
TEST SYSTEM :	DOG, 26/52 Weeks + 6 Weeks, ORAL	DATE		16-APR-91					
SPONSOR :	CIBA-GEIGY								
NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX									
STATUS AT NECROPSY: R1									
ORGAN/FINDING	DOSE GROUP:	T		A		B		C	
		M	F	M	F	M	F	M	F
	SEX:	2	2	2	2	2	2	2	2
	NO. ANIMALS:	2	2	2	2	2	2	2	2
	NO. EXAM.:	2	2	2	2	2	2	2	2
AORTA									
- CALCIFICATION			1			1	1	1	
- HAEMORRHAGE, ADVENT.			1	1					
- ARTERIT. VASO VASORUM						1			
BRAIN									
- MONONUCL. CEL. AGGREG.		2	2	2	2	2	2	2	2
- CAPILLAR. HAEMORRHAGE		1							1
- OEDEMA CHOROID PLEX.			2	1		2			
DUODENUM									
- CAPELL. ECTASIA MUCO.		2	2	2	2	2	2	2	2
RECTUM									
- CYSTIC GLANDS		2	2	2	2	2	2	2	2
LIVER									
- BILIARY THROMBI		2	2	2	2	2	2	2	2
- POSITIVE HALL REACT.				1	2	2	2	2	1
- POSITIVE PERLS' REACT.		1		1		1		1	2
- POSI. PERLS' REAC. KUP.				2		1		1	2
- NEGATIVE PERLS' REACT.		2	1	1	1	1	2	1	
- NEGATIVE HALL REACT.		2	2	1					1
- BROWN/YEL. PIGM. ACCU.				2		1	2	2	2
- GREEN. PIGMENT ACCUM.						2		1	1
- PERIVASCULITIS		1		2	2	2	2	1	1
- INFLAM. CEL. INFILTR.				2	2	2	2	2	1
- UNICELLULAR NECROSIS						1			
- MONONUCL. CEL. AGGREG.		1		1					1
- MICROGRANULOMA		1	2		1	2	1		1
PRIMARY GLAND									
- PROOESTRUS		2	2	2	2	2	2	1	2
- METOESTRUS			2			2			
- ANOESTRUS				1					1
PAROTID GLAND									
- FATY INFILTRATION		2	2	2	2	2	2	2	2
- LYMPHOID CEL. AGGREG.			1	2		1	2	1	1
THYROID + PARATH. GL.									
- PARATHYROID MISSING		2	2	2	2	2	2	2	2
- INTERFOLL. ADENOMAT.		2	2	1		2	2	2	2
- DEVELOPMENTAL CYST			1			2	1		
- CYST, PARATHYROID GL.		1	1	1	1	1	1	1	1
- CYSTIC FOLLICLE(S)								1	

b(4)

Table IVB.6.3

Dose (mg/kg)	Time (Day)	C _{max} (µmol/L)		AUC _(0-24 hr) (µmol hr/L)	
		Male	Female	Male	Female
20	1	41	23	549	310
200		37	97	560	1776
20	182	42	36	549	456
200		60	88	964	1366
20	363	54	29	734	352
200		65	185	991	3580

7. CGP 33101 13-Week Oral Toxicity Study in Monkeys (MIN 924143) (Test No. 92-6094, conducted by Ciba-Geigy, England, report dated, GLP)

a. Methods

CGP 33101 (0, 35, 100 or 300 mg/kg; suspension in aqueous 3% corn starch) was given orally via nasogastric intubation or gavage to cynomolgus monkeys (3 or 6/sex/group) for 13 weeks. At the end of the dosing period, 2 or 3/sex from the C and HD groups were allowed a 4-week recovery period. Clinical observations, body weight and food consumption, physical/auditory and ophthalmoscopic examinations, ECG (4-6 h after dosing during weeks 4/5, 13, and recovery), clinical pathology and gross pathological examinations were performed on all animals. Microscopic examinations were performed on all gross lesions and on a standard list of tissues from all monkeys that were necropsied at the end of the dosing period and monkeys that died or were sacrificed prior to scheduled necropsy. The livers and gallbladders were examined from all recovery animals. Plasma drug analyses were performed on main study animals during weeks 1 and 12.

Drug Lot: #800189

b. Results

i. Mortality, Clinical Signs, Body Weight

There were no deaths considered treatment-related. The death of 1 MD male (No. 12, found dead on day 18) was attributed to a dosing accident. One HD male (No. 18) was euthanized for humane reasons on day 68 after recurring incidences of self-inflicted wounds of increasing severity (clinical observations of lacerations of the right medial lower leg). Treatment-related pathology findings in this animal consisted of a gross accumulation of choleliths in the gallbladder.

Treatment-related clinical signs were limited to emesis with and/or without compound in HD males and MD and HD females, mainly during the first week of dosing.

There were no apparent T-R changes in body weight or body weight gain.

ii. EKG, Physical/Auditory, and Ophthalmology

Statistically significant decreases in mean QT were observed in males at all doses on day 28 and at the HD on day 86 compared to C (IVB.7.1). Part of this change was due to an increase in C, but there appeared to be a possible effect at the HD. QTc was not calculated, but HR was not significantly changed.

There were no physical/auditory findings considered to be related to treatment. No statistically significant differences were observed between the mean rectal temperatures of treated and control groups during the dosing or recovery periods.

Ophthalmoscopic examinations revealed no ocular changes attributable to treatment.

iii. Clinical pathology

There were no clearly treatment-related changes in hematological or clinical chemistry parameters, although creatinine was increased (SS) in males at all doses and SGPT and alkaline phosphatase was elevated somewhat in HD females on day 89 (IVB.7.2).

iv. Pathology

T-R lesions were found in the gallbladder at the MD and HD (IVB.7.3). Gallbladders were described as containing "pale, yellow-brown material that exhibited white, delicate, fan-shaped birefringence under polarized light." Increased numbers of inflammatory cells composed of an increased proportion of granulocytes were present in the lamina propria of the gallbladder of the affected animals. According to the report, "there was no evidence of bile stasis or epithelial damage in the hepatobiliary system." There was an increase of relative spleen weight in HD females that was thought to reflect an antigenic stimulus that was associated with microscopic evidence of lymphoid hyperplasia in two animals (# 31, # 32) and was not considered to be T-R. Morphological changes that were not considered T-R included lymphoid depletion of the thymus, oral and esophageal candidiasis, bacterial colonization of the surface epithelium and protozoiasis of the large intestine, parasitism and evidence of viral infection. Animals in all treatment groups had evidence of latent malaria infection, and 2 HD females (31 and 32) had minimal, focal glomerulonephritis that was thought to be probably related to parasitism.

v. Plasma levels (IVB.7.4)

Exposure was less than dose-proportional. There were no consistent sex or time differences.

c. Conclusions

Oral administration of rufinamide (35, 100 and 300 mg/kg) to cynomolgus monkeys for 3 months produced choleliths and inflammation in the lamina propria of the gallbladder at the MD and HD in both sexes. Possible decreases in QT were observed in males. Following a 4-week recovery period, choleliths were found only in a single HD female monkey, indicating partial reversibility. The gallbladder granules were determined to be composed primarily of a cysteine conjugate of a hydroxylated metabolite. This highly insoluble conjugate was assumed to have been formed by enzymatic degradation of the corresponding glutathione conjugate with subsequent precipitation in the bile. Metabolism studies in humans have produced no evidence that these conjugates are formed in humans. The LD was considered a NOAEL.

IVB.7

CGP 33101: 13-WEEK ORAL TOXICITY IN MONKEYS (MIN924143)

SUMMARY OF STATISTICAL ANALYSIS
ERG

MALE										
GROUP NO.	DOSE	(N)	SINRRHY (N_A)		HR (BPM)		PI (SECONDS)		PEI (MV)	
			ABN/NORM	N	MEAN±SE	N	MEAN±SE	N	MEAN±SE	
PERIOD: DAY -13										
1	0 MG/KG	6	0/6		265.0± 5.5		0.030±0.000		0.12±0.02	
2	35 MG/KG	3	0/3		261.7± 1.7		0.033±0.003		0.13±0.03	
3	100 MG/KG	3	0/3		256.7±10.1		0.033±0.003		0.17±0.03	
4	300 MG/KG	6	0/6		244.2±12.3		0.033±0.002		0.15±0.02	
TEST FOR EQUALITY					P= NS		P= NS		P= NS	
PERIOD: DAY 28										
1	0 MG/KG	6	0/6		252.5± 5.6		0.032±0.002		0.12±0.02	
2	35 MG/KG	3	0/3		256.7± 6.0		0.033±0.003		0.13±0.03	
3	100 MG/KG	3	0/2	2	265.0± 6.0		0.035±0.005	2	0.20±0.00	
4	300 MG/KG	6	0/6		264.2± 3.7		0.030±0.000		0.17±0.03	
TEST FOR TREND					P= NS		P= NS		P= NS	
PERIOD: DAY 86										
1	0 MG/KG	6	0/6		255.8± 7.6		0.032±0.002		0.13±0.02	
2	35 MG/KG	3	0/3		263.3± 4.4		0.033±0.003		0.17±0.07	
3	100 MG/KG	3	0/2	2	280.0± 5.0		0.035±0.005	2	0.20±0.00	
4	300 MG/KG	6	0/5	5	262.0± 4.9		0.034±0.002	5	0.22±0.02	
TEST FOR TREND					P= NS		P= NS		P= NS	
QT (SECONDS)										
GROUP NO.	DOSE	(N)	N	MEAN±SE	MEA (DEGREES)		ST (N_A)	T (N_A)	ABN/NORM	ABN/NORM
					N	MEAN±SE				
PERIOD: DAY -13										
1	0 MG/KG	6		0.138±0.003		38.8±22.5		0/6	0/6	
2	35 MG/KG	3		0.140±0.000		15.7±28.7		0/3	0/3	
3	100 MG/KG	3		0.140±0.006		73.0± 3.2		0/3	0/3	
4	300 MG/KG	6		0.143±0.004		11.2±34.7		0/6	0/6	
TEST FOR EQUALITY					P= NS		P= NS			
PERIOD: DAY 28										
1	0 MG/KG	6		0.147±0.002		39.0±22.1		0/6	0/6	
2	35 MG/KG	3		0.140±0.000*		36.7±19.3		0/3	0/3	
3	100 MG/KG	3	2	0.140±0.000*		2 71.0± 0.0		0/2	0/2	
4	300 MG/KG	6		0.138±0.002*		9.5±36.3		0/6	0/6	
TEST FOR TREND					* P= 0.014		P= NS			
PERIOD: DAY 86										
1	0 MG/KG	6		0.142±0.004		50.3±18.1		0/6	0/6	
2	35 MG/KG	3		0.143±0.003		35.7±16.2		0/3	0/3	
3	100 MG/KG	3	2	0.135±0.005		2 71.5± 0.5		0/2	0/2	
4	300 MG/KG	6	6	0.130±0.003*		5 37.8±32.6		0/5	0/5	
TEST FOR TREND					* P= 0.041		P= NS			

IVB.7.2

SUMMARY OF STATISTICAL ANALYSIS
BIOCHEMISTRY

40011
SMKRB

		MALE								
GROUP NO.	DOSE	(N)	ALBUMIN (GM/DL)		GLOBULIN (GM/DL)		CREAT (MG/DL)		BUN (MG/DL)	
			N	MEAN±SE	N	MEAN±SE	N	MEAN±SE	N	MEAN±SE
PERIOD: DAY 59										
1	0 MG/KG	6	4	4.23±0.15	3	3.8±0.1	1	1.09±0.028	2	23.6±1.8
2	35 MG/KG	3	4	4.37±0.03	3	4.1±0.1	1	1.287±0.064*	2	25.3±0.4
3	100 MG/KG	3	2	4.20±0.20	2	3.7±0.0	2	1.255±0.055*	2	19.3±0.5*
4	300 MG/KG	6	5	4.20±0.04	5	3.6±0.2	5	1.222±0.06/**	5	17.5±1.2**
TEST FOR TREND			P= NS		P= NS		* P= 0.040		** P= 0.003	

SUMMARY OF STATISTICAL ANALYSIS
BIOCHEMISTRY

		FEMALE						
GROUP NO.	DOSE	(N)	SGPT (U/L)		SGOT (U/L)		ALPKN (U/L)	
			N	MEAN±SE	N	MEAN±SE	N	MEAN±SE
PERIOD: DAY 59								
1	0 MG/KG	6	5	52.2± 4.2	4	74.8± 7.0	2	275.3± 28.3
2	35 MG/KG	3	3	57.3± 8.8	3	82.7±19.5	2	222.3± 53.8
3	100 MG/KG	3	3	59.7± 7.5	3	67.7± 4.8	2	320.3± 20.7
4	300 MG/KG	6	6	72.7±10.5	5	66.2± 0.1	3	391.7± 46.4*
TEST FOR TREND			P= NS		P= NS		* P= 0.029	

IVB.7.3

Cholelithiasis at Necropsy

Dose (mg/kg)	Male	Female
Terminal Sacrifice/Early Decedents		
0	0/3	0/3
35	0/3	0/3
100	1/3 ^a	3/3
300	4/4 ^b	3/3
Recovery Sacrifice		
0	0/3	0/3
300	0/2	1/3

^a#12 died on day 18

^b#18 sacrificed on day 68

IVB.7.4

Summary of AUC, C_{max}, T_{max} and C_{trough} data for CGP 33101 in samples of plasma taken from monkeys on day 78 of a Toxicology 13-week oral toxicity study (WIN 924143)

Dose (mg/kg/day)	Animal Number	Sex	AUC ^a (hr(µg/ml))	C _{max} (µg/ml)	T _{max} (hr)	C _{trough} (µg/ml)
35	7	M	254	16.0	4	4.6
	8		314	18.8	8	6.5
	9		386	23.4	4	8.2
Mean ± Std. Dev.			321 61	19.4 3.7	-	6.4 1.8
	25	F	252	14.8	8	4.4
26	277		15.4	8	6.4	
27	254		18.2	4	4.9	
Mean ± Std. Dev.			261 14	16.1 1.8	-	5.2 1.0
	100	M	577	28.4	12	17.7
11	578		28.9	4	18.7	
12 ^b	---		---	---	---	
Average ^c			577	28.7	-	18.2
	28	F	522	42.3	4	11.5
	29		429	24.5	4 & 8	10.0
	30		618	37.0	8	15.8
Mean ± Std. Dev.			523 95	34.6 9.1	-	12.4 3.0
	300	M	999	50.0	12	31.3
14	1090		59.2	12	32.4	
15	732		38.8	4	30.1	
Mean ± Std. Dev.			940 186	49.3 10.2	-	31.3 1.2
	31	F	995	60.0	4	31.7
32	695		37.7	4	17.9	
33	678		38.9	8	16.1	
Mean ± Std. Dev.			789 178	45.5 12.5	-	21.9 8.5

^a Calculated for a 24-hour dosing interval by assuming that the concentration at t = 0 was equivalent to that at 24 hr.

^b No sample obtained.

^c Mean ± standard deviation could not be calculated because n = 2.

8. CGP 33101: 6/12 Month Oral Toxicity Study in Cynomolgus Monkeys (TEST NO. 936082, conducted by Ciba-Geigy, England, report dated 2/20/95, GLP)

a. Methods

Rufinamide, batch 800389, was administered orally (gavage) to cynomolgus monkeys as follows:

	Group 1	Group 2	Group 3	Group 4
Dose (mg/kg)	0	20	60	200
Volume (ml/kg)	5	5	5	5
Number of animals	8 ♂ + 8 ♀	8 ♂ + 8 ♀	8 ♂ + 8 ♀	8 ♂ + 9 ♀ **
Interim ***	2 ♂ + 2 ♀	2 ♂ + 2 ♀	2 ♂ + 2 ♀	2 ♂ + 3 ♀
Main ****	4 ♂ + 4 ♀	4 ♂ + 4 ♀	4 ♂ + 4 ♀	4 ♂ + 4 ♀
Recovery *****	2 ♂ + 2 ♀	2 ♂ + 2 ♀	2 ♂ + 2 ♀	2 ♂ + 2 ♀

* 3% w/v aqueous corn starch suspension

** 4 000 ♀ was found dead on day 7 and was replaced with 4 016 ♀.

*** Animals scheduled for interim kill were treated for 6 months.

**** Animals scheduled for main kill were treated for 12 months.

***** Animals scheduled for recovery kill were treated for 12 months with a 4 week recovery period.

The following endpoints were evaluated: mortality and clinical signs (daily); body weight and food consumption (weekly); hearing and ophthalmology (Pre-test, weeks 25, 50 and 55); clinical chemistry, hematology, and urinalysis (weeks 0, 13, 26, 39, 51 and 56); toxicokinetics (day 1 and week 52); and organ weights, macroscopic, and microscopic histopathology (all tissues from all animals).

b. Results

i. Mortality, Clinical Signs, Body Weight

There were no deaths thought to be related to treatment. One HD female (4000) was found dead on day 7 (found to have meningitis) and 1 C female (1008) and HD male (4009) died on days 119 and 179, respectively, following accidental strangulation.

No toxicologically significant clinical signs were observed. Vomiting was observed occasionally in all groups, including controls. This was generally seen immediately before, during or in the period immediately after dosing.

No body weight differences were noted between treated and control animals.

ii. Clinical Pathology, EKG, Auditory, and Ophthalmology

No treatment related hearing abnormalities or ophthalmology findings.

There were no treatment related changes in hematology.

There was some clinical chemistry evidence of effects on liver and kidney function (IVB.8.1). Increases in Alk Phos, AST, and ALT were seen in both sexes, primarily at the MD and HD. Increases in plasma creatinine concentrations were noted in treated animals at all doses. Urea levels also tended to be increased, although not as consistently. There was generally evidence of recovery four weeks after dosing cessation, although some liver enzyme values remained higher. There were no difference in creatinine or urea values at week 56.

There were no treatment related changes in urinary composition.

iii. Pathology

Liver weights were increased in treated males and females. Kidney weights were dose-dependently increased in males, and were increased in females, but not D-D. No liver or kidney weight changes were evident after the recovery period. There were no apparent T-R changes in thyroid weights.

At necropsy of the interim study animals, various amounts of white granules were observed in the gall bladder of 3 of the 5 HD monkeys (2 males and 1 female). After 12 months, single dark granules in the gall bladder were observed macroscopically in 2 of the 7 HD monkeys (1 male, 1 female). After the recovery period, 2 females of the same dose group showed multiple white granules in their gall bladders.

After 12 months (IVB.8.2 and IVB.8.3), minimal hepatocytic hypertrophy in 2 males (one of these showed biliary granules) and 3 females at the HD, as well as in 1 MD female. No liver changes were seen in the recovery animals. Pigment deposits in the brain were seen in 1 male and 1 female from the HD group at the terminal sacrifice, but no brain lesions were noted in the recovery animals. There were no apparent T-R changes in the kidney or thyroid.

iv. Plasma levels (IVB.8.4)

Exposure to parent increased with increasing doses, but was less than dose proportional. Based on the morning pre-dose concentrations, steady-state concentrations might have been almost reached as soon as 24 h after the first dose. Due to saturation in the absorption processes, concentration-time profiles at steady-state fluctuated less at the HD than at the LD. There was no appreciable accumulation upon repeated dosing and no sex difference.

c. Conclusions

Administration of rufinamide (20, 60, or 200 mg/kg) to cynomolgus monkeys for up to 1 year produced effects on the liver and gall bladder at the MD and HD. Increases in Alk Phos, AST, and ALT were seen in both sexes, primarily at the MD and HD. These changes were associated with increased liver weight and hepatocytic hypertrophy in 5/7 HD and 1/8 MD animals. The presence of granules in the bile was seen at the HD and attributed to the metabolism and excretion of rufinamide as a conjugate which accumulated as concretions of insoluble material. Although there was no evidence microscopically of cholestatic changes, the increases in plasma alkaline phosphatase activity may be related to this finding. The LD, which was associated with an AUC about 1/2 that in humans at the MRD (~1000 umol.h/L), was considered a no adverse effect level.

IVB.8.1

DOSE		GROUP MEANS CLINICAL CHEMISTRY BLOOD SAMPLE MALE WEEK 51							
mg/kg	Group	Na	K	Gluc	Urea	ASAT	ALAT	AP	Total Prot
CONTROL	1	139.5	4.01	3.78	6.24	27	37	1587	73.7
20	2	140.9	3.91	4.06	6.24	27	51	1317	76.2
60	3	140.8	4.18	4.10	6.79	33	47	1523	72.9
200	4	140.2	4.20	4.05	6.86	40	55	2149	77.4
		% Alb	% A1	% A2	% B	% G	Ratio A:D		
CONTROL	1	63.8	2.7	13.8	6.1	13.6	1.78		
20	2	62.3	2.8	16.2	4.4	14.4	1.71		
60	3	63.7	2.8	14.8	5.1	13.7	1.77		
200	4	59.3	2.7	13.4	5.6	16.9	1.49		
		Abs Alb	Abs A1	Abs A2	Abs B	Abs G			
CONTROL	1	47.0	2.0	10.1	4.5	10.0			
20	2	47.4	2.1	12.3	3.4	11.0			
60	3	46.4	2.0	10.8	3.7	10.0			
200	4	45.7	2.1	11.9	4.4	13.3			
		Chol	TD	Ca	Mg	PO4	Creat		
CONTROL	1	2.99	0.54	2.49	0.68	1.94	71		
20	2	2.77	0.81	2.46	0.67	1.94	80		
60	3	2.88	0.87	2.46	0.65	1.80	78		
200	4	2.68	1.10	2.45	0.69	1.96	89		
		G-GT	Cl	Bili					
CONTROL	1	94	108	1.8					
20	2	66	109	2.1					
60	3	73	109	1.7					
200	4	92	108	1.6					

DOSE		GROUP MEANS CLINICAL CHEMISTRY BLOOD SAMPLE FEMALE WEEK 51							
mg/kg	Group	Na	K	Gluc	Urea	ASAT	ALAT	AP	Total Prot
CONTROL	1	141.5	3.80	3.98	5.82	30	34	892	74.5
20	2	141.3	3.98	3.87	6.22	29	37	1245	74.0
60	3	139.7	4.01	3.89	6.47	27	43	990	73.8
200	4	139.8	4.01	4.23	6.14	27	38	1722	75.2
		% Alb	% Al	% A2	% B	% G	Ratio A:G		
CONTROL	1	59.2	2.9	17.9	4.2	15.9	1.46		
20	2	58.0	2.9	18.3	4.6	16.2	1.39		
60	3	57.1	3.3	19.5	4.2	15.9	1.34		
200	4	53.7	3.6	21.8	3.8	17.2	1.17		
		Abs Alb	Abs Al	Abs A2	Abs B	Abs G			
CONTROL	1	44.0	2.1	13.3	3.1	11.9			
20	2	42.8	2.1	13.6	3.4	12.0			
60	3	42.1	2.5	14.4	3.1	11.7			
200	4	40.5	2.7	16.3	2.8	12.9			
		Chol	TG	Ca	Mg	PO4	Creat		
CONTROL	1	3.54	0.90	2.44	0.63	1.41	76		
20	2	3.09	0.56	2.40	0.67	1.60	78		
60	3	3.34	1.03	2.48	0.67	1.39	81		
200	4	2.55	0.85	2.42	0.64	1.53	84		
		B-GT	Cl	Bili					
CONTROL	1	45	109	2.2					
20	2	60	110	1.9					
60	3	47	111	1.5					
200	4	68	109	1.5					

IVB.8.2

Summary Table of Pathological Findings after 6 and 12 Months

	Group 1		Group 2		Group 3		Group 4	
	Control							
Dose (mg/kg)	0		20		60		200	
Sex (♂/♀)	♂	♀	♂	♀	♂	♀	♂	♀
ORGAN/Finding								
GALL BLADDER								
After 6 months:								
-Several white granules							2/3***	1/2*
After 12 months:								
-Single dark granule							1/3	1/4
-Several white granules								2/2**
LIVER								
After 12 months:								
-Minimal hypertrophy					1/4	2/3	3/4	

Legend: * = The 3rd female of this group was found dead on day 7 of the study, therefore it was excluded from this table.

** = Recovery animals.

*** = 3rd male found dead on study day 179, data included in interim.

IVB.8.3

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: KO
 MAIN STUDY

ORGAN/FINDING	SEX :					MALE
	DOSE GROUP:	01	02	03	04	
	NO. ANIMALS:	4	4	4	3	
HEART	NO. EXAM.:	4	4	4	3	
- Inf., Inflamm. Cells		1		2	2	
- Arteritis/Periarter.					1	
LUNGS	NO. EXAM.:	4	4	4	3	
- Inf., Inflamm. Cells					1	
- Deposition, Pigment		4	4	4	3	
TRACHEA	NO. EXAM.:	4	4	4	3	
- Inf., Inflamm. Cell			2	1		
- Edema				1		
TONGUE	NO. EXAM.:	4	4	4	3	
- Inf., Inflamm. Cells		1	1		1	
- Inflammation			1			
- Hyperplasia, Squ. Cell			1			
STOMACH	NO. EXAM.:	4	4	4	3	
- Erosion					1	
- Inf., Lymphoid Cells		1	3	3	1	
- Atrophy, Mucosa				1		
- Hemorrhage				1	2	
- Arteritis/Periarter.					1	
CECUM	NO. EXAM.:	4	4	4	3	
- Trematodes in Lumen			1			
- Ectopic tis., splenic		1				
COLON	NO. EXAM.:	4	4	4	3	
- Balantidiosis		1	2	3	2	
- Granuloma, Parasitic			1	2		
- Arteritis/Periarter.					1	

Appears This Way
 On Original

THYMUS	NO. EXAM.:	4	4	4	3
- Hyperplasia, Lymphoid					1
- Cyst, Medullary		1		1	
.....					
SPLEEN	NO. EXAM.:	4	4	4	3
- Hyperplasia, Lymphoid		1	1		3
- Eosinophil. material		2	1		3
- Inf., Inflamm. Cell					2
- Congestion					1
.....					
AXILLARY LYMPH NODES	NO. EXAM.:	4	4	4	3
- Amyloidosis			1	1	
- Fibrosis			1		
- Hyperplasia, Lymphoid			1		2
- Eosinophil. material				1	2
- Deposition, Pigment		2	3	1	
- Histiocytosis, Sinus				1	
.....					
MESENT. LYMPH NODE	NO. EXAM.:	4	4	4	3
- Hyperplasia, Lymphoid					1
- Deposition, Pigment			1		
- Histiocyt. Sin. Retic.				1	
- Arteritis/Periarter.					1
.....					
STERNUM/MARROW	NO. EXAM.:	4	4	4	3
- Lymphoid Follicles			1	1	1
.....					
FEMUR/MARROW	NO. EXAM.:	4	4	4	3
- Hypercellular marrow					2
- Lymphoid follicles		1			2
.....					
KNEE JOINT CAPSULES	NO. EXAM.:	4	4	4	3
- Arteritis/Periarter.					1
.....					
THYROID GLAND	NO. EXAM.:	4	4	4	3
- Inf., Lymphoid Cells		2	1	1	
- Cyst(s)			1		
.....					
PARATHYROID GLANDS	NO. EXAM.:	3	3	2	2
- Inf., Lymphoid Cells			1		
.....					
THIGH MUSCLE	NO. EXAM.:	4	4	4	3
- Inf., Inflamm. Cells					1
.....					
SCIATIC NERVE	NO. EXAM.:	4	4	4	3
- Inf., Inflamm. Cells			1		
.....					
EYES	NO. EXAM.:	4	4	4	3
- Inf., Lymphoid Cells			1		
- Cataract		4	2	2	3
.....					
LACRIMAL GLANDS	NO. EXAM.:	4	4	4	2
- Inf., Lymphoid Cells		1	1	2	1
.....					
BRAIN	NO. EXAM.:	4	4	4	3
- Edema					1
- Deposition, Pigment					1
- Inf., Inflamm. Cells		1			
.....					

LIVER	NO. EXAM.:	4	4	4	3
- Hypertr.,Hepatocyte					2
- Inf.,Lymphoid Cells		2		1	1
- Inflammatory Focus		1		1	
- Lipidosis,Tension				1	
- Arteritis/Periarter.					1
.....					
GALLBLADDER	NO. EXAM.:	4	4	3	3
- Inf.,Inflamm.Cells			1		
- Calculus,Biliary					1
.....					
SALIVARY GLANDS	NO. EXAM.:	4	4	4	3
- Inf.,Lymphoid Cells		3	3	3	3
- Mineralization			1		
.....					
KIDNEYS	NO. EXAM.:	4	4	4	3
- Amyloidosis		1			
- Inf.,Lymphoid Cells		2	3	1	2
- Edema				1	
- Arteritis/Periarter.					1
.....					
URINARY BLADDER	NO. EXAM.:	4	4	4	3
- Inflammation				1	
.....					
TESTES	NO. EXAM.:	4	4	4	3
- Immature		4	3	2	2
.....					
EPIDIDYMIDES	NO. EXAM.:	4	4	4	3
- Immature		4	3	2	2
.....					
PROSTATE	NO. EXAM.:	2	1	1	2
- Immature		2		1	2
- Arteritis/Periarter.					1
.....					
SEMINAL VESICLES	NO. EXAM.:	4	4	4	3
- Immature		3	3	2	2
.....					

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0
 MAIN STUDY

ORGAN/FINDING	SEX :					FEMALE
	DOSE GROUP:	01	02	03	04	
	NO. ANIMALS:	3	4	4	4	
HEART	NO. EXAM.:	3	4	4	4	
- Inf., Inflamm. Cells		2	2	4	1	
- Epicarditis/Auricle					1	
LUNGS	NO. EXAM.:	3	4	4	4	
- Adhesion, Fibrous			1			
- Fibrosis			1			
- Emphysema					1	
- Deposition, Pigment		3	4	4	4	
- Cyst					1	
STOMACH	NO. EXAM.:	3	4	4	4	
- Inf., Lymphoid Cells		2	1	3	1	
JEJUNUM	NO. EXAM.:	3	4	4	4	
- Lymphangiectasia				1		
- Arteritis/Periarter.				1		
ILEUM	NO. EXAM.:	3	4	4	4	
- Lymphangiectasia				1		
- Arteritis/Periarter.			1			
CECUM	NO. EXAM.:	3	4	4	4	
- Trematodes in Lumen		1		1		
COLON	NO. EXAM.:	3	4	4	4	
- Hemorrhage			1			
- Balantidiosis		2	1	3	3	
- Inf., Inflamm. Cells			1			
- Granuloma, Parasitic			1		2	
LIVER	NO. EXAM.:	3	4	4	4	
- Hypertr., Hepatocyte				1	3	
- Inf., Lymphoid Cells		1	3	1	3	
- Lipidosis, Tension			1			

Appears This Way
 On Original

SALIVARY GLANDS	NO. EXAM.:	3	4	4	4
- Inf.,Lymphoid Cells		1	4	2	4
.....					
KIDNEYS	NO. EXAM.:	3	4	4	4
- Inf.,Lymphoid Cells		2	2	2	2
- Arteritis/Periarter.				1	
.....					
URINARY BLADDER	NO. EXAM.:	3	4	4	4
- Inflammation				1	
.....					
OVARIES	NO. EXAM.:	3	4	4	4
- Cyst		2	1	1	
- Change,Physiological				1	
.....					
UTERUS	NO. EXAM.:	3	4	4	4
- Cycle,Menstruation				1	2
.....					
VAGINA	NO. EXAM.:	3	4	4	4
- Inflammation					1
.....					
THYMUS	NO. EXAM.:	3	4	4	4
- Atrophy				1	1
.....					
SPLEEN	NO. EXAM.:	3	4	4	4
- Hyperplasia,Lymphoid		1		2	1
- Eosinophil. material		2	1	3	2
- Nod.,Fibrosiderotic					1
- Inf.,Inflamm.Cell			1	1	
- Congestion					1
.....					
AXILLARY LYMPH NODES	NO. EXAM.:	3	4	4	4
- Hyperplasia,Lymphoid				1	3
- Eosinophil. material			1	2	1
- Inf.,Inflamm.Cell					1
- Hemorrhage					1
- Deposition,Pigment		2	2	1	
- Histiocytosis,Sinus			1		
.....					

Appears This Way
On Original

MESENT. LYMPH NODE	NO. EXAM.:	3	4	4	3
- Hyperplasia, Lymphoid		1			1
- Eosinophil. material		1			
- Inf., Inflamm. Cell			1		
- Histiocyt. Sin. Retic.		1			
- Granuloma		1			
.....					
STERNUM/MARROW	NO. EXAM.:	3	4	4	4
- Hypercellular marrow		1			
- Lymphoid Follicles		1	1		1
.....					
FEMUR/MARROW	NO. EXAM.:	3	4	4	4
- Hypercellular marrow				1	2
- Lymphoid follicles		1		1	2
- Hemorrhage/Marrow				1	
.....					
THYROID GLAND	NO. EXAM.:	3	4	4	4
- Cyst(s)			1		
.....					
PARATHYROID GLANDS	NO. EXAM.:	3	3	3	4
- Inf., Lymphoid Cells			1		
.....					
THIGH MUSCLE	NO. EXAM.:	3	4	4	4
- Sarcosporidiosis		1			
- Inf., Inflamm. Cells		1		1	1
.....					
SKIN	NO. EXAM.:	3	4	4	4
- Inf., Inflamm. Cell					1
.....					
EYES	NO. EXAM.:	3	4	4	4
- Cataract			2	2	1
- Conjunctivitis		1			
.....					
LACRIMAL GLANDS	NO. EXAM.:	3	4	4	3
- Inf., Lymphoid Cells			2	1	2
.....					
BRAIN	NO. EXAM.:	3	4	4	4
- Deposition, Pigment					1
- Inf., Lymphoid Cells					1
.....					

IVB.8.4

Sex	AUC(0-24h) [$\mu\text{mol}\cdot\text{h/L}$]		C_{max} [$\mu\text{mol/L}$]		t_{max} [h]	
	Day 1	Week 52	Day 1	Week 52	Day 1	Week 52
Daily dose: 20 mg/kg						
Male	892 \pm 112	1060 \pm 152	55.3 \pm 11.3	62.7 \pm 7.4	4	8
Female	804 \pm 94	1010 \pm 136	49.1 \pm 3.4	62.3 \pm 10.0	6	6
Daily dose: 60 mg/kg						
Male	1800 \pm 190	1690 \pm 420	104 \pm 14	106 \pm 21	12	2
Female	1950 \pm 275	2290 \pm 573	115 \pm 26	121 \pm 23	8	4
Daily dose: 200 mg/kg						
Male	2960 \pm 734	3190 \pm 536	151 \pm 42	156 \pm 33	12	6
Female	2660 \pm 529	3060 \pm 476	131 \pm 28	144 \pm 26	12	4

*: median.

C. GENETIC TOXICOLOGY

1. Bacterial Mutagenicity Test on CGP 33101 (Report No. SP 787, Dated 10/1/85, Conducted by Ciba-Geigy, Frankfurt, Germany, non-GLP)

CGP 33101 was tested for mutagenicity with Salmonella typhimurium tester strains TA 100, TA 1537, and TA 98 and with E. coli WP2 uvrA at concentrations from 15.8 to 5000 ug per plate without S-9 and from 5 to 5000 ug per plate with S-9. Precipitate was seen at doses > 500 ug per plate. In the absence of S-9 Mix, CGP 33101 was weakly cytotoxic at the highest dose. In the S-9 test no toxicity was seen. No evidence of mutagenicity was observed in this study (Table IVC.1.1).

Table IVC.1.1

WITH S-9 MIX (from liver homogenate of Aroclor 1254-treated rats)

Compound (ug/plate)	Solvent (ul DMSO/plate)	Surviving fraction	Revertant colonies per plate				
			TA 100	TA 1537	TA 98	TA 98+TCPO	WP2 uvrA
0	10	1.0	124 143	27 34 38	64 72	68 87	31 39
0	10	1.0	143 151	33 35 48	66 88	69 88	37 52
5 CGP 33101	10	0.8	137 140	37 38 41	62 68	69 78	25 28
15.8	10	0.9	127 139	26 31 42	70 70	74 74	30 37
50	10	0.9	118 138	29 33 36	77 79	88 86	38 42
158	10	0.9	104 115	29 40 41	67 69	88 73	32 46
500 §	10	0.9	115 127	33 36 46	62 69	69 71	38 44
1580 §	30	0.9	125 133	27 28 34	67 81	67 68	25 28
5000 §§	95	0.9	103 105	18 22 26	71 78	69 79	19 27
10 BaP	10	0.8	1430 1440	167 186 188	680 705	603 668	165 179
50 BaP	10	1.0	275 298	45 55 57	100 102	345 352	43 49
10 2-AA	10	0.9	4010 4250	192 197 202	2580 2610	2260 2330	685* 734*
90 3-MC	30	1.0	3330 3730	96 96 96	1480 1720	1650 1686	57 65

WITHOUT S-9 MIX

Compound (ug/plate)	Solvent (ul DMSO/plate)	Surviving fraction	Revertant colonies per plate			
			TA 100	TA 1537	TA 98	WP2 uvrA
0	10	1.0	102 103	10 11 15	21 32	71 82
0	10	1.0	103 129	10 11 16	30 38	77 85
15.8 CGP 33101	10	1.0	85 105	8 9 10	15 24	87 89
50	10	1.0	108 127	10 12 12	30 31	67 81
158	10	1.0	101 103	10 11 16	29 29	59 82
500 §	10	1.0	116 130	9 10 10	25 27	77 78
1580 §	30	1.0	113 115	7 8 8	22 25	67 68
5000 §	95	0.8	86 91	3 8 9	21 24	58 60
1 BPO	10	1.0	2180 2230	531 532 548	2130 2320	145 150
10 ENNG	10	0.9	19000 23000	25 100 150	31 33	247 271
15 ENNG	10	1.0	18000 19000	26 27 30	467 552	8000 6100

Mutagenicity experiments with his⁺ S. typhimurium were performed as described by Ames et al. (Mutat. Res. 31 (1975) 347-364) with only minimal modifications (see "Materials and Methods"). Additionally an epoxide hydrolase inhibitor and glutathione depletor, 1,1,1-trichloropropane oxide, was added to some incubations (column headed "TA 98+TCPO"). Experiments with trp⁺ E. coli WP2 uvrA were done analogously with 50 µM erythran in the top agar. The tables show the number of his⁺ or trp⁺ revertant colonies of individual plates.

DMSO: Dimethylsulfoxide; BaP: Benzo(a)pyrene; BaP: Benzo(a)pyrene; 2-AA: 2-Aminoanthracene; 3-MC: 3-Methylcholanthrene;

BPO: Benzo(a)pyrene 4,5-oxide; ENNG: N-Ethyl-N'-nitro-N-nitrosoguanidine; ENNG: N-Ethyl-N'-nitro-N-nitrosoguanidine.

§ 50 µg 2-Aminoanthracene was used.

* Macroscopically visible precipitation of test compound on the plates.

§§ A precipitate was still present at the end of the experiment.

Appears This Way
On Original

2. Salmonella and Escherichia/Liver-Microsome Test (Study no. 926056, conducted by Ciba-Geigy, Basel, report dated 7/3/92, GLP)

Rufinamide was tested with or without S9 activation. WP2 uvrA was tested at up to 2500 µg/plate (no cytotoxic effects observed). Strains TA 98, TA 100, TA 1535 and TA 1537 were tested at up to 5000 µg/plate (no cytotoxic effects observed). No increase in frequencies of mutant colonies was observed with or without metabolic activation (Tables IVC.2.1a and IVC.2.1b). The positive controls gave the appropriate responses.

Tables IVC.2.1a

SUMMARY OF THE RESULTS

Experiment without metabolic activation

Test number : 926056 Experiment : Original
 Test substance : CGP 33 101 Batch : 800189

Treatment/Strain	TA 100	TA 1535	TA 98	TA 1537
Negative control	169.7	10.3	14.3	5.3
<u>CGP 33 101:</u>				
312.5000 µg/plate	172.3	13.7	15.3	5.3
625.0000 µg/plate	165.7	9.7	11.3	5.0
1250.0000 µg/plate	167.3	10.7	10.3	7.0
2500.0000 µg/plate	175.7	10.3	15.3	5.0
5000.0000 µg/plate	166.7	8.7	8.3	4.3
<u>Positive controls:</u>				
sodium azide	909.7	896.0	-----	-----
2-nitrofluorene	-----	-----	1979.7	-----
9-aminoacridine	-----	-----	-----	2091.0

Treatment/Strain	WP2 uvrA
Negative control	20.0
<u>CGP 33 101:</u>	
156.2500 µg/plate	14.7
312.5000 µg/plate	15.3
625.0000 µg/plate	14.0
1250.0000 µg/plate	15.0
2500.0000 µg/plate	11.3
<u>Positive controls:</u>	
4-NQO	973.7

Tables IVC.2.1b

Experiment with metabolic activation

Test number : 926056 Experiment : Original
 Test substance : CGP 33 101 Batch : 800189

Treatment/strain	TA 100	TA 1535	TA 98	TA 1537
Negative control	190.3	12.0	25.7	7.0
CGP 33 101:				
312.5000 ug/plate	191.3	14.0	26.7	5.0
625.0000 ug/plate	180.7	11.3	28.3	6.0
1250.0000 ug/plate	165.0	11.3	22.3	6.7
2500.0000 ug/plate	169.3	13.0	20.7	5.7
5000.0000 ug/plate	166.3	15.7	11.3	4.0
Positive controls:				
2-aminoanthracene	2048.3	----	2305.7	172.3
cyclophosphamide	----	609.0	----	----

Treatment/strain	WP2 uvra
Negative control	15.0
CGP 33 101:	
156.2500 ug/plate	14.7
312.5000 ug/plate	17.0
625.0000 ug/plate	17.0
1250.0000 ug/plate	15.7
2500.0000 ug/plate	7.3
Positive controls:	
2-aminoanthracene	1598.0

3. Chromosome studies on Chinese Hamster Ovary cell line CCL 61 in vitro (test # 896147, conducted by Ciba-Geigy, Basle, Switzerland, completed 7/25/90, GLP)

Concentrations of 62.5, 125, and 250 ug/ml were tested for chromosome effects in four experiments: 3 hours treatment with activation and 14 hours recovery time, 3 hours treatment with activation and 21 hours recovery time, 14 hours treatment without activation, 24 hours treatment without activation. Two hundred metaphases were examined from vehicle control and drug groups. At least fifty metaphases each from the appropriate positive controls from the second experiment (3 hours treatment with activation and 21 hours recovery time) and from the fourth experiment (24 hours treatment without activation) were analyzed. The highest concentration (250 ug/ml) suppressed mitotic activity by 8, 46, 30, and 20% in the 4 experiments.

In the original and confirmatory studies, numbers of cells with specific chromosomal aberrations were similar between treated and controls under all 4 conditions (Table IVC.3.1). The positive controls (cyclophosphamide and mitomycin-C) produced the expected results.

Table IVC.3.1

3 hrs Treatment With Activation and 14 hrs Recovery					
	Vehicle Control (1% DMSO)	Rufinamide 62.5 µg/mL	Rufinamide 125 µg/mL	Rufinamide 250 µg/mL	
% of metaphases with specific aberrations	0.5 (2.5)	0 (2)	0 (1)	0 (2)	
Metaphases with:					
Chromatid breaks	- (3)	-	-	- (1)	
Iso-chromatid breaks	- (2)	- (4)	- (1)	- (3)	
Di-, polycentrics	1 (-)	-	-	-	
Iso-chromatid fragments	-	-	- (1)	-	
% of metaphases with unspecific aberrations	1.5 (1.5)	2.5 (0)	1 (0.3)	0.3 (0.5)	
Metaphases with:					
Chromatid gaps	3 (3)	5 (-)	2 (1)	1 (1)	

3 hrs Treatment With Activation and 21 hrs Recovery					
	Vehicle Control (1% DMSO)	Rufinamide 62.5 µg/mL	Rufinamide 125 µg/mL	Rufinamide 250 µg/mL	Positive Control (Cyclophosphamide 40 µg/mL)
% of metaphases with specific aberrations	0.5 (2.5)	1 (2)	1.5 (1)	3 (2.5)	38 (68)
Metaphases with:					
Chromatid breaks	-	1 (-)	-	1 (-)	5 (7)
Iso-chromatid breaks	- (3)	- (4)	- (2)	- (3)	5 (14)
Chromatid exchanges	-	-	-	-	12 (14)
Di-, polycentrics	- (1)	-	-	1 (1)	1 (-)
Ring chromosomes	- (1)	-	-	1 (-)	-
Chromatid fragments	1 (-)	-	2 (-)	3 (-)	1 (6)
Iso-chromatid fragments	-	1 (1)	1 (-)	- (2)	- (7)
% of metaphases with unspecific aberrations	3 (2)	2.5 (0.5)	3.5 (0)	0 (0.5)	22 (6)
Metaphases with:					
Chromatid gaps	6 (4)	4 (1)	7 (-)	-	11 (2)
Iso-chromatid gaps	-	1 (-)	-	- (1)	1 (1)

14 hrs Treatment Without Activation				
	Vehicle Control (1% DMSO)	Rufinamide 62.5 µg/mL	Rufinamide 125 µg/mL	Rufinamide 250 µg/mL
% of metaphases with specific aberrations	0 (1)	0 (1.5)	0.5 (3)	0 (1.5)
Metaphases with:				
Chromatid breaks	-	-	-	- (1)
Iso-chromatid breaks	- (2)	- (2)	- (4)	- (2)
Chromatid fragments	-	-	- (1)	-
Iso-chromatid fragments	-	- (1)	1 (1)	-
% of metaphases with unspecific aberrations	2 (1.5)	1.5 (0.5)	1.5 (2)	4 (1)
Metaphases with:				
Chromatid gaps	4 (3)	3 (1)	3 (4)	3 (2)

24 hrs Treatment Without Activation

	Vehicle Control (1% DMSO)	Rufinamide 62.5 µg/mL	Rufinamide 125 µg/mL	Rufinamide 250 µg/mL	Positive Control (Mitomycin-C 6.1 µg/mL)
% of metaphases with specific aberrations	1 (2)	0 (2.5)	0.5 (2.5)	1.5 (4.5)	14 (20)
Metaphases with:					
Chromatid breaks	- (1)	-	1 (-)	1 (2)	1 (4)
Iso-chromatid breaks	- (3)	- (4)	- (5)	- (3)	1 (7)
Deletions	-	-	-	-	1 (-)
Chromatid exchanges	1 (-)	-	-	-	4 (2)
Di-, polycentrics	-	-	-	1 (-)	-
Ring chromosomes	-	-	-	-	1 (1)
Chromatid fragments	1 (-)	- (1)	-	1 (-)	- (4)
Iso-chromatid fragments	2 (-)	-	-	1 (-)	- (4)
% of metaphases with unspecific aberrations	3 (2)	0.5 (0.5)	3 (1)	3.5 (1.5)	12 (1)
Metaphases with:					
Chromatid gaps	6 (4)	1 (1)	6 (2)	5 (3)	8 (1)
Iso-chromatid gaps	-	-	-	2 (-)	1 (-)

- = effect not observed

Results in brackets are from confirmatory repeat assay.
Only observed aberrations are included.

4. Point Mutation Test with Chinese Hamster Cells V79 (Test No.: 876202, conducted by Ciba-Geigy, Basle, report dated 5/17/88, non-GLP)

CGP 33101 was tested for mutagenicity in V79 Chinese hamster cells in vitro. The original and the confirmatory experiments with and without metabolic activation were performed at concentrations of 20, 40, 80, 160, 240, 320, and 400 µg/ml. Cells were treated for 21 hours in the experiment without microsomal activation and for 5 hours in the experiment with microsomal activation.

In the original and confirmatory experiments without and with metabolic activation, comparison of the numbers of mutant colonies in the control and treated cultures showed no significant differences in mutant frequencies (Table IVC.4.1). The positive controls (EMS and DMN) produced the appropriate responses.

Table IVC.4.1

Metabolic Activation	Test Article	Concentration or Dose Level	6-TG resistant clones per dish (Mean)	Viability clones per dish (Mean)	Mutant frequency (10E-6)*	Factor**
Without Activation***	1 st Negative Control	-	0.00	56.17	<4.0	-
		-	1.22	57.17	21.4	-
	2 nd Negative Control	-	0.00	61.17	<4.0	-
		-	0.94	61.00	15.5	-
	Positive Control (Ethyl methanesulphonate)	300 nL/mL	41.71	28.67	1454.9	363.7
			40.83	30.17	1353.6	73.4
	Rufinamide (CGP 33 101)	20 µg/mL	0.22	48.00	4.6	1.2
			1.89	68.33	27.6	1.5
		40 µg/mL	0.11	52.17	<4.0	1.0
			1.00	75.50	13.2	1.0
Rufinamide (CGP 33 101)	80 µg/mL	0.06	56.67	<4.0	1.0	
		1.11	57.00	19.5	1.1	

	Rufinamide (CGP 33 101)	160 µg/mL	0.00 0.72	45.00 54.67	<4.0 13.2	1.0 1.0
	Rufinamide (CGP 33 101)	240 µg/mL	0.00 0.22	39.50 50.83	<4.0 4.4	1.0 1.0
	Rufinamide (CGP 33 101)	320 µg/mL	0.07 0.00	38.33 67.17	<4.0 <4.0	1.0 1.0
	Rufinamide (CGP 33 101)	400 µg/mL	0.08 0.00	26.33 59.67	<4.0 <4.0	1.0 1.0
With Microsomal Activation (S9) ***	1 st Negative Control	-	0.06 0.17	62.33 56.17	<4.0 <4.0	-
	2 nd Negative Control	-	0.28 0.39	51.00 44.33	5.4 8.8	-
	Positive Control (N- nitroso- dimethylsulfamide)	1 µL/mL	6.00 4.78	34.33 40.83	174.8 117.0	37.0 18.3
	Rufinamide (CGP 33 101)	20 µg/mL	0.00 0.06	80.00 37.17	<4.0 <4.0	1.0 1.0
	Rufinamide (CGP 33 101)	40 µg/mL	0.00 0.11	65.83 44.33	<4.0 <4.0	1.0 1.0
	Rufinamide (CGP 33 101)	80 µg/mL	0.11 0.22	52.00 51.00	<4.0 4.4	1.0 1.0
	Rufinamide (CGP 33 101)	160 µg/mL	0.00 0.28	56.50 38.33	<4.0 7.2	1.0 1.1
	Rufinamide (CGP 33 101)	240 µg/mL	0.00 0.22	45.33 54.67	<4.0 4.1	1.0 1.0
	Rufinamide (CGP 33 101)	320 µg/mL	0.06 0.17	45.00 59.67	<4.0 <4.0	1.0 1.0
	Rufinamide (CGP 33 101)	400 µg/mL	0.00 0.11	59.17 37.83	<4.0 <4.0	1.0 1.0

* - normalized to a virtual plating efficiency of 100%

** - mutant frequency (treated) / mutant frequency (control)

*** - Results of initial (upper result) and confirmatory assays (lower result)

5. Micronucleus Test, Rat (Study No. 896146, conducted by Ciba-Geigy, Basel, dated 7/26/90, GLP)

In Part I of the study, rats (Tif:RAIf; 8/sex/dose/sampling timepoint) were dosed orally (gavage) with 0 or 5000 mg/kg. Sampling timepoints were 16 hours, 24 hours, and 48 hours post dosing. Five animals/sex/dose/timepoint were evaluated. For each animal, 1000 polychromatic erythrocytes were analyzed for micronuclei. In Part II of the study, the same strain of rats (8/sex/dose) were dosed (oral gavage) with 0, 1250, 2500, or 5000 mg/kg. Five animals/sex/dose were evaluated. A sampling time of 24 hours was used for each dose. Again, 1000 PCEs were analyzed per animal. In both parts of the study, the positive control (20 mg/kg ip cyclophosphamide, 24 hour sampling) was given to 5/sex.

There were no deaths in the study. No clinical evidence of toxicity or TK data were provided. No inhibition of cell proliferation, as measured by reductions in PCE to NCE ratio compared to C, was noted. Rufinamide did not increase the frequency of micronucleated PCE, while positive control groups showed statistically significantly increased frequencies (Table IVC.5.1). However, the failure to demonstrate exposure or toxicity and to evaluate the ICH recommended 2000 PCEs/animal may require that the study be repeated.

Table IVC.5.1

Sampling Time	Test Article	Dose (mg/kg)	Gender and No. per Group	Ratio of PCEs to NCEs	% of PCEs with micronuclei
Part I 16 hrs	Negative Control (vehicle only)	-	5F	0.4	0.02
			5M	0.3	0.10
	CGP 33 101 (Rufinamide)	5000	5F	0.6	0.02
			5M	0.4	0.04
Part I 24 hrs	Negative Control (CMC 0.5%)	-	5F	0.5	0.06
			5M	0.3	0.02
	Positive Control (Cyclophosphamide)	20	5F	0.6	1.50
			5M	0.6	1.56
	CGP 33 101 (Rufinamide)	5000	5F	0.4	0.02
			5M	0.3	0.02
Part I 48 hrs	Negative Control (CMC 0.5%)	-	5F	0.4	0.04
			5M	0.2	0.00
	CGP 33 101 (Rufinamide)	5000	5F	0.3	0.04
			5M	0.4	0.02
Part II 24 hrs	Negative Control (CMC 0.5%)	-	5F	0.8	0.06
			5M	0.7	0.00
	Positive Control (Cyclophosphamide)	20	5F	0.8	0.40
			5M	0.3	0.36
	CGP 33 101 (Rufinamide)	1250	5F	0.9	0.10
			5M	0.9	0.02
	CGP 33 101 (Rufinamide)	2500	5F	0.3	0.04
			5M	0.8	0.14
	CGP 33 101 (Rufinamide)	5000	5F	0.8	0.00
			5M	0.3	0.02

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D. CARCINOGENICITY

1. CGP 33101: 104-Week Oral Carcinogenicity Study in Mice (Report No.: T/P (US) 96005; conducted by Ciba-Geigy, Summit, NJ; completed 5/22/96; GLP)

- a. Methods

CGP 33101 (Lot #800889) was administered in the diet to CD-1 mice (60/sex/group) at daily doses of 0, 40, 120 or 400 mg/kg for 104 weeks. At initiation of dosing, animals were approximately 6 weeks of age. Clinical observations, body weight and food consumption determinations, and physical/auditory, palpable mass, and gross and microscopic pathology examinations were performed on all groups. Ophthalmology examinations were conducted on control and HD animals. TK analyses were performed on samples from 10 satellite animals/sex/group.

Dose selection was based on the results of the 13-week dietary study (Study no. 92-6060), where body weights were decreased at 600 mg/kg, food consumption was reduced at 200 mg/kg and higher, and liver toxicity was observed at 200 and 600 mg/kg.

- b. Results

- i. Non-neoplastic (**Figures IVD.1.1a and b; Tables IVD.1.1, 1.2, 1.3 and 1.5**)

Treatment-related effects consisted of increased survival (HD females); decreased body weight gain (HD; terminal BW 4% below C in M, 8% below C in F); increased ALT (all doses), alkaline phosphatase (MD & HD), and AST (HD); microscopic bone changes consisting of hyperostosis and myelofibrosis (MD & HD); microscopic hepatic changes, including leukocytic infiltration, hepatocellular hypertrophy, pigmented macrophages, and foci of cellular alterations (HD); and microscopic renal/urinary tract changes (primarily in males), consisting of hydronephrosis (MD & HD) and focal fibrosis, chronic nephropathy, and dilatation of the ureters and urinary bladder (HD). Systemic exposure to parent drug was lower in females than in males at the LD and MD, but there was no clear sex difference at the HD. The AUC at the HD was approximately 2400 $\mu\text{mol}\cdot\text{hr/L}$ (clinical exposure at MRHD = 1923 $\mu\text{mol}\cdot\text{h/L}$).

- ii. Neoplastic (**Table IVD.1.4**)

Increased incidences of osteomas (0/60, 0/60, 2/60, 3/60 in M, SS at MD and HD; 0/60, 2/60, 1/60, 6/60 in F, SS at HD) were seen at all doses. Incidences of hepatocellular adenomas (4/59, 5/59, 4/59, 13/58 in M, SS at HD; 0/59, 0/59, 1/57, 10/59 in F, SS at HD) and carcinomas (8/59, 7/59, 8/59, 14/58 in M, NS; 1/59, 0/59, 1/57, 4/59 in F, NS) were increased at the HD. The increase in the incidence of osteomas was considered to have resulted from the activation of a resident mouse retrovirus by fluoride produced during oxidative metabolism of CGP 33101. The increase in the incidence of liver tumors was considered related to hepatic microsomal enzyme induction.

c. Conclusion

Chronic oral administration of CGP 33101 to mice resulted in increased incidences of bone osteomas (SS at MD and HD) and liver hepatocellular adenomas (HD) and carcinomas (HD) in males and females. There was no clear no-effect dose for induction of osteomas. However, because a low incidence of osteomas was also observed in the control (1/70 males, 2/70 females) animals from another carcinogenicity study run concurrently in this facility with mice of same strain and source, the low incidences of osteoma in the LD and MD animals were not considered to be treatment-related by the sponsor. The no-effect dose for liver tumors was 120 mg/kg. The study appears valid.

Figure IVD.1.1a

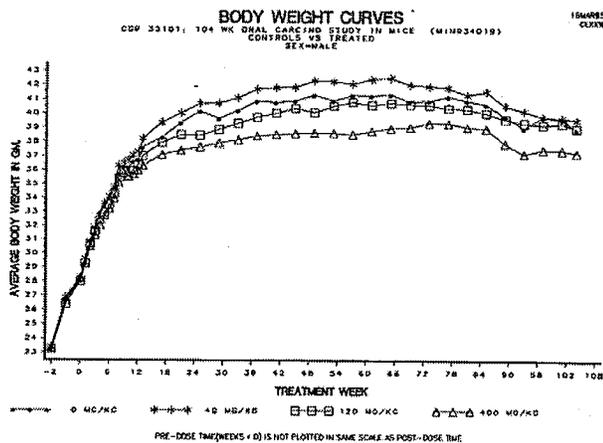


Figure IVD.1.1b

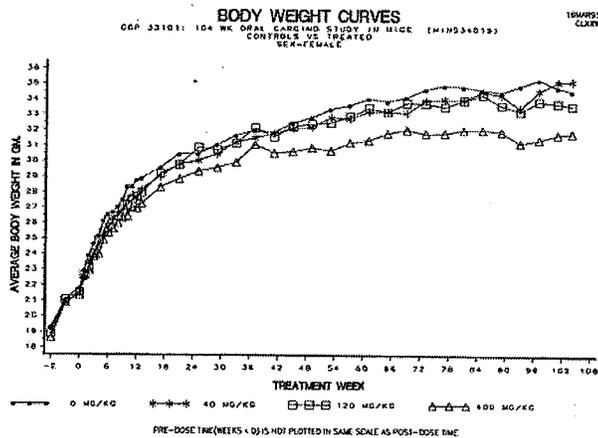


Table IVD.1.1

CGP 33101

104-week oral carcinogenicity study in mice

MIN 934019

Type of death	Summary of mortality								
	Sex:	Males				Females			
	Group no.: Dose (mg/kg): No. of mice:	1 0 60	2 40 60	3 120 60	4 400 60	1 0 60	2 40 60	3 120 60	4 400 60
Found dead		20	15	16	23	19	18	19	6
Sacrificed moribund		17	19	14	17	16	19	14	10
Other ^a		1	2	1	2	4	2	2	2
Terminal sacrifice		22	24	29	19	21	21	26	42
Percent survival at termination		36.7	40.0	48.3	30.0	35.0	35.0	43.9	70.0

^aIncludes missing animals subsequently found and sacrificed, and animals sacrificed due to physical abnormality.

Table IVD.1.2

CGP 33101

104-week oral carcinogenicity study in mice

MIN 934019

Group Dose (mg/kg)	Mean body weight change during the dosing period ^a					
	Males			Females		
	Body weight (g) Baseline	Body weight (g) Week 104	Percent change ^b	Body weight (g) Baseline	Body weight (g) Week 104	Percent change ^b
1 (0)	28.0	38.9	39.3	21.9	34.6	55.2
2 (40)	28.3	39.8	43.7 (3.7)	21.5	35.2	62.8 (7.0)
3 (120)	28.0	39.0	39.6 (0.9)	21.5	33.6	55.9 (-5.5)
4 (400)	28.2	37.3	36.3 (-16.6)	21.3	31.8**	48.3* (-18.0)

^aThese data were taken directly from the statistical printout for all surviving animals.

^bValues in parentheses represent:

Percent gain relative to control =

$$\frac{\text{weight gain of group} - \text{weight gain of control}}{\text{weight gain of control}} \times 100$$

*Statistically significant relative to the control group at p < 0.05.

**Statistically significant relative to the control group at p < 0.01.

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Table IVD.1.3

Table 3.2. Summary of compound-related lesions

Group:	Males				Females			
	1	2	3	4	1	2	3	4
Bone								
- osteoma	0	0	2	3	0	2	1	6
- hyperostosis (bone)	8	12	19	41	15	12	33	44
- hyperostosis (joint)	1	0	0	4	0	2	2	8
- hyperostosis (bone and/or joint)	8	12	19	43	15	14	33	44
- myelofibrosis	0	1	4	10	3	4	10	6
Liver								
- foci of cell alterations	0	0	0	3	1	0	0	2
- hepatocellular adenoma	4	5	5	13	0	0	1	10
- hepatocellular carcinoma	8	7	8	14	1	0	1	4
- hepatocellular hypertrophy	8	7	12	38	3	3	6	34
- pigmented macrophages	14	14	14	26	23	21	23	45
- leukocytic infiltration	17	20	16	12	18	20	24	28
Kidney								
- chronic nephropathy	7	3	6	16	17	8	6	12
- fibrosis	0	4	0	18	4	3	1	8
- hydronephrosis	6	10	16	25	4	2	1	4
Ureter								
- dilatation	1	3	1	7	0	0	0	0
Urinary bladder								
- dilatation	11	12	11	21	0	0	0	0

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Table IVD.1.4

US/09/56
PSS* (2.05)

SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

BODY SYSTEM ORGAN FINDING	DOSE GROUPS				TEST FOR TREND P-VALUE
	0 mg/kg	40 mg/kg	120 mg/kg	400 mg/kg	
DIGESTIVE SYSTEM					
ESOPHAGUS					
PAPILLOMA [B]	0/60 OBS/EXP:	1/60 3.92	0/60 0.00	0/60 0.00	0.766
GALL BLADDER ADENOMA [B]	0/47 OBS/EXP:	1/52 3.91	0/49 0.00	0/47 0.00	0.767
LIVER					
HEMANGIOMA [B]	0/59 OBS/EXP:	0/59 0.00	1/59 3.12	0/58 0.00	0.528
HEMANGIOSARCOMA [M]	2/59 OBS/EXP:	1/59 1.96	1/59 0.55	0/58 0.00	0.930
HEPATOCELLULAR ADENOMA [B]	4/59 OBS/EXP:	5/59 0.74	5/59 0.67	13/58 2.17**	0.004**
HEPATOCELLULAR CARCINOMA [M]	8/59 OBS/EXP:	7/59 0.75	8/59 0.73	14/58 1.77	0.054
PANCREAS					
ISLET CELL ADENOMA [B]	0/56 OBS/EXP:	0/60 0.00	0/57 0.00	1/59 4.64	0.216
SMALL INTESTINE					
ADENOCARCINOMA [M]	0/54 OBS/EXP:	1/57 3.83	0/54 0.00	0/50 0.00	0.761
MUSCULOSKELETAL SYSTEM					
BONE					
OSTEOMA [B]	0/60 OBS/EXP:	0/60 0.00	2/60 1.62*	3/60 2.35*	0.014*
OSTEOSARCOMA [M]	0/60 OBS/EXP:	0/60 0.00	1/60 3.11	0/60 0.00	0.532
NERVOUS SYSTEM					
BRAIN					
MENINGIOMA [M]	0/60 OBS/EXP:	0/60 0.00	1/60 3.53	0/60 0.00	0.506
REPRODUCTIVE SYSTEM					
TESTIS					
HEMANGIOMA [B]	0/60 OBS/EXP:	0/60 0.00	0/59 0.00	1/60 4.95	0.202
INTERSTITIAL-CELL TUMOR [M]	1/60 OBS/EXP:	0/60 2.14	0/59 0.00	1/60 2.47	0.617
SEMINOMA [M]	1/60 OBS/EXP:	0/60 1.42	2/59 2.16	0/60 0.00	0.690
RESPIRATORY SYSTEM					
LUNG					
ADENOCARCINOMA [M]	6/60 OBS/EXP:	6/60 0.67	10/60 1.22	5/60 0.97	0.359
ADENOMA [B]	6/60 OBS/EXP:	10/60 1.65	6/60 0.93	2/60 0.36	0.935
COMBINATIONS					
BONE					
OSTEOMA OR OSTEOSARCOMA	0/60 OBS/EXP:	0/60 0.00	3/60 1.95*	3/60 2.01*	0.014*
HARDERIAN GLAND					
ADENOMA OR ADENOCARCINOMA	9/60 OBS/EXP:	4/60 0.75	5/60 0.86	3/60 0.63	0.959
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	12/59 OBS/EXP:	12/59 0.75	13/59 0.71	27/58 1.95**	0.001**
LUNG					
ADENOMA OR ADENOCARCINOMA	12/60 OBS/EXP:	16/60 1.25	16/60 1.09	8/60 0.67	0.801

NOTE: THE P-VALUES ON THE REPORT ARE ROUNDED TO THREE DECIMALS. A * OR ** INDICATES A STATISTICAL SIGNIFICANCE AT THE 0.05 OR 0.01 LEVEL, RESPECTIVELY. WHEN RECORDED BESIDE A GROUP OBS/EXP THIS REFLECTS THE COMPARISON WITH CONTROLS.

Table IVD.1.4 (cont.)

SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
FEMALES

PG# (2.05)

BODY SYSTEM ORGAN FINDING	DOSE GROUPS				TEST FOR TREND P-VALUE
	0 mg/kg	40 mg/kg	120 mg/kg	400 mg/kg	
DIGESTIVE SYSTEM					
LARGE INTESTINE					
POLYP [B]	0/55	0/56	1/55	0/50	
	OBS/EXP:	0.00	3.86	0.00	0.553
LIVER					
HEMANGIOMA [B]	0/59	0/59	1/57	1/59	
	OBS/EXP:	0.00	2.12	1.31	0.326
HEMANGIOSARCOMA [N]	1/59	2/59	2/57	0/59	
	OBS/EXP:	0.87	1.87	1.65	0.823
HEPATOCELLULAR ADENOMA [B]	0/59	0/59	1/57	10/59	
	OBS/EXP:	0.00	0.00	0.38	2.38**
HEPATOCELLULAR CARCINOMA [M]	1/59	0/59	1/57	4/59	
	OBS/EXP:	0.77	0.00	0.70	1.96
SARCOMA [M]	0/59	0/59	0/57	1/59	
	OBS/EXP:	0.00	0.00	0.00	2.62
PANCREAS					
ISLET CELL ADENOMA [B]	1/59	0/56	0/56	0/59	
	OBS/EXP:	4.79	0.00	0.00	1.000
ISLET CELL CARCINOMA [M]	0/59	0/56	1/56	0/59	
	OBS/EXP:	0.00	0.00	4.23	0.00
STOMACH					
PAPILLOMA [B]	0/57	1/59	0/57	0/57	
	OBS/EXP:	0.00	4.91	0.00	0.80
MUSCULOSKELETAL SYSTEM					
BONE					
CHONDROMA [B]	0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.18	0.00
NERVE SHEATH TUMOR, BENIGN [B]	0/60	0/60	0/60	1/60	
	OBS/EXP:	0.00	0.00	0.00	3.74
OSTEOMA [B]	0/60	2/60	1/60	6/60	
	OBS/EXP:	0.00	0.39	0.45	2.27*
JOINT					
OSTEOMA [B]	0/60	0/60	1/60	0/60	
	OBS/EXP:	0.00	0.00	4.00	0.00
SKELETAL MUSCLE					
HEMANGIOSARCOMA [M]	0/60	0/60	1/59	0/60	
	OBS/EXP:	0.00	0.00	3.76	0.00
RHABDOMYOSARCOMA [M]	1/60	0/60	0/59	0/60	
	OBS/EXP:	4.61	0.00	0.00	0.00
COMBINATIONS					
ADRENAL GLAND					
PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	0/59	1/59	2/59	1/60	
	OBS/EXP:	0.00	2.34	1.36	0.52
ADRENAL GLAND					
ADENOMA OR ADENOCARCINOMA	2/57	2/59	6/59	5/60	
	OBS/EXP:	0.57	0.57	1.59	1.19
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	1/59	0/59	2/57	14/59	
	OBS/EXP:	0.29	0.00	0.50	2.27**

NOTE: THE P-VALUES ON THE REPORT ARE ROUNDED TO THREE DECIMALS. A * OR ** INDICATES A STATISTICAL SIGNIFICANCE AT THE 0.05 OR 0.01 LEVEL, RESPECTIVELY. WHEN RECORDED BESIDE A GROUP OBS/EXP THIS REFLECTS THE COMPARISON WITH CONTROLS.

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Table IVD.1.5 Plasma rufinamide levels in 2-year mouse carcinogenicity study

Dose (mg/kg)	Week	Time (h)	Male mice				Female mice				
			Mean conc. (µmol/L)	SD (µmol/L)	CV (%)	N	Mean conc. (µmol/L)	SD (µmol/L)	CV (%)	N	
40	26	1	12.8	3.4	27	5	10.1	4.7	47	5	
		11	4.50	3.23	72	5	*				
	52	1	15.0	4.8	32	5	9.11	8.28	91	5	
		11	8.29	4.13	66	5	4.67	7.02	150	5	
	78	1	12.5	9.0	24	5	6.58	3.53	54	5	
		11	2.35	2.47	105	5	1.43	1.68	117	5	
	104	1	17.1	2.3	14	4	8.62	8.32	97	4	
		11	6.08	4.12	68	5	*				
	120	26	1	36.7	12.1	33	5	29.7	7.6	26	5
			11	16.4	6.8	41	5	*			
52		1	47.3	9.7	20	5	30.5	14.7	48	5	
		11	22.0	7.7	35	5	6.44	6.14	95	5	
78		1	51.7	18.5	26	5	23.9	9.5	40	5	
		11	16.6	9.9	59	5	4.28	3.65	85	4	
104		1	50.9			2	29.6	5.4	18	4	
		11	29.9	1.4	5	3	*				
400		26	1	157	42	27	5	115	21	18	5
			11	59.2	22.2	38	5	58.2	25.3	44	5
	52	1	120	12	10	5	92.4	25.7	28	5	
		11	64.4	14.4	22	5	45.1	33.9	75	5	
	78	1	112	19	17	5	122	28	23	5	
		11	68.9	45.8	67	5	69.1	63.8	92	5	
	104	1	75.3	39.9	53	4	117	49	42	5	
		11	67.2			2	124	53	43	4	

Values below LOQ (1.05 µmol/L) taken as 0.

To convert into µg/mL, multiply the concentration values by 0.2382.

CV (%) = (SD/mean) x 100.

*: Not determined because half of the concentrations at least were below LOQ.

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2. CGP 33101: 104-Week Oral Carcinogenicity Study in Rats (Report No.: T/P (US) 95035, Test No.: 92-6046; conducted by Ciba-Geigy, Summit, NJ; issued 9/21/95; GLP)

a. Methods

CGP 33101 (Lot #800289) was administered in the diet to S-D rats (60/sex/group) at daily doses of 0, 20, 60 or 200 mg/kg for 97 (males) or 103 (females) weeks (sponsor says 98 and 104 weeks). Due to low survival in control males, all remaining males were sacrificed during week 98. Surviving females were sacrificed as scheduled during week 104. Clinical observations, body weight and food consumption determinations, and physical/auditory and palpable mass examinations were performed on all animals. Ophthalmology examinations were conducted on control and HD animals. Hematology and serum biochemistry evaluations were conducted on the first 10 surviving rats/sex/group. TK analyses were performed on plasma samples from the first 5 surviving rats/sex/group. Gross and microscopic pathology examinations were conducted on animals from all groups.

Dose selection was based primarily on body weight effects in the 13-week dietary study (Study No. 92100) with doses of 200, 400, and 600 mg/kg, where BW gains were decreased 31, 49, and 51% in males and 25, 28, and 32% in females compared to C. In the 1-year dietary toxicity study (20, 60 or 200 mg/kg), terminal BWs were 0.3, 4, and 24% below C in M and 2, 11, 28% below C in F at the respective doses.

b. Results

i. Non-neoplastic (**Figures IVD.2.1a and b; Tables IVD.2.1, 2, and 4**)

Treatment-related effects consisted of decreased body weight (MD & HD; terminal BWs 10 & 29% below C in M, 21 & 37% below C in F) and food consumption (MD and HD); decreased mortality (MD & HD); microscopic hepatic changes, including centrilobular hepatocellular hypertrophy, and accumulation of pigmented macrophages, apoptosis and megalocytosis (MD & HD); microscopic renal alterations consisting of pelvic epithelial hyperplasia (all doses; attributed to chronic irritation secondary to renal pelvic mineralization); and microscopic changes thought to be secondary to the decreased body weight or associated stress, including decreased bone marrow cellularity, thymic atrophy and ovarian stromal hyperplasia (all doses). Plasma rufinamide concentrations were generally somewhat lower in females. Based the data from the 13-week study, AUCs at the HD were approximately 3000 (F) and 4000 (M) $\mu\text{mol}\cdot\text{hr}/\text{L}$ (human exposure at MRD = 1923 $\mu\text{mol}\cdot\text{h}/\text{L}$).

ii. Neoplastic (**Table IVD.2.3**)

Increased incidences of thyroid follicular (0/59, 1/60, 10/60, 4/60, SS at MD and HD) and C-cell adenomas (1/59, 3/60, 6/60, 2/60, NS) were found in males. The incidence of thyroid C-cell carcinoma was also increased slightly in MD males (1/59, 1/60, 3/60, 0/60, NS). These tumors were considered a result of long-term TSH stimulation (CGP 33101 previously shown to increase the activity of thyroxine UDP-glucuronyl transferase in the rat). There were also possible small increases (NS) in liver hepatocellular adenomas in MD males (3/59, 2/60, 7/60, 4/60) and HD females (2/60, 1/60, 1/60, 5/60), and pituitary adenomas (34/59,

34/59, 43/60, 38/60) and carcinomas (0, 0, 2, 1) in MD and HD males. In addition, osteosarcoma was found in 1 HD male. Because of the excessive BW effect at the HD in both sexes (and even the MD in F), the MD should probably be considered the relevant group for comparison to C.

c. Conclusions

Chronic oral administration of CGP 33101 to rats produced an increase in the incidences of thyroid follicular adenomas and C-cell adenomas/carcinomas in males. The LD appeared to be a no-effect dose for follicular adenomas. Although the increase in C-cell adenomas was NS, there was not a clear no-effect dose. There was also a possible increase (NS) in liver hepatocellular adenomas in MD males and HD females (seen in mice). The MD was considered the MTD based on decreases in body weight gain noted in both sexes by the end of the study. However, based on the shortened duration and excessive BW effects, the validity of the study is questionable (see statistical review). Based on the results of the 3-month oral gavage study in rats (60, 200, 600 mg/kg), it appears that higher doses could have been given by that route without producing comparable BW effects. At the end of treatment in that study, BW gain was 2, 5 and 17% below C in M and 9, 12 and 30% below C in F, at the respective doses. BWs were 2, 5 and 11% lower in M and 5, 7 and 15% lower in F, respectively.

Figure IVD.2.1a

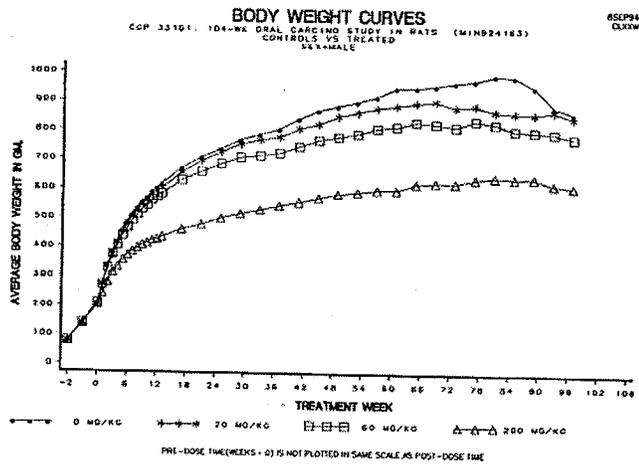


Figure IVD.2.1b

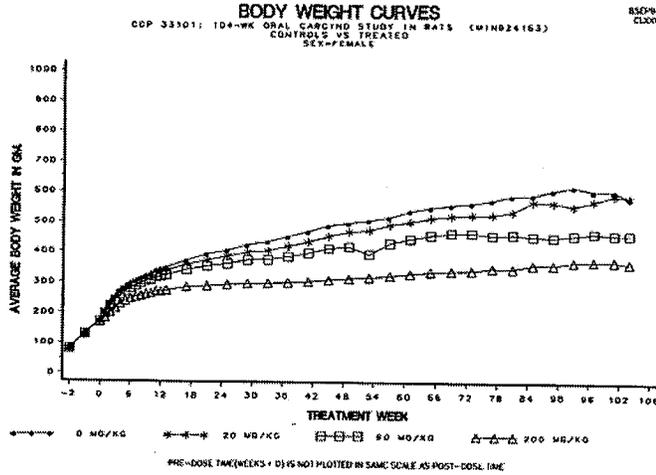


Table IVD.2.1

ODP 33101: 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS (MIN 924163)

Summary of mortality

Sex:	Males				Females				
	Group No.:	1	2	3	4	1	2	3	4
Dose (mg/kg):	0	20	60	200	0	20	60	200	
No. of Rats:	60	60	60	60	60	60	60	60	
Type of Death									
Found dead	27	21	12	17	21	12	11	17	
Sacrificed moribund	19	16	22	11	18	28	21	16	
Other*	1	0	0	0	1	0	1	2	
Terminal sacrifice (week 99-males) (week 105-females)	13	23	26	32	20	20	27	25	
Percent survival at termination	21.7	38.3	43.3	53.3	33.3	33.3	45.0	41.7	

*Includes mechanical trauma, deaths attributable to the blood collection process and animals sacrificed at the discretion of the Study Director.

Table IVD.2.2

OPF 33101: 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS (NTP 926163)

Mean body weight change during the dosing period^a

Group Dose (ng/kg)	Males			Females		
	Body Weight (g) Baseline	Week 97	Percent Change ^b	Body Weight (g) Baseline	Week 104	Percent Change ^b
1 (0)	206.5	863.7	319.2 (0.0)	170.2	583.4	232.8 (0.0)
2 (20)	205.8	847.1	310.5 (-2.4)	170.0	584.1	244.8 (0.2)
3 (60)	207.7	776.0	276.7 (-13.2)	168.9	459.2**	177.6** (-29.7)
4 (200)	203.6	613.5**	205.5** (-37.6)	170.3	366.0**	112.7** (-52.6)

a = These data were taken directly from the statistical printout for all surviving animals.

b = Values in parentheses represent:

Percent change relative to control =

$$\frac{\text{weight gain of group} - \text{weight gain of control}}{\text{weight gain of control}} \times 100$$

**Statistically significant relative to the control group at p < 0.01.

Table IVD.2.3

SUMMARY OF FINDING INCIDENCES AND STATISTICAL ANALYSIS
NEOPLASTIC HISTOPATHOLOGY
MALES

PSS* (2.05)

BODY SYSTEM ORGAN FINDING	DOSE GROUPS				TEST FOR TREND P-VALUE
	0 mg/kg	20 mg/kg	60 mg/kg	200 mg/kg	
DIGESTIVE SYSTEM					
LIVER					
HEMANGIOMA (B)	0/59 OBS/EXP: 0.00	1/60 3.96	0/60 0.00	0/60 0.00	0.752
HEPATOCELLULAR ADENOMA (B)	3/59 OBS/EXP: 1.10	2/60 0.57	7/60 1.56	4/60 0.76	0.523
HEPATOCELLULAR CARCINOMA (M)	4/59 OBS/EXP: 2.19	2/60 0.98	3/60 1.22	0/60 0.00	0.985
ENDOCRINE SYSTEM (continued)					
ADRENAL GLAND (continued)					
PHEOCHROMOCYTOMA (B)	8/59 OBS/EXP: 2.05	4/60 0.88	3/60 0.54	5/60 0.82	0.974
PHEOCHROMOCYTOMA (M)	2/59 OBS/EXP: 4.22	0/60 0.00	0/60 0.00	1/60 0.99	0.934
PARATHYROID					
ADENOMA (B)	1/52 OBS/EXP: 0.58	5/56 2.37	2/57 0.79	1/55 0.38	0.839
PITUITARY					
ADENOMA (B), pars distalis	34/59 OBS/EXP: 1.08	34/59 0.96	43/60 1.14	38/60 0.86	0.806
CARCINOMA (M), pars distalis	0/59 OBS/EXP: 0.00	0/59 0.00	2/60 2.40	1/60 1.07	0.245
THYROID					
C-CELL ADENOMA (B)	1/59 OBS/EXP: 0.37	2/60 1.03	6/60 1.90	2/60 0.62	0.282
C-CELL CARCINOMA (M)	1/59 OBS/EXP: 1.18	1/60 0.91	3/60 2.13	0/60 0.00	0.785
FOLLICULAR ADENOCARCINOMA (M)	0/59 OBS/EXP: 0.00	1/60 4.13	0/60 0.00	0/60 0.00	0.863
FOLLICULAR ADENOMA (B)	0/59 OBS/EXP: 0.00	1/60 0.29	10/60 2.43*	4/60 0.89*	0.025*

HEMATOPOIETIC-LYMPHORETICULAR SYSTEM					
LYMPH NODE					
HEMANGIOSARCOMA (M)	0/59	0/60	0/60	1/60	
	OBS/EXP: 0.00	0.00	0.00	2.00	0.347
SPLEEN					
HEMANGIOSARCOMA (M)	0/59	1/60	0/60	0/60	
	OBS/EXP: 0.00	4.84	0.00	0.00	0.018
LIPOSARCOMA (M)	1/59	0/60	0/60	0/60	
	OBS/EXP: 7.31	0.00	0.00	0.00	1.000
SYSTEMIC					
GRANULOCYTTIC LEUKEMIA (M)	1/60	0/60	0/60	0/60	
	OBS/EXP: 4.00	0.00	0.00	0.00	1.000
HISTIOCYTTIC SARCOMA (M)	2/60	1/60	1/60	0/60	
	OBS/EXP: 2.35	1.07	0.93	0.00	0.948
LYMPHOMA, MALIGNANT (M)	0/60	0/60	2/60	2/60	
	OBS/EXP: 0.00	0.00	1.00	1.00	0.076
THYMUS					
THYMOMA (B)	0/57	1/55	0/55	0/55	
	OBS/EXP: 0.00	4.00	0.00	0.00	0.750
INTEGUMENTARY SYSTEM					
MAMMARY GLAND					
ADENOCARCINOMA (M)	0/53	0/53	0/55	1/58	
	OBS/EXP: 0.00	0.00	0.00	2.66	0.376
COMBINATIONS (continued)					
BRAIN					
GRANULAR CELL TUMOR, BENIGN OR MALIGNANT	0/59	3/60	1/60	0/60	
	OBS/EXP: 0.00	3.14	0.92	0.00	0.864
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	6/59	4/60	10/60	4/60	
	OBS/EXP: 1.38	0.75	1.49	0.53	0.872
MAMMARY GLAND					
FIBROADENOMA, OR ADENOCARCINOMA	2/53	0/53	1/55	1/58	
	OBS/EXP: 2.56	0.00	0.94	0.75	0.859
PANCREAS					
ISLET CELL ADENOMA OR CARCINOMA	3/59	8/60	1/60	2/60	
	OBS/EXP: 0.96	2.39	0.27	0.52	0.943
PITUITARY					
ADENOMA OR CARCINOMA	34/59	34/59	45/60	39/60	
	OBS/EXP: 1.05	0.94	1.18	0.86	0.737
SKIN					
FIBROMA OR FIBROSARCOMA	2/59	2/60	2/60	0/60	
	OBS/EXP: 1.38	1.03	1.05	0.00	0.939
PAPILLOMA, KERATOACANTHOMA OR SQUAMOUS CELL CARCINOMA					
	4/59	1/60	0/60	4/60	
	OBS/EXP: 2.06	0.46	0.00	1.64	0.664
THYROID					
C-CELL ADENOMA OR CARCINOMA	2/59	4/60	9/60	2/60	
	OBS/EXP: 0.54	1.00	1.97	0.42	0.439
FOLLICULAR ADENOMA OR ADENOCARCINOMA	0/59	2/60	10/60	4/60	
	OBS/EXP: 0.00	0.55	2.27*	0.83*	0.042*
TOTAL BODY					
HEMANGIOMA OR HEMANGIOSARCOMA	0/59	2/60	1/60	1/60	
	OBS/EXP: 0.00	2.17	0.92	0.84	0.396
HEMANGIOSARCOMA	0/59	1/60	1/60	1/60	
	OBS/EXP: 0.00	1.49	1.20	1.07	0.323
NERVE SHEATH TUMOR, BENIGN	0/59	1/60	0/60	1/60	
	OBS/EXP: 0.00	2.02	0.00	1.67	0.468
NERVE SHEATH TUMOR, BENIGN OR MALIGNANT	0/59	1/60	0/60	2/60	
	OBS/EXP: 0.00	1.40	0.00	2.12	0.251

NOTE: THE P-VALUES ON THE REPORT ARE ROUNDED TO THREE DECIMALS. * OR ** INDICATES A STATISTICAL SIGNIFICANCE AT THE 0.05 OR 0.01 LEVEL, RESPECTIVELY. WHEN RECORDED BESIDE A GROUP OBS/EXP THIS REFLECTS THE COMPARISON WITH CONTROLS.

Table IVD.2.3 (cont.)

BODY SYSTEM ORGAN FINDING	DOSE GROUPS				TEST FOR TREND P-VALUE
	0 mg/kg	20 mg/kg	60 mg/kg	200 mg/kg	
DIGESTIVE SYSTEM					
LIVER					
HEMANGIOMA [B]	0/60	0/60	0/60	1/60	0.279
OBS/EXP:	0.00	0.00	0.00	3.58	
HEPATOCELLULAR ADENOMA [B]	2/60	1/60	1/60	5/60	0.137
OBS/EXP:	0.97	0.50	0.41	1.97	
HEPATOCELLULAR CARCINOMA [M]	1/60	0/60	1/60	1/60	0.406
OBS/EXP:	1.35	0.00	1.32	1.31	
PANCREAS					
ISLET CELL ADENOMA [B]	1/60	0/60	2/60	0/60	0.452
OBS/EXP:	1.44	0.40	2.52	0.00	
ISLET CELL CARCINOMA [M]	1/60	1/60	0/60	0/60	0.910
OBS/EXP:	2.10	2.10	0.00	0.00	
SMALL INTESTINE					
LEIOMYOSARCOMA [M]	0/60	0/60	0/60	2/60	0.040*
OBS/EXP:	0.00	0.00	0.00	3.50*	
ENDOCRINE SYSTEM					
ADRENAL GLAND					
CORTICAL ADENOMA [B]	2/60	2/60	1/60	0/59	0.924
OBS/EXP:	1.61	1.61	0.79	0.00	
CORTICAL CARCINOMA [M]	0/60	1/60	0/60	1/59	0.313
OBS/EXP:	0.00	2.31	0.00	1.75	
PHEOCHROMOCYTOMA [B]					
PHEOCHROMOCYTOMA [B]	1/60	1/60	2/60	0/59	0.763
OBS/EXP:	1.14	1.20	1.77	0.00	
PHEOCHROMOCYTOMA [M]	0/60	0/60	0/60	1/59	0.304
OBS/EXP:	0.00	0.00	0.00	3.29	
PARATHYROID					
ADENOMA [B]	1/58	0/57	2/56	1/53	0.363
OBS/EXP:	1.05	0.00	1.86	0.95	
PITUITARY					
ADENOMA [B], pars distalis	49/60	47/60	52/60	50/60	0.831
OBS/EXP:	1.08	0.93	1.01	0.93	
CARCINOMA [M], pars distalis	1/60	2/60	1/60	3/60	0.270
OBS/EXP:	0.63	1.28	0.53	1.54	
THYROID					
C-CELL ADENOMA [B]	4/60	4/60	3/60	4/60	0.593
OBS/EXP:	1.10	1.10	0.78	1.03	
C-CELL CARCINOMA [M]	1/60	0/60	0/60	0/60	1.000
OBS/EXP:	4.37	0.00	0.00	0.00	
FOLLICULAR ADENOMA [B]	1/60	0/60	1/60	2/60	0.329
OBS/EXP:	1.15	0.00	0.85	1.84	
GANGLIONEUROMA [B]	1/60	0/60	0/60	0/60	1.000
OBS/EXP:	4.60	0.00	0.00	0.00	
COMBINATIONS					
ADRENAL GLAND					
CORTICAL ADENOMA [B] OR CARCINOMA [M]	2/60	3/60	1/60	1/59	0.828
OBS/EXP:	1.18	1.77	0.56	0.55	
PHEOCHROMOCYTOMA, BENIGN OR MALIGNANT	1/60	1/60	2/60	1/59	0.518
OBS/EXP:	0.89	0.93	1.46	0.70	
BRAIN					
ASTROCYTOMA OR OLIGODENDROGLIOMA	0/60	1/60	0/60	1/60	0.426
OBS/EXP:	0.00	2.18	0.00	1.83	
LIVER					
HEPATOCELLULAR ADENOMA OR CARCINOMA	3/60	1/60	2/60	6/60	0.139
OBS/EXP:	1.08	0.36	0.63	1.83	
MAMMARY GLAND					
ADENOCARCINOMA OR CARCINOSARCOMA	7/60	20/60	15/60	15/60	0.228
OBS/EXP:	0.50	1.58	1.01	0.97	
ADENOMA OR FIBROADENOMA	37/60	28/60	30/60	20/60	1.000
OBS/EXP:	1.60	1.17	0.95	0.55	
ADENOMA, FIBROADENOMA, ADENOCARCINOMA OR CARCINOSARCOMA	39/60	38/60	37/60	26/60	1.000
OBS/EXP:	1.33	1.31	0.98	0.59	

OVARY						
GONADAL STROMAL TUMOR [B] OR SERTOLI-CELL TUMOR [B]	OBS/EXP:	0/60 0.00	1/60 2.30	1/59 1.70	0/60 0.00	0.685
GONADAL STROMAL, SERTOLI-CELL, THECAL CELL, OR YOLK SAC TUMOR	OBS/EXP:	0/60 0.00	1/60 1.49	2/59 2.41	0/60 0.00	0.568
PANCREAS						
ISLET CELL ADENOMA OR CARCINOMA	OBS/EXP:	2/60 1.71	1/60 0.86	2/60 1.53	0/60 0.00	0.876
PITUITARY						
ADENOMA OR CARCINOMA	OBS/EXP:	50/60 1.08	49/60 0.99	53/60 1.60	53/60 0.95	0.790
SKIN						
FIBROMA OR FIBROSARCOMA	OBS/EXP:	2/60 1.23	2/60 1.27	2/60 1.09	1/60 0.51	0.765
THYROID						
C-CELL ADENOMA OR CARCINOMA	OBS/EXP:	5/60 1.28	4/60 1.02	3/60 0.74	4/60 0.97	0.711
TOTAL BODY						
HEMANGIOMA	OBS/EXP:	1/60 1.32	0/60 0.00	1/60 1.34	1/60 1.22	0.434

NOTE: THE P-VALUES ON THE REPORT ARE ROUNDED TO THREE DECIMALS. A * OR ** INDICATES A STATISTICAL SIGNIFICANCE AT THE 0.05 OR 0.01 LEVEL, RESPECTIVELY. WHEN RECORDED BESIDE A GROUP OBS/EXP THIS REFLECTS THE COMPARISON WITH CONTROLS.

Table IVD.2.4 Plasma rufinamide levels in 2-year rat carcinogenicity study (n = 5)

Dose (mg/kg)	Week	Time (h)	Male rats			Female rats		
			Mean conc. (µmol/L)	SD (µmol/L)	CV (%)	Mean conc. (µmol/L)	SD (µmol/L)	CV (%)
20	12	1	29.6	3.8	13	20.7	3.9	19
		11	21.1	3.4	16	11.3	1.8	16
		25	25.6	2.2	9	18.8	4.3	23
	52	1	48.2	4.0	8	35.8	9.0	25
		11	35.5	6.1	17	22.3	5.1	23
		25	40.0	4.3	11	24.0	6.6	28
76	1	55.7	6.0	11	33.7	15.2	45	
	11	40.1	10.5	26	23.8	12.9	54	
	25	47.7	6.4	13	27.5	13.5	49	
60	12	1	92.1	7.9	9	72.2	18.2	25
		11	66.8	2.7	4	42.4	8.1	19
		25	81.1	8.3	10	62.6	15.0	24
	52	1	134	7	5	101	21	21
		11	100	10	10	73.6	27.4	37
		25	109	13	12	78.1	17.2	22
76	1	145	49	34	137	28	20	
	11	98.9	32.2	33	86.9*	35.0	40	
	25	114	35	31	97.6*	23.7	24	
200	12	1	160	16	10	191	21	11
		11	131	19	15	137	40	29
		25	170	13	8	173	28	16
	52	1	219	16	7	221	60	27
		11	184	9	5	152	56	37
		25	224	12	5	202	80	40
76	1	250	15	6	271	26	10	
	11	219	17	8	219	33	15	
	25	239	22	9	208	92	44	

*: n = 4.

E. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

1. CGP 33101: A Fertility and Reproductive Toxicity (Segment I) Study in Rats (MIN 911018) (Report 92057, dated 12/7/92, conducted by Ciba-Geigy, Summit, NJ; GLP)

a. Methods

Rufinamide was administered by oral gavage at doses of 0, 15, 50, or 150 mg/kg to male (12/group) and female (24/group) rats. Males were treated for 64 days prior to mating, during the 2-week mating period, and for approximately 3 weeks thereafter. Females were treated for 15 days prior to mating and during mating (2:1 ratio for 2 weeks), gestation, and lactation. Pregnant females were sacrificed either on gestational day 13 (12/group) or postnatal day 21 (12/group). F0 fertility and reproductive parameters were evaluated. F1 observations included: body weight, mortality, clinical signs, ophthalmological examinations, postnatal developmental parameters (righting reflex, pinna detachment, ear canal opening, eyes open, Preyer's reflex, papillary reflex both direct and indirect, testes descent, vaginal opening), and fertility assessment.

Doses were based on the 3-month oral gavage toxicity study in rats (Tif:RAIf) with doses of 60, 200 or 600 mg/kg, in which clinical signs (hypotonia, convulsions, decreased activity) were seen at the MD or greater and decreased BW gain was seen at all doses (BW gain was 2, 5 and 17% below C in M and 9, 12 and 30% below C in F at the respective doses). In the rat (Tif:RAIf) Seg II study (20, 100 or 300 mg/kg) decreased maternal BW gain was seen at all doses (14, 33, and 54% below C during dosing period).

Strain: Sprague-Dawley
Drug lot: Lot No. 800189

b. Results

i. Mortality and Clinical Observations

There were no mortalities in F0 males or females. Treatment-related clinical signs were limited to salivation at the HD in males.

ii. Body Weight

Body weight was decreased slightly in HD males on days 28 (7% below C, SS) and 84 (6%, NS) of dosing. In females, body weight was reduced slightly in the MD and HD groups at the end of the premating period (6 and 7%, respectively, both SS) and in the HD group at the end of gestation (7% on GD20, SS). However, there were no effects on corrected body weight (body weight minus the total weight of the uterus, ovaries, placenta and embryos) or body weight gain.

iii. F0 fertility and reproductive parameters

The percentage of mated females that were pregnant on either GD 13 or 21 was decreased at the HD and possibly the MD compared to C (83.3, 91.7, 79.2, and 70.8 in C, LD, MD, and HD, respectively; C lower than expected). There were no effects on reproductive parameters in females sacrificed on GD 13 (but only 8-10 pregnant females evaluated per group). Increases in postimplantation loss and stillbirths and decreased numbers of viable pups were seen at all doses (SS at HD) in females treated through

lactation (Table IVE.1.1). There were no differences among groups in duration of gestation.

iv. Litter parameters

Reductions in pup survival during postnatal days 0 to 4 were observed at the MD and HD. The percentages of pups surviving during the postculling periods, PNDs 4 to 21 and 4 to 35, were also decreased, primarily due to effects (SS) in females (Table IVE.1.2).

There were no clinical signs in the F1. There were no apparent effects on the developmental parameters evaluated (but small Ns). Decreases in pup body weights were seen in treated pups (Table IVE.1.3). There was no clear effect on F1 fertility, but % pregnant was reduced slightly in the HD group (11/11, 13/13, 9/9, and 8/9).

v. Necropsy

There were no effects on F0 male testes weights. The observation of a mammary tumor in 1 HD dam (No. 3389) was considered incidental.

3. Conclusions

Treatment of male and female rats with rufinamide (15, 50 or 150 mg/kg) prior to and during mating, gestation, and lactation resulted in decreased fertility (HD), increased postimplantation loss and stillbirth (MD and HD), and decreased pup survival (MD and HD) and growth (all doses). Dose selection was appropriate based on the level of parental toxicity. However, the number of animals used (12/group) is below the number currently specified in the ICH guidelines, which also recommend 1:1 mating.

Table IVE.1.1

7.16. Summary of the reproductive parameters derived from full-term parental females
(Mean ± Standard Deviation)

Parameter	Dose Level (mg/kg/day)			
	Control (0)	15	50	150
No. pregnant full-term females	11	13	9	9
No. implants	16.00 ± 4.34	17.08 ± 2.87	16.89 ± 1.90	15.89 ± 2.26
No. viable neonates	15.36 ± 4.11	16.00 ± 2.94	16.00 ± 1.50	14.22 ± 2.64
No. stillbirths	0.00 ± 0.00	0.15 ± 0.38	0.22 ± 0.67	0.44 ± 0.88
% Stillbirths	0.00 ± 0.00	1.03 ± 2.52	1.11 ± 3.33	2.87 ± 5.70
Postimplantation loss	0.64 ± 0.67	1.08 ± 0.95	0.89 ± 1.05	1.67 ± 1.00*
% Postimplantation loss	3.62 ± 3.92	6.34 ± 5.88	5.00 ± 5.68	10.80 ± 6.68*

*Statistically different from controls at $p \leq 0.05$. See Appendix 8.19.

Table IV.E.1.2

7.19. Summary of F₁ generation: survival and sex ratios^a

Parameter	Dose Level (mg/kg/day)			
	Control (0)	15	50	150
Number of viable litters	11	13	9	9
Mean litter size (day 0 lactation)	15.4	16.0	16.0	14.2
Number of viable males (day 0)	92	112	71	62
Number of viable females (day 0)	77	96	73	66
Sex ratio day 0 lactation (% males)	54.4	53.9	49.3	48.4
<u>Survival Indices Sexes Pooled:</u>				
Mean % pups surviving days 0-4 (precull)	97.1	100.0	94.5	93.7**
Mean % pups surviving days 4-21 (postcull)	100.0	99.0	98.6	95.8
Mean % pups surviving days 4-35 (postcull)	100.0	99.0	98.6	95.8

7.19. Summary of F₁ generation: survival and sex ratios^a (cont.)

Parameter	Dose Level (mg/kg/day)			
	Control (0)	15	50	150
<u>Survival Indices by Sex:</u>				
Mean % males surviving Days 0-4 (precull)	100.0	100.0	95.9*	93.9**
Mean % males surviving Days 4-21 (postcull)	100.0	98.1	100.0	97.2
Mean % males surviving (days 4-35 (postcull)	100.0	98.1	100.0	97.2
Mean % females surviving Days 0-4 (precull)	96.1	100.0	92.4	93.7*
Mean % females surviving Days 4-21 (postcull)	100.0	100.0	97.2	94.4*
Mean % females surviving Days 4-35 (postcull)	100.0	100.0	97.2	94.4*

Table IVE.1.3

7.21. Summary of F₁ generation: male body weight (grams)^a
(Mean ± Standard Error)

Postnatal Days	Dose Level (mg/kg/day)			
	Control (0)	15	50	150
0	6.50 ± 0.12 (11) ^b	6.31 ± 0.11 (13)	6.29 ± 0.13 (9)	6.47 ± 0.13 (9)
4 (Preacting)	10.40 ± 0.39 (11)	9.87 ± 0.35 (13)	10.04 ± 0.42 (9)	9.85 ± 0.42 (9)
4 (Postculling)	10.38 ± 0.39 (11)	9.92 ± 0.35 (13)	10.08 ± 0.42 (9)	9.84 ± 0.42 (9)
7	17.30 ± 0.52 (11)	16.51 ± 0.47 (13)	16.64 ± 0.56 (9)	15.98 ± 0.56 (9)
14	36.10 ± 0.84 (11)	33.55 ± 0.76*	33.74 ± 0.91 (9)	31.61 ± 0.91**
21	59.52 ± 1.49 (11)	55.83 ± 1.35 (13)	56.36 ± 1.62 (9)	56.87 ± 1.62 (9)
28	100.94 ± 2.09 (11)	96.10 ± 1.88 (13)	94.36 ± 2.26 (9)	95.87 ± 2.26 (9)
35	163.29 ± 3.37 (11)	160.46 ± 3.04 (13)	161.37 ± 3.65 (9)	157.46 ± 3.65 (9)

^aValues for the means and standard errors were derived from the Healy analysis. See Appendix 8.19.

^bNumber in parentheses () equals number of litters used in mean.

*Statistically different from control at $p \leq 0.05$.

**Statistically different from control at $p \leq 0.01$

7.22. Summary of F₁ generation: female body weight (grams)^a
(Mean ± Standard Error)

Postnatal Days	Dose Level (mg/kg/day)			
	Control (0)	15	50	150
0	6.19 ± 0.12 (11) ^b	5.99 ± 0.11 (13)	5.95 ± 0.13 (9)	6.19 ± 0.13 (9)
4 (Preacting)	10.10 ± 0.40 (11)	9.33 ± 0.36 (13)	9.53 ± 0.43 (9)	9.60 ± 0.44 (9)
4 (Postculling)	10.17 ± 0.41 (11)	9.40 ± 0.37 (13)	9.44 ± 0.45 (9)	9.63 ± 0.45 (9)
7	16.94 ± 0.51 (11)	15.47 ± 0.47 (13)	15.66 ± 0.56 (9)	15.60 ± 0.56 (9)
14	35.11 ± 0.70 (11)	32.21 ± 0.64**	31.90 ± 0.76**	31.50 ± 0.78**
21	57.56 ± 1.27 (11)	53.60 ± 1.16 (13)	54.13 ± 1.38 (9)	55.06 ± 1.41 (9)
28	93.59 ± 1.72 (11)	87.67 ± 1.57*	86.17 ± 1.88**	91.61 ± 1.92 (9)
35	143.32 ± 2.34 (11)	135.14 ± 2.13 (13)	138.49 ± 2.55 (9)	141.76 ± 2.61 (9)

^aValues for the means and standard errors were derived from the Healy analysis. See Appendix 8.19.

^bNumber in parentheses () equals number of litters used in mean.

*Statistically different from control at $p \leq 0.05$.

**Statistically different from control at $p \leq 0.01$

2. Developmental Toxicity (Teratogenicity) Study With CGP 33 101 In Rats (Test No. 876147, report dated 8/30/89, conducted by Ciba-Geigy, Switzerland; GLP)

a. Methods

Female rats (24/group) received oral (gavage) doses of 0, 20, 100 and 300 mg/kg on gestation days 6 through 15. Females were sacrificed on GD 21 and reproductive parameters were recorded (corpora lutea, uterine weight, live and dead fetuses, early and late resorptions, abortions, etc). Fetuses were examined for sex, external gross findings, body weight, and visceral (1/2, Wilson's) or skeletal (1/2) abnormalities.

Strain: Tif: RAI f(SPF), hybrids of RII/1 x RII/2
Batch no: LOS 800187

b. Results

i. Effects on the dam

There were no significant clinical signs. Body weight gain was dose-dependently decreased (14, 33, and 54% compared to C during dosing period) in treated groups (**Table IVE.2.1**). Gravid uterine weights were decreased at the HD compared to C (99.6 vs 110.4 g) There were no effects on reproductive parameters and no gross pathological findings in dams.

ii. Fetal evaluations

Fetal weights were decreased somewhat at the MD and HD (7 and 11% below C; combined M & F means: 5.5, 5.4, 5.1, and 4.9 g, in respective groups).

There were no apparent treatment-related differences in external or visceral abnormalities or skeletal malformations. However, incidences of fetal skeletal anomalies were increased at the MD and HD and skeletal variations were increased at all doses (**Table IVE.2.2**). (A classification scheme that included malformations, anomalies, and variations was defined.)

Irregular ossification of occipital bones (classified as an anomaly) was noted in 2 MD and 1 HD litters. Four of 6 affected MD fetuses were from the same litter (dam no. 69). This female was shown to have markedly decreased body weight between GD 7 and 11 compared to other animals in the same dose group (sponsor's effort to link effect to maternal toxicity). The incidence of asymmetrically shaped sternebra 5 (anomaly) was increased in the MD and HD groups; numbers of affected fetuses were 5 (4 litters) and 11 fetuses (7 litters). Four of the affected fetuses in the HD group were from litter no. 92. This dam showed markedly reduced body weight between days GD 8 and 11.

Overall incidences of skeletal anomalies (fetal/litter) were 4.3/27%, 4.7/22%, 12/46%, and 12/43%, respectively.

Incidences of several skeletal variants were dose-dependently increased at all doses; these included reduced ossification of digits and shortened rib 13. The skeletal anomalies and variants were considered consistent with fetal growth retardation.

c. Conclusions

Administration of rufinamide (0, 20, 100, or 300 mg/kg) to pregnant rats during organogenesis (GDs 6-15) resulted in decreased fetal weights and increased incidences of skeletal anomalies at the MD and HD and increased skeletal variations at all doses. These doses were also maternally toxic.

Table IVE.2.1

TABLE 3 : MEAN MATERNAL BODY-WEIGHT CHANGE DURING GESTATION - GRAMS

	GROUP GROUP NAME DOSE LEVEL	GROUP 1 CONTROL 0 MG/KG	GROUP 2 LOW DOSE 20 MG/KG	GROUP 3 INTERMED. DOSE 100 MG/KG	GROUP 4 HIGH DOSE 300 MG/KG
DAYS 0 TO 6	MEAN	30.3	27.3	32.3	31.0
	S.D.	5.5	5.4	6.5	6.8
	N	22	23	24	23
DAYS 6 TO 11	MEAN	29.0	25.2	16.1b	1.4b
	S.D.	6.1	3.9	6.7	15.2
	N	22	23	24	23
DAYS 11 TO 16	MEAN	42.0	35.8	30.7b	31.1b
	S.D.	5.9	9.7	10.5	14.2
	N	22	23	24	23
DAYS 16 TO 21	MEAN	72.7	71.2	71.0	71.6
	S.D.	10.2	9.0	10.4	12.4
	N	22	23	24	23
DAYS 6 TO 16	MEAN	71.0	61.0a	45.1b	32.5b
	S.D.	10.2	10.8	11.5	15.4
	N	22	23	24	23
DAYS 0 TO 21	MEAN	174.0	159.5a	150.1b	135.1b
	S.D.	15.5	16.3	20.9	22.2
	N	22	23	24	23

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

Table IVE.2.2

Daily Dose (mg/kg)	0 (Control)	20	100	300
Dams/Dose	24	24	24	24
Diaphragmatic hernia				
No. Fetus (%)	1 (0.0)	0	0	0
No. Litters (%)	1 (4.5)	0	0	0
Renal pelvic dilatation				
No. Fetus (%)	0	0	0	1 (0.6)
No. Litters (%)	0	0	0	1 (4.3)
Skeletal Malformation:				
No. Fetuses evaluated	161	170	190	174
Reduced nasal bone				
No. Fetus (%)	0	0	1 (0.5)	0
No. Litters (%)	0	0	1 (4.2)	0
Skeletal Anomalies ^b :				
Irregular ossification occipital bone				
No. Fetus (%)	0	0	6* (3.2)	1 (0.6)
No. Litters (%)	0	0	2 (8.3)	1 (4.3)
Total skeletal anomalies				
No. Fetus (%)	7 (4.3)	8 (4.7)	22* (12)	21* (12)
No. Litters (%)	6 (2.7)	5 (2.2)	11 (4.6)	10 (4.3)
Skeletal Variations ^a :				
Metatarsal 1 - absent ossification				
No. Fetus (%)	3 (1.9)	7 (4.1)	49** (26)	56** (32)
No. Litters (%)	3 (1.4)	5 (2.2)	15** (63)	18** (78)
Bipartite cervical vertebral centers				
No. Fetus (%)	21 (13)	22 (13)	10* (5.3)	2** (1.1)
No. Litters (%)	12 (5.5)	14 (6.1)	6 (2.5)	2** (8.7)

Shortened rib 13				
No. Fetus (%)	9 (5.6)	17 (10)	41** (22)	57** (33)
No. Litters (%)	5 (23)	9 (39)	13* (54)	15** (65)
Anterior digit 2 – proximal phalanx: absent ossification				
No. Fetus (%)	2 (1.2)	1 (0.6)	23** (12)	26** (15)
No. Litters (%)	2 (9.1)	1 (4.3)	7 (29)	11** (48)
Anterior digit 4 – proximal phalanx: absent ossification				
No. Fetus (%)	0	0	4 (2.1)	7* (4.0)
No. Litters (%)	0	0	2 (8.3)	5* (22)
Anterior digit 5 – proximal phalanx: absent ossification				
No. Fetus (%)	3 (1.9)	5 (2.9)	34** (18)	47** (27)
No. Litters (%)	3 (14)	4 (17)	10 (42)	16** (70)
Anterior digit 5 – proximal phalanx: poor ossification				
No. Fetus (%)	2 (1.2)	4 (2.4)	9 (4.7)	10* (5.7)
No. Litters (%)	1 (4.5)	3 (13)	7* (29)	7* (30)
Posterior digit 2 – proximal phalanx: absent ossification				
No. Fetus (%)	18 (11)	27 (16)	89** (47)	115** (66)
No. Litters (%)	10 (45)	13 (57)	20* (83)	21** (91)
Posterior digit 3 – proximal phalanx: absent ossification				
No. Fetus (%)	10 (5.2)	14 (8.2)	72** (38)	93** (53)
No. Litters (%)	7 (32)	8 (35)	16* (67)	20** (87)
Posterior digit 4 – proximal phalanx: absent ossification				
No. Fetus (%)	8 (5.0)	11 (7.6)	76** (40)	94** (54)
No. Litters (%)	8 (36)	9 (39)	18* (75)	20** (87)
Posterior digit 5 – proximal phalanx: absent ossification				
No. Fetus (%)	34 (21)	59** (35)	116** (61)	140** (80)
No. Litters (%)	17 (77)	20 (87)	21 (88)	23* (100)

G - Day of Gestation.

* - For controls, group means are shown. For treated groups, percent differences from controls are shown.

[‡] - Only significant results presented.

NP - not performed

Dunnnett's T test: * p < 0.05, ** p < 0.01. Statistical significance is based upon actual data (not percent differences).

Noteworthy findings: - None, + Mild, ++ Moderate, +++ Marked.

3. Developmental Toxicity (Teratogenicity) Study With CGP 33 101 In Rabbits (Study No.: 876148; report dated 8/30/89, conducted by Ciba-Geigy, Switzerland, GLP)

a. Methods

Mated females (20/treatment group) were given oral (gavage) doses of 0, 30, 200, or 700 mg/kg from gestation day 7 to 19. Animals were sacrificed on GD 29 and reproductive (corpora lutea, uterine weight, live and dead fetuses, early and late resorptions, abortions) and fetal parameters (sex, body weight, external, visceral, and skeletal anomalies/malformations/variations) were evaluated. A dose range-finding study in rabbits at doses of up to 600 mg/kg showed no maternal or developmental effects.

Strain: Chinchilla rabbit
Drug lot #: Batch No.: LOS 800187

b. Results

i. Maternal effects

There were no treatment-related clinical signs or deaths. Body weight gain was only transiently slightly reduced at the MD and HD during the first week of dosing (**Figure IVE.3.1**). One LD (no. 39) and 1 HD doe (no. 74) aborted on GDs 26 and 16, respectively, and were sacrificed. Three C (nos. 2, 4 and 15), 1 LD (no. 40), 2 MD (nos. 59 and 60), and 1 HD doe (no. 63) were not pregnant. One C (no. 12), 1 LD (no. 32), and 3 HD does (nos. 64, 77 and 80) showed total resorption. Thus, the numbers of females with live fetuses on GD 29 were 16, 17, 17 and 15, respectively. At necropsy there were no T-R macroscopic pathology findings.

ii. Developmental effects

Resorptions and postimplantation loss were increased at HD, and fetal weights were dose-dependently reduced (**Table IVE.3.1**).

There were no differences in external and visceral findings.

Skeletal malformations were increased slightly at the MD and HD (**Table IVE.3.2**): 1 control fetus (no. 6/01), 2 MD fetuses (nos. 50/07 and 54/03), and 2 HD fetuses (nos. 68/01 and 76/07) showed absent ossification of pubic bones; and 1 HD fetus (no. 73/09) had thoracic scoliosis.

The HD fetus (68/01) with absent ossification of pubic bones also a number of skeletal anomalies, mainly asymmetrically shaped and fused sternebrae. Fetus no. 68/02 (same litter) showed asymmetrically shaped sternebra 5. The HD fetus (73/09) with thoracic scoliosis showed fused, displaced and asymmetrically shaped thoracic vertebral centers, reduced thoracic vertebral arches, and shortened, displaced ribs. Three MD fetuses (nos. 43/03, 44/07 and 58/03) showed asymmetrically shaped sternebra 5. Thus total skeletal anomalies were increased slightly at the MD and HD (**Table IVE.3.3**).

Increases in skeletal variations were also seen at the MD and HD: absent or poor ossification of bones including metacarpal 1, caudal vertebral centers and some phalanges at the HD, and increased incidences of shortened 13th rib and absent ossification of the medial phalanx of anterior digit 5 at the MD and HD.

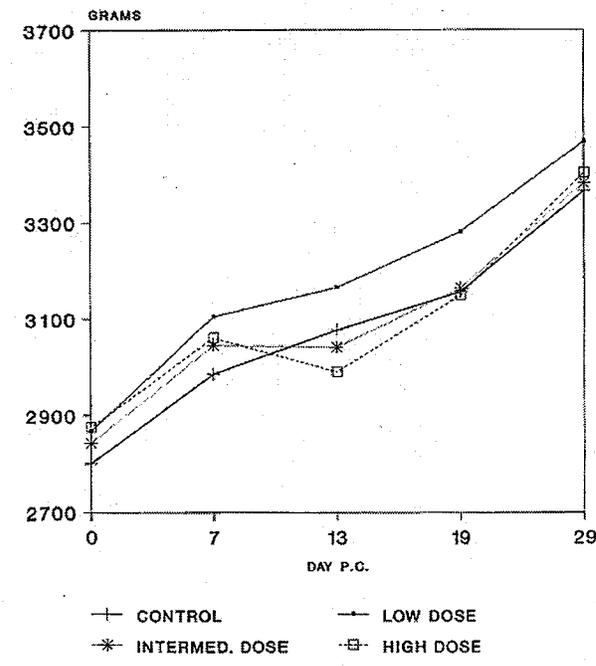
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c. Conclusions

Oral administration of rufinamide (0, 30, 200, or 700 mg/kg) to pregnant rabbits from GD 7 to 19 resulted in decreased fetal weights and increased incidences of skeletal abnormalities, including malformations, at the MD or greater. These doses produced only minimal maternal toxicity.

Figure IVE.3.1

FIGURE 1 : Mean maternal body weight during gestation



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Table IVE.3.1

TABLE 8 : SUMMARY OF CESAREAN SECTION DATA

GROUP	GROUP 1	GROUP 2	GROUP 3	GROUP 4
GROUP NAME	CONTROL	LOW DOSE	INTERMED. DOSE	HIGH DOSE
DOSE LEVEL	0 MG/KG	30 MG/KG	200 MG/KG	700 MG/KG
Pregnant, used for calculation	N 17	18	17	18
Resorptions: Early	N 8	6	7	26
No. per animal	MEAN 0.5	0.3	0.4	1.4
	S.D. 1.2	1.4	1.2	2.9
% of Impl. per group	% 4.5	4.5	5.6	14.5
% of Impl. per animal	MEAN 8.4	5.6	5.9	19.7
	S.D. 24.5	23.6	17.4	38.3
Resorptions: Late	N 2	2	4	10
No. per animal	MEAN 0.1	0.1	0.2	0.6
	S.D. 0.3	0.3	0.6	1.0
% of Impl. per group	% 1.6	1.5	3.2	6.3
% of Impl. per animal	MEAN 2.5	1.3	3.3	5.8
	S.D. 8.2	3.7	8.7	10.6
Resorptions: Total	N 10	8	11	36
No. per animal	MEAN 0.6	0.4	0.6	2.0
	S.D. 1.3	1.4	1.4	2.7
% of Impl. per group	% 8.1	6.0	8.7	22.8
% of Impl. per animal	MEAN 10.9	6.8	9.3	25.4
	S.D. 25.2	23.5	20.3	36.6
Postimplantation loss	N 10	8	11	36
No. per animal	MEAN 0.6	0.4	0.6	2.0
	S.D. 1.3	1.4	1.4	2.7
% of Impl. per group	% 8.1	6.0	8.7	22.8
% Impl. per animal	MEAN 11.6	6.8	9.3	25.4
	S.D. 25.8	23.5	20.3	36.6
Viable Male Fetuses	N 55	65	55	50
	% 48	52	48	41
Female Fetuses	N 59	60	60	72
	% 52	48	52	59
Fetal Body Weight (g)	MEAN 40.3	39.8	38.6	36.5
	S.D. 6.8	4.6	6.7	4.5
Male Fetuses	MEAN 40.9	40.4	38.8	35.7
	S.D. 7.1	5.0	6.3	5.8
Female Fetuses	MEAN 39.5	39.0	38.3	37.1
	S.D. 7.0	5.1	7.5	4.4

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

Table IVE.3.2

TABLE 13 : FETAL SKELETAL MALFORMATIONS

GROUP	GROUP 1	GROUP 2	GROUP 3	GROUP 4
GROUP NAME	CONTROL	LOW DOSE	INTERMED. DOSE	HIGH DOSE
DOSE LEVEL	0 MG/KG	30 MG/KG	200 MG/KG	700 MG/KG
Litters Evaluated	N 16	17	17	15
Fetuses Evaluated	N 114	125	115	122
PELVIC GIRDLE				
ABSENT OSSIFICATION PUBIS				
Fetal Incidence	N 1	0	2	2
	% 0.9	0.0	1.7	1.6
Litter Incidence	N 1	0	2	2
	% 6.3	0.0	12	13
MISCELLANEOUS				
THORACIC SCLYOSIS				
Fetal Incidence	N 0	0	0	1
	% 0.0	0.0	0.0	0.8
Litter Incidence	N 0	0	0	1
	% 0.0	0.0	0.0	6.7
TOTAL FETAL SKELETAL MALFORMATIONS				
Fetal Incidence	N 1	0	2	3
	% 0.9	0.0	1.7	2.5
Litter Incidence	N 1	0	2	3
	% 6.3	0.0	12	20

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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Table IVE.3.3

TABLE 36 : SUMMARY OF SKELETAL MALFORMATIONS, ANOMALIES, AND VARIATIONS

GROUP GROUP NAME DOSE LEVEL	GROUP 1 CONTROL 0 MG/KG	GROUP 2 LOW DOSE 30 MG/KG	GROUP 3 INTERMED. DOSE 200 MG/KG	GROUP 4 HIGH DOSE 700 MG/KG
Litters Evaluated	N 16	17	17	15
Fetuses Evaluated	N 114	125	115	122
Live	N 114	125	115	122
Dead	N 0	0	0	0
TOTAL MALFORMATIONS				
Fetal Incidence	N 1	0	2	3
	% 0.9	0.0	1.7	2.5
Litter Incidence	N 1	0	2	3
	% 6.3	0.0	12	20
Affected Fetuses/Litter	MEAN% 1.04	0.00	3.78	2.15
	S.D. 4.17	0.00	12.40	4.45
TOTAL ANOMALIES				
Fetal Incidence	N 2	0	3	3
	% 1.8	0.0	2.6	2.5
Litter Incidence	N 2	0	3	2
	% 13	0.0	18	13
Affected Fetuses/Litter	MEAN% 1.76	0.00	2.12	2.07
	S.D. 4.85	0.00	4.74	5.73
TOTAL VARIATIONS				
Fetal Incidence	N 114	125	115	121
	% 100	100	100	99
Litter Incidence	N 16	17	17	15
	% 100	100	100	100
Affected Fetuses/Litter	MEAN% 100.00	100.00	100.00	99.26
	S.D. 0.00	0.00	0.00	2.87

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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4. An Oral Pre- and Postnatal Development Study in Rats (Study No. 997078; report dated 4/6/00; conducted by Novartis, Summit, NJ; GLP)

a. Methods

Rufinamide was administered orally (gavage) to female rats (N=25/group) at doses of 0, 5, 30, or 150 mg/kg from GD 6 through PND 20. Females were observed for clinical signs, BW and food consumption during gestation and lactation. Following parturition, pups were counted, sexed and weighed, and surviving pups were culled into standard litter sizes on PND 21. All pups were observed for clinical signs and standard developmental parameters. Selected pups were selected for fertility and/or behavioral evaluations.

Doses were based on an earlier Segment III study in rats in which doses of 15, 50, or 150 mg/kg were given orally from GD 15 through PND 20 and pup survival during lactation days 0-4 was decreased at all doses. There were slight decreases in pup weights at the HD and decreases in maternal body weight gain at all doses (not D-R; 30% at HD during GD15-20). In a modified Segment III study in rats, pregnant rats were given 150 mg/kg from GD 15 through PND 20, and pups were cross-fostered. A treated group in which litters remained with the dams served as a positive control. Reduced pup survival and weights were observed in positive control pups and in pups from treated dams cross-fostered to vehicle-treated dams. There were also reduced number of live pups at parturition and increased post-implantation loss and stillbirth in the rufinamide-treated dams. The results of this study indicated an in utero effect.

Strain: Rat/Wistar Hannover, NI(GLX/BRL/HAN)IGS BR
Drug lot #: 800797

b(4)

b. Results

i. Effects on the dam

Mortality and clinical observations - There were no drug-related mortalities. Clinical signs were seen only at the HD and consisted of hunched posture, salivation, piloerection, and cool to touch.

Body weight and food consumptions - Statistically significant reductions in gestational body weight gain were seen at the HD only for the intervals GD 6 to 9 and 18 to 20 (Table IVE.4.1). On GD 20, mean BW was 8.5% below C at the HD. Post-partum body weight gain was similar among groups.

Parturition parameters - There were no clear effects on percent females pregnant, females surviving delivery, duration of gestation, or implantation sites per litter (Table IVE.4.2).

ii. Offspring evaluations

Survival - Increased numbers of pups found dead during PNDs 1 to 4 and decreases in the number surviving to PND 21 were seen at all doses (Table IVE.4.3). Increased stillbirth and litter loss were also seen at the HD. The LD effect was not considered treatment-related by the sponsor because it was due to the death of an entire litter (none of the pups had milk in their stomachs). The MD effect was small.

Body Weight - Pup weights were decreased at birth and throughout lactation at the MD and HD (**Table IVE.4.4**). This deficit persisted in HD offspring, particularly males (PND 91 BW 5% below C), but was eventually made up in females (PND 77 females not different).

Developmental Landmarks - No differences were noted for any of the morphological or functional parameters investigated (righting reflex, pinna detachment, eye opening, acoustic startle, pupillary reflex, vaginal opening, and preputial separation evaluated for the day on which at least 50% of pups in a litter reached criterion, the day on which 100% reached criterion, and/or the percent litters reaching 100% criterion).

Offspring Behavior - No clear treatment-related differences were seen in any of the behavioral tests administered (open field motor activity on days 56-58; passive avoidance and M-maze learning and memory on days 63 and 70 ± 2 days).

Offspring Reproductive Performance - There were no apparent differences in any of the fertility/reproductive performance parameters (mating, pregnancy rates, number of corpora lutea and implantation sites, resorptions, percent pre- or postimplantation loss, viable fetuses, fetal weights).

c. **Conclusions**

Oral administration of rufinamide (5, 30, or 150 mg/kg) to rats during gestation and lactation resulted in increased perinatal and early postnatal death and pre- and postnatal growth deficits (BW reductions) in the offspring. There was no clear no-effect dose for early death.

Table IVE.4.1

Summary of Gestation Body Weight Changes (PGBCGV)

DOSAGE		0	5	30	150
		KG/DAY	KG/DAY	KG/DAY	KG/DAY
DAYS 0 TO 3	MEAN	8	6	7	8
	S.D.	5	4	4	4
	N	24	25	23	23
DAYS 3 TO 6	MEAN	13	13	12	13
	S.D.	3	4	2	3
	N	24	25	23	23
DAYS 6 TO 9	MEAN	12	9**	9*	0**
	S.D.	5	3	4	5
	N	24	25	23	23
DAYS 9 TO 12	MEAN	15	15	15	14
	S.D.	4	4	4	5
	N	24	25	23	23
DAYS 12 TO 15	MEAN	13	14	14	10
	S.D.	4	6	7	9
	N	24	25	23	23
DAYS 15 TO 18	MEAN	16	25	24	23
	S.D.	5	6	9	14
	N	24	25	23	23
DAYS 18 TO 20	MEAN	23	19	21	16**
	S.D.	6	6	8	9
	N	24	25	23	23

Statistical key: * = p<0.05 ** = p<0.01

Table IVE.4.2

Summary of Litter Data [PLISU]					
DOSAGE		0 MG/ KG/DAY	5 MG/ KG/DAY	30 MG/ KG/DAY	150 MG/ KG/DAY
Females Mated	N	25	25	25	25
Females Pregnant	N	24	25	23	23
	%	96.0	100.0	92.0	92.0
Females Surviving Delivery	N	24	25	22	23
	%	100.0	100.0	88.7	100.0
Duration of Gestation	MEAN	21.8	21.8	21.7	22.0
	S.D.	0.4	0.5	0.5	0.5
with Stillborn Pups	N	1	1	0	2
	%	4.2	4.0	0.0	8.7
with all Stillborn/Uncertain	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
with one or more Liveborn	N	24	25	22	23
	%	100.0	100.0	100.0	100.0
with Entire Liveborn Litter Dying and/or Missing, Cannibalized, Culled					
days 0-4	N	0	1	0	2
	%	0.0	4.0	0.0	8.7
days 5-21	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
days 0-21	N	0	1	0	2
	%	0.0	4.0	0.0	13.0

Table IVE.4.3

Summary of Litter Data [PLISU]					
DOSAGE		0 MG/ KG/DAY	5 MG/ KG/DAY	30 MG/ KG/DAY	150 MG/ KG/DAY
Litters Delivered (total)	N	24	25	22	23
Pups Delivered (total)	N	232	217	215	218
	MEAN	9.7	8.7	9.8	9.5
	S.D.	2.4	2.9	2.3	2.9
Liveborn	N	231	216	215	214
Stillborn	N	1	1	0	4
	%	0.4	0.5	0.0	1.8
Uncertain	N	0	0	0	0
Culled day 21	N	0	0	0	0
Culled (total)	N	0	0	0	0
Cannibalized	N	0	0	0	0
Missing	N	0	4	5	10
Liveborn, not culled prior to day 21	N	231	216	215	214
Pups Dying, Missing, and/or Cannibalized					
day 0	N	0	0	0	3
	%	0.0	0.0	0.0	1.4
days 1-4	N	0	14**	3	17**
	%	0.0	6.5	1.4	7.9
days 5-7	N	0	2	1	0
	%	0.0	0.9	0.5	0.0
days 8-14	N	0	0	1	0
	%	0.0	0.0	0.5	0.0
days 15-21	N	0	0	0	2
	%	0.0	0.0	0.0	0.9
Pups Surviving 21 days	N	231	200**	210*	192**
	%	100.0	82.6	97.7	89.7
Implantation Sites per Litter	MEAN	248	242	232	231
	S.D.	10.3	9.7	10.5	10.0
		2.4	3.4	2.2	2.8

Statistical key: * = p<0.05 ** = p<0.01

Table IV.E.4.4

Summary of Litter Data [ELISU]

DOSAGE		0 MG/ KG/DAY	5 MG/ KG/DAY	30 MG/ KG/DAY	150 MG/ KG/DAY

Live Pups/Litter					
day 0	MEAN	9.6	8.6	9.8	9.3
	S.D.	2.4	2.9	2.3	3.1
day 4	MEAN	9.6	8.1	9.6	8.4
	S.D.	2.4	3.3	2.3	3.8
day 7	MEAN	9.6	8.0	9.6	8.4
	S.D.	2.4	3.2	2.3	3.8
day 14	MEAN	9.6	8.0	9.5	8.4
	S.D.	2.4	3.2	2.2	3.8
day 21 - Pre-culling	MEAN	9.6	8.0	9.5	8.3
	S.D.	2.4	3.2	2.2	3.9
day 21 - Post-culling	MEAN	9.6	8.0	9.5	8.3
	S.D.	2.4	3.2	2.2	3.9
Pup Weight/Litter (grams)					
day 3	MEAN	6.1	6.1	5.8	5.6**
	S.D.	0.5	0.5	0.4	0.7
day 4	MEAN	10.1	10.6	9.5	8.9**
	S.D.	1.3	1.4	1.1	1.1
day 7	MEAN	14.7	15.6	14.1	12.9**
	S.D.	1.8	2.3	1.8	1.9
day 14	MEAN	29.1	30.4	27.8	24.5**
	S.D.	3.3	4.6	3.3	5.1
day 21	MEAN	46.0	46.9	42.9	39.9**
	S.D.	5.4	6.6	5.5	5.9
day 21	MEAN	46.0	46.9	42.9	39.9**
	S.D.	5.4	6.6	5.5	5.9
Sex Ratio - Male Pups:Total Pups					
day 0	N	112	112	102	101
	%	48.5	51.9	47.4	47.2
day 21	N	112	108	101	94
	%	48.5	54.0	48.1	49.0

Statistical key: ** = p<0.01

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5. A 10-Week Oral (Gavage) Toxicity Study of RUF331 in Neonatal Albino Rats (Study no. 998010, report dated 9/30/99, conducted by _____, GLP)

b(4)

a. Methods

Rat pups (12 litters of 4 pups/sex per group) received rufinamide (Lot No. 800797) oral (gavage) doses of 0, 15, 50, or 150 mg/kg from PND 7 to 21. At weaning on PND 21, each treatment group was divided into 4 subgroups (A, B, C and D) consisting of 10 pups/sex for continued dosing for up to a total of 10 weeks. The subgroups were designated as follows:

Subgroup	Duration of Dosing	Investigations	Recovery Period	Number of animals	
				Males	Females
A	10 weeks	Body weight and food intake, ophthalmoscopy, laboratory investigations, toxicokinetic bleeds, necropsy at the end of dosing, histopathology	None	40	40
B	10 weeks	Body weight and food intake, behavioral testing, laboratory investigations, necropsy at the end of the recovery period, histopathology	~ 4 weeks	40	40
C	2 weeks	Body weight and food intake, behavioral testing, necropsy at the end of the recovery period	~ 10 weeks	40	40
D	2 weeks	Toxicokinetic bleeds, necropsy at the end of dosing	None	40	40

Observations included mortality, clinical observations, body weights and food consumption, reflex development (negative geotaxis, auditory startle, air righting; assessed daily until all pups in the litter had a positive response or up to PND 21), sexual maturation (vaginal opening, preputial separation), ophthalmology (subgroups A and B), functional observational battery (subgroups B and C), motor activity (subgroups B and C during Weeks 4, 7 and 10; subgroup B during the recovery period Week 12), auditory startle habituation (subgroups B and C once during Weeks 4, 7 and 10; subgroup B during the recovery period Week 12; 4-minute acclimation period and then the startle response measured in 50 identical trials at a sound level of 120 dBA with an 8-second intertrial interval), Cincinnati water maze (during weeks 10 and 11 for Subgroup C or weeks 12 and 13 for Subgroup B), clinical pathology (subgroups A and B), complete gross pathology (subgroup A, B, C and D on completion of the treatment/recovery period), and microscopic examination of selected tissues (subgroup A and B at the end of the treatment and recovery periods). Dose selection was based on findings in a range-finding study (0, 20, 60, 200, and 600 mg/kg) in which mortality was increased at the HD (although not clearly T-R) and BW gain reductions were seen at ≥ 200 mg/kg (primarily during the early pre-weaning phase).

Strain: Sprague-Dawley CD-1 [CD(SD)IGS BR]
 Drug Lot #: 800797

b(4)

b. Results

i. Mortality, clinical signs, and body weight

Although several pups in the control and treated groups died, these were not considered drug-related. Clinical signs were limited to decreased activity for the first few days of dosing at the HD. Pup body weights were significantly decreased in the HD group (16% on PND 21; Table IVE.5.1). Reflex development was unaffected by treatment. Postweaning, no mortality or overt clinical signs were observed, but body weights and food consumption were reduced somewhat at the HD (Wk 11 BWs 9 and 13% below C in

Subgroup A males and females). Sexual maturation was not clearly affected, although preputial separation appeared to be delayed very slightly at the HD (NS; **Table IVE.5.2**). No ocular changes were observed that were considered related to treatment.

ii. Clinical pathology

Hematology - In subgroup A, MPV was significantly reduced in MD and HD females. In subgroup B, WBCs were significantly reduced in HD males and HD females showed a significant decrease in RBCs. These differences were not considered to be toxicologically significant.

Clinical chemistry - In subgroup A, BUN was significantly increased in HD females.

Urinalysis - There were no clear differences among groups.

ii. Pathology

Organ weights and Macroscopic - At the end of treatment, brain weights were dose-dependently decreased in males and females (**Table IVE.5.3-6**). Following fixation, whole brain and regional (cerebrum) weights were significantly reduced in MD and HD males and females. Thymus weights (abs and rel) tended to be decreased but not as consistently. Absolute but not relative kidney weights were significantly reduced in HD females. Liver and spleen weights were significantly increased. No gross pathological findings attributed to treatment were observed.

Microscopic - Histopathologically, centrilobular hepatocellular hypertrophy was noted in HD males after 10 weeks of treatment (**Table IVE.5.7**). At this time there was also an increased incidence of cytoplasmic vacuolation in the pituitary in MD and HD males. The liver hypertrophy was not seen after the 4 week recovery period, but the pituitary changes were still present at a lower severity.

d. Behavioral evaluation

Motor activity - In subgroup C at week 10, HD females showed a significant decrease in total activity counts (**Table IVE.5.8**). However, there were no apparent differences among treatment groups in subgroup B at week 12.

Auditory startle habituation - In subgroup B, HD females showed significant increases in maximum startle amplitude at week 4, but there were no clear or consistent changes in startle at week 12. In subgroup C, maximum startle was significantly increased in HD males at week 4, maximum and average startle were significantly increased in HD females at week 10, and HD males showed a significant decrease in time to maximum startle at week 10.

Cincinnati maze - In subgroup B, there were no significant differences between the control and treated groups on paths A or B. In subgroup C, the number of errors to swim path B on trial 5 was significantly increased in HD males.

e. Toxicokinetics

The toxicokinetics results are shown in **Table IVE.5.9**. Both AUC and Cmax values increased in a less than dose proportional manner. No clear sex differences were observed. AUCs after 2 and 10 weeks of treatment were somewhat lower than exposures after a single dose.

c. Conclusions

Oral gavage administration of rufinamide (15, 50, or 150 mg/kg) to young rats for 10 weeks starting on PND 7 resulted in clinical signs (decreased activity) and decreased pup body weights pre- and postweaning at the HD. There were no T-R deaths and no clearly T-R neurobehavioral changes. It should be noted, however, that group sizes (N=10/sex/grp) were small for neurobehavioral testing. Terminal evaluations indicated D-R reductions in brain weights (whole and regional; SS at MD and HD; terminal and recovery) and histopathological findings in the liver (HD) and pituitary (MD and HD). The liver and pituitary findings were also seen in adults at similar exposures; thus, there was no apparent age-related difference in sensitivity. Based on these results, the LD was considered to be a no-effect level.

Table IVE.5.1

TABLE NO. 1.3	GROUP LITTER MEAN (S.D.) PUP BODY WEIGHTS (G)						PROJECT NO :96488
	TOTAL - PHASE I - PREWEANING						
	DAY POST PARTUM						
	DAY 4	DAY 7	DAY 11	DAY 14	DAY 17	DAY 21	
GROUP 1 - VEHICLE CONTROL	10.3 1.04	16.3 1.78	26.9 2.64	35.9 3.11	44.5 4.18	57.9 4.53	
GROUP 2 - PUF331 15 mg/kg/day	10.7 1.36	17.1 2.09	27.4 3.04	35.3 3.91	42.7 4.89	55.5 8.09	
GROUP 3 - PUF331 50 mg/kg/day	10.7 .99	17.0 1.52	26.9 2.56	34.6 3.48	41.6 3.84	54.1 4.74	
GROUP 4 - PUF331 150 mg/kg/day	9.8 1.20	15.8 1.84	24.6 2.63	31.8 * 3.14	39.1 ** 3.85	48.7 ** 5.23	

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

Table IVE.5.2

TABLE NO. 1.11	GROUP MEAN (S.D.) PREPUDIUM SEPARATION PHASE I - SUBGROUP B	PROJECT NO :96488
	DAY OF DEVELOPMENT	
GROUP 1 - VEHICLE CONTROL	42.6 1.35	
GROUP 2 - RUF331 15 mg/kg/day	43.2 1.32	
GROUP 3 - RUF331 50 mg/kg/day	42.9 1.10	
GROUP 4 - RUF331 150 mg/kg/day	44.1 2.02	

Table IVE.5.3a

TABLE NO. 3.3	GROUP MEAN (S.D.) RELATIVE ORGAN WEIGHTS (G%) (RELATIVE TO BRAIN WEIGHT)	PROJECT NO :96488		
	PHASE I - SUBGROUP A WEEK 11 - MALES			
	BRAIN WEIGHT (G)	LIVER	SPLLEN	HEART
GROUP 1 - VEHICLE CONTROL	2.189 .0459	590.660 48.5078	40.168 3.5279	67.952 8.7338
GROUP 2 - RUF331 15 mg/kg/day	2.123 .0572	571.427 53.7517	40.333 5.8257	65.732 7.2297
GROUP 3 - RUF331 50 mg/kg/day	2.044 ** .1053	616.231 49.1021	39.446 4.8824	65.445 5.1647
GROUP 4 - RUF331 150 mg/kg/day	2.099 * .0757	604.921 51.6297	35.708 7.3990	62.969 4.5300

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

	GONADS	PROS- TATE	PITU- ITARY	THYMUS
GROUP 1 - VEHICLE CONTROL	158.923 27.5943	42.432 7.3187	.583 .0681	31.306 6.0843
GROUP 2 - RUF331 15 mg/kg/day	155.477 9.0415	46.140 6.7356	.575 .0742	27.345 3.3824
GROUP 3 - RUF331 50 mg/kg/day	177.218 18.6752	48.730 5.8569	.605 .0827	23.348 ** 4.9398
GROUP 4 - RUF331 150 mg/kg/day	186.695 * 26.4013	48.403 11.0186	.547 .0477	22.836 ** 3.2737

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

Table IVE.5.3b

TABLE NO. 3.3		GROUP MEAN (S.D.) RELATIVE ORGAN WEIGHTS (G%) (RELATIVE TO BRAIN WEIGHT)			PROJECT NO :96488
PHASE I - SUBGROUP A WEEK 11 - FEMALES					
	BRAIN WEIGHT (G)	LIVER	SPLEEN	HEART	
GROUP 1 - VEHICLE CONTROL	1.977 .0551	356.541 45.7788	26.419 3.3302	47.190 5.2093	
GROUP 2 - RUF331 15 mg/kg/day	1.962 .1128	355.625 38.3842	27.891 4.1346	47.298 5.6090	
GROUP 3 - RUF331 50 mg/kg/day	1.883 .1006	359.585 46.4721	28.470 4.6907	46.763 6.9924	
GROUP 4 - RUF331 150 mg/kg/day	1.863 * .0744	368.054 47.5705	28.820 3.3446	46.593 5.3476	

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 (DUNNETT'S)

Table IVE.5.4a

TABLE NO. 3.3		GROUP MEAN (S.D.) RELATIVE ORGAN WEIGHTS (G%) (RELATIVE TO BRAIN WEIGHT)			PROJECT NO 196488
PHASE I - SUBGROUP B WEEK 15 - MALES					
	BRAIN WEIGHT (G)	LIVER	SPLEEN	HEART	
GROUP 1 - VEHICLE CONTROL	2.259 .0825	643.788 120.1677	42.252 6.7293	77.766 8.0093	
GROUP 2 - RUF331 15 mg/kg/day	2.203 .0903	583.805 41.4034	42.191 6.8055	75.759 8.0514	
GROUP 3 - RUF331 50 mg/kg/day	2.147 * .1239	620.896 75.1738	42.418 4.8022	76.047 5.7537	
GROUP 4 - RUF331 150 mg/kg/day	2.099 ** .0887	611.972 50.6071	41.447 4.9743	79.656 11.1699	

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

Table IVE.5.4b

TABLE NO.3.3		GROUP MEAN (S.D.) RELATIVE ORGAN WEIGHTS (G%) (RELATIVE TO BRAIN WEIGHT)			PROJECT NO :96488
PHASE I - SUBGROUP B WEEK 15 - FEMALES					
	BRAIN WEIGHT (G)	LIVER	SPLEEN	HEART	
GROUP 1 - VEHICLE CONTROL	2.070 .0747	344.179 42.0257	27.077 1.5645	52.414 6.0494	
GROUP 2 - RUF331 15 mg/kg/day	2.035 .1020	353.092 26.8200	27.834 3.3250	52.481 5.6449	
GROUP 3 - RUF331 50 mg/kg/day	1.983 .1165	363.200 36.7307	29.026 1.4589	53.399 6.8395	
GROUP 4 - RUF331 150 mg/kg/day	1.928 ** .0646	360.479 36.4494	30.881 * 3.6497	53.711 5.9259	

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

Table IVE.5.5a

TABLE NO.3.4		GROUP MEAN (S.D.) TERMINAL BODY WEIGHTS AND BRAIN WEIGHTS (G)				PROJECT NO :96488
PHASE I - SUBGROUP A WEEK 11 - MALES						
	TERMINAL BODY WEIGHT (G)	BRAIN WEIGHT	CEREBELLUM	CEREBRUM	MEDULLA AND PONS	
GROUP 1 - VEHICLE CONTROL	430.2 25.55	2.458 .0780	.342 .0239	1.803 .0516	.263 .0135	
GROUP 2 - RUF331 15 mg/kg/day	416.3 43.88	2.398 .0803	.343 .0184	1.741 .0595	.257 .0228	
GROUP 3 - RUF331 50 mg/kg/day	415.7 43.92	2.289 ** .1484	.337 .0222	1.678 ** .0968	.241 .0295	
GROUP 4 - RUF331 150 mg/kg/day	391.2 32.77	2.348 * .0618	.341 .0174	1.720 * .0523	.248 .0109	

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)

Table IVE.5.5b

TABLE NO. 3.4		GROUP MEAN (S.D.) TERMINAL BODY WEIGHTS AND BRAIN WEIGHTS (G)			PROJECT NO :96488	
PHASE I - SUBGROUP A WEEK 11 - FEMALES						
	TERMINAL BODY WEIGHT (G)	BRAIN WEIGHT	CEREBELLUM	CEREBRUM	MEDULLA AND PONS	
GROUP 1 - VEHICLE CONTROL	248.4 22.03	2.254 .0489	.318 .0182	1.657 .0559	.239 .0166	
GROUP 2 - RUF331 15 mg/kg/day	243.6 29.13	2.223 .1228	.311 .0238	1.625 .0960	.232 .0123	
GROUP 3 - RUF331 50 mg/kg/day	230.6 23.59	2.120 * .1214	.296 .0261	1.562 * .0847	.227 .0205	
GROUP 4 - RUF331 150 mg/kg/day	215.4 * 25.48	2.109 ** .0779	.303 .0428	1.549 * .0759	.225 .0228	
SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)						

Table IVE.5.6a

TABLE NO. 3.4		GROUP MEAN (S.D.) TERMINAL BODY WEIGHTS AND BRAIN WEIGHTS (G)			PROJECT NO :96488	
PHASE I - SUBGROUP B WEEK 15 - MALES						
	TERMINAL BODY WEIGHT (G)	BRAIN WEIGHT	CEREBELLUM	CEREBRUM	MEDULLA AND PONS	
GROUP 1 - VEHICLE CONTROL	532.0 78.28	2.497 .0878	.355 .0164	1.825 .0611	.274 .0147	
GROUP 2 - RUF331 15 mg/kg/day	486.5 37.35	2.455 .1105	.346 .0238	1.793 .0856	.269 .0139	
GROUP 3 - RUF331 50 mg/kg/day	503.7 44.57	2.396 .1361	.341 .0365	1.730 * .0856	.267 .0255	
GROUP 4 - RUF331 150 mg/kg/day	479.5 41.62	2.372 .1064	.339 .0178	1.713 ** .0708	.255 .0239	
SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: * P<0.05 ** P<0.01 (DUNNETT'S)						

Table IVE.5.8

TABLE NO. 1.13

GROUP MEAN ACTIVITY COUNTS
PHASE I - SUBGROUP C : FEMALES
WEEK 10

PRO

INTERVAL NO.		GROUP 1 VEHICLE CONTROL	GROUP 2 RUF331 15 mg/kg/day	GROUP 3 RUF331 50 mg/kg/day	GROUP 4 RUF331 150 mg/kg/day
1	MEAN	156.5	150.7	132.4	140.4
	S.D.	25.6	32.7	27.6	17.9
	N	10	10	10	10
2	MEAN	114.7	93.5	86.3	98.0
	S.D.	32.2	30.2	32.3	26.3
	N	10	10	10	10
3	MEAN	86.0	66.5	59.1	52.2
	S.D.	28.3	38.4	32.5	38.0
	N	10	10	10	10
4	MEAN	70.0	36.5	42.6	32.3
	S.D.	41.1	37.0	34.6	24.7
	N	10	10	10	10
5	MEAN	65.0	26.2	46.3	25.5
	S.D.	43.0	27.0	25.9	26.0
	N	10	10	10	10
6	MEAN	48.9	24.6	30.9	12.7
	S.D.	33.4	21.1	24.3	14.1
	N	10	10	10	10
TOTAL	MEAN	541.1	398.0	397.6	361.1 +
	S.D.	168.4	163.0	129.8	100.7
	N	10	10	10	10

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: + P<0.05 (T-TEST), TOTAL

Table IVE.5.9

Table 7.1-9.: Mean (± SE) toxicokinetic parameters of RUF331 after oral (gavage) administration of RUF331 to neonatal rats (Study# 998010)

Dose (mg/kg)	Sex	Single dose			Week 2			Week 10		
		AUC ±SE (ng*hr/mL)	C _{max} (ng/mL)	t _{max} (h)	AUC ±SE (ng*hr/mL)	C _{max} (ng/mL)	t _{max} (h)	AUC (ng*hr/mL)	C _{max} (ng/mL)	t _{max} (h)
15	Male	234926 ±4184	12781	4	118387 ±14459	15182	2	153188 ±19319	11281	2
	Female	242850 ±952	12287	8	118804 ±22946	12520	2	138965 ±21441	13023	2
50	Male	533669 ±13142	25330	8	288785 ±11426	24882	4	452014 ±13475	30765	4
	Female	642603 ±15865	30834	8	362830 ±51436	34836	2	441771 ±5464	33861	4
150	Male	1025621 ±18825	48059	8	882839 ±25552	48297	4	811156 ±87515	44061	4
	Female	1112959 ±170572	65405	8	721872 ±41448	59328	4	952878 ±119135	53077	2

6. CGP 33101: 13-Week Oral (Capsule) Toxicity Study In Young Dogs (MIN 951058) (Report No.: T/P (US) 95004, dated 3/28/96, conducted by Ciba-Geigy, Summit, NJ, GLP)

a. Methods

Rufinamide (Lot #800889) was administered orally (capsule) to beagle dogs (3 or 6/sex/group) at doses of 0, 1, 5, or 200 mg/kg for 13 weeks. At the end of the dosing period, 3/sex from the control and HD groups were allowed a 4-week recovery period. At initiation of dosing, dogs were approximately 4 months of age. Endpoints included: clinical observations, body weight and food consumption, clinical pathology (hematology, clinical chemistry, and urinalysis), auditory and ophthalmoscopic examinations (weeks -2, 7, and 13), ECG evaluations (4-6 hr after dosing during weeks -1, 5, 9, 12, and 17), gross pathology and organ weights, and microscopic examinations (standard list of tissues/organs from all animals at the end of the dosing period and on liver and gross lesions from animals sacrificed after recovery period). Samples for TK analyses were collected from 3 dogs/sex/group. Dose selection was based on the results of a 2-week study in young dogs (0, 6, 200, and 600 mg/kg) in which yellow-brown pigment deposits in the liver were seen at all doses.

b. Results

i. Mortality and Clinical signs

There were no deaths. Treatment-related clinical signs were limited to vomiting and various fecal changes, found primarily at the HD. Feces with apparent compound, indicating incomplete absorption, were observed in all HD animals throughout the treatment period, and isolated occurrences were noted in both sexes at the LD and MD. Vomit with apparent compound was sporadically observed in the majority of HD animals.

ii. Body weight

There were no treatment-related changes in body weights.

iii. Electrocardiographic examinations

There were no EKG abnormalities considered T-R. Animal nos. 30 (MD female) and 32 (HD female) had what was called occasional second-degree A-V block during weeks 5 and 9, respectively, but these were considered incidental by the sponsor because of "the absence of a dose- and/or time-relationship or increase in incidence."

iv. Ophthalmology

Ophthalmoscopic examinations did not indicate any ocular changes attributable to treatment.

v. Clinical pathology

Increases in ALT were seen in HD animals during dosing, particularly in 1 male and 1 female (nos. 17 and 34) in which values were up 5X predose values (Table IVE.6.1). Transaminase activity remained elevated during the recovery period. Creatinine and BUN also tended to be increased (<2X) in HD dogs.

Hematology and urinalysis parameters were not clearly affected by treatment at all dose levels.

vi. Anatomic pathology Tables IVE.6.2-3

There were no treatment-related organ weight alterations or gross pathology findings.

Microscopic changes were seen in the livers of all HD animals, including those in the recovery group. These consisted primarily of pigment deposits of unknown composition (minimal to moderate) which, according to the pathology report, were found centrilobularly within hepatocytes or bile canaliculi, but were also present in midzonal regions. The pigment was described as medium to dark brown in color, partially birefringent under polarized light, and not staining for bile or iron. One male and 1 female (nos. 17 and 34, above) sacrificed after the recovery period also exhibited minimal amounts of a coarsely granular, dark brown pigment within the Kupffer cells that stained partially for lipofuscin. The majority of HD females, from both the terminal sacrifice and recovery groups, also exhibited what was described as a primarily neutrophilic focal infiltrate that either surrounded the intrahepatic bile ducts or was perivascular. Despite the clinical chemistry findings, there were no apparent microscopic changes in the kidney.

vii. Toxicokinetics Tables IVE.6.4-5

Plasma concentrations of rufinamide increased in a D-R but less than dose-proportional manner over the dose range studied. No significant differences in systemic exposure were observed between sexes following 2 weeks of treatment at the LD and MD. After 11 weeks of dosing, no differences were observed between sexes in the LD dose group, but systemic exposure appeared to be higher in females than in males at the MD. At the HD, non-steady-state plasma profiles were obtained, presumably due to dosing and/or absorption irregularities (unexplained, significance unclear); at both 2 and 11 weeks, concentrations before dosing were markedly higher than at 24 h post-dosing. Therefore, C_{max} and AUC values could not be accurately determined.

c. Conclusions

When rufinamide (1, 5, or 200 mg/kg) was administered orally to young dogs for 13 weeks beginning at 4 months of age, clinical chemistry and histopathological evidence of hepatotoxicity was seen, primarily at the HD, at both the terminal and recovery sacrifices. Microscopic liver findings in HD animals consisted of pigment deposits of unknown composition in hepatocytes, bile canaliculi, and Kupffer cells and neutrophilic infiltrates around intrahepatic bile ducts or blood vessels (females).

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 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Table IVE.6.2

BODY SYSTEM ORGAN FINDING SEX	TERMINAL SEGMENT SUMMARY OF FINDING INCIDENCES				12/22/95 PSS* (2.05)
	0 mg/kg	1 mg/kg	5 mg/kg	200 mg/kg	
DIGESTIVE SYSTEM					
ESOPHAGUS					
Infiltration, leukocytic, submucosal, glandular.					
MALES	0/3	0/3	1/3	1/3	
GALL BLADDER					
Infiltration, leukocytic.					
MALES	2/3	0/3	0/3	0/3	
LARGE INTESTINE					
Attenuated, surface, epithelial cell.					
MALES	2/3	0/3	0/3	0/3	
FEMALES	0/3	0/3	0/3	1/3	
Bacteria, surface, epithelial cell.					
MALES	3/3	2/3	0/3	1/3	
FEMALES	0/3	0/3	0/3	1/3	
Infiltration, leukocytic.					
MALES	1/3	1/3	2/3	0/3	
LIVER					
Infiltration, leukocytic.					
MALES	1/3	1/3	1/3	2/3	
FEMALES	0/3	0/3	0/3	3/3	
Pigment deposit(s).					
MALES	0/3	0/3	0/3	3/3	
FEMALES	0/3	0/3	0/3	3/3	
Pigment.					
MALES	1/3	1/3	1/3	0/3	
FEMALES	0/3	1/3	1/3	0/3	
SALIVARY GLAND					
Infiltration, leukocytic					
MALES	1/3	0/3	1/3	0/3	
FEMALES	2/3	1/3	2/3	0/3	
SMALL INTESTINE					
Congestion, villi.					
MALES	0/3	0/3	0/3	1/3	
Dilatation, crypt.					
FEMALES	0/3	0/3	1/3	0/3	

Table IVE.6.3

BODY SYSTEM ORGAN FINDING SEX	RECOVERY SEGMENT SUMMARY OF FINDING INCIDENCES		12/22/95 PSS* (2.05)
	0 mg/kg	200 mg/kg	
DIGESTIVE SYSTEM			
LIVER			
Infiltration, leukocytic.			
MALES	1/3	0/3	
Infiltration, neutrophil, focal.			
FEMALES	0/3	2/3	
Pigment deposit(s).			
MALES	0/3	3/3	
FEMALES	0/3	1/3	
Pigment.			
FEMALES	1/3	0/3	
ENDOCRINE SYSTEM			
PITUITARY			
Cyst			
FEMALES	1	2	
REPRODUCTIVE SYSTEM			
PROSTATE			
Immature.			
MALES	0	1	

Table IVE.6.4 AUC(0-24h) (umol.h/L) in young dogs treated with rufinamide for 13 weeks

Dose (mg/kg)	Week 2		Week 11	
	Males	Females	Males	Females
1	15.6 ± 5.6	16.4 ± 1.6	19.7 ± 9.5	20.0 ± 3.9
5	68.2 ± 46.7	63.1 ± 16.6	58.3 ± 11.4	105 ± 21

Table IVE.6.5

Table 6: CGP 33101 plasma concentrations in treated animals
(Dose: 200 mg/kg)

13-week oral toxicity study in young dogs.

Time (h)	Animal					
	Male dogs			Female dogs		
	13	14	15	31	32	33
Week 2 - Concentrations (µmol/L)						
0	←			→		
2						
4						
6						
8						
24						
Week 11 - Concentrations (µmol/L)						
0	←			→		
2						
4						
6						
8						
24						

To convert into µg/mL, multiply the concentration values by 0.2382.

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V. SUMMARY AND EVALUATION

General toxicology

Important findings in general toxicology studies provided in support of this application are shown in Table V.1 (note: NOAEL incorrect for monkeys). In rats, the most prominent effect was on the pituitary gland, and this resulted in the drug being placed on hold earlier in its development. Subsequent information suggesting a plausible mechanism involving thyroid suppression and indicating that the effect was specific to rats was considered adequate to allow clinical development to proceed (P/T review dated 9/15/95). There has apparently been no evidence of a disruption of thyroid or pituitary function in humans (adequacy of clinical monitoring needs to be established). The sponsor has also provided arguments that the cholestasis and biliary thrombus formation seen in dogs and the formation of choleliths in the gallbladder of monkeys are species specific effects, primarily based on metabolism data. Putative mechanisms for drug-induced cholestasis in humans include those involving the parent drug or a normal metabolite, a relatively rare metabolite, or an immunological reaction. So, while the clinical data in the NDA do not indicate that these effects were present in humans, the potential for such effects in some susceptible individuals may exist (evidence of possible drug-induced immune reaction was noted in 3-month dog study).

Table V.1

Table 2 Notable changes found in the pivotal repeat-dose toxicity studies and drug exposure (Study Nos. 90-6147, 89-6305, 936082, 93027).

Species	Noteworthy findings	Dose (mg/kg)	C _{max} * (µmol/L)		AUC _(0-24 hr) * (µmol/hr/L)	
			Male	Female	Male	Female
Rats	None (NOAEL)	20	NP	NP	NP	NP
	Reduced body weight gain and food consumption. Liver: increased (relative) weight and centrilobular hepatocellular hypertrophy. Pituitary: vacuolation. Thyroid: follicular hypertrophy. Increased T4.	200	223 (2.3)	223 (2.3)	4320 (2.2)	3652 (1.9)
Dogs	Liver: biliary thrombi and brown/yellow pigment accumulation	20	54 (0.6)	29 (0.3)	734 (0.4)	352 (0.2)
	Increased ALP	200	65 (0.7)	185 (1.9)	991 (0.5)	3580 (1.9)
Cynomolgus monkeys	None (NOAEL)	60	106 (1.1)	121 (1.3)	1690 (0.9)	2290 (1.2)
	Increased AST and ALP. Liver: increased weight and minimal hepatocellular hypertrophy. Gall bladder: granules (choleliths)	200	156 (1.6)	144 (1.5)	3190 (1.7)	3060 (1.6)
Human**			97		1923	

NP = not performed

*Ratios to human C_{max} and exposure levels are presented in the parentheses.

**Human C_{max} and exposure levels are shown as means of ten healthy subjects observed at steady state at a dose of 3200 mg/day (given as 1600 mg b.i.d.) in Study No. A001-001. AUC_(0-12 hr) was multiplied by 2 to obtain AUC_(0-24 hr).

Mouse

In the 13-week study in mice (CD-1; 10/sex/group), dietary administration of 60, 200, and 600 mg/kg for 13 weeks produced increased enzyme activities (SGOT, SGPT, ALK Phos) and microscopic changes in the liver and salivary glands, primarily at the MD and HD. These changes were characterized as centrilobular hepatocellular hypertrophy, single cell necrosis and periportal pigment and were generally more severe in the males than in the females. The pigment did not stain for bile and only partially stained for iron and lipofuscin. The LD was considered to be a NOAEL.

Table V.2

Table 3 Rufinamide exposure in mouse (Study No. 93041).

Dose (mg/kg)	C _{max} * (µmol/L)		AUC _(0-24 hr) * (µmol/hr/L)		C _{min} * (µmol/L)	
	Male	Female	Male	Female	Male	Female
60	19	17	285	260	ND	3
200	66	93	1297	1306	39	17
600	212	171	3883	3195	109	95

* = at end of dosing period
 ND = not detected

Rats

Oral (gavage) administration of rufinamide (0, 60, 200, or 600 mg/kg) to rats (Tf:RAIf; 10/sex/group) for 3 months produced pituitary TSH-secreting cell vacuolation and ballooning at all doses in males, and convulsions (transient in 1/10 MD and 2/10 HD males), increased BUN and creatinine, and centrilobular hepatocellular hypertrophy in both sexes at the MD and HD. White particles, presumed to be test material, were observed in the feces of all rufinamide-treated animals, indicating poor absorption.

Dietary administration of rufinamide (0, 200, 400, or 600 mg/kg) to rats (S-D; 20/sex/group) for 3-months produced microscopic findings of centrilobular hepatocellular hypertrophy and vacuolation in the pituitary gland in both sexes (more severe in males) at all doses. Pituitary vacuolation was observed in all males at all doses. The vacuolation was described as being characterized by swollen cells containing numerous finely demarcated cytoplasmic vacuoles. The severity ranged from minimal to moderate in a non-dose-related fashion. In females, minimal to mild pituitary vacuolation was D-R (0/20, 1/20, 5/20 and 7/20). Other findings included polyuria at all doses and increased water consumption at the MD and HD. There were also increases in serum creatinine in both sexes at the HD and in BUN in males at the MD and HD. Although there were no associated histopathological changes in renal glomeruli or tubules, an increased incidence of renal pelvic mineralization was seen in males at the MD and HD. The dose recommended in the study report for the chronic rat studies, based primarily on the body weight effects in this study, was 200 mg/kg.

Table V.3

Table 4 Rufinamide exposure in rat (Study No. 93027).

Dose (mg/kg)	Time (Week)	C _{max} (µmol/L)		AUC _(0-24 hr) (µmol/hr/L)		C _{min} (µmol/L)	
		Male	Female	Male	Female	Male	Female
200	2	182	149	3724	2918	128	99
400		223	205	4442	4081	154	143
600		210	174	4433	3724	154	144
200	10	223	223	4320	3652	121	89
400		256	254	5428	4706	183	160
600		262	258	5655	5378	204	175

Dietary administration of rufinamide (20, 60 and 200 mg/kg) to rats (S-D; 26/sex/grp) for 52 weeks rats produced centrilobular liver cell hypertrophy and an increased severity of pituitary cell vacuolation (males), primarily at the MD and HD. Slightly increased incidences and severity of thyroid follicular cell hypertrophy were also seen in both sexes at the MD and HD. Because of the high background incidence seen in this study, the pituitary effect was thought to represent a treatment-related exacerbation of an existing species specific condition. These changes were partially or completely reversible. Total and free T4 were increased slightly to moderately at the

MD and HD at Weeks 27, 40, and 53 in a few animals. TSH levels were increased in some MD and HD males at Weeks 40 and 53, with partial to full reversibility observed. The LD was considered to be a NOAEL.

Dogs

Oral (capsule) administration of rufinamide (0, 60, 200, or 600 mg/kg) to dogs (Beagle; 3/sex/dose) for 3 months produced clinical signs (MD and HD), anemia (MD and HD), increased liver enzyme activities (all doses), and pathological changes consisting of perivascular cellularity in the liver and kidney, intracytoplasmic inclusions in the kidney (males), eosinophilic hepatocytes, sinusoidal cell hypertrophy, and periacinar canalicular bile (MD and HD). After recovery, alkaline phosphatase levels were still increased, and bile was still present in the canaliculi. According to the pathology report, "the pathological lesions, when associated with hematological data, suggested a possible drug-induced autoimmune reaction." There was no NOAEL.

Oral (capsule) administration of rufinamide (0, 20, 60, or 200 mg/kg) to dogs (Beagle; 8/sex/dose) for up to 1 year produced dose-related biliary thrombi and accumulation of pigment (of biliary origin or iron containing) in hepatocytes and Kupffer cells, which was associated with inflammatory cell infiltration and perivascularitis, in all treated groups. Partial reversibility of biliary thrombi was noted after 4 weeks recovery. A slight to moderate increase in alkaline phosphatase activity was observed at the HD, thought to be possibly related to the retardation of bile flow. There was evidence of reversibility for this effect after 4-weeks. No effects on total and free T4 and T3 were seen in this study.

Table V.4

Table 5 Rufinamide exposure in dog (Study No. R 50/1991).

Dose (mg/kg)	Time (Day)	C _{max} (µmol/L)		AUC _(0-24 hr) (µmol/hr/L)	
		Male	Female	Male	Female
20	1	41	23	549	310
200		37	97	560	1776
20	182	42	36	549	456
200		60	88	964	1366
20	363	54	29	734	352
200		65	185	991	3580

Monkeys

Oral administration of rufinamide (35, 100, or 300 mg/kg) to cynomolgus monkeys (3/sex/dose) for 13 weeks produced choleliths and inflammation in the lamina propria of the gallbladder at the MD and HD in both sexes. Possible decreases in QT were observed in males. After a four week recovery period, choleliths were only found in 1 HD female, indicating partial reversibility. The gallbladder granules were determined to be composed primarily of a cysteine conjugate of a hydroxylated metabolite. This insoluble conjugate was thought to have been formed by enzymatic degradation of the corresponding glutathione conjugate with subsequent precipitation in the bile. Metabolism studies in humans have not indicated that such conjugates are formed in humans. The LD was considered a NOAEL.

Administration of rufinamide (20, 60, or 200 mg/kg) to cynomolgus monkeys for 1 year produced effects on the liver and gall bladder at the MD and HD. Increases in Alk Phos, AST, and ALT

were seen in both sexes, primarily at the MD and HD. These changes were associated with increased liver weight and hepatocytic hypertrophy. The presence of granules in the bile was seen at the HD and attributed to the metabolism and excretion of rufinamide as a conjugate which accumulated as concretions of insoluble material. Although there was no microscopic evidence of cholestatic changes, the increased alkaline phosphatase activity was thought to be related to this finding. The LD, which was associated with an AUC about 1/2 that in humans at the MRD (~1000 vs 2000 $\mu\text{mol}\cdot\text{h/L}$), was considered a NOAEL.

Table V.5

Table 6 Rufinamide exposure in monkey (Study No. BPK 1995/020).

Dose (mg/kg)	Time	C_{max} ($\mu\text{mol/L}$)		$\text{AUC}_{(0-24\text{ hr})}$ ($\mu\text{mol}\cdot\text{hr/L}$)	
		Male	Female	Male	Female
20	Day 1	55	49	892	804
60		104	115	1800	1950
200		151	131	2960	2660
20	Week 52	63	62	1060	1010
60		106	121	1690	2290
200		156	144	3190	3060

Genetic toxicology

Rufinamide was negative in vitro in the Ames test, a mammalian cell forward mutation study (Chinese Hamster Cells V79), and a mammalian chromosome aberration study (Chinese Hamster Ovary). An in vivo rat micronucleus assay did not indicate any effect of rufinamide, but the study failed to demonstrate exposure or toxicity at the highest dose tested (5000 mg/kg) and only evaluated 1000 cells/animal.

Reproductive and developmental toxicology

When male and female rats (S-D) were treated with 15, 50, or 150 mg/kg (by oral gavage) prior to and during mating, gestation, and lactation, effects consisted of decreased fertility (HD), increased postimplantation loss and stillbirths (MD and HD), and decreased pup survival (MD and HD) and growth (all doses). Dose selection was appropriate based on the level of parental toxicity. However, this study should be considered inadequate based on the small numbers evaluated (12/sex/group) and the 2:1 mating ratio employed. It is possible that the reproductive effects seen with rufinamide are related to the triazole structure, since several azole antifungals which have been shown to have effects on steroid metabolism have also demonstrated reproductive toxicity in animals (Waller et al, Contraception 41:411-417, 1990), although there was no clear evidence of such sex steroid effects of rufinamide in general toxicity testing.

In the rat embryofetal development study, oral (gavage) administration of rufinamide (0, 20, 100, or 300 mg/kg) to pregnant rats (Tif:RAIf) during organogenesis (GDs 6-15) resulted in decreased fetal weights and increased incidences of skeletal anomalies at the MD or greater and increased skeletal variations at all doses. These doses were also maternally toxic, probably excessively so at the HD, based on BW effects (BW gain 54% below C during treatment period). Structurally related azole antifungals, such as fluconazole, have been reported to have teratogenic effects in animals and possibly humans, including skeletal and, specifically, digit effects (Lopez-Rangel and Van Allen, Birth Defects Research Part A, 73:919-923, 2005).

In the rabbit embryofetal development study, oral (gavage) administration of rufinamide (0, 30, 200, or 700 mg/kg) to pregnant rabbits during organogenesis (GD 7 to 19) resulted in decreased

fetal weights and increased incidences of skeletal abnormalities, including malformations, at the MD or greater. While the effect was fairly modest, these doses produced no significant maternal toxicity. Because adequate maternal toxicity was not shown at the HD, this study should be repeated.

In the rat pre- and postnatal development study, oral (gavage) administration of rufinamide (5, 30, or 150 mg/kg) to rats during gestation and lactation (GD 6–PND 20) resulted in reduced fetal growth, early postnatal death, and pre- and postnatal BW reductions in the offspring. There was no clear no-effect dose for early death, although the sponsor questioned the LD and MD effects. A mouse study conducted with oral (gavage) doses of 50, 150, and 500 mg/kg given from GD15–PND 20 did not show a comparable effect on pup viability (small increase in stillbirth at MD and HD, but only a slight decrease in PND 0–4 survival at HD), but no maternal toxicity was evident at the doses tested and no plasma level data were provided. Additional rat pre- and postnatal studies with cross-fostering were conducted with rufinamide and indicated an in utero effect (P/T review dated 9/15/95).

A juvenile rat study was conducted with oral (gavage) doses of 15, 50, or 150 mg/kg given for 10 weeks starting on PND 7. Clinical signs (decreased activity) and decreased pup body weights were seen at the HD. There were no T-R deaths and no clearly T-R neurobehavioral changes. It should be noted, however, that group sizes (N=10/sex/grp) were less than what is generally considered adequate for neurobehavioral testing. Terminal evaluations indicated D-R reductions in brain weights (total and regional; persisting into the recovery period) and histopathological findings in the liver and pituitary (similar to adult) at the MD and HD. Based on these results, the LD was considered to be a NOAEL. The effect on brain weight at doses that did not appreciably alter BW is of considerable concern and should be described in labeling and further investigated, eg, with extended neurohistopathology and brain morphometry.

When doses of 1, 5, or 200 mg/kg were administered orally (capsules) to young dogs for 13 weeks beginning at 4 months of age, clinical chemistry and histopathological evidence of hepatotoxicity was seen, primarily at the HD. Pigment deposits of unknown composition were present in the livers of all HD animals at the terminal and recovery sacrifices. HD females also had neutrophilic infiltrates around intrahepatic bile ducts or blood vessels. These findings appear to be similar to those seen in adults and, based on dose, do not indicate increased sensitivity in dogs of this age (although there were irregularities in TK). However, the developmental age range studied in dogs is limited and inadequate for the clinical population. A request for a dog study that covers early postnatal development and includes bone measurements and thorough brain histopathology should be considered.

Carcinogenicity

Mouse

In the mouse study, rufinamide was administered in the diet to CD-1 mice at approximate daily doses of 40, 120 or 400 mg/kg for 103 weeks. Effects consisted of increased survival (HD females); decreased body weight gain (HD; terminal BW 4% below control in males, 8% below control in females); increased liver enzymes (all doses); and non-neoplastic microscopic bone, liver, kidney and urinary tract changes. Systemic exposure to parent drug was lower in females than in males at the LD and MD, but there was no clear sex difference at the HD. Based on data from the 13-week study, the AUC at the HD was approximately 2400 $\mu\text{mol}\cdot\text{hr}/\text{L}$ (human exposure at MRD = 1923 $\mu\text{mol}\cdot\text{hr}/\text{L}$).

The main neoplastic findings were increased incidences of osteomas (benign neoplasms of the bone; reportedly <1% background incidence in CD-1 mice) at all doses (0/60, 0/60, 2/60, 3/60 in males, statistically significant; 0/60, 2/60, 1/60, 6/60 in females, statistically significant) and of hepatocellular adenomas (4/59, 5/59, 4/59, 13/58 in males, statistically significant; 0/59, 0/59,

1/57, 10/59 in females, statistically significant) and carcinomas (8/59, 7/59, 8/59, 14/58 in males, not significant; 1/59, 0/59, 1/57, 4/59 in females, not significant) at the HD.

According to the pathology report, osteomas had the following characteristics: diameter ranging from 0.1 to 1 cm; no associated clinical signs or effects on mortality; multiple osteomas in 7/14 osteoma-bearing mice; periosteal origin as indicated by location; and most common locations in the skull and pelvis. These features were thought to be consistent with virus-induced osteomas, as distinct from chemically-induced bone tumors which were said to tend to be malignant and affect the medullary cavity near the ends of long bones. It was reported that similar osteomas were observed in control and treated animals from another carcinogenicity study run concurrently in the same facility with mice of the same strain and source (data not provided). Electron microscopic examination of selected osteomas from the rufinamide study showed variable numbers of retroviral (based on morphology) particles associated with osteoblasts, osteocytes, and endothelial cells from the tumor masses. These virus particles were not found in bone from controls without gross lesions. The viral particles were said to be morphologically the same as those reported by Maurer et al. (*Regul Toxicol Pharmacol*, 18:154-68,1993) in a carcinogenicity study of sodium fluoride in CD-1 mice conducted by Proctor and Gamble in which osteomas were increased. This suggested to the sponsor that a retrovirus may have played a role in the development of the bone tumors observed with rufinamide. A non-neoplastic bone lesion (hyperostosis) increased in the rufinamide study was also observed in the P&G study. (However, the finding of increased myelofibrosis in the rufinamide study was not reported in the P&G study). Fluoride has a strong affinity for bone and has been shown to stimulate proliferation of osteoblasts. It was postulated that in the present study, the increased incidences of osteomas resulted from a combined action of mouse retrovirus and fluoride released by oxidative metabolism of rufinamide. No evidence was found for oxidative metabolism of rufinamide to monofluorinated products in humans. According to the sponsor, retroviruses are not known to play a role in the formation of human bone tumors (but are suspected according to Nilsson and Stanton, *IARC Sci Publ* 111:681-729, 1994). Based on this information, the rufinamide-induced increase in bone tumors in mice was not considered clinically relevant by the sponsor.

While the proposed mechanism is theoretically plausible, it is not well-established and the evidence for its operation in either study is too circumstantial at this point to rule out clinical relevance. While viruses are considered a well-established cause of osteoma in mice (Nilsson and Stanton, *ibid.*), the role they may have played in the P&G study and their apparent interaction with fluoride in that study are not understood. The retrovirus particles seen by EM were not identified in either the P&G or rufinamide study. In addition, viral particles were found in controls with osteomas as well as in both control and treated mice without bone tumors in the P&G fluoride study, and a variety of tooth changes associated with fluoride toxicity were seen in the treated mice, while none of these was found in the rufinamide study. It is also not clear how the doses of fluoride compare in the 2 studies. In the P&G study, incidences of osteoma were increased primarily at the high dose of 25 mg NaF/kg (associated with about 25% incidence of osteoma). Urine fluoride concentrations at that dose were reported to be approximately 50 and 10 ug/ml in males and females at the end of the study, but no details of how the urine was collected are given in the paper (presumably aspirated from bladder at sacrifice). In a PK study in which the same doses of rufinamide as in the carcinogenicity study were given for 14 days and fluoride was measured in 24 hr urine samples collected at the end of dosing, fluoride concentrations averaged approximately 6 ug/ml at the HD of 400 mg/kg rufinamide. Another possible mechanism for bone tumor induction could involve an effect on steroidogenesis. Estrogenic compounds have been shown to induce osteomas in mice, and triazole antifungals structurally related to rufinamide are known to have effects on mammalian steroid metabolism (Zarn et al., *Environmental Health Perspectives* 111:255-261, 2003).

Rat

In the rat study, rufinamide was administered in the diet to S-D rats at approximate daily doses of 0, 20, 60 or 200 mg/kg for 97 (males) or 103 (females) weeks. (Due to low survival in controls, all remaining males were sacrificed during week 98. Surviving females were sacrificed as scheduled during week 104.) Effects consisted of decreased body weight gain (MD & HD; terminal BWs 10 & 29% below controls in males, 21 & 37% below controls in females); decreased mortality (MD & HD); and non-neoplastic microscopic changes in the liver and kidney. Plasma rufinamide concentrations were generally somewhat lower in females at the LD and MD but not at the HD. Based on TK from the 13-week dietary study, the AUC at the HD was approximately 4000 $\mu\text{mol}\cdot\text{hr}/\text{L}$ (human exposure at MRD = 1923 $\mu\text{mol}\cdot\text{hr}/\text{L}$).

Neoplastic findings consisted of increased incidences of thyroid follicular (0/59, 1/60, 10/60, 4/60; statistically significant) and thyroid C-cell adenomas (1/59, 3/60, 6/60, 2/60; not significant) in males. The incidence of thyroid C-cell carcinoma was increased somewhat in MD males (1/59, 1/60, 3/60, 0/60; not significant). There was also a possible increase (not significant) in liver hepatocellular adenomas in MD males (3/59, 2/60, 7/60, 4/60) and HD females (2/60, 1/60, 1/60, 5/60).

The MD was considered the MTD based on decreases in body weight gain noted in both sexes by the end of the study. However, in view of the shortened duration and excessive BW effects, even at the MD in females (and the resulting reduced sensitivity to detect potential carcinogenic effects), the validity of the study is questionable (see statistical review). Since estimated plasma exposures in the groups that did not have excessive weight loss were similar to or below those anticipated in humans, the tumorigenic potential of rufinamide has not been adequately assessed at clinically relevant exposures. Based on the results of the 3-month oral gavage study in rats (60, 200, 600 mg/kg), it appears that higher doses could have been given by that route without producing comparable BW effects. At the end of treatment in that study, BW gain was 2, 5 and 17% below C in M and 9, 12 and 30% below C in F, at the respective doses. BWs were 2, 5 and 11% lower in M and 5, 7 and 15% lower in F, respectively. While no TK data were collected in the 3-month gavage study, oral gavage TK data is available from the juvenile rat study. Comparing AUCs at 10 weeks, which should be comparable to adult data, with those from the 13 week dietary study, it appears as if exposures are similar at similar doses (ie, 811 and 953 $\mu\text{g}\cdot\text{h}/\text{ml}$ in males and females at 150 mg/kg by oral gavage vs 1029 and 870 $\mu\text{g}\cdot\text{h}/\text{ml}$ in males in females at 200 mg/kg in the diet). The body weight effects in the juvenile study are not as useful for comparison, since most of the effect was seen in the preweaning period, but at the end of the 10 week study, BWs were about 10% below controls at the HD of 150 mg/kg.

Thyroid follicular cell tumors in rats have typically been dismissed as not relevant to humans. According to Greaves (Histopathology of Preclinical Toxicology Studies, Elsevier, 1990), "on the basis of comparisons of thyroid follicular cell tumor development in laboratory animals following derangement of thyroid and pituitary homeostasis and epidemiological data relating to thyroid neoplasm development in human populations, it has been suggested that humans are less sensitive than commonly used animal models to the tumor-inducing effects of long-term derangement of thyroid status." However, this does not appear to apply to C-cell tumors, which were also increased in rufinamide-treated rats. In fact, as pointed out by Greaves (ibid.), radioactive iodine, which induces follicular cell tumors in rats, reduced incidences of C-cell tumors. Investigative studies by the sponsor indicating a direct effect of rufinamide on the thyroid in addition to an effect on thyroid hormone metabolism suggest the possibility of a direct tumorigenic effect unrelated to the effect on thyroid function. This, as well as the finding of osteosarcoma in a HD male provide some additional support for recommending that the study be repeated.

VI. RECOMMENDATIONS

The application is approvable from a pharm/tox standpoint. The sponsor should address the following deficiencies:

- 1) Because of the excessive reductions in body weight seen in the HD male and MD and HD female groups, and the resulting decreased sensitivity to detect carcinogenic potential, the rat carcinogenicity study is considered inadequate. Based on the results of the 3-month oral gavage study in rats, it appears that higher doses could have been given by that route without producing comparable BW effects. Therefore, it is recommended that the sponsor conduct a 2-year carcinogenicity study in rats by oral gavage at appropriate (based on MTD) doses.
- 2) Several critical studies do not conform to current standards and are, therefore, inadequate: a) the in vivo micronucleus assay in rats did not evaluate the recommended 2000 micronucleated polychromatic erythrocytes per animal, b) the rat fertility study evaluated too few animals (12/group) and did not employ 1:1 mating, and c) the rabbit embryofetal development study did not evaluate a maternally toxic high dose. These studies need to be repeated.
- 3) The finding of decreased whole and regional brain weights in the juvenile rat study should be further investigated, e.g., using expanded neurohistopathology and brain morphometry.
- 4) The developmental age range studied in juvenile dogs was inadequate. A dog study in which dosing is initiated at an earlier age (corresponding to the clinical age range) should be conducted, and endpoints of particular concern, such as bone growth and brain development should be included (in addition to the standard toxicity endpoints).

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