

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-911

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 21-911
Drug Name: Rufinamide tablets 100, 200, and 400 mg
Indication(s): Partial seizures in adults
Applicant: Eisai Medical Research Inc.
Date of Document: Nov. 17, 2005
Review Priority: Standard

Biometrics Division: Division of Biometrics 1 (HFD-710)
Statistical Reviewer: Ohidul Siddiqui, Ph.D
Concurring Reviewers: Kun Jin, Ph.D; James Hung, Ph.D

Medical Division: HFD-120
Clinical Team: Norman Hershkowitz MD, PhD
Project Manager: Courtney Calder

Keywords: *NDA review, endpoint analysis/LOCF, multi-center*

Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES	1
FOOD AND DRUG ADMINISTRATION	1
STATISTICAL REVIEW AND EVALUATION	1
1. EXECUTIVE SUMMARY	3
1.1. CONCLUSIONS AND RECOMMENDATIONS	3
1.2. BRIEF OVERVIEW OF REVIEWED CLINICAL STUDIES	3
1.2.1. PIVOTAL STUDIES	3
1.3. STATISTICAL ISSUES AND FINDINGS	4
2. INTRODUCTION	6
2.1. OVERVIEW	6
2.2. DATA SOURCES	7
3. STATISTICAL EVALUATION	7
3.1. STUDY REVIEWED	7
3.1.1. STUDY AE/PT2	7
PRIMARY AND SECONDARY EFFICACY VARIABLES IN STUDY AE/PT2	8
ANALYSIS POPULATION	8
SPONSOR'S FINDINGS: STUDY AE/PT2	8
PATIENT DISPOSITION AND DEMOGRAPHICS	8
PRIMARY EFFICACY VARIABLE: SEIZURE FREQUENCY RATIO	8
SECONDARY EFFICACY VARIABLE:	9
RESPONSE RATE	9
FDA REVIEWER'S DATA ANALYSES AND COMMENTS (STUDY AE/PT2)	9
3.2.1. STUDY AE/ET1	10
PRIMARY AND SECONDARY EFFICACY VARIABLES IN STUDY AE/ET1	11
FDA REVIEWER'S DATA ANALYSES AND COMMENT (STUDY AE/ET1)	12
STUDY 21A	13
PRIMARY AND SECONDARY EFFICACY VARIABLES IN STUDY 21A	14
FDA REVIEWER'S DATA ANALYSES AND COMMENT (STUDY 21A)	15
STUDY #022	16
PRIMARY AND SECONDARY EFFICACY VARIABLES IN STUDY#22	17
FDA REVIEWER'S DATA ANALYSES AND COMMENT (STUDY #22)	21
4. SUBGROUP ANALYSES	21
4.1. SUBGROUP ANALYSES – STUDIES AE/PT2, AE/ET1, AND 21A.	21
4.2. SUBGROUP ANALYSES – STUDY #22	22
5. SUMMARY AND CONCLUSIONS	22
5.1. COLLECTIVE EVIDENCE OF EFFICACY IN STUDIES AE/PT2, AE/ET1, 21A, AND 022.	22
5.3. CONCLUSIONS AND RECOMMENDATIONS	24

1. EXECUTIVE SUMMARY

The sponsor submitted findings of three phase III trials to support the efficacy of rufinamide as an adjunctive therapy of partial seizures in adults. According to the sponsor's findings, all three studies were positive studies to demonstrate the efficacy of rufinamide. However, based on the statistical analyses done in this statistical review, two studies (AE/ET1 and #21A) succeeded to demonstrate the efficacy of rufinamide reducing partial seizures in adults for the ITT sample. Another study (AE/PT2) failed to demonstrate the efficacy of rufinamide in reducing partial seizures in adults.

The sponsor also submitted findings of one study (#022) to support the efficacy of rufinamide, as adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over. This statistical review confirms the significant efficacy of rufinamide as adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over.

1.1. Conclusions and Recommendations

In this statistical review, evidence of efficacy was found in study #21A to conclude that rufinamide was effective as an adjunctive therapy of partial seizures in adults. In Study AE/ET1, the efficacy of 800 mg of rufinamide was found to be marginally significant to demonstrate the efficacy of rufinamide for treating patients with partial seizures in adults.

Study#22 succeeded to demonstrate that rufinamide was effective as an adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over.

1.2. Brief Overview of Reviewed Clinical Studies

1.2.1. Pivotal Studies

The submitted three pivotal studies (to demonstrate the efficacy of rufinamide as an adjunctive therapy of partial seizures in adults) were Phase 3, multicenter, multinational, randomized, double-blind, and parallel group trials. One of the studies was dose titration study - dose levels were escalated weekly (400 mg/day at Week 1, rising weekly to 1600 mg/day at Week 4), and the other two studies were fixed doses studies. The treatment duration in one study was 28 days, and in another two studies, the durations were 90 days. Two studies were conducted at Italy, Netherlands, Norway, Sweden, Argentina, Belgium, Canada, Denmark, Finland, France, Germany, and Spain (i.e., non-US studies). The third study was conducted at US (about 50% of the randomized patients at US), Argentina, Chile, France, Germany, Great Britain, Italy, Russia, Slovakia, South Africa, Spain, and Switzerland. In two studies, patients were enrolled in between 1991 to 1994. In the third study, the patients were enrolled in between 1997 to 1999.

The submitted one pivotal study (#022) (to demonstrate the efficacy of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with LGS) was a multicenter, double-blind, placebo-controlled, randomized, parallel-group study. The study was conducted at

36 centers in the following countries: Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and United States. About 46% patients were randomized in USA.

1.3 Statistical Issues and Findings

The statistical issues of the pivotal studies are presented as follows:

Study AE/PT2:

- No primary efficacy variable was identified in the protocol. The efficacy variables were defined retrospectively after database was locked and unblinded.
- The defined primary efficacy analysis population consisted of all patients who received treatment, except those who were seizure-free for the durations of both the Baseline and Double blind Phases. That is, the sponsor did not analyze the ITT sample for the primary analysis.
- There were two patients belonged to placebo group whose seizure frequency ratios were outliers. Without these two patients' data, the Wilcoxon rank-sum test produced p-values of 0.1696. According to the sponsor's analysis (Wilcoxon rank-sums test, ITT sample) on Seizure frequency ratio, the study was also a failed study (p-value=0.071). Therefore, the study AE/PT2 was a fail study to demonstrate the efficacy of rufinamide.

Study AE/ET1:

- The study had fixed doses of rufinamide 200 mg/day, 400 mg/day, 800 mg/day, 1600 mg/day b.i.d., and Placebo. In the study report, the primary statistical analysis for seizure frequency per 28 days (log,-transformed) was a normal multiple regression model. The slope was used to show the efficacy of rufinamide. However, the numerical results suggested that the dose response is not linear; thus, the slope is difficult to interpret though it is statistically significantly positive.
- The sponsor did not compare each dose group with placebo in the primary analysis after controlling multiplicity adjustment. In this review, data were re-analyzed to compare each dose group with placebo after controlling the multiplicity adjustments. After multiplicity adjustment for the fixed doses in the LSMEAN comparisons (in ANCOVA analysis), 800 mg of rufinamide was marginally significant efficacious as compared to placebo. The other three doses were statistically insignificant from placebo.

Study Q21A:

- About 50% patients were randomized in USA. Among the USA randomized patients, there was no difference between the rufinamide and placebo with respect to the percent change in total seizure frequency per 28 days from baseline (P-value=0.106, Wilcoxon Rank Sums test).

Study 022:

- No statistical issues were found in this study. The study was a positive study in demonstrating the efficacy of rufinamide.

**Appears This Way
On Original**

2. INTRODUCTION

2.1. Overview

The sponsor was seeking approval for two indications for rufinamide, as an adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over and also as an adjunctive therapy for partial-onset seizures with and without secondary generalization in adults. Table 1 lists an overview of the submitted studies.

Table 1: Overview of the four pivotal studies.

Study ID	No. of centers Location(s)	Study dates Enrollment: Total/goal	Design	Study & control drugs: dose, route, regimen
AE/PT2	9 Italy Netherlands Norway Sweden	Jun-91 to Jan-92 50/48	Randomized, DB, placebo-controlled, parallel group	RUF: 400 mg/day at Week 1, rising weekly to 1600 mg/day at Week 4 b.i.d. PLA
AE/ET1	67 Argentina Belgium Canada Denmark Finland France Germany Italy Netherlands Norway Spain Sweden	Nov-92 to Dec-94 647/500	Randomized, DB, placebo-controlled, parallel group	RUF: 200 mg/day 400 mg/day 800 mg/day 1600 mg/day b.i.d. PLA
021A	48 Argentina Chile France Germany Great Britain Italy Russia Slovakia South Africa Spain Switzerland USA Uruguay	Nov-97 to May-99 313/274	Randomized, DB, placebo-controlled, parallel group	RUF: 3200 mg/day b.i.d. PLA
022	Belgium Brazil Germany Hungary Italy Norway Poland Spain USA	Mar-98 to Sep-00 139/128	Randomized, DB, placebo-controlled, parallel group	RUF: 45 mg/kg/day b.i.d. PLA

Table 1 (continued)

Study ID	Duration of treatment	Diagnosis and main inclusion criteria	Primary endpoint(s)
AE/PT2	28 days	Adults with partial seizures who were using no more than 2 fixed-dose AEDs	Seizure frequency ratio (ratio of seizure frequency during DB Phase to seizure frequency during 3-month retrospective Baseline Phase)
AE/ET1	3 months	Adults with inadequately controlled partial seizures who were using 1 to 3 fixed-dose AEDs	Total seizure frequency per 28 days
021A	91 days-- Titration: 14 days & Maintenance: 77 days	Adults with inadequately controlled partial seizures who were using 1 or 2 fixed-dose AEDs	Percentage change in partial seizure frequency per 28 days, relative to baseline
022	84 days Titration: 14 days Maintenance: 70 days	Children or adults with inadequately controlled seizures associated with LGS and using 1 to 3 fixed-dose AEDs	1) Percentage change in total seizure frequency per 28 days, relative to baseline, 2) Percentage change in tonic-atonic seizure frequency per 28 days, relative to baseline, 3) Seizure severity rating

Source: Individual study reports

2.2. Data Sources

SAS data sets of the pivotal studies are available at \\CDSESUB1\N21911\N-000\2005-11-17. The study reports are available at \\CDSESUB1\N21911\N-000\2005-11-17.

3. STATISTICAL EVALUATION

3.1. Study reviewed

In this statistical review, the efficacy findings of the four studies (Studies AE/PT2, AE/ET1, 021A, and 022) are reviewed as follows.

3.1.1. Study AE/PT2

Study AE/PT2 was a multicenter, double-blind, placebo-controlled, randomized, parallel-group, weekly rising-dose study. The randomized patients were from both genders and aged in the range of 18 to 60 years. The patients were included if they had a diagnosis of PGTC seizures, simple partial seizures, and/or complex partial seizures with or without secondarily generalized seizures. The study did not require patients to experience seizures during the Baseline Phase as a prerequisite for enrollment. Eligible patients were supposed to receive no more than 2 of the following fixed-dose AEDs: phenobarbital, carbamazepine, phenytoin, or valproate.

No trial entry requirements concerning seizure frequency at baseline were defined in the protocol. Therefore, some patients entered the trial without seizures during the Baseline Phase.

Patients were randomized to receive either rufinamide or placebo during the 28-day Double-blind Phase. The daily dose was 400 mg of rufinamide or placebo during the first week, given on a b.i.d. schedule. The dose was increased by 400 mg/day each week, so that the dose during the fourth week was 1600 mg/day, given on a b.i.d. schedule. Figure 1 lists the design of the study.

Figure 1: Schematic design diagram (Study AE/PT2)

Phase (Series)	Baseline ¹ /Screen	Single-dose PK Phase (A)	Double-blind Treatment Phase (B)	Single-dose PK Phase (C)
	Randomisation ↓			
Exam/Report No.	1	2	3 4 5 6	7 8
Days	0 *	1 5	8 15 22 29	35 up to 42 **
Dose CGP 33101(mg)		↑ 800	400 800 1200 1600	↑ 800
Design		Open	Double-blind	Open

Source: Study report

Primary and secondary efficacy variables in Study AE/PT2

No primary efficacy variables were identified in the protocol. The efficacy variables were defined retrospectively after database lock and unblinding of the trial. The primary variable was the seizure frequency ratio during the Double-blind Phase, based on all types of seizures. A patient's seizure frequency ratio was defined as the seizure frequency in the Double-blind Treatment Phase divided by the seizure frequency in the retrospective Baseline Phase. The secondary efficacy variable was response to treatment, defined as experiencing at least a 25% reduction or at least a 50% reduction in seizure frequency during the Double-blind Phase relative to the Baseline Phase.

Analysis Population

The primary efficacy analysis population consisted of all patients who received treatment, except those who were seizure-free for the durations of both the Baseline and Double blind Phases, called data set (i). This data set included 44 of 50 patients enrolled in the trial. Secondary efficacy analysis populations consisted of all patients who received treatment, except those who were seizure free during the Baseline Phase, called data set (ii), and all patients who received treatment (intent-to-treat population), called data set (iii). This reviewer considered data set (iii) as the primary analysis population instead of data set (i) in this analysis. The primary analysis of seizure frequency ratio was performed using Wilcoxon rank-sums test.

Sponsor's Findings: Study AE/PT2

Patient disposition and demographics

A total of fifty patients (25 patients in each group) were randomized in the study. Of the 25 patients who received double-blind rufinamide, 23 (92%) completed the study and 2 (8%) were withdrawn prematurely due to adverse events. All 25 patients who received double-blind placebo completed the study.

The median baseline seizure frequency was 3.69 (range, 0 to 64.62) per 28 days in the rufinamide group and 4.62 (range, 0 to 76.92) per 28 days in the placebo group.

Primary efficacy variable: seizure frequency ratio

The primary analysis of seizure frequency ratio was performed using data set (i). The median seizure frequency ratio was 0.593 for the rufinamide group and 1.520 for the placebo group ($p=0.0397$; Wilcoxon rank-sums test). Secondary analyses performed using data sets (ii) and (iii) demonstrated trends in favor of rufinamide ($p=0.1029$ and $p=0.0708$, respectively).

Table 2: Median seizure frequency per 28 days in the Baseline and Double-blind Phases --Study AE/PT2)

Data seta	Treatment	No. of patients			Median % change relative to Baseline Phase	P-Value
			Baseline Phase	Double-blind Phase		
(i)	Placebo	21	6.46	8.30	52	0.0397
	Rufinamide(400 mg to 1600 mg)	23	4.00	3.11	-41	
(ii)	Placebo	19	8.62	9.33	8	0.1029
	Rufinamide (400 mg to 1600 mg)	23	4.00	3.11	-41	
(iii) ITT sample	Placebo	25	4.62	5.19	0	0.0708
	Rufinamide (400 mg to 1600 mg)	25	3.69	3.11	0	

Data set (i) included all patients who received treatment, except those who were seizure-free for the duration of both the Baseline and Double-blind Phases.

Data set (ii) included all patients who received treatment, except those who were seizure-free during the Baseline Phase.

Data set (iii) included all patients who received treatment (intent-to-treat population).

Source: ISE report

Secondary efficacy variable:

Response rate

With respect to the secondary measure - at least a 25% reduction in seizure frequency, the rufinamide group (48% patients) was statistically significant (p-value=0.012, ITT sample, Fisher Exact test) from placebo group (12% patients). However, for at least 50% reduction in seizure frequency, the rufinamide group (36% patients) was not statistically significant (p-value=0.0955, ITT sample, Fisher Exact test), as compared to the placebo group (12%).

FDA Reviewer's Data Analyses and Comments (Study AE/PT2)

In study AE/PT2, the patients who had a diagnosis of PGTC seizures, simple partial seizures, and/or complex partial seizures with or without secondarily generalized seizures were randomized. In the primary statistical analyses, the sponsor excluded the patients who had not experienced any seizure at baseline and post baseline. That is, ITT sample was not considered in evaluating the efficacy of rufinamide. In addition the sponsor used Wilcoxon rank-sums test to evaluate treatment efficacy. In this test, the country effect was not controlled. This reviewer reanalyzed the ITT sample.

This reviewer re-analyzed the ITT data (i.e. Data (iii)) set using Wilcoxon rank-sums test (sponsor's proposed method). The findings based on Wilcoxon rank-sums test were similar to the sponsor's findings, and rufinamide was not statistically significant (p-value=0.0708) compared to placebo. There were two patients belonged to placebo group whose seizure frequency ratios were outliers. Without these two patients' data, the Wilcoxon rank-sums test

produced p-values of 0.1696. Based on the sponsor's analyses as well as this reviewer's analyses, the study AE/PT2 was a failed study.

With respect to the secondary measure- at least a 50% reduction in seizure frequency, the rufinamide group was not statistically significant ((p-value=0.0955, ITT sample, Fisher Exact test)) from placebo group.

3.2.1. Study AE/ET1

Study AE/ET1 was a multicenter, double-blind, placebo-controlled, randomized, 5-arm parallel (fixed dose) both inpatients and outpatients with seizures on up to three concomitant antiepileptic drugs to investigate efficacy and tolerability of rufinamide doses 200, 400, 800, and 1600 mg/day. Patients from both genders (ages 15 to 65 years) were randomized if they had a diagnosis of simple partial seizures (including auras), and/or complex partial seizures with or without secondarily generalized seizures. The patients were required be taking 1 to 3 fixed-dose AEDs with poor control of seizures, i.e., 4 seizures per month during the 6 months preceding the Baseline Phase. The trial design was summarized in Figure 2. The study was conducted at 67 centers in 12 countries (Argentina, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, and Sweden).

Figure 2. Schematic design diagram (Study AE/ET1)

Phase	Baseline	Double-blind Treatment	Extension
Design	Open, prospective	Double-blind	Double-blind or Open-label
		Randomization ↓	
Examination/ Report No.	1 2 3	4 (5, 6*) 7, 8, 9, 10, 11, 12, Final**	DB Ext Open Ext
Week	0 4 8	12/0 D4, 1, 2, 3, 4, 8, 12	every 4 weeks
rufinamide (mg)/ placebo		↑ 200, 400, 800, 1600/day or placebo	a b

Source: Study Report

The baseline seizure frequency was determined during a 3-month prospective Baseline Phase. A patient must have experienced 9 or more seizures during the Baseline Phase to be eligible to continue in the study. After completing the Baseline Phase, 647 patients (ITT sample) were randomized to 1 of 5 treatment groups (rufinamide 200, 400, 800, or 1600 mg/day or placebo, given on a b.i.d. schedule) for the 3-month Double-blind Phase. There was no Titration Period (i.e., it was a fixed dose trial).

Primary and secondary efficacy variables in Study AE/ET1

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

The secondary efficacy variables were (i) Seizure frequency ratio, based on total seizure frequency per 28 days, (ii) Response to treatment, defined as experiencing at least a 25% or at least a 50% reduction in seizure frequency during the Double-blind Phase relative to the Baseline Phase.

Statistical Method

The primary statistical analysis for seizure frequency per 28 days (log,-transformed) was a normal multiple regression model. In the analysis, all seizure frequencies were shifted by a value of 1/3 prior to the logarithmic transformation to account for a small number of patients who experienced zero seizures during the Double-blind Treatment Phase. Statistical significance of the linear component of ordinal dose was determined from the p-value associated with the estimate of the linear component of the treatment contrast for ordinal dose. The ITT patients (who have baseline measures and at least one post baseline measures) were included in the analysis.

Additional exploratory analyses were performed to make multiple comparisons of the seizure frequency per 28 days for each of the four rufinamide doses relative to placebo. (Sponsor statement)--Since these multiple comparisons are supplementary to the primary analysis that tests for the linear trend of dose response, adjustments to the p-values for the multiple comparisons were not performed.

The secondary measures (i) seizure frequency ratio was analyzed by computing pairwise Wilcoxon rank-sums test for each dose of rufinamide relative to placebo; (ii) Response to treatment was analyzed using a logistic regression model. No adjustment for multiple testing was made for the analysis of the secondary efficacy variables.

Sponsor's Findings

A total of 554 patients (85.6%) completed the Double-blind Treatment Phase. The percentage of patients who completed this phase of the trial was similar across the treatment groups (placebo 87.2%, relative to 87.4%, 84.0%, 85.3% and 84.2% for rufinamide 200, 400, 800, and 1600 mg/day, respectively).

The percentage of patients prematurely discontinuing from the trial due to adverse experiences was lowest among placebo-treated patients (6.8%), similar among the three lower dose rufinamide treatment groups (9.4%, 9.6%, and 9.3% for rufinamide 200, 400, 800 mg/day) and slightly higher for patients in the rufinamide 1600 mg/day treatment group (12.0%). The other

reasons for discontinuation were: unsatisfactory therapeutic effect, withdrawal of consent, non-compliance, failure to meet the protocol criteria, and loss to follow-up.

Demographic and baseline data

The randomized patients were from both genders (about 50% males). The mean patient age was 36.1 years (range=14-68 years). Majority of the patients received trial drug as outpatients; only 31 of 647 patients (4.8%) received trial drug on an inpatient basis. Baseline seizure subtype was similar between treatment groups. Patients could have more than one of these seizure subtypes. The most common seizure subtype was complex partial seizures (90.6%). The median baseline seizure frequency per 28 days was similar between rufinamide- and placebo-treated patients ranging from 11.1 to 12.7.

Efficacy Findings

The estimated dose response slope in the linear regression model (using all four doses of rufinamide and placebo) for seizure frequency per 28 days in the Double-blind Treatment Phase, was statistically significant in favor of rufinamide (p-value=0.003). The estimated slope of -0.049 implied that seizure frequency per 28 days in the Double-blind Treatment Phase decreased as the dose of rufinamide increased from placebo.

The secondary measure- Seizure frequency ratio was statistically significantly lower for the 400 mg/day, 800 mg/day, and 1600 mg/day treatment groups compared with placebo (all p-values < 0.0274, Wilcoxon rank-sums test). These significant differences corresponded to a reduction in median seizure frequency ratio of 11%, 16%, and 17%, respectively, compared with placebo. The median seizure frequency ratio for the 200 mg/day group was only 4% lower than placebo and was not statistically significant from placebo.

With respect to the secondary measure - at least a 25% reduction in seizure frequency per 28 days from baseline, 1600 mg/day group (37.6% responders) was statistically significant (p-value 0.0238) compared to placebo group (24.1% responders).

FDA Reviewer's Data Analyses and Comment (Study AE/ET1)

This reviewer was able to reproduce the sponsor's reported primary and secondary efficacy results. Since there were four fixed dose groups (200mg, 400mg, 800mg, and 1600 mg), a comparison of individual dose group vs. placebo was important to determine the efficacy of rufinamide, as well as in the statistical comparisons, a multiplicity adjustment was also important to be carried out. This reviewer compared individual dose group vs. placebo after considering the multiplicity adjustments.

Based on the ANCOVA model (including Country as a factor, and log,-transformed seizure frequency per 28 days at baseline as a covariate), only 800mg dose group (LSMEAN comparison) appeared to be statistically significant (p-value= 0.014) compared to placebo group (Table 3). The p-values of the other doses vs. placebo comparisons were greater than or equal to 0.078. After multiplicity adjustment (either using Hochberg's method or Bonferroni

adjustment), none of the four dose groups (800 mg missed to be significant marginally) of rufinamide were statistically significantly different from placebo group.

The percent reductions in seizure frequency for the rufinamide groups over placebo group were not linear (see Table 3). For the 1600 mg, the reduction was lower than the reduction for the 800 mg. Although the slope was statistically significant, the slope is very difficult to interpret if the trend is not linear. Only 800 mg dose showed some efficacy of rufinamide. Hence the study results were inconclusive to demonstrate the efficacy of rufinamide.

Table 3: Median seizure frequency per 28 days in the Baseline and Double-blind Phases --Study AE/ET1)

Data seta	Treatment	No. of patients	Median seizure frequency per 28		ANCOVA ^s model Analysis on seizure frequency per 28 days (log,-transformed) at double-blind phase		
			Basel-ine Phase	Double-blind Phase	LSMEAN	%Reduction in Seizure Frequency over Placebo **	P-value (RUF vs. Placebo) from ANCOVA
ITT	Placebo	133	11.67	11.86	2.633		
	Ruf 200 mg	127	11.08	11.00	2.665	-3.251	0.661
	Ruf 400 mg	125	11.83	10.67	2.516	11.041	0.114
	Ruf 800 mg	129	12.67	11.00	2.452	16.556	0.014
	Ruf 1600 mg	133	11.33	10.67	2.502	12.278	0.078

^s The sponsor used the same model to estimate regression slope.

^{**}% Reduction over placebo = 100 x [1-exp (LSMEAN rufinamide- LSMEAN placebo)]

LSMEAN: Least Square Mean.

Study 21A

Study 21A was a multicenter, double-blind, placebo-control, randomized, parallel-group study of rufinamide (3200 mg vs. placebo) as adjunctive therapy in adults (age ≥ 16 years) patients with inadequately controlled partial seizures. The study consisted of three phases. The Baseline Phase consisted of 56 days during which patients must have experienced at least six partial seizures (with at least one seizure in each of the 28-day periods) and been treated with a fixed dose of one or two concomitant AEDs. During the 91-day Double-blind Phase patients were randomized to either rufinamide or placebo. This phase had a Titration Period (during which the dose of rufinamide was to be increased to 3200 mg/day vs. placebo) and a Maintenance Period (during which patients remained at either 3200 mg/day or placebo). Dose reductions of up to one 400 mg tablet were allowed in the event of tolerability issues. The trial design was summarized in Figure 3. The study was conducted at 48 centers from 13 countries. Centers included: Argentina (7), Chile (1), France (4), Germany (1), Great Britain (2), Italy (3), Russia (4), Slovakia (2), South Africa (3), Spain (2), Switzerland (1), United States (17), and Uruguay (1). About 50% patients were randomized in USA.

Figure 3. Schematic design diagram (Study 21A)

Phase	Baseline (56 days)	Double - blind (91 days)					Extension	
Period		Titration (14 days)			Maintenance (77 days)		C*	OL
		Randomization ↓						
Visit		1 2	3 4	5	6	6.1 Post-taper		
Day	-56 to -7	0 7	14 35	63	91			
Treatment	1 - 2 AEDs	Rufinamide (RFA) + 1 - 2 AEDs						
	1 - 2 AEDs	Placebo (PLB) + 1 - 2 AEDs						

*C = Blinded conversion OL = Open label

Source: Study Report

A patient must have experienced 6 or more seizures during the Baseline Phase, and may have been taking up to two additional AEDs on fixed doses to be eligible to study. Patients included male and female adult (age ≥ 16 years) patients with partial seizures, which included the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures.

Primary and secondary efficacy variables in Study 21A

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

The secondary efficacy variables were (i) the total partial seizure frequency per 28 days during the Double-blind Phase, (ii) Response to treatment, defined as experiencing at least a 25% or at least a 50% reduction in seizure frequency during the Double-blind Phase relative to the Baseline Phase.

Statistical Method

The primary statistical method was Wilcoxon rank-sums test to compare between-treatment differences for the primary efficacy variable. The secondary measures (at least 25% reduction, at least 50% reduction) were evaluated using a logistic regression model.

Sponsor's Findings

A total of 313 adult patients were randomized with 156 randomized to rufinamide and 157 randomized to placebo. Among the randomized patients, 257 patients (82.1%) completed the Double-blind Treatment Phase. The percentages of patients who completed this phase of the trial were 76.9% and 87.3% for rufinamide and placebo groups, respectively.

The percentages of patients prematurely discontinuing from the trial due to adverse experiences were 13.5% and 3.2% for rufinamide and placebo groups, respectively. The percentages of discontinuation due to other reasons were similar between the two groups.

Demographic and baseline data

All randomized patients included in the adult stratum were at least 16 years of age and all had a baseline body weight of at least 40 kilograms. There were no notable differences between the two treatment groups with respect to sex, race, age, body weight, or the percentage of patients experiencing secondarily generalized seizures during the Baseline Phase.

Efficacy Findings

The primary efficacy variable, percentage change in partial seizure frequency per 28 days of the Double-blind Phase from the Baseline Phase appeared to be statistically significant in favor of the rufinamide treatment group relative to the placebo treatment group (Wilcoxon rank-sums test, $p=0.0158$). Rufinamide-treated patients experienced a 20.4% median reduction in partial seizure frequency per 28 days from the Baseline Phase compared to a 1.6% median increase for placebo-treated patients.

With respect to the secondary measures – (i) at least a 25% reduction in seizure frequency per 28 days from baseline, and (ii) at least a 50% reduction in seizure frequency per 28 days from baseline, the rufinamide group had statistically significantly higher reductions in partial seizure frequency relative to baseline during double-blind period compared to placebo group (p -value=.038 for 50% reduction & p -value=.001 for 25% reduction).

FDA Reviewer's Data Analyses and Comment (Study 21A)

This reviewer was able to reproduce the sponsor's reported primary and secondary efficacy results. Since about 50% patients were randomized from USA, it was important to evaluate the efficacy of rufinamide for the USA patients. Therefore, the efficacy of rufinamide was evaluated for the USA and non-USA patients separately using Wilcoxon Rank Sums test. Table 4 lists the efficacy findings by USA vs. non-USA patients.

For the USA and Non-USA randomized patients, the median percentage changes in seizure frequency relative to baseline of the two treatment groups were very similar. However, for the USA patients (with 77 placebo patients and 80 Ruf patients), the rufinamide group was not statistically significantly (p -value=0.106, Wilcoxon Rank Sums test) different from placebo.

Table 4: Median seizure frequency per 28 days in the Baseline and Double-blind Phases --Study 21A)

Data seta	Treatment	No. of patients			Median % change relative to Baseline Phase	P-Value (Ruf. Vs. Placebo)
			Baseline Phase	Double-blind Phase		Wilcoxon Rank sum test
ITT	Placebo	156	8.00	8.66	1.609	
	Ruf 3200 mg	156	8.50	7.55	-20.416	0.016
ITT USA	Placebo	77	8.00	8.00	2.564	
	Ruf 3200 mg	80	8.00	7.42	-15.39	0.106
ITT NON-USA	Placebo	79	8.5	8.71	-3.21	
	Ruf 3200 mg	76	9.25	7.59	-22.12	0.067

Study #022

Study#022 was a multicenter, double-blind, placebo-controlled, randomized, parallel-group study of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with LGS. The study consisted of a 28-day prospective Baseline Phase and an 84-day Double-blind Phase during which patients received either rufinamide or placebo. During the Double-blind Phase, visits to the study site occurred on the first day of treatment (Visit 1), Day 7 (Visit 2), Day 14 (Visit 3), Day 28 (Visit 4), Day 56 (Visit 5), and Day 84 (Visit 6). The trial design is summarized in Figure 4. A total of 138 patients were randomized (74 in the rufinamide group and 64 in the placebo group) to receive either rufinamide or placebo. Both rufinamide and placebo were administered orally as 100, 200, or 400 mg tablets in a b.i.d. dosage regimen. The dosage administered was based on the patient's weight. Dosing started at approximately 10 mg/kg/day, and the dosage was titrated to approximately 45 mg/kg/day over a 1- to 2- week period. The study was conducted at 36 centers in the following countries: Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and United States. About 46% patients were randomized from USA.

Male or female patients (between 4 and 30 years of age) were included if they had a diagnosis of inadequately controlled seizures associated with LGS (including both atypical absence seizures and drop attacks) and were being treated with one to three concomitant fixed-dose antiepileptic drugs (AEDs).

Figure 4. Schematic design diagram (Study 22)

Phase	Baseline (28 days)	Double-blind (84 days)						
Period		Titration (14 days)			Maintenance (70 days)			
		↓ Randomization						
Visit	Baseline	1	2	3	4	5	6	6.1 Post ^a
Day	-28	0	7	14	28	56	84	Taper

Phase III, double-blind, placebo-controlled study

Treatment	1-3 AEDs	Rufinamide + 1-3 AEDs
	1-3 AEDs	Placebo + 1-3 AEDs

Source: Study Report

Primary and secondary efficacy variables in Study#22

The primary efficacy variables were as follows:

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

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

Variable 3- Seizure severity rating from the Global Evaluation of the patient's condition.

The secondary efficacy variables were as follows:

Variable 4- Response to treatment, defined as experiencing at least a 50% reduction in tonic-atonic seizure frequency during the Double-blind Phase relative to the Baseline Phase.

Variable 5- The percent change in seizure frequency per 28 days in the Double-blind Phase relative to the Baseline Phase for each seizure subtype other than tonic-atonic seizures.

Variable 6- Composite score for the Global Evaluation of the patient's condition.

Statistical Methods

The primary statistical method was Wilcoxon rank-sum test to compare between-treatment differences for each of the three primary efficacy measures. Significance of the difference between treatment groups was tested at the two-sided, 2.5% level. Rufinamide was considered effective if

(1) (Variable 1) The percent reduction in total seizure frequency in the Double-blind Phase relative to the Baseline Phase was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo and/or

2) both of the following were true:

(i) (Variable 2) The percent reduction in tonic-atonic seizure frequency in the Double-blind Phase relative to the Baseline Phase was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo.

(ii) (Variable 3) The seizure severity rating from the Global Evaluation performed by the parent/guardian at the end of the Double-blind Phase was significantly ($p < 0.025$, two-sided) greater for rufinamide than placebo. The adjustment of the alpha level was made by Novartis in response to recommendations by the FDA as noted in the minutes of the End of Phase 2 meeting on 23-Apr-98.

The secondary measure -at least 50% reduction in tonic-atonic seizure frequency were evaluated using a logistic regression model. The model included treatment, region (US, Brazil, Europe), sex, and age as explanatory variables. Significance of the difference between treatment groups was tested at the two-sided, 5% level. The other two secondary measures were evaluated using Wilcoxon rank-sum test. Significance of the difference between the treatment groups was tested at the two-sided, 5% level.

Sponsor's Findings

A total of 123 patients (89%) out of 138 randomized patients completed the Double-blind Treatment Phase. The percentages of patients who completed this phase of the trial were 85% and 92% for rufinamide and placebo groups, respectively.

The percentages of patients prematurely discontinuing from the trial due to adverse experiences were 8% from rufinamide group and none from placebo group. The percentages of discontinuation due to other reasons were similar between the two groups.

Demographic and baseline data

About two-thirds of the patients were males. The mean age was 14 years, and more than 70% of the patients were younger than 17 years. The mean weight was approximately 40 kg. There were no notable differences between the two treatment groups with respect to sex, race, age, body weight, or region/country.

Efficacy Findings

Primary efficacy results

Variable 1- The percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p = 0.0015$, Wilcoxon rank-sum test). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency. A brief summary of the results is presented in Table 5.

Table 5. Summary of percent change in total seizure frequency per 28 days relative to baseline (Intent-to-treat patients)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	74	290.0	(48.0, 53760.0)	64	205.0	(21.0, 109714.0)
Double-blind seizure frequency per 28 days	74	204.1	(5.4, 43262.3)	64	205.4	(50.7, 113165.0)
Percent change in seizure frequency per 28 days from baseline ^a	74	-32.7	(-92.3, 381.4)	64	-11.7	(-82.8, 550.6)

^a Between-group comparison using Wilcoxon rank-sum test p -value = 0.0015

Source: Study report

Variable 2- The percent change in tonic-atonic seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p < 0.0001$, Wilcoxon rank-sum test). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 days. A brief summary of the results is presented in Table 6.

Table 6. Summary of percent change in tonic-atonic seizure frequency per 28 (Intent-to-treat patients)

	Rufinamide			Placebo		
	n ^a	Median	Range	n ^a	Median	Range
Baseline tonic-atonic seizure frequency per 28 days	73	92.0	(5.0, 14304)	60	92.5	(1.0, 13122)
Double-blind tonic-atonic seizure frequency per 28 days	73	60.7	(0.0, 12036.1)	60	76.2	(0, 17500)
Percent change in tonic-atonic seizure frequency per 28 days from baseline ^b	73	-42.5	(-100, 1190.8)	60	1.4	(-100, 709.6)

^b Between-group comparison using Wilcoxon rank-sum test p -value = 0.0001

Source: Study report

Variable 3- The seizure severity rating at the end of the Double-blind Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p = 0.0041$, Wilcoxon rank-sum test). An improvement in seizure severity was observed in 39 (53.4%) of the 73 rufinamide-treated patients compared to 19 (30.6%) of the 62 placebo-treated patients. A brief summary of the results is presented in Table 7.

Table 7. Summary of seizure severity rating of the Global Evaluation of the (Intent-to-treat patients)

Seizure severity	Rufinamide (N=73)		Placebo (N=62)	
	n ^a	%	n ^a	%
Very much worse	0	0.0	0	0.0
Much worse	3	4.1	4	6.5
Minimally worse	3	4.1	4	6.5
No change	28	38.4	35	56.5
Minimally improved	14	19.2	10	16.1
Much improved	16	21.9	8	12.9
Very much improved	9	12.3	1	1.6

Between-group comparison using Wilcoxon rank-sum test p-value = 0.0041

Source: Study report

The primary efficacy analysis showed statistically significant results in favor of rufinamide for all three primary variables at a 0.025 level.

Secondary efficacy findings

Variable 4: The percent of patients who experienced at least a 50% reduction in tonic-atonic seizure frequency per 28 days, relative to baseline, was significantly higher in the rufinamide group (42.5%) than in the placebo group (16.7%) ($p = 0.0020$; logistic model). The observed odds ratio of 3.81 indicates that patients who received rufinamide were approximately four times more likely to experience at least a 50% reduction in tonic-atonic seizure frequency, compared with those receiving placebo.

Variable 5: There were median reductions in the frequencies of all seizure types with rufinamide were considerably larger than those with placebo. The difference between the groups favoring rufinamide was statistically significant for atonic seizures ($p=0.0125$; Wilcoxon rank-sum test) and combined absence and atypical absence seizures ($p=0.0222$; Wilcoxon rank-sum test). The efficacy in tonic seizures was not significant ($p=0.0821$; Wilcoxon rank-sum test).

Variable 6: The composite score for the Global Evaluation of the patient's condition was the sum of five 7-point assessments performed by the parent/guardian at the end of the trial. The five assessments were level of alertness, level of interaction with the environment, responsiveness to verbal requests, ability to perform activities of daily living, and seizure severity. The mean total score at the end of the Double-blind Phase was 2.30 in the rufinamide group and 1.77 in the placebo group, with median scores of 1 and 0, respectively. The difference between the groups was not statistically significant ($p = 0.3492$)

FDA Reviewer's Data Analyses and Comment (Study #22)

This reviewer was able to reproduce the sponsor's reported primary and secondary efficacy results. For the USA randomized patients, the rufinamide group was also statistically significantly (p-value=0.030, Wilcoxon Rank Sums test-sponsor's method for variable 1 & (p-value <0.001, Wilcoxon Rank Sums test-sponsor's method for variable 2) different from placebo.

Based on the clinical inspection summary report, four patients' data from one USA center were dropped from the analyses. These four patients' data had no impact on the significance of rufinamide.

4. Subgroup Analyses

4.1. Subgroup Analyses – studies AE/PT2, AE/ET1, and 21A.

Within each study, subgroup analyses on the primary efficacy measure were performed to evaluate the uniformity of treatment effect within patient subgroup (gender and age group). No subgroup analyses were done on race because nearly all patients were whites. Table 6 lists the median seizure frequency per 28 days by gender and age groups. Within each study, subgroup analyses showed no substantial differences in efficacy of rufinamide across the subgroups.

The FDA reviewer also did the subgroup analyses on the studies. The reviewer's conclusions based on the findings were comparable with the sponsor's conclusions.

Table 6. Subgroup Analysis - the median seizure frequency per 28 days-ITT Population (With LOCF)

Study AE/PT2	Median seizure frequency per 28 days									
	Placebo		Rufinamide(titrated from 400 mg to 1600 mg)							
	n	Median	n	Median						
Gender : Male	16	7.2	18	3.1						
Female	9	5.18	7	7.25						
Age: <40 years	17	8.3	18	3.1						
>=40 years	8	2.6	7	3.1						
Study AE/ET1	Median seizure frequency per 28 days									
	Placebo		Rufinamide (fixed dose)							
			200 mg/day		400 per/day		800 per/day		1600 per/day	
	n	Median	n	Median	n	Median	n	Median	n	Median
Gender : Male	80	13.4	64	11.2	74	11.6	68	12.6	61	9.0
Female	53	11.0	63	11.0	51	9.6	61	9.5	72	12.0
Age: <40 years	78	14.7	82	13.0	81	11.6	79	13.0	85	8.6
>=40 years	55	10.0	45	8.0	44	8.6	50	9.2	48	11.2
Study 21A	Median seizure frequency per 28 days									
	Placebo		Rufinamide (Titrated to 3200 mg/day)							
	n	Median	n	Median						
Gender : Male	75	8.6	61	10.1						
Female	81	8.7	93	7.1						
Age: <40 years	90	10.4	103	7.4						
>=40 years	66	6.7	51	6.8						

Note: In the studies, majority of patients are Whites. So, no subgroup analysis has been done on race.

4.2. Subgroup Analyses – Study #22

Median percentage changes in seizure frequency by age and gender are summarized in Table 7. The patients within each age subgroup who received rufinamide had larger median decreases in seizure frequency than did the patients who received placebo. The results were generally similar across different age groups and male and female patients.

Table 7. Median percentage change in seizure frequency in the Double-blind phase relative to baseline, by age group (Intent-to-treat patients)

Study	Seizure Type		4-<12 yr		12-<17 yr		17-<65yr	
			RUF	PLA	RUF	PLA	RUF	PLA
022	Total	N	31	33	19	17	24	14
	Seizure	Median % change	-29.5	-15.9	-40.5	-11.6	-32.7	14.1
	Tonic- atonic	N	31	30	18	16	24	14
		Median % change	-34.5	-14.2	-47.5	12.7	-55.7	16.3
			Female		Male			
			RUF	PLA	RUF	PLA		
	Total	N	28	24	46	40		
	Seizure	Median % change	-29.5	-4.7	-37.0	-12.0		
Tonic- atonic	N	28	24	45	36			
	Median % change	-32.0	-14.2	-44.8	3.5			

Note: In the study, majority of patients are Whites. So, no subgroup analysis has been done on race.

5. SUMMARY AND CONCLUSIONS

5.1. Collective Evidence of Efficacy in Studies AE/PT2, AE/ET1, 21A, and 022.

Although the sponsor claimed that the efficacy of rufinamide was supported by the findings of three double-blind placebo-controlled studies (i.e. rufinamide group demonstrated significant median reduction in partial seizure frequency as compared to placebo group), FDA statistical reviewer found that Study#21A succeeded to demonstrate the efficacy of rufinamide in reducing the partial seizure frequency compared to placebo for the ITT sample, but it did not provide a clear evidence to demonstrate the efficacy for the USA randomized patients. Study AE/ET1 also marginally succeeded to demonstrate the efficacy of 800 mg dose of rufinamide. The other three doses of rufinamide (200 mg, 400 mg, and 1600 mg) failed to demonstrate the efficacy. Study AE/PT2 failed to demonstrate the efficacy of rufinamide in reducing the partial seizure frequency compared to placebo.

Study#22 demonstrated that rufinamide was significantly effective than placebo as adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over.

In study AE/PT2, there was no statistical analysis plan in the protocol. According to the sponsor's analysis, the primary efficacy analysis population consisted of all patients who received treatment, except those who were seizure-free for the duration of both the Baseline and Double blind Phases. This data set includes 44 of 50 patients enrolled in the trial. This sample

was not an ITT sample. Based on this sample, the rufinamide was statistically significant compared to placebo. The sponsor also did a secondary analysis based on the ITT sample, and found that rufinamide group was not statistically different from placebo group in reducing the seizure frequency.

This reviewer re-analyzed the ITT data set using Wilcoxon rank-sums test (sponsor's proposed method). The finding based on Wilcoxon rank-sums test was similar to the sponsor's finding, and rufinamide was not statistically significantly different from placebo. There were two patients belonged to placebo group whose seizure frequency ratios were outliers. Without these two patients' data, the Wilcoxon Rank-Sums test produced a p-value=0.1696. Based on the sponsor's finding as well as this reviewer's finding using the ITT sample in the analyses, it may be concluded that the study AE/PT2 was a fail study.

In study AE/ET1, according to the sponsor- the primary statistical analysis of the seizure frequency per 28 days (log-transformed) was a normal multiple regression model. The ITT patients were included in the analysis. The estimated dose response slope in the linear regression model (using all four doses of rufinamide and placebo) for seizure frequency per 28 days in the Double-blind Treatment Phase, was statistically significant in favor of rufinamide. This reviewer was able to reproduce the sponsor's reported efficacy results. However, the numerical results did not support a linear dose-response; thus the slope is very difficult to interpret.

However, the sponsor did not compare each fixed dose group with placebo and did not take care of multiplicity adjustment. This reviewer re-analyzed the data and took care of multiplicity adjustment. Based on the ANCOVA model (including Country as a factor, and log-transformed seizure frequency per 28 days at baseline as a covariate), only 800mg dose group (LSMEAN comparison) was statistically significant (p-value: 0.0143) compared to placebo group. The p-values of the other doses vs. placebo comparisons were greater than or equal to 0.074. After multiplicity adjustment, none of the four dose groups (although 800 mg was borderline significant) of rufinamide were statistically significantly different from placebo group. Therefore, based on the above ANCOVA analysis, the 800 mg of rufinamide showed some evidence of efficacy of rufinamide.

In study 21A, the primary statistical method was Wilcoxon rank-sums test to compare between-treatment differences for the primary efficacy variable the percent change in partial seizure frequency during the Double-blind Phase relative to the Baseline Phase. This reviewer was able to reproduce the sponsor's reported primary efficacy result. The rufinamide group demonstrated significant efficacy compared to placebo (p-value=0.016). This reviewer also re-analyzed the efficacy data of USA and Non-USA randomized patients separately.

For the USA and Non-USA randomized patients, the rufinamide group was not statistically significantly (p-value=0.104, & p-value=0.067, Wilcoxon Rank Sums test--sponsor's method) different from placebo. Although the study a positive study, it failed to provide clear evidence of efficacy of rufinamide for US randomized patients.

Study #022 demonstrated that rufinamide was significantly effective than placebo as adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over.

5.3. Conclusions and Recommendations

Study AE/ET1 was able to demonstrate that 800 mg of rufinamide was (marginally significant) effective in reducing partial seizure frequency of the adult patients with partial seizures. The other three doses 200 mg, 400 mg, and 1600 mg failed to demonstrate the efficacy of rufinamide.

Study #21A succeeded to demonstrate the efficacy of rufinamide for the ITT sample, but it did not provide a clear evidence to demonstrate the efficacy for the USA randomized patients.

Study AE/PT2 failed to show the efficacy of rufinamide as an adjunctive therapy in reducing partial seizure frequency of the adult patients with partial seizures.

Study#022 succeeded to demonstrate the efficacy of rufinamide as adjunctive therapy for Lennox-Gastaut syndrome (LGS) in children ages 4 and over.

Appears This Way
On Original

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

/s/

Ohidul Siddiqui
8/28/2006 09:04:42 AM
BIOMETRICS

Kun Jin
8/28/2006 09:10:09 AM
BIOMETRICS

James Hung
8/28/2006 09:44:38 AM
BIOMETRICS

Statistical Review and Evaluation
Clinical Studies

NDA/Serial Number: NDA 21-911 (Resubmission)
Drug Name: Rufinamide
Indication(s): Partial seizures in adults
Applicant: Eisai Medical Research Inc.
Date of Document: Feb 29, 2008
Review Priority: Standard
Biometrics Division: Division of Biometrics 1 (HFD-710)
Statistical Reviewer: Ohidul Siddiqui, Ph.D
Concurring Reviewers: Kun Jin, Ph.D; James Hung, Ph.D
Medical Division: HFD-120
Clinical Team: Norman Hershkowitz MD, PhD
Project Manager: Courtney Calder
Keywords: *NDA review, endpoint analysis/LOCF, multi-center*

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1. CONCLUSIONS AND RECOMMENDATIONS	3
1.2. BRIEF OVERVIEW OF REVIEWED CLINICAL STUDIES	3
1.2.1. PIVOTAL STUDIES.....	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION.....	4
2.1. OVERVIEW.....	4
2.2. DATA SOURCES	4
3. STUDIES REVIEWED.....	4
3.1. STUDY AE/ET1	4
3.2. FDA REVIEWER’S COMMENT ON STUDY AE/ET1.....	5
3.3 STUDY 21A	8
3.4. FDA REVIEWER’S COMMENTS ON STUDY 21A	9
3.5. FDA REVIEWER’S COMMENTS ON STUDY 22- LENNOX GASTAUT SYNDROME STUDY	10
CONCLUSIONS.....	12
5. APPENDIX-1-ORIGINAL STATISTICAL REVIEW	13

1. EXECUTIVE SUMMARY

The sponsor submitted a 'complete response' of the NDA 21-911 (Rufinamide) to address the issues listed in the September 15, 2006 Approvable Letter. In the original submission, the sponsor submitted efficacy findings of two studies (Study AE/ET1, and Study 21A) to support an approval claim of Rufinamide (an antiepileptic drug). In the Approval letter, the agency stated that the efficacy results were inconsistent, and the appropriate recommending dose was unclear. In this complete response, the sponsor included several statistical analyses of efficacy data of the two pivotal studies (AE/ET1 and 21A) to claim the appropriate recommending dose of rufinamide.

The sponsor also included some statistical findings on the study 22 (Lennox Gastaut Syndrome Study) to claim the efficacy of rufinamide to treat Lennox Gastaut Syndrome.

1.1. Conclusions and Recommendations

In the current resubmission, the sponsor submitted several sensitivity analyses findings of the efficacy data of Studies AE/ET1 and 21A to support a minimally efficacious dose of ~~2~~ mg/day (per study AE/ET1), and an acceptable maximum dose of 3,200 mg/day (per study 21A). According to this review, the sponsor's submitted sensitivity analyses findings of the efficacy data of two studies do not consistently support the claims of a minimally efficacious dose of ~~2~~ mg/day, and an acceptable defined maximum dose of 3,200 mg/day.

b(4)

The Study 22 (Lennox Gastaut Syndrome Study) was a positive study with respect to three co-primary efficacy measures. The imbalance seizure frequencies at baseline for the two groups might be a concern in considering the study as a positive study.

1.2. Brief Overview of Reviewed Clinical Studies

1.2.1. Pivotal Studies

The original statistical review is included in Appendix-1.

1.3 Statistical Issues and Findings

The statistical issues are stated in the original statistical review (enclosed in Appendix-1).

2. INTRODUCTION

2.1. Overview

The sponsor submitted a 'complete response' of the NDA 21-911 (Rufinamide) to address the issues listed in the September 15, 2006 Approvable Letter. In the original submission, the sponsor submitted the efficacy findings of two studies (Study AE/ET1, and Study 21A) to support an approval claim of Rufinamide (an antiepileptic drug). The original statistical review of the NDA is enclosed in Appendix-I.

In the Approvable letter, the agency stated that the efficacy results were inconsistent, and the appropriate recommending dose was unclear. In this complete response, the sponsor included several statistical analyses findings of the efficacy data of the two pivotal studies (AE/ET1 and 21A) to establish the appropriate recommending dose of rufinamide. Next, the included statistical results of the two studies are reviewed.

2.2. Data Sources

SAS data sets of the pivotal studies are available at \\CDSESUB1\EVSPROD\NDA021911\0000.

3. Studies Reviewed

3.1. Study AE/ET1

Sponsor's Findings

Study AE/ET1 was conducted to explore the effective dose range and to figure out a minimum effective dose. The primary outcome, the linear trend of dose-response for seizure frequency per 28 days, was significant (P=0.003).

In finding the minimum effective dose, the sponsor stated that due to the lack of normality in the seizure frequency per 28 days despite log transformation, the linear model failed to find the minimum effective dose. In Table 1, the sponsor listed the analyses of four secondary endpoints and claimed that the seizure frequency ratio of each treatment group in comparison to the placebo group showed a statistically significant reduction of seizure frequency for the doses of 400 mg/day, 800 mg/day and 1600 mg/day (all $P \leq 0.0274$).

Table 1: Secondary endpoints for AE/ET1

	Seizure frequency ratio ¹		Percentage of patients with a 25% reduction in seizure frequency ²		Percentage of patients with a 50% reduction in seizure frequency ²		Estimated odds-ratio for GATE ³	
	Median	P value		P value		P value		P value
Placebo	1.05		14		9			
200 mg/day	1.01	0.8116	22.8	0.7847	4.7	0.1822	1.452	0.1164
400 mg/day	0.93	0.0274	32.8	0.1198	16	0.0875	1.744	0.0197
800 mg/day	0.88	0.0123	34.1	0.0803	11.6	0.4812	1.781	0.0143
1600 mg/day	0.87	0.0163	37.6	0.0238	14.3	0.1978	2.238	0.0005

¹ The seizure frequency ratio for each patient was the number of seizures that occurred during the Double-blind Phase divided by the number of seizures that occurred during the Baseline Phase. This was expressed per 28-day intervals. Wilcoxon rank-sum test was used to compare the seizure frequency ratio.

^{2, 3, 4} Based on Logistic Regression

Source: clinical overview of the submission dated Feb 29, 2008

The sponsor also performed Poisson regression on the double-blind phase for dose response and minimum dose selection. Table 2 lists the results of the analysis on the primary outcome measure.

Table 2. Poisson Regression Analysis on Seizure Frequency during the administration double-blind Phase

Treatment Group	Percent reduction relative to placebo	Pair-wise comparisons to placebo		
		Estimate (SE)	95%CI	P-value
200mg	6.7%	0.933 (0.0640)	0.816, 1.068	0.3136
400mg	14.5%	0.855 (0.0635)	0.739, 0.989	0.0347
800mg	12.8%	0.872 (0.0593)	0.763, 0.996	0.0436
1600mg	15.6%	0.844 (0.0565)	0.740, 0.962	0.0112
Linear Trend of Dose-response				
Dose-Response		0.665 (0.1020)	0.493, 0.898	0.0078

Note: Results are based on a generalized linear model with ordinal dose, country, sex, age, and log (baseline counts) as covariates and adjusted for over-dispersion using Pearson Chi-square as a scale factor.

Source: clinical overview of the submission dated Feb 29, 2008

The sponsor believes that the ANCOVA based on ranks presented in Table 3 is a better approach and standard analysis in seizure trials analysis.

Table 3: ANCOVA on Ranks of Percentage Change in Total Seizure Frequency Per 28 Days

Treatment Group	Descriptive Statistics		Comparison to Placebo P-value ^a
	N	Mean (SD)	
Placebo	N	133	
	Mean (SD)	13.2 (69.1)	
	Median	4.9	
	Min., Max.	-100, 417	
200mg	N	127	0.9066
	Mean (SD)	8.0 (46.9)	
	Median	0.5	
	Min., Max.	-71, 185	
400mg	N	125	0.0273
	Mean (SD)	-2.7 (54.3)	
	Median	-6.9	
	Min., Max.	-87, 319	
800mg	N	129	0.0131
	Mean (SD)	-4.4 (51.2)	
	Median	-12.5	
	Min., Max.	-100, 225	
1600mg	N	133	0.0113
	Mean (SD)	-2.4 (58.4)	
	Median	-13.2	
	Min., Max.	-100, 417	

^a -P-value based on ANCOVA model on ranks with baseline and country as covariates

Source: clinical overview of the submission dated Feb 29, 2008

3.2. FDA Reviewer's Comment on Study AE/ET1

The objectives of Study AE/ET1 were to (i) find an effective dose-response trend, and (ii) figure out a minimum effective dose of rufinamide. To achieve the first objective, the sponsor needed first to demonstrate a significant dose-response trend among the selected doses (200mg, 400mg, 800mg, and 1600mg). If there was a statistically significant dose-response trend, then a minimum effective dose among the selected doses (i.e., objective #2) should be explored.

The sponsor included placebo group with the selected four doses in the dose response analysis, and the dose-response trend was statistically significant. The significance of this

dose response analysis might be due to either (i) there was a linear dose-response trend or (ii) there was no linear trend but a difference in responses between Placebo vs. all doses together (in presence of plateau dose response of the selected doses).

In finding the dose-response analysis, the sponsor recoded the doses as 0 (=placebo), 1 (=200mg), 2 (=400mg), 3 (=800mg) and (4=1600mg). Since the dose was considered as a continuous covariate in the model, it was meaningful (to keep proportionality of the dose amounts) to recode the doses as 2, 4, 8, and 16 instead of 1, 2, 3, and 4¹. In addition, in the dose response analysis, the main interest was to estimate the slope for the selected doses of interest. So, the selected doses (200mg, 400mg, 800mg, and 1600mg) were needed to be included in estimating the slope of the dose response trend.

Table 4 lists the impact of coding the doses as 1, 2, 3, and 4 instead of 2, 4, 8, and 16; and the impact of including the placebo arm in estimating the slope for the dose response. When the placebo arm was dropped from the analysis and the doses were coded as 2, 4, 8, and 16, then the estimated slope of dose response was insignificant (p-value=0.086). The insignificant slope means that the efficacy of the four doses 200mg, 400mg, 800mg, and 1600mg were similar. In presence of the placebo group in the slope analysis, the slope is significant (p-value=0.015), and this significance means that the efficacy of the dose groups were different from the efficacy of the placebo group. Since the slope of the four doses were not significant, one can pick up either 200mg or 1600mg as a minimal effective dose given that the safety profiles of the doses were similar.

Table 4: Regression Analysis for dose response

Regression Analysis [§]	Estimated Slope	P-value
Sponsor's analysis: Placebo arm was included in the model, and doses were coded as 0, 1, 2, 3, and 4	-0.048	0.003
Reviewer's analysis: Placebo arm is included in the model, and doses were coded as 0, 2, 4, 8, and 16	-0.0001	0.015
Reviewer's analysis: Placebo arm is dropped, and doses were coded as 1, 2, 3 and 4	-0.055	0.019
Reviewer's analysis: Placebo arm is dropped, and doses were coded as 2, 4, 8, and 16	-0.00008	0.086

[§]The primary statistical analysis for seizure frequency per 28 days (log,-transformed) was a normal multiple regression model.

In Table 1, Wilcoxon rank-sum test was used to compare the seizure frequency ratio (a secondary measure) of each individual dose vs. placebo. After multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment), only 800 mg of rufinamide was statistically significantly different from the placebo group. The sponsor did not consider any multiplicity adjustment in stating the significance of the dose vs. placebo comparisons.

¹ In evaluating an effective dose (i.e., individual doses vs. placebo), the dose were considered as FACTOR (i.e., categorical variable), and hence it was not an issue how the doses were coded in finding an effective dose.

In the logistic regression analyses on the other secondary measures 25% reduction or 50% reduction, none of the doses were statistically significant after multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment).

In the logistic regression analysis of Global Assessment of Therapeutic Effect test (GATE) scale, only 1600mg of rufinamide was statistically significantly different from the placebo group after multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment).

In Table 2, only 1600mg of rufinamide was statistically significantly different from the placebo group after multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment).

This reviewer dropped 200mg (since p-value=.906) from the Poisson model and refitted the Poisson regression model. Table 5 lists the findings of the analysis. In absence of the 200mg in the model, the 400mg and 800mg failed to retain the significance levels as reported in Table 2. Each dose group should have its own power to demonstrate its significant efficacy.

Table 5. Poisson Regression Analysis on Seizure Frequency during the administration double-blind Phase (excluded 200 mg)

Treatment group	Estimate (SE)	P-value (dose vs. placebo)
400 mg vs. Placebo	0.888 (0.080)	0.139
800 mg vs. Placebo	0.887 (0.073)	0.101
1600 mg vs. Placebo	0.856 (0.072)	0.030

The sponsor included log-transformed baseline seizure count as a covariate in the Poisson model. Since the seizure frequency data of post-baseline was modeled as count data, it was meaningful to include the baseline seizure frequency data as a covariate without any transformation. This reviewer included baseline seizure frequency data as a covariate in the model without any transformation, and found that none of the doses were statistically significantly (p-values ≥ 0.245) different from placebo.

In Table 3, a regular ANCOVA analysis was done on the rank of Percent Change in Total Seizure Frequency Per 28 Days to compare the efficacy of the individual doses vs. placebo. After multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment), only 1600 mg of rufinamide was statistically significantly different from the placebo group.

This reviewer did an ANCOVA analysis on the rank of Total Seizure Frequency Per 28 Days at Post-baseline instead of considering rank of the percent change of seizure frequency. In the analysis, the rank of baseline total seizure frequency per 28 days and country (land) were included as covariates (i.e., the same covariates that were used by the sponsor in Table 6). Table 6 lists the p-values of the analysis. After multiplicity

adjustment (either using Hochberg’s method or Bonferroni adjustment), none of the doses were statistically significantly different from placebo in the rank based ANCOVA analysis.

Table 6: ANCOVA on Ranks of Total Seizure Frequency Per 28 Days at Post-baseline

	Dependent Measure: Rank of Total Seizure Frequency Per 28 Days at Post-baseline
	P-value [‡]
200mg vs. Plb	0.962
400mg vs. Plb	0.033
800mg vs. Plb	0.034
1600mg vs. Plb	0.0601

[‡] P-value based on ANCOVA model with ranked baseline Seizure and country as covariates

The sponsor submitted several sensitivity analyses to support the significances of 400 mg/day, 800 mg/day and 1600 mg/day of rufinamide in reducing total seizure frequency per 28 days. In this review, it was found that the efficacy results of the doses across the submitted sensitivity analyses were still inconsistent as reported in the Approval letter, dated Sept. 15, 2006.

3.3 Study 21A

The study 21A was a positive study with respect to the protocol specified primary efficacy measure- percentage change in partial seizure frequency per 28 days of the Double-blind Phase from the Baseline Phase. Rufinamide 3200 mg appeared to be significantly different from the placebo group (Wilcoxon rank-sums test, P-value=0.0158) as adjunctive therapy in adults (age ≥ 16 years) patients with inadequately controlled partial seizures.

In the study report, an ANCOVA analysis (as a secondary analysis) was done on log of seizure frequency at post-baseline including the log transformed total partial seizure frequency per 28 days during the baseline phase, Treatment, Country, Sex, and Age as covariates . The analysis indicated that Rufinamide 3200mg was not statistically significantly (P-value=0.092) different from placebo. In other previously reviewed NDAs [e.g., NDA#22253 (Lacosamide); NDA#21035 (Keppra)], ANCOVA on post-baseline log transformed total partial seizure frequency per 28 days was used as the primary statistical analysis, and hence the ANCOVA analysis on log-transformed post-baseline analysis is also an acceptable analysis. In the previous reviewed NDAs, the statistical findings based on both the ANCOVA analysis and Willcoxon rank-sum test analysis were consistent (i.e., provided similar p-values) regarding the efficacy conclusions of the drugs.

In this submission, the sponsor reported results of an ANCOVA on rank of percent change from baseline in seizure frequency including baseline (rank of seizure freq) and country as covariates. In the rank ANCOVA analysis, Rufinamide 3200mg was highly significant (P-value=0.008) compared to placebo.

3.4. FDA Reviewer's Comments on Study 21A

This reviewer did a secondary analysis on the efficacy data of the study 21A (reported in section 9.2.1, page 45 of the study report). Table 7 lists the p-values for the comparison of rufinamide 3200mg vs. placebo for the secondary analyses. According to the sponsor, the lack of statistical significance in the ANCOVA analysis (i.e., Model#1) was due to the lack of normality in this variable despite the log transformation. The sponsor stated that an ANCOVA rank analysis is more appropriate in analyzing seizure frequency data. Therefore, as a remedy of the lack of normality, one can use an ANCOVA model (Model#2) on rank data of total partial seizure frequency per 28 days during the Double-blind Phase including rank of total partial seizure frequency per 28 days during the baseline and age as covariates, and treatment, Country, gender as factors in the model. The model provided a p-value of 0.118. So, rufinamide was not statistically significantly different from placebo based on ANCOVA model on rank data of post-baseline seizure frequency.

Table 7. Study 21A- Comparison of Rufinamide 32mg vs. Placebo

Secondary Efficacy Measures	P-value
Model #1: ANCOVA: Log (total partial seizure frequency per 28 days during the Double-blind Phase) = Log (Total partial seizure frequency per 28 days during the baseline Phase)+ Treatment +Country+sex+age	0.092
Model#2:ANCOVA: (comparable to Model#1): Rank of total partial seizure frequency per 28 days during the Double-blind Phase = Rank of total partial seizure frequency per 28 days during the baseline Phase+ Treatment + Country +Age +Sex	0.118

Therefore, although Study 21A was a positive study with respect to the protocol specified primary efficacy measure and primary statistical method, the findings of sensitivity analyses put some uncertainties in the efficacy conclusion of rufinamide.

Table 8 lists the mean and median seizure frequency per 28 days in the baseline and double-blind phases for the studies AE/ET1 and 21A. The changes in median seizure frequency from baseline to double-blind period were in the range of -1.16 to -0.95 for the doses of 400mg to 3200mg. The changes in median seizure frequency from baseline to double-blind period did not support any evidence of efficacy trend of the doses range 400mg to 3200mg. The same was true for the mean changes in seizure frequency.

Table 8: Median and Mean seizure frequency per 28 days in the Baseline and Double-blind Phases --Studies AE/ET1 and 21A)

Data set (ITT sample)		N	Mean seizure freq per 28			Median seizure freq per 28			Median % Change from Base
			Base Phase	Double-blind Phase	Change from Base	Base Phase	Double-blind Phase	Change from Base	
Study-AE/ET 1	Placebo	133	36.3	44.4	8.1	11.67	11.86	0.19	4.89
	200 mg	127	24.3	25.1	0.8	11.08	11.00	-0.08	0.45
	400 mg	125	23.8	21.5	-2.3	11.83	10.67	-1.16	-6.93
	800 mg	129	28.1	26.4	-1.7	12.67	11.00	-1.67	-12.5
	1600 mg	133	26.3	26.2	-0.1	11.33	10.67	-0.66	-13.18
Study-21A	Placebo	156	20.7	21.8	1.1	8.00	8.66	-0.66	1.61
	3200 mg	156	21.8	20.9	-0.9	8.50	7.55	-0.95	-20.42

3.5. FDA Reviewer's Comments on Study 22- Lennox Gastaut Syndrome Study

Primary variable 1: Total seizure frequency per 28 days

Rufinamide was effective (p-value=0.0015) in reducing the percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase. However, the median total seizure frequency per 28 days at double-blind period was almost same for the two groups (Table 9). Therefore, the statistical significance of the difference of the two groups might be due to the imbalance baseline seizure frequency per 28 days for the two groups at baseline.

Table 9: Summary of percent change in total seizure frequency per 28 days relative to baseline (Intent-to-treat patients)

	Rufinamide			Placebo		
	n	Median	Range	n	Median	Range
Baseline seizure frequency per 28 days	74	290.0	(48.0, 53760.0)	64	205.0	(21.0, 109714.0)
Double-blind seizure frequency per 28 days	74	204.1	(5.4, 43262.3)	64	205.4	(50.7, 113165.0)
Percent change in seizure frequency per 28 days from baseline*	74	-32.7	(-92.3, 381.4)	64	-11.7	(-82.8, 550.6)

Cross-reference: Post-text Table 9.1-1; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.

* Between-group comparison using Wilcoxon rank-sum test p-value = 0.0015

Source: Study report

Primary efficacy variable 2: Tonic-atonic seizure frequency per 28 days

In comparison to placebo, rufinamide was effective (p-value<0.0001) in reducing the percent change in tonic-atonic seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase (Table 10).

Table 10: Summary of percent change in tonic-atonic seizure frequency per 28 days relative to baseline (Intent-to-treat patients)

	Rufinamide			Placebo		
	n ^a	Median	Range	n ^a	Median	Range
Baseline tonic-atonic seizure frequency per 28 days	73	92.0	(5.0, 14304)	60	92.5	(1.0, 13122)
Double-blind tonic-atonic seizure frequency per 28 days	73	60.7	(0.0, 12036.1)	60	76.2	(0, 17500)
Percent change in tonic-atonic seizure frequency per 28 days from baseline ^b	73	-42.5	(-100, 1190.8)	60	1.4	(-100, 709.6)

Cross reference: Post-text Table 9.1-2; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.

^a 5 patients (1 rufinamide, 4 placebo) did not experience tonic-atonic seizures during the Baseline Phase.

^b Between-group comparison using Wilcoxon rank-sum test p-value < 0.0001.

Source: Study report

Primary efficacy variable 3: Seizure severity subscale of Global Evaluation of patient's condition

Rufinamide was also effective (p-value=0.0041) compared to placebo with respect to the changes in seizure severity rating at the end of the Double-blind Phase.

Secondary measures: Seizure frequency for other subtypes

Table 11 lists the median number of atypical absence, tonic, myoclonic, partial, and absence seizures that occurred during the Baseline Phase was higher in the rufinamide group than in the placebo group. That is, the two groups were imbalanced at baseline with respect to the subtypes seizure frequency.

Among the atypical absence, tonic, myoclonic, partial, and absence seizures subtypes seizure frequency, rufinamide was significantly effective in controlling atonic seizures (p-value = 0.0125) and combined absence and atypical absence seizures (p-value = 0.0222). The median percent decreases in other subtypes of seizures for the rufinamide group were numerically higher but not statistically significant as compared to the placebo group.

Imbalanced Seizure Frequency at Baseline

Tables 9 and 11 list the median number of total seizures, atypical absence, tonic, myoclonic, partial, and absence seizures that occurred during the Baseline Phase. The two groups were imbalanced at baseline with respect to all subtypes seizure frequencies, and hence also with respect to total seizure frequency. The imbalance baseline seizure frequency indicated that patients who had higher severity of the disease were more likely to be randomized into the rufinamide group instead of the placebo group. In a recent communication with the sponsor regarding this issue, the sponsor stated that the imbalance seizure frequencies at baseline for the two groups were by chance. The sponsor strongly believed that there was no issue regarding randomization scheme of the trial. However, the imbalance seizure frequency for each subtype (i.e., the patients who had higher seizure frequency were more likely to receive rufinamide) might not be occurred by chance.

Table 11: Summary of percent change in frequency of other seizure types per 28 days relative to baseline (Intent-to-treat patients)

	Rufinamide			Placebo			p-Value ^b
	n ^a	Median	Range	n ^a	Median	Range	
Absence & atypical absence seizures							
Baseline frequency/ 28 days	66	63.5	(1, 2171)	56	53.0	(1, 4009)	
Double-blind frequency/ 28 days	66	39.1	(0, 2793.7)	56	43.0	(0, 5828.3)	
% change in frequency/ 28 days	66	-50.6	(-100, 1729.2)	56	-29.8	(-100, 584.3)	0.0222
Tonic seizures							
Baseline frequency/ 28 days	52	66.3	(1, 1450.4)	43	49.0	(1, 1066)	
Double-blind frequency/ 28 days	52	47.0	(0, 12036.1)	43	55.3	(0, 1228.6)	
% change in frequency/ 28 days	52	-27.8	(-100, 3003.6)	43	1.6	(-100, 300)	0.0421
Atonic seizures							
Baseline frequency/ 28 days	45	56.0	(1, 4037)	33	49.0	(2, 13122)	
Double-blind frequency/ 28 days	45	24.6	(0, 5450.2)	33	60.3	(0, 16946.7)	
% change in frequency/ 28 days	45	-44.8	(-100, 13660)	33	-21.0	(-100, 709.6)	0.0125
Myoclonic seizures							
Baseline frequency/ 28 days	37	80.0	(1, 38928)	31	50.8	(1, 92583)	
Double-blind frequency/ 28 days	37	52.3	(0.3, 30352.8)	31	39.3	(0, 90350.7)	
% change in frequency/ 28 days	37	-30.4	(-98.7, 338.6)	31	-13.6	(-100, 184.7)	0.5711
Tonic-clonic seizures							
Baseline frequency/ 28 days	37	18.0	(1, 336)	27	15.0	(1, 788)	
Double-blind frequency/ 28 days	37	9.8	(0, 71.4)	27	14.7	(0, 200)	
% change in frequency/ 28 days	37	-45.6	(-100, 789.2)	27	-18.1	(-100, 729.6)	0.3306
Partial seizures							
Baseline frequency/ 28 days	11	49.0	(1, 4195)	9	41.0	(3, 723)	
Double-blind frequency/ 28 days	11	14.3	(0, 7862)	9	23.6	(0, 600.7)	
% change in frequency/ 28 days	11	-71.9	(-100, 126.1)	9	-11.1	(-100, 43.4)	*** ^c

Cross reference: Post-text Tables 9.2-2 to 9.2-11; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.

^a Number of patients who experienced a given type of seizure during the Baseline Phase.

^b Wilcoxon rank-sum test.

^c No p-value reported because this type of seizure occurred in <20% of the patients.

Source: Study report

Conclusions

In the current resubmission, the sponsor submitted several secondary analyses on the efficacy data of the studies AE/ET1 and 21A to support a minimally efficacious dose of _____ /day (per study AE/ET1), and acceptable a defined maximum dose of 3,200 mg/day (per study 21A)

In this review, the sensitivity analyses of the two studies do not consistently support the claims of a minimally efficacious dose of _____ /day, and an acceptable defined maximum dose of 3,200 mg/day.

The Study 22 (Lennox Gastaut Syndrome Study) was a positive study with respect to three co-primary efficacy measures. The imbalance seizure frequencies at baseline for the two groups might be a concern in considering the study as a positive study.

b(4)

5. Appendix-1-Original Statistical Review

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

/s/

Ohidul Siddiqui
8/22/2008 12:23:57 PM
BIOMETRICS

Kun Jin
8/22/2008 01:24:28 PM
BIOMETRICS

James Hung
8/26/2008 09:38:46 AM
BIOMETRICS



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Carcinogenicity Studies

NDA/Serial Number:	21-911
Drug Name:	Inovelon (Rufinamide) 100, 200, and 400 mg Tablets
Indication:	Adjunctive Treatment of Partial Seizures and Seizures Associated with Lennox-Gastaut Syndrome
Applicant:	Eisai Medical Research, Inc.
Date:	November 17, 2005
Biometrics Division:	Division of Biometrics 6
Statistical Reviewer:	Roswitha Kelly, M.S.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Neurology Products
Pharm/Tox Reviewer:	Edward J. Fisher, Ph.D.
Pharm/Tox Team Leader	Lois Freed, Ph.D.
Project Manager:	Courtney Calder

Distribution: NDA 21911/Inovelon
HFD-120/C. Calder
HFD-120/E. Fisher, Ph.D.
HFD-120/L. Freed, Ph.D.
HFD-715/K. Lin, Ph.D.
HFD-705/S.Machado Ph.D.
HFD-710/Roswitha Kelly, M.S.
HFD-700/R. O'Neill, Ph. D.
HFD-700/L. Patrician, M.S.

File Directory: C:\Data\N21911_Rufi_Carc_2.doc

Table of Contents

1.	Executive Summary	3
1.1.	Conclusions and Recommendations	3
1.2.	Brief Overview of Carcinogenicity Studies	4
1.3.	Statistical Issues and Findings	4
2.	Introduction	5
2.1.	Overview	5
2.2.	Data Sources	5
3.	Statistical Evaluation	5
3.1.	Rat Study # 926046.....	5
3.1.1.	Statistical Methods	6
3.1.2.	Sponsor's Results	6
3.1.3.	Reviewer's Results	7
3.2.	Mouse Study #926045	18
3.2.1.	Statistical Methods	18
3.2.2.	Sponsor's Results	18
3.2.3.	Reviewer's Results	19
4.	Conclusions	27

List of Tables

Table 1: Summary of Important Trends in Tumor Findings among Rats and Mice	3
Table 2: Female Rats, Mortality by Time Interval and Dose	9
Table 3: Female Rats, Mortality Trend with Dose	9
Table 4: Female Rats, Tumor Incidences and P-values for Trend.....	10
Table 5: Female Rats: Tumor Incidences for Selected Combined Tumors	12
Table 6: Male Rats, Mortality by Time Interval and Dose	14
Table 7: Male Rats, Mortality Trend with Dose	15
Table 8: Male Rats, Tumor Incidences and P-values for Trend	15
Table 9: Male Rats: Tumor Incidences of Selected Combined Tumors	17
Table 10: Female Mice, Mortality by Time Interval and Dose	19
Table 11: Female Mice, Mortality Trend with Dose	20
Table 12: Female Mice, Tumor Incidences and P-values for Trend.....	21
Table 13: Female Mice, Selected Combined Tumors.....	23
Table 14: Male Mice, Mortality by Time Interval and Dose	24
Table 15: Male Mice, Mortality trend with Dose	24
Table 16: Male Mice, Tumor Incidences and P-Values for Trend	26
Table 17: Male Mice, Selected Combined Tumors	27

List of Figures

Figure 1: Female Rats, Kaplan Meier Survival Functions.....	10
Figure 2: Female Rats Mean Body Weight Curves by Dose	12
Figure 3: Male Rats, Kaplan Meier Survival Functions	15
Figure 4: Male Rats Mean Body Weight Curves by Dose.....	18
Figure 5: Female Mice, Kaplan Meier Survival Functions.....	20
Figure 6: Male Mice, Kaplan Meier Survival Functions	25

1. Executive Summary

1.1. Conclusions and Recommendations

Based on the standard Office of Biometrics analysis of carcinogenicity data, the reviewer observed the following statistically significant trends with dose in single and combined tumor types (Table 1). These analyses took intercurrent mortality and the context of observation into account and used all four treatment groups. Statistical significance was declared at different levels for rare and common tumors.

Table 1: Summary of Important Trends in Tumor Findings among Rats and Mice

TUMOR	FEMALE RATS	MALE RATS	FEMALE MICE	MALE MICE
Bone/Osteoma	No Tumors	No Tumors	Significant P=0.0102	Significant P=0.0245
Bone/Osteosarcoma	No Tumors	Slight Increase P=0.3367	No Tumors	No increase P=0.5315
Bone/Combined Osteoma and Osteosarcoma	n/a	Same as Osteosarcoma P=0.3367	Same as Osteoma P=0.0102	Slight Increase p=0.0415
Liver/Hepatocellular Adenoma	Slight Increase p=0.0534	No Increase P=0.6225	Significant P=0.0001	Significant P=0.0012
Liver/Hepatocellular Carcinoma	No Increase P=0.3812*	No Increase P=0.9894	Increase P=0.0724	Increase P=0.0158
Liver/Combined Hepatocellular Adenoma and Carcinoma	Same as Hepatocellular Adenoma p=0.0534	No Increase P=0.9224	Highly Significant P=0.0000	Highly significant P=0.0001

*These tumors were reported as incidental

Among the female rats no statistically significant increase in any tumor type was observed. The validity of this study may be in question as mean body weights would indicate that the high dose exceeded the MTD. Excluding the high dose from the analyses led to similar conclusions, i.e. no significant increases in either mortality or tumors. Though to a lesser degree than the high dose, the mid dose had also substantially lower mean body weights than the controls and hence may have exceeded the MTD as well. This is in contrast to the sponsor's conclusion that the mid dose represented the MTD. The final decision with respect to the validity of this study is left to the expertise of the reviewing pharmacologist.

Among the male rats unusually high mortality among the controls caused an early termination of the whole study and a highly significant increase in survival with dose. After 97 weeks of treatment no statistically significant increase in tumor incidences was observed across the four treatment groups. Similarly to the female rats, the mean body weights of the male high dose group were greatly lower than the controls' and hence the high dose likely exceeded the MTD. Excluding the high dose from analysis resulted again in a significant increase in survival with dose with the mid dose experiencing the best survival. With the high dose excluded, the increase with dose in follicular cell adenoma in the thyroid reached statistical significance. This was in agreement with the sponsor's conclusion that the increase in this tumor type did not reach statistical significance across all treatment groups due to the severe body weight suppression in the high dose. It needs to be determined whether a study trimmed in length and in the number of treatment groups is still valid to assess the tumorigenic potential of the compound.

Among the female and male mice the same two tumor types showed statistically significant increases, namely osteoma in the bone and hepatocellular adenoma in the liver. Among the female mice, no osteosarcomas were observed. For the male mice the combination of osteomas and osteosarcomas led to a non-significant increase. There were non-significant increases in hepatocellular carcinomas and their combination with the hepatocellular adenomas resulted in highly significant trends with dose in both genders.

No other tumor type or combination of certain tumors reached statistical significance at the usual levels.

1.2. Brief Overview of Carcinogenicity Studies

The sponsor provided the study reports and tumor data files for the rat carcinogenicity and mouse carcinogenicity studies with the November 17, 2005, electronic submission. Study # 92-6046 was a whole life study in Sprague-Dawley rats with doses of 0, 20, 60, and 200 mg/kg/day of rufinamide mixed into the feed. The female rats were treated for 103 weeks. The male rats were terminated early after 97 weeks of dosing because of high mortality among the controls. Study # 92-6045 was a whole life study in CD-1 mice with doses of 0, 40, 120, and 400 mg/kg/day of rufinamide mixed into the feed. Both genders were treated for 103 weeks. In both species, the group size was 60 animals per dose and gender.

1.3. Statistical Issues and Findings

There are two major influences on tumor detection in the rat study. For both genders the mean body weights of the high dose groups were much lower than the controls' and may have masked any tumorigenic potential of the compound. In addition, the male controls experienced unusually high mortality which resulted in early termination of this study, a factor which can also influence the detection of late developing tumors.

Excluding the high dose group from analysis did not alter the overall conclusions for the females and the validity of this study is in question. For the males, excluding the high dose group from analysis resulted in a significant increase in one tumor type and in one combination of tumors. Though a significant tumor finding validates a study, it is pointed out that the study was terminated early due to unexpected high mortality among the male control rats. The reviewer has some concern that findings may not be clearly interpretable when a study was trimmed in length and in treatment groups. The final decision with respect to the validity of this study is left to the expertise of the reviewing pharmacologist.

Among the mice a strong signal of tumorigenicity was observed by the same two tumor types showing statistically significant increases in both the males and females. When combining these tumors with related ones, one of the tumor types resulted again in a highly significant increase in both genders.

2. Introduction

2.1. Overview

This review addresses the sponsor's reports and findings of the rat and mice carcinogenicity studies (#92-6046 and #92-6045). In addition, the reviewer independently analyzed the tumor files for each gender of each species. In discussion with the reviewing pharmacologist, some tumor types were combined for additional analyses.

2.2. Data Sources

The rat and the mouse tumor data were submitted as SAS transport files following the electronic submission guidance. They and the sponsor's study reports can be found in the EDR at \\CDSESUB1\N21911\N_000\2005-11-17.

3. Statistical Evaluation

3.1. Rat Study # 926046

This was an oral feed whole life study in Sprague-Dawley rats to determine the carcinogenic potential of rufinamide. The study was conducted and evaluated by Ciba-Geigy in Summit, NJ. Sixty animals per sex were exposed to daily doses of 0, 20, 60, or 200 mg/kg for at least 98 (males) or 104 weeks (females). Due to low survival among control males all remaining males were sacrificed during weeks 98-99. Surviving female rats were sacrificed as scheduled during weeks 104-105. The animals were housed singly and had feed and water available ad lib. The study was initiated Aug. 12, 1992 and

terminated Aug. 21, 1994. A complete necropsy and microscopic examination was conducted on all tissues and organs from all rats.

3.1.1. Statistical Methods

Among other methods, the sponsor tested for equality of and trend in survival curves by the Mantel-Cox log rank test and by presenting Kaplan-Meier estimates. Tumor incidences were analyzed by one-sided trend tests adjusted for mortality differences following the general method of Peto et al., i.e. taking the context of observation into account. Palpable lesions were classified as mortality independent and analyzed as if fatal with the tumor onset time used as the death time. For incidental tumors the specific method of analysis was determined by whether or not animals shared the same death time. For fatal and palpable tumors the specific method depended on the number of animals with tumor. The sponsor followed significant trend tests involving all treatment groups with trend tests sequentially removing the highest remaining dose until no further significant results were observed or all groups had been compared. As the increase in follicular cell adenomas among the male rats did not reach statistical significance when all dose groups were used, the sponsor did not test for trend with the high dose removed. However, the sponsor noted the increase in this tumor type.

The reviewer used the standard Office of Biometrics (OB) software for carcinogenicity studies which followed similar principles as the sponsor had adopted. For all tumor types, OB's primary statistic is the exact permutation trend test. The context of observation is addressed by using different numbers at risk and by specifying different time intervals for fatal/palpable and incidental tumors. Usually only the trend test involving all treatment groups is performed. When extraneous factors suggest that the results from the high dose animals are invalid, the same method is applied to the data with the high dose removed. The reviewer's statistical approach follows the draft guidance found at <http://www.fda.gov/cder/guidance/815dft.pdf>. Though the references of this draft guidance include most of the authors the sponsor has cited, they refer to different publications. Hence it is not surprising that the p-values observed by the sponsor and by the reviewer are not identical. There was no consistent direction in this difference. At times the differences were small, at others quite substantial. For example, the sponsor observed a p-value of 0.025 for trend in benign follicular adenomas in the thyroid of the male rats. The reviewer observed a p-value of 0.2007 for the same incidences. It is noted that both approaches led to similar conclusions. The reviewer relied on the results produced by the OB software, as these are consistently applied to carcinogenicity study submissions.

3.1.2. Sponsor's Results

The sponsor observed a dose-related trend in mortality among the female rats at $p=0.080$ (two-sided). Among the male rats, the dose-related trend in mortality was highly

significant ($p=0.000$) with the high dose males having the best survival. In fact, this study was terminated early (week 99) due to increased mortality among the male controls.

The sponsor noted no treatment related increases in any neoplasm among the female rats. A treatment related increase in the incidence of thyroid follicular adenomas was observed among the male rats but did not reach statistical significance. The sponsor contributed the lack of statistical significance to the severely reduced body weights of the high dose males. As their testing procedure stopped with a non-significant trend, they did not test for any increase in this tumor type when the high dose was excluded.

The sponsor concluded that the maximum tolerated dose (MTD) was established at 60 mg/kg for both genders based on the body weight gain reductions.

The sponsor reported that one male control animal apparently was treated with 20 mg/kg/day. When this was detected, the animal was sacrificed and removed from the group. Hence there are only 59 male controls.

3.1.3. Reviewer's Results

It is noted that the length of treatment seems to be one week shorter than the sponsor stated. The sponsor's data set for the females indicated treatment for 103 weeks and the data set for the males reported treatment for 97 weeks. Terminal sacrifice started the week immediately following and lasted 2 weeks.

3.1.3.1 Female Rats

Tables 2 and 3 and Figure 1 show that there was a somewhat better survival in the mid and high dose groups than in the control and low dose groups, but not to a statistically significant degree. Though the p-values between the sponsor and the reviewer differed, both reached the same conclusion.

All trend tests in tumor incidences were adjusted for intercurrent mortality and tested for linear increase in tumors with dose. In addition to the context of observation (fatal or incidental), the incidence among the concurrent controls determined whether the tumor was rare or common. The trend tests were declared statistically significant at $\alpha=0.025$ and $\alpha=0.005$ for rare and common tumors, respectively. With this approach, Table 4 shows no statistically significant increase in any single tumor type among the female rats. The following tumors were combined: alveolar/bronchiolar adenoma and adenocarcinoma in the lung, islet cell adenoma and carcinoma in the pancreas, adenoma and carcinoma, pars distalis, in the pituitary, benign and malignant pheochromocytoma in the adrenal gland, c-cell adenoma and carcinoma in the thyroid, adenoma and adenocarcinoma in the Zymbal's gland, and hepatocellular adenoma and carcinoma in the liver. None of these combinations resulted in a statistically significant increase (Table 5). These conclusions are consistent with the sponsor's findings.

As no statistically significant increase in tumor incidences was observed among the female rats, the validity of this study was evaluated. From Table 2 it is clear that sufficient numbers of animals were exposed to the compound sufficiently long, namely the animals' expected life span, and that the administration of the compound did not increase mortality with dose. Using the sponsor's mean body weight graph (Figure 2) and corresponding tables, the reviewer noted that the treated groups had mean body weights lower than the controls at all times. Specifically, at the end of week 1 the difference between the high dose and control groups' mean body weight was about 11 percent. By the end of the study the mean body weight of the high dose females was 37 percent lower than the mean body weight of the controls. These numbers suggest that the high dose had exceeded the MTD.

As the mean body weights of the high dose were so much lower than the controls' one could look for the mid-dose as a potential MTD. Excluding the high dose from the analyses of the female rats resulted in similar findings and conclusions as when all treatment groups were analyzed: Trends in mortality were still not significant ($p=0.1516$) and no tumor findings approached statistical significance ($p>0.2500$). The mid dose females had mean body weights of about 22 percent lower than their controls at one year and of about 26 percent towards the end of the study, indicating that even the mid dose may have exceeded the MTD. The final determination of the validity of the female rat study is left to the expertise of the reviewing pharmacologist.

Appears This Way
On Original

Table 2: Female Rats, Mortality by Time Interval and Dose

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-52	60	7	53	88.3	11.7
	53-78	53	11	42	70.0	30.0
	79-91	42	12	30	50.0	50.0
	92-103	30	10	20	33.3	66.7
	FINALKILL104-105	20	20	0		
LOW	0-52	60	3	57	95.0	5.0
	53-78	57	15	42	70.0	30.0
	79-91	42	14	28	46.7	53.3
	92-103	28	8	20	33.3	66.7
	FINALKILL104-105	20	20	0		
MED	0-52	60	1	59	98.3	1.7
	53-78	59	11	48	80.0	20.0
	79-91	48	15	33	55.0	45.0
	92-103	33	6	27	45.0	55.0
	FINALKILL104-105	27	27	0		
HIGH	0-52	60	2	58	96.7	3.3
	53-78	58	9	49	81.7	18.3
	79-91	49	13	36	60.0	40.0
	92-103	36	11	25	41.7	58.3
	FINALKILL104-105	25	25	0		

Table 3: Female Rats, Mortality Trend with Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	1.6730	0.4332	1.3884	0.4995
Depart from Trend				
Dose-Mortality Trend	1.9605	0.1615	2.8046	0.0940
Homogeneity	3.6336	0.3038	4.1930	0.2414

Figure 1: Female Rats, Kaplan Meier Survival Functions

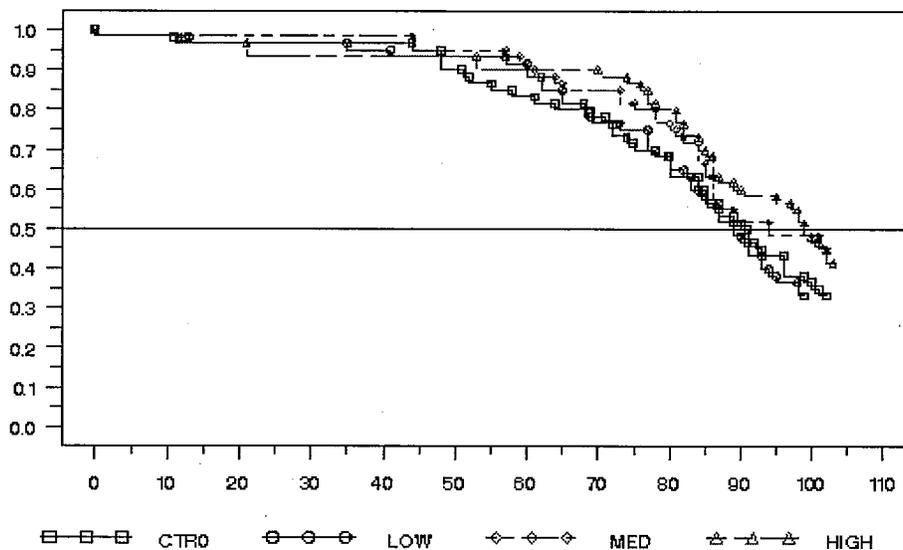


Table 4: Female Rats, Tumor Incidences and P-values for Trend

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
10	LUNG	23	ADENOCARCINOMA [M], alveolar/b	1	0	0	0	1.0000	0.8355
10	LUNG	24	ADENOMA [B], alveolar/bronchio	1	0	0	0	1.0000	0.8220
10	LUNG	25	LEIOMYOMA [B]	1	0	0	0	1.0000	0.8220
10	LYMPH NODE	84	HEMANGIOMA [B]	0	0	1	0	0.8043	0.5028
11	MAMMARY GLAND	27	ADENOCARCINOMA [M]	6	20	15	15	0.4026	0.3995
11	MAMMARY GLAND	28	ADENOMA [B]	2	3	3	3	0.4289	0.4332
11	MAMMARY GLAND	29	CARCINOSARCOMA [M]	1	0	0	0	1.0000	0.8355
11	MAMMARY GLAND	30	FIBROADENOMA [B]	36	27	27	19	0.9999	0.9999
11	MAMMARY GLAND	31	HEMANGIOMA [B]	1	0	0	0	1.0000	0.8355
11	MAMMARY GLAND	32	SARCOMA [M]	0	0	0	1	0.3143	0.0762
13	OVARY	36	GONADAL STROMAL TUMOR, BENIGN	0	0	1	0	0.5652	0.5846
13	OVARY	37	SERTOLI-CELL TUMOR [B]	0	1	0	0	0.7826	0.7648
13	OVARY	38	THECAL-CELL TUMOR, MALIGNANT [0	0	1	0	0.5185	0.5547

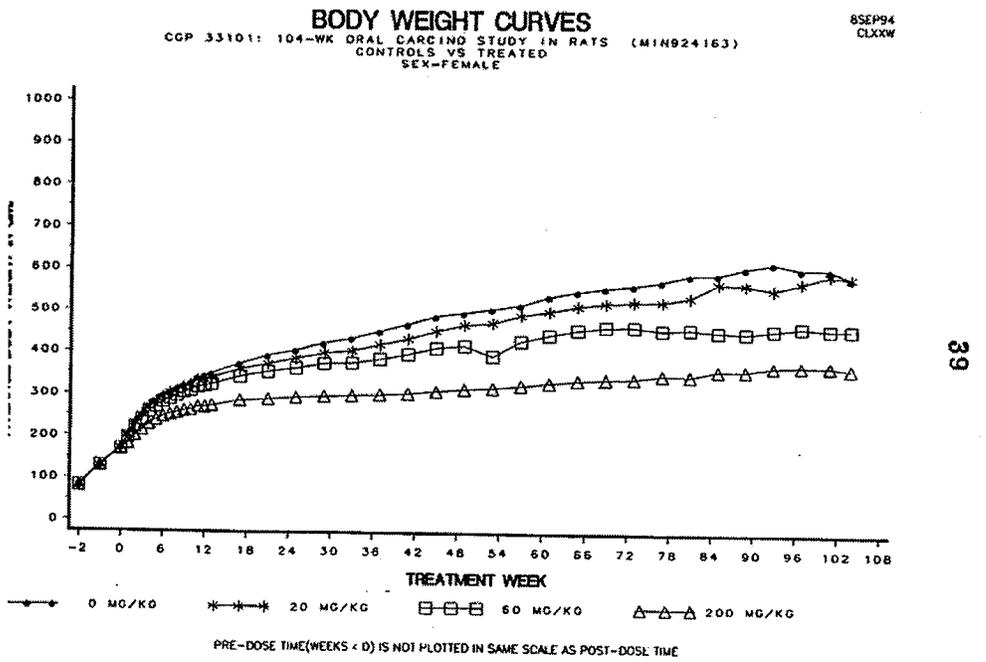
13	OVARY	39	YOLK SAC CARCINOMA [M]	0	0	1	0	0.5145	0.5734
14	PANCREAS	41	ISLET CELL ADENOMA [B]	1	0	2	0	0.7343	0.7784
14	PANCREAS	42	ISLET CELL CARCINOMA [M]	1	1	0	0	0.9365	0.8689
15	PARATHYROID	43	ADENOMA [B]	1	0	2	1	0.4365	0.4612
16	PITUITARY	44	ADENOMA [B], pars distalis	49	47	52	50	0.8186	0.8162
16	PITUITARY	45	CARCINOMA [M], pars distalis	1	2	1	3	0.2154	0.1936
18	SKIN	48	FIBROMA [B]	2	2	1	1	0.7759	0.7637
18	SKIN	49	FIBROSARCOMA [M]	0	0	1	0	0.5652	0.5846
18	SKIN	50	HEMANGIOSARCOMA [M]	0	0	1	0	0.5115	0.5627
18	SKIN	53	LIPOMA [B]	5	0	1	0	0.9965	0.9759
18	SKIN	55	RHABDOMYOSARCOMA [M]	0	1	0	0	0.7679	0.7707
19	SMALL INTESTINE	59	LEIOMYOSARCOMA [M]	0	0	0	2	0.0854	0.0171
2	ADRENAL GLAND	2	CORTICAL ADENOMA [B]	2	2	1	0	0.9469	0.9296
2	ADRENAL GLAND	3	PHEOCHROMOCYTOMA [B]	1	1	2	0	0.8368	0.8528
2	ADRENAL GLAND	4	PHEOCHROMOCYTOMA [M]	0	0	0	1	0.3143	0.0762
2	ADRENAL GLAND	83	CORTICAL CARCINOMA [M]	0	1	0	1	0.3547	0.2860
21	SYSTEMIC	62	HISTIOCYTIC SARCOMA [M]	0	1	1	2	0.1512	0.1280
21	SYSTEMIC	63	LYMPHOMA, MALIGNANT [M]	2	2	0	4	0.1265	0.1134
24	THYMUS	81	THYMOMA [M]	1	0	0	0	1.0000	0.8261
25	THYROID	68	C-CELL ADENOMA [B]	4	4	3	4	0.5288	0.5290
25	THYROID	69	C-CELL CARCINOMA [M]	1	0	0	0	1.0000	0.7989
25	THYROID	71	FOLLICULAR ADENOMA [B]	1	0	1	2	0.2133	0.1594
25	THYROID	72	GANGLIONEUROMA [B]	1	0	0	0	1.0000	0.8355
27	URINARY BLADDER	75	TRANSITIONAL CELL CARCINOMA [M]	0	0	0	1	0.2741	0.0593
28	UTERUS	76	ADENOCARCINOMA [M]	1	0	0	1	0.4826	0.3433
28	UTERUS	77	FIBROSARCOMA [M]	0	0	0	1	0.2952	0.0694
28	UTERUS	78	POLYP [B]	3	5	2	2	0.8433	0.8362
29	VAGINA	78	POLYP [B]	0	1	0	0	0.7826	0.7648
30	ZYMBAL'S GLAND	79	ADENOCARCINOMA [M]	0	1	0	1	0.3468	0.2708
30	ZYMBAL'S GLAND	80	ADENOMA [B]	0	1	0	1	0.3513	0.2944
4	BRAIN	10	OLIGODENDROGLIOMA [M]	0	0	0	1	0.2737	0.0590
4	BRAIN	7	ASTROCYTOMA [M]	0	1	0	0	0.7826	0.7648
4	BRAIN	8	GRANULAR CELL TUMOR, BENIGN [B]	1	0	0	0	1.0000	0.8220
5	CERVIX	11	ENDOMETRIAL STROMAL SARCOMA [M]	0	0	0	1	0.2407	0.0450
7	EYE	13	FIBROMA [B]	1	0	0	0	1.0000	0.8355
8	KIDNEY	18	TRANSITIONAL CELL CARCINOMA [M]	0	0	0	1	0.2747	0.0599
9	LIVER	19	HEMANGIOMA [B]	0	0	0	1	0.2407	0.0450

9	LIVER	21	HEPATOCELLULAR ADENOMA [B]	2	1	1	5	0.0534	0.0408
9	LIVER	22	HEPATOCELLULAR CARCINOMA [M]	1	0	1	1	0.3812	0.3427

Table 5: Female Rats: Tumor Incidences for Selected Combined Tumors

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
10	LUNG	23	[C]ADENOCARCINOMA [M], alveola	2	0	0	0	1.0000	0.9097
14	PANCREAS	41	[C]ISLET CELL ADENOMA [B]	2	1	2	0	0.9099	0.9053
16	PITUITARY	44	[C]ADENOMA [B], pars distalis	50	49	53	53	0.7581	0.7562
2	ADRENAL GLAND	3	[C]PHEOCHROMOCYTOMA [B]	1	1	2	1	0.5770	0.5986
25	THYROID	68	[C]C-CELL ADENOMA [B]	5	4	3	4	0.6055	0.6060
30	ZYMBAL'S GLAND	79	[C]ADENOCARCINOMA [M]	0	2	0	2	0.2410	0.2074
9	LIVER	21	[C]HEPATOCELLULAR ADENOMA [B]	2	1	1	5	0.0534	0.0408
[O]	[OTHER]	[O]	[OTHER]	47	43	39	37	0.9935	0.9927

Figure 2: Female Rats Mean Body Weight Curves by Dose



3.1.3.2 Male Rats

Like the sponsor, the reviewer observed a statistically significant trend in survival. The control animals experienced the highest mortality and the high dose males the best survival (Tables 6, 7 and Figure 3). In fact the study was terminated after week 97 due to the poor survival among the control animals.

The sponsor noted a treatment related increase in thyroid follicular adenomas and attributed the lack of statistical significance to the reduced body weight in the high dose animals. The incidences of 0, 1, 10, 4 of follicular adenoma in the thyroid of the control, low, medium and high dose groups respectively followed a non-linear pattern and the reviewer's test for linear increase with dose did not approach statistical significance ($p=0.2007$) (Table 8). As a matter of fact, the reviewer did not observe any statistically significant linear increases in tumor incidences. None of the tumor combinations, similar to those performed for the females, (Table 9), reached statistical significance either.

As no statistically significant increases in tumor incidences were observed among the male rats, the validity of this study was evaluated. Though the study was terminated after 97 weeks of treatment its length (in itself) and the number of animals exposed can be considered adequate. As the high dose animals experienced the best survival, increased mortality cannot be used as a measure for assessing the validity of the study. Using the sponsor's mean body weight graph (Figure 4) and corresponding tables, the reviewer noted that the treated groups had mean body weights lower than the controls at all times. In particular, at the end of week 1, the difference between the mean body weights of the high dose and control group was about 12 percent. By the end of one year the difference was 34 percent and by the end of the study, week 97, the mean body weight of the high dose males was 29 percent lower than the mean body weight of the controls. These numbers suggest that the high dose had exceeded the MTD.

For the males, it does appear that the mid-dose could serve as an MTD based on mean body weights. By the end of one year, the mid dose males' mean body weights were up to 12 percent lower than the controls and towards study end by up to 17 percent. When analyzing the data without the high dose, the trend for mortality remained statistically significant ($p=0.0133$) showing that the mid dose had significantly better survival than the controls. The sponsor had noted the non-linear increase in follicular adenoma in the thyroid which did not reach statistical significance when all four dose groups were analyzed. When excluding the high dose, the trend in follicular adenomas was highly statistically significant ($p=0.0002$). No other single tumor type reached statistical significance. However, the trend for the combined follicular adenoma and adenocarcinomas in the thyroid was also significant ($p=0.0006$). The increase for the combined c-cell adenoma and carcinoma in the thyroid did not reach statistical significance ($p=0.0361$).

The duration of the male rat study was reduced because of high mortality among the controls and the power of the statistical tests (the probability of detecting a true effect) was reduced because of the exclusion of the high dose from analysis. The observance of a

statistically significant increase in a tumor seems to validate a study, but the reviewer is concerned in this particular situation. The sponsor considers the tumor finding not relevant to humans, and if their argument is accepted, lack of tumorigenic potential could be established based on a study reduced in length of exposure and in power, both being factors which tend to decrease the observance of tumors. Of course, one does not know whether a study with a normally accepted duration and high dose would have revealed increases in additional tumor types. However, a full standard study may have shed light on the potential importance of osteosarcoma among the high dose male rats. Both osteomas (M and F) and osteosarcomas (M) were observed among the mice. The final determination of the validity of the male rat study is left to the expertise of the reviewing pharmacologist.

Table 6: Male Rats, Mortality by Time Interval and Dose

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTRO	0-52	59	3	56	94.9	5.1
	53-78	56	19	37	62.7	37.3
	79-91	37	13	24	40.7	59.3
	92-97	24	10	14	23.7	76.3
	FINALKILL 98-99	14	14	0		
LOW	0-52	60	3	57	95.0	5.0
	53-78	57	14	43	71.7	28.3
	79-91	43	17	26	43.3	56.7
	92-97	26	3	23	38.3	61.7
	FINALKILL 98-99	23	23	0		
MED	0-52	60	2	58	96.7	3.3
	53-78	58	11	47	78.3	21.7
	79-91	47	13	34	56.7	43.3
	92-97	34	6	28	46.7	53.3
	FINALKILL 98-99	28	28	0		
HIGH	0-52	60	4	56	93.3	6.7
	53-78	56	9	47	78.3	21.7
	79-91	47	7	40	66.7	33.3
	92-97	40	7	33	55.0	45.0
	FINALKILL 98-99	33	33	0		

Table 7: Male Rats, Mortality Trend with Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	3.9765	0.1369	3.3692	0.1855
Depart from Trend				
Dose-Mortality Trend	9.2798	0.0023	7.8986	0.0049
Homogeneity	13.2562	0.0041	11.2679	0.0104

Figure 3: Male Rats, Kaplan Meier Survival Functions

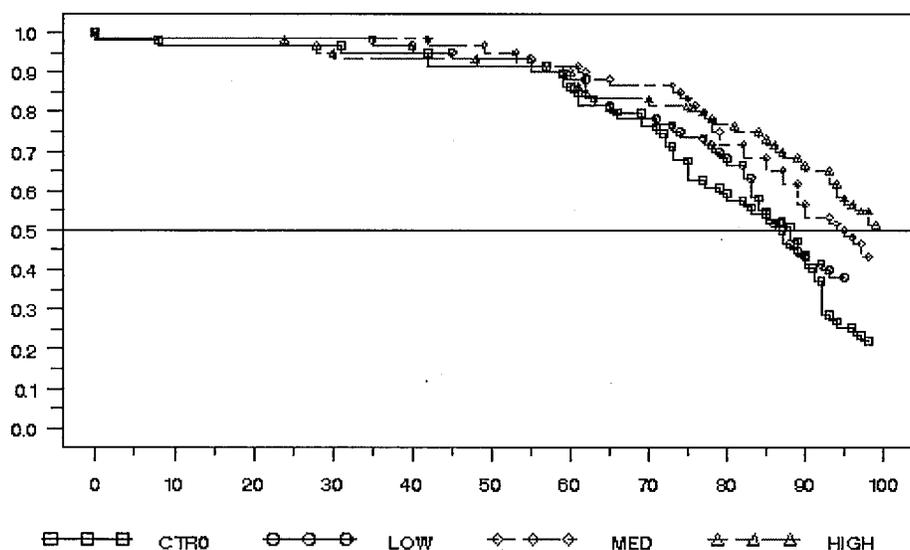


Table 8: Male Rats, Tumor Incidences and P-values for Trend

Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
10	LUNG	24	ADENOMA [B], alveolar/bronchio	0	0	1	0	0.5000	0.5509
10	LYMPH NODE	26	HEMANGIOSARCOMA [M]	0	0	0	1	0.3367	0.0879
11	MAMMARY	27	ADENOCARCINOMA [M]	0	0	0	1	0.3636	0.1007

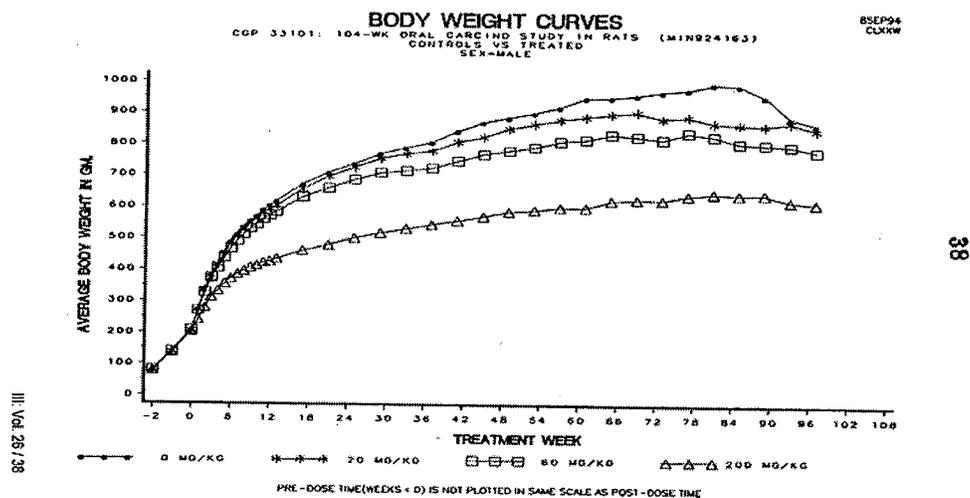
	GLAND								
11	MAMMARY GLAND	30	FIBROADENOMA [B]	2	0	1	0	0.9013	0.8744
12	OTHER TISSUE(S)	34	NERVE SHEATH TUMOR, MALIGNANT	0	0	0	1	0.5000	0.1599
12	OTHER TISSUE(S)	35	SQUAMOUS CELL CARCINOMA [M], o	0	0	0	1	0.6667	0.2414
14	PANCREAS	40	ACINAR ADENOMA [B]	0	1	0	0	0.8571	0.8038
14	PANCREAS	41	ISLET CELL ADENOMA [B]	2	5	1	1	0.9021	0.8880
14	PANCREAS	42	ISLET CELL CARCINOMA [M]	1	3	0	1	0.7562	0.7352
15	PARATHYROID	43	ADENOMA [B]	1	5	2	1	0.9071	0.8976
16	PITUITARY	44	ADENOMA [B], pars distalis	34	34	43	38	0.8802	0.8774
16	PITUITARY	45	CARCINOMA [M], pars distalis	0	0	2	1	0.2945	0.3021
17	PROSTATE	46	ADENOMA [B]	1	0	1	0	0.7735	0.7798
18	SKIN	47	BASAL CELL CARCINOMA [M]	1	0	0	0	1.0000	0.7858
18	SKIN	48	FIBROMA [B]	2	3	1	0	0.9864	0.9704
18	SKIN	49	FIBROSARCOMA [M]	0	0	1	0	0.5122	0.5560
18	SKIN	51	KERATOACANTHOMA [B]	3	1	0	3	0.2871	0.2878
18	SKIN	52	LEIOMYOSARCOMA [M]	0	1	0	0	0.7626	0.7475
18	SKIN	53	LIPOMA [B]	2	2	0	1	0.7934	0.7792
18	SKIN	54	PAPILLOMA [B]	1	0	0	0	1.0000	0.7858
18	SKIN	55	RHABDOMYOSARCOMA [M]	1	0	0	0	1.0000	0.8645
18	SKIN	56	SEBACEOUS GLAND ADENOMA [B]	0	1	2	2	0.1575	0.1515
18	SKIN	57	SQUAMOUS CELL CARCINOMA [M]	0	0	0	1	0.3367	0.0879
19	SMALL INTESTINE	58	ADENOCARCINOMA [M]	0	1	1	0	0.7774	0.8058
2	ADRENAL GLAND	2	CORTICAL ADENOMA [B]	0	1	0	1	0.1886	0.0935
2	ADRENAL GLAND	3	PHEOCHROMOCYTOMA [B]	8	4	3	5	0.8306	0.8256
2	ADRENAL GLAND	4	PHEOCHROMOCYTOMA [M]	2	0	0	1	0.7013	0.6717
20	SPLEEN	60	LIPOSARCOMA [M]	1	0	0	0	1.0000	0.8645
20	SPLEEN	82	HEMANGIOSARCOMA [M]	0	1	0	0	0.6154	0.7307
21	SYSTEMIC	61	GRANULOCYTTIC LEUKEMIA [M]	1	0	0	0	1.0000	0.8325
21	SYSTEMIC	62	HISTIOCYTIC SARCOMA [M]	2	1	1	0	0.9487	0.9214
21	SYSTEMIC	63	LYMPHOMA, MALIGNANT [M]	0	0	2	2	0.0937	0.0824
23	TESTIS	65	INTERSTITIAL-CELL TUMOR [B]	2	2	3	3	0.5894	0.5848
23	TESTIS	66	MESOTHELIOMA [M]	0	0	2	1	0.2416	0.2532
24	THYMUS	67	THYMOMA [B]	0	1	0	0	0.6042	0.6650
25	THYROID	68	C-CELL ADENOMA [B]	1	3	6	2	0.6753	0.6720
25	THYROID	69	C-CELL CARCINOMA [M]	1	1	3	0	0.9007	0.8963
25	THYROID	70	FOLLICULAR ADENOCARCINOMA [M]	0	1	0	0	0.8571	0.8038
25	THYROID	71	FOLLICULAR ADENOMA [B]	0	1	10	4	0.2007	0.1907

26	TRACHEA	73	NERVE SHEATH TUMOR, BENIGN [B]	0	0	0	1	0.3367	0.0879
27	URINARY BLADDER	74	PAPILLOMA [B]	0	1	0	0	0.8571	0.8038
3	BONE	5	CHONDROSARCOMA [M]	1	0	0	0	1.0000	0.8179
3	BONE	6	OSTEOSARCOMA [M]	0	0	0	1	0.3367	0.0879
30	ZYMBAL'S GLAND	79	ADENOCARCINOMA [M]	0	2	0	2	0.2470	0.2064
4	BRAIN	7	ASTROCYTOMA [M]	0	2	0	1	0.5870	0.5507
4	BRAIN	8	GRANULAR CELL TUMOR, BENIGN [B]	0	2	1	0	0.8469	0.8670
4	BRAIN	9	GRANULAR CELL TUMOR, MALIGNANT	0	1	0	0	0.7938	0.7688
6	EAR	12	NERVE SHEATH TUMOR, BENIGN [B]	0	1	0	0	0.7400	0.6846
8	KIDNEY	14	ADENOMA [B]	1	1	0	0	0.9451	0.8864
8	KIDNEY	15	HEMANGIOSARCOMA [M]	0	0	1	0	0.6224	0.6422
8	KIDNEY	16	LIPOSARCOMA [M]	0	0	1	0	0.5000	0.5509
8	KIDNEY	17	NEPHROBLASTOMA [M]	1	0	0	0	1.0000	0.8156
9	LIVER	19	HEMANGIOMA [B]	0	1	0	0	0.7522	0.7407
9	LIVER	21	HEPATOCELLULAR ADENOMA [B]	3	2	7	4	0.6225	0.6187
9	LIVER	22	HEPATOCELLULAR CARCINOMA [M]	4	2	3	0	0.9894	0.9798

Table 9: Male Rats: Tumor Incidences of Selected Combined Tumors

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
14	PANCREAS	41	[C] ISLET CELL ADENOMA [B]	3	8	1	2	0.9190	0.9089
16	PITUITARY	44	[C] ADENOMA [B], pars distalis	34	34	45	39	0.8577	0.8550
2	ADRENAL GLAND	3	[C] PHEOCHROMOCYTOMA [B]	10	4	3	6	0.8346	0.8295
25	THYROID	70	[C] FOLLICULAR ADENOCARCINOMA [0	2	10	4	0.2538	0.2458
4	BRAIN	8	[C] GRANULAR CELL TUMOR, BENIGN	0	3	1	0	0.9086	0.9078
9	LIVER	21	[C] HEPATOCELLULAR ADENOMA [B]	6	4	10	4	0.9224	0.9162
[O]	[OTHER]	[O]	[OTHER]	22	28	25	23	0.8689	0.8654
25	THYROID	68+69	[C] C-CELL ADENOMA AND CARCINOMA WITHOUT HD	2	4	9	-----	0.0361	0.0255

Figure 4: Male Rats Mean Body Weight Curves by Dose



3.2 Mouse Study #926045

This was an oral feed whole life study in CD-1 mice to determine the carcinogenic potential of rufinamide. The study was conducted and evaluated by Ciba-Geigy in Summit, NJ. Sixty animals per sex were exposed to daily doses of 0, 40, 120, or 400 mg/kg for 103 weeks. The animals were housed singly and had feed and water available ad lib. The study was initiated Feb. 3, 1993 and terminated March 1, 1995. A complete necropsy and microscopic examination was conducted on all tissues and organs from all mice.

3.2.1 Statistical Methods

Both the sponsor and the reviewer applied their respective statistical methods to the mice tumor data as they had done to the rat data. For details of the methods please see section 3.1.1.

3.2.2 Sponsor's Results

The sponsor reported a significant dose-related trend in mortality among the female mice with a two-sided p-value of 0.000. There was no dose-related trend in mortality among the male mice.

The sponsor reported compound-related increases in osteoma, hepatocellular adenomas and hepatocellular carcinomas but considered them not biologically or clinically relevant to humans. Specifically, among the female mice, the sponsor observed a significant increase in osteoma in the bone with $p=0.011$ and a significant increase in hepatocellular adenoma in the liver with $p=0.001$. Combining hepatocellular adenoma with carcinoma resulted in a highly significant increase with dose ($p=0.000$). Among the male mice, the sponsor reported the increase in osteoma in the bone significant with $p=0.014$ and the increase in hepatocellular adenoma in the liver significant with $p=0.004$. For the combined osteoma and osteosarcoma in the bone the p-value for trend was 0.014 and for the combined hepatocellular adenoma and carcinoma the p-value was 0.001.

3.2.3 Reviewer's Results

3.2.3.1 Female Mice

Table 10 shows that survival was acceptable for all groups of female mice but was by far the best among the high dose females. The inverse relationship between mortality and dose was reflected in the highly significant trend tests (Table 11) and the Kaplan-Meier survival functions (Figure 5).

Table 10: Female Mice, Mortality by Time Interval and Dose

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR0	0-52	60	5	55	91.7	8.3
	53-78	55	9	46	76.7	23.3
	79-91	46	15	31	51.7	48.3
	92-103	31	10	21	35.0	65.0
	FINALKILL104-105	21	21	0		
LOW	0-52	60	6	54	90.0	10.0
	53-78	54	13	41	68.3	31.7
	79-91	41	10	31	51.7	48.3
	92-103	31	10	21	35.0	65.0
	FINALKILL104-105	21	21	0		
MED	0-52	60	2	58	96.7	3.3
	53-78	58	9	49	81.7	18.3
	79-91	49	14	35	58.3	41.7
	92-103	35	9	26	43.3	56.7
	FINALKILL104-105	26	26	0		

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
	53-78	60	9	51	85.0	15.0
HIGH	79-91	51	3	48	80.0	20.0
	92-103	48	6	42	70.0	30.0
	FINALKILL104-105	42	42	0		

Table 11: Female Mice, Mortality Trend with Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.4661	0.7921	0.7720	0.6798
Depart from Trend				
Dose-Mortality Trend	16.9727	0.0000	14.9632	0.0001
Homogeneity	17.4387	0.0006	15.7352	0.0013

Figure 5: Female Mice, Kaplan Meier Survival Functions

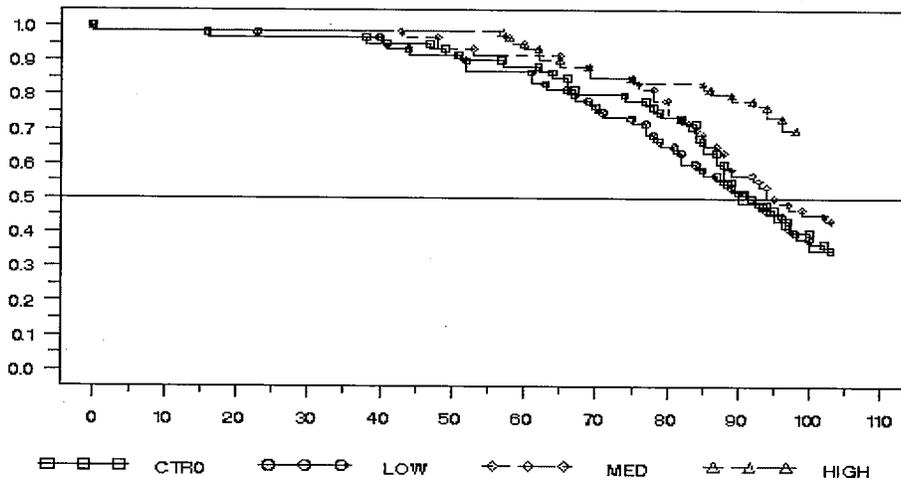


Table 12 gives the mortality adjusted trends in tumor findings. The p-values reflect one-sided tests for increases in tumors with dose. Increases in osteoma in the bone and in hepatocellular adenoma in the liver reached statistical significance. Both tumors are considered rare based on the incidence among the concurrent controls, but the finding for hepatocellular adenoma in the liver would remain statistically significant even when the

tumor is considered common. Hepatocellular carcinomas showed a non-significant increase. The combined hepatocellular adenomas and carcinomas showed a highly significant increase ($p=0.0000$, Table 13).

Table 12: Female Mice, Tumor Incidences and P-values for Trend

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0001	ADRENAL GLAND	00039	PHEOCHROMOCYTOMA [B].	0	0	1	1	0.1705	0.1035
0001	ADRENAL GLAND	00040	PHEOCHROMOCYTOMA [M].	0	3	1	0	0.8987	0.9050
0001	ADRENAL GLAND	00047	SPINDLE CELL TUMOR, BENIGN [B]	1	0	0	0	1.0000	0.8660
0002	BONE	00006	CHONDROMA [B].	0	0	1	0	0.4286	0.4752
0002	BONE	00031	NERVE SHEATH TUMOR, BENIGN [B]	0	0	0	1	0.2250	0.0373
0002	BONE	00034	OSTEOMA [B].	0	2	1	6	0.0102 !	0.0072
0003	BRAIN	00033	OLIGODENDROGLIOMA [B].	0	1	0	0	0.7534	0.7449
0004	CERVIX	00008	ENDOMETRIAL STROMAL SARCOMA [M]	0	2	1	0	0.8340	0.8678
0004	CERVIX	00024	LEIOMYOMA [B].	1	0	1	0	0.7818	0.7933
0004	CERVIX	00041	POLYP [B].	0	0	0	1	0.3818	0.1086
0006	FORELEG	00034	OSTEOMA [B].	0	0	0	1	0.3818	0.1086
0008	HARDERIAN GLAND	00001	ADENOCARCINOMA [M].	0	0	1	0	0.4103	0.3537
0008	HARDERIAN GLAND	00004	ADENOMA [B].	2	2	5	5	0.1925	0.1816
0009	JOINT	00034	OSTEOMA [B].	0	0	1	0	0.4048	0.3432
0010	KIDNEY	00004	ADENOMA [B].	0	0	1	0	0.4000	0.3459
0011	LARGE INTESTINE	00041	POLYP [B].	0	0	1	0	0.5529	0.5910
0012	LIVER	00015	HEMANGIOMA [B].	0	0	1	1	0.3258	0.2774
0012	LIVER	00016	HEMANGIOSARCOMA [M].	1	2	2	0	0.9103	0.9126
0012	LIVER	00017	HEPATOCELLULAR ADENOMA [B].	0	0	1	10	0.0001 !	0.0001
0012	LIVER	00018	HEPATOCELLULAR CARCINOMA [M].	1	0	1	4	0.0724	0.0498
0012	LIVER	00043	SARCOMA [M].	0	0	0	1	0.3818	0.1086
0013	LUNG	00001	ADENOCARCINOMA [M].	3	4	4	2	0.9298	0.9232
0013	LUNG	00004	ADENOMA [B].	8	5	6	6	0.8523	0.8469
0014	MAMMARY GLAND	00001	ADENOCARCINOMA [M].	1	3	2	3	0.4976	0.4984
0014	MAMMARY GLAND	00010	FIBROADENOMA [B].	0	0	0	1	0.3939	0.1145
0014	MAMMARY GLAND	00036	PAPILLOMA [B], intraductal.	0	0	0	1	0.3939	0.1145
0015	OVARY	00001	ADENOCARCINOMA [M].	0	0	1	0	0.6147	0.6535
0015	OVARY	00004	ADENOMA [B].	1	2	3	2	0.6234	0.6261
0015	OVARY	00012	GONADAL STROMAL TUMOR, BENIGN	0	0	1	0	0.6147	0.6535
0015	OVARY	00014	GRANULOSA-THECA CELL TUMOR [B]	0	1	1	0	0.6911	0.7550

0015	OVARY	00016	HEMANGIOSARCOMA [M].	0	1	0	0	0.7546	0.7452
0015	OVARY	00024	LEIOMYOMA [B].	1	0	0	0	1.0000	0.7679
0015	OVARY	00025	LEIOMYOSARCOMA [M].	0	1	0	0	0.7500	0.7579
0015	OVARY	00026	LUTEAL CELL TUMOR, BENIGN [B].	1	0	0	2	0.3164	0.2067
0015	OVARY	00027	LUTEAL CELL TUMOR, MALIGNANT [0	1	0	0	0.7353	0.7035
0015	OVARY	00046	SERTOLI-CELL TUMOR [B].	0	0	0	1	0.1765	0.0205
0016	PANCREAS	00021	ISLET CELL ADENOMA [B].	1	0	0	0	1.0000	0.7970
0016	PANCREAS	00022	ISLET CELL CARCINOMA [M].	0	0	1	0	0.6182	0.6574
0017	PITUITARY	00002	ADENOMA [B], pars distalis, ac	1	0	0	0	1.0000	0.8645
0018	SKELETAL MUSCLE	00016	HEMANGIOSARCOMA [M].	0	0	1	0	0.5268	0.5675
0018	SKELETAL MUSCLE	00042	RHABDOMYOSARCOMA [M].	1	0	0	0	1.0000	0.8479
0018	SKELETAL MUSCLE	00043	SARCOMA [M].	0	0	1	0	0.6182	0.6574
0019	SKIN	00005	BASAL-CELL EPITHELIOMA [B].	1	0	0	0	1.0000	0.7731
0019	SKIN	00016	HEMANGIOSARCOMA [M].	0	1	0	1	0.3460	0.2626
0019	SKIN	00030	MYXOSARCOMA [M].	0	0	1	0	0.6053	0.6476
0019	SKIN	00032	NERVE SHEATH TUMOR, MALIGNANT	0	0	1	0	0.5868	0.6300
0019	SKIN	00042	RHABDOMYOSARCOMA [M].	0	1	1	0	0.6928	0.7630
0019	SKIN	00044	SEBACEOUS ADENOCARCINOMA [M].	0	0	1	0	0.5303	0.5705
0019	SKIN	00048	SQUAMOUS CELL CARCINOMA [M].	2	0	0	1	0.6440	0.5905
0021	SPLEEN	00016	HEMANGIOSARCOMA [M].	1	2	1	0	0.9376	0.9338
0022	STOMACH	00038	PAPILLOMA [B].	0	1	0	0	0.7419	0.7190
0023	SYSTEMIC	00019	HISTIOCYTIC SARCOMA [M].	11	5	3	1	0.9999	0.9994
0023	SYSTEMIC	00028	LYMPHOMA, MALIGNANT [M].	17	17	17	13	0.9981	0.9974
0026	THYMUS	00049	THYMOMA [M].	0	1	0	0	0.7188	0.6869
0027	THYROID	00011	FOLLICULAR ADENOMA [B].	0	1	0	0	0.8091	0.8088
0029	UTERUS	00008	ENDOMETRIAL STROMAL SARCOMA [M]	0	0	0	1	0.3761	0.1060
0029	UTERUS	00015	HEMANGIOMA [B].	0	0	0	1	0.3761	0.1060
0029	UTERUS	00016	HEMANGIOSARCOMA [M].	1	0	0	1	0.5548	0.4001
0029	UTERUS	00024	LEIOMYOMA [B].	3	2	1	0	0.9870	0.9726
0029	UTERUS	00025	LEIOMYOSARCOMA [M].	2	1	1	2	0.5855	0.5640
0029	UTERUS	00041	POLYP [B].	5	7	4	7	0.5348	0.5308
0030	VAGINA	00024	LEIOMYOMA [B].	2	1	0	0	0.9869	0.9422
0030	VAGINA	00025	LEIOMYOSARCOMA [M].	2	0	0	1	0.6195	0.5653
0030	VAGINA	00041	POLYP [B].	0	0	1	1	0.2021	0.1565
0031	ZYMBAL'S GLAND	00001	ADENOCARCINOMA [M].	0	0	0	1	0.3818	0.1086

In discussion with the reviewing pharmacologist, the reviewer combined adenomas and carcinomas or adenomas and adenocarcinomas, or the benign and malignant types of selected tumors at given sites. Of these only hepatocellular adenomas and carcinomas in the liver reached statistical significance. In addition, hemangiomas and hemangiosarcomas were grouped over all body systems. Neither tumor type approached statistical significance.

Table 13: Female Mice, Selected Combined Tumors

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0001	ADRENAL GLAND	00039	[C]PHEOCHROMOCYTOMA [B].	0	3	2	1	0.6596	0.6758
0008	HARDERIAN GLAND	00001	[C]ADENOCARCINOMA [M].	2	2	6	5	0.1782	0.1667
0012	LIVER	00017	[C]HEPATOCELLULAR ADENOMA [B].	1	0	2	14	0.0000	0.0000
0013	LUNG	00001	[C]ADENOCARCINOMA [M].	11	9	10	8	0.9642	0.9603
0015	OVARY	00026	[C]LUTEAL CELL TUMOR, BENIGN [1	1	0	2	0.3659	0.3053
0016	PANCREAS	00021	[C]ISLET CELL ADENOMA [B].	1	0	1	0	0.7964	0.8014
0012	[C]LIVER	00015	HEMANGIOMA [B].	0	0	1	2	0.1569	0.1141
0012	[C]LIVER	00016	HEMANGIOSARCOMA [M].	2	4	4	2	0.8114	0.8075
0012	[C]LIVER	00015	[C]HEMANGIOMA, SARCOMA	2	4	5	4	0.5834	0.5805

3.2.3.2 Male Mice

Table 14 shows that survival was about equal among all dose groups of the male mice. The number of terminally killed animals ranged from 20 (high dose) to 30 (mid dose). Hence the test for linear increase in mortality with dose was statistically non-significant (Table 15). The Kaplan-Meier survival curves (Figure 6) also reflect these findings.

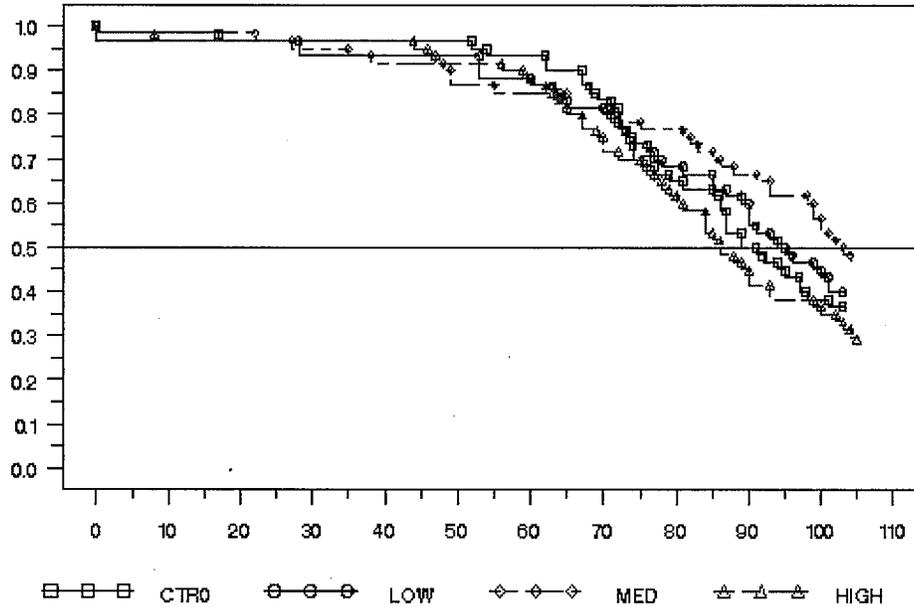
Table 14: Male Mice, Mortality by Time Interval and Dose

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
TR0	0-52	60	2	58	96.7	3.3
	53-78	58	17	41	68.3	31.7
	79-91	41	11	30	50.0	50.0
	92-103	30	8	22	36.7	63.3
	FINALKILL104-105	22	22	0		
LOW	0-52	60	2	58	96.7	3.3
	53-78	58	16	42	70.0	30.0
	79-91	42	9	33	55.0	45.0
	92-103	33	9	24	40.0	60.0
	FINALKILL104-105	24	24	0		
MED	0-52	60	6	54	90.0	10.0
	53-78	54	7	47	78.3	21.7
	79-91	47	7	40	66.7	33.3
	92-103	40	10	30	50.0	50.0
	FINALKILL104-105	30	30	0		
HIGH	0-52	60	4	56	93.3	6.7
	53-78	56	17	39	65.0	35.0
	79-91	39	12	27	45.0	55.0
	92-103	27	7	20	33.3	66.7
	FINALKILL104-105	20	20	0		

Table 15: Male Mice, Mortality trend with Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	3.6091	0.1646	2.9611	0.2275
Depart from Trend				
Dose-Mortality Trend	1.3543	0.2445	1.5365	0.2151
Homogeneity	4.9634	0.1745	4.4976	0.2125

Figure 6: Male Mice, Kaplan Meier Survival Functions



It is important to note that the significant increases were observed in the same tumor types as had been found among the female mice. Osteoma in the bone was significant for a rare tumor with $p=0.0245$ and hepatocellular adenoma in the liver was significant for a common tumor with $p<0.0012$ (Table 16). The increase in hepatocellular carcinoma did not reach statistical significance by itself. However, the combined hepatocellular adenomas and carcinomas in the liver were highly statistically significant ($p<0.0001$, Table 17). There was a single case of osteosarcoma (mid dose) and its combination with the osteomas was not statistically significant for linear trend (0.0415). No increases in other single or combined tumor types reached statistical significance.

Table 16: Male Mice, Tumor Incidences and P-Values for Trend

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0001	ADRENAL GLAND	00007	CORTICAL ADENOMA [B].	1	1	3	1	0.4593	0.4776
0001	ADRENAL GLAND	00040	PHEOCHROMOCYTOMA [M].	0	0	1	1	0.1732	0.1036
0001	ADRENAL GLAND	00047	SPINDLE CELL TUMOR, BENIGN [B]	1	0	0	0	1.0000	0.8169
0002	BONE	00034	OSTEOMA [B].	0	0	2	3	0.0245	0.0188
0002	BONE	00035	OSTEOSARCOMA [M].	0	0	1	0	0.5315	0.5342
0003	BRAIN	00029	MENINGIOMA [M].	0	0	1	0	0.5060	0.5366
0005	ESOPHAGUS	00038	PAPILLOMA [B].	0	1	0	0	0.7708	0.7352
0007	GALL BLADDER	00004	ADENOMA [B].	0	1	0	0	0.7667	0.7301
0008	HARDERIAN GLAND	00001	ADENOCARCINOMA [M].	5	0	1	2	0.6321	0.6416
0008	HARDERIAN GLAND	00004	ADENOMA [B].	4	4	4	1	0.9185	0.9081
0010	KIDNEY	00004	ADENOMA [B].	0	2	0	1	0.4777	0.4748
0012	LIVER	00015	HEMANGIOMA [B].	0	0	1	0	0.5000	0.5239
0012	LIVER	00016	HEMANGIOSARCOMA [M].	2	3	1	0	0.9612	0.9328
0012	LIVER	00017	HEPATOCELLULAR ADENOMA [B].	4	5	5	13	0.0012	0.0006
0012	LIVER	00018	HEPATOCELLULAR CARCINOMA [M].	8	7	8	14	0.0158	0.0121
0013	LUNG	00001	ADENOCARCINOMA [M].	6	6	10	6	0.4485	0.4496
0013	LUNG	00004	ADENOMA [B].	6	10	6	2	0.9850	0.9791
0016	PANCREAS	00021	ISLET CELL ADENOMA [B].	0	0	0	1	0.2121	0.0332
0017	PITUITARY	00003	ADENOMA [B], pars distalis, ch	0	0	1	0	0.5172	0.5194
0019	SKIN	00016	HEMANGIOSARCOMA [M].	0	0	1	0	0.4880	0.5407
0019	SKIN	00023	KERATOACANTHOMA [B].	0	0	1	0	0.7143	0.6348
0019	SKIN	00038	PAPILLOMA [B].	0	0	2	1	0.2206	0.2082
0019	SKIN	00043	SARCOMA [M].	0	1	0	0	0.7371	0.7342
0020	SMALL INTESTINE	00001	ADENOCARCINOMA [M].	0	1	0	0	0.7609	0.7226
0021	SPLEEN	00015	HEMANGIOMA [B].	0	0	1	0	0.5208	0.5311
0021	SPLEEN	00016	HEMANGIOSARCOMA [M].	3	0	0	0	1.0000	0.9364
0022	STOMACH	00001	ADENOCARCINOMA [M].	1	1	0	0	0.9381	0.8522
0022	STOMACH	00004	ADENOMA [B].	0	1	0	0	0.7634	0.7266
0023	SYSTEMIC	00013	GRANULOCYTIC LEUKEMIA [M].	0	1	0	1	0.3033	0.2245
0023	SYSTEMIC	00019	HISTIOCYTIC SARCOMA [M].	0	2	2	0	0.6997	0.7494
0023	SYSTEMIC	00028	LYMPHOMA, MALIGNANT [M].	13	12	11	15	0.1588	0.1535
0024	TEETH	00009	FIBRO-ODONTOMA, AMELOBLASTIC [M].	0	1	0	0	0.7708	0.7352

0025	TESTIS	00015	HEMANGIOMA [B].	0	0	0	1	0.2083	0.0322
0025	TESTIS	00020	INTERSTITIAL-CELL TUMOR [M].	1	0	0	1	0.3750	0.2501
0025	TESTIS	00045	SEMINOMA [M].	1	0	2	0	0.6764	0.7305
0027	THYROID	00011	FOLLICULAR ADENOMA [B].	1	0	0	0	1.0000	0.8254
0028	URETHRA	00037	PAPILLOMA [B], transitional-ce	0	1	0	0	0.7647	0.7291

Table 17: Male Mice, Selected Combined Tumors

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR0	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
0002	BONE	00034	[C]OSTEOMA [B].	0	0	3	3	0.0415	0.0296
0008	HARDERIAN GLAND	00001	[C]ADENOCARCINOMA [M].	9	4	5	3	0.9107	0.9025
0012	LIVER	00017	[C]HEPATOCELLULAR ADENOMA [B].	12	12	13	27	0.0001	0.0000 !
0013	LUNG	00001	[C]ADENOCARCINOMA [M].	12	16	16	8	0.9260	0.9208
0022	STOMACH	00001	[C]ADENOCARCINOMA [M].	1	2	0	0	0.9397	0.8861
[OTH	[OTHER]	[OTHE	[OTHER]	20	22	23	21	0.3653	0.3633

4. Conclusions

Study 92-6046 was a feed study in Sprague-Dawley rats with daily doses of 0, 20, 60, or 200 mg/kg. Group size was 60 animals per gender and dose. The female rats were dosed for 103 weeks. The male rats were dose only for 97 weeks. A complete necropsy and microscopic examination was conducted on all tissues and organs from all rats.

The female rat study lasted the full two years with good survival across all groups. No statistically significant increases in tumor incidences were observed using mortality adjusted trend tests and hence the validity of the study had to be evaluated. The reviewer concluded that sufficient numbers of animals were exposed to the compound for a sufficient length of time. However, the high dose exceeded the MTD based on mean body weights. There was a dose-related reduction in mean body weights with the high dose females experiencing as much as 37 percent lower mean body weights than their controls. In order to entertain whether the mid-dose could serve as an MTD, the reviewer reanalyzed the data without the high dose. Again, no statistically significant increases in tumor findings were observed. The mid-dose female rats experienced mean body weights of 22 percent lower than the controls' at one year and even higher towards the end of the study, which is again excessive for representing an MTD. It is therefore left to the expertise of the reviewing pharmacologist to determine whether the study can be considered adequate.

The male rat study was terminated in week 98 due to increased mortality among the controls. There was a highly significant decrease in mortality with dose. No significant increases in tumor findings were observed using mortality adjusted trend tests. In evaluating the adequacy of the tumor challenge it was found that the high dose exceeded the MTD for the males as well based on the reduced mean body weights. All treated groups had mean body weights lower than the controls throughout the study. The high dose mean body weight was 34 percent lower than the controls' by one year. Hence the high dose exceeded the MTD. When excluding the high dose from analysis, a significant increase in follicular adenomas in the thyroid emerged. This finding had not reached statistical significance when all groups were analyzed. The sponsor attributed the lack of statistical significance for this tumor type across all treatment groups to a reduction in tumors among the high dose animals secondary to the severely reduced mean body weights. Also the trend in the combined follicular adenomas and adenocarcinomas in the thyroid was statistically significant when the high dose was excluded from analysis. It is not clear to the reviewer whether the validity of the study can be established when the study is reduced both in length of time (to 97 weeks of treatment) and in the number of treatment groups (exclusion of the high dose). One cannot know whether increases in additional tumor types would have been observed had the study lasted the full two years and had the high dose been appropriate, but the observance of a single osteosarcoma in the bone of a high dose male rat may be of concern as this tumor and related ones were observed in both genders of the mice. For completeness sake it is reported that based on mean body weights, the mid dose may be close to the MTD with experiencing about 12 percent lower mean body weight at one year. Towards the end of the (shortened) study, the differential reached about 17 percent. The final determination of the validity of the male rat study is left to the expertise of the reviewing pharmacologist.

Study 92-6045 was a feed study in CD-1 mice with daily doses of 0, 40, 120, or 400 mg/kg. Group size was 60 animals per gender and dose. Treatment lasted 103 weeks for both genders. A complete necropsy and microscopic examination was conducted on all tissues and organs from all mice.

The female mouse study lasted two years and showed superior survival for the high dose animals. The trend in survival with dose was highly significant. There were statistically significant increases in osteoma in the bone and in hepatocellular adenoma in the liver. Hepatocellular carcinoma showed a non-significant increase, but the trend test for the combined hepatocellular adenomas and carcinomas was highly statistically significant.

The male mouse study also lasted the planned two years. Survival was not influenced by drug treatment. It is important to note that the same two tumor types observed among the female mice (osteoma in bone and hepatocellular adenoma in the liver) also showed significant increases among the male mice. Among this gender a combination of osteoma and osteosarcoma in the bone did not reach statistical significance but the combination of hepatocellular adenoma and hepatocellular carcinoma of the liver did. Hence the validity of the mouse study was established in both genders.

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

/s/

Roswitha Kelly
8/9/2006 01:12:20 PM
BIOMETRICS

Karl Lin
8/9/2006 01:39:19 PM
BIOMETRICS
Concur with review