

Clinical Review
 Norman Herszkowitz, MD, PhD
 21911 (000)
 Rufinamide (Invelon ®)

Characteristic	Rufinamide (N=74)		Placebo (N=64)		All treatments (N=138)	
	n	%	n	%	n	%
Sex						
Male	46	62.2	40	62.5	86	62.3
Female	28	37.8	24	37.5	52	37.7
Race						
White/Caucasian	62	83.8	53	82.8	115	83.3
Black	6	8.1	4	6.3	10	7.2
Other	6	8.1	7	10.9	13	9.4
Age (years)						
Mean (Range)	14.5 (4, 35)		13.6 (4, 37)		14.1 (4, 37)	
≥4 - <12	31	41.9	33	51.6	64	46.4
≥12 - <17	19	25.7	17	26.6	36	26.1
≥17	24	32.4	14	21.9	38	27.5
Weight (kgs)						
Mean (Range)	44.1 (15.5, 138.5)		40.2 (16.2, 86.0)		42.3 (15.5, 138.5)	
18 - 29.0	24	32.4	24	37.5	48	34.8
29.1 - 50.0	25	33.8	20	31.3	45	32.6
50.1 - 70.0	13	17.6	14	21.9	27	19.6
≥70.1	12	16.2	6	9.4	18	13.0
Region/Country						
Europe	29	39.2	27	42.2	56	40.6
Brazil	10	13.5	9	14.1	19	13.8
USA	35	47.3	28	43.8	63	45.7

The 28 day baseline seizure frequency for a variety of seizure classifications is presented in the table below. There were significant differences between seizure frequencies for almost every sub-classification, except tonic-atonic, with placebo patients exhibiting a lower baseline seizure frequency. This would suggest that a statistical correction for baseline is important. This was performed, as noted in the discussion on the design in the Appendix, as part of a post-hoc exploratory analysis.

	Rufinamide (N=74)			Placebo (N=64)		
	n	Median	Range	n	Median	Range
All types of seizures	74	290.0	48, 53760	64	205.0	21, 109714
Tonic-atonic seizures ^a	73	92.0	5, 14304	60	92.5	1, 13122
Atypical absence seizures	59	76.0	1, 2171	55	52.0	1, 4009
Tonic seizures	52	66.3	1, 14304	43	49.0	1, 1066
Atonic seizures	45	56.0	1, 4037	33	49.0	2, 13122
Myoclonic seizures	37	80.0	1, 38928	31	50.8	1, 92583
Tonic-clonic seizure	37	18.0	1, 336	27	15.0	1, 788
Unclassified	12	17.5	1, 202	13	16.0	1, 72
Partial seizures	11	49.0	1, 4195	9	41.0	3, 723
Absence seizures	8	31.0	1, 192	5	22.0	3, 84
Clonic seizures	7	36.0	1, 6021	1	51.0	--

Concomitant AED treatment was generally well matched with no greater than 5% difference in the incidence in use between placebo and control. The one exception to this was a more common use of clonazepam in the rufinamide group. Drugs used in 10% or greater patients are presented in the table below.

Preferred term	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
ANY ANTI-EPILEPTIC DRUGS	74	(100.0)	64	(100.0)
VALPROATE	44	(59.5)	35	(54.7)
LAMOTRIGINE	30	(40.5)	19	(29.7)
TOPIRAMATE	20	(27.0)	17	(26.6)
CLONAZEPAM	14	(18.9)	7	(10.9)
CARBAMAZEPINE	12	(16.2)	12	(18.8)
GLOBAZAM	10	(13.5)	8	(12.5)
PHENYTOIN	10	(13.5)	12	(18.8)
PHENOBARBITAL	6	(8.1)	9	(14.1)

The majority of patients were on 2 or 3 concomitant AEDs. The number of concomitant AEDs was well matched across treatment groups. This information is presented in the table below.

Total Number of Concomitant AEDs	Rufinamide (N=74)		Placebo (N=64)	
	n	%	n	%
One	8	10.8	8	12.5
Two	38	51.4	35	54.7
Three	28	37.8	21	32.8

The targeted dose of rufinamide was 45/mg/kg/day or 3200 mg/day, whichever was lowest. Adjustment was permitted in the final dose during titration, based upon tolerability and, with permission of the Sponsor. Reductions in dosage were permitted during the maintenance dose, based upon tolerability. Targeted dose was reached by 7.8% of rufinamide patients and 100% of placebo patients.

6.1.4.4.3 Primary Endpoints

6.1.4.4.3.1 Sponsors Analysis

6.1.4.4.3.1.1 Percent change in total seizure frequency

The table presents the median 28 day total seizure frequency at baseline and final endpoint evaluation along with the percent change. As is apparent there was a reduction over baseline of approximately 21% from the rufinamide as compared to the placebo. A Wilcoxon rank-sum test revealed this to be statistically significant (p=0.0015). This met the criteria of 0.025,

established for correcting for multiple endpoints. The Sponsor performed an ANCOVA, with treatment and region as factors and baseline frequency as a covariate that verified statistical significance ($p = 0.0026$). This suggests that baseline was not an important factor in rufinamide's effect. Another secondary analysis factored in the number of concomitant AEDs (Cochran-Mantel-Haenszel) and demonstrated that the observed therapeutic effect was independent of this factor.

	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 ^z	74	-32.7	(-92.3, 381.4)	64	-11.7	(-82.8, 550.6)

6.1.4.4.3.1.2 Percent change in tonic and atonic seizure frequency.

The table presents the median 28 seizure tonic/atonic frequency at baseline and final endpoint evaluation along with the percent change. As is apparent, the rufinamide treatment group experienced a 41% reduction of seizures over placebo. This was observed to be statistically significant ($p < 0.0001$, Wilcoxon rank-sum). This meets the criteria of 0.025, established to correct for multiple endpoints. An ANCOVA, with treatment and region as factors and baseline frequency as a covariate, verified statistical significance (p value of < 0.0001). Similar to total seizures, this effect appeared to be independent to the number of concomitant AEDs.

	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)

6.1.4.4.3.1.3 Global-seizure severity subscale

The table below presents the final endpoint evaluation of the Global Evaluation for the seizure-severity at the final double-blind visit. As is apparent, more patients in the rufinamide groups were classified as having improved with most of the improved patients where in the much improved category or better. The improvement in scores was statistically significant (Wilcoxon

rank-sum, p=0.0041). This met the criteria of 0.025, established for correcting of multiple endpoints.

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

6.1.4.4.3.2 FDA Statistics Analysis

The statistical reviewer was able to reproduce the Sponsor's statistical analysis. The statistical reviewer performed a secondary analysis examining only US patients for "all seizure" frequency and tonic/atonic- seizure frequency change. This analysis revealed a significant rufinamide therapeutic effect for both endpoints with a p of 0.03 and <0.001, respectively.

DSI discovered on audit a problem with 1 of the 2 sites audited that may potentially affect the study results. These involved some inconsistencies in seizure rates. Thus, inconsistencies were observed when rates reported in the CRFs were compared to those reported in source tables for 4 patients. The FDA statistical reviewer performed a statistical analysis of the primary endpoint with the 4 patients in question excluded. Moreover, at the request of this medical reviewer, the statistical reviewer performed an analysis of the primary endpoints after excluding the entire center (1553). Following both analyses, the primary endpoints were still highly significant using both a parametric and non-parametric method. The table below presents this data.

Study#22	After excluded four patients: P-value		After excluding the center#1553	
	Wilcoxon	ANOVA	Wilcoxon	AVONA
% change in seizure freq. from baseline	<.001	.001	.004	<.001
%change in tonic-atonic seizure from baseline	<.001	<.001	<.001	.001
Seizure severity	.002	Not Applicable	.001	Not Applicable

Not applicable because the Seizure severity is ordinal outcome measure

The statistical reviewer performed a subgroup analysis for primary endpoint seizure frequency changes to examine the uniformity of the therapeutic effect based upon gender and age. While there are some differences in magnitude of response, there was a clear trend for a therapeutic effect in all subgroups. The table below presents this analysis. No analysis was performed on racial subclasses as non-Caucasians made up very small percent of the studied population.

Study	Seizure Type		4-<12 yr		12-<17 yr		17-<65yr	
			RUF	PLA	RUF	PLA	RUF	PLA
022	Total Seizure	N	31	33	19	17	24	14
		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 Seizure	N	28	24	46	40		
		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.

6.1.4.4.3 Reviewers Comments

All primary endpoints of the protocol were satisfied at the required p value even when correcting for multiple endpoints.

6.1.4.4.4 Secondary Endpoints

6.1.4.4.1 Sponsors Analysis

- *The 50% responder rate for all tonic and atonic seizures:* The table below presents the 50% responder rate for tonic-atonic seizures. There were a statistically significant greater number of responders in the rufinamide treatment group (p=0.002, logistic regression model).

Responder Rate	Rufinamide		Placebo		Odds Ratio ^a	P-value ^b
	#	%	#	%		
50%	31/73	42.5	10/60	16.7	3.81	0.0020

- *Percent change in 28 day seizure frequency in seizure subtypes:* Percent in seizure frequency is presented for seizure subtypes experienced by at least 10 patients. The Sponsor has combined absence and atypical absence because of the difficulty in clinically distinguishing between these. A “p” value is not presented for partial seizures because of the small number of patients examined. Of these data only 2 subclasses exhibited a

statistically significance ($p < 0.05$, Wilcoxon rank-sum not corrected for multiple comparison). These included atonic and the combined absence. There, however, was a trend toward a greater reduction in the rufinamide group with all seizure subtypes. This analysis has some limitations as it only examines patients with this subclass of seizures at baseline and is therefore not a true random sample.

	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)	0.0222
Double-blind frequency/ 28 days	66	39.1	(0, 2793.7)	56	43.0	(0, 5628.3)	
% change in frequency/ 28 days	66	-50.6	(-100, 1729.2)	56	-29.8	(-100, 584.3)	
Tonic seizures							
Baseline frequency/ 28 days	52	66.3	(1, 14304)	43	49.0	(1, 1066)	0.0821
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)	
Atonic seizures							
Baseline frequency/ 28 days	45	56.0	(1, 4037)	33	49.0	(2, 13122)	0.0125
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)	
Myoclonic seizures							
Baseline frequency/ 28 days	37	80.0	(1, 38928)	31	50.8	(1, 92583)	0.5711
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)	
Tonic-clonic seizures							
Baseline frequency/ 28 days	37	18.0	(1, 336)	27	15.0	(1, 788)	0.3306
Double-blind frequency/ 28 days	37	9.8	(0, 714)	27	14.7	(0, 200)	
% change in frequency/ 28 days	37	-45.6	(-100, 789.2)	27	-18.1	(-100, 729.6)	
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)	

- *Global evaluation of the “patients condition:”* The results of the global evaluation, which as noted above is the mean of a global evaluation for 5 categories of symptoms, is presented in the table below (-3 of very much worse to +3 of very much improved). While there was a trend toward improvement in the rufinamide group as compared to placebo this was not found to be statistically significant (Wilcoxon rank-sum, $p = 0.3492$).

	Rufinamide	Placebo
n ^a	73	62
Mean	2.30	1.77
Median	1	0
Range	(-10, 13)	(-6, 13)

6.1.4.4.4.2 FDA Statistical Reviewer’s Analysis

As noted above, while the study in Lennox-Gastaut was strongly positive, a final conclusion of efficacy in this disorder must be delayed until confirmatory data is provided. This may be provided in the form of a resolution of the confounding data from the partial seizure studies (e.g. an additional adjunctive study, perhaps at higher doses) or a second study in Lennox-Gastaut.

7 APPENDICES

7.1 Review of Individual Study Reports

7.1.1 Study AE/ET1 –Partial Epilepsy

7.1.1.1 Design

This is a multicenter (multi-international), double-blind, placebo-control, multiple dose (200, 400, 800 and 1,600 mg/day), parallel group design study that examined the therapeutic benefit of adjunctive treatment with rufinamide in patients with inadequately controls seizures of partial origin who were already being treated with at least 1 anticonvulsant.

7.1.1.2 Sample Size

A sample size of 500 patients was selected to allow for 100 patients in the 5 treatment groups. The Sponsor notes that 100 patients in each group will allow for a power of 80% at an alpha of 0.05 with no correction for multiple comparisons. While this study contains a large number of patients it uses a somewhat uncommon primary endpoint for such epilepsy study analysis. That is, it uses a regression analysis to examine for a positive slope. This may be because the study was originally designed as a large phase 2 dose finding study. As a result the “n” size per dose group was probably not adequately large for optimal power to distinguish individual dose differences from placebo.

7.1.1.3 Dosing

There was one placebo group and 4 drug groups (200, 400, 800 and 1,600 mg/day). Doses were administered in a bid regimen. There was no up-titration during the double blind period. According to the Sponsor, the dose selection was based upon animal studies, PK/tolerability studies and small and short duration, double-blind, placebo-control, sequential titration PD study AE/PT2.

Dosing was administered as 100 and 200 mg tablets. Because these tablets were of different size a double-dummy dosing technique was used to maintain the blind: i.e. 5 tablets were administered to all patients.

The formulation used in this trial, the Clinical Service Form (CSF), exhibited a slightly greater bioavailability than the to be marketed formulation that was used in the remaining two pivotal trials (see PK section).

7.1.1.4 Principal Inclusion Criteria

- Male or female patients age 15 to 65 years of age under.
- Female were required to be non-lactating, none pregnant, incapable of becoming pregnant or, under continuous supervision of a health professional, were using a reliable method contraception.
- A diagnosis of simple partial (including aura) and /or complex partial seizures with or without secondary generalization.
- Patients should have poorly controlled seizures, defined as 4 seizures/month during the 6 months prior to baseline, while on 1 to 3 AEDs.
- Constant dosages of current AEDs (1 to 3) for at least 4 weeks before the baseline phase.

7.1.1.5 Principal Exclusion Criteria

- Females who are pregnant or lactating.
- Patients with a history of any seizure type other than that of partial origin.
- Patients with a history of status epilepticus within the last 24 months.
- Patients with a progressive neurological degenerative condition.
- Patients with history of suicidal ideation or suicidal attempts.

- Patients with a history of clinically relevant psychiatric disorders within the last 24 months.
- Patients with a history of hypersensitivity to rufinamide or any of its metabolites.
- Patients with clinically relevant abnormalities in pre-trial screen (e.g. in CBC and serum chemistries).
- Patients with clinically relevant hepatic, renal, cardiopulmonary, metabolic or endocrinological disorders.
- Patients with acute hepatitis or AIDS.
- History of drug or alcohol abuse within 12 months prior to the study.
- Patients using ethosuximide, felbamate (added in an amendment) or hormonal contraceptives.
- Patients who received an investigational drug within the last 3 months prior to the trial.

7.1.1.6 Concomitant Medication

As noted one to three anticonvulsant drugs were permitted during the study. As this study was performed about 10 years ago, patients were not exposed to recent anticonvulsants such as levetiracetam, oxcarbazepine, zonisamide etc. Ethosuximide and felbamate (see amendment) were not permitted. Hormonal contraceptives were not permitted as a form of birth control.

7.1.1.7 Amendments

There were 5 official amendments. The first two amendments were made before the trial was initiated. Neither of these amendments would affect efficacy determination. These included:

- The first amendment increased the restrictions for study entry and monitoring during the study regarding pregnancy and reduced some laboratory safety monitoring during the study that were felt to be redundant.
- The second amendment corrected a very important error in the protocol that would have labeled the blister pack with the treatment code instead of the country code. This would not affect the blind as it was initiated before the initiation of the study.

The remaining amendments were implemented during the study. None of these amendments should effect efficacy conclusions. These are described as follows.

- The third amendment altered the time for evaluation of one of the secondary endpoints, the FePsy. It was determined that more time was required for the test and the intervening break. As a secondary cognitive endpoint this would have no impact on the primary conclusion of the study. Another part of this amendment changed the wording for seizure reporting in the CRF to better concur with other parts of the CRF. Examination of this

change by this reviewer suggests that it should not affect seizure reporting rate. For example “simple seizures without secondary generalization” was changed to “simple seizures only.”

- The fourth amendment was made to reduce a redundancy for requested concomitant medication information on the PK and clinical trial CRF.
- The Fifth Amendment was to exclude patients on Felbamate when serious adverse events associated with this anticonvulsant were identified.

There was on very important post-hoc change in data analysis that was established prior to the breaking of the blind. Thus the original protocol specified primary endpoint was time to the fourth seizure. In a meeting of a working group, which occurred prior to unblinding (8/30/94), it was decided that such an endpoint was not ideal. One reason for this is that it “penalizes those patients who experience high baseline seizure frequencies.” The Sponsor notes a formal letter was issued 2/9/95). This information was not available in the submitted NDA. It is unknown whether this information for this major change was sent to the FDA at the time of change. Consequently, in a teleconference with the Sponsor, Eisai (9/6/06) was requested to provide the division of the documentation of these events. This was provided in an e-mail sent on 9/8/06. Included were two documents dated 2/9/95 that included an internal letter with a new SAP (labeled to supersede original plan). Consequently, log transformed seizure frequency per 28 days during the double blind phase was examined using a linear regression to determine a dose trend as a primary endpoint. Other secondary endpoints and secondary analyses were specified in this updated SAP (see below). The original endpoint was maintained as a secondary endpoint.

7.1.1.7.1 Study Schedule

The study included a 12 week prospective baseline period and a 12 week prospective double-blind treatment period.

The table below presents the schedule for procedures performed during the study.

*Appears This Way
On Original*

Week	---pre trial check---	Prospective Baseline				Double-blind treatment							
		0	4	8	12 ^r	D4	1	2	3	4	8	12	
Examination /report no.		1	2	3	4*	7	8	9	10	11	12	13/F	
Informed consent, personal data, history, concomitant diseases, previous/current medication, non-drug therapy		X											
Check of inclusion/exclusion criteria		X			X								
12-lead ECG		X			X	X	X	X	X	X	X	X	
Nicotine/alcohol consumption, weight, PR, bp, respiratory rate, temperature		X	X	X	X	X	X	X	X	X	X	X	
Physical examination		X	X	X	X	X	X	X	X	X	X	X	
Neurological examination		X	X	X	X	X				X	X	X	
Seizure record, sleep quality and duration, adverse experiences, concomitant medication, non drug treatment			X	X	X	X	X	X	X	X	X	X	
EEG				X	e						X	e	
Routine laboratory examinations		X			X	X		X		X	X	X	
Psychometric battery (selected centers)					X						X		
Seizure record (Patient Diary) ---daily---		---	---	---	---	---	---	---	---	---	---	---	
Liverpool Seizure Severity Scale		X	X	X	X					X	X	X	
Patient's satisfaction with antiepileptic treatment					X							X	
Global assessment of efficacy and tolerability												X	
Plasma levels current concomitant AEDs		X	X	X	X	X	X	X	X	X	X	X	
Plasma levels of rufinamide					X ^a	X	X	X	X	X	X	X	
Tablet count					X	X	X	X	X	X	X	X	

^x Exam 4 = end of prospective baseline with randomization and start of Double-blind Treatment Phase
^{*} Examinations 5 and 6 (Days 2 and 3) optional for outpatients, mandatory for inpatients (see text for procedures - Section 3.6. - not included in this exhibit).
 D4 = Day 4 of trial treatment, F = final or in event of premature discontinuation, e = evaluation of previous week's trace, a = baseline measurement

Patients first entered the baseline period following inclusion and exclusion criteria evaluation at "Examination 1." They were subsequently evaluated at monthly intervals (see table above) for baseline features and safety.

Patients are randomized into the double-blind study after completing the baseline period. In order to continue to the double-blind phase patients were required to have demonstrated during the baseline period at least nine seizures, continued use of AEDs at a constant dose and good compliance. Patients received their first dose of rufinamide on "Examination 4." The investigator was permitted to maintain the patient in the hospital if it was thought to be in the patient's best interest at this time (these subsequent days were then referred to as "Examination 5" and "examination 6." The final examination in this study occurred 3 months after treatment was initiated at "Examination 13." The table above presents the scheduled procedures during this period.

7.1.1.8 Endpoints

7.1.1.8.1 Primary Endpoint

As noted above the original protocol specified primary endpoint was time to the fourth seizure. For reasons stated above this was changed to a measure of seizure frequency.

7.1.1.8.2 Secondary Endpoints

According to the study report the following were considered secondary endpoints.

- *Comparison of seizure frequency between dose and placebo groups: This was performed to be two ways: 1) Comparison of seizure counts during administration between dose groups and placebo, 2) Comparison of Seizure frequency ratio was calculated as the 28 day seizure frequency during the double-blind phase divided by the seizure frequency during the baseline period.*
- *Time to forth seizure: As noted above this was the original primary endpoint.*
- *Response to treatment: Although the Sponsor notes in the study report that this was not specified as an endpoint in the protocol it was included in the revised SAP. This response to treatment was defined as the number of patients who experienced a 25% reduction in seizure frequency from baseline.*
- *Global Assessment of Therapeutic Effect, (GATE): This is an investigator rater assessment of therapeutic effect of treatment. It is based upon a 4 point scale from none to very good.*

Other secondary endpoints were noted in the revised SAP but were not enumerated as secondary endpoints in the study reports. These included:

- Time to first seizure.
- Time to first complex partial seizure.
- Time to first generalized seizure.

7.1.1.8.3 Exploratory Endpoint

The Liverpool Seizure Severity Scale (LSS) was used as an exploratory endpoint. This survey consists of 20 questions addressing seizure severity.

7.1.1.9 Analysis

The intent to treat patient set was used in the primary analysis of all endpoints. This was defined as any patient who provided a seizure diary from the baseline and the double-blind phase. All analyses were two tailed with an alpha of 0.05.

7.1.1.9.1 Primary Endpoint

This analysis examined the dose relationship of seizure frequency during the double-blind treatment phase. An inverse relationship was interpreted as demonstrating efficacy.

Seizure frequency per 28 days was log transformed (Log_e) and analyzed with a normal multiple regression model. All values were first shifted by 1/3 prior to transformation to account for the small number of patients with zero seizures during the double-blind phase. Thus the final measure was Log_e seizure frequency + 1/3. Explanatory variables included baseline frequency, ordinal dose, country, sex and age. Statistical significance for which ordinal dose was determined.

7.1.1.9.2 Secondary Endpoint

There was no adjustment for multiple comparisons on any of these endpoints.

- *Comparison of seizure frequency between dose and placebo groups:* This was planned to be performed in 2 ways according to the revised SAP: 1) Using a Poisson analyses the seizure counts in different treatment doses with explanatory variables of baseline frequency, ordinal dose, country, and sex and age, 2) seizure frequency ratio (frequency during administration divided by baseline frequency) using a Wilcoxin rank-sum test without correction for multiple comparisons. Only the latter analysis was performed in the final study report.
- *Time to forth seizure:* Analysis was performed with the use of a Cox proportional hazard regression model. Explanatory variables included were baseline frequency, dose, sex and age.
- *Response to treatment:* This was analyzed through a logistic regression model with explanatory variables of dose, country, baseline frequency, sex and age.

- *Global Assessment of Therapeutic Effect, (GATE)*: This was analyzed using the same method as was the Response to Therapy.

7.1.2 Exploratory Endpoint

The LSS was to be analyzed using an ANCOVA.

7.1.2.1 Results

See “Efficacy Findings” in the “Integrative Review of Efficacy.”

7.1.3 Study 021A–Partial Epilepsy

7.1.3.1 Design

This is a multicenter (multi-international), double-blind, placebo-control (single dose), parallel group design study that examined the therapeutic benefit of adjunctive treatment with rufinamide in patients with inadequately controls seizures of partial origin who were already being treated with at least 1 anticonvulsant.

7.1.3.2 Sample Size

A sample of 274 (1:1) was determined to be adequate for demonstrating an effect,

7.1.3.3 Dosing

The targeted dose for study was 3200 mg/day. All dosing was administered in two divided doses at 7 to 8 AM and 7 to 8 PM. Dose titration occurred over a period of one week according to the schedule below. If a problem in tolerability arose, titration could occur at a slower rate over the period of two weeks. If tolerability was a problem during the maintenance phase the dose could be reduced by no more than 400 mg after discussion with the trial monitor.

Rufinamide was administered as 400 mg tablets and patients were instructed to take their dose with food. The FMI, to be marketed, formulation was used.

Adults ≥16 years				
Study day	Dose (mg/kg)	Daily dose (mg)	AM	PM
			Bottle C - tablets	Bottle C - tablets
1 - 2	10	800	1	1
3 - 4	20	1600	2	2
5 - 6	30	2400	3	3
7	45	3200	4	4

Bottle C contained 400 mg tablets of rufinamide or matching placebo.
 * The above doses were recommended, however, each dose level increase was at the discretion of the investigator based on tolerability.

Taper off of drug occurred at a rate of a 25% dose reduction every other day.

The Sponsor notes that dosing of 3200 mg/day was based upon the efficacy data in study AE/ET1 that demonstrated that “doses of 400-1600 mg produced a significant reduction in seizure frequency,” and an extension phase of AE/ET1 that demonstrated that doses of 3200 mg/day were “well tolerated.”

7.1.3.4 Principal Inclusion Criteria

- The patient should have been 16 years or older and weigh at least 40 lbs.
- The patient should have had a diagnosis of partial seizures with at least one complex partial or secondary generalized seizure.
- The patient should have been on a fixed dose of one to two concomitant anticonvulsants during the 56-day Baseline Phase.
- Additional AEDs or non-allowed medications must have been discontinued 30 days prior to this period.
- The patient should have at least 6 documented partial seizures during the 56-day baseline phase of the study, with at least one partial seizure occurring in each 28-day baseline Phase period.
- The patient should have had a CT or MRI confirming the absence of a progressive CNS lesion and interim exams confirming the absence of such lesions.

- EEG evidence prior to, or during, the 56 day baseline period consistent with a diagnosis of partial seizures.
- Females were to be incapable of child birth base upon menarche status, be surgically sterile or used adequate contraception (IUD or spermicidal and barrier): hormonal contraception was not considered adequate. Abstinence was considered adequate if confirmed by parent/guardian.
- If a female was capable of child birth they must have had normal menstrual cycles 3 months prior to study entrance and had a negative pregnancy test at time of randomization.

7.1.3.5 Principal Exclusion Criteria

- Patient had a treatable etiology for seizures (e.g. neoplasm).
- Patient had a diagnosis of generalized seizures, with the exception of secondary generalized seizures.
- Patient had a generalized status within 2 months prior to the 56-day Baseline Phase while complying with appropriate AED therapy.
- Patient who had seizures occurring only in clusters.
- Patient had used benzodiazepines with a frequency of greater the twice a month unless used as a concomitant anticonvulsant.
- Patient had evidence on exam, or by history, of significant medial disease or progressive neurological disease requiring current medical intervention or likely to have a significant impact on the outcome of the study.
- Patient had a history of schizophrenia or any psychotic symptom (excluding post-ictal phenomena).
- Patient had a history of suicide attempt.
- Patient had a history of drug abuse or has a positive drug screen.
- Patient had received rufinamide in the past.
- Patient had participated in a study of another investigational study within 30 days of the baseline phase.
- Patient had received felbamate within 30 days of the baseline phase.
- Patient had a history of no non-compliance or was potentially unreliable.
- Patient was unable to maintain a seizure calendar a/or unable to take medication either independently or with assistance.

7.1.3.6 Concomitant Medication

Patients were allowed to be on a stable dose of 1 to 2 concomitant AEDs (see inclusion criteria). They were to maintain these doses throughout the baseline and double-blind phases. Other AEDs must have been discontinued 30 days prior to the baseline phase. Use of non-AEDs “were to be avoided” and patients or the caregivers were advised to consult either the investigator before any drug was initiated.

7.1.3.7 Amendments

One amendment (8/3/98) is noted. This amendment increased the sample size in order to increase the power to detect statistically significant differences between the treatment groups in both the adult and pediatric strata as these were now going to be evaluated as separate populations: i.e. the study had been divided into an adult study (21A) and a pediatric study (21P). This allowed each stratum to be analyzed independently as a stand-alone study without loss in the power of the study.

Although not issued as an amendment the Sponsor notes that later on in the conduct of the study, centers enrolled at a rate faster than anticipated. Because of this unexpected over-enrollment, a separate sensitivity analysis was conducted to ensure that the additional patients did not influence the outcome of the overall analysis.

7.1.3.7.1 Study Schedule

The schedule for study procedures is presented in the table below. The study consisted of two principal phases, the baseline and double-blind treatment phase.

The baseline phase was 8 weeks in duration. Patients were monitored for seizure activity during this period and were required to have a prescribed number of partial seizures during this phase (see inclusion criteria) to continue to the double-blind experimental phase. Up to 6 weeks of retrospective seizure accounting information could be used in lieu of the baseline monitoring if diaries containing this information were considered "accurate and complete." The baseline visit occurred during this period from day -56 to day-7. The timing is dependent on the amount of retrospective baseline data available. Testing, clinical history and examination, required for screening, were performed at this time.

Patients who meet screening criteria were randomized at visit1, during the double blind treatment phase. This phase consisted of a one week titration period and a 12 week maintenance period. Clinic visits occurred during this phase at a frequency of every week to every month.

Seizure diaries were monitored at each visit as was various testing for safety monitoring according to schedule below.

Phase	Base-line	Double-blind Treatment						
		Titration		Maintenance				
Visit (Examination/Report No).		1	2	3	4	5	6	6.1
Day	-56 to -7	0	7	14	35	63	91/ or Term.	Post-tapering
Written informed consent	X							
Inclusion and Exclusion checklist		X						
Seizure history & current classification		X						
Medical and neurological history		X						
Physical and neurological examination		X					X	
Electrocardiogram	X						X	
Interim physical examination			X	X	X	X		
Seizure frequency	X ^a	X	X	X	X	X	X	
Concomitant medication / therapy		X	X	X	X	X	X	X
Concomitant AEDs and doses	X ^a	X	X	X	X	X	X	X
Adverse experience(s)			X	X	X	X	X	X
Routine laboratory analysis	X	X		X	X	X	X	
Drug screen	X							
Serum β-HCG pregnancy test		X					X	
Urine pregnancy test (dip stick)		X						
Thyroid function tests	X	X					X	
Study drug levels (Rufinamide)				X	X	X	X	
Concomitant AED levels (AED-1, AED-2)	X	X		X	X	X	X	
Dispense study drug		X	X	X	X	X	X ^b	
Global tolerability scale							X	
Termination sheet							X	

^a To be recorded in the source documents; details then transcribed on to the CRF at Visit 1.
^b Dispense tapering medication or enter patient into long-term extension.

7.1.3.8 Endpoints

7.1.3.8.1 Primary Endpoint

The primary endpoint was the percent change in partial seizure frequency during the double-blind phase as compared to the Baseline Phase. The frequency was based upon the number of seizures per 28 days.

7.1.3.8.2 Secondary Endpoints

- *The total partial seizure frequency per 28 days during the Double-blind Phase.* This was calculated as the total partial seizure frequency during the Double-blind Phase divided by the number of days in the double-blind seizure diary. This was then multiplied by 28.
- *Response to treatment:* Patients experiencing a 25% and 50% reduction in 28 day seizure frequency during the double-Blind placebo control phase as compared to the Baseline Phase.
- *Change in the 28 day frequency of secondarily generalized seizure:* This was determined in two different ways for 2 separate populations of patients. Thus, for those experiencing secondarily generalized seizures during the baseline phase a simple percent change from baseline is calculated in a manner similar to that of the primary endpoint. For those who did not experience such seizures during the baseline phase a difference between the Double-Blind and the Baseline phase was calculated.

7.1.3.9 Analysis

A sample size of 274 patients were calculated as being required to detect a 25% difference in the percentage reduction in partial seizure frequency from baseline between rufinamide and placebo at a power of 80%. This calculation was based upon the assumption of a standard deviation of 69.5% at a p of 0.05. The standard deviation was derived from the prior oxcarbazepine pediatric studies performed by Novartis and is similar to that used in the AE/ET 1 protocol.

7.1.3.9.1 Primary Endpoint

The primary endpoint was the percent change in the 28 day partial seizure frequency calculated as $PCH = 100 * (T - B) / B$; where T = 28 day seizure frequency during the double-Blind Experimental Phase and B = 28 day seizure frequency during the baseline phase. The difference between placebo and rufinamide was determined by a two sided Wilcoxon rank-sum test ($p < 0.05$).

Two sensitivity analyses were also performed for the primary endpoint: 1) only those patients who completed the Double-blind Phase, 2) for the first 274 patients randomized to evaluate the impact of over-enrollment beyond the planned sample size (see amendments).

7.1.3.9.2 Secondary Endpoint

- *The total partial seizure frequency per 28 days during the Double-blind Phase:* This was analyzed by using the natural logarithm of the partial seizure frequency per 28 days during the Double-blind Phase. The Sponsor notes that because a small number of patients with partial seizure frequencies of zero were expected during the Double-blind Phase, a positive constant, chosen as 1/3, was added to all partial seizure frequencies logarithmic transformation. The analysis was carried out with an analysis of covariance model. The analysis was fitted with treatment, age-group, country and sex as factors and \log_e (28-day seizure frequency in the Baseline Phase) as a covariate. This model was also used to investigate treatment-by-factor interactions as follows: 1) treatment-by-country interaction was examined, 2) treatment-by-sex interaction was tested in the same manner as treatment-by-country interaction, 3) assuming that the interaction terms are not statistically significant, estimates of the treatment difference between rufinamide and placebo were produced along with 95% confidence interval
- *Response to treatment:* Both 25% and 50% responder rates were using a logistic regression model. This model included treatment, country, sex and age as explanatory variables. The presence of interactions of treatment with country and sex was examined using a tabular presentation.
- *Change in the 28 day frequency of secondarily generalized seizure in patients:* All analyses for this endpoint utilized the Wilcoxon rank-sum test.

7.1.3.10 Results

See “Efficacy Findings” in the “Integrative Review of Efficacy.”

7.1.4 Supportive Non-Pivotal Trials in Partial Epilepsy

In addition to the two pivotal trials described above the Sponsor has submitted 7 additional double-blind controlled trials in epilepsy that should be examined when considering approval for rufinamide as adjunctive treatment in this seizure disorder. One trial, AE/PT2 was a small (n=48), short duration, adjunctive trial in adults. Another trial, 021P, examined adjunctive use in a pediatric population. This was originally combined with the adult adjunctive trial (021A), but was separated prior to unbinding. Three studies (038, 016 and 039) were small to moderate size

studies that examined monotherapy in a patient population .12 years old. One of these studies (039) was terminated because of recruitment difficulties. One additional trial examines primary generalized Tonic Clonic seizures. These trials are summarized in the table below:

Appears This Way
On Original

Clinical Review
 Norman Hershkowitz, MD, PhD
 21911 (000)
 Rufinamide (Invelon®)

Study ID	No. of centers Location(s)	Study dates Enrollment: Total/goal	Design	Study & control drugs: dose, route, regimen	Study objective	No. subjects by arm entered/ completed	Duration of treatment	No. M/F* Mean age* (range)	Diagnosis and main inclusion criteria	Primary endpoint(s)
ADULTS WITH PARTIAL SEIZURES: CONTROLLED STUDIES										
Double-blind, placebo-controlled adjunctive therapy studies in adults with partial seizures										
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	Efficacy and safety	25/23 25/25	28 days	34/16 34 ^b (20-60)	Adults with partial seizures who were using no more than 2 fixed-dose AEDs	Seizure frequency ratio (ratio of seizure frequency during DB Phase to seizure frequency during 3-month retrospective Baseline Phase)
Double-blind, controlled studies of monotherapy and monotherapy substitution in patients with partial seizures										
038*	18 USA	May-99 to Feb-01 104/102	Randomized, DB, placebo-controlled, parallel group	RUF: 3200 mg/day t.i.d. PLA	Efficacy and safety	52/47 52/45	10 days Titration: 1 day Maintenance: 9 days	43/61 35.4 (12-70)	Patients (≥12 years) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery and completed a 48-hour Baseline Phase when no AEDs were taken	Time to meeting 1 of 4 exit criteria defined in the protocol, all indicating increased severity or frequency of seizures
016*	16 Canada Poland USA	Nov-97 to Oct-00 142/160	Randomized, DB, controlled, 2-dose group	RUF: 300 mg/day 3200 mg/day t.i.d.	Efficacy and safety	70/69 72/66	112 days Titration: 7 days Maintenance: 105 days	55/87 39.4 (17-76)	Patients (≥12 years) with inadequately controlled partial seizures who were using 1 or 2 fixed-dose AEDs	Percentage of patients meeting 1 of 4 exit criteria defined in the protocol, all indicating increased severity or frequency of seizures
039**	10 Mexico Sweden USA	Dec-98 to Sep-00 29/118	Randomized, DB, placebo-controlled, parallel group	RUF: 1200 mg/day b.i.d. PLA	Efficacy and safety	14/11 15/13	56 days	8/21 42.2 (15-87)	Patients (≥12 years) with recent-onset partial seizures who had not received AEDs for at least 84 days	The study was terminated early due to lack of enrollment; no efficacy analysis was performed.
OTHER INDICATIONS: CONTROLLED STUDIES										
Double-blind, placebo-controlled adjunctive therapy study in primary generalized epilepsy										
018*	42 Argentina Austria Belgium Chile Great Britain Poland USA	Jun-97 to Apr-00 155/144	Randomized, DB, placebo-controlled, parallel group	RUF: 800 mg/day b.i.d. PLA	Efficacy and safety	80 ^b /64 75/66	140 days	59/94 29.3 (4-63)	Patients (≥4 years) with inadequately controlled PGTC who were using 1 or 2 fixed-dose AEDs	Percentage change in PGTC seizure frequency per 28 days, relative to baseline
Double-blind, placebo-controlled adjunctive therapy study in children with partial seizures										
021P*	58 Argentina Brazil Chile France Germany Hungary Italy Russia Slovakia South Africa Spain Switzerland USA	Nov-97 to May-00 269/274	Randomized, DB, placebo-controlled, parallel group	RUF: 45 mg/kg/day b.i.d. PLA	Efficacy and safety	137 ^c /117 132/122	91 days Titration: 14 days Maintenance: 77 days	156/ 112 10.5 (3-17)	Children (4 to <16 years) with inadequately controlled partial seizures who were using 1 or 2 fixed-dose AEDs	Percentage change in partial seizure frequency per 28 days, relative to baseline

*, ** Indicate that the rufinamide formulation used in the study was the newer Final Market Image (*) or the older Clinical Service Form (**).

^a Results are based on the number of patients who received at least 1 dose of study medication.

As noted above all studies were double-blind control studies. With some exceptions all studies contained similar key inclusion criteria. Differences included one study that examined pediatric patients; one study examined primary generalized tonic-clonic seizures and not partial seizures. Baseline seizure frequency moderately varied between studies but was very high in the monotherapy surgical trial (study 038: 90 seizures/month).

The table below is copied from the Sponsors ISE and presents a summary of supplemental studies information with doses, primary endpoint, primary endpoint value and p-value summarized.

Study	Treatment arm	No. entered/ completed	Primary endpoint	Result	p-value	Statistical test	Other comment
ADULTS WITH PARTIAL SEIZURES							
Double-blind, placebo-controlled adjunctive therapy studies in adults with partial seizures							
AE/PT2	RUF 400 to 1600 mg/day PLA	25/23 25/25	Seizure frequency ratio	0.593 1.520	0.0397*	Wilcoxon-Mann-Whitney (alpha level 0.05)	
Double-blind, controlled studies of monotherapy and monotherapy substitution in patients with partial seizures							
038	RUF 3200 mg/day PLA	52/47 52/45	Time to meeting at least one exit criterion	4.8 days 2.4 days	0.0499*	Log-rank (alpha level 0.05)	When a Weibull parametric regression model with baseline seizure frequency as covariate was used, the treatment effect was significant (p=0.0271)
016	RUF 300 mg/day 3200 mg/day	70/69 72/66	Percentage of patients meeting at least one exit criterion	72.5% 66.7%	0.4402	CMH (alpha level 0.05)	Trend (0.0968) favoring 3200 mg/day in time to meeting one of the exit criteria (median of 56 vs 32 days)
Double-blind, placebo-controlled adjunctive therapy study in primary generalized epilepsy							
018	RUF 800 mg/day PLA	80/64 75/66	Median percentage change in PGTC seizure frequency per 28 days, relative to baseline	-36.4% -25.6%	0.6330	Wilcoxon rank-sum (alpha level 0.05)	Country that enrolled 53% of patients (USA) showed advantage for rufinamide (-55.6%) over placebo (-32.9%)
Double-blind, placebo-controlled adjunctive therapy study in children with partial seizures							
021P	RUF 45 mg/kg/day PLA	137/117 132/122	Median percentage change in partial seizure frequency per 28 days, relative to baseline	-7.0% -12.8%	0.6214	Wilcoxon rank-sum (alpha level 0.05)	Trend (p=0.0596) favoring rufinamide in percentage of patients with at least 50% decrease in frequency (27.2% vs 18.3%)

* Indicates statistical significance according to the Sponsors analysis.

For a discussion of the results and potential significance of supportive studies see “Efficacy Findings” in the “Integrative Review of Efficacy.”

7.1.5 Study 22 –Lennox-Gastaut

7.1.5.1 Design

This was a multinational, multicenter, double-blind, placebo-controlled, randomized, parallel group study of rufinamide as adjunctive therapy in patients with inadequately controlled LGS.

7.1.5.2 Sample Size

A total of 128 were estimated to be necessary to demonstrated efficacy.

7.1.5.3 Dosing

Patients were to be treated with a target dose of 45 mg/kg/day (3200 mg/day in an adult of ≥ 70 kg). Drug was administered twice daily at 7:00-8:00 AM and 7:00-8:00 PM. Patients were to undergo a 14 day titration period. The rate of titration and final mg dose was dependent on the patient's weight. The titration regimen is presented in the table below. The dose achieved after this period would be maintained for the remainder of the double-blind phase (maintenance period). Titration schedule could be altered if problems with tolerability were encountered. If problems in tolerability were observed during the maintenance period dosage reductions were permitted after discussions with the Sponsor.

*Appears This Way
On Original*

Trial day	Dose mg/kg	18 – 29.0 kg						29.1 – 50.0 kg							
		Daily dose (mg)	AM			PM			Daily dose (mg)	AM			PM		
			A	B	C	A	B	C		A	B	C	A	B	C
1-2	≈10	200	1			1			400	1			1		
3-4	≈20	400		1			1		800	2				2	
5-6	≈30	800		2			2		1200	3				3	
7	≈45	1000		2			3		1800	4				5	

Trial day	Dose mg/kg	50.1 – 70.0 kg						
		Daily dose (mg)	AM			PM		
			A	B	C	A	B	C
1-2	≈10	600		1			2	
3-4	≈20	1200		3			3	
5-6	≈30	1800		4			5	
7	≈45	2400		6			6	

Trial day	Dose mg/kg	≥70.1 kg						
		Daily dose (mg)	AM			PM		
			A	B	C	A	B	C
1-2	≈10	800			1			1
3-4	≈20	1600			2			2
5-6	≈30	2400			3			3
7	≈45	3200			4			4

A = Bottle A containing 100 mg tablets of rufinamide or matching placebo.

B = Bottle B containing 200 mg tablets of rufinamide or matching placebo.

C = Bottle C containing 400 mg tablets of rufinamide or matching placebo.

Note: the above titration schedules were recommended for each weight category; however, a slower titration (over 14 days) was allowable at the discretion of the investigator.

The dose selected for this study was based upon study AE/ET1, which was previously discussed, and which examined therapeutic safety and tolerability in patients with partial seizures.

The FMI, to be marketed, formulation was used.

7.1.5.4 Principal Inclusion Criteria

- Patient should be between 4 and 30 years of age at Visit 1 (randomization) and weigh at least 18 kg (40 pounds) at Visit 1.
- Patient should have inadequately controlled LGS which must include both atypical absence seizures and drop attacks (or other nomenclature that defines identical seizure types such as tonic-atic or astatic seizures). Other seizure types may have included tonic, tonic-clonic or myoclonic.
- Patient should be on a fixed dose of one to two concomitant AEDs (changed to one to three concomitant AEDs by Amendment 1) during the 28-day Baseline Phase (additional

AEDs or non-allowed medication must have been discontinued 30 days prior to the 28-day Baseline Phase).

- Patient should have at least 90 seizures in the month prior to the 28-day Baseline Phase of the trial.
- Patient should have an EEG within 6 months prior to the baseline demonstrating a slow spike-and-wave pattern.
- If female, patient should be either: 1) premenarchal, or 2) surgically incapable of bearing children, or 3) practicing contraception for at least 1 month prior to entering the trial by means of an intrauterine device or spermicidal and barrier. Abstinence was considered as an acceptable method of contraception on a case-by-case basis upon discussion with the responsible Novartis representative. Oral contraceptives/ hormonal contraceptive techniques were not considered adequate contraception during this trial.
- If female and capable of bearing children, patient should have a normal menstrual cycle during the 3 months prior to baseline and have a negative urine pregnancy test at Visit 1 (prior to first dose of trial drug).
- Patient should have a computed tomography (CT) scan or magnetic resonance imaging (MRI) study confirming the absence of a progressive lesion and no physical examination changes suggesting such a lesion should have occurred since that imaging procedure.

7.1.5.5 Principal Exclusion Criteria

- Patient has a treatable etiology of seizures, such as active infection, neoplasm, metabolic disturbance, etc.
- Patient has a history of generalized tonic-clonic status epilepticus within the 30 days prior to baseline while complying with appropriate AED therapy.
- Patient has intermittent benzodiazepine use of more than four single administrations per month prior to baseline.
- Patient has evidence on physical examination, or a history (within the 2 years prior to baseline), of any clinically significant cardiac, respiratory, hepatic, gastrointestinal, renal, hematological, or progressive neurologic disorder requiring current medical intervention/therapy or likely to have a significant impact on the outcome of the trial.
- Patient has clinically significant ECG abnormalities.
- Patient has a malignancy or history of a malignancy (within the 5 years prior to baseline).
- Patient has a history (within the 6 months prior to baseline) of a psychiatric/mood disorder (DSM IV), not consistent with LGS, which required medical and/or electroconvulsive therapy. Antidepressants such as tricyclic antidepressants or selective serotonin reuptake inhibitors may have been used in low doses (if discussed with the responsible Novartis representative).
- Patient has a history of substance abuse (including alcohol) or a positive drug screen.
- Patient has a history of a suicide attempt.
- Patient has a history of rufinamide (CGP 33101) therapy.

- Patient has participated in another trial of an investigational drug/device within the 30 days prior to baseline.
- Patient has a history of anoxic episodes requiring resuscitation within the 12 months prior to baseline.
- Patient is on a ketogenic diet or has received adrenocorticotrophic hormone within the 6 months prior to baseline.
- Patient has received felbamate treatment within the 2 months prior to baseline. Felbamate was a non allowed medication in this study.
- Patient is pregnant, trying to become pregnant, or nursing an infant.

7.1.5.6 Concomitant Medication

Patients must be on a fixed dose of 1 or 2 AEDs for at least 28 days prior to randomization. This was increased to 3 (see amendment 1). Any additional AEDs should have been discontinued 30 days prior to entry into the baseline phase. Concomitant AED treatment was to remain unchanged throughout the study. Felbamate was not permitted. Use of other medications was noted to “be avoided whenever possible.” Patients were asked to consult the investigator prior to starting any new medications (including over the counter medications).

7.1.5.7 Amendments

- Amendment 1: This amendment increased the maximum number of allowed concomitant AEDs from two to three. It was instituted during the course of the study to increase recruitment as many patients with LGS received more than two AEDs.
- Amendment 2: At a meeting with the FDA (April 23, 1998) the Sponsor was told by the FDA that because of the problem of multiple comparisons for the primary endpoint the analysis did not correct for type I error. A correction was therefore made for the efficacy analysis (see analysis).

7.1.5.7.1 Study Schedule

A schedule of study procedures is presented in the table below.

Phase Period Visit (Examination/Report No). Day	Baseline ^a	Double-blind Treatment						
		Titration			Maintenance			
		1 0	2 7	3 14	4 28	5 56	6 \$4/ or Term.	6.1 Post- taper
Written informed consent	X							
Inclusion and Exclusion checklist		X						
Seizure history & current classification	X							
Medical and neurological history	X							
Physical and neurological examination		X					X	
Electrocardiogram	X						X	
Interim physical examination			X	X	X	X		
Seizure frequency	X	X	X	X	X	X	X	
Record concomitant medication / therapy	X	X	X	X	X	X	X	X
Record concomitant AEDs and doses	X	X	X	X	X	X	X	X
Adverse experience(s)			X	X	X	X	X	X
Routine laboratory analysis	X	X			X		X	
Drug screen	X							
Serum β -HCG pregnancy test		X					X	
Urine pregnancy test (dip stick)		X						
Thyroid function tests	X	X					X	
Trial drug levels (rufinamide)					X		X	
Concomitant AED levels	X	X			X		X	
Dispense trial drug		X	X	X	X	X	X ^b	
Collect and count returned trial drug			X	X	X	X	X	X
Global Evaluation		X					X	
Termination sheet							X	

Term. = Termination
^a CCTV/EEG was to be performed prior to the baseline visit.
^b Taper medication or double-blind conversion medication dispensed.

The study consisted of two phases, the baseline and double-blind treatment phase.

The baseline phase was 28 days in duration. The patient was required to have a 6-24 hours baseline closed-circuit video/EEG 6 months prior to entry into this phase. During the baseline visit (-28 days) the investigators and patient/caregiver reviewed the video/EEG and developed a strategy for naming and counting seizures. The patient was instructed on the seizure diary. Additional safety and PK laboratories and testing was performed at this visit (see table above).

The double-blind phase was 3 months long and consisted of 2 periods, the 2 week titration and the 10 week maintenance treatment periods. Patient who meet criteria were randomized on the first day of the phase (visit 1). Routine laboratories, adverse event monitoring was performed at 2 to 4 weeks intervals (see the above table).

Of note seizures in this disorder may occur in clusters and are sometimes difficult to count. The investigator strategy meeting with the patient may assist the patient in counting such events. Errors introduced in counting such events may be expected to be equally distributed between placebo and rufinamide group and therefore should not bias the results in any direction but simply increase the variance and make the rejecting of the null hypothesis more difficult.

Endpoints

7.1.5.7.2 *Primary Endpoint*

The primary endpoint included 3 individual variables: 1) percent change in seizure frequency per 28 days in the double-blind phase as compared to the baseline phase for all seizure types, 2) percent change in seizure frequency per 28 days in the double-blind phase as compared to the baseline phase for all tonic and atonic seizures (referred to from herein as tonic/atonic), 3) “Seizure severity” rating using a Global Evaluation scale (based upon a 7 point scale with +3 as very much improve, -3 as very much worse and 0 as no change) rated by parent/guardian.

7.1.5.7.3 *Secondary Endpoints*

- The 50% responder rate for all tonic and atonic seizures. Note, this was originally to be all seizure types, but changes prior to braking of the blind because it was believed that drop attack was the most significant type of seizure. According to the study report this was not made as an amendment but was made as part of an SAP issued prior to study unblinding.
- Percent change in 28 day seizure frequency during the double-blind phase from baseline in each subtype of seizure other then tonic-atonic seizures.
- Global evaluation of the “patient’s condition.” This was rated by the parent/guardian and consisted of 5 categories of evaluation, each rated on a 7-pint scale similar to the primary endpoint of seizure severity (-3 to +3 of very much improved to very much worse). The categories included level of alertness, level of interaction with environment, responsiveness to verbal requests, ability to perform activities of daily life and seizures severity. A mean of categories were taken for the final analysis.

7.1.5.8 *Analysis*

All statistical analyses were two tailed. Because of the multiple endpoints used in the analysis the primary endpoints utilized an alpha of 0.025 (see below) whereas analysis of secondary endpoints utilized an alpha of 0.05.

7.1.5.8.1 *Primary Endpoint*

Each of the three primary endpoints was analyzed using a Wilcoxon rank sum test with an alpha of 0.025. Efficacy was concluded if 1 of the following 2 criterion were met: 1) the percent reduction in total seizures frequency was greater for the rufinamide then for placebo group at an alpha of 0.025, and/or 2) Superiority for the rufinamide group over placebo in the global and both percent reduction in tonic and atonic seizures (both must be significant at an alpha of 0.025). This was changed from the original 0.05 level based upon recommendations of the FDA (4/23/98) to correct for multiple comparisons. The overall alpha level was 0.05 as per a Bonferroni correction.

7.1.5.8.2 Secondary Endpoint

- The 50% responder rate in atonic + tonic seizure types. Treatment group difference in this variable was analyzed using a logistic regression model that included treatment, region (US, Brazil, Europe), sex, and age as explanatory variables.
- Percent change in 28 day seizure frequency during the double-blind phase from baseline in each subtype of seizure other then tonic-tonic seizures was analyzed by the Wilcoxon rank-sum test. Only patients experiencing the particular subtype of seizures were evaluated.
- Global evaluation of the “patient’s condition” was analyzed with a Wilcoxon rank-sum test.

7.1.5.8.3 Exploratory Endpoint

A number of exploratory analyses were performed by Eisai that were not included in Novartis’ protocol and amendments. This was done to verify the “robustness of the results of the original analyses performed by Novartis.”

This analysis included an ANCOVA evaluation of the change in total frequency and in the frequency of tonic and atonic seizures. This parametric evaluation contrasted to the non-parametric primary evaluation and allowed the exploration of other potential significant covariates. This analysis used treatment and region as factors and baseline as a covariate. A reduced ANCOVA model (treatment, region, and baseline as a covariate) was used for subgroup analyses by sex, age (< 12 yrs, ≥ 12 yrs), and weight (< 25 kg, 25-50 kg, > 50kg), number of AEDs used (1, 2, 3), and type of AED used (lamotrigine, topiramate, valproate). In addition, an ANCOVA model with treatment and region as factors and covariates (sex, age, weight) was used to determine the association between response and covariates.

An alternative analysis of Global seizure severity used a Cochran-Mantel-Haenszel test adjusted for region.

7.1.5.9 Results

See “Efficacy Findings” in the “Integrative Review of Efficacy.”

7.2 Line-by-Line Labeling Review

Labeling review was not performed.

Appears This Way
On Original

Clinical Review
Norman Hershkowitz, MD, PhD
21911 (000)
Rufinamide (Invelon ®)

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/

Norman Hershkowitz
3/21/2008 09:40:12 AM
MEDICAL OFFICER

MEMORANDUM

NDA 21-911 ~~_____~~ **Tablets (rufinamide) 100, 200, and 400 mg**

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Rufinamide for the Adjunctive Treatment of 1) Partial Seizures in Adolescents and Adults, and 2) Seizures Associated With Lenox-Gastaut Syndrome in Pediatric Patients, 4 Years of Age and Older

DATE: September 15, 2006

Regulatory History

Rufinamide was developed by Novartis under IND 35,534, opened in 1990. IND ownership was transferred to Eisai in 2004 and Eisai is the sponsor of the current NDA. The NDA was submitted in late 2005, but after discussions with the division about problems with the electronic datasets for the carcinogenicity data, the sponsor made the decision to withdraw the NDA (November 3, 2005). The NDA was re-submitted on November 17, 2005. The filing letter, dated January 24, 2006, raised a number of issues ~~_____~~ of the then proposed name Inovelon with other b(4)

~~_____~~ There were also a number of chemistry and clinical pharmacology issues noted in the letter. On May 23, 2006, the sponsor amended the NDA with a proposal to change the proprietary name to ~~_____~~ instead of Inovelon.

The NDA was reviewed by Dr. Norman Hershkowitz (clinical efficacy), Dr. Ohid Siddiqui (statistics), Dr. Ramesh Raman (clinical safety), Dr. Lisa Jones (cardiac safety), Dr. Veneeta Tandon (clinical pharmacology), Dr. Ed Fisher (pharmacology/toxicology), and Linda Wisniewski, R.N. (DMETS). Dr. Patricia Beaston performed a consult for the Controlled Substances Staff (CSS).

DMETS

In the 74-day letter, the sponsor was notified that the proprietary name Inovelon was unacceptable because of ~~_____~~. The sponsor has proposed a new name in a letter dated May 23, 2006. b(4)

The DMETS consult dated 9/5/2006, responds to the sponsor's proposed name ~~_____~~. DMETS believes the new name has the potential ~~_____~~ and does not recommend the use of the new name.

Clinical Pharmacology

Rufinamide is almost entirely metabolized by hydrolysis. As such, there is almost no involvement of the P450 system. Thus, rufinamide would not be expected to have great potential to inhibit or induce P450 enzymes. In fact, it does show some tendency to induce 3A4. No more than 2% of the parent is excreted by the kidneys, with almost all of the drug excreted as the main metabolite. The half-life is roughly 8-12 hours.

Food increases the bioavailability of rufinamide; rufinamide was administered with food in clinical trials.

Controlled Substances Staff

Dr. Beaston reviewed data bearing on the abuse potential of ~~_____~~ Formal testing of the abuse potential in humans was not formally tested, but none of the other available data suggest an abuse potential for rufinamide. Specifically, rufinamide does not bind to receptors associated with drugs of abuse and nonclinical studies in monkeys did not show evidence of withdrawal or a pattern of self administration. Clinical studies did not show a pattern of adverse events suggestive of abuse liability.

b(4)

DSI Inspections

A number of clinical site inspections were performed: 2 centers from Argentina for Study ET1, 1 center from the US for Study 21A, and 1 center from the US for Study 22 and 1 center from Brazil for Study 22. One site, Dr. Sachdeo's site (a US site in Study 22), was found to have discrepancies in outcome data recorded in the CRF compared to source data. Because of this, his site probably needs to be dropped from consideration in the primary analysis of Study 22. Dr. Sachdeo's site enrolled 14 patients or 10% of enrolled patients. Dr. Siddiqui has informed me that dropping these patients does not affect the overall results for Study 22.

There was also an inspection of Novartis for their own inspection process. It was noted that study drug continued to be shipped to an investigator even after Novartis' own internal inspections revealed problems at that site. Even with this observation, though, DSI has concluded that data monitored by Novartis are acceptable to support the NDA.

*Appears This Way
On Original*

Efficacy Data

See the **Table of Studies** at the end of this memorandum.

Adjunctive Treatment of Partial Seizures

The sponsor performed 4 studies bearing on the efficacy of  as adjunctive treatment of partial seizures: Study PT2, Study ET1, Study 21A, and Study 21P. b(4)

Study PT2 was an early (1991-1992) exploratory study with only a 1-month treatment period. Such a study would not usually be considered supportive of an application for a chronically administered AED and, as a result, will not be discussed at great length in this memo. Additionally, the standard controlled trial of an AED incorporates a prospective baseline period during which seizure frequency is recorded. As an early study, Study PT2 had a retrospective baseline period making baseline seizure data less reliable. Additionally, there was no prospectively defined analysis plan and the FDA statistical team believes the study fails on a reasonable post hoc analysis.

Study ET1 (1992-1994) was a randomized, double-blind, placebo-controlled parallel group study with multiple fixed dose groups. Patients were randomized to receive 200mg/day, 400mg/day, 800mg/day, 1600mg/day, or placebo and followed for 3 months. Note that the formulation of rufinamide used in Study ET1 (formulation CSF) was not the to-be-marketed formulation (formulation FMI). The CSF and FMI formulations are not bioequivalent in the fed state.

The primary protocol-specified analysis of ET1 was a dose-response analysis using the seizure frequency on treatment for each of the dose groups. Dr. Siddiqui has reproduced the sponsor's analysis, estimating the dose response slope in the linear regression model using all 5 dosing groups in the trial, and confirmed that the trial is positive by the primary analysis, $p=0.003$. However, Dr. Siddiqui does not believe this primary protocol-specified analysis is valid because of the nonlinearity of the data. The protocol did not clearly state how pairwise comparisons of each dose group to placebo would be addressed in this situation. Using a parametric approach, Dr. Siddiqui did pairwise-comparisons of each dose group to placebo, finding that only the 800mg/day dose group comparison to placebo was nominally statistically significant. When adjusted for multiple comparisons, none of the pairwise comparisons was positive. Note that by a Wilcoxon rank sum test, using a stepwise approach starting with the highest dose, the top 3 dose comparisons (400 mg/day, 800 mg/day, and 1600 mg/day) are significant. The median percent reductions in seizure frequency compared to baseline were +5%, 0%, -7%, -13%, and -13% for the placebo, 200, 400, 800, and 1600 mg/day groups respectively.

Study 21A (1997-1999) was also a randomized, double-blind, placebo-controlled parallel group adult study, but there was only one dose group for rufinamide, 3200mg/day. Patients were randomized to rufinamide or placebo and followed for 3 months. Roughly half the patients enrolled were from the US.

The primary protocol-specified analysis of 21A was a non-parametric analysis of change-from-baseline seizure frequency. Dr.Siddiqui has also performed another analysis, an ANCOVA, which he believes to be a more reasonable analysis, given the uncertainty presented in interpreting the non-parametric analysis.

A total of 274 patients were randomized. During the baseline period, the median number of partial seizures per month was 8.5 for the rufinamide group and 8 for the placebo group. The predominant concomitant AEDs used by both groups were, in order of frequency, carbamazepine, lamotrigine, valproate, gabapentin, and phenytoin.

Concomitant AED	Rufinamide, n=156		Placebo, n=156	
	n	%	n	%
Carbamazepine	96	62	91	58
Lamotrigine	36	23	28	18
Valproate sodium	22	14	15	10
Gabapentin	19	12	20	13
Phenytoin	16	10	24	15
Valproate semisodium	15	10	16	10
Phenobarbital	8	5	19	12

The median percent change from baseline for the rufinamide group was -20% while the median percent change from baseline for the placebo group was +2%. This difference was statistically significant by the Wilcoxon rank sum analysis, p=0.016. By the ANCOVA analysis performed by Dr.Siddiqui, the difference was not statistically significant, p=0.094.

Dr.Hershkovitz has pointed to several analyses showing a difference by gender in Study 21A. First, for females, the median percent change from baseline for all partial seizures is -24% for the rufinamide group and +10% for the placebo group, a difference of -34%. The between-group difference is much smaller for males enrolled in the study: -12% for the rufinamide group and -4% for the placebo group, a difference of -8%. Second, the responder rate, measured as the proportion of patients with at least a 50% reduction in seizure frequency, shows no difference between rufinamide and placebo for males, 24% vs 21%. For females, the same responder rates are 31% for rufinamide and 16% for placebo.

	Percent Change in Seizure Frequency Compared to Baseline					
		Rufinamide		Placebo		
		Median	Mean	Median	Mean	
Male	63	-12%	+16%	75	-4%	-6%
Female	93	-24%	0	81	+10%	+109%

When looking at a breakdown of results by type of partial seizures, the overall between-group difference is maintained for simple partial and complex partial seizures. For partial seizures with secondary generalization, there is no difference between the rufinamide group and the placebo group. However, only about 100 of all patients randomized actually experienced secondarily generalized seizures.

The effect size, measured as median percent change from baseline, by concomitant AED is shown in the table below:

Concomitant AED	Rufinamide		Placebo	
	n	Median %	n	Median %
Valproate alone	17	-47	15	-9
Carbamazepine and/or lamotrigine; Plus Valproate	21	-24	18	-20
Carbamazepine and/or Lamotrigine; No Valproate	88	-7	89	+3
Other AEDs	30	-41	34	+7

For the significant proportion of patients taking carbamazepine and/or lamotrigine, the between-group difference is surprisingly small.

Study 21P (1997-2000) began as the pediatric stratum of Study 21 above, and evolved into an independent pediatric study after discussions with the agency. At a 1998 End-of-Phase II meeting with DNDP, the agency noted that the sponsor would need a separate, adequately-powered study in the pediatric population in order to support approval of a pediatric indication. The minutes from that meeting note that Study 21, as it existed at that time, was not powered for the pediatric subgroup. Subsequently, the sponsor amended the protocol, powering for the adult and pediatric strata of Study 21 separately as Study 21A and Study 21P. Study 21P failed on the primary analysis, and the sponsor is not seeking a pediatric claim at this time.

A total of 269 pediatric patients, age 4 years to less than 16 years of age, were randomized to 45 mg/kg/day rufinamide or placebo in this study. The primary outcome was the percent change in seizure frequency compared to baseline, evaluated using a Wilcoxon rank-sum test. The median percent change from baseline for all partial seizures was -7% for the rufinamide group and -13% for the placebo group, $p=0.62$.

The predominant concomitant AEDs used by both groups are shown in the table below:

Concomitant AED	Rufinamide, n=136		Placebo, n=132	
	n	%	n	%
Carbamazepine	70	52	67	51
Valproate	42	31	44	33
Lamotrigine	24	18	28	21
Phenytoin	16	12	10	8

Between-group differences were not presented in the study report by concomitant AED.

Monotherapy of Partial Seizures

There were 2 studies performed investigating the efficacy of rufinamide as monotherapy for partial seizures, Study 16 and Study 38.

The first study, **Study 16** (1997-2000), followed a withdrawal-to-monotherapy design. Patients (n=142) with CPS or partial seizures with secondary generalization (simple partial seizures were not allowed) who were inadequately controlled with 1-2 AEDs were randomized to have either low-dose or high-dose rufinamide added to their regimen. The low dose was 300mg/day administered tid. The high dose was 3200mg/day administered tid. Once randomized, the concomitant AEDs were tapered and withdrawn by the end of week 6, leaving patients on rufinamide alone. The total treatment period was roughly 16 weeks. The primary analysis was a comparison of the proportions of patients meeting the exit criteria in the 2 randomized groups.

Exit criteria included: 1) a doubling of the monthly seizure frequency during baseline, 2) a doubling of the highest consecutive 2-day seizure frequency, 3) a single generalized seizure if none in the past 6 months, and 4) a clinically significant worsening of seizure duration or frequency that requires intervention.

The study report reflects that 44/66 patients in the high-dose group met one of the exit criteria, while 50/69 in the low-dose group met one of the exit criteria, p=0.44.

The second study, **Study 38** (1999-2001), enrolled inpatients in an epilepsy monitoring unit. These patients underwent withdrawal of all their background AEDs as part of a pre-surgical evaluation and were then randomized to receive rufinamide or placebo. The study had a time-to-failure outcome with failure defined operationally to capture significant seizure worsening: 1) 4 partial seizures, 2) 2 generalized seizures if none in prior year, 3) serial seizures requiring intervention, or 4) status epilepticus. The primary analysis compared the time-to-event data for failures.

A total of 102 patients were randomized to either placebo or 3200 mg/day of rufinamide. The median time to failure for the placebo group was 2.4 days, compared to 4.8 days for rufinamide, p=0.0499. The proportions of patients meeting the exit criteria were 69% for the placebo group and 67% for the rufinamide group (by the protocol-specified,

worst-case scenario which counted discontinuations for other reasons in the drug group as failures, but in the placebo group as completers).

The presurgical trial design used in Study 38 must be viewed as an early surrogate for AED efficacy; it cannot speak to the efficacy of a drug during chronic treatment of epilepsy. Any positive results would only prompt further longterm trials. At the same time, it is worth asking how the 2-day difference in median time to failure in Study 38 compares with the results for other drugs in similar study designs. For oxcarbazepine, 24/51 patients (47%) randomized to rufinamide met the exit criteria during a similar trial, compared to 43/51 patients (84%) randomized to placebo. For gabapentin, 47% of patients on gabapentin failed, compared to 83% on placebo. Although it is hazardous to compare results across studies, the results for rufinamide are much less persuasive compared to these other 2 examples. In fact, it is worth noting that Study 38 was powered assuming that 55% of the rufinamide patients and 85% of the placebo patients would meet the exit criteria.

Lenox-Gastaut Syndrome

There was one study, Study 22, done to support the efficacy of rufinamide in LGS.

Study 22 (1998-2000) was a randomized, double-blind, placebo-controlled parallel group study of rufinamide 45 mg/kg/day vs. placebo. Children or adults (between 4 and 30 years of age) with LGS were enrolled and treated for 3 months. LGS was diagnosed based on the presence of a mixed seizure disorder, mental retardation, and the characteristic EEG pattern described for LGS, the slow spike-and-wave pattern. The primary outcome included 3 variables. The first was the percentage change in total seizure frequency per 28 days relative to baseline. The second was the percentage change in tonic-atonic seizures. The third was a seizure severity rating from the global evaluation; this was a 7 point scale performed by the parent/guardian at the end of the treatment period.

A total of 139 patients were randomized, but only 138 received randomized treatment. The majority of patients were male and the majority were less than 17 years of age. During the 1-month baseline period, the median number of all seizures was 290 for the rufinamide group and 205 for the placebo group. The median number of tonic-atonic seizures was 92 for the rufinamide group and 92 also for the placebo group. The predominant concomitant AEDs used by both groups were, in order of frequency, valproate, lamotrigine, topiramate, clonazepam, and carbamazepine. Clobazam, phenytoin, and phenobarbital were also used.

Concomitant AED	Rufinamide, n=74		Placebo, n=64	
	n	%	n	%
Valproate	44	59	35	55
Lamotrigine	30	41	19	30
Topiramate	20	27	17	27
Clonazepam	14	19	7	11

Carbamazepine	12	16	12	19
Clobazam	10	13	8	13
Phenytoin	10	13	12	19
Phenobarbital	6	8	9	14

The primary efficacy analysis showed statistically significant results in favor of rufinamide for all three primary variables; by protocol, the study would be considered if rufinamide won on the first variable at 0.025 or rufinamide was superior at 0.025 on both the second and third variables. The median percent change from baseline for all seizures was -33% for rufinamide and -12% for placebo. For only tonic-atonic seizures, the median percent change from baseline was -43% for rufinamide and +1% for placebo. Improved seizure severity was reported for 53% of rufinamide patients compared to 31% of placebo patients.

The sponsor points out that the reduction seen for tonic-atonic seizures, or drop attacks, was 44% when compared to placebo. The other drugs approved for LGS have been shown to have reductions of 20% (topiramate), 25% (lamotrigine), and 25% (felbamate).

As mentioned above, the US site of Dr.Sachdeo had record-keeping errors for the 4 patients audited there. Even if the whole site (n=14) is excluded from consideration, Dr.Siddiqui has informed me that the study is still positive.

The effect size, measured as median percent change from baseline, by concomitant AED is shown in the table below:

	Rufinamide		Placebo	
	n	Median %	n	Median %
Valproate	44	-36	33	-1
Lamotrigine	29	-15	19	+22
Topiramate	19	-40	17	-12

Although the between-group difference for the concomitant lamotrigine group is -37 in favor of rufinamide, the absolute median percent change for the rufinamide group is relatively small compared to the concomitant valproate and concomitant topiramate groups.

Primary Generalized Tonic-Clonic Seizures

PGTC seizures were studied in **Study 18** (1997-2000). This was a randomized, double-blind, placebo-controlled parallel group, add-on study of rufinamide 800 mg/day vs. placebo. After the 56 day baseline period, patients were followed on double-blind treatment for 140 days.

This study enrolled children and adults with inadequately controlled primary generalized tonic-clonic seizures. In addition to PGTC seizures, patients could have other seizure

subtypes, with the exception of partial-onset seizures. These other subtypes included absence, myoclonic, atypical absence, tonic, and clonic seizures. However, patients with a clinical diagnosis of LGS, characterized by mental retardation, multiple seizure types, and an EEG pattern of slow spike waves (< 3 Hz), were excluded. To be included, patients 4 years of age or older (ultimately, 16% of enrolled patients were < 16 years of age) were required to have at least 3 PGTC seizures during a 56-day prospective baseline period, with at least one per month.

The primary outcome variable was the percent change in PGTC seizure frequency, evaluated using a Wilcoxon rank-sum test.

A total of 155 patients were randomized, 80 to rufinamide and 75 to placebo. Roughly 15% of patients in both treatment groups were less than 16 years of age. During the 2-month baseline period, the median number of PGTC seizures was 3.5 for the rufinamide group and 4 for the placebo group. The median number of all seizures was 6 for the rufinamide group and 6 also for the placebo group. Absence seizures and atypical absence seizures occurred in only a fraction of randomized patients. The predominant concomitant AEDs used by both groups were, in order of frequency, valproate, carbamazepine, lamotrigine, and phenytoin. Clonazepam, topiramate, phenobarbital, and gabapentin were also used.

The median percent change from baseline for PGTC seizures was -36% for the rufinamide group and -26% for the placebo group, $p=0.63$. The sponsor's conclusion was that "...the reason for the lack of significant efficacy in this setting is not clear, although it should be noted that the dose of 800 mg/day was lower than that used in the phase III studies in partial seizures and Lennox-Gastaut syndrome, in which a trend for increase efficacy at higher plasma concentrations was observed." "There is the possibility that the dose of rufinamide was lower than the optimal dose for many of the patients with this type of highly refractory seizure disorder." Of course, while the FDA clinical pharmacology review has confirmed that a concentration-response relationship has been shown, it is not true that a trend for increased efficacy was shown at doses higher than 800 mg/day.

Secondary outcome variables in Study 18 included the percent change in seizure frequency for all seizure subtypes, including PGTC seizures. The median percent reductions by treatment group for all seizures are shown below:

	Rufinamide	Placebo
All seizures	-30	-19

There were too few patients with other seizure types to provide meaningful results for those subgroups.

Safety Data

The overall exposure in the NDA was 1978 patients. Roughly 900 adult patients were exposed to rufinamide in adjunctive partial seizure studies. Roughly 135 pediatric and adult pts were exposed to rufinamide in Lennox-Gastaut studies.

Overall, about 600 pts were exposed to a median daily dose of 2400-3200 mg/day.

Dr.Ramesh Raman's review of the safety data is ongoing.

There were 23 deaths in patients who received rufinamide, but 5 of these occurred more than 30 days after the last dose of rufinamide.

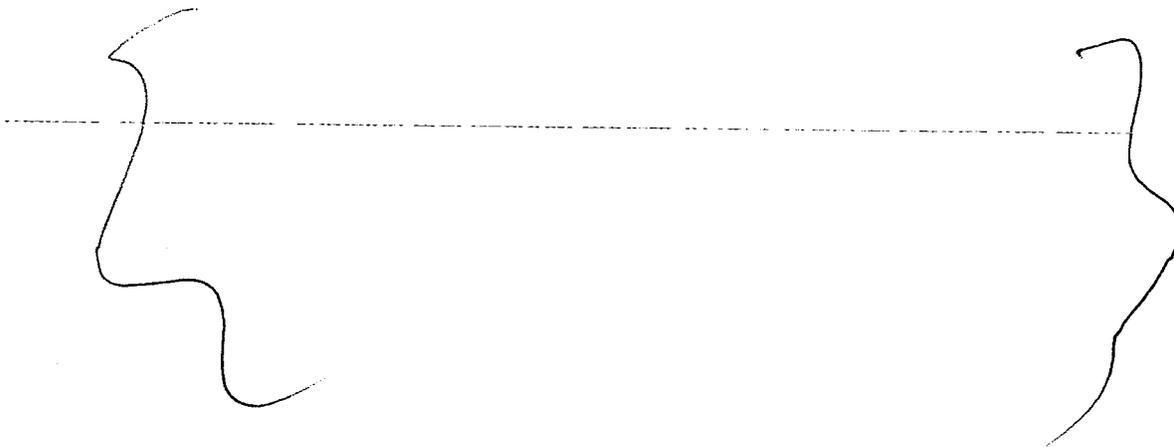
Of the 23 deaths, Dr.Raman identified 9 that could potentially be classified as sudden unexplained deaths of epilepsy, a phenomenon that is described in the literature and which has been explored during NDA reviews for other AEDs. Importantly, in light of the QT interval discussion below, Dr.Raman has found the incidence of sudden unexplained death in epilepsy (SUDEP) in the rufinamide safety database to be roughly the same as in other AED NDAs approved by the division.

Dr.Lisa Jones of the DNP Safety Team performed a targeted review of the NDA safety data based on the finding that rufinamide has the potential to decrease the QT interval. At clinically relevant plasma levels, rufinamide has the potential to shorten QT by about 20 msec, perhaps the most dramatic example of QT shortening encountered by the agency's cardio-renal division to date. Several cardiology experts who were contacted by the cardio-renal division agree that QT shortening might be expected to put patients at risk of rhythm disturbances just as QT lengthening. However, the degree of shortening that would do this is uncertain. As a result, Dr.Jones reviewed the safety experience, looking for any adverse events that might reflect cardiac rhythm disturbance (sudden death, arrhythmias, etc.). She did not identify any particular signal that might arise from this issue.

DNP consulted with the agency's Cardio-Renal Division about the significance of the QT shortening. Dr.Shari Targum addressed the issue in an 8/31/06 consult. She points out that their concerns are based on a genetic Short QT Syndrome first described in 2000. Affected patients can experience syncope, atrial fibrillation, life-threatening arrhythmias, or sudden death. A theoretical argument has also been proposed that would put patients with shortened QT at risk for ventricular fibrillation. However, no acceptable cutoff for degree of QT shortening can be proposed at this time and Dr.Targum's consult did not propose that the observed phenomenon with rufinamide should stand in the way of an approval action.

Common Adverse Events

The most common adverse events seen across the NDA include headache, somnolence, nausea, dizziness, and fatigue. For labeling, the sponsor has proposed —



b(4)

Malignant Hyperthermia

In his review, Dr. Raman has described 2 cases of possible "malignant hyperthermia." I have reviewed these 2 cases with him. The first case, Patient 6419, occurred in a patient who was having serial partial seizures bordering on status. The patient received several other medications in an attempt to stop these seizure flurries. Then the patient developed hemorrhagic pancreatitis with a fever. After a laparotomy was performed, the patient developed cerebral edema, herniated, and died. (Note that the patient had a prior history of recurring increased intracranial hypertension for which acetazolamide was prescribed.) I believe this is a complicated case of hemorrhagic pancreatitis s/p administration of numerous drugs to break the seizures. The terminal event of cerebral edema is not well-explained but may have been related to the history of increased intracranial hypertension.

The second case described in Dr. Raman's review, Patient 2071, is a child that was admitted with fevers as high as 107. Concomitant medications included topiramate, which is labeled for oligohydrosis and hyperpyrexia. An evaluation was unrevealing for a source of the fever. Rufinamide was stopped and the child was discharged with a diagnosis of "malignant hyperthermia." The criteria for this diagnosis are not stated. Rufinamide was re-started and, apparently months later, the patient died of SUDEP (sudden unexplained death of epilepsy). Like the first case, the events of this case do not seem well-explained; at least the concomitant topiramate might be a potential suspect drug for hyperthermia.

Serious Hepatic Adverse Events

Dr. Raman's review of the lab data did not reveal any tendency toward elevation of hepatic enzymes. However, his review does include descriptions of several patients with potential liver events: Patient 4408, Patient 4216, Patient 3159, and Patient 8019. The first 2 cases appeared to be cases of hypersensitivity and are discussed in the next section. Patient 3159 was unusual in that the laboratory elevations resolved in one day

while still on treatment; hemolysis of the specimen might explain some of the results. Patient 8019 had a seizure and a "post-seizure muscle entrapment syndrome." SGOT, SGPT, and bilirubin were all elevated (result for alkaline phosphatase was not available), but returned to normal within 2 weeks with discontinuation of drug.

Hypersensitivity Reaction

There are a number of cases of hypersensitivity reaction in the NDA. Patient 4408, a 12-year old, developed fever, rash, and facial edema on day 29 of rufinamide and then went on to become stuporous with labs on admission to the hospital showing elevations of AST, ALT, and total bilirubin. The patient improved with drug discontinuation.

Patient 4216, a 7-year old, developed fever, rash, and hematuria after a couple of weeks on drug. Unfortunately, further details, especially lab data, are lacking for this case. However, the hematuria is noted to be "microscopic" hematuria.

Status Epilepticus

Across the double-blind portions of the controlled trials, status epilepticus occurred only in rufinamide treated patients, roughly 1%; there were no placebo cases. Further consideration of this finding seems appropriate; the presentation of cumulative distribution functions (CDFs) for percent change from baseline for the different treatment groups in all studies would be helpful in this regard.

Discussion

Over the past 10 years, the usual development program presented in an NDA for a new chemical entity for the treatment of epilepsy has included at least 2 positive controlled trials of the new drug used as adjunctive treatment in partial seizures in adult patients. Having established the efficacy in partial seizures, it has been standard for sponsors to perform only one additional study in patients with LGS (enrolling patients roughly 4 years of age through 30 years of age) to support approval of an adjunctive claim in LGS. Likewise, a single study of adjunctive therapy for partial seizures in pediatric patients will support a pediatric claim and a single study of adjunctive therapy for PGTC seizures will support a PGTC seizure claim (for pediatric patients, adult patients, or both, depending on the age range studied).

The NDA for _____ has raised the question whether a single positive study of adjunctive therapy for partial seizures in adults, along with a positive study of adjunctive therapy for LGS would support either or both claims. I think the answer could be yes. However, to support such an approach to approval, I believe each study would need to be robustly positive and contradictory evidence from other studies should be lacking. Neither condition applies in the case of _____

b(4)

Study 22, the study of adjunctive therapy in LGS, is robustly positive. The p-value is significant and is not analysis-dependent. The effect size is comparable to the effect size seen with the other 3 AEDs approved for LGS. And the effect is consistent across the different seizure types analyzed.

I do not consider Study 21A, the study of adjunctive therapy in adult partial seizures, robustly positive. The p-value is positive, $p=0.016$, by the protocol-specified non-parametric analysis (Wilcoxon rank sum), but the p-value is not positive, $p=0.094$, by another very reasonable analysis, ANCOVA with adjustment for center and country.

Studies 22 and 21A are 2 of the 4 clinical trials presented in the NDA to incorporate the high dose, 3200 mg/day. The other such studies are Study 21P and Study 16, both failed studies. [Study 38 also included the 3200 mg/day dose, but is not considered here because of the unique in-patient design in patients undergoing a pre-surgical evaluation for epilepsy surgery.] Study 21P was essentially identical in design to Study 21A, except that it included pediatric, not adult patients. It is highly unusual for DNP to see the results of large controlled trials of AEDs where the placebo group performs numerically better than the active group, but such is the case in Study 21P.

Study 16 was a failed study in monotherapy. The low dose of 300 mg/day was chosen by the sponsor as likely to be ineffective based on other study results. Yet the 3200 mg/day dose group did not perform better than this pseudo-placebo. To have no difference in performance across such a large dose range is highly unusual. Recently, DNP has had discussions with numerous sponsors about AED monotherapy study designs that would be practical and ethically acceptable by today's standards. _____ compiled the results of all available

monotherapy controlled trials where patients with refractory partial seizures were withdrawn to monotherapy with either a pseudo-placebo or a presumably effective dose of the study drug. As a result of her efforts, a historical control group has been established which can serve as a comparator for other AEDs. By her analyses, the upper limit of the 95% CI for failure rate for the active comparator might be reasonably set at about 68%. Compared to this number, the failure rate for the _____ 3200 mg/day arm in Study 16 would not support the efficacy of _____ as monotherapy in partial seizures.

b(4)

Historically, adjunctive trials for AEDs evolved because of the view that placebo-controlled monotherapy trials in epilepsy were unethical because of 1) the serious and life-threatening sequelae of seizures in the unprotected placebo group and 2) the availability of other drugs to prevent seizures. Until general proof of principle of AED activity is shown in adjunctive trials, it is deemed unethical to place a patient on a totally unproven medication for epilepsy. Adjunctive trials really serve as a convenient tool in the road to approval for AEDs. While the formal indication granted in labeling may only allow for adjunctive use, it is understood that these AEDs will be used for both monotherapy and adjunctive therapy even before formal monotherapy studies are eventually done. Given that fact, it is perhaps even more disturbing that the NDA for _____ includes a failed study in monotherapy.

b(4)

At this point, it is probably worth noting the fifth study of the 3200 mg/day dose, Study 38, a placebo-controlled monotherapy study conducted during presurgical evaluations. The median time to failure for placebo patients in this study was 2 days while the median time to failure for Inavra patients was 4 days. It is impossible to translate this result into the everyday world of chronic AED therapy for epilepsy. As described above in the description of Study 38, the proportions of patients meeting the exit criteria in the 2 arms of the trial were very similar, a finding that is different and unexpected based on the results seen in similar trial designs of at least 2 other approved AEDs. Overall, I have not factored the results of Study 38 heavily into my discussion and conclusion for the overall NDA.

b(4)

To summarize the above, then, of the 4 studies of 3200 mg/day that I believe should have a bearing on the action on the ~~_____~~ NDA, 2 of the 4 are clearly failed studies. One of the failed studies, Study 21P, is almost identical in design to Study 21A, and therefore directly casts a cloud over the results of 21A. As mentioned, The results of 21A cannot be considered especially robust because a very reasonable analysis, in fact the more standard analysis for such a study (an ANCOVA), is not positive even though the protocol-specified analysis is positive. Study 16 is the other failed study. Because we know that approved AEDs are used as monotherapy in practice even when the formal indication in labeling is for adjunctive therapy, it is disturbing to know that the only relevant monotherapy trial with ~~_____~~ is a failed study.

b(4)

Neither of the other 2 studies, Study 18 and Study ET1, provide robust evidence of effectiveness either. Study 18 incorporated a high dose of 800 mg/day and was a failed study. Study ET1 incorporated doses up to 1600 mg/day, but did not clearly establish that any one dose was superior to placebo.

Dose-Response

Even if DNP was prepared to accept that there was substantial evidence to support approval for partial seizures or LGS, there would not seem to be enough information available to provide adequate dosing guidelines for labeling. Generally, labeling will not support a higher dose if there is no demonstrated benefit over a lower dose. Across the studies presented in this NDA, there is no evidence that 3200 mg/day performs better than 1600 mg/day or even 800 mg/day. At the same time, there are independent studies that failed to show an effect of ~~_____~~ at doses of 800 mg/day and 3200 mg/day, raising discomfort with the notion of making a recommendation to use less than a dose of 3200 mg/day.

b(4)

Efficacy by Concomitant AED

As mentioned in the description of Study 21A, for the significant proportion of patients taking carbamazepine and/or lamotrigine, the between-group difference was surprisingly small. The suggestion might be that, if effective ~~_____~~ effect might not be seen in patients taking concomitant carbamazepine and/or lamotrigine.

b(4)

Following on that point, the most commonly used AED in the positive study, Study 22, was valproate. Although the between-group difference for the concomitant lamotrigine group in Study 22 is -37 in favor of rufinamide, the absolute median percent change for the active arm (with lamotrigine) is relatively small compared to the concomitant valproate and concomitant topiramate groups.

Further analyses based on concomitant AED use seem warranted, especially in the failed adjunctive studies, Study 21P and Study 18.

What additional evidence would support approval?

At this time, I believe the sponsor should be sent a Not-Approvable Letter. To support approval for either indication, LGS or partial seizures, a controlled trial of adjunctive therapy in partial seizures (incorporating multiple fixed dose groups of 800 mg/day, 1600 mg/day, 2400 mg/day, and 3200 mg/day and perhaps even higher doses) would seem to be the most appropriate study to perform. Such a study (if positive), along with Study 21A, would provide substantial evidence of effectiveness: _____

_____ It would also provide much-needed dose-response information. At the same time, with that evidence in place, Study 22 would support a LGS indication.

b(4)

Even then, before approval, the sponsor should be asked for at least the following:

1. The theoretical possibility exists that a new AED would be effective only when used concomitantly with certain other AEDs, due to specific pharmacodynamic interactions. For this reason, sponsors usually provide subgroup analyses of efficacy with concomitant AEDs. The sponsor should provide such information for the existing studies and any new studies. This might be especially important in light of the failed trial as monotherapy.
2. For all dose groups in all controlled trials, the sponsor should create graphs of the cumulative distribution functions for percent change from baseline seizure frequency, drug vs. placebo. Such graphs provide a visual understanding of a drug's efficacy across the range of possible outcomes.

Table of Studies

	Placebo	200 mg/day	300 mg/day	400 mg/day	800 mg/day	1600 mg/day	3200 mg/day or 45mg/kg/day
Adjunctive Therapy of Partial Seizures							
Study ET1 N=550	X	X		X	X	X	
Study 21A N=300	X						X
Study 21P N=269	X						X
Monotherapy for Partial Seizures							
Study 16 N=142			X				X
Study 38 N=104	X						X
Adjunctive Therapy in Lennox-Gastaut Syndrome							
Study 22 N=138	X						X
Adjunctive Therapy of Primary Generalized Tonic-Clonic in Children and Adults with Multiple Seizure Types							
Study 18 N=155	X				X		

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

/s/

John Feeney
9/19/2006 04:37:29 PM
MEDICAL OFFICER

**NDA SAFETY REVIEW:
SHORTENED QT INTERVAL WITHIN THE
RUFINAMIDE DEVELOPMENT PROGRAM**

Application Type NDA
Submission Number 021-911

Letter Date September 8, 2005
Stamp Date September 8, 2005

Reviewer Name M. Lisa Jones, MD, MPH
Review Completion Date August 11, 2006

Established Name Rufinamide
(Proposed) Trade Name Inovelon®
Therapeutic Class Triazole
Applicant Eisai Medical Research, Inc.

Priority Designation Standard

Formulation Oral (100, 200 and 400 mg)
Dosing Regimen Adults: 800 to 3200 mg/day
Children: _____

Indication Adjunctive Therapy for Partial
Seizures, Lennox-Gastaut
Syndrome or Primary
Generalized Tonic Clonic
Seizures

Intended Population Patients with Epilepsy

b(4)

TABLE OF CONTENTS

1. INTRODUCTION AND BACKGROUND	4
1.1 PRODUCT INFORMATION	4
1.2 REVIEW CONTENT	4
1.3 SHORTENED QT INTERVAL: INFORMATION FROM THE LITERATURE	5
1.3.1 Overview	5
1.3.2 Risks of Short QT Familial Syndrome	5
1.3.3 Short QT as a Drug Effect: Digoxin	6
2. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	6
2.1 SPONSOR DOCUMENTS	6
2.2 FDA DOCUMENTS	7
2.3 OTHER DOCUMENTS	7
3. ECG ANALYSIS: OVERVIEW OF ECG TESTING IN THE RUFINAMIDE DEVELOPMENT PROGRAM, INCLUDING PRECLINICAL RESULTS	8
3.1 OVERVIEW OF RELEVANT STUDIES	8
3.2 PRECLINICAL CARDIOVASCULAR STUDIES	9
3.2.1 <i>In Vitro</i> IKr Channel	9
3.2.2 Canine Dose-Toxicity Studies	9
3.2.3 Primate Study	10
3.3 ECG DATA COLLECTION STUDIES	10
3.3.1 E2080-A001-001	10
3.3.2 E2080-A001-002	10
3.3.3 Phase 3 Studies	13
4. ECG ANALYSIS: SELECTION OF STUDIES AND ANALYSES FOR OVERALL DRUG CONTROL COMPARISONS	13
4.1 E2080-A001-001 METHODS	13
4.2 E2080-A001-002 METHODS	14
4.2.1 Overview	14
4.2.2 Subjects	14
4.2.3 Dose	14
4.2.4 Moxifloxacin Positive Control	15
4.3 PHASE III STUDY METHODS	15
4.3.1 CRUF331 0022	15
4.3.2 AE/ET 1	16
5. ECG ANALYSIS: RESULTS OF STANDARD ANALYSES AND EXPLORATIONS OF ECG DATA	16
5.1 E2080-A001-001 RESULTS	16
5.2 MEASURES OF CENTRAL TENDENCY	16
5.2.1 <i>Healthy Volunteers</i>	16
5.2.2 <i>Patients with Epilepsy</i>	17
5.3 OUTLIERS OR SHIFTS FROM NORMAL TO ABNORMAL	17
5.3.1 <i>Healthy Volunteers</i>	17
5.4 MARKED OUTLIERS AND DROPOUTS FOR ECG ABNORMALITIES	20
5.4.1 <i>Outliers</i>	20
5.4.2 <i>Deaths</i>	21
5.4.3 <i>ECG-Related Serious Adverse Events</i>	23

5.4.4 ECG-Related Adverse Events.....	24
5.4.5 Discontinuations due to ECG- and Cardiovascular-Related Adverse Events.....	25
5.5 OTHER ECG RELATED DATA	27
5.5.1 Dose/Concentration Response Analysis.....	27
6. FDA QT REVIEW TEAM: RESPONSE TO DNP REQUEST FOR CONSULTATION.....	30
7. CONCLUSIONS AND RECOMMENDATIONS.....	31
7.1 CONCLUSIONS.....	31
7.2 REGULATORY ACTIONS	31
7.3 LABELING AND OTHER CONSIDERATIONS	32

1. INTRODUCTION AND BACKGROUND

1.1 Product Information

Eisai Medical Research, Inc. has submitted a New Drug Application (NDA) seeking FDA approval to market Rufinamide (Inovelon®) as an adjunctive therapy for partial seizures (in adults and adolescents over 12), or Lennox-Gastaut syndrome (in adults and children over 4 years). Rufinamide has not been previously marketed outside the United States.

Rufinamide is a triazole derivative, which the sponsor stated is structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide's mechanism of action is not completely understood, but *in vitro* studies suggest that rufinamide modulates the activity of sodium channels by prolonging their inactive state (Eisai Proposed Labeling, pg. 2).

1.2 Review Content

This review addresses electrocardiogram (ECG)-related safety data within the rufinamide development program, focusing on the finding, which emerged during phase 1 clinical studies, that rufinamide shortens the QT interval. In a thorough QT study with 88 subjects, rufinamide was associated with a QT interval shortening ranging from -2.1 to -21.3 msec, depending on the dose and heart rate correction employed.

The ECG-related safety data reviewed in this document include:

- Data collection, methodology, and results of the rufinamide “thorough QT” study
- Sudden deaths
- ECG-related Adverse Events (Serious and otherwise)
- Discontinuations due to ECG

The shortening of the QT interval with rufinamide administration was reproducible, with an apparent dose-response relationship, in adequately designed studies, one of which utilized a positive control (moxifloxacin) to verify the sensitivity of the assay. In addition, it is biologically plausible that rufinamide shortens the QT interval, as other drugs which act at the sodium/potassium ATPase pump, such as digoxin, have been shown to do so. This strongly suggests that the shortening of the QT interval is causally associated with rufinamide. Although there is a scarcity of literature on the clinical consequences of drugs which shorten the QT interval, some information on possible adverse events can be gained from the literature describing a familial form of Short QT syndrome. Examinations of families with Short QT syndrome have shown a greater risk for palpitations, atrial fibrillation and cardiac arrest (two-fold higher risk).

The remainder of safety data (that which is not related or potentially related to effects on cardiac repolarization) within the rufinamide development program is reviewed by Dr. Ramesh Raman in a separate document.

1.3 Shortened QT Interval: Information from the Literature

1.3.1 Overview

In contrast to an extensive literature on prolonged QT interval, relatively little information is available on the clinical consequences of a shortened QT interval. Furthermore, much of the short QT literature is focused on a familial form of Short QT syndrome.

1.3.2 Risks of Short QT Familial Syndrome

Assuming that a shortened QT interval from either an inherited defect or a drug effect has the same clinical sequelae, the literature on the familial Short QT syndrome can provide information on the potential risks associated with drug-induced short QT. There is some support for this assumption in the literature, as Cheng et al. conjectured that the mechanism of arrhythmogenesis seen with the drug digoxin could be similar to that for familial QT syndrome.^{1 2}

Familial Short QT syndrome has only been recognized as a clinical entity since approximately 2000.³ Despite the relative newness of the syndrome, a number of cardiac adverse events have been documented in association with the syndrome. Specifically, the literature reports that patients with familial Short QT syndrome have an increased risk of palpitation, syncope, atrial/ventricular arrhythmias and sudden cardiac death.⁴

A number of studies have attempted to better quantify the increased risk of these cardiac adverse events in persons with a short QT interval, including:

- In a study of 6693 Holter recordings, Algra et al. found that both long and short QT intervals were associated with a two-fold higher risk of sudden death.⁵ The subjects were composed of 6693 consecutive patients referred to one of the four participating Rotterdam hospitals for a 24-hour ECG over a four-year period. Deaths were

¹ Antzelevitch C, Francis J. Congenital Short QT Syndrome. *Indian Pacing and Electrophysiology Journal* 2004;4(2):46-49.

² Cheng TO. Digitalis administration: an underappreciated but common cause of short QT interval. *Circulation* 2004;109:e152.

³ Schulze-Bahr E, Breithardt G. Short QT and short QT syndromes. *J Cardiovasc Electrophysiol* 2005;16:397-8.

⁴ Schulze-Bahr E, Breithardt G. Short QT and short QT syndromes. *J Cardiovasc Electrophysiol* 2005;16:397-8.

⁵ Algra A, JG Tijssen JR, Roelandt JR et al. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. *Br Heart J* 1993;70:43-8.

recorded for up to two years after the 24-hour ambulatory electrocardiography, with 99.5% follow-up. Patients with a shortened mean QTc (<400 msec) had a higher risk of sudden death (relative risk 2.4, 95% C.I. 1.4 to 4.3), than patients with a normal mean QTc (400 to 440 msec). These results were based on 104 sudden deaths observed in the study.

- Gaita et al. examined six patients from two different families with familial Short QT syndrome. These patients had experienced syncope, palpitations, resuscitated cardiac arrest and a family history of sudden cardiac death.

The Gaita et al. report noted that the QT interval in the six patients with familial Short QT syndrome did not exceed 280 msec (or a QTc of 300 msec). Another study measuring QT interval in persons with Short QT syndrome demonstrated an interval of 220 to 290 ms.⁶

Reviewer comment: The QT data in the rufinamide development program was not presented as absolute QT intervals, but instead as msec shortened compared to a time-matched placebo control (See Section 5.1 of this review). Because of this, it is difficult to make direct comparisons between the degree of QT interval shortening in familial Short QT syndrome, with digoxin treatment (see below) and with rufinamide treatment.

1.3.3 Short QT as a Drug Effect: Digoxin

With regards to shortened QT as a drug effect, the principle drug recognized to shorten QT is digoxin. The shortened QT interval with digoxin toxicity (~280 msec QTc) overlaps the shortening of the QT interval seen in familial Short QT syndrome. Digoxin glycosides bind specifically to the sodium-potassium ATP-ase pumps, decreasing the active transport of sodium, which in turn is thought to increase outward current during the plateau phase of the cardiac action potential and decrease the subsequent refractory period.⁷

Reviewer comment: The digoxin label notes that digoxin may cause various conduction disorders and rhythm disturbances, but does not specifically discuss digoxin's effects on the QT interval.

2. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

2.1 Sponsor Documents

1. NDA 021-911 (Rufinamide). Electronic NDA Submission: Integrated Summary of Safety. Prepared by Eisai Medical Research, Inc. Dated September 8, 2005.

⁶ Schulze-Bahr E, Breithardt G. Short QT and short QT syndromes. J Cardiovasc Electrophysiol 2005;16:397-8.

⁷ Cheng et al. Digitalis administration: an underappreciated but common cause of Short QT interval. Circulation 2004;109:e152.

2. NDA 021-911 (Rufinamide). Electronic NDA Submission: Clinical Overview. Prepared by Eisai Medical Research, Inc. Dated May 15, 2006.
3. NDA 021-911 (Rufinamide). E2080-A001-001 NDA Study Report "A Double-Blind, Placebo-Controlled, Ascending Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rufinamide in Healthy Subjects. Prepared by Eisai Medical Research Inc. Dated March 2005.
4. NDA 021-911 (Rufinamide). E2080-A001-002 NDA Study Report "A Double-Blind, Placebo-Controlled, Parallel-Design Trial of the Electrocardiographic Effect of Rufinamide in Healthy Subjects: A Definitive QT Study." Prepared by Eisai Medical Research Inc. Dated August 12, 2005.
5. NDA 021-911 (Rufinamide). Cardiac Safety Report: The Effect of Rufinamide on Cardiac Repolarization. A Definitive QTc Study (E2080-A001-002). Prepared by _____ . Dated June 26 2005.
6. NDA 021-911 (Rufinamide). Statistical Report for Evaluation of the Effect of Rufinamide on Ventricular Repolarization. Prepared by _____ . Dated August 3, 2005.
7. NDA 021-911 (Rufinamide). Sponsor-proposed labeling within the Rufinamide NDA. Prepared by Eisai Medical Research Inc.

b(4)

2.2 FDA Documents

8. NDA 021-911 (Rufinamide). Statistical Review and Evaluation: Clinical Studies. Prepared by Ohidul Siddiqui, Ph.D., Kun Jim Ph.D. and James Hung Ph. D. Documents reviewed dated November 17, 2005.
9. International Conference on Harmonization (ICH) Guideline E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Prepared by the ICH Expert Working Group. Dated May, 2005.
10. NDA 021-911 (Rufinamide). Interdisciplinary Review Team: Response to Request for Consultation on QT Interval Shortening. Prepared by Shari Targum MD, and Norman Stockbridge MD. Dated August 31, 2006.

2.3 Other Documents

11. Schulze-Bahr E, Breithardt G. Short QT and short QT syndromes. J Cardiovasc Electrophysiol 2005;16:397-8.
12. Agabiti-Rosei et al. Short QT Syndrome. European Cardiac Journal 2005. <http://www.servier.com/pro/cardiology/pdfs/bay14gb.asp>.
13. Algra A, JG Tijssen JR. Contribution of the 24 hour electrocardiogram to the prediction of sudden coronary death. Br Heart J 1993;70:421-427.
14. Antzelevitch C, Francis J. Congenital Short QT Syndrome. Indian Pacing and Electrophysiology Journal 2004;4(2):46-49.
15. Cheng TO. Digitalis administration: an underappreciated but common cause of short QT interval. Circulation 2004;109:e152.

3. ECG ANALYSIS: OVERVIEW OF ECG TESTING IN THE RUFINAMIDE DEVELOPMENT PROGRAM, INCLUDING PRECLINICAL RESULTS

3.1 Overview of Relevant Studies

The table below summarizes the studies which collected ECG data within the rufinamide development program. The sponsor reported that ECG data were not available for Phase III Studies 9209, 9213, A233, A184, A202, A237, and AE/MD2.

FDA Table 1: Studies Collecting ECG Data in the Rufinamide Development Program (Adapted from Sponsor Table 5.2, Tabular Listing of All Clinical Studies)

Study	Site ^a	Description	Dose (mg/day)	Length (Days)	Number of Subjects ^b
E2080-A001-001	US	Phase 1 DB, PC Maximum Dose Study in Healthy Volunteers (Ages 19 - 43)	800 -7200	18	20
E2080-A001-002	US	Phase 1 DB, PC “Definitive QT” study in Healthy Volunteers (Ages 19 – 54)	800-7200	20	88
CRUF331 0022	Multi-national	Phase 3 DB, PC, Parallel Study in LGS Pts. (Ages 4 - 30)	45 mg/kg/day b.i.d.	84	128
AE/ET1	Multi-National	Phase 3 DB, PC, Parallel Study in Epilepsy Pts. (Ages 14 – 65)	200-1600	90	554

a. Site refers to location of the study sites.

b. Number of subjects refers to subjects who completed the study per protocol.

Abbreviations: DB = Double-blind, PC = Placebo-controlled, LGS=Lennox-Gastaut Syndrome, Pts. = Patients

The sponsor characterized Study E2080-A001-002 as the “definitive QT study” within the rufinamide development program. This study is described in more detail in Sections 3.3.1 and 4.2 of this review.

3.2 Patient Populations

As shown in Table 1 above, clinical QT data was collected in two subject populations: healthy volunteers and patients with epilepsy.

Reviewer comment: *In this review, ECG data is presented separately for healthy volunteers and for patients with epilepsy.*

3.2 Preclinical Cardiovascular Studies

The sponsor asserted that preclinical testing for rufinamide “demonstrated no important cardiovascular effects in a range of standard pharmacologic and toxicologic tests.” The specific nonclinical studies referenced by the sponsor included the following (ISS, Section 9.3.1).

3.2.1 In Vitro IKr Channel

In a hERG in vitro inhibition study of the human IKr channel (Study DJNR1037), the sponsor reported that 100 µmol/L rufinamide inhibited hERG-induced tail currents by an average of 35.9% (n=5), which was equivalent to the inhibition seen with the vehicle control. The positive control compound E-4031, which Eisai described as a well-established hERG blocker, induced inhibition of 87.1% at 100 nmol/L. The sponsor concluded that rufinamide did not inhibit hERG-induced tail currents at concentrations up to 100 µmol/L (ISS, pg.313).

Reviewer comment: *FDA pharmacologist John Koerner considered the hERG studies for rufinamide to not have been well performed,⁸ which may have impaired the ability of the study to detect hERG inhibition.*

3.2.2 Canine Dose-Toxicity Studies

3.2.2.1 Canine Study 982069

Eisai performed a dog study in beagles (Study 982069) with escalating IV doses of 1, 3, and 10 mg/kg at 45-minute intervals. At 3 mg/kg, Eisai stated that the heart rate changes in both the treated and vehicle animals were comparable. At 10 mg/kg, the decrease in heart rate with rufinamide was less pronounced than for the vehicle control. Eisai believed that these data indicated a vehicle-related effect on heart rate, rather than an effect due to rufinamide, and in addition that the effects were not clinically significant (ISS, pg. 80).

Reviewer comment: *Eisai did not note whether a decrease in heart rate is expected with the control vehicle.*

3.2.2.2 Canine Study 896305

Electrocardiography was also assessed in a pivotal repeat-dose toxicity study in beagle dogs (Study 896305). The sponsor stated that no notable treatment-related effects on

⁸ Electronic mail communication received August 31, 2006.

heart parameters were observed following daily doses of up to 200 mg/kg for a maximum of 52 weeks.

Eisai stated that these canine studies (Studies 982069 and 896305) confirmed the absence of any effect on cardiovascular function and on the duration of the QT interval in particular.

3.2.3 Primate Study

Eisai stated that no cardiovascular treatment-related findings were observed in a 13-week study in Cynomolgus monkeys (Study No. 92-6094)(ISS, pg. 80).

3.3 ECG Data Collection Studies

3.3.1 E2080-A001-001

Eisai described the ECG collection within Study E2080-A001-001 as follows. Three pre-dose (baseline) ECGs were recorded on Day 1 (as per Amendment 02) prior to the first dose). On Days 3, 6, 9, 12, 15, and 18, ECGs (one ECG per time point) were recorded pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, and 12 hours after the morning dose. On Days 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, and 17, ECGs (one ECG per time point) were recorded four to six hours after the morning dose. ECGs were also recorded at screening, check-in, and study discharge. ECGs were complete, standardized, 12-lead recordings and were taken by an ECG machine capable of storing the data electronically. The ECGs were reviewed by the Investigator (paper or electronic tracing) for safety and were available for comparison to subsequent ECGs by the Investigator for safety. ECGs were transmitted electronically to a central laboratory () and were analyzed at () according to their specified protocol (ISS).

b(4)

3.3.2 E2080-A001-002

3.3.2.1 Holter Monitoring

Eisai stated that ECG monitoring in Study E2080-A001-002 was performed through a combination of Holter recordings and standard ECGs, as per the following protocol. Twelve-lead continuous Holter recordings were obtained for a 25-hour period at Baseline (Day -1) and on Day 18, and for a 24-hour period on Day 19. In addition, Holter recordings were obtained from one hour pre-dose until 12 hours post-dose⁹ on Days 9, 12, 15, and 20. Individual ECGs were extracted from Holter recordings (three ECGs per PK time point, approximately two minutes apart, just prior to PK sample collection) at pre-dose and at 0.5, 1, 1.5, 2, 3, 4 hours, 5 hours and 25 minutes, 6, 7, 8, 10, and 12 hours after the first dose on Days 9, 12, 15, 18, and 20, and at 16, 20 hours, 24 hours and 25

⁹ "Post-dose" refers to the morning dose of rufinamide, which was taken twice daily.

minutes, 30, and 36 hours after the dose administered on Day 18 (E2080-A001-002 Study Report).

Reviewer comment: ICH E14 guidance to industry on performing a thorough QT study states the following with regard to the use of ambulatory ECGs, such as Holter monitoring:

“While ambulatory ECG monitoring has historically not been considered sufficiently validated to be used as the primary assessment of QT/QTc interval, newer systems that allow for the collection of multiple leads that more closely approximate a surface ECG have potential value to collect interval data. The use of ambulatory ECG monitors might additionally allow detection of extreme QT/QTc interval events that occur infrequently during the day and asymptomatic arrhythmias. Data on the QT/RR from ambulatory ECG monitoring can also prove useful in the calculation of individualized QT corrections. However, as QT/QTc intervals measured by this methodology might not correspond quantitatively to those standard surface ECGs, data obtained from the two methodologies might not be suitable for direct comparison, pooling, or interpretation using the same threshold of concern (pg. 7).”

Eisai pooled data from ambulatory monitoring and surface ECGs, which the FDA guidance states “might not be suitable.” Based on the consistent and biologically plausible QT measurements with increasing doses, as well as the validation from a positive control, I believe the pooling of the ECG data did not compromise the QT interval results within the rufinamide development program.

3.3.2.2 Standard 12-Lead ECGs

Standard 12-lead ECGs were also performed at Screening, Baseline (Day -1), at study discharge, and on Days 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, and 17, approximately four to six hours post-dose. In addition, standard 12-lead ECGs were obtained at pre-dose and 2, 4, 6, and 8 hours after the first dose on Days 3, 6, 9, 12, 15, and 18, and at pre-dose and 1, 2, 4, and 6 hours post-dose on Day 20. The sponsor reported that subjects were in a supine position attached to the continuous Holter monitor for 20 minutes prior to all PK samples being drawn. The ECGs were reviewed by the site investigator and by a central laboratory (E2080-A001-002 study report, pg. 43). b(4)

Eisai stated that all QT intervals were measured using the median representative beat of the entire 10 second recordings. The RR interval calculated as the average of all the RR intervals contained within the same time frame. The sponsor explained that this validation method was specifically selected for its proven reduction in variability. QT and RR intervals were identified by computer and adjusted by certified cardiovascular technicians, and then visually validated or manually adjusted by Board Certified cardiologists (Report, pg. 4). b(4)

Eisai noted that the primary lead used in the ECG evaluations was Lead II, which the sponsor stated was in accordance with regulatory guidance, with Lead V5 as the secondary choice (_____ Report, pg. 4).

b(4)

3.3.2.3 QT Rate Correction

The sponsor stated that all QTc data was calculated as the means of three intervals, based on ECGs taken at two minute intervals. Three corrections (QTc) methods for heart rate were used:

1. Fridericia correction: $QTcF = QT/RR^{0.333}$
2. Bazett correction: $QTcB = QT/RR^{0.5}$
3. Individual subject specific correction (QTci). All pairs of QT and RR interval data collected on Day -1 each subject were analyzed by the following linear regression:
 $\log(QT) = \log(a) + b \log(RR)$

The sponsor noted that the Bazett formula over-corrects at faster heart rates, and that the Fridericia correction performs better in these situations. Eisai used QTcF as the primary endpoint for the analyses, with the other two correction methods as secondary endpoints (_____ Study Report).

b(4)

Reviewer comment: Rufinamide administration produced a 4.4 to 10.4 beats per minute increase in heart rate between two and eight hours after the highest dose in Study E2080-A001-002 (See Section 5.5.2). Fridericia's correction is generally considered more accurate in drugs with a bradycardic or tachycardic effect, so I concur with the sponsor's choice of Fridericia's correction for the primary endpoint.

3.3.2.4 Analysis Overview

The primary statistical analysis in Study E2080-A001-002 was the measure of central tendency, calculated as the largest time-matched baseline corrected mean difference in QTcF between the rufinamide and the placebo group over the collection period. Eisai stated that this protocol was in accordance with the recommendations in the ICH E14 guideline for analysis of QT/QTc interval data, dated May, 2005. The sponsor's null hypothesis (i.e. that this difference is 10 msec versus the alternative that it is less than 10 msec) was tested by comparing the largest one-sided 95% upper confidence bound on the baseline-corrected mean difference between the supra-therapeutic dose level of rufinamide (7200 mg/day) on Study Day 18 with the corresponding time-matched ECG. Categorical analyses of specific QT changes (number of subjects having QTc intervals >450, >480, and >500 msec, and QTc interval increases from Day -1 Baseline >30 and >60 msec at each dose) were also conducted (E2080-A001-002 Study Report).

Reviewer comment: *As noted in the results sections of this review, the categorical analysis above was designed to examine QT prolongation, and is less well suited to characterizing a shortening of the QT interval (See also Section 7 of this review describing the FDA's request to Eisai for additional data tables).*

A PK/PD analysis using mixed effects population modeling was conducted to evaluate the effect of rufinamide and moxifloxacin plasma concentrations on QT interval calculated with a subject specific correction factor (QTcSS)(E2080-A001-002 study report).

3.3.2.5 Time-Matching Protocol

Eisai stated that assay sensitivity was evaluated through use of a moxifloxacin positive control. Subjects originally randomized to placebo received moxifloxacin on Day 20, and the time-matched Day 19 baselines were subtracted. For comparison, the first day of ECG collection times for the placebo group (Day 9) was used, with the Day -1 time-matched baseline subtracted. The Day 20 baseline-subtracted moxifloxacin data was then compared with the Day 9 baseline-subtracted placebo data by a paired t test at each ECG time, including one-sided 95% lower confidence bounds on the differences from placebo (Moxifloxacin minus placebo) (Report, pg. 6).

b(4)

3.3.3 Phase 3 Studies

The sponsor reported that the ECGs recorded in the clinical studies¹⁰ did not undergo centralized review. Instead, each center provided ECGs with an "automatic readout," confirmed by the principal investigator, designating the ECG as normal or abnormal. The results were summarized in shift tables comparing the interpretations at baseline and at the final post-baseline evaluation. In addition, potential effects of rufinamide on cardiac related parameters were examined by a review of ECG- and cardiovascular-related adverse events, serious adverse events, and discontinuations due to adverse events (ISS, Section 2.7.4.4.2.3).

Reviewer comment: *Although more information on adverse events was available from the clinical studies, the QT data with regards to ECGs interval was only collected in the Phase 1 studies, primarily the QT study E2080-A001-002.*

4. ECG ANALYSIS: SELECTION OF STUDIES AND ANALYSES FOR OVERALL DRUG CONTROL COMPARISONS

4.1 E2080-A001-001 Methods

Eisai described Study E2080-A001-001 as a multiple-dose, double-blind, placebo-controlled, randomized, dose escalation trial. Subjects (20 healthy volunteers) received

¹⁰ The clinical trials in which ECG data was collected were CRUF331 0022 and AE/ET 1.

multiple ascending doses of rufinamide in total daily doses of 800, 1600, 2400, 3200, 4800, and 7200 mg, administered twice daily with food, over a period of 18 days. Subjects were to remain at each dose level for 3 days before moving to the next higher dose level. After the subjects received the maximum dose of 7200 mg/day, rufinamide was abruptly discontinued and the subjects were discharged the next day. The subjects were contacted by telephone five days later to inquire about adverse events (E2080-A001-001 Study Report, pg.7).

Reviewer comment: The patient population and methodology of Study E2080-A001-001 is very similar to that of Study E2080-A001-002 (described below), which allows for the corroboration of ECG results between these two studies.

4.2 E2080-A001-002 Methods

4.2.1 Overview

The sponsor characterized Study E2080-A001-002 as the “definitive QT study” within the rufinamide development program. Study E2080-A001-002 was a double-blind, parallel-group study with concurrent placebo and positive (moxifloxacin) controls. Studies were stratified by gender at study entry (E2080-A001-002 study report).

4.2.2 Subjects

Eisai described the inclusion/exclusion criteria as being typical of cardiac safety Phase 1 investigations in healthy volunteers - notably, requiring a normal physical examination and screening ECG. The subject age span was 18 to 55 years, with a nearly equal gender distribution. One hundred and seventeen (117) subjects were enrolled, 100 subjects completed the study, and 88 subjects completed the study per protocol (E2080-A001-002 study report).

4.2.3 Dose

Rufinamide subjects received step-wise increasing doses of rufinamide (three days at each dose level of 800, 1600, 2400, 3200, 4800 and 7200 mg/day¹¹, over a period of 17 days. On Day 18, only a single dose of 3600 mg rufinamide was to be administered in the morning, followed by a washout on Day 19 and a single dose of placebo on Day 20. Subjects in the placebo group received placebo according to the same dosing schedule and over the same time period (from Days 1-18), and then received a single dose of 400 mg moxifloxacin on Day 20 (E2080-A001-002 study report).

Reviewer comment: Of note, the proposed therapeutic dose in the rufinamide development program was 2400 mg/day. The 3200, 4800 and 7200 mg/day doses in the Study E2080-A001-002 are therefore supratherapeutic doses.

¹¹ Rufinamide was administered as a twice a day dosing following a standardized meal.

4.2.4 Moxifloxacin Positive Control

To test assay sensitivity, placebo subjects received a single dose of moxifloxacin (400 mg) on Day 20, and the rufinamide subjects received a matching placebo capsule. The time-matched mean change from baseline in subjects randomized to placebo following the single dose of moxifloxacin (Study Day 20 minus Study Day 19) and following placebo (Study Day 9 minus Study Day -1) were then compared (E2080-A001-002 study report).

The sponsor explained that six subjects in the rufinamide treatment group were inadvertently given moxifloxacin on Day 20, instead of the placebo. These subjects were excluded from the Day 20 PK and QT/QTc analyses of moxifloxacin. All data prior to Day 20 were included in the analyses for these subjects, and all 117 subjects enrolled were analyzed for safety (E2080-A001-002 summary).

Eisai stated that the moxifloxacin-treated group, with placebo subtracted, demonstrated a mean QTc_i increase of 12.5 ms, with the 95% lower confidence interval predicting that the lowest increase with 95% assurance would be 9.51 ms. The sponsor noted that the differences in means were always greater than 10 msec between two and eight hours post-dose (the time period covering T_{max} for moxifloxacin). The sponsor therefore concluded that the subjects given moxifloxacin demonstrated a prolongation of the QT interval, verifying the ability of the study assay to detect such changes (report, pg. 8).

b(4)

Reviewer comment: In light of the finding of a shortened QT interval in the rufinamide-treated subjects, the use of a moxifloxacin positive control arm to verify that the E2080-A001-002 study protocol can detect prolonged QT changes is particularly helpful.

4.3 Phase III Study Methods

Reviewer comment: The detailed review of the Phase 3 studies within the rufinamide NDA is addressed by other FDA reviewers. The summary of methods below is provided for reference.

4.3.1 CRUF331 0022

Study CRUF331 0022 was a multinational, randomized, double-blind, placebo-controlled, parallel trial of rufinamide as an adjunctive therapy for patients with inadequately controlled Lennox-Gastaut syndrome. The study consisted of a 28-day prospective baseline phase (which enrolled 138 patients [74 rufinamide and 64 placebo]) followed by an 84-day double-blind phase and a subsequent open-label phase. Subjects were initially dosed at approximately 10 mg/kg/day, and titrated to approximately 45 mg/kg/day over a one- to two-week period (CRUF331 0022 Study Report, pg. 12).

4.3.2 AE/ET 1

Study AE/ET1 was multinational, double-blind, placebo-controlled randomized, 5-arm parallel (fixed dose) study of epilepsy patients with inadequately controlled seizures receiving up to three concomitant AED drugs. After completion of a baseline phase, 647 patients were randomized to placebo or one of four treatment groups (rufinamide 200, 400, 800, or 1600 mg/day). The double-blind phase lasted three months.¹²

5. ECG ANALYSIS: RESULTS OF STANDARD ANALYSES AND EXPLORATIONS OF ECG DATA

5.1 E2080-A001-001 RESULTS

Eisai performed a dose-response analysis to characterize the results of Study E2080-A001-001. The sponsor found that for each 1 ug/ml increase in rufinamide, the QT interval decreased 0.5 ms, which resulted in - 7.5 msec at “typical” patient concentrations (15 ug/ml) (E2080-A001-001 Study Report).

Reviewer comment: The sponsor did not perform as extensive an analysis on Study E2080-A001-001 as for Study E2080-A001-002, and the statement above was essentially all the results provided. It can be stated, however, that the results of Study E2080-A001-001 are generally consistent with the results of Study E2080-A001-002, in that both show a comparable decrease in the QT interval with rufinamide use.

5.2 Measures of Central Tendency

5.2.1 Healthy Volunteers

The sponsor indicated that the analysis of central tendency within Study E2080-A001-002 did not demonstrate an increase in QTcF, QTcB or QTci with rufinamide. In fact, rufinamide treatment was associated with a decrease in these parameters relative to placebo, as shown in FDA Figure 1 below.

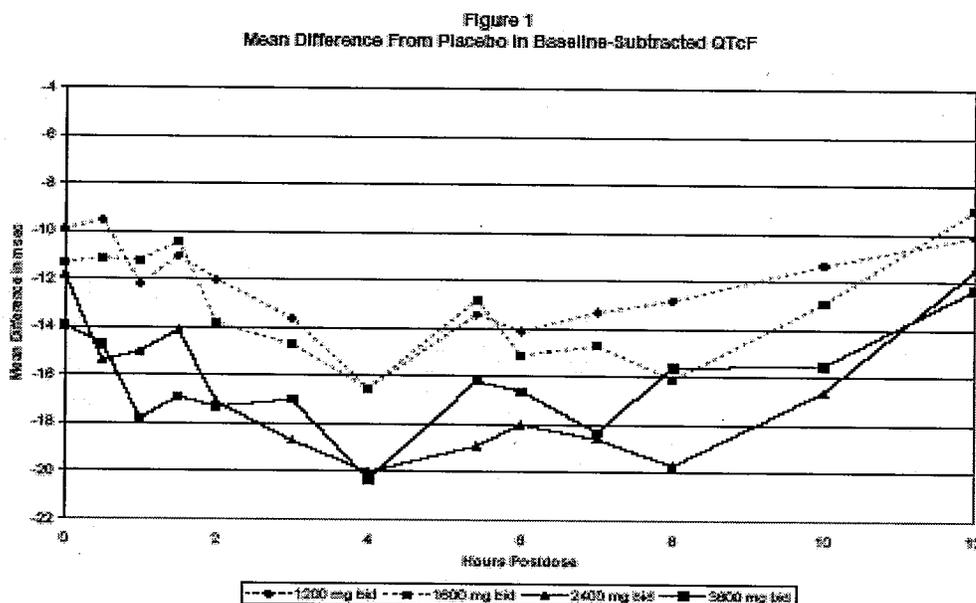
At a dose of 2400 mg/day, the change from placebo ranged from -16.7 msec to -9.6 msec for QTcF and from -18.0 msec to -9.3 msec for QTci. At the supra-therapeutic dose of 7200 mg/day, the changes ranged from -20.2 msec to -2.1 msec and from -21.3 msec to -3.7 msec, for QTcF and QTci respectively.

Eisai provided the figure below summarizing the effect of dose on the QTcF interval.

Reviewer comment: The sponsor presented equivalent figures for the other correction methods, which were similar in appearance.

¹² This summary of Study AE/ET1 was adapted from the FDA Statistical Review of Ohidul Siddiqui.

FDA Figure 1. Mean Difference from Placebo in Baseline-Subtracted QTcF in Study E2080-A001-002 (Adapted from Sponsor Figure 1, Statistical Report, pg.9)



Eisai noted that the greatest decreases in QT interval seen in the figure above occurred at the two higher dose levels. In addition, the greatest decreases were generally between four and eight hours post-dose, which were the times with the highest plasma concentrations of rufinamide (Statistical Report, pg.8).

b(4)

Reviewer comment: The presence of a dose/concentration response relationship is discussed in more detail in Section 5.5.1 of this review.

5.2.2 Patients with Epilepsy

Reviewer comment: Analysis of the ECGs in the clinical studies consisted of classifying them as normal or abnormal, so measures of central tendency are not available.

5.3 Outliers or Shifts from Normal to Abnormal

5.3.1 Healthy Volunteers

Eisai stated that categorical outlier analysis of QTc intervals in rufinamide subjects within Study E2080-A001-002 revealed no significant outliers. Specifically, no subject had a QTc value of >500 msec. In addition, there were no rufinamide subjects with QTcF values >480 msec; although one subject had QTcB values that ranged from 481 to

489 msec and another subject had *QTci* values that ranged from 481 to 494 msec at various times during the study (ISS, 2.7.4.4.2 ECGs).

At the therapeutic rufinamide dose (2400 mg/day), there were no *QTcF* values >450 msec; however, four rufinamide subjects reached that category at the supra-therapeutic dose level (7200 mg/day), as did five subjects in the corresponding placebo group. There were one and three subjects with *QTci* >450 msec at the clinical and the supra-therapeutic dose levels of rufinamide, respectively, and one in the corresponding placebo group. Only one subject in the placebo group had an increase from baseline of >60 msec (increase in *QTcB* from 370 msec at baseline to 433 msec at 12 hours post-dose on Day 1 (ISS, 2.7.4.4.2 ECGs).

Reviewer comment: *The outlier analysis described above was designed to characterize prolongation of the QT interval, and so is less informative when used with a drug such as rufinamide which is associated with a shortening of the QT interval. In the NDA Action Letter, Eisai was requested to submit a table which better reflects outliers with regard to shortening of the QT interval (see Section 3.3.2.4 of this review for details).*

In the table below, Eisai summarized the number of subjects with ECGs changing from "normal" to "abnormal," or vice versa, comparing their ECG at the end of the study to their baseline ECG.

FDA Table 2: ECG Shift Table for Healthy Volunteers in Studies E2080-A001-001 and E2080-A001-002 (Adapted from Sponsor Table9.4.1-10, ISS, pg. 308)

Post-text table 9.4.1-10
Summary of changes from the baseline ECG result to the final ECG result
(Healthy Volunteers)

ECG baseline	Final ECG			
	Rufinamide(N=326)			
	Missing	Normal	Abnormal	Total
Normal	44(13.50)	113(34.70)	22(6.70)	179(54.90)
Abnormal	10(3.10)	11(3.40)	23(7.10)	44(13.50)
Missing	0	0	0	0
Total	54(16.60)	124(38.00)	45(13.80)	223(68.40)

Reviewer comment: *Eisai described the classification of ECGs into the categories of normal or abnormal in the following statement: "Each ECG that was recorded was*

given an overall interpretation of normal or abnormal (ISS, Section 3.4.3.4).” Beyond this statement, the sponsor did not provide any criteria used to classify the ECGs as normal or abnormal. The subjectiveness of such classifications compromises the utility of the shift tables. In addition, I presume that the abnormal ECGs included various types of abnormalities, and were not limited to interval abnormalities.

5.3.2 Patients with Epilepsy

Patients with Epilepsy – Double-Blind Phase: The shift table below compares baseline ECGs with the final ECGs for all patients with epilepsy who received study drug in the Phase 3 double-blind studies. Eisai summarized that ECGs were interpreted as normal at baseline and abnormal at the final evaluation for 9.4% of the rufinamide-treated patients and 8.8% of the placebo-treated patients. Conversely, ECGs were interpreted as abnormal at baseline and normal at the final evaluation for 7.1% of the rufinamide-treated patients and 11.7% of the placebo-treated patients (ISS, pg. 304).

Reviewer comment: See preceding reviewer comment on Eisai’s criteria for classifying ECGs as normal or abnormal.

FDA Table 3: ECG Shift Table for All Patients with Epilepsy within the Double-Blind Studies (Adapted from Sponsor Table 9.3-1, ISS, pg.304)

Baseline ECG interpretation	Final ECG interpretation							
	Rufinamide (N=1240)				Placebo (N=635)			
	Missing	Abnormal	Normal	Total	Missing	Abnormal	Normal	Total
Missing	11 (0.9)	0	1 (0.1)		7 (1.1)	1 (0.2)	3 (0.5)	
Abnormal	5 (0.4)	188 (15.2)	88 (7.1)		5 (0.8)	126 (19.8)	74 (11.7)	
Normal	16 (1.3)	117 (9.4)	812 (65.5)		10 (1.6)	56 (8.8)	350 (55.1)	
Total				1238 (99.8)				632 (99.5)

Note: Two patients in the rufinamide group and 3 patients in the placebo group had no ECG information reported in their CRFs and are therefore excluded from this table. The remaining 1238 rufinamide-treated patients and 632 placebo-treated patients had ECG information reported. “Missing” in this table indicates that the ECG interpretation was not included among the information reported in the CRF.

Cross reference: Appendix I, Table 9.4.1-0

All Rufinamide-Treated Patients with Epilepsy: The following shift table summarizes ECG shifts between the normal and abnormal categories for all rufinamide-treated patients with epilepsy. Eisai stated that ECGs were interpreted as normal at baseline and abnormal at the final evaluation for 10.7% of the patients who received rufinamide, and as abnormal at baseline and normal at the final evaluation for 7.4%.

FDA Table 4: ECG Shift Table for All Rufinamide-Treated Patients with Epilepsy (Adapted from Sponsor Table 9.3-2, ISS, pg.305)

Baseline ECG interpretation	Final ECG interpretation			
	Rufinamide (N=1978)			
	Missing	Abnormal	Normal	Total
Missing	23 (1.2)	22 (1.1)	39 (2.0)	1963 (99.2)
Abnormal	141 (7.1)	190 (9.6)	146 (7.4)	
Normal	266 (13.4)	212 (10.7)	924 (46.7)	
Total				

Note: Fifteen patients had no ECG information reported in their CRFs and are therefore excluded from this table. The remaining 1963 patients had ECG information reported. "Missing" in this table indicates that the ECG interpretation was not included among the information reported in the CRF.

Cross reference: Appendix I, Table 9.4.1-1

Patients with Partial Seizures: Eisai stated that ECGs were interpreted as normal at baseline and abnormal at the final evaluation for 8.6% of the rufinamide-treated patients and 9.3% of the placebo-treated patients. ECGs were interpreted as abnormal at baseline and normal at the final evaluation for 5.7% of the rufinamide-treated patients and 11.7% of the placebo-treated patients.

LGS Patients: ECGs were interpreted as normal at baseline and abnormal at the final evaluation for 13.5% of the rufinamide-treated patients and 6.3% of the placebo-treated patients. Conversely, ECGs were interpreted as abnormal at baseline and normal at the final evaluation for 9.5% of the rufinamide-treated patients and 17.2% of the placebo-treated patients.

Reviewer comment: *Although shift tables may provide an overview of the effect of rufinamide on ECGs, several factors limit their utility. In particular, the nature of the ECG abnormalities is not clear, and multiple types of abnormalities are likely pooled within the abnormal category, which could obscure the effect of any particular abnormality (such as QT-related abnormalities).*

5.4 Marked Outliers and Dropouts for ECG Abnormalities

5.4.1 Outliers

5.4.1.1 Healthy Volunteers

Eisai reported that at no time (for any of the four dose levels or for any of the three methods of QTc correction) was the observed mean time-matched change from baseline for rufinamide subjects greater than that among placebo subjects. The sponsor noted that the greatest decreases in QT intervals were seen at the two higher doses. In addition, the greatest decreases tended to be between four and eight hours which were the times with the highest plasma concentrations of rufinamide (See Section 5.4.1 for further discussion of a dose-response relationship).

Eisai stated that at rufinamide doses of 1200 mg and 3600mg no subject experienced an increase in baseline QTcF greater than 30 ms. When the QTci formula was applied there

were two in the rufinamide treated subjects (1200 mg and 3600 mg respectively) and two in corresponding placebo groups, which accounted for 1.9% of the total sample.

The sponsor reported that there were no QTcF values greater than 450 ms at rufinamide 2400mg; however, four subjects did reach that category at 3600mg, as did five subjects in the corresponding placebo group. There was one QTci greater than 450 ms at rufinamide 1200mg, and three at 3600mg with one in the corresponding placebo group.

Reviewer comment: See Section 5.3.1 for comments on the design of Eisai's outlier analysis.

5.4.1.2 Patients with Epilepsy

Reviewer comment: Because the analysis of the ECGs within the Phase 3 studies consisted of broadly classifying ECGs as normal or abnormal, no information on ECG intervals or outliers is available for patients with epilepsy.

5.4.2 Deaths

5.4.2.1 Healthy Volunteers

Eisai stated there were no deaths within studies E2080-A001-001 and E2080-A001-002.

5.4.2.2 Patients with Epilepsy

Eisai reported that sudden death occurred in eight (0.4%) rufinamide-treated patients and four (0.6%) placebo-treated patients within the rufinamide development program. The sponsor defined sudden deaths as deaths without any obvious cause, regardless of the investigators' term for cause of death (ISS, pg. 148).

FDA Table 5: Summary of the Sudden Death in Rufinamide-Treated Subjects (N=8)(Adapted from Sponsor Table 7.1-1, ISS, pg. 146)

Subject	Description
016E 1255-00557	This 19-year-old woman had no notable medical history except inadequately controlled partial seizures and "drug hypersensitivity." She received rufinamide for 28 days during the DB phase until she met the exit criteria of "prolongation or clinically significant worsening of generalized seizure duration or frequency." Concomitant medications as she entered the OL extension phase were lamotrigine, topiramate, lorazepam, and naproxen. On Day 569 of the Extension Phase, while receiving 4000 mg rufinamide daily, the patient was found dead in her dormitory bed. An autopsy revealed findings consistent with seizure disorder. Tests for alcohol or illicit drugs were negative.
021AE	This 20-year-old woman with no notable medical history except

1257-05122	inadequately controlled partial seizures and viral encephalitis received placebo during the DB phase followed by rufinamide during the OL extension phase. Concomitant medications were folic acid, Depo-Provera, lamotrigine, tiagabine, lorazepam, and topiramate. An ECG in August 2001 was read as normal. On Day 948 of the Extension Phase, while receiving 3200 mg rufinamide daily, the patient died suddenly. No other information regarding the death was available. In the opinion of the autopsy medical examiner, the death was due to the patient's epileptic seizure disorder.
021AE 1282-05025	This 59-year-old woman entered the study with a medical history notable for inadequately controlled partial seizures and a benign breast lumpectomy. She received placebo during the DB phase and entered the OL extension phase. Concomitant medications included aspirin, ofloxacin, Acular, Maxitrol, phenytoin, lamotrigine, and topiramate. An ECG in February 2000 was reported as normal. On Day 828 of the extension phase, while receiving 3600 mg rufinamide and 800 mg topiramate daily, the patient was found dead on the floor of her home. There was no blood or evidence of trauma found at the scene. An autopsy was not performed. The death certificate indicated the cause of death as hypoxia/anoxia, probably secondary to seizure.
021PE 0006-04411	This 6-year-old girl entered the study with a medical history notable for inadequately controlled partial seizures since age of 5 months, dementia, and "drug intolerance NOS." She received rufinamide during the DB and subsequent OL phase, titrated to 1000 mg/day. Concomitant medications were benzobarbital and valproate. On Day 743 of the extension study, the patient was found dead. Examination revealed her tongue had been bitten. The day before she was "dysphoric, excited, and aggressive." She was thought to have died of "status epilepticus during the patient's sleep complicated by acute cardiovascular failure." No autopsy was performed and the death certificate reported cause of death as "unclear cerebral impairment." Follow-up information stated that the assumption of "the complication of acute cardiovascular failure was based on clinical findings, but could not be confirmed because an autopsy was not performed." The patient had no known history of cardiovascular disease.
0101 0052-00011	This 65-year-old man entered the study with a medical history notable for symptomatic secondarily generalized seizures, depression, hypercholesterolemia, hypertension, hypothyroidism, hyperhomocystinemia and an apparent cerebrovascular accident. On Day 47 of rufinamide therapy, while receiving rufinamide 1200 mg/day, he experienced "moderate sleep apnea syndrome." Study treatment was continued unchanged. On Day 119, while receiving rufinamide and carbamazepine, the patient died in bed following an epileptic seizure. Prior to the event, the patient had experienced persisting epileptic seizures and ongoing nocturnal apneas.
0101	This 33-year-old man entered the DB phase with a "seizures NOS." On

0052-00016	Day 86, while receiving rufinamide 800 mg/day and carbamazepine, the patient was found dead in bed. An autopsy provided no information. The investigator believed the death may have resulted from an epileptic seizure, since blood was found in the patient's mouth.
AE/ET1 0001-09009	This 34-year-old woman entered the study with a history of inadequately controlled partial seizures and fatigue. She received placebo during the DB phase and began receiving rufinamide during the OL extension phase. Her concomitant medications were carbamazepine and valproate. On Day 237, while receiving rufinamide 1200 mg/day, the patient was found dead in bed. An autopsy revealed "mild brain congestion" and "a finding consistent with mild temporal lobe atrophy." Mild congestion of the lungs was also noted. On the basis of the autopsy, the potential cause of death was given as epileptic seizure.
AE/ET1 0002-02056	This 33-year-old woman entered the study with a history of inadequately controlled partial seizures, asthma, muscle spasms, and head injury. She received rufinamide during the DB phase and then entered the OL extension phase. Her concomitant medications were cyclobenzaprine, imipramine, paracetamol, and carbamazepine. On Day 189 of rufinamide therapy, the patient experienced a seizure and died. The autopsy designated the cause of death as asphyxia.

Reviewer comment: I reviewed the eight sudden deaths among rufinamide-treated patients summarized in the table above. These subjects all had inadequately controlled epilepsy, and in several cases there was evidence that they had died from seizure activity. However, the possibility of an arrhythmia secondary to a shortening of the QT interval cannot be ruled out. In fact, the ICH E14 guidance to industry on QT studies notes that arrhythmic events may be mistaken for seizures.

5.4.3 ECG-Related Serious Adverse Events

5.4.3.1 Healthy Volunteers

Eisai stated that no serious adverse events were reported in E2080-A001-001 or E2080-A001-002 (ISS, pg. 307).

5.4.3.2 Patients with Epilepsy

The table below summarizes serious adverse events related to ECGs or the SOCs¹³ of cardiac/vascular disorders during the Phase 3 studies. Eisai stated that no such events occurred in either treatment group during any of the double-blind studies in patients with epilepsy. Of the events that occurred during open-label treatment with rufinamide, the only event that was serious and occurred in more than one patient was deep vein thrombosis, which occurred in two patients (ISS, pg. 305).

¹³ SOC= System Organ Class

FDA Table 6: ECG-Related Serious Adverse Events in Epilepsy Patients treated with Rufinamide (Adapted from Sponsor Table 9.3-4, ISS, pg. 305)

Table 9.3-4. ECG- and cardiovascular-related serious adverse events

Population		Rufinamide
SOC	Preferred term	n (%)
All treated patients with epilepsy (N=1978)		
Cardiac disorders	Angina pectoris	1 (0.1)
	Arrhythmia	1 (0.1)
	Palpitations	1 (0.1)
	Ventricular extrasystoles	1 (0.1)
Investigations	Electrocardiogram abnormal	1 (0.1)
Vascular disorders	Deep vein thrombosis	2 (0.1)
	Infarction	1 (0.1)
	Thrombophlebitis	1 (0.1)
Double-blind, adjunctive therapy studies in adults with partial seizures (with open-label extensions)		(N=932)
Cardiac disorders	Palpitations	1 (0.1)
Investigations	Electrocardiogram abnormal	1 (0.1)
Vascular disorders	Deep vein thrombosis	1 (0.1)
	Thrombophlebitis	1 (0.1)
Double-blind studies in pediatric patients (with open-label extensions)		(N=391)
Cardiac disorders	Arrhythmia	1 (0.3)

Cross reference: Appendix I, Table 7.7.1-1

Reviewer comment: Eisai described the SAE of “electrocardiogram abnormal” as occurring in a 49-year-old man who underwent an ECG prior to elective surgery while receiving rufinamide 4800 mg/day. The ECG showed normal sinus rhythm with right atrial abnormality and non-specific ST-T wave changes. The sponsor maintained that these abnormal ECG findings were also present at study entry. The patient was hospitalized for cardiac catheterization, which revealed no significant findings.

5.4.4 ECG-Related Adverse Events

5.4.4.1 Healthy Volunteers

Eisai stated that no healthy volunteer experienced an ECG-related adverse event (ISS, pg. 309).

Reviewer comment: I searched the adverse events among the healthy volunteers for reports of syncope, and found one case among the rufinamide-treated subjects, compared to no cases among the placebo-treated subjects.

5.4.4.2 Patients with Epilepsy

FDA Table 7: ECG-Related Adverse Events in Epilepsy Patients treated with Rufinamide (Adapted from Sponsor Table 9.3-3, ISS, pg. 307)

Table 9.3-3. ECG-related adverse events

	Rufinamide		Placebo	
	n	(%)	n	(%)
All treated patients with epilepsy (double-blind studies)	(N=1240)		(N=635)	
Electrocardiogram change	2	(0.2)	0	
Electrocardiogram abnormal	1	(0.1)	0	
Electrocardiogram ST segment elevation	1	(0.1)	0	
All treated patients with epilepsy	(N=1978)			
Electrocardiogram change	3	(0.2)		
Electrocardiogram abnormal	2	(0.1)		
Electrocardiogram QT prolonged	1	(0.1)		
Electrocardiogram QT shortened	1	(0.1)		
Electrocardiogram ST segment elevation	1	(0.1)		
Double-blind, adjunctive therapy studies in adults with partial seizures	(N=720)		(N=290)	
Electrocardiogram change	2	(0.3)	0	
Electrocardiogram abnormal	1	(0.1)	0	
Electrocardiogram ST segment elevation	1	(0.1)	0	
Double-blind, adjunctive therapy studies in adults with partial seizures (with open-label extensions)	(N=932)			
Electrocardiogram change	2	(0.2)		
Electrocardiogram abnormal	2	(0.2)		
Electrocardiogram ST segment elevation	1	(0.1)		
Double-blind studies in pediatric patients (with open-label extensions)	(N=391)			
Electrocardiogram change	1	(0.3)		
Electrocardiogram QT prolonged	1	(0.3)		

Cross reference: Appendix I, Tables 6.2.1-2, 6.3.1-2, 6.4.1-2, 6.5.1-2, 6.6.1-2, 6.7.1-2, 6.8.1-2, 6.9.1-2, 6.10.1-2

Eisai noted that there were no ECG-related adverse events in either treatment group in the monotherapy substitution studies, in the LGS study or its extension, or either treatment group in the double-blind portion of the pediatric studies (ISS, pg.309).

5.4.5 Discontinuations due to ECG- and Cardiovascular-Related Adverse Events

5.4.5.1 Healthy Volunteers

Eisai stated that one rufinamide-treated subject (0.3%) in Studies E2080-A001-001 and E2080-A001-002 discontinued due to palpitations. There were no other discontinuations in healthy volunteers due to cardiovascular-related adverse events (ISS Appendix I, Table 7.5.12-1).

Reviewer comment: *A request has been made to the sponsor for more information on the subject who discontinued due to palpitations, specifically for a description of the patient's ECG.*

One rufinamide-treated subject experienced an adverse event *after* discontinuation (verbatim term: feeling shaky). This adverse event occurred two days after discontinuation, and the subject recovered completely three days later (E2080-A001-001 Study Report, pg. 51).

5.4.5.2 Patients with Epilepsy

Eisai provided the table below summarizing discontinuations due to adverse events related to ECGs or the SOCs of cardiac/vascular disorders within the clinical studies. The sponsor noted that no such discontinuations occurred in the LGS study, in the double-blind phases of the monotherapy studies or in the studies in pediatric patients. The only events leading to discontinuation in more than one patient were palpitations and hypertension (two patients each)(ISS, pg. 308).

Reviewer comment: *More information on the subject who discontinued due to arrhythmia has been requested from the sponsor, including a description of the patient's ECG.*

FDA Table 8: Discontinuations from the Clinical Studies due to ECG- or Cardiovascular-Related Adverse Events (Adapted from Sponsor Table 9.3.5, ISS, pg. 308)

Appears This Way
On Original

Table 9.3-5. Discontinuations due to ECG- and cardiovascular-related adverse events

Population		Rufinamide	Placebo
SOC	Preferred term	n (%)	n (%)
All treated patients with epilepsy (double-blind studies)		(N=1240)	(N=635)
Cardiac disorders	Palpitations	1 (0.1)	0
Investigations	Blood pressure decreased	0	1 (0.2)
Vascular disorders	Flushing	1 (0.1)	0
	Hypertension	1 (0.1)	0
All treated patients with epilepsy		(N=1978)	
Cardiac disorders	Palpitations	2 (0.1)	
	Arrhythmia	1 (0.1)	
Vascular disorders	Hypertension	2 (0.1)	
	Flushing	1 (0.1)	
	Hypotension	1 (0.1)	
	Pallor	1 (0.1)	
Double-blind, adjunctive therapy studies in adults with partial seizures		(N=720)	(N=290)
Cardiac disorders	Palpitations	1 (0.1)	0
Investigations	Blood pressure decreased	0	1 (0.3)
Vascular disorders	Hypertension	1 (0.1)	0
Double-blind, adjunctive therapy studies in adults with partial seizures (with open-label extensions)		(N=932)	
Cardiac disorders	Palpitations	2 (0.2)	
Vascular disorders	Hypertension	2 (0.2)	
Double-blind studies in pediatric patients (with open-label extensions)		(N=391)	
Cardiac disorders	Arrhythmia	1 (0.3)	
Vascular disorders	Hypotension	1 (0.3)	
	Pallor	1 (0.3)	

Cross reference: Appendix I, Table 7.7.1-2

5.5 Other ECG Related Data

5.5.1 Dose/Concentration Response Analysis

Eisai provided the following table summarizing the maximum decrease in mean time-matched change from baseline in QTcF among subjects receiving rufinamide minus that among subjects receiving placebo.

b(4)

FDA Table 9: Maximum Decrease in QTcF Relative to Placebo by Dose in Study E2080-A001-002 (Adapted from Sponsor Table on pg. 8 of the _____ ; Statistical Report)

Clinical Review

27

M. Lisa Jones MD, MPH

Rufinamide

Inovelon®

Maximum Decrease in QTcF Relative to Placebo Following Each Dose

Dose	Maximum Observed Mean (Minimum) Difference From Placebo (msec)	95% Upper Confidence Bound (msec) on Maximum Difference
1200 mg bid	-16.66 (-9.57)	-13.0
1600 mg bid	-16.11 (-9.12)	-12.7
2400 mg bid	-20.17 (-11.45)	-16.2
3600 mg bid	-20.18 (-12.88) ¹	-16.1

¹Through 12 hours post dose

Eisai's statistical analysis plan did not specify an analysis for dose-response, however, a post-hoc analysis was performed to assess the dose response relationship statistically. A test for trend was performed among the differences in baseline-subtracted changes in QTcF between rufinamide and placebo, assuming the four rufinamide doses to be equally spaced. At the following times postdose the test for trend achieved nominal statistical significance (p<0.05): hour 0.5 (p=0.005), hour 1 (p=0.010), hour 1.5 (p=0.005), hour 2 (p=0.009), hour 3 (p=0.030), hour 4 (p=0.026), hour 6 (p=0.048), hour 7 (p=0.011), and hour 10 (p=0.023) (Report, pg. 7).

b(4)

The sponsor stated that the time to maximal serum concentration of rufinamide in Study E2080-A001-002 was 5.15 hours, with a range of approximately three to eight hours. Eisai reported that the decrease in QTc consistently peaked at four hours, irrespective of dose. Using a proportion of a 0.5 msec decrease per 1µg/mL, the sponsor estimated a decrease of 7.5 msec at a typical concentration in patients (15 µg/mL) (Report, pg. 7).

b(4)

FDA Table 10: Mean Change from Time-Matched Baseline in QTcF by Hour Post-Dose in Study E2080-A001-002 (Adapted from Sponsor Table 10, Statistical Report, pg. 20)

b(4)

Appears This Way
On Original

Table 10
Mean Change From Time-Matched Baseline in QTcF
Day 18

Hours Postdose	Rufinamide 3600 mg bid (N=49)	Placebo (N=52)	Difference	95% Upper Confidence Bound
0	-15.32	-1.32	-14.00	-9.49
0.5	-24.83	-9.45	-15.38	-11.21
1	-24.56	-6.54	-18.02	-14.08
1.5	-23.49	-6.65	-16.84	-13.06
2	-23.63	-6.15	-17.49	-13.66
3	-24.24	-7.16	-17.08	-13.12
4	-23.74	-3.55	-20.18	-16.07
5.417	-23.34	-7.32	-16.02	-11.91
6	-24.80	-7.86	-16.94	-13.70
7	-22.54	-4.59	-17.94	-13.96
8	-20.01	-4.60	-15.41	-11.61
10	-17.69	-2.26	-15.43	-11.37
12	-14.56	-1.68	-12.88	-8.21
16	-17.82	-9.64	-8.18	-4.15
20	-15.60	-7.82	-7.78	-3.54
24.417	-13.58	-5.88	-7.70	-3.39
30	-13.79	-9.17	-4.63	-0.43
36	-6.07	-3.97	-2.10	2.11

5.5.2 Rufinamide Effect on Heart Rate

Eisai noted that there was a moderate rise in heart rate induced by rufinamide in Study E2080-A001-002. The mean differences from placebo ranged from 4.4 to 10.4 beats per minute between two and eight hours after the highest dose (Day 18).

To assess whether the decreases in QTc were related to changes in heart rate, Eisai calculated mean changes in heart rate from the time-matched baseline following the highest dose. The mean differences from placebo ranged from 4.4 to 10.4 bpm between two and eight hours post-dose (Day 18). Changes in heart rate were then added as a covariate to the analysis of time-matched changes in QTcF. However, adjustment for change in heart rate had only a minimal effect on the differences in means between rufinamide and placebo, as these results were very similar to the unadjusted results. The sponsor noted that the increases in heart rate observed following administration of rufinamide were too small to explain the magnitude of the reduction in the QT interval (ISS, 2.7.4.4.2 ECGs).

5.5.3 Gender Sub-analysis

To assess whether the changes in QTc were comparable between males and females, Eisai calculated the time-matched changes from baseline in QTc at two to eight hours following the highest dose on Study Day 18, as shown in the table below.

FDA Table 11: Mean Change from Time-Matched Baseline in QTcF by Treatment Group and Sex (Adapted from Sponsor Table 54, _____ ; Statistical Report, pg. 64)

b(4)

Table 54
 Mean Change From Time-Matched Baseline in QTcF by Treatment Group and Sex
 Day 18

Hours Postdose	Rufinamide Males (N=27)	Rufinamide Females (N=22)	Placebo Males (N=26)	Placebo Females (N=26)	Interaction P-Value
2	-23.4	-23.3	-5.2	-6.8	0.74
3	-23.3	-24.9	-6.5	-7.6	0.92
4	-21.3	-26.3	-4.1	-2.6	0.20
5.417	-22.6	-24.3	-7.6	-6.9	0.64
6	-24.8	-24.4	-8.5	-7.5	0.90
7	-24.0	-21.5	-3.7	-5.5	0.38
8	-19.9	-20.7	-5.3	-3.9	0.66

The sponsor concluded from this table that both the rufinamide results and the placebo results were comparable between males and females (Report, pg. 9).

b(4)

6. FDA QT REVIEW TEAM: RESPONSE TO DNP REQUEST FOR CONSULTATION

To assist in this review, the DNP¹⁴ consulted the FDA's Interdisciplinary Review Team for QT Studies. In their response¹⁵, the QT team expressed their concern regarding the clinical significance of the QT interval shortening. As in this review, the concern was largely based on adverse outcomes associated with familial short QT syndrome. The QT team provided the following recommendations for the evaluation of the QT shortening with the rufinamide use:

1. Given the characteristics of familial Short QT syndrome, in addition to cases of sudden death, cases of atrial fibrillation should be reviewed for imbalances between placebo and rufinamide-treated subjects.

Reviewer comment: In response to the suggestion above, I searched the ISS (Integrated Summary of Safety) for cases of atrial fibrillation¹⁶. The search did not yield any results, and a request has been forwarded to the sponsor to look further for cases and for any imbalance between the rufinamide and placebo groups.

2. If this drug were to be approved, a post-marketing surveillance program should be considered.

Reviewer comment: I agree with this suggestion, and will pursue further discussions should rufinamide be approved.

¹⁴ DNP=Division of Neurology Products

¹⁵ NDA 021-911 (Rufinamide). FDA Interdisciplinary Review Team: Response to Request for Consultation on QT Interval Shortening. Prepared by Shari Targum MD, and Norman Stockbridge MD. Dated August 31, 2006.

¹⁶ I searched using the key words "atrial" and "fibrillation," both separately and combined.

3. The sponsor should be asked to submit ECGs from the thorough QT Study E2080-A001-002 to the FDA's ECG warehouse.

Reviewer comment: This request has been forwarded to the sponsor.

7. CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

During the "definitive QT" study in the rufinamide development program (Study E2080-A001-002), a shortening of the QT interval was observed in association with rufinamide treatment. The degree of shortening ranged from -2.1 to -21.3, depending on the dose, time from dose and heart rate correction method employed. Several factors suggest a causal relationship between rufinamide treatment and shortening of the QT interval:

- The degree of shortening of the QT interval rose with increasing dose, and was greatest when measured at times corresponding to the highest rufinamide plasma concentrations.
- Although the QT Study E2080-A001-002 utilized ambulatory ECG monitoring in a way not endorsed by the ICH E14 guidance to industry on assessing QT interval, the study was of adequate overall design. A moxifloxacin positive control arm demonstrated the ability of the study to appropriately measure a prolonging effect on the QT interval.
- The shortening of the QT interval in E2080-A001-002 was also observed in another Phase 1 study, E2080-A001-001, so the results are reproducible.
- It is biologically plausible that rufinamide may shorten the QT interval, as other drugs which act at the sodium/potassium ATP-ase pump, such as digoxin, also shorten of the QT interval.

7.2 Regulatory Actions

In October 2006, the DPP issued an Approvable Action Letter for rufinamide. With regards to the QT review, the letter made the following request to Eisai:

The results of Study E2080-A001-002, which examined QT intervals, found rufinamide to be associated with reduction of the QT interval ranging from approximately 2 to 20 msec. For this study (E2080-A001-002) and for the ECG data collected in the clinical trials, please provide outlier tables summarizing the number and percent of subjects with QT intervals in each of the following categories. We ask that you provide this table for each dose level and stratify by heart rate correction method.

Absolute QT:

- < 420 msec*
- < 410 msec*
- < 400 msec*
- < 390 msec*
- < 350 msec*
- < 300 msec*

QT Reduction from Baseline:

- QT interval decreases < 5 msec from baseline*
- QT interval decreases < 10 msec from baseline*
- QT interval decreases < 15 msec from baseline*
- QT interval decreases < 20 msec from baseline*

7.3 Labeling and Other Considerations

The sponsor did not address the clinical implications of a shortened QT interval within the NDA submission. Eisai's proposed labeling with regards to the QT interval was limited to a statement within the

_____ Clearly, such a statement is inadequate, and should rufinamide be approved a more appropriate statement describing the QT shortening effect observed in Study E2080-A001-002 should be included in labeling. In addition, I believe, at a minimum, a recommendation that patients with known short QT not be treated with rufinamide should also be included in labeling.

Quantifying the risk posed by shortening of the QT to rufinamide patients in labeling is difficult. As noted by Dr. Shari Targum of the FDA QT Review Team, there are no guidelines on the topic, and indeed relatively little information of any type.

Whether patients receiving rufinamide should have a screening ECG prior to treatment is a matter for discussion. In his review of the rufinamide safety profile, Dr. Raman noted that some patients with familial short QT may present with seizures. It is plausible that these patients will not respond to first-line anti-epileptic drugs, and if the etiology remains unrecognized these patients could be considered candidates for rufinamide treatment and be at increased risk for QT-related adverse events.

b(4)

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

/s/

M. Lisa Jones
1/8/2007 11:57:36 AM
MEDICAL OFFICER

Alice T. Hughes
1/9/2007 11:43:07 AM
MEDICAL OFFICER

MEMORANDUM

DATE: September 15, 2006

FROM: Division Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-911

SUBJECT: Recommendation for action on NDA 21-911, for the use of rufinamide as adjunctive treatment for partial seizures and the seizures of Lennox-Gastaut Syndrome (LGS)

NDA 21-911, for the use of rufinamide as adjunctive treatment for partial seizures and the seizures of Lennox-Gastaut Syndrome (LGS), was submitted by Eisai Medical Research, Inc., on 11/17/05. The application contains the results of four randomized controlled trials in patients with partial seizures receiving other antiepileptic drugs (Studies PT2, ET1, 21A, and 21P), two studies of rufinamide as monotherapy (Studies 16 and 38), one study as adjunctive treatment in patients with LGS (Study 22), and one study as adjunctive therapy for primary generalized tonic-clonic seizures in patients with multiple seizure types (Study 18). In addition, the application contains safety data, CMC data, and non-clinical studies. The application has been reviewed by Drs. Norman Hershkowitz, Ramesh Ramen, and Lisa Jones, medical officers in HFD-120, Dr. Shari Targum, cardiology consultant, Dr. Ohidul Siddiqui, statistician, Dr. Ed Fisher, pharmacologist, Dr. David Claffey, chemist, Dr. Patricia Beaston, Controlled Substances Staff, Dr. Roswitha Kelly, statistician for carcinogenicity, Drs. Vaneeta Tandon and Atul Bhattaram, Office of Clinical Pharmacology, and Dr. John Feeney, neurology drugs team leader. I will briefly review the relevant data, and present the division's recommendation for action on the application.

EFFECTIVENESS

As noted, the sponsor has submitted the results of 8 randomized controlled trials assessing the effectiveness of rufinamide against various seizure types. The sponsor has identified three of these studies as establishing substantial evidence of effectiveness: Studies ET1 and 21A as adjunctive therapy in the treatment of partial seizures, and Study 22, as adjunctive therapy in patients with LGS. Here, however, I will briefly present the results of all eight randomized trials.

Adjunctive Studies

Study PT2

This was a multi-center, double blind study in which patients with partial seizures receiving other AEDs were randomized to receive either placebo or increasing

doses of rufinamide over the 4 weeks of the double blind phase. Patients were initially treated with 200 mg BID for one week, then had their dose increased by 400 mg/day each week, until they reached the maximum dose of 800 mg BID (1600 mg/day) during the last week. No primary efficacy measure or statistical analysis was prospectively designated in the protocol.

A total of 50 patients were randomized in this trial; 25 to each treatment. The sponsor presented as primary an analysis of all patients except those who were seizure free during both the (retrospective) baseline and double-blind periods. A total of 44 patients were included in this analysis. According to this analysis, the median seizure frequency ratio was 0.59 for the rufinamide group and 1.52 for the placebo group ($p=0.04$). Dr. Siddiqui analyzed the standard intent-to-treat population with a Wilcoxon rank-sums test; this yielded a p-value for the between-treatment contrast of 0.071 (median seizure frequency of 5.19 and 3.11 for the placebo and rufinamide groups, respectively). Analysis of the percentage of patients with at least a 50% reduction of seizures compared to baseline, the between-treatment contrast yielded a p-value of 0.096 (36% vs 19%).

Study ET1

This was a multi-center, randomized, double blind study in which patients with partial seizures being treated with 1-3 AEDs were randomized to receive either placebo, or rufinamide 200, 400, 800, or 1600 mg/day, given as a BID dose. There was a 3 month prospective baseline, followed by a 3 month double blind phase. The primary efficacy variable was the seizure frequency/28 days, and the primary analysis was a linear trend for dose response. Secondary analyses included comparisons of the individual doses to placebo on seizure frequency/28 days.

The study was conducted at 67 centers in 12 countries (Argentina, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, and Sweden). A total of 554 patients were randomized, with about 85% of patients in each group completing the double-blind portion of the study.

The p-value for the linear dose response was $p=0.003$. In addition, the sponsor compared each dose to placebo, using a Wilcoxon rank-sum test to analyze the seizure frequency ratio. All p-values for the individual contrasts were < 0.027 , corresponding to a decrease in median seizure frequency compared to placebo of 11%, 16%, and 17%, for the 400, 800, and 1600 mg/day doses, respectively.

However, Dr. Siddiqui has concluded that the seizure frequency data were not linear, and that, therefore, the results of the linear trend test are difficult, at best, to interpret; although this test does establish an effect of rufinamide, it is difficult to assess the effects of the individual doses. Such an examination is critical for being able to draft labeling recommendations. The amended protocol called for several analyses of the effects of the individual doses. The first analysis listed

was a Poisson regression, the results of which the sponsor did not provide. The sponsor has presented the results of the Wilcoxon test described above. These results, taken at face value, support the conclusion that each dose is superior to placebo. However, the sponsor also presented the results of an ANCOVA. As Dr. Siddiqui notes, this analysis is also appropriate, given that the protocol specified primary outcome (linear dose response) was also analyzed with an ANCOVA, and the ANCOVA adjusts for country; it is also the more generally used analysis for this sort of data. The results of the ANCOVA, including country as a factor and log-transformed seizure frequency as a covariate, were as follows (the p-values obtained were not adjusted for multiple comparisons):

Dose	LS Mean sz frequency	% Reduction vs pbo	P-value
Pbo	2.63		
200 mg	2.67	-3.3	0.66
400 mg	2.52	11	0.11
800 mg	2.45	16.6	0.014
1600 mg	2.5	12.3	0.08

The sponsor also notes that the nominally significant result for the 800 mg dose group is related to the inclusion of an outlier. Removal of this outlier presumably results in the loss of nominal significance of this contrast.

Study 21A

This was a multi-center, double-blind comparison of rufinamide 3200 mg and placebo in adult patients with partial seizures receiving other AEDs. The trial consisted of a two month prospective baseline period and a 3 month double blind phase. The double blind phase consisted of a 2 week titration phase, and a 77 day maintenance phase. The primary outcome was the percent change in seizure frequency. The primary analysis was to be a Wilcoxon rank-sums test. Secondary variables included the proportion of patients experiencing at least 25% and 50% reduction in seizure frequency compared to baseline.

The study was performed in 48 centers in 13 countries, including Argentina, Chile, France, Germany, Great Britain, Italy, Russia, Slovakia, South Africa, Spain, Switzerland, United States (about 50% of the patients were in the US), and Uruguay. A total of 313 patients were enrolled; about 80% of patients in both groups completed the double blind phase.

Rufinamide patients experienced a 20.4% median reduction in seizure frequency compared to a 1.6% median increase in frequency in the placebo patients (p=0.016). The p-values for the between-treatment contrasts for the secondary

outcomes of proportion of patients with at least a 25% and 50% reduction in seizure frequency were 0.001 and 0.04, respectively. Patients in the US had treatment effects similar to that for other patients.

Although the Wilcoxon test was prospectively designated as primary, Dr. Siddiqui points out that the Wilcoxon test cannot distinguish between a true difference between medians and differences between the shapes of the distributions. In this case, the variances are different between the treatment groups, raising the possibility that the distributions have different shapes. In addition, as noted earlier, the usual analytic technique used for data of this sort is an ANCOVA, adjusting for country and baseline frequency. For this reason, Dr. Siddiqui also performed an ANCOVA on 28 day seizure frequency with log-transformed data with country in the model; the resultant p-value for the drug-placebo contrast was 0.09.

Study 22

This was a multi-center, double blind trial in patients with LGS on other AEDs in which patients were randomized to receive either rufinamide 45 mg/kg/day or placebo. The trial consisted of a 1 month prospective baseline phase and a 3 month double blind phase. Patients were titrated to their final dose of rufinamide over the first 1-2 weeks of the double-blind phase.

The primary outcomes were:

- 1) Percent change in 28 day total seizure frequency
- 2) Percent change in the sum of tonic/atonic 28 day seizure frequency
- 3) Seizure severity rating on a Global Evaluation

Secondary outcomes included the proportion of patients experiencing at least a 50% reduction in seizure frequency, the percent change in seizure frequency of seizure types other than tonic/atonic, and the composite score for the Global Evaluation.

A total of 138 patients were randomized (74 rufinamide, 64 placebo) in 36 centers in Belgium, Brazil, Germany, Hungary, Italy, Norway, Poland, Spain, and the United States (about 46% of patients were in the US).

The primary analysis was to be the Wilcoxon rank sums test according to the following algorithm: the study would be considered successful if Variable 1 was significant at $p=0.025$, or if Variables 2 and 3 were both significant at 0.025 each.

A total of about 85-90% of patients completed the double blind phase. The mean age was 14 years, with about 70% of the patients below the age of 17.

Variable 1

Rufinamide patients experienced a 32.7% median reduction in total seizure frequency, compared to an 11.7% median reduction in placebo patients (p=0.0015).

Variable 2

Rufinamide patients had a median percent reduction in tonic/atonic seizure frequency of 42.5%, compared to a 1.4% median increase in the placebo patients (p<0.0001).

Variable 3

Seizure severity improved in 53.4% of rufinamide patients compared to 30.6% of the placebo patients (p=0.004).

Secondary outcomes

A total of 42.5% of rufinamide patients experienced at least a 50% reduction in tonic/atonic seizure frequency compared to 16.7% of the placebo patients (p=0.002).

The between treatment contrasts on median reduction of atonic seizures and combined absence and atypical absence seizures reached nominal significance (p=0.013 and 0.02, respectively), but did not reach significance for tonic seizures (p=0.08).

There was no significant difference between treatments on the composite Global Evaluation (p=0.35).

Study 21P

This was similar in design to Study 21A but was performed in pediatric patients ages 4-16 years old (it began as a subset of Study 21A). A total of 269 patients were randomized to either rufinamide 45 mg/kg/day or placebo. As for Study 21A, the primary outcome was the percent change in 28 day seizure frequency, analyzed with the Wilcoxon rank-sums test. As noted by Dr. Feeney, the outcome numerically favored the placebo patients, with a median percent change from baseline in partial seizure frequency of -7% in the rufinamide patients and -13% in the placebo patients (p=0.62).

Study 18

This was a randomized, double blind multi-center study in which patients with primary generalized tonic-clonic (PGTC) seizures (patients were permitted in the study who also had other seizure types as well) were randomized to receive

either rufinamide 800 mg/day or placebo. In this study, patients were enrolled in a 56 day baseline period, followed by a 140 day double blind treatment phase.

The primary outcome was the median percent change from baseline in PGTC seizures. A total of 155 patients were randomized (80 rufinamide, 75 placebo). The median percent change in PGTC seizure frequency in the rufinamide group was -36%, compared to -26% in the placebo group ($p=0.63$).

Monotherapy Studies

Study 16

This was a multi-center study in which patients on 1-2 AEDs were randomized to receive either 300 mg/day or 3200 mg/day of rufinamide given in a TID regimen. After randomization, patients had their rufinamide dose increased simultaneously while having their AEDs withdrawn over 6 weeks, so that for the remainder of the study (about another 10 weeks) they were treated with rufinamide monotherapy. Patients were treated until they completed the study, or met one of four exit criteria: 1) a doubling of their monthly baseline seizure frequency; 2) a doubling of their greatest consecutive 2 day seizure frequency; 3) a single generalized seizure (if they had not experienced such a seizure in the last 6 months; or 4) a clinically significant worsening of their seizures (e.g., increased duration or frequency) that required intervention. The primary outcome measure was the proportion of patients meeting exit criteria

A total of 44/66 high dose patients met exit criteria, compared to 50/69 low dose patients ($p=0.44$).

Study 38

In this study, patients had all of their previous AEDs withdrawn in preparation for epilepsy monitoring as a prelude to potential epilepsy surgery. Patients were treated for 10 days or until they met one of the following exit criteria: 1) 4 partial seizures; 2) 2 generalized seizures if they had none in the prior year; 3) serial seizures requiring intervention; or 4) status epilepticus. The primary analysis was a comparison of the time to meeting exit criteria.

A total of 102 patients were randomized to either rufinamide 3200 mg/day or placebo. The median time to failure in the rufinamide group was 4.8 days, compared to 2.4 days for the placebo patients ($p=0.05$). As Dr. Feeney notes, the proportion of patients who met exit criteria on a worst-case analysis (and presented by the sponsor as primary in their study report) were essentially the same in the two treatment groups (67% in the rufinamide, and 69% in the placebo groups).

Non-clinical

The sponsor has submitted the results of 2 lifetime in vivo carcinogenicity studies; one in mice, one in rat.

The mouse study revealed a statistically significant increased trend in the incidence of benign osteomas in this study, largely accounted for by the high dose animals (400 mg/kg/day): 3/60 males and 6/60 females. Although the sponsor proposed a mechanism for these tumors, the support for this is meager. No tumors were seen in the control group, although the sponsor states that in other control groups, run concurrently with this study, 1-2 osteomas were seen. Also, there was an increased trend for the occurrence of combined liver hepatocellular adenomas/carcinomas, due largely to an increase in adenomas.

No tumors were seen in the rat study, but this study was considered inadequate (a conclusion also reached by the CAC) because of excessive decrease in body weight in the high dose (200 mg/kg/day) males (about 30% less than the control males) and in the mid (60 mg/kg/day) and high dose females (about 25% and 37% lower than the controls, respectively). It is possible that this decrease in body weight may in part be due to a lack of palatability of the drug, given that this study was done with dietary drug administration, as opposed to with gavage dosing. There is evidence that there is also some loss of body weight with gavage dosing, but it is possible that increased exposure can still be achieved with gavage dosing, and there is reason to believe that the safety margins are inadequate at the doses that were not associated with excessive body weight loss.

In addition, several nonclinical studies have been deemed unacceptable by the pharmacology team. Specifically, the in vivo micronucleus assay in the rat, the rat fertility study, the rabbit embryofetal study, and the juvenile dog study are all deficient and need to be repeated. The specific deficiencies in each study are described in the letter to the sponsor.

Finally, Drs. Fisher and Freed note a finding of decreased brain weights in the juvenile rat study, and they request additional investigation of this finding

SAFETY

Data from a total of 1978 patients with epilepsy, in both double blind and open label studies, were included in the sponsor's submission. A total of 1240 patients were enrolled in double blind trials; 720 adults were enrolled in trials of patients with partial seizures in which rufinamide was given as adjunctive therapy, and

208 adults were enrolled in trials in which rufinamide was given as monotherapy. A total of 212 pediatric patients were enrolled in double blind trials, 74 of whom were enrolled in a trial of LGS. The NDA contains additional safety data on 60 patients with diabetic neuropathy and 326 healthy volunteers.

A total of 1239 patients were treated for at least 6 months, and 922 patients were treated for at least one year. A total of 445 patients were treated for at least 2 years. A total of 731 received a median daily dose of at least 1600 mg for at least 6 months. An additional 467 patients received a median daily dose of between 400-1600 mg for at least 6 months. A total of 595 patients received a median daily dose of at least 1600 mg for 2 years.

A total of 965 adults received rufinamide for at least 6 months; 698 adults received treatment for at least one year. A total of 280 pediatric patients received treatment for at least 6 months, with 224 receiving treatment for at least one year.

Deaths

A total of 2/1240 (0.2%) patients receiving rufinamide died in controlled trials (both adults), compared to 4/635 (0.4%) of placebo patients. An additional 16 patients died during open-label studies or within 30 days of discontinuing treatment.

One of the patients who died in the double blind studies was a 26 year old man who received rufinamide for 69 days. This patient fever, abdominal pain and vomiting after recovery from a series of seizures. At laparotomy, hemorrhagic pancreatitis and peritonitis were noted. Over the next several days, the patient's condition worsened, with persistent fever despite antibiotic therapy, and ultimately he died. An autopsy revealed cerebral edema and herniation.

The other death was in a 40 year old man who suffered a head injury after a fall; it is not clear if the fall was preceded by dizziness.

Of the remaining deaths, a total of 9 (the sponsor considered there to be 8 cases, but Dr. Raman suggests that there could be an additional case) could have been considered sudden, although there is evidence that in 6, the deaths closely followed seizure activity, resulting in 3 sudden unexplained deaths (SUDs). The rate of SUDs in this development program (including all 9 deaths) was 0.0035/patient year, well within the estimates for the recently approved AEDs.

No other death appeared to be reasonably related to treatment with rufinamide.

Discontinuations

A total of 19% of patients discontinued treatment with rufinamide in controlled trials compared to 14% in the placebo group. The corresponding numbers are 25% and 19%, respectively, in adult partial seizure studies, and 14% and 9%, respectively, in pediatric controlled trials. In adult partial seizure studies, 10% of patients discontinued due to adverse events, compared to 6% in the placebo group. In pediatric studies, the corresponding numbers are 7% and 2%, respectively. About 10% of patients discontinued treatment in open-label experience.

In controlled trials in adults, the following table presents the most common adverse events (incidence of at least 1%) responsible for treatment discontinuation:

Event	Rufinamide (N=720)	Placebo (N=290)
Dizziness	19 (2.6%)	3 (1%)
Headache	13 (1.8%)	3 (1%)
Diplopia	11 (1.5%)	1 (0.3%)
Nausea	10 (1.4%)	0
Ataxia	8 (1.1%)	0
Convulsion	7 (1%)	3 (1%)
Vertigo	7 (1%)	0

Dizziness, headache, and diplopia appear to be dose related (see Sponsor's table 7.4-5, reproduced in Dr. Raman's review, Appendix Table 8), although this table pools dose groups among studies.

The following table presents the analogous data for pediatric controlled trials:

Event	Rufinamide (N=212)	Placebo (N=197)
Fatigue	3 (1.4%)	0
Convulsion	3 (1.4%)	1 (0.5%)
Rash	3 (1.4%)	1 (0.5%)
Vomiting	2 (0.9%)	0

Serious Adverse Events

A total of 7% of rufinamide treated patients in adult controlled trials experienced a serious adverse event, compared to 3.4% of placebo patients. In pediatric studies, 7.5% of rufinamide patients discontinued due to an AE, compared to 5.6% of placebo patients.

The following table displays the incidence of the most common serious adverse events (at least 0.5%) in adult controlled trials:

Event	Rufinamide (N=720)	Placebo (N=290)
Diplopia	6 (0.8%)	0
Fatigue	5 (0.7%)	0
Partial seizures With gen'l	4 (0.6%)	0

The following table displays the analogous data for pediatric controlled trials:

Event	Rufinamide (N=212)	Placebo (N=197)
Vomiting	2 (0.9%)	0
Convulsion	2 (0.9%)	0
Status epilepticus	2 (0.9%)	0

Two serious adverse events are worthy of description.

A 28 year old man experienced a prolonged secondarily generalized seizure after 10 days of treatment with rufinamide. He had a post-ictal muscle entrapment, hemiparesis, and dysphasia. Upon hospitalization, his SGOT was >40 times the ULN, SGPT was >20 times the ULN, and his bilirubin was 2 times the ULN. The drug was discontinued 2 days after the seizure, and laboratory values were normal 2 weeks later.

Another adult patient (previously described) had an episode of complex-partial status epilepticus, followed the next day by abdominal pain. A laparotomy revealed hemorrhagic pancreatitis and peritonitis. Over the next 2 days, the patient became stuporous, and he died. An autopsy revealed cerebral edema and herniation.

Common Adverse Events

In adult controlled trials the following AEs in at least 2% of rufinamide patients and with an appreciably greater incidence than placebo were seen:

Event	Rufinamide	Placebo
--------------	-------------------	----------------

	(N=720)	(N=290)
Dizziness	19.4%	11.4%
Fatigue	17.6%	11.7%
Somnolence	10.4%	7.2%
Diplopia	9.9%	3.1%
Blurred Vision	6.0%	3.1%
Anxiety	3.6%	1.7%
Ataxia	3.6%	0.3%
Vertigo	3.1%	0.7%
Anorexia	2.2%	0.7%

Of the events listed above, headache, dizziness, and somnolence appeared to be dose related. Although not listed in the table above, Nausea appeared dose related (by examination of pooled data), with an incidence of 23% in patients whose median daily dose was between 2400-3200 mg.

The analogous table for pediatric patients in the LGS study follows, including those events that occurred in at least 3 rufinamide patients:

Event	Rufinamide (N=74)	Placebo (N=64)
Somnolence	24.3%	12.5%
Vomiting	21.6%	6.3%
Decreased appetite	9.5%	4.7%
Nasopharyngitis	9.5%	3.1%
Headache	6.8%	4.7%
Rash	6.8%	1.6%
Ataxia	5.4%	0
Convulsion	4.1%	1.6%
Ear infection	4.1%	1.6%
Epistaxis	4.1%	0
Nystagmus	4.1%	0
Status epilepticus	4.1%	0

There were no multiple fixed dose studies in pediatric patients; for this reason, it is difficult to assess whether or not any specific AE was dose related.

Labs and Vital Signs

Although there were minor changes in laboratory values and vital signs, there were no systematic clinically meaningful changes in either laboratory values or vital signs, with the possible exception in the number of patients with clinically

notable decreases in WBC in adult controlled trials (5.2% vs 2.15 in drug and placebo patients, respectively). However, there were a number of patients whose last laboratory values (typically in open-label exposure) met criteria for "clinically notable changes". The sponsor should obtain follow-up information in these patients, if possible.

Laboratory abnormalities were associated with several serious adverse events (1 leucopenia, 2 neutropenia, and one each of anemia, hemolytic anemia, and leukocytosis).

One case each of anemia, disseminated intravascular coagulation, hemolytic anemia, leucopenia, and neutropenia led to discontinuations. It was not obvious in all cases that rufinamide was the cause, and patients in whom the drug was discontinued recovered off drug.

A 6 year old boy was noted to have DIC after having been found in the bathtub unconscious one month after starting rufinamide. He had been intubated after this event. The drug was discontinued (as was his concomitant valproate), and he recovered in about one week.

Three patients had serious adverse events associated with hyponatremia and one with hypochloremia.

One patient was a 39 year old woman with a history of hyponatremia was receiving carbamazepine and lamotrigine was admitted to the hospital with chest pain 6 days after beginning treatment with rufinamide. An MI was ruled out, and 6 weeks later, a day after discontinuing rufinamide, she was hospitalized for apathy and constipation. She had decreased sodium (129 mEq/l), chloride (94 mEq/l) and mild anemia. She improved after treatment.

Another patient, a 54 year old woman, experienced hyponatremia on Day 1111 of rufinamide treatment (she was receiving multiple other medications). The hyponatremia appeared to resolve while continuing treatment with rufinamide.

A third patient had several episodes of hyponatremia while receiving rufinamide that each spontaneously resolved while on continued treatment.

Other Potential Adverse Events of Interest

Rash

No cases of SJS, TEN, or EM occurred in the development program. There was no difference in the incidence of rash in adult controlled trials, but in pediatric controlled trials, 5.2% of rufinamide and 2% of placebo patients had a rash. These rashes typically occurred during the first two weeks of treatment.

A total of 3 patients had a serious hypersensitivity reaction and 4 patients discontinued secondary to hypersensitivity reaction. All of these events occurred in children within 4 weeks of initiation of treatment with rufinamide.

One patient was a 12 year old boy who developed mild elevation of liver enzymes (PT and OT) and rash about 2 weeks after starting rufinamide and 8 weeks after starting lamotrigine. He recovered after both rufinamide and lamotrigine were discontinued.

An 8 year old girl developed facial swelling, rash, cervical lymphadenopathy, decreased appetite, and lethargy. She also had bilateral otitis media and fever (cefuroxime axetil was started for the otitis 6 days before the appearance of the rash). Within two weeks of discontinuation of the rufinamide, she recovered.

A 12 year old girl had a complicated course in which she developed fever, facial, neck, and tongue edema with markedly elevated temperature and stupor, and "abundant popular rash" on Day 39 of treatment with rufinamide. She also developed markedly elevated SGPT, SGOT, LDH, and bilirubin on Day 59. Drug was discontinued on day 60. About 10 days later the patient had recovered.

An 8 year old boy developed a fever and rash on Day 11 of treatment. This was accompanied by elevated LDH, SGPT, and SGOT. He recovered 3 days after discontinuation of the rufinamide.

A 7 year old boy developed a fever and rash 12-15 days after treatment initiation. He also developed "bilateral conjunctival discoloration" and hematuria. He was recovering by 10 days.

Cognitive and Psychiatric Adverse Events

The following cognitive and psychiatric adverse events were seen in greater than 1% of rufinamide controlled trials and at a greater incidence than in the placebo group:

Event	Rufinamide (N=1240)	Placebo (N=635)
Somnolence	11.8%	9.1%
Anxiety	2.7%	1.4%
Disturbance in attention	1.7%	1.4%
Nervousness	1.5%	0.8%
Depression	1.5%	0.9%

QT

The sponsor has performed a thorough QT study. This was a double blind placebo and positive (moxifloxacin) controlled parallel group study in healthy volunteers. A total of 117 subjects were enrolled, 100 completed the study, and 88 completed the study per protocol.

In this study, patients received increasing doses of rufinamide over 17 days in the following order: 800, 1600, 2400, 3200, 4800, and 7200 mg/day. On Day 18, a single dose of 3200 mg was given, followed by a washout on Day 19, and then placebo on Day 20. Placebo patients received placebo throughout, and then a single 400 mg dose of moxifloxacin on Day 20. The mean change in QT on moxifloxacin was calculated (Day 20-Day 19) and following placebo (Day 9 minus Day -1) and then compared. The mean change in QTc on moxifloxacin was +12.5 msec, with the difference always at least +10 msec from hours 2-8 after dosing, consistent with the expected Tmax for moxifloxacin, documenting the study's ability to detect the expected moxifloxacin increase (assay sensitivity). Dr. Jones describes the details of the type and frequency of EKG recordings in this study, which were considered acceptable.

As described by Dr. Jones, in this study, significant decreases in QTc were seen after dosing, with the greatest decreases seen 4-8 hours after dosing. The maximum observed mean decreases at the following doses were seen:

Dose	Maximum Observed Mean Change in QTc
1200 mg BID	-16.7 msec
1600 mg BID	-16.1 msec
2400 mg BID	-20.2 msec
3600 mg BID	-20.2 msec

Although the sponsor presented these changes, they did not present the range of absolute QT durations, nor did they present any categorical outlier analyses.

Dr. Jones also evaluated the safety database for potentially clinically important cardiac adverse events.

There were a total of 8 sudden unexplained deaths in rufinamide treated patients (0.4%), compared to four (0.6%) in placebo patients. The rate of sudden unexplained deaths in this development program was consistent with that seen in other AED development programs. There were few important clinical cardiac adverse events (see, for example, Dr. Jones's Table 8, Discontinuations due to ECG or Cardiovascular Adverse Events, page 25 of her review).

CMC

Dr. Claffey recommends that the application be approved.

DMETS

b(4)

The sponsor has proposed the tradename _____ (a previously proposed tradename Inuvelon had been rejected). DMETS has recommended that _____ be rejected as well, because of the potential for medication errors involving _____.

Clinical Pharmacology

The Clinical Pharmacology review describes a positive concentration-effect response for both Studies ET1 and 22.

COMMENTS

The sponsor has submitted the results of seven randomized controlled trials (excluding Study PT2) that by design appeared adequate and well-controlled, although they have presented only three (ET1, 21A, and 22) as establishing substantial evidence of effectiveness.

Study ET1 examined the effects of several doses of rufinamide as adjunctive therapy in patients with partial seizures. Although the primary outcome analysis (the linear trend test) was positive, thereby establishing a drug effect, it is difficult to determine the effects of the individual doses. The amended protocol stated that the effects of the individual doses would be analyzed with a Poisson regression; the results of this analysis were not presented. The sponsor presented the result of a Wilcoxon test for the individual doses (also described in the amended statistical plan), and these results appear to support a conclusion that the 400, 800, and 1600 mg/day doses are effective. However, because the primary analysis of this study was performed using an ANCOVA, it is also appropriate for a similar parametric approach to be applied to the analyses of the individual doses (indeed, the sponsor performed such an analysis, but did not present it as primary). In addition, the ANCOVA can adjust for country, and this is the typical analysis applied to data of this sort. When such an analysis is performed on the (log transformed) percent reduction in 28 day seizure frequency, only the 800 mg dose appears nominally significantly superior to placebo, a result that is difficult to interpret, and speaks to the lack of robustness of the ostensibly strongly positive result from the Wilcoxon test.

Study 21A appears to be a study that demonstrates a statistically significant difference of rufinamide 3200 mg/day compared to placebo on the protocol-specified Wilcoxon rank sums test in a similar population of patients as those

enrolled in Study ET1. However, the a statistically significant finding on the Wilcoxon test cannot distinguish between a true difference in medians and a difference in the shape of the distributions. In this case, because the variances are different between the treatments, a positive finding is difficult to interpret. For this reason, and for the reasons described to justify the ANCOVA above, Dr. Siddiqui performed an ANCOVA on log transformed 28 day seizure frequency, with baseline seizure frequency and country as covariates. The result of this test yielded a p-value for the between-treatment contrast of 0.09, again, suggesting that the result of this study is not robust.

Study 22, a study of adjunctive rufinamide in patients with LGS, is a clearly positive study.

The only other study that could be considered to have documented a statistically significant difference between rufinamide and placebo is Study 38, the pre-surgical study, in which a significant difference between treatments of about 2 days was seen on the primary outcome of time to meeting exit criteria. However, this finding is undermined by the essential identity between treatments in the proportion of patients who met exit criteria in the analysis presented by the sponsor as primary (apparently a worst case analysis). Although this study design is not routinely used, in those previous cases in which known effective drugs have been studied in this paradigm, this latter measure routinely demonstrates a clear separation between treatments. Again, the array of findings in this study suggests a less than robust treatment effect.

Against these four studies, only one of which is clearly positive and unambiguously identifies an effective dose, the sponsor has presented the results of at least three other studies that by design appear capable of demonstrating an effect of the drug, but that are negative. Study 21P, a study of rufinamide as adjunctive therapy in pediatric patients, presents the disturbing result of numerical superiority of the placebo group, with no obvious explanation for this outcome. Study 18, a study of the effects of rufinamide 800 mg/day (a dose that the sponsor asserts is effective, based on their analysis of Study ET1) versus placebo as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures, is clearly negative, and Study 16, a study comparing rufinamide 300 mg to rufinamide 3200 mg as monotherapy, failed to demonstrate a difference between the treatments. Although it is theoretically possible that both of these doses are equi-effective as monotherapy, the study obviously does not establish this conclusion. The sponsor has provided no independent replication of a positive finding for any specific dose.

Beyond the fact that two of the studies the sponsor presents as positive do not appear to be unambiguously so, the treatment effect sizes seen in these ostensibly positive studies are quite small in comparison to those seen in studies of recently approved anti-seizure medications, where treatment effects on the order of approximately 30% improvement compared to placebo are routinely

seen. In Study ET1, the treatment differences in 28 day seizure frequency ratio vary from 11-17% and on mean percent reduction in seizure frequency from 11-16%. Similarly, the treatment effect in Study 21A is about 20%.

Although the data presented strongly suggest that rufinamide is active as an anticonvulsant (the linear trend test in Study ET1 and Study 22 alone suggest so), it is difficult to understand what dose(s) is/are effective. Perhaps 800 mg is seen to be effective in Study ET1, but this dose shows no effect in Study 18. Perhaps Study 21A suggests that a dose of 3200 mg/day is effective, but this finding is not replicated in Study 21P. If both 3200 and 300 mg are effective (one theoretical interpretation of Study 16), it is unclear why a dose of 3200 mg should be recommended, as Study 21A seems to suggest. The results taken in toto do not provide a clear picture of which dose(s) should be recommended. Further, as discussed above, the treatment effect in those studies that did identify an effect, is quite small compared to recently approved AEDs.

I do acknowledge that Study 22, in patients with LGS, is clearly positive. One could argue, therefore, that rufinamide could be approved for this indication. Although the sponsor has presented only one study in this indication, it could be argued that this study, taken in conjunction with the other data in partial seizures, could serve as substantial evidence of effectiveness for the treatment of LGS.

In previous cases in which we have granted an indication for a specific seizure type on the basis of only a single study in that seizure type, we have done so only when there exists substantial evidence of effectiveness for a different seizure type (in the typical case, this has meant at least two positive trials in patients with partial seizures). Although I acknowledge that the data in partial seizures for rufinamide are certainly suggestive of an effect, as I have described above, I do not believe that substantial evidence of rufinamide's effectiveness has been submitted. Even if one were to argue that only a single study in partial seizures and a single study in LGS should support approval for LGS (logically, if this conclusion could be drawn,

b(4)

_____ For these reasons, then, I do not believe that rufinamide should be approved at this time for any indication.

There are no safety issues that would preclude approval, although I do not the occurrence of several cases of hypersensitivity reactions, and a marked effect of shortening of the QT interval, a finding that at the moment is difficult to interpret. Although Dr. Raman suggests that there are several cases of malignant hyperthermia, I am not convinced.

As noted above, there are numerous nonclinical deficiencies that need to be communicated to the sponsor. The timing of these studies (i.e., prior to, or after approval), is an open question.

There are also additional clinical issues that the sponsor should be asked to address. These include obtaining follow-up of those patients whose last laboratory values reached clinically notable criteria, providing an analysis of the increased incidence of status epilepticus in patients on rufinamide compared to placebo, a revised analysis of patients with simultaneous elevated TSH and decreased thyroxine levels (there is some hint in the data that there may be some patients with what appears to be primary hypothyroidism), providing an analysis of effectiveness by specific concomitant AEDs, and further analysis of the QT data. Finally, the sponsor will be asked to provide a new proposed tradename.

For the reasons cited above, we recommend that the sponsor be issued an Approvable letter, with a request for an additional study in partial seizures that examines the appropriate dose range. Because we have fundamental questions about the effectiveness of rufinamide, especially with regard to appropriate dosing recommendations, we are not including draft labeling at this time.

Russell Katz, M.D.

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

/s/

Russell Katz
9/15/2006 05:53:45 PM
MEDICAL OFFICER

**Interdisciplinary Review Team for QT Studies
Response to a Request for Consultation**

NDA	#21911
Brand Name	Inovelon®
Generic Name	Rufinamide
Sponsor	Eisai Medical Research
Indication	Epilepsy
Dosage Form	Oral
Therapeutic Dose	800 to 3200 mg/day (adults); 10-45 mg/kg/day (children) -
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	
Application Submission Date	September 8, 2005
Review Classification	NDA Review
Date Consult Received	August 16, 2006
Date Consult Due	August 31, 2006
Clinical Division	Division of Neurology Products (Safety Team)
PDUFA Date	September 17, 2006

1.0 PURPOSE OF THE CONSULTATION: The Neurology Division is currently reviewing the NDA for the anti-epileptic drug rufinamide, a triazole derivative (NDA due date: 9/17/06). The safety team within the Neurology Division was asked to review the ECG-related safety data within the rufinamide development program.

Rufinamide appears to shorten the QT interval (from -2.1 to -21.3 msec, depending on the dose and heart rate correction method employed).

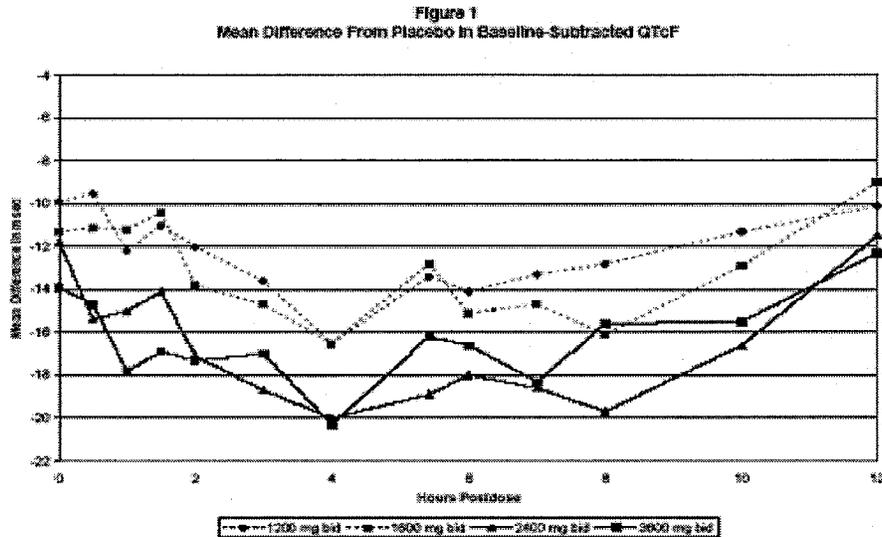
At this point, the safety team is requesting our assistance in understanding the clinical consequences of the shortening of the QT interval seen with rufinamide treatment.

2.0 SUMMARY OF FINDINGS

The NDA database included a thorough QT study (E2080-A001-002) which has been reviewed by the safety and clinical pharmacology reviewers.

In brief, the QT study was a randomized, double-blind, placebo-controlled parallel-group study which included step-wise increasing doses of rufinamide and a blinded single-dose of over-encapsulated moxifloxacin (400 mg) for assay sensitivity. The study enrolled 117 healthy males and females. ECGs were collected via 12-lead Holter monitoring and utilized a time-matched baseline on the day prior to dosing. The primary endpoint was the change from time-matched baseline in QTcF.

FDA Figure 1. Mean Difference from Placebo in Baseline-Subtracted QTcF (Adapted from Sponsor Figure 1, Cardiocore Statistical Report, pg.9)



(taken from Safety review, NDA 21911)

Table 1. Maximum Decrease in QTcF relative to placebo by Dose (from Sponsor Table on page 8 of Cardiocore Statistical Report).

The sponsor reported that the decrease in QTc consistently peaked at 4 hours, irrespective of dose.

Maximum Decrease in QTcF Relative to Placebo Following Each Dose		
Dose	Maximum Observed Mean (Minimum) Difference From Placebo (msec)	95% Upper Confidence Bound (msec) on Maximum Difference
1200 mg bid	-16.66 (-9.57)	-13.0
1600 mg bid	-16.11 (-9.12)	-12.7
2400 mg bid	-20.17 (-11.45)	-16.2
3600 mg bid	-20.18 (-12.88) ¹	-16.1

¹Through 12 hours post dose

(taken from Safety review, NDA 21911)

Assay sensitivity for moxifloxacin was demonstrated in this study (though QTcF decreases in placebo are noted also):

Table 2. Mean Change from Time-matched Baseline in QTcF Day 20 Moxifloxacin vs. Day 9 Placebo among subjects originally randomized to placebo and received moxifloxacin on Day 20. (Source: Sponsor)

Hours Postdose	Moxifloxacin 400 mg (N=45)	Placebo (N=45)	Difference	95% Lower Confidence Bound
0	-1.19	-3.49	2.30	-1.25
0.5	2.99	-11.15	14.14	10.39
1	1.24	-8.38	9.62	5.22
1.5	-0.04	-10.62	10.58	7.14
2	4.48	-9.59	14.07	10.44
3	9.06	-9.63	18.69	14.88
4	9.04	-5.40	14.44	10.95
5.417	8.78	-7.69	16.47	13.33
6	8.59	-7.84	16.43	12.80
7	7.11	-6.39	13.51	10.03
8	8.65	-5.13	13.77	10.16
10	6.00	-5.24	11.24	7.08
12	2.63	-3.30	5.93	1.73

2.0 CLINICAL SIGNIFICANCE OF QT SHORTENING:

We are concerned about QT shortening. These concerns are based on the following:

1. The Short QT Syndrome: This genetic condition, first described in 2000, is characterized by a shortened QT interval and episodes of syncope, paroxysmal atrial fibrillation or life-threatening cardiac arrhythmias/family history of sudden death. To date, three genetic mutations encoding potassium ion channels have been identified.
2. The theoretic concern, promulgated by Dr. Hondeghem (1) that electrophysiologic effects such as triangulation, reverse use dependence, instability and dispersion (TRIaD) with QT shortening predisposes patients toward ventricular fibrillation.

However, we have little experience with drug-induced QT shortening and we have no algorithm for risk assessment.

We can suggest the following:

1. We note that you have already reviewed the cases of sudden death in the NDA database. Given the characteristics of Short QT syndrome, you might consider looking to see if there are imbalances in cases of atrial fibrillation.
2. If this drug were to be approved, you might consider a post-marketing surveillance program.
3. Please have the sponsor submit the ECGs from study E2080-A001-002 to the ECG warehouse. Please contact us if the sponsor needs more information on how to submit the ECGs.

References:

1. Hondeghem LM. Thorough QT/QTc Not So Thorough: Removes Torsadogenic Predictors from the T-Wave, Incriminates Safe Drugs, and Misses Profibrillatory Drugs. J of Cardiovascular Electrophysiology 2006; 17 (3): 337- 340.

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

/s/

Shari Targum
8/31/2006 06:06:33 PM
MEDICAL OFFICER

Norman Stockbridge
9/1/2006 07:22:17 AM
MEDICAL OFFICER