

Table 6.1.4.3.5 Summary of seizure frequency ratio relative to baseline by number and type of AEDs (Intent-to-treat patients) in Study AE/PT2

	Rufinamide			Placebo			
	N	Median	Range	N	Median	Range	p-Value*
1 AED							
Seizure frequency ratio (i)	10	0.51	(0.0, 10.1)	11	1.59	(0.34, 20.0)	0.0973
Seizure frequency ratio (ii)	10	0.51	(0.0, 10.1)	9	0.96	(0.34, 6.7)	0.2693
Seizure frequency ratio (iii)	11	0.52	(0.0, 10.1)	14	1.00	(0.34, 20.0)	0.1382
2 AEDs							
Seizure frequency ratio (i)	12	0.80	(0.0, 3.3)	10	1.30	(0.27, 4.8)	0.1871
Seizure frequency ratio (ii)	12	0.80	(0.0, 3.3)	10	1.30	(0.27, 4.8)	0.1871
Seizure frequency ratio (iii)	12	0.80	(0.0, 3.3)	11	1.08	(0.27, 4.8)	0.2182
Carbamazepine							
Seizure frequency ratio (i)	14	0.80	(0.0, 10.1)	16	1.55	(0.27, 20.0)	0.0882
Seizure frequency ratio (ii)	14	0.80	(0.0, 10.1)	14	1.30	(0.27, 6.7)	0.2147
Seizure frequency ratio (iii)	16	1.0	(0.0, 10.1)	18	1.30	(0.27, 20.0)	0.1202
Phenytoin							
Seizure frequency ratio (i)	7	0.52	(0.27, 2.02)	7	0.89	(0.27, 1.52)	0.6547
Seizure frequency ratio (ii)	7	0.52	(0.27, 2.02)	7	0.89	(0.27, 1.52)	0.6547
Seizure frequency ratio (iii)	7	0.52	(0.27, 2.02)	9	0.89	(0.27, 1.52)	0.7911
Valproate							
Seizure frequency ratio (i)	8	1.01	(0.0, 2.02)	6	2.4	(0.80, 5.06)	0.0926
Seizure frequency ratio (ii)	8	1.01	(0.0, 2.02)	6	2.4	(0.80, 5.06)	0.0926
Seizure frequency ratio (iii)	9	1.01	(0.0, 2.02)	7	1.87	(0.80, 5.06)	0.1679

Data set (i) consists of all patients who had seizures in any phase of the trial; all patients who were seizure free during both the Baseline and Double-blind Treatment Phases are excluded.

Data set (ii) Consists of all patients who had at least one seizure during the Baseline Phase; all patients who were seizure free during the Baseline Phase are excluded.

Data set (iii) Includes all randomized patients who received double-blind trial medication and provided seizure information during the Baseline and Double-blind Treatment Phases.

* P-value based on Wilcoxon Rank-Sum Test.

Table 10.6-5

10.5 Drugs associated with sodium channel blocking and QT shortening

FDA REQUEST TO SPONSOR ON CONCOMITANT MEDICATIONS IN RUFINAMIDE-TREATED PATIENTS

NON-RUFINAMIDE DRUGS THOUGHT TO SHORTEN THE QT INTERVAL:

1. Digoxin
2. Lamictal
3. Ranolazine (Ranexa ®) – Treatment for familial Long QT syndrome
4. Mexiletine
5. Magnesium

SODIUM CHANNEL BLOCKING DRUGS:

1. Procainamide
2. Disopyramide
3. Tocainide
4. Mexiletine
5. Phenytoin
6. Flecainide
7. Propafenone
8. Moricizine
9. Lidocaine
10. Propofol
11. Carbamazepine
12. Amitriptyline
13. Imipramine
14. Haloperidol
15. Chlorpromazine
16. Digoxin
17. Metoclopramide
18. Isoproterenol

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REFERENCES

1. Verrotti A, Scardapane A, et.al. Antiepileptic Drugs and Thyroid Function. Journal of Pediatric Endocrinology & Metabolism, 21, 401-408 (2008)

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Norman Hershkowitz
11/14/2008 05:13:49 PM
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**NDA SAFETY REVIEW:
SHORTENED QT INTERVAL WITHIN THE
RUFINAMIDE DEVELOPMENT PROGRAM -
ADDITIONAL DATA FOLLOWING THE APPROVABLE
ACTION LETTER OF SEPTEMBER 2006**

Application Type NDA
Submission Number 021-911

Reviewer Name M. Lisa Jones, MD, MPH
Review Completion Date August 7, 2008

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 Variable
Indication Adjunctive Therapy for Partial
 Seizures, Lennox-Gastaut
 Syndrome _____

Intended Population Patients with Epilepsy

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1. INTRODUCTION

1.1 Documents Used in this Review

1.1.1 FDA Documents

1. Rufinamide (021-911). NDA Safety Review: Shortened QT Interval within the Rufinamide Development Program. Prepared by M. Lisa Jones MD, MPH. Dated August 11, 2006.
2. Rufinamide (021-911). Approvable Action Letter. Prepared by the Division of Neurology Products (DNP). Dated September 16, 2006.
3. Rufinamide (021-911). Interdisciplinary Review Team (IRT) for QT Studies Response to a Request for Consultation. Prepared by Shari Targum MD and Norman Stockbridge MD. Dated September 1, 2006.

1.1.2 Sponsor Documents

1. Rufinamide (021-911). Integrated Summary of Safety: Addendum, pg. 636-694. Prepared by Eisai Medical Research, Inc. Dated February 27, 2008.
2. Rufinamide (IND 35-534). IND Annual Report of data from September 2006 to September 2007. Prepared by Eisai Medical Research, Inc.

1.2 Background

In 2006, Eisai Inc. submitted a New Drug Application (NDA) seeking permission to market rufinamide in the United States as an anti-epileptic agent. The studies supporting the application included a “thorough” QT study with a moxifloxacin positive control. During this “definitive QT” study (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 msec, depending on the dose, the time from dose and the heart rate correction method.

The DNP performed an initial review of the issue¹, completed in August 2006. The review found several factors suggesting a causal relationship between rufinamide treatment and shortening of the QT interval:

1. The degree of shortening of the QT interval generally rose with increasing dose, and was usually greatest when measured at times corresponding to the highest rufinamide plasma concentrations (See Section 2.1 of this review for additional information on dose-response patterns).

¹ Rufinamide (021-911). NDA Safety Review: Shortened QT Interval within the Rufinamide Development Program. Prepared by M. Lisa Jones MD, MPH. Dated August 11, 2006.

2. 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.
3. A number of subjects showed a decrease in the QT interval of 20 msec (see Section 2.1 of this review for more information), and an effect to this degree is less likely to be a chance occurrence.
4. 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.
5. 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 the QT interval.

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

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Reviewer comment: Clearly, such a statement is inadequate, and should rufinamide be approved a more thorough description of the issue should be included in labeling (See Section 3 "Conclusions and Recommendations" of this review for further discussion of potential labeling).

Quantifying the risk posed to patients by their shortening of the QT interval is difficult. As part of the NDA review, the DNP² consulted the Interdisciplinary Review Team (IRT) on QT issues for assistance in evaluating the presence of and clinical consequences of the decrease in the QT interval. As noted by Dr. Shari Targum in the resulting QT Team review, the FDA has no official guidelines on the topic.

1.3 Review Content

This review examines data that has been accumulated since the time of the first NDA review and the September 2006 Approvable Action letter to the sponsor. Specifically, the data consists of:

1. A request in the Approvable Action letter to have the QT data displayed in a manner which allowed for better evaluation.
2. Additional adverse event data since the time of the initial NDA review.

² DNP=Division of Neurology Products

2. DATA ON SHORTENED QT INTERVAL SINCE LAST REVIEW

2.1 Tabular Data

2.1.1 FDA Request to Sponsor

In the Approvable Action letter sent to Eisai in September 2006, the FDA made the following request regarding the presentation of QT-related data:

“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

2.1.2 Sponsor Response

The tables prepared by the sponsor in response to the request above are contained in Attachment 4.1 of this review.

Reviewer comment: *The FDA's request asked that tables be prepared using each heart rate correction method, but as the total number of tables is excessive for inclusion in this review, I have included only tables using the Fridericia correction. The numbers in the tables differed minimally across the different heart correction method (by ~5%), and given that rufinamide increases the heart rate by about 4 to 10 beats per minute, Fridericia is an appropriate correction method.*

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M. Lisa Jones MD, MPH

Rufinamide

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In the tables below, I summarize the information contained in the separate tables shown in Attachment 4.1. In the tables prepared by the sponsor, the data was stratified by the hour after dosing, but the table below shows the QT measurement at 5.4 hours post-dosing, which corresponds to the Tmax. The data in the tables was collected from approximately 100 patients (52 rufinamide, 58 placebo), belonging primarily to the definitive QT study E2080-A001-002.

Reviewer comment: The sponsor did not note the total number of patients from which the data was collected in the attachment containing the tables. I therefore calculated the number of subjects from the percents and number of subjects affected within the cells of the table.

FDA Table 1: Summary of QT-Related Data in the Rufinamide Development Program – Percent Subjects with QTcF from <410 to <300 msec at 5.4 hours (Tmax) after dosing

Percent (N) of Patients with QTcF <410 msec		
Dose (mg)	Rufinamide	Placebo
2400	92.3 (n=48)	81.0 (n=47)
3200	94.2 (n=49)	82.7 (n=43)
4800	93.9 (n=46)	84.6 (n=44)
7200	97.9 (n=47)	84.6 (n=44)
Percent (N) of Patients with QTcF <400 msec		
Dose (mg)	Rufinamide	Placebo
2400	88.5 (n=46)	60.3 (n=35)
3200	82.7 (n=43)	50.0 (n=26)
4800	91.8 (n=45)	53.8 (n=28)
7200	91.7 (n=44)	55.8 (n=29)
Percent (N) of Patients with QTcF <390 msec		
Dose (mg)	Rufinamide	Placebo
2400	63.5 (n=33)	31.0 (n=18)
3200	61.5 (n=32)	32.7 (n=17)
4800	69.4 (n=34)	28.8 (n=15)
7200	62.5 (n=30)	34.6 (n=18)
Percent (N) of Patients with QTcF <350 msec		
Dose (mg)	Rufinamide	Placebo
2400	0 (n=0)	0 (n=0)
3200	3.8 (n=2)	0 (n=0)
4800	4.1 (n=2)	0 (n=0)

7200	6.3 (n=3)	1.9 (n=1)
Percent (N) of Patients with QTcF <300 msec		
Dose (mg)	Rufinamide	Placebo
2400	0 (n=0)	0 (n=0)
3200	0 (n=0)	0 (n=0)
4800	0 (n=0)	0 (n=0)
7200	0 (n=0)	0 (n=0)

Reviewer comment: As acknowledged by the IRT QT team during the NDA review, there is “no algorithm for risk assessment” regarding QT reduction, and even the FDAs QT team has “little experience with drug-induced QT shortening.” As such, as noted in the prior review of the issue, there are no threshold values that are known to mark an increased risk for clinical consequences. However, as summarized in the initial Safety Team review, a few literature references offer some data on the subject. For instance, in familial syndromes of shortened QT interval, in which patients are at an increased risk for sudden cardiac death, the QTc interval falls within the range of 280 to 300 msec³. It is reassuring that none of the rufinamide-treated patients showed a QT interval shortened to this degree. However, another study⁴ found that of 6693 patients undergoing Holter recordings, those with a QTc of <400 msec had a higher risk of sudden death (relative risk 2.4, 95% C.I. 1.4 to 4.3) within a two-year follow-up period. Although the preceding study has a number of limitations, it is notable that for all patients for whom QT data is available, at the 3200 mg dose 83% of subjects had a QT interval in this range (<400 msec) when measured at Tmax. This compares to 50% of the parallel placebo patients.

Other notable findings of the table above include:

- Although some doses and time points show a relatively linear dose-response pattern, the pattern in many others is not as clear (See Attachment 4.1 of this review for additional data points).
- The number of rufinamide-treated patients with a QT interval of less than 390 msec is roughly twice that of placebo-treated patients (~63 percent of rufinamide patients versus 30% of placebo patients).

The table below present the QT data as the decrease in the QT interval compared to baseline values in rufinamide-and placebo-treated patients.

FDA Table 2: Summary of All QT-Related Data in the Rufinamide Development Program – Percent and Number of Subjects with QTcF Decrease from Baseline of >5msec to >20 msec at 5.4 hours (Tmax) after dosing

³ Antzelevitch C, Francis J. Congenital Short QT syndrome. Indian Pacing Electrophysiol J. 2004 Apr–Jun; 4(2): 46–49.

⁴ Algra A, Tijssen JG, Roeland 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.

	Percent (N) of Patients with QTcF decrease from baseline >5 msec	
Dose (mg)	Rufinamide	Placebo
2400	90.4 (n=47)	56.9 (n=33)
3200	86.5 (n=45)	44.2 (n=23)
4800	98.0 (n=48)	53.8 (n=28)
7200	91.7 (n=44)	59.6 (n=31)
	Percent (N) of Patients >10 msec	
Dose (mg)	Rufinamide	Placebo
2400	86.5 (n=45)	34.5 (n=20)
3200	76.9 (n=40)	34.6 (n=18)
4800	85.7 (n=42)	30.8 (n=16)
7200	79.2 (n=38)	40.4 (n=21)
	Percent (N) of Patients with QTcF >15 msec	
Dose (mg)	Rufinamide	Placebo
2400	71.2 (n=37)	19.0 (n=11)
3200	65.4 (n=34)	15.4 (n=8)
4800	77.6 (n=38)	17.3 (n=9)
7200	68.8 (n=34)	25.0 (n=13)
	Percent (N) of Patients with QTcF >20 msec	
Dose (mg)	Rufinamide	Placebo
2400	46.2 (n=24)	5.2 (n=3)
3200	46.2 (n=24)	7.7 (n=4)
4800	65.3 (n=32)	9.6 (n=5)
7200	60.4 (n=29)	13.5 (n=7)

Reviewer comment: In the table above, the difference between the rufinamide- and placebo-treated patients is substantial. Approximately half of the patients treated with rufinamide showed a decrease in their QT interval of >20 msec, compared to about 10% in the placebo group.

2.2 Adverse Event Data

In the initial review of shortened QT interval with rufinamide use, there were eight cases of sudden death among rufinamide-treated patients. 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.

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M. Lisa Jones MD, MPH

Rufinamide

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At the time of the current review, some additional patient data was available and was reviewed for any evidence of adverse events (AEs) related to a decrease in the QT interval. The adverse events that had the greatest potential to be associated with the QT interval decrease are sudden death and ventricular arrhythmias, particularly ventricular fibrillation, which was noted as a theoretical possibility in the IRT QT review. Other adverse events with a potential link to the QT interval decrease include syncope, ventricular flutter and cardiac dysrhythmia unspecified.

The additional rufinamide patient data that was available for review included:

- *15 day AE reports:* A total of six reports were submitted since the time of the NDA. None were cardiac or hemodynamic in nature.
- *Annual report* encompassing the time period from September 29, 2006 to September 29, 2007: This data included studies E2080-AOOI-301 (165 active patients), E2080-AOOI-302 (76 active patients) and CRUFI-331-2301 (a continued, open-label study following initial trials in the 1990's with only 2 active subjects).
 - Within the IND Safety Reports, the sponsor stated that there were no deaths during the time period covered by the annual report.
 - In the common adverse event listing, with the exception of 17 reports of dizziness, there were no events which were apparent manifestations of a short QT interval. Clearly, the finding of dizziness in the reports is not unexpected, and likely has other etiologies.
 - In the listing of AEs leading to discontinuation, there were no cardiac, hemodynamic or other adverse events (apart from dizziness) with a potential to be related to a decrease in the QT interval.

***Reviewer comment:** As noted by the primary reviewer Dr. Steven Dinsmore, ECG data is being collected in studies E2080-AOOI-301 and E2080-AOOI-302. This data was not available at the time of this review.*

3. CONCLUSIONS AND RECOMMENDATIONS

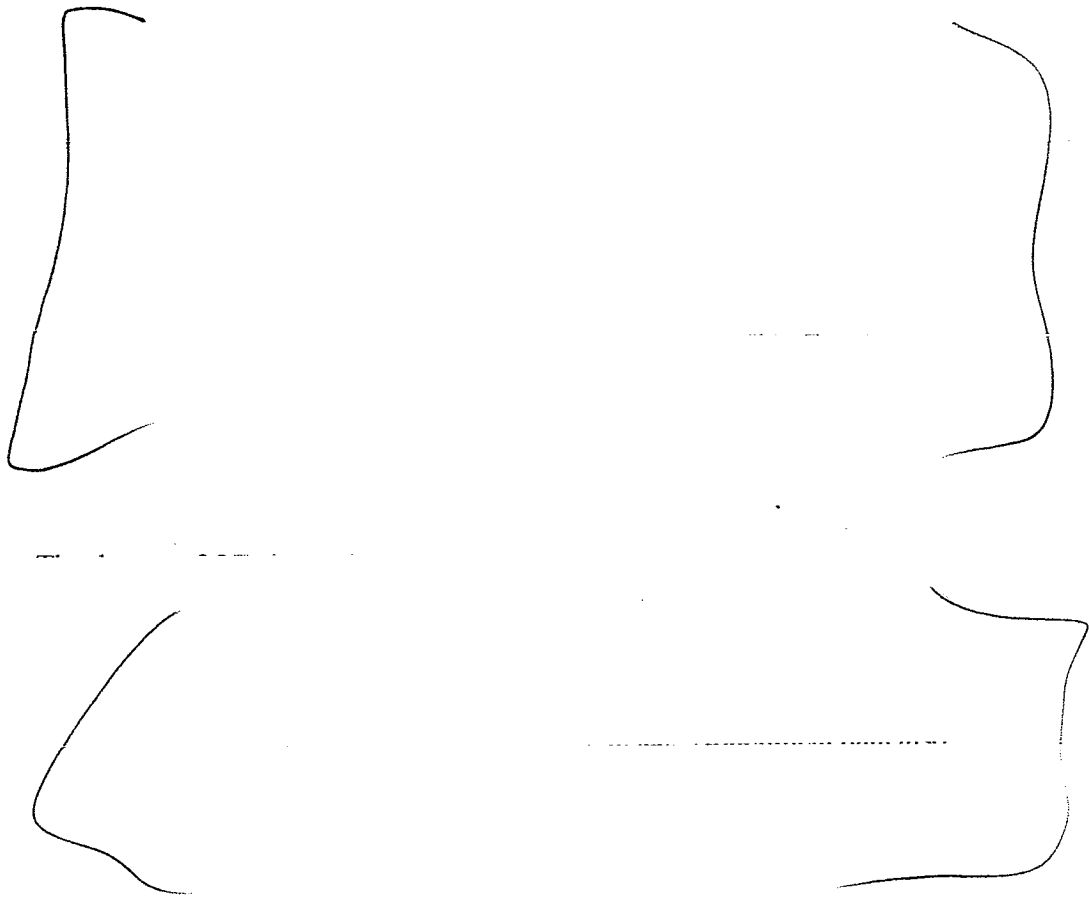
The additional data contained in Eisai's response to the Approvable Action letter has provided a clearer picture of the consistency and extent of rufinamide's ability to shorten the QT interval. Although it was apparent in the initial review that the QT shortening effect could extend to 20 msec, the most recent data presentation highlights the number of patients experiencing this degree of effect; in the data available, 92% (3200 mg) to 100% (7200 mg) of subjects recorded a QT interval decrease of >20 msec during at least one of the time points after dosing.

Review of adverse event listings available since the time of the initial review of the issue revealed no deaths and no adverse events with a strong potential to be related to a shortened QT syndrome.

The potential risk to patients from a QT decrease of the degree observed with rufinamide treatment remains unclear. Should rufinamide be approved for marketing, the issue should clearly be addressed in labeling. The FDA's Division of Neurology Products (DPP), with input from the FDA's IRT QT Team, has drafted the proposed labeling below to include in the rufinamide labeling.

FDA PROPOSED LABELING:

RUFINAMIDE LABEL (relevant sections)



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4. ATTACHMENTS

4.1 Sponsor Response to FDA Request for QT Data Stratified by QTc Interval and QTc Reductions from Baseline

(Adapted from the Integrated Summary of Safety, Addendum: Section 3.4, pg. 636 – 694.
Prepared by Eisai Medical Research. Dated February 27, 2008)

Table 1.1
Number (%) of Subjects With a QTcF Interval < 420 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	53	98.1	52	91.2
	0.5	54	100.0	52	89.7
	1	53	96.4	53	91.4
	1.5	55	100.0	53	91.4
	2	54	100.0	53	94.6
	3	54	100.0	55	94.8
	4	52	98.1	54	93.1
	5.417	51	98.1	55	94.8
	6	51	98.1	52	89.7
	7	51	98.1	53	91.4
	8	52	100.0	53	91.4
	10	50	96.2	51	89.5
	12	50	96.2	51	91.1
	Any Time	55	100.0	57	98.3
3200 mg	0	49	96.1	45	88.2
	0.5	49	96.1	49	94.2
	1	52	98.1	47	90.4
	1.5	51	96.2	49	94.2
	2	52	98.1	45	88.2
	3	51	96.2	49	94.2
	4	51	98.1	46	90.2
	5.417	50	96.2	48	92.3
	6	51	98.1	49	94.2
	7	51	98.1	48	92.3
	8	52	98.1	48	92.3
	10	50	96.2	46	88.5
	12	50	94.3	45	88.2
	Any Time	52	98.1	50	96.2
4800 mg	0	46	93.9	49	94.2
	0.5	46	93.9	49	94.2
	1	45	93.8	48	90.6
	1.5	47	95.9	49	92.5
	2	47	95.9	49	92.5
	3	48	98.0	48	90.6
	4	48	98.0	48	90.6
	5.417	48	98.0	49	94.2
	6	47	95.9	49	92.5
	7	47	95.9	49	92.5
	8	47	97.9	49	92.5
	10	47	97.9	47	92.2
	12	45	93.8	48	90.6
	Any Time	48	98.0	51	96.2

Table 1.1
Number (%) of subjects with a QTcF Interval < 420 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	45	93.8	45	88.2
	0.5	47	97.9	49	94.2
	1	47	97.9	47	92.2
	1.5	47	97.9	46	90.2
	2	47	97.9	47	94.0
	3	47	97.9	47	92.2
	4	47	97.9	49	94.2
	5.417	47	97.9	47	90.4
	6	47	97.9	49	94.2
	7	47	97.9	46	90.2
	8	47	95.9	47	92.2
	10	46	95.8	45	86.5
	12	47	95.9	43	82.7
	16	48	98.0	48	92.3
	20	46	93.9	45	88.2
	24.417	45	91.8	45	88.2
	30	45	91.8	45	91.8
	36	45	91.8	44	88.0
	Any Time	48	98.0	50	96.2

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Table 2.1
Number (%) of Subjects With a QTcF Interval < 410 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	51	94.4	44	77.2
	0.5	47	87.0	46	79.3
	1	50	90.9	48	82.8
	1.5	52	94.5	49	84.5
	2	49	90.7	48	85.7
	3	52	96.3	49	84.5
	4	52	98.1	46	79.3
	5.417	48	92.3	47	81.0
	6	50	96.2	46	79.3
	7	45	86.5	47	81.0
	8	48	92.3	51	87.9
	10	48	92.3	44	77.2
	12	48	92.3	44	78.6
	Any Time	55	100.0	55	94.8
3200 mg	0	44	86.3	41	80.4
	0.5	46	90.2	40	76.9
	1	49	92.5	43	82.7
	1.5	48	90.6	40	76.9
	2	50	94.3	39	76.5
	3	51	96.2	44	84.6
	4	50	96.2	41	80.4
	5.417	49	94.2	43	82.7
	6	48	92.3	41	78.8
	7	48	92.3	43	82.7
	8	50	94.3	44	84.6
	10	46	88.5	41	78.8
	12	46	86.8	40	78.4
	Any Time	52	98.1	49	94.2
4800 mg	0	45	91.8	42	80.8
	0.5	45	91.8	39	75.0
	1	42	87.5	42	79.2
	1.5	45	91.8	45	84.9
	2	46	93.9	42	79.2
	3	47	95.9	45	84.9
	4	47	95.9	41	77.4
	5.417	46	93.9	44	84.6
	6	46	93.9	41	77.4
	7	45	91.8	43	81.1
	8	45	93.8	42	79.2
	10	45	93.8	40	78.4
	12	42	87.5	40	75.5
	Any Time	48	98.0	49	92.5

Table 2.1
Number (%) of Subjects With a QTcF Interval < 410 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	42	87.5	39	76.5
	0.5	44	91.7	44	84.6
	1	46	95.8	37	72.5
	1.5	44	91.7	38	74.5
	2	44	91.7	36	72.0
	3	46	95.8	41	80.4
	4	47	97.9	37	71.2
	5.417	47	97.9	44	84.6
	6	45	93.8	42	80.8
	7	45	93.8	42	82.4
	8	47	95.9	41	80.4
	10	44	91.7	36	69.2
	12	44	89.8	37	71.2
	16	43	87.8	42	80.8
	20	35	71.4	36	70.6
	24.417	37	75.5	40	78.4
	30	42	85.7	39	79.6
	36	36	73.5	38	76.0
	Any Time	48	98.0	49	94.2

Appears This Way
On Original

Table 3.1
Number (%) of Subjects With a QTcF Interval < 400 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	38	70.4	28	49.1
	0.5	39	72.2	35	60.3
	1	42	76.4	33	56.9
	1.5	44	80.0	33	56.9
	2	46	85.2	36	64.3
	3	49	90.7	38	65.5
	4	46	86.8	32	55.2
	5.417	46	88.5	35	60.3
	6	40	76.9	31	53.4
	7	43	82.7	36	62.1
	8	42	80.8	38	65.5
	10	39	75.0	33	57.9
	12	38	73.1	29	51.8
	Any Time	53	96.4	50	86.2
3200 mg	0	36	70.6	26	51.0
	0.5	35	68.6	30	57.7
	1	40	75.5	30	57.7
	1.5	38	71.7	28	53.8
	2	44	83.0	33	64.7
	3	48	90.6	35	67.3
	4	45	86.5	32	62.7
	5.417	43	82.7	26	50.0
	6	42	80.8	30	57.7
	7	44	84.6	35	67.3
	8	44	83.0	34	65.4
	10	39	75.0	31	59.6
	12	34	64.2	29	56.9
	Any Time	50	94.3	45	86.5
4800 mg	0	37	75.5	29	55.8
	0.5	36	73.5	28	53.8
	1	36	75.0	30	56.6
	1.5	39	79.6	30	56.6
	2	42	85.7	31	58.5
	3	45	91.8	34	64.2
	4	44	89.8	27	50.9
	5.417	45	91.8	28	53.8
	6	40	81.6	26	49.1
	7	44	89.8	32	60.4
	8	42	87.5	32	60.4
	10	39	81.3	26	51.0
	12	39	81.3	30	56.6
	Any Time	47	95.9	44	83.0

Table 3.1
Number (%) of subjects With a QTcF Interval < 400 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	35	72.9	26	51.0
	0.5	38	79.2	31	59.6
	1	37	77.1	27	52.9
	1.5	37	77.1	27	52.9
	2	38	79.2	27	54.0
	3	43	89.6	34	66.7
	4	46	95.8	30	57.7
	5.417	44	91.7	29	55.8
	6	41	85.4	31	59.6
	7	43	89.6	31	60.8
	8	41	83.7	36	70.6
	10	35	72.9	29	55.8
	12	38	77.6	27	51.9
	16	33	67.3	32	61.5
	20	24	49.0	19	37.3
	24.417	29	59.2	25	49.0
	30	32	65.3	26	53.1
	36	24	49.0	26	52.0
	Any Time	48	98.0	44	84.6

Appears This Way
On Original

Table 4.1
Number (%) of Subjects With a QTcF Interval < 390 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	25	46.3	18	31.6
	0.5	25	46.3	20	34.5
	1	30	54.5	16	27.6
	1.5	30	54.5	22	37.9
	2	32	59.3	21	37.5
	3	39	72.2	28	48.3
	4	35	66.0	18	31.0
	5.417	33	63.5	18	31.0
	6	31	59.6	18	31.0
	7	30	57.7	20	34.5
	8	31	59.6	22	37.9
	10	28	53.8	18	31.6
	12	22	42.3	15	26.8
	Any Time	47	85.5	36	62.1
3200 mg	0	26	51.0	12	23.5
	0.5	26	51.0	16	30.8
	1	26	49.1	16	30.8
	1.5	29	54.7	17	32.7
	2	30	56.6	19	37.3
	3	35	66.0	22	42.3
	4	32	61.5	21	41.2
	5.417	32	61.5	17	32.7
	6	31	59.6	20	38.5
	7	33	63.5	22	42.3
	8	37	69.8	22	42.3
	10	29	55.8	18	34.6
	12	25	47.2	17	33.3
	Any Time	42	79.2	34	65.4
4800 mg	0	25	51.0	15	28.8
	0.5	27	55.1	15	28.8
	1	25	52.1	16	30.2
	1.5	27	55.1	16	30.2
	2	32	65.3	18	34.0
	3	38	77.6	15	28.3
	4	38	77.6	17	32.1
	5.417	34	69.4	15	28.8
	6	32	65.3	13	24.5
	7	35	71.4	17	32.1
	8	33	68.8	18	34.0
	10	28	58.3	17	33.3
	12	24	50.0	16	30.2
	Any Time	43	87.8	30	56.6

Table 4.1
Number (%) of Subjects With a QTcF Interval < 390 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	28	58.3	12	23.5
	0.5	25	52.1	15	28.8
	1	27	56.3	16	31.4
	1.5	27	56.3	15	29.4
	2	31	64.6	18	36.0
	3	37	77.1	17	33.3
	4	36	75.0	13	25.0
	5.417	30	62.5	18	34.6
	6	33	68.8	16	30.8
	7	33	68.8	18	35.3
	8	36	73.5	23	45.1
	10	25	52.1	17	32.7
	12	27	55.1	16	30.8
	16	24	49.0	17	32.7
	20	18	36.7	7	13.7
	24.417	18	36.7	11	21.6
	30	18	36.7	17	34.7
	36	15	30.6	20	40.0
	Any Time	46	93.9	36	69.2

Appears This Way
On Original

Table S.1
Number (%) of Subjects With a QTcF Interval < 350 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	0	0.0	0	0.0
	0.5	1	1.9	0	0.0
	1	1	1.8	0	0.0
	1.5	0	0.0	0	0.0
	2	2	3.7	0	0.0
	3	2	3.7	0	0.0
	4	2	3.8	0	0.0
	5.417	0	0.0	0	0.0
	6	1	1.9	0	0.0
	7	2	3.8	0	0.0
	8	2	3.8	0	0.0
	10	0	0.0	0	0.0
	12	0	0.0	0	0.0
	Any Time	5	9.1	0	0.0
3200 mg	0	0	0.0	0	0.0
	0.5	0	0.0	0	0.0
	1	0	0.0	0	0.0
	1.5	0	0.0	0	0.0
	2	2	3.8	0	0.0
	3	3	5.7	0	0.0
	4	5	9.6	0	0.0
	5.417	2	3.8	0	0.0
	6	0	0.0	0	0.0
	7	1	1.9	0	0.0
	8	3	5.7	0	0.0
	10	2	3.8	0	0.0
	12	1	1.9	0	0.0
	Any Time	10	18.9	0	0.0
4800 mg	0	1	2.0	0	0.0
	0.5	1	2.0	0	0.0
	1	1	2.1	0	0.0
	1.5	1	2.0	0	0.0
	2	1	2.0	0	0.0
	3	1	2.0	0	0.0
	4	2	4.1	0	0.0
	5.417	2	4.1	0	0.0
	6	1	2.0	0	0.0
	7	1	2.0	0	0.0
	8	0	0.0	0	0.0
	10	1	2.1	0	0.0
	12	1	2.1	0	0.0
	Any Time	4	8.2	0	0.0

Table 5.1
Number (%) of Subjects With a QTcF Interval < 350 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	0	0.0	0	0.0
	0.5	1	2.1	0	0.0
	1	2	4.2	0	0.0
	1.5	2	4.2	1	2.0
	2	1	2.1	0	0.0
	3	1	2.1	0	0.0
	4	0	0.0	0	0.0
	5.417	3	6.3	0	0.0
	6	2	4.2	0	0.0
	7	3	6.3	0	0.0
	8	1	2.0	0	0.0
	10	2	4.2	0	0.0
	12	1	2.0	0	0.0
	16	1	2.0	0	0.0
	20	0	0.0	0	0.0
	24.417	1	2.0	0	0.0
	30	1	2.0	0	0.0
	36	0	0.0	0	0.0
	Any Time	6	12.2	1	1.9

Appears This Way
On Original

Table 6.1
Number (%) of Subjects With a QTcF Interval < 300 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	0	0.0	0	0.0
	0.5	0	0.0	0	0.0
	1	0	0.0	0	0.0
	1.5	0	0.0	0	0.0
	2	0	0.0	0	0.0
	3	0	0.0	0	0.0
	4	0	0.0	0	0.0
	5.417	0	0.0	0	0.0
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	10	0	0.0	0	0.0
	12	0	0.0	0	0.0
	Any Time	0	0.0	0	0.0
3200 mg	0	0	0.0	0	0.0
	0.5	0	0.0	0	0.0
	1	0	0.0	0	0.0
	1.5	0	0.0	0	0.0
	2	0	0.0	0	0.0
	3	0	0.0	0	0.0
	4	0	0.0	0	0.0
	5.417	0	0.0	0	0.0
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	10	0	0.0	0	0.0
	12	0	0.0	0	0.0
	Any Time	0	0.0	0	0.0
4800 mg	0	0	0.0	0	0.0
	0.5	0	0.0	0	0.0
	1	0	0.0	0	0.0
	1.5	0	0.0	0	0.0
	2	0	0.0	0	0.0
	3	0	0.0	0	0.0
	4	0	0.0	0	0.0
	5.417	0	0.0	0	0.0
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	10	0	0.0	0	0.0
	12	0	0.0	0	0.0
	Any Time	0	0.0	0	0.0

Table 6.1
Number (%) of Subjects With a QTcF Interval < 300 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	0	0.0	0	0.0
	0.5	0	0.0	0	0.0
	1	0	0.0	0	0.0
	1.5	0	0.0	0	0.0
	2	0	0.0	0	0.0
	3	0	0.0	0	0.0
	4	0	0.0	0	0.0
	5.417	0	0.0	0	0.0
	6	0	0.0	0	0.0
	7	0	0.0	0	0.0
	8	0	0.0	0	0.0
	10	0	0.0	0	0.0
	12	0	0.0	0	0.0
	16	0	0.0	0	0.0
	20	0	0.0	0	0.0
	24.417	0	0.0	0	0.0
	30	0	0.0	0	0.0
	36	0	0.0	0	0.0
	Any Time	0	0.0	0	0.0

Appears This Way
On Original

Table 7.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 5 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	36	66.7	24	42.9
	0.5	45	84.9	38	65.5
	1	47	87.0	35	60.3
	1.5	49	89.1	38	65.5
	2	48	88.9	34	60.7
	3	48	88.9	41	70.7
	4	46	86.8	31	53.4
	5.417	47	90.4	33	56.9
	6	51	98.1	31	53.4
	7	46	88.5	27	46.6
	8	47	92.2	32	55.2
	10	42	80.8	20	36.4
	12	43	82.7	25	45.5
	Any Time	55	100.0	57	98.3
3200 mg	0	35	68.6	19	38.0
	0.5	46	90.2	30	57.7
	1	46	86.8	34	65.4
	1.5	47	88.7	34	65.4
	2	48	90.6	24	47.1
	3	47	88.7	34	65.4
	4	49	94.2	29	56.9
	5.417	45	86.5	23	44.2
	6	47	90.4	32	61.5
	7	47	90.4	28	53.8
	8	47	90.4	25	48.1
	10	46	88.5	21	42.0
	12	41	77.4	22	44.0
	Any Time	53	100.0	51	98.1
4800 mg	0	38	77.6	23	45.1
	0.5	47	95.9	33	63.5
	1	42	87.5	30	56.6
	1.5	46	93.9	34	64.2
	2	46	93.9	28	52.8
	3	45	91.8	27	50.9
	4	47	95.9	23	43.4
	5.417	48	98.0	28	53.8
	6	47	95.9	27	50.9
	7	47	95.9	22	41.5
	8	44	93.6	18	34.0
	10	42	87.5	21	42.9
	12	33	68.8	27	51.9
	Any Time	49	100.0	51	96.2

Table 7.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 5 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	34	70.8	17	34.0
	0.5	47	97.9	34	65.4
	1	46	95.8	27	52.9
	1.5	45	93.8	24	47.1
	2	46	95.8	24	48.0
	3	45	93.8	29	56.9
	4	46	95.8	26	50.0
	5.417	44	91.7	31	59.6
	6	47	97.9	29	55.8
	7	45	93.8	22	43.1
	8	43	89.6	26	51.0
	10	41	85.4	19	38.0
	12	33	67.3	21	41.2
	16	41	85.4	28	56.0
	20	38	77.6	28	56.0
	24.417	35	71.4	23	46.0
	30	36	73.5	30	61.2
	36	28	57.1	20	40.8
	Any Time	49	100.0	50	96.2

Appears This Way
On Original

Appears This Way
On Original

Table 8.1
Number (%) of Subjects With a Decrease From Baseline in QTcF Interval > 10 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	30	55.6	17	30.4
	0.5	43	81.1	32	55.2
	1	43	79.6	22	37.9
	1.5	42	76.4	28	48.3
	2	43	79.6	24	42.9
	3	46	85.2	24	41.4
	4	44	83.0	15	25.9
	5.417	45	86.5	20	34.5
	6	47	90.4	21	36.2
	7	41	78.8	19	32.8
	8	37	72.5	16	27.6
	10	38	73.1	14	25.5
	12	28	53.8	15	27.3
	Any Time	55	100.0	52	89.7
3200 mg	0	31	60.8	8	16.0
	0.5	40	78.4	24	46.2
	1	40	75.5	24	46.2
	1.5	43	81.1	22	42.3
	2	45	84.9	20	39.2
	3	43	81.1	19	36.5
	4	41	78.8	18	35.3
	5.417	40	76.9	18	34.6
	6	44	84.6	21	40.4
	7	43	82.7	17	32.7
	8	43	82.7	14	26.9
	10	43	82.7	15	30.0
	12	33	62.3	18	36.0
	Any Time	53	100.0	47	90.4
4800 mg	0	32	65.3	10	19.6
	0.5	44	89.8	23	44.2
	1	39	81.3	21	39.6
	1.5	45	91.8	23	43.4
	2	40	81.6	19	35.8
	3	42	85.7	19	35.8
	4	44	89.8	16	30.2
	5.417	42	85.7	16	30.8
	6	44	89.8	18	34.0
	7	41	83.7	13	24.5
	8	42	89.4	11	20.8
	10	36	75.0	11	22.4
	12	28	58.3	16	30.8
	Any Time	49	100.0	48	90.6

Table 8.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 10 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	29	60.4	5	10.0
	0.5	41	85.4	25	48.1
	1	43	89.6	19	37.3
	1.5	43	89.6	18	35.3
	2	39	81.3	18	36.0
	3	44	91.7	17	33.3
	4	41	85.4	10	19.2
	5.417	38	79.2	21	40.4
	6	46	95.8	21	40.4
	7	41	85.4	16	31.4
	8	37	77.1	12	23.5
	10	35	72.9	11	22.0
	12	31	63.3	12	23.5
	16	36	75.0	20	40.0
	20	31	63.3	16	32.0
	24.417	26	53.1	15	30.0
	30	33	67.3	21	42.9
	36	19	38.8	13	26.5
	Any Time	49	100.0	47	90.4

Appears This Way
On Original

Table 9.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 15 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	22	40.7	10	17.9
	0.5	37	69.8	18	31.0
	1	38	70.4	12	20.7
	1.5	37	67.3	17	29.3
	2	36	66.7	16	28.6
	3	42	77.8	16	27.6
	4	37	69.8	5	8.6
	5.417	37	71.2	11	19.0
	6	37	71.2	12	20.7
	7	32	61.5	10	17.2
	8	28	54.9	6	10.3
	10	23	44.2	8	14.5
	12	20	38.5	8	14.5
	Any Time	54	98.2	43	74.1
3200 mg	0	24	47.1	5	10.0
	0.5	32	62.7	14	26.9
	1	33	62.3	14	26.9
	1.5	32	60.4	11	21.2
	2	37	69.8	9	17.6
	3	37	69.8	9	17.3
	4	35	67.3	8	15.7
	5.417	34	65.4	8	15.4
	6	37	71.2	10	19.2
	7	35	67.3	9	17.3
	8	37	71.2	6	11.5
	10	32	61.5	11	22.0
	12	25	47.2	10	20.0
	Any Time	53	100.0	35	67.3
4800 mg	0	22	44.9	5	9.8
	0.5	35	71.4	17	32.7
	1	33	68.8	15	28.3
	1.5	34	69.4	12	22.6
	2	37	75.5	9	17.0
	3	37	75.5	12	22.6
	4	38	77.6	8	15.1
	5.417	38	77.6	9	17.3
	6	39	79.6	10	18.9
	7	33	67.3	6	11.3
	8	37	78.7	5	9.4
	10	31	64.6	6	12.2
	12	23	47.9	7	13.5
	Any Time	49	100.0	36	67.9

Table 9.1
Number (%) of Subjects With a Decrease From Baseline in QTcF Interval > 15 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	25	52.1	5	10.0
	0.5	36	75.0	13	25.0
	1	35	72.9	13	25.5
	1.5	37	77.1	7	13.7
	2	36	75.0	9	18.0
	3	34	70.8	10	19.6
	4	34	70.8	6	11.5
	5.417	33	68.8	13	25.0
	6	42	87.5	14	26.9
	7	36	75.0	8	15.7
	8	34	70.8	8	15.7
	10	25	52.1	9	18.0
	12	22	44.9	8	15.7
	16	25	52.1	17	34.0
	20	23	46.9	12	24.0
	24.417	20	40.8	13	26.0
	30	23	46.9	14	28.6
	36	11	22.4	10	20.4
	Any Time	49	100.0	38	73.1

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Table 10.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 20 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
2400 mg	0	13	24.1	3	5.4
	0.5	25	47.2	6	10.3
	1	27	50.0	5	8.6
	1.5	28	50.9	12	20.7
	2	28	51.9	6	10.7
	3	34	63.0	8	13.8
	4	28	52.8	1	1.7
	5.417	24	46.2	3	5.2
	6	28	53.8	5	8.6
	7	23	44.2	6	10.3
	8	21	41.2	3	5.2
	10	16	30.8	3	5.5
	12	15	28.8	4	7.3
	Any Time	51	92.7	26	44.8
3200 mg	0	17	33.3	2	4.0
	0.5	24	47.1	8	15.4
	1	28	52.8	7	13.5
	1.5	24	45.3	7	13.5
	2	25	47.2	5	9.8
	3	31	58.5	5	9.6
	4	26	50.0	3	5.9
	5.417	24	46.2	4	7.7
	6	33	63.5	4	7.7
	7	29	55.8	4	7.7
	8	25	48.1	4	7.7
	10	17	32.7	4	8.0
	12	19	35.8	1	2.0
	Any Time	52	98.1	23	44.2
4800 mg	0	16	32.7	3	5.9
	0.5	27	55.1	6	11.5
	1	28	58.3	5	9.4
	1.5	28	57.1	7	13.2
	2	29	59.2	7	13.2
	3	31	63.3	5	9.4
	4	31	63.3	4	7.5
	5.417	32	65.3	5	9.6
	6	33	67.3	4	7.5
	7	23	46.9	2	3.8
	8	24	51.1	2	3.8
	10	24	50.0	3	6.1
	12	14	29.2	6	11.5
	Any Time	48	98.0	23	43.4

Table 10.1
Number (%) of Subjects with a Decrease From Baseline in QTcF Interval > 20 msec

Daily Dose	Hours Postdose	Rufinamide n	Rufinamide %	Placebo n	Placebo %
7200 mg	0	18	37.5	4	8.0
	0.5	27	56.3	9	17.3
	1	26	54.2	7	13.7
	1.5	27	56.3	5	9.8
	2	28	58.3	6	12.0
	3	32	66.7	8	15.7
	4	30	62.5	4	7.7
	5.417	29	60.4	7	13.5
	6	30	62.5	6	11.5
	7	28	58.3	4	7.8
	8	24	50.0	5	9.8
	10	19	39.6	7	14.0
	12	16	32.7	4	7.8
	16	19	39.6	9	18.0
	20	15	30.6	9	18.0
	24.417	16	32.7	5	10.0
	30	13	26.5	9	18.4
	36	8	16.3	8	16.3
	Any Time	49	100.0	32	61.5

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M. Lisa Jones
10/10/2008 02:06:29 PM
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10/15/2008 11:57:49 AM
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CLINICAL REVIEW

Application Type NDA
Submission Number 021911
Submission Code

Letter Date NOV 17 2005
Stamp Date
PDUFA Goal Date

Reviewer Name Ramesh Raman, MD
Review Completion Date 9/8/2006

Established Name
(Proposed) Trade Name
Therapeutic Class Anticonvulsant
Applicant Eisai Medical Research, NJ, USA

Priority Designation {enter P or S}

Formulation Oral
Dosing Regimen 7 to 3200 mg/d in divided doses twice daily b(4)
Indication Partial-Onset Seizures (epilepsy)
Intended Population Adults and Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Safety

Approvable.

The following reasons justify the recommendation.

1. Efficacy has not yet been established. Without established effectiveness, administration of any drug although safe is not justified.
2. The behavior and safety of rufinamide in the adolescent population has not been adequately studied or characterized. The sought indication in adolescents is therefore not justified.
3. The behavior and safety of rufinamide has not been adequately studied or characterized in the African/Black and Hispanic/Latino population.
4. The confirmed QT shortening via the validated thorough QT study is unique to rufinamide and is the first in its class as an anticonvulsant to demonstrate this potentially serious inherent capability. Although no fatal cardiac arrhythmias were noted, the concerns would be greater in certain predisposed populations such as those with congenital QT abnormalities who may additionally present with seizures. Sufficient information on the absolute QT values was not provided to fully characterize this concern. The sponsor has not recognized or the addressed the concerns related to QT shortening. Further, the observed QT shortening that ranged from 2 to 20 msec was not adequately stratified.
5. Laboratory abnormalities related to TFT were not adequately analyzed in a clinically meaningful way.
6. The disposition and outcome of those patients with a final clinically notable value post-treatment was not provided.

In order to resolve these issues, the sponsor should provide the following-

1. Submit adequate data or justification that can support the use of rufinamide in the adolescent population or alternately, amend the indication to exclude this population.
2. Submit adequate data or justification that can support the use of rufinamide in the African/Black and Hispanic/Latino population or alternately, amend the label to indicate that this population was not adequately studied.
3. An assessment and a risk-benefit management plan of addressing the short QT concern that would justify approval preferably based on the additional benefit that rufinamide could provide in the context of the presence of other class agents in the market. In addition, for the ECG data collected in the clinical trials, the sponsor should provide outlier tables summarizing the number and percent of subjects with QT intervals in each of the following categories as shown below. These tables should be provided for each dose level and stratified by heart rate correction method.

Absolute QT: < 420 msec, < 410 msec, < 400 msec, < 390 msec, < 350 msec and < 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, and QT interval decreases < 20 msec from baseline.

4. An integrated safety analysis of all TFT abnormalities that is clinically meaningful suggesting a hypothyroid response. For the different subgroups of patients in the safety database, the re-analyses should include the proportions of patients who simultaneously experienced an increase in serum TSH and a decrease in serum thyroxine (T3, T4, free and bound) or vice versa by treatment.
5. Re-examine the records for those patients with a clinically notable change in lab parameters and, for each patient, clearly state whether there was follow-up on the abnormal lab value, the nature of the follow-up if one existed, and the final outcome if known.
6. Demonstrate effectiveness.

1.2 Recommendation on Postmarketing Actions

Not applicable.

1.2.1 Risk Management Activity

Not applicable.

1.2.2 Required Phase 4 Commitments

Not Applicable.

1.2.3 Other Phase 4 Requests

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical safety program is discussed under 1.3.3.

1.3.2 Efficacy

See Efficacy review by Dr. Herschkowitz.

1.3.3 Safety

General Comments to the Reader

The clinical data was reviewed by three reviewers. The efficacy data and related components were reviewed by Dr. Herschkowitz while all the safety data and related components (except comprehensive ECG/QT/CVS) were reviewed by this reviewer. The ECG/QT/CVS related safety was comprehensively reviewed by Dr. Lisa Jones (safety team). Comments on ECG/QT/CVS by this reviewer were limited. Comments relevant to clinical safety may appear in the various non-clinical safety sections of this review. These safety comments therefore, may not be comprehensive to the section under which they appear since additional comments that are not related to clinical safety may be required to fully address the issue. In these situations, comments from the respective disciplines should additionally be sought.

Every attempt was made to conform to the FDA clinical review template (of July 2004). For ease of reference, the safety tables under each section were numbered to match the numbers of the respective sections in the review template. However, tables from other sections retaining their original numbers may have been re-presented in the executive summary section (1.3.3).

It is to be noted that throughout the safety review, the names rufinamide, Rufinamide, Inovelon and ~~many~~ many have been used interchangeably. They mean the same. While the sponsor's proposed trade name (s) for rufinamide has (ve) been found to be _____

b(4)

_____ If one such previously proposed but disputed trade name appears in this safety review, it is not implied that the name has been found acceptable.

The complexities in the regulatory drug development of rufinamide (see background below) influenced the approach to the review. Several companies were involved in its development and the studies that contributed to the data submitted for review were conducted many years ago, starting as early as 1989, and many studies were performed outside the US. Based on the interactions with the sponsor during the review cycle when clarifications were needed, it was apparent that some of the discrepancies and lapses in information were either due to the complex changing of ownership and or the standards and conditions that existed at the time when the trials were conducted particularly those that were outside the US.

Background

Ciba-Geigy in Europe initiated the earliest clinical studies with rufinamide, an anticonvulsant, known at that time by the product name CGP 33101. Novartis, formed from the merger of Ciba-Geigy and Sandoz, continued the global development, using the product name RUF 331. Eisai Company, Ltd. acquired the rights to rufinamide from Novartis on 6 February 2004. Since that time, Eisai (hereon sponsor) has been managing the development program and is the sponsor for the submitted NDA 021911.

Rufinamide, under NDA 021911, was resubmitted on November 17, 2005. It was initially submitted on September 8, 2005 and later withdrawn (due to lack of adequate preclinical information) on November 2, 2005. On March 13, 2006, the sponsor submitted a 4-month safety update. On June 23, 2006, the sponsor submitted a 95 page safety amendment document that provided corrections to the previously submitted numbers on AE and SAE. The sponsor has formally submitted a request for deferral of pediatric studies for ages 0-4 years _____

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Rufinamide, according to the sponsor, is not

marketed (registered) elsewhere and hence there is no post-marketing experience or post-market data.

The clinical safety profile of rufinamide can be discussed under the following headings-

- I. Drug, Sought Indication and Dosage and Administration
- II. The Submission, Data, Safety Studies, Monitoring and Assessments
- III. Extent of Exposure, Demographics and Disposition of Study Population
- IV. Safety Summary and Discussions on - Adequacy of Assessments; Treatment Emergent Findings; and Risk Benefit Assessments
- V. Conclusions

I. DRUG, INDICATION, DOSAGE AND ADMINISTRATION

Drug

Rufinamide, an anticonvulsant, is a triazole derivative, which according to the sponsor, is structurally unrelated to currently available antiepileptic drugs (AEDs) in the US market. Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1*H*-1,2,3-triazole-4 carboxamide. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile. The drug is available for oral administration in film-coated tablets containing 100, 200, and 400 mg of rufinamide.

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. Based on in vitro studies, it was noted that rufinamide limited the frequency of firing of sodium-dependent action potentials in rat neurons, an effect that could contribute to blocking the spread of seizure activity from an epileptogenic focus.

Rufinamide was well absorbed after oral administration. However, the rate of absorption was relatively slow and the extent of absorption was decreased as dose was increased. The pharmacokinetics did not change with multiple dosing. Rufinamide has low protein binding (approximately 34% of rufinamide was bound to human serum proteins, predominantly to albumin). Rufinamide was evenly distributed between erythrocytes and plasma. Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid. This metabolic route is not cytochrome P450 dependent. The metabolite has no known pharmacological activity and is primarily renally excreted. Renal excretion was the predominant route of elimination for drug related material, accounting for 84.7% of the dose. The renal excretion of unchanged rufinamide accounted for less than 2% of the dose. Plasma half-life of rufinamide is approximately 6-10 hours. Half-life was unaffected by renal impairment and did not change notably with age. When given twice daily at 12-hourly intervals, rufinamide accumulated to the extent predicted by its terminal half-life, indicating that the pharmacokinetics of rufinamide were time-independent (i.e. no autoinduction of metabolism).

Since rufinamide did not induce its own metabolism, nor did it act as an inhibitor of carboxylesterase activity, it is not expected to have significant drug-drug interactions with other substrates for this enzyme. Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide. Drug-drug interactions are discussed in section 8.2.

The essence of the findings of drug-drug interactions with other anticonvulsants that is summarized in a table in section 8.2 is presented here for ease of reference. Rufinamide may increase phenytoin levels by up to 21% but effects on other AEDs were minimal. Valproate co-administration may lead to elevation in rufinamide plasma levels, especially in children.

SAFETY TABLE 8.2.A DRUG-DRUG INTERACTIONS WITH OTHER ANTI-EPILEPTIC DRUGS		
AED Co-administered	Influence of Rufinamide on AED concentration ^{a)}	Influence of AED on Rufinamide concentration
Carbamazepine	Decrease by 7 to 13% ^{b)}	Decrease by <30%. Dependent on dose of carbamazepine
Lamotrigine	Decrease by 7 to 13% ^{b)}	No Effect
Phenobarbital	Increase by 8 to 13% ^{b)}	Decrease by 25 to 46% ^{d), e)} . Independent on dose or concentration of phenobarbital
Phenytoin	Increase by 7 to 21% ^{b)}	Decrease by 25 to 46% ^{d), e)} . Independent on dose or concentration of phenytoin
Topiramate	No Effect	No Effect
Valproate	No Effect	Increase by <16 to 70% ^{d)} . Dependent on concentration of valproate
Vigabatrin	Not Investigated	Decrease by <30%. Independent on dose or concentration of vigabatrin
Primidone	Not Investigated	Decrease by 25 to 46% ^{d), e)} . Independent on dose or concentration of primidone
Benzodiazepines ^{e)}	Not Investigated	No Effect

Ref: Modified Sponsor's Table 3, 

Note:

^{a)} Predictions are based on rufinamide concentrations at the maximum recommended dose of INOVELON®.

^{b)} Maximum changes predicted to be in children and in patients who achieve significantly higher levels of rufinamide, as the effect of rufinamide of these AEDs is concentration-dependent.

^{c)} All compounds of the benzodiazepine class were pooled to examine for 'class effect' on rufinamide clearance.

^{d)} Larger effects in children at high doses/concentrations of AEDs.

^{e)} Phenobarbital, primidone and phenytoin were treated as a single covariate (phenobarbital-type inducers) to examine the effect of these agents on rufinamide clearance.

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Indication

The sought indication is –

INOVELON® (rufinamide) is indicated as:

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

Dosage and Administration

The sought dosage and administration is-

Adjunctive therapy in Adults and Adolescents with partial-onset seizures (12 Years of Age and Over)

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Adjunctive therapy in pediatric (4 - 15 years) and adult patients with Lennox-Gastaut syndrome.

Children: Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a maximum of 45 mg/kg/day or 3200 mg/day whichever is less, administered in two equally divided doses.

Adults: Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg/day every 2 days until a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached.

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INOVELON[®] is given orally with food.

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II. THE SUBMISSION, DATA, SAFETY STUDIES, MONITORING AND ASSESSMENTS AND METHODS

Submission, Studies, Data and Analysis Population

This safety review addressed information that was submitted from the time of the filing date of November 17, 2005 through September 2006. The database lock date for the integrated safety data presented in this submission was February 1, 2005.

The clinical studies that contributed to the safety database are listed in Appendix Table 1. The Integrated Summary of Safety (ISS) included data from 20 studies involving 1978 unique patients (adults and pediatrics combined- see Tables 7.2.1.1.A-C) with epilepsy who were exposed to rufinamide. It should be noted that the clinical drug development program began as early as 1989.

These studies (listed in Appendix Table 1) included data from 8 controlled studies in patients with epilepsy (including one study—Study 021—which was summarized in 2 reports, 1 for the adult patients and 1 for the pediatric patients); 2 open-label studies in patients with epilepsy; and 2 controlled pharmacokinetic studies in patients with epilepsy. Eight of the studies, including the adult (021A) and pediatric (021P) parts of Study 021, had open-label extension phases in which long-term safety data were collected. Also included in this summary were safety results that were presented separately from the results in patients with epilepsy. This included data from the only study in a non-epilepsy indication (diabetic neuropathy), 22 biopharmaceutic / pharmacokinetic studies performed in healthy volunteers, and 2 studies (1 with an extension) performed in Japan for which only translated study reports were available.

The information that was presented regarding the 2 ongoing studies (Studies 2301 [N=70 patients) and E2080-A001-002 [definitive QT study in healthy volunteers completed May 2005]), the 120-day safety update and studies conducted in Japan is discussed in section 4.1 and 8.8.

The safety analyses population included data from 1978 unique rufinamide patients. The data was broken down into various subgroups by population and study type and integrated. These integrated subgroups were-a) All double-blind studies, b) All studies combined, c) Adult double-blind studies, d) Adult double-blind with open-label extensions studies, e) Mono-therapy double-blind studies, f) LGS double-blind study (s), g) LGS double-blind with open-label extension study, h) Pediatric double-blind studies and i) Pediatric double-blind with open label extension studies. Study design, including criteria, is discussed in 7.2.1.1.

These subgroups were further broadly identified into double-blind studies and double-blind studies with open-label extensions (if these were conducted) and by population (adult vs. pediatric). While the safety of the entire 1978 rufinamide patients was evaluated, emphasis was placed on double-blind studies (because of the possibility of clinically meaningful interpretations of data) and those that would support the sought indication, viz., double-blind adjuvant partial seizure studies in adolescents (defined as ages 12 to < 16 years) and adults (defined as ages ≥16 years) and double-blind LGS study (s) in pediatrics (defined as ages > 4 years to <16 years) and adults. The LGS indication, in essence, was supported by a single LGS double-blind study. The direct support for the sought indications could therefore potentially originate only from a subset of the presented subgroups. Patient enumeration is discussed in section 7.2.1.1. The relevant epilepsy safety analysis population that is based on the type of study, age and indication and summarized in a table in section 7.2.1.1 is presented here for ease of reference.

SAFETY TABLE 7.2.1.1.C		
OVERVIEW OF EPILEPSY POPULATION BY AGE, SUBGROUP, INDICATION		
Criteria	Pediatric (N) [Age < 16 yrs]	Adult (N) [Age ≥ 16 yrs]
Number of Unique Patients (N= 1978)	397	1581
All Double-blind (N = 1240)	203	1037
All Open-label	194	544
LGS Double-blind (N=74)	49	25
LGS Open-label	41	20
Partial Epilepsy Indication (double-blind) (N= 720)	4	716
LGS Indication (double-blind) (N= 74)	49	25
Ref: Sponsor's Information submitted Sep 7, 2006; Table 7.2.1.2.A		

Monitoring and Assessments

The safety variables that were evaluated were: Adverse events; Clinical laboratory tests (blood chemistry, hematology, and urinalysis); tests of Thyroid function were performed in some protocols; Vital sign measurements and body weight; ECGs; Physical examinations/Neurological examinations.

An overview of the safety parameters evaluated in each of the clinical trials in epilepsy that is summarized in a table in section 7.1 is presented here for ease of reference.

SAFETY TABLE 7.1.A				
OVERVIEW OF EVALUATED SAFETY PARAMETERS				
Referenced Study	AE	Vitals & Weight	Laboratory ^A	ECG
AE/ET1 & AE/ET1E	X	X	X ^B	X
AE/PT1	X	X	X ^B	X
AE/PT2	X	X	X ^B	X
AE/PT3	X	X	X ^B	X
016 & 016E	X	X	X ^B	X
018 & 018E	X	X	X ^B	X
021A & 021AE	X	X	X ^B	X
021P & 021PE	X	X	X ^B	X
022 & 022E	X	X	X ^B	X
027 & 027E	X	X	X ^B	X
038 & 038E	X	X	X ^C	X
039 & 039E	X	X	X	X
0101	X	X	X	X
2301	X	X	X	X
Ref: Modified from Sponsor's Table 3.3-1, ISS, p. 52				
Note:				
A = Included Standard hematology, Blood Chemistry and UA				
B = Included Thyroid Function Tests				
C = Included Thyroid Function Tests at Baseline Only				

Methods

Analysis of Extent of Exposure

The methods involving the extent of exposure to study drug was analyzed in three ways-

1. the median daily dose of rufinamide that a patient received during his or her entire duration of exposure to the drug;
2. the daily dose that the patient received for the longest period of time (called daily dose of maximum duration); and
3. the maximum daily dose that the patient received. The daily dose was calculated from doses taken during the maintenance period in studies that included both titration and maintenance periods, i.e., Studies 016, 021A and 021P, 022, and 038. These data were summarized using descriptive statistics (mean, median, standard deviation, range).

Duration of exposure to rufinamide was summarized by median daily dose, maximum daily dose, and daily dose of maximum duration. The distribution of patients was shown for the following intervals: 0 to <1 month, 1 to <3 months, 3 to <6 months, 6 to <12 months, 12 to <24 months, 24 to <36 months, 36 to <48 months, and ≥ 48 months. The distribution was shown for doses in mg/kg/day (<10, 10 to <20, 20 to <30, 30 to ≤ 45 , >45 mg/kg/day) or in mg/day (<400,

400 to <1600, 1600 to <2400, 2400 to ≤3200, >3200 mg/day). For the population of all treated patients with epilepsy, distributions of duration by median daily dose were also generated for subgroups of patients categorized by their weight at baseline (<18.0, 18.0 to 29.0, 29.1 to 50.0, 50.1 to 70.0, ≥70.1 kg).

Analyses of Adverse events

In the rufinamide studies, an adverse event was defined as any undesirable sign, symptom, laboratory abnormality, or medical condition occurring after study treatment, even if the event was not considered to be treatment-related. Information was recorded on the adverse event CRF about all adverse events, whether volunteered by the patient, discovered by investigator, or detected through physical examination, laboratory test, or other means.

In all epilepsy trials, events that are to be expected due to the trial indication (such as seizures in patients with epilepsy) were not be treated as adverse events or serious adverse events, unless the event represented a significant worsening of the symptom (e.g., new seizure type, clinically significant increase in seizure severity, status epilepticus or hospitalization, etc.).

The investigators were instructed to record adverse events using standard medical terminology. For the CSRs, the specific terms that the investigators recorded were coded to Low Level Terms and to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 6.0. Coding to Version 6.0 was done either as part of the original CSR or as an addendum to the original CSR.

Adverse events data were pooled using the analysis populations defined above. Tables within the text that displayed the overall incidence of patients with at least one adverse event and adverse events by MedDRA SOC showed the results for every adverse event reported. Additional tables were focused on very common adverse events, defined as any adverse event that occurred in 10.0% or more of the patients within a treatment group. The very common adverse events were summarized by Preferred Term, by severity, and by dose of rufinamide. All of these presentations were based on adverse events regardless of causality.

The relation between the occurrence of adverse events and the dose of rufinamide was evaluated for 1) the median dose of rufinamide that a patient received during his or her entire duration of exposure to the drug, excluding exposure during titration; 2) the dose that the patient received for the longest period of time (called daily dose of maximum duration); and 3) the maximum daily dose that the patient received. Most of the double-blind studies evaluated stable doses of rufinamide, so the median dose, dose of maximum duration, and maximum dose were generally the same for patients in those studies. Adjustments of dose were allowed during open-label extensions.

Serious adverse events were summarized by showing the number and percent of patients who experienced at least one event and each specific event. The total number of events per treatment group, and the number of events leading to discontinuation, was also noted for each analysis population. The number of events was based on the serious adverse event reports received by the sponsor. Some of these included multiple events that occurred concurrently in a single patient. Such concurrent events were counted as a single serious adverse event only when determining the total number of events.

Analysis of Laboratory tests

Clinical laboratory data were summarized using descriptive statistics for values obtained at baseline and at the last post-baseline visit, and for the difference between those two evaluations. Two distinct definitions of baseline were used: 1) in analyses of populations from well-controlled studies, the baseline measure of a parameter was the last reported value prior to initiation of randomized study treatment; 2) in analyses of the remaining populations, where the interest was in change since initiation of rufinamide, the baseline measure was the last reported value for a parameter prior to initiation of treatment with rufinamide. The last post-baseline value was defined as the last reported value within the Double-blind Phase for the analyses of data from controlled studies. For the remaining populations, the last post-baseline value was defined as the last reported value after initiation of rufinamide treatment. Individual patients with changes in laboratory parameters of potential clinical significance were identified in two ways. First, shift tables were generated to show the number of patients with values for each parameter that were below, within, or above the normal range at baseline and below, within, or above the normal range at the last post-baseline evaluation. Second, the numbers and percentages of patients who had changes in any laboratory parameter that met predefined criteria for clinically notable values were calculated.

Normal ranges and clinically notable criteria used in the analyses of individual studies, and reported in the individual CSRs, varied. They were not always modified appropriately depending on the patients' ages, and the clinically notable criteria were not in accordance with current standards. Therefore, for consistency and accuracy, a single set of age-adjusted normal ranges and clinically notable criteria was used for this ISS. The age-adjusted normal ranges, those that were recommended by the Mayo Medical Laboratories Test Catalog, were presented in Appendix I, Table 8.1.0 of the submission.

The standard definitions/criteria of clinically notable values of lower limit and upper limit for hepatobiliary, renal (BUN and Cr), hematology, general chemistry and thyroid functions used in the ISS analyses that were presented in Table 3.4-1, ISS, p. 55 has been included in Appendix-Table 2. International units rather than conventional units were used to measure changes. The disposition of patients with clinically notable values (changes from baseline), were not specified. How these patients with clinically notable changes were managed or followed was not provided and the outcome was unknown.

Analysis of Vital signs and Body Weight

Vital signs and weight were evaluated two ways viz., summary statistics and incidences based on identifying clinically notable changes.

Summary statistics (means, medians, standard deviations, ranges) were calculated (but not integrated- see comments below) at baseline and at the last post-baseline evaluation, and for the difference between those two evaluations. Two distinct definitions of baseline were used: 1) in analyses of populations from well-controlled studies, the baseline measure of a parameter was the last reported value prior to initiation of randomized study treatment; 2) in analyses of the remaining populations, where the interest was in change since initiation of rufinamide, the baseline measure was the last reported value for a parameter prior to initiation of treatment with rufinamide. The last post-baseline value was defined as the last reported value within the Double-blind Phase for the analyses of data from controlled studies. For the remaining populations, the last post-baseline value was defined as the last reported value after initiation of rufinamide treatment.

The incidence of patients with clinically notable changes was determined, using the definitions of clinically notable changes that was presented in Table 3.4-2, ISS, p. 56, for pulse rate, SBP, DBP and Weight has been included in this review for reference (Appendix Table 3). Patients were included in the evaluation of clinically notable changes only if they had both a baseline value and at least 1 post-baseline value for vital signs and weight.

Analysis of ECG

The ECGs recorded in the clinical studies did not undergo centralized review. Instead, each center provided each patient's ECG with an automatic readout, confirmed by the principal investigator. Each ECG that was recorded was given an overall interpretation of 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.

The ECG, QT and related CVS safety data has been reviewed by the DNDP safety team (Dr. Lisa Jones).

Analysis of Physical and Neurological Examinations

According to the sponsor, no summaries or tabulations for these findings were integrated or submitted in the ISS (3.4.3.5, ISS, p. 56).

III. EXPOSURE, DEMOGRAPHICS AND DISPOSITION

Exposure

The overall extent of exposure was summarized by median dose, age and or sex for each of the epilepsy analysis population (All double-blind, All Epilepsy, Adult Double-blind, Adult Double-blind with open-label extension, Mono-therapy double-blind, LGS double-blind, LGS double-blind with open-label extension, Pediatric double-blind and Pediatric double-blind with open label extension). Although not part of the epilepsy population, an overview for the diabetic neuropathy subgroup and healthy volunteer subgroup was additionally presented. A comprehensive discussion on exposure, on other subgroups, including the diabetic neuropathy subgroup and healthy volunteer subgroup, is presented in section 7.2.1.3. Appendix Table 4 includes relevant exposure related tables.

In placebo-controlled clinical studies, doses ranged from 200 to 3200 mg/day.

In adults with partial seizures enrolled in adjunctive therapy studies, 932 patients received rufinamide during the Double-blind Phase, the Extension Phase, or both phases of Studies AE/PT2, AE/ET1, or 021A. The total exposure to rufinamide in this population was 1190.94 patient-years. The mean daily dose was 1568 mg/day. The duration of exposure ranged from less than 1 month to 4 years or more. More than half of the 682 patients with median doses of less than 2400 mg/day were treated for at least 6 months. More than half of the 250 patients with median doses of 2400 mg/day were treated for at least 12 months.

In the LGS study, 135 patients received rufinamide during the Double-blind Phase, the Extension

Phase, or both phases in this study. The median duration of exposure was 14.3 months. The mean dose was 45 mg/kg/day. The cumulative duration of exposure during the Double-blind and Extension Phases was at least 12 months for more than half of the patients. Approximately one-quarter of the patients with LGS were exposed to rufinamide for at least 24 months. The total exposure to rufinamide in this population was 166.6 patient-years.

In the population of all rufinamide-treated patients with epilepsy, 1978 patients received rufinamide during the Double-blind Phase, the Extension Phase, or both. The total exposure to rufinamide in this population was 2552.96 patient-years. The mean daily dose was 1700 mg/day. The duration of exposure ranged from less than 1 month to 4 years or more. More than half of the 939 patients with median doses of less than 1600 mg/day were treated for at least 6 months. More than half of the 1039 patients with median doses of 1600 mg/day or more were treated for at least 12 months.

Demographic and Other Characteristics of the Study Population

The population in whom safety of rufinamide was evaluated included adult and pediatric patients (on multiple medications) with a variety of seizure disorders. These included the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures, primary generalized seizures and seizures associated with the LGS.

Demographic information, including concomitant medications, of the different subsets of the patient population is summarized in section 7.2.1.2. The clinically meaningful demographic profiles of those patients representative of the sought indications were not submitted with the original application. These were subsequently submitted (essentially information presented in Table 7.2.1.2.B below) upon request. The demographic characteristics, for the important subgroups, viz., 1) all double-blind, 2) adult double-blind and 3) LGS double-blind and 4) Indication Relevant Subgroups were-

1. All double-blind subgroup

The profiles were similar for the 2 treatment (rufinamide and placebo) groups. Approximately half of the patients were males. The mean age was 31.7 years in the rufinamide group and 28.6 years in the placebo group; a larger percentage of the patients in the rufinamide group (82.2%) than in the placebo group (68.2%) were between the ages of 17 and 64 years. The mean weights were 67.6 kg and 64.2 kg, respectively; more than 73% of the patients weighed more than 50 kg.

Concomitant AEDs and non-AEDs, received by more than 5% and 10% of the patients respectively in either treatment group (rufinamide or placebo) were analyzed. Most of the studies included in this pool enrolled patients who were receiving stable doses of one to three AEDs. The concomitant AEDs used most frequently in both treatment groups were carbamazepine (55.6% of patients in the rufinamide group and 46.1% of patients in the placebo group) and valproate (27.6% and 29.8%, respectively). The percentages of patients who received other individual AEDs were generally similar in the 2 treatment groups. Similar percentages of rufinamide-treated patients (73.7%) and placebo-treated patients (74.0%) received non-AED concomitant therapy. However, only 2 medications (paracetamol and ibuprofen) were taken by more than 10% of the patients in either group.

2. Adult double-blind subgroup

As in the all double-blind subgroup, the profiles were similar for the 2 treatment (rufinamide and placebo) groups. Approximately half of the patients were males. The mean age was 35.8 years in the rufinamide group and 37.7 years in the placebo group; more than 98% of patients in each group were between the ages of 17 and 64 years. The mean weights were 72.2 kg and 74.7 kg, respectively; more than 93% of the patients weighed more than 50 kg.

Concomitant AEDs and non-AEDs, received by more than 5% and 10% of the patients respectively in either treatment group (rufinamide or placebo) were analyzed. All of the studies included in the AED pool, enrolled patients who were receiving stable doses of one to three AEDs. The most frequently used concomitant AEDs in both treatment groups were carbamazepine (68.3% of patients in the rufinamide group and 64.1% of patients in the placebo group), valproate (25.6% and 25.9%), and phenytoin (22.2% and 19.0%). The percentages of patients who received other concomitant AEDs were similar in the 2 treatment groups. Overall, 65.4% of rufinamide-treated patients and 80.3% of placebo-treated patients received non-AED concomitant therapy. However, only one medication (paracetamol) was taken by more than 10% of the patients in either group.

3. LGS double-blind subgroup

In these analyses, approximately 62% of the patients were males in each group (rufinamide and placebo). The mean age was approximately 14 years in each group, with 42% (rufinamide) and 52% (placebo) of the patients being less than 12 years old. The mean weight was 44.1 kg in the rufinamide group and 40.2 kg in the placebo group.

Patients in the LGS study were to be receiving stable doses of one to three AEDs. The concomitant AEDs used most frequently in more than 5% of patients were the same in both treatment groups: valproate, lamotrigine, clonazepam, and topiramate. Overall, 81.1% of rufinamide-treated patients and 73.4% of placebo-treated patients received non-AED concomitant therapy. However, only 2 medications (paracetamol and amoxicillin) were taken by more than 10% of the patients in either group.

4. Indication Relevant Subgroups

The demographics of the relevant representative population based on the two sought indications that include adolescents and adults for the partial epilepsy indication and pediatrics and adults for the LGS indication that is summarized in a table in section 7.2.1.2 is presented here for ease of reference.

SAFETY TABLE 7.2.1.2.B									
DEMOGRAPHICS OF POPULATION RELEVANT TO INDICATION									
Study Subgroup		Partial Seizures Double-blind				LGS Double-blind			
Population		Adolescent		Adult		Pediatric		Adult LGS	
Age Groups (years)		12 - < 16		≥ 16		4 - < 16		≥ 16	
Number Treated		N		N		N		N	
Percent		(%)		(%)		(%)		(%)	
Treatment		R = 4	P = 0	R = 716	P = 290	R = 49	P = 43	R = 25	P = 21
CHARACTERISTICS									
Sex	Male	3	0	361	156	29	28	17	12
		75	0	50.4	53.8	59.2	65.1	68.0	57.1
	Female	1	0	355	134	20	15	8	9
		25	0	49.6	46.2	40.8	34.9	32.0	42.9

Race ^a	White / Caucasian	0	0	130		39	34	23	19
		0	0	18.2		79.6	79.1	92.0	90.5
	Black	0	0	8		5	3	1	1
		0	0	1.1		10.2	7.0	4.0	4.8
	Oriental	0	0	3		0	0	1	0
		0	0	0.4		0	0	4.0	0
	Other	0	0	15		5	6	0	1
		0	0	2.1		10.2	14.0	0	4.8
	Not reported ^b	4	0	560		0	0	0	0
		100	0	78.2		0	0	0	0
Age (yrs)	Mean	14.75	0	35.91	37.65	9.71	9.23	23.88	22.52
	Range	14-15	0	16-72	17-68	4-15	4-15	16-35	16-37
	Median	15	0	35	37	10.00	9.00	23	17
Weight (kg)	N	4	0	711	288	49	43	25	21
	Mean	51.75	0	72.27	74.70	34.06	31.19	63.74	58.77
	Median	48.0	0	71.0	72.15	29.10	27.0	61.80	64
	Range	36-75	0	40-129	34.60-145.40	15.50-138.50	16.20-76.0	34.60-113.40	34.10-86.00
	< 29	0	0	0	0	24	24	0	0
		0	0	0	0	49.0	55.8	0	0
	> 29-50	2	0	47	9	18	13	7	7
		50.0	0	6.6	3.1	36.7	30.2	28.0	33.3
	> 50	2	0	664	279	7	6	18	14
		50.0	0	92.7	96.2	14.3	14.0	72.0	66.7
	Missing	5	2	0	0	0	0	0	0
		0.7	0.7	0	0	0	0	0	0

Ref: Sponsor's Post-text Tables 9 and 10, submitted Sep 6, 2006

Note:

a= The possible choices for race on the rufinamide CRFs that collected this information were White/Caucasian, Black, Oriental, or Other. b = information about race was not collected in all studies. Hatched areas indicate areas of concern (see comments in review); Treatment R= Rufinamide, P= Placebo

Disposition and Overall Profile of Dropouts

The disposition of the subjects that is discussed and summarized in a table in section 7.1.3.1 is presented here for ease of reference.

SAFETY TABLE 7.1.3.1.A												
OVERVIEW OF PATIENT DISPOSITION BY TREATMENT & STUDY												
Criteria		ALL DOUBLE-BLIND + OPEN-LABEL			DOUBLE-BLIND SUBGROUPS							
		Double-Blind		Extension	Adult		Monotherapy		LGS		Pediatric	
		R	P	R	R	P	R	P	R	P	R	P
		N	N	N	N	N	N	N	N	N	N	N
		(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Number Treated		1240	635	1382 [#]	720	290	208	67	74	64	212	197
		100	100	100 [#]	100	100	100	100	100	100	100	100
Number Completed		997	547	416 [#]	536	236	193	58	64	59	183	180
		80.4	86.1	30.1 [#]	74.4	81.4	92.8	86.6	86.5	92.2	86.3	91.4
Number Discontinued		241	88	945	182	54	15	9	10	5	29	17
		19.4	13.9	68.4	25.3	18.6	7.2	13.4	13.5	7.8	13.7	8.6
Reason	Unsatisfactory Therapeutic Effect	80	27	575	71	22	0	0	3	1	5	4
		6.5	4.3	41.6	9.9	7.6	0	0	4.1	1.6	2.4	2.0
	Adverse Experience	100	27	134	74	18	7	2	6	0	15	4
		8.1	4.3	9.7	10.3	6.2	3.4	3.0	8.1	0	7.1	2.0

Consent	17	10	79	11	5	2	3	1	1	2	2
	1.4	1.6	5.7	1.5	1.7	1.0	4.5	1.4	1.6	0.9	1.0
Withdrawal	13	5	71	7	1	3	1	0	1	3	2
	1.0	0.8	5.1	1.0	0.3	1.4	1.5	0	1.6	1.4	1.0
Administrative problem	4	3	21	0	1	1	0	0	0	1	0
	0.3	0.5	1.5	0	0.3	0.5	0	0	0	0.5	0
Lost to Follow-up	12	11	14	6	4	1	3	0	2	3	4
	1.0	1.7	1.0	0.8	1.4	0.5	4.5	0	3.1	1.4	2.0
Does Not Meet Protocol Criteria	2	3	13	2	2	0	0	0	0	0	1
	0.2	0.5	0.9	0.3	0.7	0	0	0	0	0	0.5
Death	4	0	3	2	0	1	0	0	0	0	0
	0.3	0	0.2	0.3	0	0.5	0	0	0	0	0
Abnormal Lab Value	9	2	35	9	1	0	0	0	0	0	0
	0.7	0.3	2.5	1.3	0.3	0	0	0	0	0	0
Other	2	0	21	2	0	0	0	0	0	0	0
	0.2	0	1.5	0.3	0	0	0	0	0	0	0
No Information on Disposition											

Ref: Sponsor's Tables 2.1-1 and 2.1-2, pp 44-45, ISS, Section 2

Note:

= In the open-label extensions, "completed" patients were those who were still participating in the study when Sponsor ended product development and who returned to the study site for a termination visit.

R= Rufinamide; P= Placebo; LGS= Lennox-Gastaut syndrome; Hatched areas

The disposition of the subjects included in Table 7.1.3.1.A can be discussed under two broad categories, viz., 1) Patients in All Double-blind with open-label extension subgroup and 2) Patients in Double-blind studies by subgroup. Under the latter, information from the subgroup of patients representative of the sought indication, viz., the adult double-blind and the LGS double-blind subgroups is also presented.

1. Disposition of Patients in All Double-blind with open-label extension subgroup

As shown in Table 7.1.3.1.A, similar percentages of patients in the rufinamide group (80.4%) and the placebo group (86.1%) completed double-blind treatment. The most common reasons for premature discontinuation were adverse events (8.1% with rufinamide and 4.3% with placebo) and unsatisfactory therapeutic effect (6.5% and 4.3%, respectively). Other reasons for premature discontinuation occurred in similar percents of patients in the two treatment groups.

According to the sponsor, patients participating in the open-label extensions could continue receiving rufinamide indefinitely. When the sponsor discontinued development of rufinamide, 30.1% of the patients were still receiving drug and returned to the study sites for termination visits. The most common reason for premature discontinuation of the remaining patients in the open-label extensions was unsatisfactory therapeutic effect (41.6%). However, it is important to note that the maximum duration of exposure to rufinamide in these studies was long, ranging from 3 to 8.5 years.

2. Disposition of Patients in Double-blind studies by subgroups

As shown in Table 7.1.3.1.A for double-blind studies, among the patients who received rufinamide, 74.4% to 92.8% completed the studies, as did 81.4% to 92.2% of the patients who received placebo depending on the subgroup. The most common reasons for premature discontinuation of rufinamide were unsatisfactory therapeutic effect (0% to 9.9%) and adverse events (3.4% to 10.3%), depending on the subgroup. They were also the most common reasons for premature discontinuation of placebo (0% to 7.6%) and (0% to 6.2%). Other reasons for

premature discontinuation occurred in similar percents of patients in the 2 treatment groups within each study category for the four subgroups.

Disposition of the diabetic neuropathy subgroup and healthy volunteer subgroup is discussed in section 7.1.3.1.

IV. SUMMARY AND DISCUSSION ON ASSESSMENTS AND FINDINGS

The final recommendations on the safety of rufinamide were driven by the ensuing conclusions and discussions involving safety evaluations.

The clinical safety data of rufinamide can be discussed and summarized under the following broad headings of:

- A) Adequacy of Safety Assessments
- B) Treatment Emergent Findings
- C) Risk-Benefit Assessments

A) Adequacy of rufinamide safety data base and assessments

In the rufinamide drug development program certain limitations questioned the adequacy of some aspects of the safety data base. These inadequacies were related to a) safety assessments and b) population studied.

a) Safety Assessments

For some of the chosen parameters in vitals and labs, their respective set criteria that were considered significant changes or those changes thought to be clinically notable, were liberal (e.g., BUN, diastolic BP). However, with such larger margins, the results for isolated parameters generally did not seem to influence the assessments because there were no worrisome signals when the evaluations involved other parameters that typically constituted a clinically meaningful panel. For e.g., isolated BUN elevations without creatinine elevations or isolated diastolic BP changes without other changes in SBP or HR or when DBP mean changes were not significant did not raise concerns.

Sufficient information was sometimes lacking or inadequate- a) disposition of patients with clinically notable changes was not provided and the outcome was unknown, b) insufficient parameters such as an incomplete thyroid panel due to missing thyroxine levels or an incomplete LFT assessment due to missing alkaline phosphatase values, c) insufficient information such as the lack serum sodium values in patients flagged as an SAE due to hyponatremia, d) the lack of absolute QT/QTc values in the TQT database, etc.

Sometimes the data was not presented in a clinically meaningful manner (changes in lab values configured to represent a condition such as elevated TSH and decreased thyroxine to suggest hypothyroidism).

Sometimes the lack of recognition and or the characterization of a signal such as QT shortening, status epilepticus, leucopenia, neutropenia, etc., resulted in the lack of acquiring additional data or making assessments that perhaps may have been achieved otherwise.

b) Population

As noted in section 7.2.1.2 (Table 7.2.1.2 A) and table 7.2.1.2.B above, it is quiet eminent that not enough adolescents (only 4 were studied) were studied

b(4)

Based on the demographics of the population that was exposed to rufinamide in clinical trials, all races that are congruent with the demographics of the US population were not studied (Table 7.2.1.2.A). Further, race was not reported in nearly half of the patients in clinical studies.

As of July 1, 2005 (based on Census 2000; <http://www.infoplease.com/ipa/A0762156.html>) the US population consists of, amongst others, 80.2% Whites, 12.8% Black/African Americans, 14.4% Hispanic/Latino, and 4.3% Asian. Specifically, not enough African / Black patients were studied (all double-blind = 4.2%, all studies combined = 4.3%, adult double-blind = 1.1 and LGS double-blind = 8.1%) and Hispanic population demographics is unknown. The inadequacy with respect to the African / Black population is highlighted further by the fact that complications, including SUDEP (see findings below), are known to occur at a higher frequency in the African / Black population. If a licensure is sought for marketing rufinamide (or any drug) in the US, it is imperative that a demographically similar patient population representative of the US general population is evaluated in clinical trials for which the drug is intended.

The aforementioned safety related inadequacies and lapses, however, did not significantly impact the overall recommendation. These deficiencies, coupled with the treatment emergent findings (see below) were of the magnitude that was generally comparable (see risk-benefit below) to the approved agents (other than short QT). Overall, these inadequacies and lapses did not impact approvability and could be addressed in labeling.

B) Treatment Emergent Findings

Treatment emergent findings were related to-

- Adverse Events (AE)
- Laboratory Findings
- Cardiac (QTc/ECG) Findings
- Vital Signs Findings
- Physical Examination Findings
- Tolerance, Abuse and Dependence
- Effects of Withdrawal and Rebound
- Drug Overdose

ADVERSE EVENTS (AE)

Treatment emergent AEs that occurred in this drug development program can be discussed under the following broad headings-

1. Overview of AE
2. Fatal AE (Deaths)
3. Non-fatal SAE
4. Discontinuations due to AE

5. Other Significant Adverse Events- Rash, Hypersensitivity, CNS/Neurocognitive, Status Epilepticus
6. Common AE by Study Population Subgroup, Preferred Term, Severity and Dose
7. Occurrence of Adverse Events in Subpopulations of Patients by Age, Sex, Race and Concomitant Medication
8. Adverse Events and Rufinamide Plasma Concentration

1. Overview of All Treatment Emergent AE

Table 1.3.3.A provides an overview of treatment emergent adverse events (deaths, non-fatal SAEs, Discontinuations due to AE, Common AE with severity) for the adult double-blind and LGS double-blind subgroups- _____ Appendix

Table 5 provides an overview of all treatment emergent AE for all the subgroups that were analyzed.

b(4)

As shown in Table 1.3.3.A (hatched areas), AEs that were non-fatal and serious or those that led to discontinuations occurred at a greater incidence in the rufinamide treated patients compared to placebo (controlled trials). Further, AEs that were moderate and severe in intensity also occurred at a greater incidence in the rufinamide treated patients compared to placebo (hatched areas in Table 1.3.3.A). Such results were also generally true for the all double-blind subgroups combined, monotherapy double-blind subgroup (except events that were of moderate severity) and the pediatric double-blind subgroup (Appendix Table 5).

SAFETY TABLE 1.3.3.A OVERVIEW OF ALL ADVERSE EVENTS				
Event	Adult Partial Seizures, DB, Adjunctive Therapy		LGS, DB, Adjunctive Therapy	
	Rufinamide (N=720) N (%)	Placebo (N=290) N (%)	Rufinamide (N=74) N (%)	Placebo (N=64) N (%)
Deaths	2 (0.3)	3 (1.0)	0	0
Non-fatal SAE	51 (7.1)	10 (3.4)	3 (4.1)	2 (3.1)
AE → DC	74 (10.3)	18 (6.2)	6 (8.1)	0
Any AE	580 (80.6)	236 (81.4)	60 (81.1)	52 (81.3)
Mild AE	215 (29.9)	110 (37.9)	17 (23)	31 (48.4)
Moderate AE	274 (38.1)	96 (33.1)	33 (44.6)	15 (23.4)
Severe AE	91 (12.6)	30 (10.3)	10 (13.5)	6 (9.4)
Ref: Modified Sponsor's Table 2.7.4.2-1, p 25, 2.7.4, Module 2				

Discussions on treatment emergent Fatal AE (deaths), non-fatal SAE, Discontinuations due to AE, Other significant AE and Common Adverse Events will ensue.

2. Treatment Emergent Deaths

Twenty-three of the unique 1978 patients who received rufinamide (and an additional 5 patients who received placebo) died in this drug development program (Table 7.1.1.A). The overview of deaths that is discussed and summarized in a table in section 7.1.1 is presented here for ease of reference.

SAFETY TABLE 7.1.1.B OVERVIEW OF DEATHS	
All Deaths (all treatments) (N)	28
During Placebo treatment (N)	5

During Rufinamide treatment (N)	23
Deaths during study or < 30 days after last dose of Rufinamide (N)	18
Deaths > 30 days after last dose of Rufinamide (N)	5
Sudden Death - during study or < 30 days after last dose of Rufinamide (N)	Sponsor = 8*, FDA = 9*
Sudden Death - > 30 days after last dose of Rufinamide (N)	0
Deaths Attributable to other underlying causes (N)	12
Deaths indeterminable if it was sudden or not (N)	2
Rufinamide Treatment Gender (N)	Male = 11, Female = 12
Rufinamide Treatment Age (N)	> 18 = 20, < 18 = 3
Deaths in DB Studies	2 R, 5 P
Deaths in OL and or OL Extension of DB Studies	21 R, 0 P
Deaths in Mono-therapy DB Studies	0
Deaths in LGS DB Studies	0
Deaths in Diabetic Neuropathy or Healthy Volunteer Subset	0
Sudden Deaths in DB Studies	0
Autopsy (N)	Yes= 8, No= 8, Unknown [#] =7
Autopsy (N) in Sudden Death Cases (N=9)	Yes=5, No= 3, Unknown [#] =1
Sudden Death with Autopsy Findings Suggestive of Seizure as cause of Sudden death- Definite SUDEP***	5
Sudden Death following witnessed seizure or signs suggestive of seizure and no Autopsy- Probable SUDEP***	2 (0006-04411, 0052-00011)
Sudden Death without witnessed seizures or signs of seizure and no Autopsy – Probable SUDEP***	2** (3054-02071, 1282-05025)
Ref: See Table Above; Sponsor's Table 7.1-1, ISS, pp 146-147	
Note: DB= Double-blind; OL= Open-label; R = Rufinamide; P= Placebo; *=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor and therefore sponsor's calculations are based on the 8 cases. Comments are based on the 9 sudden deaths; #Unknown= Not specified if autopsy was conducted or not- most likely not conducted; **= Two cases of Sudden death (1282-05025, 3054-02071) in whom there was no autopsy and sudden death could not be attributed to witnessed seizure or signs of seizures or other causes. ***= see SUDEP discussion in text (section 7.1.1).	

In all, 28 patients died in this drug development program. Eighteen rufinamide patients died either during the clinical studies or within 30 days after receiving the last dose of study drug and 5 rufinamide patients died > 30 days after receiving the last dose of rufinamide. Seven patients (2 who received rufinamide and 5 who received placebo) died during double-blind studies, and 21 patients died while taking rufinamide either during open-label studies or open-label extension studies.

Based on a thorough understanding of sudden deaths in epilepsy and SUDEP (see SUDPEP definition, criteria and discussion in 7.1.1), the rufinamide death cases were critically examined.

As indicated in Table 7.1.1.A, in 12 cases, the deaths were attributable to other underlying causes. In two cases (patient 0008-01159 and patient 1146-00069), it was not possible to determine if these deaths were sudden or not. In one case no information was provided and in the second case, no meaningful deductions were possible because the body was found decomposed 87 days after the last dose and the autopsy was reported to be consistent with seizure.

8 deaths were considered sudden deaths by the sponsor. However, following a thorough review of the cases, in the opinion of this reviewer, an additional sudden death case was identified (Case 3054-02071). In all, there were 9 sudden death cases (witnessed or un-witnessed) in whom no other obvious underlying cause was found. Brief narratives for these 9 sudden deaths followed by reviewer comments are provided in section 7.1.1.

In 5 of the 9 sudden death cases, the cause of death was reported in the autopsy as being most consistent due to seizures (details were lacking). In two cases, although an autopsy was not performed, the most likely causes for the sudden death were seizure related- in one case (patient 0052-00011) a witnessed seizure preceded death and in a second case, (patient 006-04411) while no seizures were witnessed, there were tongue bite marks suggesting that the patient had a seizure. Therefore, 5 of the 9 sudden death cases met the definite SUDEP criteria (see section 7.1.1) because of sudden death and autopsy findings. Two (patient 0006-04411 and patient 0052-0008) of the remaining 4 sudden death cases met the probable SUDEP criteria of the sudden death (no autopsy and the death occurred following a witnessed seizure in one and with signs of a seizure [tongue biting] in the other). The remaining 2 sudden death cases (patients 3054-02071 and 1282-05025) without an autopsy (or associated seizures or evidences of a seizure) and with no other identifiable causes, also met a probable SUDEP criteria based on the circumstances surrounding the deaths. In essence, 5 sudden deaths met the definite SUDEP criteria and 4 sudden deaths met the probable SUDEP criteria. All rufinamide deaths could therefore be considered SUDEP. The comparative SUDEP rates are discussed in section 7.1.1 (Table 7.1.1.C).

However, in the context that QT shortening is known to occur with rufinamide (see Safety QT review by Dr. Jones, PK review on special cardiac QT studies and QT discussion below) and the concerns that QT shortening like QT prolongation is also associated with the risk of sudden cardiac death, the importance of the causes of the sudden deaths and their attribution to whether they were SUDEP or due to a specific rufinamide induced fatal cardiac arrhythmia, become important and relevant particularly when rufinamide is the first antiepileptic that carries this recognized pro-arrhythmic trait.

To further explore the extent of the plausibility of a rufinamide induced QT abnormality as the cause of death in all the 9 sudden deaths, additional critical analyses were conducted by this reviewer. These involved estimates on sudden deaths in drug development programs for approved drugs with respect to the background SUDEP death rate and their comparison to the rufinamide death rate. The notion for such a comparative approach resided in the logic that the rufinamide death rates, if found to be greater than the background SUDEP rate and or greater than the SUDEP rates for the approved drugs, was indicative of the existence of a direct relation between rufinamide and the sudden deaths. The death rates within the rufinamide program for the different subgroups are discussed in section 7.1.1 (Table 7.1.1.C). The comparative rate of sudden death for some of the approved drugs and the background SUDEP rate that is discussed and summarized in a table in section 7.1.1 are presented here for ease of reference.

SAFETY TABLE 7.1.1.D				
RATES OF SUDDEN UNEXPLAINED DEATHS IN EPILEPSY (SUDEP) - COMPARISON				
Name (Approval Date ^D)	Exposed (N)	Patient-years ^A	SUDEP (N)	SUDEP Rate ^B
Rufinamide (approval date not applicable)	1978	2552.96	8 (Sponsor)	0.0031*
	1978	2552.96	9 (Reviewer)	0.0035*
Lamictal (Lamotrigine) (1994)	4700	5747	20	0.0035
Topamax (Topiramate) (1996)	?	2796	10	0.0035
Neurontin (Gabapentin) (1993)	2203	2103	8	0.0038
Gabitril (Tiagabine) (1997)	2531	3831	10	0.0026
Zonegran (Zonisamide) (2000)	991	??	9	0.0077 (7.7/1000)
SUDEP Background Rate ^C	0.0005 For General Population with Epilepsy 0.005 For Patients with Refractory Epilepsy			
Ref: 2006 PDR; pp 1452, 2441, 2500, 998, 1090; Table 7.1.1.C;				
Note:				

A= Exposure Rate, B= Incidence Per Patient Year (also called Incidence Density); C= Source- 2006, PDR, Lamictal, p. 1452; D= Source: <http://cdernet.cder.fda.gov/>- Drugs at FDA; Lyrica (pregabalin) was approved for epilepsy in 2005 (earlier approval for neuropathy) but information on SUDEP is not mentioned. Hence this was not included in this table.

*=Case 3054-02071 was not identified as a case of Sudden Death by the Sponsor and therefore sponsor's rates were based on the 8 cases. The rates based on the 9 sudden deaths were calculated by this reviewer.

As shown in Table 7.1.1.D, the rufinamide SUDEP rate is similar to those drugs in the market and well within the background SUDEP rate. These results did not raise concerns even if such an association between rufinamide and QT is known to exist because the observed QT shortenings were not associated with fatal cardiac arrhythmias or other CVS related AEs in these clinical trials. Further, all the approved agents, have neither been tested formally for QT effects nor have they hitherto caused worrisome fatal arrhythmias. Although different chemically, but like rufinamide, with a similar mechanism of action on the sodium dependent channels, it appears that such pro-arrhythmic potential whether established (as in the case of rufinamide) or not (as in the others), based on the SUDEP estimates, does not appear to manifest as sudden deaths over and beyond the background rates of SUDEP. Of course, this does not alleviate the concern on the effects of rufinamide on QT or that it has the potential to cause fatal arrhythmias in predisposed populations such as those with congenital QT abnormalities (see QT/ECG below).

In addition to these issues involving sudden deaths, there were other findings of concern in patients who died. In two death cases hyperthermia was an observed associated event.

In one complicated case (patient 0003-06419 in Table 7.1.1.A) that is discussed in detail in section 7.1.1, while the death was not considered sudden, there were several unusual adverse events that this patient experienced before dying. These were hyperthermia, hemorrhagic pancreatitis and the autopsy findings of cerebral edema and herniation. This patient, following full recovery from a series of (5) seizures, developed fever, abdominal pain and vomiting. A diagnostic laparotomy revealed hemorrhagic pancreatitis, peritonitis and intestinal paresis (no details as to how one arrived at such diagnoses). The WBC count was noted to be 14.6×10^9 /L (55% N, 39% bands, 9% L and 7% M) with normal LFTs and other CBC parameters (amylase and lipase not reported). Over the next 48 hours, the patient became stuporous with rising temperatures (106.16°F and 107.24°F) and a clinical diagnosis of cerebral edema was made (no details as to how one arrived at such a diagnosis). Repeat WBC continued to show a shift to the left (with bands) and the patient's clinical condition continued to deteriorate with continued fever and requiring intubation with mechanical ventilation. Subsequently the patient died and autopsy showed cerebral edema and herniation. In this case, the peritonitis, although on antibiotic therapy, probably continued to contribute to the fever, the resilient high fever coupled with unexplained cerebral edema and herniation could not be solely attributable to the underlying "peritonitis" or seizures. Of note, the patient was on a carbonic anhydrase inhibitor, and it is known that patients are at greater risk of developing a heat related disorder with the concomitant administration of anticonvulsants and carbonic anhydrase inhibitors (see 2006 PDR, Topamax [p. 2441]).

In a second case (patient Number 3054/2071), while the cause of sudden death was not known, approximately 6 months before death, this 4 year old female, while receiving rufinamide (started Sep 1999), experienced several episodes of high fever (Oct 99, Nov 99, ~~Feb 00~~) that was not associated with status or seizures or an infective focus (workup during ~~Feb 00~~ hospitalization between the 1st and 17th, was negative for an infective source). A diagnosis of malignant hyperthermia (neurogenic origin per sponsor) was made. She recovered fully and was

b(6)

discharged from the hospital after a stay of 17 days in — No details or criteria that led to the diagnosis of malignant hyperthermia were provided.

These two death cases, thus, brought the plausibility of the association of hyperthermia and rufinamide.

While the full picture of the clinical syndrome of malignant hyperthermia was not provided (either it did not occur or it was not described adequately) and therefore the rufinamide-hyperthermia association arguable, other considerations that further favor such plausibility of this association are-

- a. Hyperthermia with oligohidrosis (no indication that rufinamide patients experienced oligohidrosis) is reported in the warning section of the labels of other anticonvulsants that have a similar mechanism of action as rufinamide on the sodium channels (Zonegran and Topamax, see Table 1.3.3.B),
- b. In malignant hyperthermia, a genetically heterogeneous disorder, disease-causing mutations have been identified in the genes encoding the α -subunit of the voltage gated sodium channels in addition to the ryanodine receptor (that interacts with L-type calcium channel) (ref: Neurology in Clinical Practice, Bradley et al, 4th edition, Chapter 70, p. 1856 [ISBN 0-7506-7469-5), and
- c. The known (as noted in the Topamax label) predisposition for hyperthermia in patients simultaneously receiving drugs such as carbonic anhydrase inhibitors or anticholinergics (as was the case in patient 0003-06419 who was receiving acetazolamide).

In summary, all the 9 sudden deaths best matched the profile of SUDEP (5 definite and 4 probable). The rufinamide SUDEP rates were comparable to the rates of the anticonvulsants in the US market most of which, additionally, had a similar mechanism of action. Because the observed death rates were well below the background SUDEP rate, the likelihood of the influence of a specific cause for sudden death such as QT shortening, at best, is remote. Overall, with respect to deaths, rufinamide exhibited a safety profile comparable to the approved agents. However, the concern of QT in some predisposed populations (congenital QT) persists (see QT/ECG below). SUDEP as ϵ should be included in the label.

b(4)

Despite the lack of details and confirmation of the occurrence of the syndrome of malignant hyperthermia, the association between rufinamide and hyperthermia, as with the class agents, was recognizable (see Table 1.3.3.B).

b(4)

3. Rufinamide and Non-Fatal Serious Adverse Events

Overview of All Non-Fatal SAE

The overview of all non-fatal SAE that is discussed and summarized in a table in section 7.1.2 is presented here for ease of reference. Table 7.1.2.A provides an overview of all the non-fatal SAEs by subgroups of the study analysis population. Table 6 in the Appendix displays the non-fatal serious adverse events (by SOC) that occurred in more than one patient per treatment group for all the double-blind subgroups (all combined, adult, monotherapy, LGS and pediatric).

As shown in Table 7.1.2.A (hatched areas), *the incidence of any non-fatal SAE (by SOC term) experienced was greater across all the subgroups for those patients who received rufinamide compared to those who received placebo.*

SAFETY TABLE 7.1.2.A OVERVIEW OF TREATMENT EMERGENT ANY NON-FATAL SAE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				
Exposed	1240	100	635	100
Any AE (Patient N)	78	6.3	25	3.9
All Study Subgroups Combined*				
Exposed	1978	100	--	--
Any AE (Patient N)	268	13.5	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE (Patient N)	51	7.1	10	3.4
Adult Double-blind with Open-label*				
Exposed	932	100	--	--
Any AE (Patient N)	124	13.3	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE (Patient N)	7	3.4	0	0
LGS Double-blind				
Exposed	74	100	64	100
Any AE (Patient N)	3	4.1	2	3.1
LGS Double-blind with Open-label*				
Exposed	135	100	--	--
Any AE (Patient N)	22	16.3		
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE (Patient N)	16	7.5	11	5.6
Pediatric Double-blind with Open-label*				
Exposed	391	100	--	--
Any AE (Patient N)	66	16.9	--	--
Ref: Tables 7.2-1, 7.2-2, 7.2-4, 7.2-5, 7.2-7, 7.2-8, 7.2-9, 7.2-12, 7.2-13, ISS, pp 151-165; *Information presented were extracted from the Safety Addendum, Jun 2006, pp 1-97				
Note: Hatched areas = greater incidence with rufinamide compared to placebo.				

Treatment emergent non-fatal SAE findings for the double-blind subgroups were as indicated below. Some of the non-fatal SAE were listed more than once depending on the subgroup under which they were analyzed. While each of the listed events were not discussed individually, those non-fatal SAEs that were either unique to the class of anticonvulsants or those of clinical relevance are discussed in other sections. Under Other significant AE, the CNS/neuropsychiatric, Rash, Hypersensitivity, and Status epilepticus related events are discussed. Those significant events related to labs (leucopenia [3 cases], neutropenia [2 cases], hyponatremia [3 cases]) are discussed under laboratory findings.

Treatment Emergent Non-fatal SAE in All Double-blind Subgroup

As shown in Table 6 in the Appendix, there were a total of 98 serious adverse event reports for 78 (6.3%) rufinamide-treated patients and a total of 28 serious adverse event reports for 25 (3.9%) placebo-treated patients. The estimated exposure in this population was 291.51 patient-

years for rufinamide and 149.60 patient-years for placebo. The rates of serious adverse events were therefore 26.76 and 16.71 per 100 patient-years, respectively.

The most frequently reported serious events in both treatment groups were related to epilepsy: convulsion (0.6% of patients in both treatment groups), grand mal convulsion (0.4% in the rufinamide group versus 0.6% in the placebo group), partial seizures with secondary generalization (0.3% versus 0%), status epilepticus (0.3% versus 0%), complex partial seizures (0.2% versus 0%), epilepsy (0.1% versus 0%), and petit mal epilepsy (0% versus 0.2%).

Twenty-three serious adverse event reports in the rufinamide group and 7 serious adverse event reports in the placebo group led to discontinuation of treatment.

Treatment Emergent Non-fatal SAE in Adult Double-blind Subgroup

As shown in Table 6 in the Appendix, there were a total of 56 serious adverse event reports for 51 (7.1%) rufinamide-treated patients and a total of 11 serious adverse event reports for 10 (3.4%) placebo-treated patients. The estimated exposure in this population was 187.49 patient-years for rufinamide and 74.17 patient-years for placebo. The rates of serious adverse events were therefore 27.20 and 13.48 per 100 patient-years, respectively (Ref: Sponsor's Appendix I, Table 7.3.2-2). No serious adverse events occurred at an incidence greater than 1.0%.

The most frequently reported serious events in both treatment groups were related to epilepsy: partial seizures with secondary generalization (0.6% in the rufinamide group versus 0% in the placebo group), convulsion (0.4% versus 1.0%), grand mal convulsion (0.3% in each group), and complex partial seizures (0.3% versus 0%). The most common serious event not related to epilepsy was diplopia (0.8% in the rufinamide group versus 0% in the placebo group).

Sixteen serious adverse event reports in the rufinamide group and 4 serious adverse event reports in the placebo group led to discontinuation of treatment.

Treatment Emergent Non-fatal SAE in Double-blind Mono-therapy Subgroup

As shown in Table 6 in the Appendix, no placebo-treated patient in this population experienced a serious adverse event. There were a total of 7 serious adverse event reports for 7 (3.4%) rufinamide-treated patients. The estimated exposure in this population was 27.80 patient-years for rufinamide and 2.89 patient-years for placebo. The rates of serious adverse events were therefore 25.18 and 0 per 100 patient-years, respectively. No serious adverse events occurred at an incidence greater than 1.0%.

The most frequently reported serious events were convulsion and status epilepticus, which each occurred in 2 patients. Two of the patients with serious adverse events (convulsion and epilepsy) received median doses of <400 mg/day, whereas the remaining 5 patients with serious adverse events received median doses of 2400 to 3200 mg/day.

No patient discontinued treatment because of a serious adverse event.

Treatment Emergent Non-fatal SAE in LGS Double-blind Subgroup

As shown in Table 6 of the Appendix, there were a total of 5 serious adverse event reports for 3 (4.1%) rufinamide-treated patients and a total of 2 serious adverse event reports for 2 (3.1%)

placebo-treated patients. The estimated exposure in this population was 16.04 patient-years for rufinamide and 14.19 patient-years for placebo. The rates of serious adverse events were therefore 18.71 and 14.10 per 100 patient-years, respectively. Serious adverse events led to discontinuation of treatment in 1 patient, who was in the rufinamide group and had serious adverse events of vomiting, fatigue, and rash.

Treatment Emergent Non-fatal SAE in Pediatric Double-blind Subgroup

As shown in Table 6 of the Appendix, there were a total of 17 serious adverse event reports for 16 (7.5%) rufinamide-treated patients and a total of 11 serious adverse event reports for 11 (5.6%) placebo-treated patients. The estimated exposure in this population was 50.32 patient-years for rufinamide and 46.54 patient-years for placebo. The rates of serious adverse events were therefore 31.80 and 23.63 per 100 patient-years, respectively.

Serious epilepsy-related events were convulsion (2 patients), status epilepticus (2 patients), and grand mal convulsion (1 patient) in the rufinamide group, and grand mal convulsion (2 patients) and petit mal epilepsy (1 patient) in the placebo group. Seven serious adverse event reports led to discontinuation of treatment in the rufinamide group and 2 serious adverse event reports led to discontinuation of treatment in the placebo group.

See section 7.1.2 for the treatment emergent non-fatal SAE findings in All Subgroups Combined, Adult Double-blind with Open-label Extension Subgroup, LGS Double-blind with Open-label Extension Subgroup and Pediatric Double-blind with Open-label Extension Subgroup, Diabetic Neuropathy Subgroup and Healthy Volunteer Subgroup.

4. Rufinamide and Treatment Emergent Discontinuations Due to Adverse Events

Overview of All AE → DC

The overview of all AE → DC that is discussed and summarized in a table in section 7.1.3 is presented here for ease of reference. Table 8 in the Appendix displays the adverse events (by SOC) that led to discontinuation that occurred in more than one patient per treatment group for all the double-blind subgroups (all combined, adult, monotherapy, LGS and pediatric).

Discontinuations due to treatment induced cognitive and psychiatric disorders are discussed under Other Significant AE (section 7.1.3.3)

Table 7.1.3.A provides an overview of the incidence of treatment emergent discontinuations due to any AE that occurred in each of the subgroups that the population was categorized for safety analysis. As shown in Table 7.1.3.A (hatched areas), *the incidence of any adverse events that resulted in discontinuation from the study (by SOC term) was greater across all the subgroups for those patients who received rufinamide compared to those who received placebo.*

SAFETY TABLE 7.1.3.A OVERVIEW OF TREATMENT EMERGENT DISCONTINUATIONS DUE TO ANY AE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				

Exposed	1240	100	635	100
Any AE →DC (Patient N)	100	8.1	27	4.3
All Study Subgroups Combined				
Exposed	1978	100	--	--
Any AE →DC (Patient N)	259	13.1	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE →DC (Patient N)	74	10.3	18	6.2
Adult Double-blind with Open-label				
Exposed	932	100	--	--
Any AE →DC (Patient N)	138	14.8	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE →DC (Patient N)	7	3.4	2	3.0
LGS Double-blind				
Exposed	74	100	64	100
Any AE →DC (Patient N)	6	8.1	0	0
LGS Double-blind with Open-label				
Exposed	135	100	--	--
Any AE →DC (Patient N)	18	13.3	--	--
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE →DC (Patient N)	15	7.1	4	2.0
Pediatric Double-blind with Open-label				
Exposed	391	100	--	--
Any AE →DC (Patient N)	49	12.5	--	--
Ref: Tables 7.4-1, 7.-3, 7.4-5, 7.4-7, 7.4.9, 7.4-10, 7.4-11, 7.4-14, 7.4-18, ISS, pp 181-204;				
Note:				
Hatched areas = greater incidence with rufinamide compared to placebo.				

Treatment emergent findings on AE that led to discontinuation for the various double-blind subgroups are discussed below. Some of the events were listed more than once depending on the subgroup under which they were analyzed. While each of the listed events were not discussed individually, those events that were either unique to the class of anticonvulsants or those of clinical relevance are discussed in other sections. Under Other significant AE, the CNS/neuropsychiatric, Rash, Hypersensitivity, and Status epilepticus related events are discussed. Those significant events related to labs (leucopenia [3 cases], neutropenia [2 cases], hyponatremia [3 cases]) are discussed under laboratory findings.

AEs → DC All Double-blind Subgroup

As shown in Table 8 in the Appendix, 100 (8.1%) of 1240 rufinamide-treated patients and 27 (4.3%) of 635 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 1.8% of the patients. The events most frequently leading to discontinuation with rufinamide were dizziness (22 patients), fatigue (20 patients), headache (14 patients), nausea (13 patients), and diplopia (12 patients). Rash was the cause of discontinuation for 6 (0.5%) rufinamide-treated patients and 1 (0.2%) placebo-treated patient. The occurrence of rash/ hypersensitivity is discussed in detail under other significant AE.

Also as shown in Table 8 in the Appendix, the distribution of adverse events leading to discontinuation which occurred in 5 or more patients in the rufinamide group and by median dose in mg/day, there were no apparent dose-response relationships. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken

for the maximum duration. Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups that were presented indicated that in both groups (rufinamide and placebo), a majority of patients who discontinued did so as a result of adverse events within the first 10 days of treatment.

AEs → DC Adult Double-blind Subgroup

As shown in Table 8 in the Appendix, 74 (10.3%) of 720 rufinamide-treated patients and 18 (6.2%) of 290 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 2.6% of the patients. The events most frequently leading to discontinuation of rufinamide were dizziness (19 patients), fatigue (17 patients), headache (13 patients), and diplopia (11 patients).

Also as shown in Table 8 in the Appendix, the distribution of adverse events leading to discontinuation which occurred in 5 or more patients in the rufinamide group and by median dose in mg/day, *dizziness, headache, and diplopia led to discontinuation of higher percentages of patients with median doses of 2400 to 3200 mg/day*, relative to patients with lower median doses. The results were similar when the occurrence of adverse events leading to discontinuation was examined by dose taken for the maximum duration or by maximum daily dose taken. Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups that were presented indicated that in both groups (rufinamide and placebo), a majority of patients who discontinued in the adult double-blind subgroup (as in the all double-blind combined subgroup) did so as a result of adverse events within the first 10 days of treatment.

AEs → DC Mono-therapy Double-blind Subgroup

As shown in Table 8 in the Appendix, 7 (3.4%) of 208 rufinamide-treated patients and 2 (3.0%) of 67 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 1.5% of the patients in either group. The events most frequently leading to discontinuation of rufinamide were anxiety (3 patients), nausea (2 patients), paresthesia (2 patients), and rash (2 patients). The occurrence of rash is discussed in detail in the other significant AE Section (Rash/hypersensitivity). No event led to the discontinuation of more than one placebo-treated patient.

Also as shown in Table 8 in the Appendix, the patients in the rufinamide group who discontinued because of adverse events each received the same median dose, maximum dose, and dose of maximum duration. One patient, who discontinued because of nausea, dizziness, headache, received 400 to less than 1600 mg/day. The remaining 6 patients were among the 125 patients in this population who had median doses, maximum doses, and doses of maximum duration within the range of 2400 to 3200 mg/day.

AEs → DC LGS Double-blind Subgroup

As shown in Table 8 of the Appendix, six (8.1%) of 74 rufinamide-treated patients and no placebo-treated patients discontinued study drug during the double-blind study in LGS due to adverse events. The events leading to discontinuation of more than one patient were vomiting (3 patients), somnolence (2 patients), and rash (2 patients). No patient had laboratory abnormalities as a primary reason for discontinuation. Rash is discussed separately under Other Significant AE.

Of the 6 patients in this LGS double-blind population with adverse events leading to discontinuation, one (who discontinued due to rash) received a median dose of <10 mg/kg/day, one (who discontinued due to somnolence) received a median dose of 10 to <20 mg/kg/day, and one (who discontinued due to pneumonia) received a median dose of more than 45 mg/kg/day. The remaining three patients (who discontinued due to a combination of the remaining events as shown in Table 8 of the Appendix) received median doses of 30 to 45 mg/kg/day. The results were similar by the dose of maximum duration and by maximum daily dose. Three of the 6 patients discontinued due to adverse events that began between Day 2 and Day 17 of treatment. The remaining 3 patients discontinued due to adverse events that began on Day 34 (anorexia, somnolence, and vomiting), Day 36 (somnolence), and Day 59 (pneumonia).

AEs → DC Pediatric Double-blind Subgroup

As shown in Table 8 of the Appendix, in the double-blind studies in pediatric patients, 15 (7.1%) of 212 rufinamide-treated patients and 4 (2.0%) of 197 placebo-treated patients discontinued treatment due to adverse events. No adverse event was cited as a reason for discontinuation of more than 1.4% of the patients. The events most frequently leading to discontinuation of rufinamide were fatigue, convulsion, and rash (3 patients each). Rash is discussed separately under Other Significant AE.

As shown in Table 8 in the Appendix, the distribution of adverse events that led to discontinuation in more than one rufinamide-treated patient, by median dose in mg/kg/day and in mg/day, respectively, did not suggest an apparent dose-response relationship. But the small number of events limited the ability to draw conclusions from these data.

The results were similar when analyzed by the dose taken for the maximum duration or by the maximum daily dose taken. Kaplan-Meier curves of the time to onset of the first adverse event leading to discontinuation in the 2 treatment groups were presented. In both groups, a majority of patients who discontinued did so as a result of adverse events with early onset (within the first week of treatment).

See section 7.1.3 for the treatment emergent AEs → DC findings in All Study Subgroups Combined, Adult Double-blind with Open-label Extension Subgroup, LGS Double-blind with Open-label Extension Subgroup, Pediatric Double-blind with Open-label Extension Subgroup, Diabetic neuropathy Subgroup and Healthy Volunteer Subgroup.

5. Treatment Emergent Other Significant Adverse Events

Under this subset analyses, the sponsor provided results on certain conditions of interest that are known to occur typically with antiepileptics. These were related to rash, hypersensitivity reaction, cognitive and psychiatric effects and status epilepticus.

Skin Rash & Hypersensitivity Reactions as Other Significant AE

Table 7 in the Appendix shows the incidence of rash (using MedDRA Preferred Terms individually and pooled together into an overall category of rash) for all patients with epilepsy who received study drug in double-blind studies by subgroups. Table 7.1.3.3.A (re-presented for convenience) provides an overview of all rashes that occurred in the pediatric and adult double-blind subgroups with reference to all skin/subcutaneous adverse events.

SAFETY TABLE 7.1.3.3.A OVERVIEW OF RASH						
SOC	All Double-blind		Pediatrics Double-blind		Adult Double-blind	
	Rufinamide N = 1240	Placebo N = 635	Rufinamide N = 212	Placebo N = 197	Rufinamide N = 720	Placebo N = 290
Skin/Subcutaneous n (%)	122 (9.8)	52 (8.2)	25 (11.8)	8 (4.1)	73 (10.1)	30 (10.3)
All Rash n (%)	38 (3.1)	21 (3.3)	11 (5.2)	4 (2.0)	21 (2.9)	11 (3.8)
Ref: Sponsor's Appendix I, Table 7.4.1-1 for All Double-blind combined; Appendix I, Table 7.4.1-2 for pediatric patients; Appendix I, Table 7.4.1-3 for adults with partial seizures; Sponsor's Table 7.3-1, ISS. Note: Hatched areas indicate significance (see comments in the review section) in the pediatric population.						

Rash occurred in similar percentages of rufinamide-treated patients (3.1%) and placebo-treated patients (3.3%) in the all double-blind combined subgroup, even when the incidence was not corrected for duration of exposure. Rash was a serious adverse event in 3 (0.2%) and 1 (0.2%) patients, who received rufinamide and placebo respectively. Rash led to discontinuation of treatment in 10 (0.8%) and 1 (0.2%) patients, who received rufinamide and placebo respectively. The incidence of rash in the pediatric double-blind subgroup showed the greatest differences between rufinamide and placebo (11 [5.2%] vs. 4 [2.0] respectively).

None of the 1978 patients (all subgroups combined) experienced erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Overall, rash was a serious adverse event in 5 (0.3%) patients and led to the discontinuation of treatment in 24 (1.2%) patients.

Kaplan-Meier curves of the time to first occurrence of rash for all double-blind studies combined, adult double-blind subgroup, LGS double-blind subgroup, and the pediatric double-blind subgroup were plotted. In the all double-blind subgroup and in adult double-blind subgroup, the curves showed that the onset of rash was similar in both treatment groups, and that the onset of rash was distributed over the course of treatment. There was no sudden increase in onset early or late in treatment. However, in the LGS and pediatric populations, rash tended to occur during the first 2 weeks of treatment.

Three patients had a serious adverse event coded as hypersensitivity and 4 patients (1 of those 3, plus 3 more) discontinued due to hypersensitivity. A total of 5 patients (2 with serious adverse events coded as hypersensitivity and 3 others with serious adverse events coded as pyrexia or rash) suffered an antiepileptic drug hypersensitivity syndrome (fever, rash, and any evidence of internal organ involvement). In all cases, the reaction appeared during the first 4 weeks of treatment. All patients were children. None of them had mucosal involvement or blistering of the skin. All patients quickly recovered after discontinuation of rufinamide. These five patients were-

Patient 0005-02670 (Study 022): SAE- Rash, Allergic Reaction, Fatigue + Discontinuation

About 2 weeks after start of rufinamide therapy, the patient, a 12-year old male experienced a morbilliform rash (fever was not mentioned as an adverse event) and elevated LFTs (moderate increase in SGPT, from 69 U/L at baseline to 127 U/L, and in SGOT, from 56 U/L at baseline to 147 U/L and increase in GGT). Concomitant AEDs were lamotrigine, valproate, and ethosuximide. Lamotrigine had been started about 8 weeks before the baseline visit. Both rufinamide and lamotrigine were discontinued and the patient recovered completely within 4 days of this event.

Patient 1260-03117 (Study 021P): SAE- Hypersensitivity (Allergic reaction) + Discontinuation

This 8-year-old female, 12 days after the start of rufinamide, experienced facial edema, dermatitis (rash), lethargy, and decreased appetite. The patient was described as ill-appearing with fever, facial swelling, abdominal discomfort, bilateral otitis, and enlarged left preauricular cervical lymph nodes. Cefuroxime axetil had been started 6 days before the onset of the rash for otitis media. Liver enzymes and eosinophils were within normal limits performed 3 days after the onset of the rash. The patient was discontinued from the study. Within 15 days of the onset of the adverse events, the patient completely recovered.

Patient 0005-04408 (Study 021PE): SAE- Hypersensitivity

This 12-year-old female received placebo during the double-blind phase of Study 021P and then entered the open-label Extension Phase. Laboratory tests obtained at that time revealed all values within the normal ranges. On Day 29 of rufinamide treatment, she developed a fever, throat hyperemia, and general weakness, diagnosed as a cold. She was treated with metamizole and acetylsalicylic acid/paracetamol/caffeine. Three days later, she developed a punctate confluent rash that disappeared. The fever recurred on Day 39, and throat hyperemia was again observed. The patient received co-trimoxazol. Three days later, she had darkened urine (note-hematuria was not confirmed), facial edema, and confluent spotted rash. Treatment consisted of ampicillin and taverfyl. The patient was hospitalized on Day 43 in a stuporous state (regarded as life-threatening), suffering from high temperature, intoxication, severe facial edema, edema of neck, tongue and facies, abundant papular rash, and urticaria. Acute respiratory viral infection, toxic allergic rash, and hepatitis were diagnosed. Rufinamide treatment was stopped on Day 60 due to adverse events. Laboratory tests performed on Day 59 revealed values of 82.08 mmol/L for total bilirubin (normal range, 0-42.75 mmol/L), 49.59 mmol/L for direct/conjugated bilirubin (normal range, 0-5.10 mmol/L), 1335 U/L for LDH (normal range, 0-500 U/L), 1345 U/L for SGOT (normal range, 0-100 U/L), and 2165 U/L for SGPT (normal range, 0-110 U/L). The patient was discharged in satisfactory condition on Day 71. No follow-up laboratory data were recorded. The investigator considered the hypersensitivity event not related to study medication but considered it possible that an interaction between anti-epileptic medication and co-medication in the presence of a viral infection could have contributed to the onset of the event. See also Section 8.1.2.3, Clinically Notable Values.

Patient 1266-03109 (Study 021PE): SAE- Rash, Pyrexia (fever)

This 8-year-old black male developed fever and a rash on day 11 of rufinamide treatment. No laboratory data were reported prior to these events. A laboratory test performed 3 days later revealed a normal value for eosinophils; slightly low values for WBCs ($2.90 \times 10^9/L$; normal range, $3-15 \times 10^9/L$) and neutrophils (28.37%; normal range, 30-90%); an elevated value for monocytes (20.44%; normal range, 0-20%); and elevated values for LDH (614 U/L; normal range, 0-500 U/L), SGOT (278 U/L; normal range, 0-100 U/L), and SGPT (322 U/L (normal range, 0-110 U/L). Rufinamide was discontinued, and the events resolved by 3 days after their occurrence. A follow-up laboratory test 10 days later revealed a tendency to normalization for LDH (380 U/L; normal range, 0-500 U/L), SGOT (49 U/L; normal range, 0-100 U/L), and SGPT (102 U/L (normal range, 0-110 U/L).

Patient 0008-04216 (Study 021PE): SAE- Allergic Rash, Hematuria

This 7-year-old Caucasian male patient presented with skin erythema on day 12 after the start of rufinamide treatment, which was followed the next day by fever of 39°C, and then on day 15 by morbilliform exanthema on his face and body, bilateral conjunctival discoloration, and hematuria. The only laboratory values reported for this patient were from samples obtained approximately 2 weeks before the onset of these adverse events. He had normal values for eosinophils (2.0%; normal range, 0-10%) and WBCs (6.1 x 10⁹/L; normal range, 3-15 x 10⁹/L) at that time. According to the sponsor, the patient was seen by the investigator approximately 10 days later and his condition was improving, but he still exhibited some erythema.

It should be noted that the proposed rufinamide package insert _____ The concerns based on cases of hypersensitivity reactions were captured in the proposed rufinamide label under the precautions section as hypersensitivity reactions with the following language -

b(4)

b(4)

Rash and hypersensitivity reactions are not unique to rufinamide as several approved anticonvulsants are also known to cause one or both. Information on skin/dermatology rash and hypersensitivity reactions contained in the labels of some of the approved anticonvulsants was reviewed to determine their extent of comparability compared to those induced by rufinamide. The overview of rash and hypersensitivity that is discussed and summarized in Table 7.1.3.3.B in section 7.1.3.3 is presented here for ease of reference.

SAFETY TABLE 7.1.3.3.B OVERVIEW OF SKIN & HYPERSENSITIVITY REACTIONS OF SOME APPROVED ANTIEPILEPTICS					
Trade Name (Chemical)		AE	LABEL SECTION		Comments/Findings
			Warning	Precautions	
1	Carbotrol, Tegretol (Carbamazepine)	Skin / Rash	x	--	Fatal SJ Reaction, Toxic Epi. Necrolysis (Lyell's syndrome)
		Hypersensitivity	--	--	Not mentioned
2	Trileptal (Oxcarbazepine)	Skin / Rash	x	--	S J Reaction, Toxic Epi. Necrolysis (Lyell's syndrome)
		Hypersensitivity	x	--	Multi-organ hypersensitivity under precautions
3	Gabitril (Tiagabine)	Skin / Rash	--	x	4 cases (one SJ)
		Hypersensitivity	--	--	None mentioned
4	Zonegran (Zonisamide)	Skin / Rash	x	--	Sulfa like drug; 7 skin related SJ deaths in the Japan (postmarket)
		Hypersensitivity	--	--	Not mentioned
5	Lamictal (Lamotrigine)	Skin / Rash	x	x	Black Box Warning
		Hypersensitivity	x	--	None
6	Lyrica (Pregabalin)	Skin / Rash	--	x	Based on preclinical findings
		Hypersensitivity	--	--	Not mentioned in label
7	Keppra	--	--	--	Not mentioned in label

	(Levetiracetam)				
8	Depacon (Valproate)	--	--	--	Not mentioned in label
9	Topamax (Topiramate)	--	--	--	Not mentioned in label
10	Neurontin (Gabapentin)	--	--	--	Not mentioned in label
Ref: 2006 PDR, pp 412, 998, 1089, 1449, 2279, 2281, 2438, 2499, 2525, 3307, 3175					
Note: Hatched areas = Both skin and hypersensitivity reactions were noted in the label.					

Based on such assessments, rufinamide, like two other approved agents Tripletal and Lamictal, (hatched areas in Table 7.1.3.3.B) caused both skin rash and hypersensitivity reaction. However, these events were not captured appropriately in the Rufinamide label. *It is recommended that a section be added to the Rufinamide label with the inclusion of hypersensitivity under this section. The greater incidence of rash and serious adverse events of rash and or hypersensitivity reactions in the pediatric population should also be included in the Rufinamide label.*

b(4)

Cognitive Adverse Events & Discontinuations as Other Significant AE

As shown in Table 7 in the Appendix that displays the incidence of cognitive events (all Preferred Terms individually pooled together into an overall category of cognitive disorder) for all patients with epilepsy who received study drug in double-blind studies, cognitive disorder occurred in 16.6% of the rufinamide-treated patients and 13.9% of the placebo-treated patients (N= 1240 for rufinamide and N= 635 for placebo). As shown, one of these was a serious adverse event: aphasia in 1 (0.1%) rufinamide-treated patient (Patient 0002-08019 who had a seizure and a prolonged post-ictal phase characterized by hemiparesis and aphasia).

As shown, cognitive disorder led to discontinuation of treatment in 19 (1.5%) rufinamide-treated patients and 4 (0.6%) placebo-treated patients. The most frequently cited reason for discontinuation was somnolence (8 rufinamide-treated patients and 2 placebo-treated patients) followed by disturbance in attention, sedation and others.

Serious cognitive adverse events that occurred in all 1978 treated patients with epilepsy occurred in 5 (0.3%) patients and led to the discontinuation of treatment in 36 (1.8%) patients.

Psychiatric Adverse Events & Discontinuations as Other Significant AE

As shown in Table 7 of the Appendix (psychiatric events [within the MedDRA SOC] and the psychiatric disorder as SAE leading to discontinuation from the study for all patients with epilepsy who received study drug in double-blind studies), the incidences of any psychiatric disorder (14.0% rufinamide vs. 13.9% placebo) and of specific psychiatric adverse events were similar for the two treatment groups. The most frequently reported event in both groups was insomnia, which occurred in 3.0% of the rufinamide-treated patients and 2.5% of the placebo-treated patients. The next most frequently reported events were anxiety (2.7%) in the rufinamide group (vs. 1.4% placebo) and irritability (1.6%) in the placebo group (vs. 1.2% rufinamide).

As shown in Table 7 of the Appendix, psychiatric disorders were serious adverse events in fewer than 1% of the patients in both treatment groups. The only events that were serious in more than 1 patient per group were psychotic disorder (3 patients) and apathy (2 patients), which were serious events in the rufinamide group only.

As shown in Table 7 of the Appendix, psychiatric disorders led to the discontinuation of treatment in 1.5% of the rufinamide-treated patients and 1.6% of the placebo-treated patients. The events most commonly leading to discontinuation of rufinamide treatment were anxiety and irritability (4 patients each).

Suicide and Suicide Attempt as Other Significant AE

As shown in Table 7.1.1.A (deaths), no patient who died in any of the rufinamide clinical studies committed suicide. Three patients in the clinical studies had adverse event that was coded to the Preferred Term of suicide attempt.

In the double-blind, adjunctive therapy studies in adults with partial seizures, this event occurred in 1 (0.1%) of the 720 patients in the rufinamide group and 1 (0.3%) of the 290 patients in the placebo group. One additional adult with partial seizures had an adverse event of suicide attempt during the Extension Phase of a double-blind study. Therefore, the overall rate of suicide attempt among the 1978 patients who received at least 1 dose of rufinamide was 0.1% (2 patients).

Brief narratives for these suicide related patients who received rufinamide are provided below.

Patient 0004-03048 (Study AE/ET1): SAE- Suicide Attempt + Discontinuation

Patient was a 38-year-old female with partial seizures whose medical history included a suicide attempt approximately 10 years before she entered the study, although this information had not been provided to the investigator when the patient enrolled in the study. She was randomly assigned to receive rufinamide 800 mg/day and began treatment on _____. Concomitant medications included phenytoin and clonazepam. On Day 152 of treatment, the patient attempted to commit suicide by ingesting 5 g of phenytoin. She was hospitalized and treated, and subsequently referred to a psychiatric hospital. Rufinamide treatment was discontinued at the time of the event. The investigator considered the suicide attempt to be unrelated to study medication.

b(6)

Patient 0003-01614 (Study AE/ET1E): SAE- Suicide Attempt + Discontinuation, SAE- Osteoarthritis

Patient was a 37-year-old male who received rufinamide during the double-blind portion of Study AE/ET1 and entered the open-label extension on 07-Jul-94. On _____ of rufinamide therapy), while receiving 1200 mg/day of rufinamide, the patient was hospitalized following a suicide attempt (not involving rufinamide). Although not reported at study entry, the patient had a history of depression but not suicide attempt. The patient was assessed as recovered with sequelae on the day of admission, but remained hospitalized to undergo psychiatric follow-up. Study drug was discontinued as a result of the suicide attempt, with the last dose given on _____ (the day of admission). In the investigator's opinion, the suicide attempt was not suspected to be related to study medication.

b(6)

Two additional rufinamide-treated patients had adverse events that coded to the Preferred Term of overdose, but neither overdose was connected with a suicide attempt.

Patient 1284-05045 (Study 021A) experienced SAE- Depression aggravated (Suicide attempt) and discontinued. This patient was treated with placebo.

The incidences of CNS AEs under the common AE and very common AE (section 7.1.5), coupled with those discussed under the Other significant AE (section 7.1.3.3 under the CNS and psychiatric), were similar and comparable to those reflected in the labels of the some of the approved antiepileptics. This review of AE under CNS/Neuropsychiatric AEs for some of the approved agents (names listed in Table 7.1.3.3.B and Table 7.1.3.3.C]) from the labels indicated the following- a) the CNS/Neuropsychiatric AEs were either listed under the precaution or warning section of the label, b) the rates of incidences listed under the preferred terms either under common AE, discontinuations, or SAEs when indicated appeared to be generally comparable to rufinamide. *These suggested that both qualitatively and quantitatively, the CNS/Neuropsychiatric AE profile of rufinamide was no better or no worse than those of some of the approved agents.*

It is recommended that under a new warning section in the label neuropsychiatric AEs be included.

b(4)

Status Epilepticus/Convulsions as Other Significant AE

Table 7 in the Appendix displays the incidence of selected epilepsy-related events for all patients with epilepsy who received study drug in double-blind studies.

The incidences of convulsion as an adverse event, a serious adverse event, and an adverse event leading to discontinuation were similar in the two treatment groups. The incidences of grand mal convulsion as an adverse event, a serious adverse event, and an adverse event leading to discontinuation were lower in the rufinamide group than in the placebo group. *Status epilepticus occurred only in the rufinamide group and in 0.9% of the patients.*

The interpretation and significance of these results on epilepsy-related events were difficult because the placebo rates were generally equal or greater than rufinamide rates for convulsions and grand mal in contrast to status rates. While it can be argued that the lower rates with rufinamide compared to placebo for the categories of convulsion and grand mal convulsion may reflect drug benefit, the rates of 0.9% and 0% for rufinamide and placebo respectively, for the category of status, however questioned this benefit. Because standard definitions were not implemented (as acknowledged by the sponsor- see below for language in proposed label) and in order to further assess the higher incidence of status, the comparative status epilepticus rates for the approved antiepileptics were sought. The overview of status epilepticus that is discussed and summarized in a table in section 7.1.3.3 is re-presented here for ease of reference. As shown in Table 7.1.3.3.C, while no firm conclusions can be drawn, rufinamide's safety profile with respect to status epilepticus generally appeared to be no better or worse than the others.

SAFETY TABLE 7.1.3.3.C						
OVERVIEW OF STATUS EPILEPTICUS OF SOME APPROVED ANTIEPILEPTICS						
Trade Name (Chemical)	LABEL SECTION		Controlled		All Studies	
	Warning	Precautions	Drug	Placebo		
1 Rufinamide	--	Proposed	N=1240 11 (0.9%)	635 0 (0)	NP	
2 Gabitril (Tiagabine)	x	--	N=494 4 (0.8%)	N=275 2 (0.7%)	N=NP (5%)	

3	Zonegran (Zonisamide)	--	x	N= NP (1.1%)	N=NP (0%)	N=NP (1%)
4	Lamictal (Lamotrigine)	--	x	NP	NP	7/2343 (0.29%)
5	Neurontin (Gabapentin)	x	--	N=543 3 (0.6%)	N=378 2 (0.5%)	31/2074 (1.5%)
6	Trileptal (Oxcarbazepine)	Not mentioned				
7	Lyrica (Pregabalin)	Not mentioned				
8	Keppra (Levetiracetam)	Not mentioned				
9	Depacon (Valproate)	Not mentioned				
10	Topamax (Topiramte)	Not mentioned				
11	Carbotrol, Tegretol (Carbamazepine)	Not mentioned				
Ref: 2006 PDR, pp 999, 1090, 1452, 2500; Sponsor's Table 7.3-7, ISS						
Note: NP=Not Provided						

Although it is premature to negotiate label language at this time, it is worth noting that the following language was included in the proposed label under the precaution section-

Although the sponsor did not use standard definitions, it is recommended that additional information from the sponsor should be sought- such as those with previous history of status, to assess the possibility if there was a particular subgroup of patients in whom such exacerbations occurred. The concern on status epilepticus eventually should be included under the section of the label.

6. Treatment Emergent Common Adverse Event

Overview of Any Common AE Occurrence All Study Subgroups

The overview of incidences of treatment emergent any common AEs that is discussed and summarized in a table in section 7.1.5 are presented below for ease of reference. As shown in Table 7.1.5.A, except for the pediatric double-blind subgroup, the incidence of common AE between the rufinamide and placebo treated subjects were comparable. The rates for the pediatric double-blind subgroup are shown as hatched areas in Table 7.1.5.A.

SAFETY TABLE 7.1.5.A				
OVERVIEW OF TREATMENT EMERGENT ANY COMMON AE ALL STUDY SUBGROUPS				
STUDY ANALYSIS POPULATION	Rufinamide (R)		Placebo (P)	
	N (Patient)	%	N (Patient)	%
All Double-blind				
Exposed	1240	100	635	100
Any AE (Patient N)	975	78.6	497	78.3
All Study Subgroups Combined				

Exposed	1978	100	--	--
Any AE (Patient N)	1761	89.0	--	--
Adult Double-blind				
Exposed	720	100	290	100
Any AE (Patient N)	580	80.6	236	81.4
Adult Double-blind with Open-label				
Exposed	932	100	--	--
Any AE (Patient N)	806	86.5	--	--
Mono-therapy Double-blind				
Exposed	208	100	67	100
Any AE (Patient N)	135	64.9	47	70.1
LGS Double-blind				
Exposed	74	100	64	100
Any AE (Patient N)	60	81.1	52	81.3
LGS Double-blind with Open-label				
Exposed	135	100	--	--
Any AE (Patient N)	124	91.9		
Pediatric Double-blind				
Exposed	212	100	197	100
Any AE (Patient N)	177	83.5	147	74.6
Pediatric Double-blind with Open-label				
Exposed	391	100	--	--
Any AE (Patient N)	357	91.3	--	--
Ref: Tables 6.2-1, 6.2-5, 6.2-9, 6.2-13, 6.2-14, 6.2-18, 6.2-22, 6.2-27, 6.2-28, 6.2-33, 6.2-37 ISS, pp 88-122				
Note:				
Hatched areas = greater incidence with rufinamide compared to placebo.				

Common AE Occurrence in All Double-blind Subgroup

As shown in Table 5 of the Appendix (the incidence of common treatment emergent AE by SOC) at least one adverse event occurred in 78.6% of the rufinamide-treated patients and 78.3% of the placebo-treated patients. The rates of common adverse events by most SOC's were similar in the two treatment groups, except that nervous system disorders, general disorders and administration site conditions, and eye disorders occurred at higher rates in the rufinamide group.

Very common adverse events by Preferred Term in All Double-blind Subgroup

As shown in Table 5 of the Appendix, (the incidence of very common adverse events, i.e., those that occurred in 10.0% or more of the patients in either treatment group, by Preferred Term), while the overall incidence rates for common AE in All Double-blind subgroup were comparable between the two treatment groups (78.6 and 78.3 for rufinamide and placebo respectively), the very common AE rates by preferred term for rufinamide were greater compared to placebo. The most frequently reported events in both groups were headache (22.9% vs. 18.8%), dizziness (15.5% vs. 9.4%), fatigue (13.6% vs. 9.0), somnolence (11.8% vs. 9.1%), and nausea (11.4% vs. 7.6%).

Very Common Adverse Events by Severity in All Double-blind Subgroup

As shown in Appendix Table 5, adverse events were judged by the investigators to be mild in 394 (31.8%) of the 1240 patients who received rufinamide and in 240 (37.8%) of the 635 patients who received placebo. At least one adverse event was considered moderate in an

additional 448 (36.1%) and 199 (31.3%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 133 (10.7%) rufinamide-treated patients and 58 (9.1%) placebo-treated patients.

The majority of the events that occurred in 10% or more of the patients, were mild or moderate in severity. The overall rates by severity for the most common events of headache, dizziness, fatigue, somnolence and nausea in patients who received rufinamide was greater than those who received placebo in the All double-blind combined data. The highest rates of severe events were for headache, which was severe in 1.6% of rufinamide-treated patients and 1.9% of placebo-treated patients. The remaining very common adverse events were severe in 1% or fewer patients in either group.

Very Common Adverse Events by Dose in All Double-blind Subgroup

The incidence of adverse events that occurred in 10.0% or more of the patients is presented by median dose in Table 5 of the Appendix for all patients with epilepsy who received study drug during double-blind studies. The results were generally similar when adverse events were analyzed by the dose of maximum duration. *There was an apparent dose-response relationship between the doses administered and the occurrence of dizziness, somnolence, and nausea in these analyses involving the all double-blind combined data.*

Common AE Occurrence in Adult Double-blind Subgroup

As shown in Table 5 of the Appendix (the incidence of adverse events by SOC), at least one adverse event occurred in 80.6% of the rufinamide-treated patients and 81.4% of the placebo-treated patients. The rates of adverse events by most SOC were similar in the two treatment groups. Eye disorders, musculoskeletal and connective tissue disorders, metabolism and nutrition disorders, and ear and labyrinth disorders occurred at higher rates in the rufinamide group compared to placebo.

Very Common Adverse Events by Preferred Term Adult Double-blind Subgroup

As shown in Table 5 of the Appendix (the incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group) while the overall incidence rates for common AE in the Adult double-blind subgroup were comparable between the two treatment groups (80.6 and 81.4 for rufinamide and placebo respectively), the very common AE rates by preferred term for rufinamide were greater for dizziness (19.4% vs. 11.4%), fatigue (17.6% vs. 11.7%), and somnolence (10.4% vs. 7.2) compared to placebo. The differences in the occurrence of headache and nausea were not remarkable in the 2 treatment groups.

Very Common Adverse Events by Severity Adult Double-blind Subgroup

As shown in Table 5 of the Appendix (events that occurred in 10% or more of the patients, by severity), adverse events were judged by the investigators to be mild in 215 (29.9%) of the 720 patients who received rufinamide and in 110 (37.9%) of the 290 patients who received placebo. At least one adverse event was moderate in 274 (38.1%) and 96 (33.1%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 91 (12.6%) rufinamide-treated patients and 30 (10.3%) placebo-treated patients. *The overall rates by severity for the most common events of headache, dizziness, fatigue, somnolence and nausea in patients who received rufinamide was greater than those who received placebo in this adult double-blind*

data. The majority were mild or moderate in severity. The highest rates of severe events were for headache, which was severe in 2.2% of rufinamide-treated patients and 2.4% of placebo-treated patients. The remaining very common adverse events were severe in 1.4% or fewer patients in either group.

Very Common Adverse Events by Dose Adult Double-blind Subgroup

As shown in Table 5 of the Appendix (incidence of adverse events that occurred in 10.0% or more of the rufinamide-treated patients by median dose), the rates of any adverse event and of each of the most frequently occurring adverse events were generally higher in the 2 highest dose groups (2400 - $\leq$ 3200). According to the sponsor, interpretation of the results for the lower median dose ranges was confounded by the inclusion of a relatively large number of patients who were enrolled in studies (primarily Studies AE/ET1 and AE/PT2) that evaluated lower doses and that used the older Clinical Service Form of rufinamide tablets, which is known to have lower bioavailability than the newer Final Market Image formulation. The results were similar for median dose and dose of maximum duration. The dose-related trend was somewhat more pronounced when the results were analyzed by maximum dose.

The table of occurrence of Common AE $> \text{—}$ and $>$ Placebo in adult double-blind subgroup was presented in the proposed label.

b(4)

Common AE Occurrence in Double-blind Mono-therapy Substitution Subgroup

At least one adverse event by SOC occurred in 64.9% of the rufinamide-treated patients and 70.1% of the placebo-treated patients in the double-blind mono-therapy substitution studies. The rates of adverse events by most SOCs were similar in the two treatment groups. General disorders, psychiatric disorders, infections and infestations, and metabolism and nutrition disorders occurred at higher rates in the rufinamide group, whereas musculoskeletal and connective tissue disorders and injury, poisoning, and procedural complications occurred at higher rates in the placebo group.

Very Common AE Occurrence by Preferred Term in Double-blind Mono-therapy Substitution Subgroup

Three events occurred at a rate of 10% or more in each treatment group. Nausea and headache occurred in comparable percentages of patients in the 2 groups, whereas somnolence occurred in a higher percentage of patients in the placebo group than the rufinamide group.

Very Common AE Occurrence by Severity in Double-blind Mono-therapy Substitution Subgroup

Adverse events that occurred in 10% or more of the patients, by severity, were judged by the investigators to be mild in 75 (36.1%) of the 208 patients who received rufinamide and in 26 (38.8%) of the 67 patients who received placebo. At least one adverse event was moderate in an additional 49 (23.6%) and 21 (31.3%) patients, respectively. At least one severe adverse event occurred in 11 (5.3%) rufinamide-treated patients and 0 placebo-treated patients. The majority were mild or moderate in severity.

Very Common AE Occurrence by Dose in Double-blind Mono-therapy Substitution Subgroup

The incidence of the very common adverse events in this population was presented by median dose. There were essentially 2 median dose groups for this population, and the overall rate of adverse events was similar for the 2 groups. Nausea occurred at a higher rate in the higher dose group.

Common AE Occurrence in LGS Double-blind Subgroup (Single study)

As shown in Table 5 of the Appendix, the incidences of any adverse events and of adverse events by most SOCs were similar in the two treatment groups (placebo and rufinamide).

Very Common AE Occurrence by Preferred Term in LGS Double-blind Subgroup

As shown in Table 5 of the Appendix, (incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group), the patients in the two treatment groups had similar durations of exposure to study drug (median of 2.8 months in both groups). Four events occurred in 10% or more of the patients in either group. *Somnolence and vomiting were more frequent with rufinamide (somnolence 24.3% vs. 12.5% and vomiting 21.6% vs. 6.3%) than placebo and pyrexia and diarrhea were more frequent with placebo than rufinamide.*

Very Common AE Occurrence by Severity Term in LGS Double-blind Subgroup

As shown in Table 5 of the Appendix (events that occurred in 10% or more of the patients by severity), adverse events were judged by the investigators to be mild in 17 (23.0%) of the 74 patients who received rufinamide and in 31 (48.4%) of the 64 patients who received placebo. At least one adverse event was moderate in an additional 33 (44.6%) and 15 (23.4%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 10 (13.5%) rufinamide-treated patients and 6 (9.4%) placebo-treated patients. The majority were mild or moderate in severity. The highest rate of severe events was for somnolence, which was severe in 4.1% of rufinamide-treated patients and 0% of placebo-treated patients. *The more frequent events of somnolence and vomiting in patients in the LGS double-blind study (s) were also greater in severity compared to placebo.*

Very Common AE Occurrence by Dose in LGS Double-blind Subgroup

As shown in Table 5 of the Appendix (incidence of adverse events that occurred in 10.0% or more of the patients by median dose), doses in this study were administered based on each patient's body weight, so the results were shown for median doses in mg/kg/day. It was difficult to draw firm conclusions about dose response from these data because, the study was designed to have patients attain a maintenance dose of approximately 45 mg/kg/day, and most of the patients had median doses near that target and the sample sizes were small.

Also shown in Table 5 in the Appendix, in addition to the results in mg/kg/day, were the results based on median doses in mg/day (the actual doses received). The results were generally similar when the incidence of adverse events was analyzed by the dose of maximum duration and by the maximum daily dose. The dose-related trend for somnolence was somewhat more pronounced when the results were analyzed by maximum dose.

The table of occurrence of Common AE ~~>~~, and > Placebo in LGS Double-blind Subgroup was presented in the proposed label.

Common AE Occurrence in Pediatrics Double-blind Subgroup

As shown in Table 5 of the Appendix, (incidence of adverse events by SOC) the incidences of any adverse events and of adverse events by most SOC were generally greater for the patients exposed to rufinamide than those exposed to placebo (83.5% vs. 74.6%). In particular, the incidences of nervous system disorders, gastrointestinal disorders, eye disorders, and general disorders and administration site conditions were higher in the rufinamide group.

Very Common AE Occurrence by Preferred Term in Pediatrics Double-blind Subgroup

As shown in Table 5 of the Appendix (incidence of adverse events that occurred in 10.0% or more of the patients in either treatment group), except for upper respiratory tract infection (placebo > rufinamide), *somnolence* (17.0% vs. 8.1%), *vomiting* (16.5% vs. 7.1%), *headache* (16.0% vs. 8.1%) and pyrexia (difference not remarkable) occurred at a greater frequency with rufinamide.

Very Common AE Occurrence by Severity in Pediatrics Double-blind Subgroup

As shown in Table 5 of the Appendix (events that occurred in 10% or more of the patients by severity), all adverse events were judged by the investigators to be mild in 65 (30.7%) of the 212 patients who received rufinamide and in 82 (41.6%) of the 197 patients who received placebo. At least one adverse event was moderate in an additional 93 (43.9%) and 52 (26.4%) rufinamide and placebo patients, respectively. At least one severe adverse event occurred in 19 (9.0%) rufinamide-treated patients and 13 (6.6%) placebo-treated patients. The majority were mild or moderate in severity. The highest rates of severe events were for vomiting, which was severe in 1.4% of rufinamide-treated patients and 0% of placebo-treated patients. The remaining very common adverse events were severe in fewer than 1% of the patients. *The more frequent events of somnolence, vomiting and headache in patients in the pediatric double-blind studies were also greater in severity compared to placebo.*

Very Common AE Occurrence by Dose in Pediatrics Double-blind Subgroup

Also shown in Table 5 of the Appendix was the incidence of adverse events that occurred in 10.0% or more of the patients by median dose. There was no apparent dose-response relationship based on the submitted results. Discernable differences in AE by dose that were clinically meaningful were not seen.

See section 7.1.5 for discussions and comments on Treatment Emergent Common AE Occurrence in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup, in Pediatrics Double-blind with Open-label Extension Subgroup, in the Diabetic Neuropathy Subgroup and in the Healthy Volunteer Subgroup.

7. Occurrence of Adverse Events in Subpopulations of Patients

Adverse Events by Age

Analyses of adverse events were performed for the following age subgroups: <12 years, 12 to 16 years, 17 to 64 years, ≥65 years. Some of the analysis populations had small numbers of patients

(or no patients) in the youngest and oldest categories, limiting the ability to draw conclusions about possible age-related effects.

AE by Age in All Double-blind Subgroup

The incidence of adverse events reported by 10% or more of all treated patients with epilepsy (double-blind studies) within each age group were similar to those for all treated patients, i.e., rates of the very common adverse events were higher with rufinamide than with placebo. There were few discernible age-related patterns. Headache, dizziness, and nausea occurred at lowest rates in the youngest group, and at comparable rates in the three older groups. This was true in both the rufinamide and placebo groups for headache and nausea, but not dizziness. Somnolence occurred at the highest rate in the youngest group of rufinamide-treated patients; rates were comparable by age in placebo-treated patients. Small sample sizes restricted interpretation in the lower age groups.

AE by Age in Adult Double-blind Subgroup

No patient in this population (incidence of adverse events reported by 10% or more of the patients in rufinamide and placebo treatment group) was <12 years old. More than 98% of the patients were between the ages of 17 and 64 years. Headache and nausea occurred in similar percentages of patients in the rufinamide and placebo groups, whereas dizziness, fatigue, and somnolence occurred in higher percentages of rufinamide-treated than placebo-treated patients.

AE by Age in LGS Double-blind Subgroup

No patient in this population (incidence of adverse events reported by 10% or more of the patients with LGS) was ≥65 years old. The rates of any adverse event and of pyrexia were highest in the youngest age group, for both rufinamide- and placebo-treated patients. Somnolence occurred at lower rates in the youngest age group than in the 2 older age groups. *Vomiting occurred in higher percentages of rufinamide-treated patients than placebo-treated patients in all age groups.* Diarrhea occurred at similar rates in the rufinamide and placebo groups for patients who were <12 years old, but occurred only in placebo-treated patients in the older age groups. Interpretations were limited due to small sample sizes.

See section 7.1.5 for discussions and comments on Treatment Emergent Common AE Occurrence by Age in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup and in Pediatrics Double-blind with Open-label Extension Subgroup.

Adverse Events by Sex

AE by Sex in All Double-blind Study Subgroup

The pattern of results for rufinamide versus placebo was similar for the two groups (rufinamide and placebo), except with respect to nausea, which showed a larger difference between treatment groups in females than in males (Sponsor's Table 6.3-7, ISS).

AE by Sex in Adult Double-blind Studies Subgroup

Any adverse event, headache, dizziness, fatigue, and nausea occurred in higher percentages of female patients than male patients. Nausea occurred in higher percentages of rufinamide-treated female patients than placebo-treated female patients (16.6% vs. 12.7%), whereas nausea occurred in similar percentages of rufinamide- and placebo-treated male patients.

AE by Sex in LGS Double-blind Subgroup

The percentage of patients with at least one adverse event was similar with rufinamide and with placebo for both males and females. Somnolence and vomiting occurred at higher rates with rufinamide than with placebo in both males and females. Pyrexia occurred at a higher rate with placebo than rufinamide in male patients, but at similar rates with both treatments in female patients. Diarrhea occurred at a higher rate with placebo than rufinamide in female patients, but at similar rates with both treatments in male patients.

See section 7.1.5 for discussions and comments on Treatment Emergent Common AE Occurrence by Sex in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup and in Pediatrics Double-blind with Open-label Extension Subgroup.

Adverse Events by Race

As discussed in section 7.2.1.2 (Demographics Table 7.2.1.2.A), 58% of the patients in the all-treated population were white, 4% were black, 0.3% were oriental, and 5% belonged to other races. 33% did not have race reported (was also called 'Other' by the sponsor), which according to the sponsor, was primarily because enrollment in these studies did not require collecting information on race. Because most of the latter studies were conducted in Europe or Eastern Europe, it is likely that a majority of the patients without race recorded were Caucasian (white). These results by race must therefore be interpreted with caution particularly with respect to the non-Caucasian population.

AE by Race in All Double-blind Study Subgroup

The pattern of results for rufinamide versus placebo within each race subgroup was generally similar to that for the entire population, i.e., adverse events occurred in higher percents of rufinamide-treated patients than placebo-treated patients.

AE by Race in Adult Double-blind Subgroup

In white patients, all of the very common adverse events (incidence of adverse events reported by 10%) occurred in higher percentages of rufinamide-treated patients than placebo-treated patients. This was also true for headache and dizziness among black patients, and for dizziness and somnolence among patients of other races (patients whose race was not reported). Fatigue, somnolence, and nausea occurred at similar rates in the 2 treatment groups in black patients, as did headache, fatigue, and nausea in patients of other races.

AE by Race in LGS Double-blind Subgroup

A majority of the patients were white, and the pattern of results for that group was similar to that for all patients in this population, i.e., somnolence and vomiting occurred in higher percentages of rufinamide-treated patients than placebo-treated patients, pyrexia occurred in higher

percentages of placebo-treated patients than rufinamide-treated patients, and diarrhea occurred in similar percentages of patients in the 2 treatment groups. The numbers of patients who were African/black or of other races were too small for conclusions to be drawn.

See section 7.1.5 for discussions and comments on Treatment Emergent Common AE Occurrence by Race in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup and in Pediatrics Double-blind with Open-label Extension Subgroup.

In summary, while the race based AE analyses shed some light on incidences based on race in the Caucasian (white) population which was the majority, small sample sizes limited interpretations in the non-Caucasian populations and the conclusions that could be drawn. Even within this limited analyses, there was an increased incidence of somnolence in the black compared to white in the adult subgroup. Further, as discussed in section 7.2.1.2 (demographics), given the concerns of the greater occurrence of sudden deaths in the African/Black epilepsy population compared to the Caucasian epilepsy population, the safety evaluations in the rufinamide program were not adequate in this population and generally in the other non-Caucasian populations. *It is therefore recommended that the concern of lack of adequate exposures of African (black) and other populations to rufinamide be discussed with the sponsor. The sponsor should provide justification and or data that can support the use of rufinamide in these populations. The outcome of these discussions may require label changes.*

Adverse Events by Concomitant AED

In concordance with the sought adjuvant indication most of the double-blind studies in the clinical development program mandated that patients receive stable doses of 1 to 3 AEDs throughout their treatment with rufinamide. There were notable exceptions to this (the double-blind mono-therapy and mono-therapy substitution studies received one concomitant AED for the first 6 weeks of treatment, with reduction of the dose over time and most patients in open-label extensions of double-blind studies continued to receive standard AEDs, but doses and medications were allowed to be changed at the discretion of the investigators). However, it should be noted that the clinical studies were not designed to investigate possible interactions between rufinamide and the standard AEDs. In addition, most patients received more than one AED. Despite these limitations, analysis of the rates of adverse events in subgroups of patients who received different AEDs could suggest potential interactions that might be encountered in clinical practice and can also indicate events that may be attributed, at least in part, to the standard AED regimen rather than to rufinamide. To provide meaningful numbers of patients, these analyses were performed by the sponsor for all AEDs that were taken by at least 10% of the rufinamide-treated patients in the relevant population. The relationship of plasma concentrations and AE with concomitant AEDs as co-variants is discussed under section 7.4.2.1 and summarized below.

AE by Concomitant AED in All Double-blind Subgroup

Within most of the AED subgroups, the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups (Sponsor's Table 6.3-19, ISS). For the 5 very common adverse events in this population, the results within each AED subgroup were generally similar to those for all treated patients, i.e., generally, adverse events occurred in higher percentages of patients in the rufinamide group than in the placebo group. Headache occurred at comparable rates in the 2 groups among patients who received concomitant

carbamazepine, phenytoin, or vigabatrin, and at a higher rate in the placebo group than the rufinamide group among those who received concomitant clonazepam. Nausea occurred at the lowest rates in both rufinamide- and placebo-treated patients who received concomitant vigabatrin. *Generally, the incidence rates were higher for rufinamide compared to placebo in patients who received lamotrigine for headache (30.6% vs. 16.8), dizziness (21.6% vs. 9.9%), fatigue (11.9% vs. 5.0%), somnolence (16.4% vs. 8.95) and nausea (17.2% vs. 4.0%). Like wise, the incidence rates were higher for rufinamide compared to placebo in patients who received vigabatrin for dizziness (13.6% vs. 7.1 %), fatigue (21.6% vs. 17.9%), somnolence (11.2% vs. 3.6%) and nausea (5.6% vs. 3.6%).*

AE by Concomitant AED in Adult Double-blind Studies Subgroup

Within the AED subgroups shown (Sponsor's Table 6.3-21, ISS), the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups (rufinamide > placebo). For the 5 very common adverse events in this population, the results within each AED subgroup were generally similar to those for all treated patients, i.e., dizziness, fatigue, and somnolence occurred in higher percentages of patients in the rufinamide group than in the placebo group, whereas headache and nausea occurred in similar percentages of patients in the 2 groups. In the subgroups of patients receiving phenytoin or clonazepam, all of the very common adverse events occurred at similar rates in the 2 treatment groups or at higher rates with placebo than with rufinamide (except for somnolence in the subgroup that received clonazepam).

AE by Concomitant AED in LGS Double-blind (Study) Subgroup

Within most of the AED subgroups (Sponsor's Table 6.3-23, ISS), the percentages of patients with at least one adverse event were similar in the rufinamide and placebo treatment groups. There were a few exceptions: no patients in the rufinamide group who used concomitant phenytoin and no patients in the placebo group who used concomitant diazepam had any adverse events. In the remaining subgroups, the pattern of the very common adverse events generally followed that seen in the total population, i.e., somnolence and vomiting occurred in higher percentages of patients who received rufinamide, whereas pyrexia and diarrhea occurred in higher percentages of patients who received placebo. One notable exception was the subgroup of patients who received clonazepam, in whom the rates of these events in the rufinamide group were similar to, or lower than, the rates in the placebo group. Small sample sizes limited meaningful interpretations.

See section 7.1.5 for discussions and comments on Treatment Emergent Common AE Occurrence by Concomitant AED in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup and in Pediatrics Double-blind with Open-label Extension Subgroup.

8. Adverse Events and Rufinamide Plasma Concentration

An exploratory analysis of the relationship between exposure and the occurrence of adverse events which occurred in at least 20% subjects was undertaken (Study EMFFR2004/014/01) by the sponsor. The adverse events were extracted from the clinical safety database, with one record for each day when the selected adverse event was present during the double-blind period only. Exposure parameters for rufinamide and other AEDs were derived from the PK models at each visit and on the day of the adverse events. Only those subjects included in the efficacy PK/PD analyses and in the PK drug-drug interaction analyses were included in the exposure-

safety analysis (N=1398). Each adverse event dataset contained demography data (sex, age and weight at baseline), predicted rufinamide, carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate C_{avss} and presence or absence of vigabatrin. The probability of occurrence was analyzed using logistic regression with stepwise inclusion of the covariates. The main significant factors in the models are listed below; however, most covariates were significant at a level of $p < 0.10$.

- Nausea occurrence was mostly explained by increasing age, rufinamide C_{avss} , weight and valproate concentrations, and less frequently with carbamazepine, phenobarbital or vigabatrin.
- Vomiting was more frequent with increased rufinamide and phenytoin concentrations.
- The most important factors of fatigue were age, phenobarbital and topiramate concentrations.
- The major factors affecting the somnolence model were: rufinamide C_{avss} , concentrations of phenytoin and weight.
- The most important factors of dizziness were: age, rufinamide C_{avss} , valproate, topiramate and lamotrigine concentrations.
- The factors affecting diplopia were predominantly: carbamazepine, rufinamide concentrations, age, phenobarbital and valproate concentrations.

Overall, the occurrence of the AEs was greater in adults than in the pediatric population. It increased with rufinamide concentrations and with concomitant administration of other AEDs. However, increasing age was associated with a decreased risk of occurrence of vomiting. The occurrence of all adverse events investigated was greater with increased rufinamide concentrations, especially vomiting, somnolence, dizziness and nausea. Other AEDs had significant effects on the likelihood of the selected adverse events occurring, although the numbers of subjects given phenobarbital, topiramate or vigabatrin was small, and so conclusions regarding these treatments were less robust than for others. Carbamazepine concentrations were very strongly correlated with the occurrence of diplopia, and treatment with this compound was most likely cause of diplopia in epileptic patients.

TREATMENT EMERGENT LABORATORY FINDINGS

Sponsor's normal laboratory values (age-adjusted normal ranges [lowest and highest values] referenced from Mayo Medical Laboratories Test Catalog [Sponsor's Appendix I, Table 8.1-0]) used in the analyses was compared to those from The Merck Manual, 17th edition, pp. 2526-2543. These sponsor's lowest and highest values are italicized and presented alongside the normal values from the Merck Manual in the discussions in section 7.1.7. Such cross referencing was required because the normal ranges and clinically notable criteria used in the analyses of individual studies, and reported in the individual CSRs, varied. For consistency and accuracy, the sponsor chose a single set of age-adjusted normal ranges and clinically notable criteria to integrate the safety data. Further, the reported values for most parameters were expressed in standard international (SI) units rather than the usual conventional units.

Hepatic and thyroid related laboratory assessments were comprehensively investigated in the clinical program for potential abnormalities because of species-specific toxicology pre-clinical findings. These were centri-lobular hepatic hypertrophy and disturbance of the pituitary-thyroid axis in rats, cholestasis in dogs, gallbladder crystals in monkeys, liver tumors in mice and thyroid follicular adenomas in rats. There was also an increased incidence of benign bone tumors

(osteomas) at 400 mg/kg in rat carcinogenicity study that was considered species specific by the sponsor.

The disposition of patients with clinically notable values (changes from baseline), were not specified. How these patients with clinically notable changes in value were managed, followed and the outcome was not provided. *It is recommended that this information be requested from the sponsor.*

The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo).

Treatment emergent laboratory changes can be discussed under those related to the Hepatobiliary system (LFTs), Renal, Hematology, General Chemistry and Thyroid (TFTs)

Treatment Emergent Hepatobiliary (LFT) Laboratory Changes

The parameters that were evaluated, their normal ranges (sponsor vs. referenced from Merck Manual) and the inconsistencies in reporting due to variations in the denominators are discussed in 7.1.7. The interpretation of the results, therefore, depended on such variations in the denominators.

Treatment Emergent LFT Lab Changes in All Double-blind Studies Subgroup

Discernable differences in mean changes or shifts or clinically notable changes that were clinically meaningful were not seen. There were no reports of serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. One rufinamide-treated patient (0005-02670 in Study 022) discontinued due to hepatic enzymes increase. This case was discussed under Other Significant AE (Skin Rash/Hypersensitivity) above and under section 7.1.3.3. The LFTs normalized in 4 days after discontinuation of Rufinamide and Lamotrigine.

Treatment Emergent LFT Lab Changes in Adult Double-blind Subgroup

Gamma-GTP was not measured under this subgroup analysis. Discernable differences in mean changes or shifts or clinically notable changes that were clinically meaningful were not seen. There were no reports of serious adverse events or discontinuations due to adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group in the adult double-blind subgroup population.

Treatment Emergent LFT Lab Changes in LGS Double-blind Subgroup (Study 022)

Gamma-GTP was not measured. Discernable differences in mean changes or shifts or clinically notable changes that were clinically meaningful were not seen. Adverse events related to hepatobiliary laboratory tests occurred in less than 1% of rufinamide-treated patients (Ref: Sponsor's Appendix I, Table 6.7.1-3). No patient in either treatment group was reported to have a serious adverse event. One patient in the rufinamide group (Patient 0005-02670, Study 022) discontinued treatment due to rash, fatigue, vomiting, and hepatic enzymes increased (moderate increased in SGOT and SGPT); the increase in hepatic enzymes was not considered the primary reason for discontinuation (see discussion and narrative under Other Significant AE [Rash/Hypersensitivity], section 7.1.3.3 for this patient). See All Subgroups Combined below.

Treatment Emergent LFT Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline value were small for every hepatobiliary laboratory parameter and were generally similar in the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-31). Discernable differences that were clinically meaningful were not seen. There were no significant changes in clinically notable values in this population. There were no reports of serious adverse events or discontinuations due to adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group.

Treatment Emergent LFT Lab Changes in Pediatric Double-blind Subgroup

Discernable differences in mean changes or shifts that were clinically meaningful were not seen. Likewise, the observed changes in the clinically notable values were not meaningful.

Treatment Emergent LFT Lab Changes in All Subgroups Combined

Treatment emergent LFT lab changes that were clinically notable when all subgroups were combined for SGOT and SGPT that were more than 5 times the upper limit of the normal range were further reviewed by the sponsor. There were 11 patients with increased SGOT and 12 with increased SGPT. Four patients had increases in both parameters. None of these patients had elevated bilirubin values more than 1.5 times the upper limit of the normal range, except for those described below. Of the 11 patients with elevations in SGOT, 3 had elevations at a single time while receiving placebo (1 of these later had a single elevation while receiving open-label rufinamide), 5 had single elevations with several normal values before and after while receiving rufinamide, 2 had elevated values at the last laboratory evaluation, and 1 had elevations both before and after randomization. Of the 12 patients with elevations in SGPT, one had an elevation at a single time while receiving placebo, one had the elevation at baseline, 6 had single elevations with several normal values before and after while receiving rufinamide, 3 had elevated values at the last laboratory evaluation, and one (the same patient noted in the SGOT group) had elevations before randomization that worsened during rufinamide treatment.

Three patients had a value for either SGOT or SGPT that was 2 or 3 times the upper limit of normal and a value for bilirubin that was 1.5 times the upper limit of normal, which were chronologically contiguous.

Patient 0005-04408 (Study 021PE) a 12 year old female, was discussed under Other Significant AE (Skin Rash/Hypersensitivity). As previously noted, the elevated LFTs were noted on Day 59 after entry into the open-label extension phase and according to the sponsor, the patient was discharged in satisfactory condition on Day 71 and no follow-up labs were recorded. The 2 other patients were - Patient 1274-03159 (13-year-old female, Study 021PE) and Patient 0002-08019 (28-year-old male, Study AE/ET1). In patient 127-03159, the elevation in LFTs (not all parameters) occurred at a single time point and the specimen was reported to be grossly hemolyzed. The labs returned to normal without any changes in treatment. In patient 0002-08019, the elevation in LFTs was noted subsequent to the patient experiencing a prolonged secondary generalized seizure with post-ictal hemiparesis and dysphasia. The patient discontinued treatment 2 days after the seizure occurred. Blood parameters reportedly returned to normal in approximately 2 weeks.

Adverse events related to hepatobiliary laboratory tests occurred in less than 1% of rufinamide-treated patients (Sponsor's Appendix I, Table 6.10.1-1). One patient had a serious adverse event related to the hepatobiliary system (unrelated cholecystitis; Patient 0045-00022 in Study 0101- see section 7.1.7). One patient discontinued due to hepatitis toxic (0001-04618 in Study 021PE), and another patient (0005- 02670 in Study 022) discontinued due to hepatic enzymes increased. In each of the patient who experienced 'acute cholecystitis' and 'hepatitis toxic', the sequence of clinical events that led to their respective clinical diagnoses and their relation to abnormal LFTs were not congruent and meaningful. Their relationship to rufinamide, at best, was remote. Short narratives for Patients 0045-00022 (acute cholecystitis) and 0001-04618 (hepatitis toxic) are presented in section 7.1.7. Patient 0005-02670 who experienced elevated LFTs and rash and who in addition was receiving Lamotrigine simultaneously is discussed under Other Significant AE (under Rash/Hypersensitivity) in section 7.1.3.3.

See section 7.1.7 for further discussions and comments on Treatment Emergent Lab changes in All Subgroups Combined, in Adult Double-blind with Open-label Extension Subgroup, in LGS Double-blind with Open-label Extension Subgroup and in Pediatrics Double-blind with Open-label Extension Subgroup.

Treatment Emergent Renal Laboratory Changes

For purposes of easy reference, the sponsor's normal laboratory values (age-adjusted normal ranges [lowest and highest values] referenced from Mayo Medical Laboratories Test Catalog [Sponsor's Appendix I, Table 8.1-0]) used in the analyses were compared to those from The Merck Manual, 17th edition, pp. 2526-2543. These sponsor's lowest and highest values are italicized and presented alongside the normal values from the Merck Manual in the discussions in section 7.1.7. The parameters that were evaluated under this panel were BUN and creatinine. The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo). These numbers varied further between the rufinamide and placebo treatment groups for the same parameter. Hence, the interpretation of the results required allowances for such variations in the denominators.

Treatment Emergent Renal Lab Changes in All Double-blind Studies Subgroup

Mean changes were small and were similar in the rufinamide and placebo groups (Sponsor's Table 8.2-1, ISS). The percentages of patients with upward or downward shifts were similar for rufinamide and placebo (Sponsor's Table 8.2-2, ISS). The incidences of clinically abnormal values for BUN and creatinine were similar (Sponsor's Table 8.2-3, ISS) in the rufinamide group and the placebo group with an increase in BUN for the rufinamide (1.8 vs. 1.6). Overall, discernable differences in mean changes or shifts or clinically notable changes that were clinically meaningful were not seen. There were no reports of serious adverse events related to renal laboratory tests or renal disorders, nor were there reports of any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in Adult Double-blind Subgroup

The mean changes were small and were similar in the rufinamide and placebo groups (Sponsor's Table 8.2-7, ISS). The mean change in creatinine was 2.3 and 0.9 with rufinamide and placebo respectively in the adult double-blind subgroup. The majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Sponsor's Table 8.2-8, ISS). Shifts from within the normal range at baseline to

above the normal range at the last evaluation occurred in small percentages of patients (<3%) in both groups. But these shifts were greater with rifinamide compared to placebo (2.6 vs. 2.1 for BUN and 1.0 vs. 0.3 for creatinine) in the adult double-blind subgroup. The incidences of clinically abnormal values for BUN and creatinine were similar in the rifinamide group and the placebo group (Sponsor's Table 8.2-9, ISS) and no clinically meaningful discernable trends were observed. Overall, discernable differences in mean changes or shifts or clinically notable changes that were clinically meaningful were not seen. There were no reports of serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in LGS Double-blind Subgroup

Mean changes were small and were similar in the rifinamide and placebo groups (Sponsor's Table 8.2-10, ISS). Discernable differences that were clinically meaningful, however, were not seen. Both upward and downward shifts from normal in BUN occurred in lower percentages of patients in the rifinamide group than the placebo group (Sponsor's Table 8.2-11, ISS). Both upward and downward shifts from normal in creatinine occurred in higher percentages of rifinamide-treated patients than placebo-treated patients. The creatinine upward shift was 8.1 and 1.6 for rifinamide and placebo respectively. Upward shifts in BUN, however, were greater with placebo (10.9 vs. 2.7). Sample sizes were small. No patient in either treatment group had a post-baseline, clinically notable value for BUN or creatinine. There were no reports of serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline evaluation were small and were comparable in the rifinamide and placebo groups: -0.1 mmol/L in the rifinamide group and -0.0 mmol/L in the placebo group for BUN, and 4.0 and 2.2 μ mol/L, respectively, for creatinine (Ref: Sponsor's Appendix I, Table 8.1.1-32). Downward shifts in BUN occurred in 3.4% of the rifinamide-treated patients and 0% of the placebo-treated patients, whereas upward shifts occurred in 1.0% and 3.0%, respectively (Ref: Sponsor's Appendix I, Table 8.4.7-2). Downward shifts in creatinine occurred in 1.0% of the rifinamide-treated patients and 3.0% of the placebo-treated patients, whereas upward shifts occurred in 1.4% and 4.5%, respectively. No patient in either treatment group had a normal baseline value for BUN or creatinine and at least 1 post-baseline, clinically notable value (Ref: Sponsor's Appendix I, Table 8.3.1-32). There were no reports of serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in Pediatric Double-blind Subgroup

Mean changes in BUN were small and were identical in the rifinamide and placebo groups (Sponsor's Table 8.2-12, ISS). The mean change in creatinine was greater in the rifinamide group (2.7) than in the placebo group (0.3) in the pediatric double-blind subgroup. The percentages of patients with upward or downward shifts in BUN and creatinine were similar for the rifinamide and placebo groups (Sponsor's Table 8.2-13, ISS). The shift in creatinine from normal baseline to high post treatment in the pediatric double-blind subgroup was greater with rifinamide than placebo (10.8 vs. 8.1). No patient in either treatment group had a clinically notable value for BUN. One (0.6%) of 168 patients in the placebo group and none of 185 patients in the rifinamide group had a clinically notable increase in creatinine. There were no

reports of serious adverse events related to renal laboratory tests or renal disorders, nor were there any discontinuations due to such adverse events, in either treatment group.

Treatment Emergent Renal Lab Changes in All Subgroups Combined

The lack of a placebo arm made meaningful interpretations in mean changes, shifts or clinically notable changes difficult.

15 patients with increased creatinine, 14 had one or two isolated elevated values (Sponsor's Appendix I, Table 8.6-8). Thirteen of the 14 patients continued therapy and had normal values at later evaluations; the 13th patient had relatively high creatinine values throughout treatment, with a minor increase relative to the other values. One of 15 patients had multiple values that were elevated. This patient had fluctuating values throughout placebo and rufinamide treatment; the baseline creatinine value was the same as the final on-therapy value.

Adverse events related to renal laboratory tests or renal disorders occurred in less than 1% of the rufinamide-treated patients (Sponsor's Appendix I, Table 6.10.1-1). One patient (0514-00005, Study 0101) had a serious adverse event of renal failure acute due to a prolonged seizure that was associated with dehydration and rhabdomyolysis. The patient recovered and was later restarted on rufinamide. This case is discussed in detail in section 7.1.7. There were no reports of discontinuations due to renal adverse events.

Treatment Emergent Hematology Laboratory Changes

For purposes of easy reference, the sponsor's normal laboratory values (age-adjusted normal ranges [lowest and highest values] referenced from Mayo Medical Laboratories Test Catalog [Sponsor's Appendix I, Table 8.1-0]) used in the analyses were compared to those from The Merck Manual, 17th edition, pp. 2526-2543. These sponsor's lowest and highest values are italicized and presented alongside the normal values from the Merck Manual in the discussions in section 7.1.7. The parameters that were evaluated under this panel were RBC, WBC, Platelets, Hb, HCT, and a differential WBC. The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo). These numbers varied further between the rufinamide and placebo treatment groups for the same parameter. Hence, the interpretation of the results required allowances for such variations in the denominators.

Treatment Emergent Hematology Lab Changes in All Double-blind Studies Subgroup

Mean changes were small and were generally similar in the rufinamide and placebo groups (Sponsor's Table 8.3-1, ISS). The majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Sponsor's Table 8.3-2, ISS). The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups. The incidences of changes in values under the clinically notable changes were similar with rufinamide and placebo (Sponsor's Table 8.3-3, ISS). Overall, discernable differences that were clinically meaningful, however, were not seen in mean changes, in shift tables and or in clinically notable changes.

Serious adverse events related to hematology, which occurred in the rufinamide group, were leukopenia (3 patients), neutropenia (2 patients), and anemia (1 patient). One rufinamide-treated patient discontinued due to disseminated intravascular coagulation, and one discontinued due to

neutropenia. These are discussed in section 7.1.7 and summarized below under All Subgroups. No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Treatment Emergent Hematology Lab Changes in All Subgroups Combined

The lack of a placebo arm made meaningful interpretations difficult.

Mean Changes

Sponsor's Table 8.3-4, ISS, displayed mean values for hematology laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small for every parameter and were similar to those seen in the double-blind studies. Discernable differences that were clinically meaningful, however, were not seen.

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-5, ISS for all treated patients who received study drug in all subgroups combined. A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation. Two hundred fifteen (10.9%) patients had downward shifts in monocytes, 180 (9.1%) patients had downward shifts in hemoglobin, and 154 (7.8%) patients had downward shifts in RBCs. Fewer than 6% of the patients had upward or downward shifts in the remaining parameters. The lack of a placebo arm made meaningful interpretations difficult.

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-6, ISS for all patients with epilepsy who received study drug in all subgroups combined. The incidences of such values were generally higher than those in the double-blind studies, reflecting the longer duration of treatment in this population. The lack of a placebo arm made meaningful interpretations difficult.

A series of tables were included in Sponsor's Appendix I identifying patients in this population (all subgroup combined) with clinically notable values (Table 8.6-2 [neutrophils or WBCs], Table 8.6-3 [hematocrit, hemoglobin, or RBCs], Table 8.6-4 [platelet count], Table 8.6-5 [eosinophils], and Table 8.6-6 [lymphocytes]). These tables displayed, for each of the patients, demographic information, treatment information, and relevant hematology laboratory results.

The following is a summary of these clinically notable changes in labs -

Neutrophils as a Clinically Notable Change- low value

There were at least 20 patients out of 26 in whom the final neutrophil count was categorized as clinically notable (Appendix Table 2 for definition and criteria for clinically notable change) drop than the previous ones. While the temporal relation to the last dose was not provided, the shortest interval between the noted abnormal value and the preceding value was 4 weeks,

implying that the earliest time at which neutropenia was seen was 4 weeks. In the remainder 6 patients with clinically notable low neutrophil value, it was not possible to make such determinations.

Hematocrit, Hb or RBC as a Clinically Notable- low value

All clinically notable values occurred at only one or 2 evaluations with subsequent values that were not clinically notable or were within normal ranges, with no evidence of progressive decline, except in 5 patients who had clinically notable values for RBCs at the final evaluation.

Platelets as a Clinically Notable Change- low value

Abnormal platelet values that were considered clinically notable included the following subgroups-

- a) The clinically abnormal values were reported for 19 patients. These were likely laboratory errors, i.e., very low values (0-4,000 platelets) with no thrombocytopenia reported as an adverse event, and the patients continued in the study with subsequent values that were not clinically notable.
- b) ~ 23 patients had one determination with low platelets (<150,000) before drug intake, that were subsequently followed by values of >100,000. Two patients had an AE of thrombocytopenia. In one, the AE was thought to be due to valproate.
- c) 3 patients had low values at one determination, which was the final laboratory evaluation performed. The reported values were 1000 (patient M7143W-00105), 2600 (this patient 0008-08071 discontinued due to fatigue and was also on valproate), and 73000.
- d) Seven patients had thrombocytopenia as an adverse event. Two of the 7 had clinically notable values (see above). The remaining 5 had values that were not clinically notable.
- e) There were no serious adverse events of thrombocytopenia and no discontinuations due to adverse events related to thrombocytopenia.

Reviewer Comments

In a majority of the cases of thrombocytopenia, valproate was thought to be the primary cause. It should be noted that in the label for valproate [2006 PDR, p. 413], thrombocytopenia is listed as a warning.

Laboratory-related AE

Anemia was reported as an adverse event in 2.1% of female patients who were treated with rufinamide and 0.6% of male patients (Ref: Sponsor's Appendix I, Table 6.3.1-9). All other adverse events related to hematology laboratory parameters occurred in less than 1% of the rufinamide-treated patients (Ref; Sponsor's Appendix I, Table 6.10.1-1).

Serious adverse events related to hematology were leucopenia (3 patients: 0003-06026 in Study AE/ET1, 1553-02028 in Study 022, 1747-02023 in Study 022E), neutropenia (2 patients: 0002-04024 in Study AE/ET1, 1553-02028 in Study 022), anemia (1 patient: 1276-05044 in Study 021A), hemolytic anemia (1 patient: 1747-02023 in Study 022E), and leukocytosis (1 patient: 0001-07515 in Study AE/ET1E). Note that more than one SAE occurred in the same patient (s).

Discontinuations related to hematology included anemia (1 patient: 0512-00001 in Study 0101), disseminated intravascular coagulation (1 patient: 0004- 04209 in Study 021P), hemolytic anemia (1 patient: 1747-02023 in Study 022E), leukopenia (1 patient: 0512-00001 in Study 0101), and neutropenia (1 patient: 0003-04265 in Study AE/ET1). Note that more than one event occurred in the same patient.

Patient 0003-06026 (Study AE/ET1): SAE Leucopenia and discontinuation

This 18 year old female, on carbamazepine since 1992, was started on 400 mg rufinamide in Jan 04. Base line labs were- WBC = 4.6×10^9 , HCT = 37, Plt = 194×10^9 . Three days after starting rufinamide, the WBC was 3.4×10^9 and ~ 4 weeks later it was 2.7×10^9 (HCT=34 and Plt= 168×10^9). Patient was discontinued and 5 days later the WBC count was 6.5×10^9 .

Reviewer Comments

SAE of leucopenia and discontinuation in Patient 0003-06026 (Study AE/ET1) is most likely related to rufinamide administration. See label recommendations below.

Patient 1553-02028 (Study 022): SAE Leucopenia and Neutropenia

This was a 13-year-old male patient with a diagnosis of Lennox-Gastaut syndrome and baseline WBC of $5.8 \times 10^9/L$ and neutrophils of 63.15%. Following therapy with cefixime (400 mg/day) for streptococcal pharyngitis and one day prior to receiving rufinamide (on the day of randomization) the laboratory tests revealed a WBC of $2.9 \times 10^9/L$ with 7.24% neutrophils. Concomitant medications were lamotrigine 500 mg/day, and carbamazepine 600 mg/day. On the following day, prior to the knowledge of the abnormal results of the WBC count from the previous day, patient received a single dose of 600 mg of rufinamide. Rufinamide and cefixime were discontinued and patient was hospitalized for observation and monitoring. Within 5 days of the onset of adverse experience, the patient was discharged from the hospital in improved condition. The patient remained off rufinamide until the neutropenia was resolved. Approximately 16 days after discharge from the hospital WBC was $4.4 \times 10^9/L$ with 35.73% neutrophils. On 05-Nov-1998 the patient reinitiated blinded rufinamide treatment.

Reviewer Comments

SAE of leucopenia and neutropenia in Patient 1553-02028 (Study 022) is not related to rufinamide administration because these events occurred before the patient was exposed to rufinamide.

Patient 1747-02023 (Study 022E): SAE Leucopenia, Hemolytic anemia and Discontinuation

This 14-year-old Caucasian female patient was enrolled in the open-label extension trial of rufinamide Protocol 022 for patients with inadequately controlled seizures associated with Lennox-Gastaut syndrome. The patient was randomly assigned to receive rufinamide during the Double-blind Phase of study 022. She then entered the Extension Phase and began receiving open-label rufinamide treatment on 25-Aug-99. Concomitant AEDs included clonazepam, lamotrigine and tiagabine. Concomitant non-AEDs included alendronate sodium, amoxicillin, bisacodyl, cefuroxime axetil, chloral hydrate, clavulin, diphenhydramine, epinephrine, folic acid, ibuprofen, lorazepam, methylprednisolone, multivitamins, naproxen, paracetamol, prednisone and Respire SR-120. On 25-Aug-99 (Day 83 of double-blind treatment), while receiving 1000

mg/day of rufinamide, the patient developed a rash. Total and differential white blood counts and bilirubin remained within normal limits. The rash completely resolved on 29-Aug-99.

On 09-Jun-00 (Day 372 of rufinamide), while receiving 1400 mg/day of rufinamide, leukopenia was reported. She had an abnormally low absolute neutrophil count ($0.473 \times 10^9/L$) and WBC ($1.8 \times 10^9/L$) on that day. A bone marrow biopsy performed on 16-Jun-00 revealed no cancer cells and an abundance of neutrophils.

On 09-Sep-00 (Day 464 of rufinamide), while still receiving 1400 mg/day of rufinamide, antinuclear antibody and anti-DS-DNA tests were found positive. The diagnosis of systemic lupus erythematosus (SLE) was made on 29-Sep-00 by a pediatric immunologist. She was started on naproxen, prednisone and alendronate. On 17-Oct-00, her white blood cell count was $4.1 \times 10^9/L$ and neutrophils were $1.763 \times 10^9/L$. Although the values for white cells, neutrophils and bilirubin were within the normal range both total and direct bilirubin were elevated over previous values on 14-Sep-00 and by 17-Oct-00 the total bilirubin was $17.10 \mu\text{mol/L}$. The investigator assessed this adverse event as not related to rufinamide because anti-DS-DNA is not expected to be found in drug-induced SLE. On _____ of rufinamide), while receiving 1400 mg/day of rufinamide, the patient's hematocrit had fallen to 22% and she was diagnosed with hemolytic anemia secondary to systemic lupus erythematosus and hyperbilirubinemia secondary to hemolytic anemia. She was admitted to the hospital for treatment with intravenous methylprednisolone. The hematocrit increased to 26 percent after the first intravenous dose. Due to the diagnosis of SLE, rufinamide was discontinued after 511 days of treatment. The hemolytic anemia was reported as resolved by 31-Oct-00. After rufinamide was discontinued for 76 days, the white blood cell count was $4.4 \times 10^9/L$, neutrophils were $1.09 \times 10^9/L$, and total bilirubin was at the pre-study level.

b(6)

Reviewer Comment

In this complex case, with underlying immunosuppressive medical condition of SLE and concurrent poly-drug treatment, it is difficult to determine the extent of the role of rufinamide particularly in the context of its prolonged use. *While direct relationship either to leucopenia or hemolytic anemia is unlikely, the possibility of a remote association either because of the presence of other medications or underlying lupus cannot be fully excluded.*

Patient 0002-04024 (Study AE/ET1): SAE Neutropenia

A 31 year F on carbamazepine, 27 days after initiation with rufinamide, was noted to have neutropenia WBC= 4.5×10^9 and neutrophil = 1.08×10^9 (baseline WBC= 5.0×10^9 and Neutrophil= 2.0×10^9). With no treatment or intervention, repeat values ~ 4 weeks later, the counts were WBC 4.9×10^9 and neutrophils were 2.35×10^9 .

Reviewer Comment

While the report at ~ 4 week post-exposure showed improvement, whether based on this single value one can conclude that rufinamide was not the cause for the SAE of neutropenia can be questioned. However, under the assumption that rufinamide was not discontinued (if no treatment of intervention also means no changes in medications) the resolution of the values towards baseline is re-assuring. Without further information, whether rufinamide was or was not the cause of neutropenia is not determinable.

Patient 1276-05044 (Study 021A): SAE Anemia, Hyponatremia, Hypochloremia, Non-Cardiogenic Chest pain, Apathy, Constipation

This patient has been discussed under the all double-blind subgroup treatment emergent chemistry lab changes (see below). Details of the description of the anemia were not provided other than a single HCT and Hb value (hematocrit [33%] and hemoglobin [10.8 g/dl]). The primary SAE of concern was metabolic (hyponatremia) and it appears that anemia was a coincidental finding that was listed automatically as a SAE along with the others.

Reviewer Comments

The SAE of anemia, as listed, was probably not the main event of concern.

Patient 0001-07515 (Study AE/ET1E): SAE Leukocytosis

This 61-year-old female patient, with a history involving multiple medical problems, on multiple non-AEDs and AEDs, entered the double-blind phase of the study AE/ET1 with a diagnosis of inadequately controlled partial seizures. On Day 2520 of rufinamide therapy, while receiving 3200 mg/day of rufinamide, the patient was noted to have leukocytosis (results not available). WBCs at study entry and throughout the study period were within the normal range and the last recorded value was $6.4 \times 10^9/L$. The patient was withdrawn from the study due to the abnormal laboratory value, with the last dose taken on Day 2547 of rufinamide therapy (value not provided). The patient was subsequently diagnosed with chronic myeloid leukemia.

Reviewer Comments

In a majority of the cases of thrombocytopenia, valproate was thought to be the primary cause (in the label for valproate, thrombocytopenia is listed under the warning).

Patient 0512-00001 (Study 0101): Discontinuation Leucopenia and Anemia

The patient had underlying SLE which was the most likely cause for the leucopenia and anemia. The actual cause for discontinuation was most likely fever.

Patient 0004- 04209 (Study 021P): Discontinuation DIC

This 6-year-old male patient entered the study with a diagnosis of partial seizures. The patient's significant medical history included mild mental retardation. The patient began rufinamide on 23-Sep-1998. Approximately 1 month after entry into the double-blind phase, the patient was alone taking a bath when his parents found him unconscious in the water. The rufinamide dose at the time of the adverse event was 1000 mg/day. Concomitant medications were phenobarbital 60 mg/day and valproic acid 1000 mg/day. The patient was hospitalized and intubated. Disseminated intravascular coagulation was diagnosed. Rufinamide and valproic acid were stopped on the same day the patient was discontinued from the study. Within 8 days of the onset of the adverse event, the patient completely recovered from asphyxia.

Reviewer Comments

The primary inciting cause for DIC was most likely related to the shock as a result of profound systemic cardiovascular and respiratory decompensation due to asphyxia. Asphyxia and unconsciousness were probably due to an un-witnessed seizure.

Patient: 0003-04265 (Study AE/ET1): Discontinuation Neutropenia

This 36 year old female patient with history of partial seizures on clobazam (benzodiazepine not approved in the US) and phenytoin (x ~ 8 months) was enrolled and started on 1600 mg of rufinamide. The following were the WBC ($\times 10^9$)/neutrophil (%) counts and associated events following rufinamide administration-

Day 3 = 5.7/56, Day 13 = 4.2/58, Day 28 = 7.3/61, Day 29 – developed furuncles, Day 55 = 3.5/43% and developed lingual mycosis. Following this, patient was discontinued. There was no further follow up.

Reviewer Comments

The patient continued to receive phenytoin and rufinamide while leucopenia and neutropenia was being monitored. In the absence of other information or follow up, it is not possible to determine the actual cause. Cessation of one medication at a time with continued WBC/differential monitoring may have provided the answer. However, it is also likely that the combination of phenytoin and rufinamide may have resulted in this problem.

Downward WBC shifts from a normal baseline that were greater than placebo were seen (4.3 vs. 2.4) in the adult double-blind subgroup analysis (see below) suggesting a tendency for rufinamide to cause leucopenia. Clinically notable decreases in WBCs occurred in 37 (5.2%) rufinamide-treated patients and 6 (2.1%) placebo-treated patients in the adult double-blind subgroup analysis (see below). These coupled with the findings from Patient 0003-04265 (Study AE/ET1) who discontinued due to neutropenia that was associated with furuncle and localized mycosis and the discontinuation of Patient 0003-06026 (Study AE/ET1) due to SAE of leucopenia raises the concern further.

It is recommended that based on the greater incidence of WBC shifts from normal baseline or the clinically notable changes compared to placebo and the development of furuncles and localized mycosis that led to discontinuation in a patient who was also receiving phenytoin, the occurrence of the possibility of leucopenia and neutropenia during Rufinamide therapy be included in the _____ label.

b(4)

Patient 1747-02023 who discontinued was discussed under SAE above.

Treatment Emergent Hematology Lab Changes in Adult Double-blind Subgroup

Mean Changes

Sponsor's Table 8.3-7, ISS, displays mean values for hematology laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small and were generally similar in the rufinamide and placebo groups. Discernable differences that were clinically meaningful, however, were not seen.

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-8 for adults with partial seizures who received study drug in double-blind studies. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups. The largest percentages of patients with shifts in both groups were for hemoglobin (downward shifts for 9.9% of the rufinamide-treated patients and 10.7% of the placebo treated patients) and monocytes (downward shifts for 10.4% and 13.4%, respectively). Upward and downward WBC shifts from a normal baseline that were greater than placebo were seen (upward 1.8 vs. 0 and downward 4.3 vs. 2.4).

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least 1 post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-9, ISS, for adults with partial seizures who received study drug in double-blind studies. Clinically notable decreases in WBCs occurred in 37 (5.2%) rufinamide-treated patients and 6 (2.1%) placebo-treated patients. All other incidences of clinically notable values were <3% and were comparable in the 2 treatment groups with no discernable trends.

Serious adverse events related to hematology, which each occurred in one patient in the rufinamide group, were leukopenia, neutropenia, and anemia. One rufinamide-treated patient discontinued due to neutropenia. These were described and discussed above under all subgroups combined including label recommendations. No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Treatment Emergent Hematology Lab Changes in Mono-therapy Double-blind Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were generally comparable for the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-33). A majority of the patients in each treatment group had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were generally similar in the two treatment groups (Ref: Sponsor's Appendix I, Table 8.4.7-3).

Clinically notable increases in eosinophils occurred in 5 (2.8%) rufinamide-treated patients and no placebo-treated patients (Ref: Sponsor's Appendix I, Table 8.3.1-33). Other clinically notable values occurred in, at most, 1 to 3 patients per group. No patient in either group had a serious adverse event related to hematology, and there were no discontinuations due to hematology-related adverse events.

Treatment Emergent Hematology Lab Changes in LGS Double-blind Subgroup

Mean Changes

Sponsor's Table 8.3-10, ISS, displayed mean values for hematology laboratory parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between

those 2 visits. Mean changes were small and were comparable in the rufinamide and placebo groups. Discernable differences that were clinically meaningful, however, were not seen.

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-11, ISS for the LGS study. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were generally similar in the two treatment groups. Higher percentages of patients in the rufinamide group than in the placebo group had downward shifts in hemoglobin (13.5% versus 3.1%) and RBCs (10.8% versus 4.7%). Discernable differences that were clinically meaningful, however, were not seen. Small sample sizes further limited interpretations.

Clinically Notable Changes

The incidence of patients with normal values for hematology parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.3-12, ISS for the double-blind adjunctive therapy study in LGS. The rates were generally similar in the two treatment groups. Discernable differences that were clinically meaningful, however, were not seen. Small sample sizes further limited interpretations.

Serious adverse events of leukopenia and neutropenia each occurred in one rufinamide-treated patient (patient: 1553-02028 in Study 022) which was probably not related to rufinamide (low counts were reported the day prior to the patient receiving rufinamide and with re-instatement and maintenance on rufinamide for 14 months there were no problems- see description and discussion above under all subgroups combined). No placebo-treated patient had a serious adverse event related to hematology. No patient in either treatment group discontinued due to such events.

Treatment Emergent Hematology Lab Changes in LGS Double-blind with Open-label Extension Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable to those seen in the double-blind study (Ref: Sponsor's Appendix I, Table 8.1.1-13). A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Ref: Sponsor's Appendix I, Table 8.4.5-3). Twenty (14.8%) patients had downward shifts in hemoglobin, 14 (10.4%) patients had downward shifts in hematocrit, and 12 (8.9%) patients had downward shifts in monocytes. All other upward and downward shifts occurred in $\leq 7.4\%$ of the patients. The rates of clinically notable values were somewhat higher than those seen during the Double-blind Phase, reflecting the longer duration of treatment in this population (Ref: Sponsor's Appendix I, 8.3.1-13). Serious adverse events of leukopenia and neutropenia occurred in the same patient (1553-02028 in Study 022- described above), and an additional patient had a serious adverse event of hemolytic anemia on Day 511 of rufinamide therapy (1747-02023 in Study 022E- see description and discussion above under all subgroups combined). The latter patient was the only patient whose treatment was discontinued due to an adverse event related to hematology.

Treatment Emergent Hematology Lab Changes in Pediatric Double-blind Subgroup

Mean Changes

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were generally comparable in the rufinamide and placebo groups (Ref: Sponsor's Appendix I, Table 8.1.1-23).

Shift Table Changes

The numbers of patients with shifts in hematology parameters, relative to the normal range, was summarized in Sponsor's Table 8.3-13, ISS for the pediatric patients who received study drug in double-blind studies. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were generally similar in the two treatment groups. A higher percentage of patients in the rufinamide group (9.4%) than in the placebo group (5.6%) had downward shifts in hemoglobin.

Clinically Notable Changes

The rates of clinically notable values were generally similar in the two treatment groups (Ref: Sponsor's Appendix I, Table 8.3.1-23). Serious adverse events of leukopenia and neutropenia each occurred in one rufinamide-treated patient (patient: 1553-02028 in Study 022- see above). One rufinamide-treated patient (0004- 04209 in Study 021P) discontinued due to disseminated intravascular coagulation, which occurred on Day 35 of rufinamide therapy, after immersion asphyxia (see description and discussion above under all subgroups combined). No placebo-treated patient had a serious adverse event related to hematology or discontinued due to such events.

Treatment Emergent Hematology Lab Changes in Pediatric Double-blind with Open-label Extension Subgroup

Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable to those seen in the double-blind studies (Ref: Sponsor's Appendix I, Table 8.1.1-18). A majority of the patients had no shifts relative to the normal range between baseline and the last post-baseline evaluation (Ref: Sponsor's Appendix I, Table 8.4.4-3). Thirty-six (9.2%) patients had downward shifts in hemoglobin, and 36 (9.2%) patients had downward shifts in RBCs. Fewer than 7.5% of the patients had upward or downward shifts in any other parameters. The rates of clinically notable values were higher than those seen in the double-blind studies, reflecting the longer duration of treatment in this population (Appendix I, Table 8.3.1-18). Serious adverse events related to hematology were leukopenia (Patients 1553-02028 in Study 022 and 1747- 02023 in Study 022E), neutropenia (Patient 1553-02028 in Study 022), and hemolytic anemia (Patient 1747-02023 in Study 022E). One rufinamide-treated patient discontinued due to disseminated intravascular coagulation (Patient 0004-04209 in Study 021P), and one discontinued due to hemolytic anemia (Patient 1747-02023 in Study 022E). These cases were described and discussed above under all subgroups combined.

Treatment Emergent General Chemistry Lab Changes

Reviewer Comments

For purposes of easy reference, the sponsor's normal laboratory values (age-adjusted normal ranges [lowest and highest values] referenced from Mayo Medical Laboratories Test Catalog [Sponsor's Appendix I, Table 8.1-0]) used in the analyses were compared to those from The Merck Manual, 17th edition, pp. 2526-2543. These sponsor's lowest and highest values are italicized and presented alongside the normal values from the Merck Manual in the discussions in section 7.1.7. The parameters that were evaluated under this panel were Bicarbonate, Calcium, Chloride, Cholesterol, Glucose, Potassium, Sodium and Uric acid. The number of patients who were evaluated varied depending on the assessed parameter, the analysis subgroup and the treatment (rufinamide or placebo). These numbers varied further between the rufinamide and placebo treatment groups for the same parameter. Bicarbonate and cholesterol were not measured in the LGS study. Hence, the interpretation of the results required allowances for such variations in the denominators.

Treatment Emergent General Chemistry Lab Changes in All Double-blind Studies Subgroup

Mean Changes

Sponsor's Table 8.4-1, ISS, displayed mean values for general chemistry parameters at baseline, the last post-baseline evaluation for each patient (Termination), and the change between those 2 visits. Mean changes were small and were comparable in the rufinamide and placebo groups. Discernable differences that were clinically meaningful, however, were not seen.

Shift Table Changes

The numbers of patients with shifts in general chemistry parameters, relative to the normal range, was summarized in Sponsor's Table 8.4-2, ISS. The table showed that the majority of patients in both treatment groups had no shifts relative to the normal range between baseline and the last post-baseline evaluation. The percentages of patients with upward or downward shifts from normal were similar in the two treatment groups. Discernable differences that were clinically meaningful, however, were not seen. However, the shifts in sodium from normal baseline to low post-treatment in this all double-blind subgroup (rufinamide = 26 [2.1%] and placebo = 11 [1.7%], may have any significance in the context of the SAE described below (Patient 1276-05044 [Study 021A])

Clinically Notable Changes

The incidence of patients with normal values for general chemistry parameters at baseline and at least one post-baseline, clinically notable value was summarized in Sponsor's Table 8.4-3, ISS for the all double-blind studies subgroup. The rates were generally similar in the two treatment groups. Discernable differences that were clinically meaningful, however, were not seen.

Two patients had serious adverse events of hyponatremia (0008-01168 in Study AE/ET1 and 1276-05044 in Study 021A), and one patient had a serious adverse event of hypochloremia (1276-05044 in Study 021A); these patients were all in the rufinamide group. These are described below. One additional hyponatremia patient (1284-5033) was reported in the June 2006 safety addendum submission under the SAE update. Further information (patient narrative) could not be accessed via the provided hyperlink. In a TCON on Sep 11, 2006, this information was sought. The sponsor acknowledged that the hyperlink was not working. However, sponsor identified the narrative in another folder of the submission.