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APPLICATION NUMBER:

21-911

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	21911
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Letter Date	February 29, 2008
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Reviewer Name	Steven Dinsmore, DO
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Established Name	rufinamide
(Proposed) Trade Name	Banzel
Therapeutic Class	anticonvulsant
Applicant	Eisai Inc.
Priority Designation	S
Formulation	Tablets 100mg, 200mg, 400mg
Dosing Regimen	LGS, (Adults) 1600mg BID LGS (children) 22.5mg/kg BID to maximum of 1600mg BID
Indication	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome
Intended Population	Children 4 years or older, Adults

TABLE OF CONTENTS1 **EXECUTIVE SUMMARY** 4

1.1 RECOMMENDATION ON REGULATORY ACTION 4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 5
1.2.1 Risk Management Activity 5
1.2.2 Required Phase 4 Commitments 5
1.2.3 Other Phase 4 Requests 6
1.3 SUMMARY OF CLINICAL FINDINGS 6
1.3.1 Brief Overview of Clinical Program 6
1.3.2 Efficacy 8
1.3.3 Safety 9
1.3.4 Dosing Regimen and Administration 13
Drug-Drug Interactions 13
Special Populations 14

2 INTRODUCTION AND BACKGROUND 16

2.1 PRODUCT INFORMATION 16
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 16
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 16
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 16
2.5 PRESUBMISSION REGULATORY ACTIVITY 16
2.6 OTHER RELEVANT BACKGROUND INFORMATION 17

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 18

4.4 DATA QUALITY AND INTEGRITY 18

6 INTEGRATED REVIEW OF EFFICACY 18

6.1 INDICATION 19
6.1.1 Methods 19
6.1.2 General Discussion of Endpoints 20
6.1.3 Study Design 22
6.1.4 Efficacy Findings 22
6.1.5 Efficacy Conclusions 44

7 INTEGRATED REVIEW OF SAFETY ONGOING TRIALS 44

7.1 METHODS AND FINDINGS 44
7.1.1 Deaths 45
7.1.2 Other Serious Adverse Events 45
7.1.4 Other Search Strategies- 48
7.1.5 Common Adverse Events 48
7.1.6 Less Common Adverse Events 50
7.1.7 Laboratory Findings 50
7.1.8 Vital Signs 50
7.1.9 Electrocardiograms (ECGs) 50
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 50
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 50
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 51

8 INTEGRATED REVIEW OF SAFETY SECOND CYCLE SUBMISSION 51

8.1 METHODS AND FINDINGS 51
8.1.1 Deaths 52
8.1.2 Other Serious Adverse Events 52

8.1.3 Dropouts and Other Significant Adverse Events (abnormalities *related to initial NDA submission safety review, including Thyroid abnormalities 8.1.3.1.3)* 52
Table 8.1.3-3, Δ baseline to final, means/medians, treatment/placebo, corrected-pooled studies 016, 018, 021A, 021P, 022, 038....57
Table 8.1.3-4 shift, baseline to final, low-normal-high, corrected-pooled studies 016, 018, 021A, 021P, 022, 038. 58
Table 8.1.3-5 clinically notable, ↑ or ↓ in value, corrected-pooled studies 016, 018, 021A, 021P, 022, 038. ...59
Table 8.1.3-6 Δ baseline to final, means/medians, treatment/placebo, corrected studies AE/ET1-AE/PT2. 60
Table 8.1.3-7 shift, baseline to final value, low-normal-high, corrected studies AE/ET1-AE/PT2 61
Table 8.1.3-8 clinically notable, ↑ or ↓in value, corrected studies AE/ET1-AE/PT2....62
8.1.4 Other Search Strategies 65
8.1.5 Common Adverse Events....65
8.1.6 Less Common Adverse Events 65
8.1.7 Laboratory Findings-as addressed in approvable letter: clinically notable changes in final visit laboratory values. 65
8.1.8 Special Safety Studies 69
8.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 75
8.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 75
8.2.2 Adequacy of Overall Clinical Experience....75

9 OVERALL ASSESSMENT 76

9.1 CONCLUSIONS....76
Partial Seizures....76
LGS....77
Safety 77
9.2 RECOMMENDATION ON REGULATORY ACTION 78
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 78
9.3.1 Risk Management Activity....78
9.3.2 Required Phase 4 Commitments 78
9.3.3 Other Phase 4 Requests....79
9.4 LABELING REVIEW....79
9.5 COMMENTS TO APPLICANT 79

10 APPENDICES....80

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 80
10.2 LINE-BY-LINE LABELING REVIEW 80
10.3 RANDOMIZATION ERRORS- CASE NARRATIVE....80
10.4 EFFICACY SUBGROUP ANALYSIS FOR INTERACTION WITH CONCOMITANT AED'S 80
Table 10.6-1 81
Table 10.6-2 82
Table 10.6-3 83
Table 10.6-4 84
Table 10.6-5 85
10.5 DRUGS ASSOCIATED WITH SODIUM CHANNEL BLOCKING AND QT SHORTENING....85

REFERENCES 87

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In this second submission for approval of rufinamide as adjunctive treatment of partial seizures in adults the re-evaluation does not identify further evidence to [redacted]. This reviewer recommends rufinamide be granted an complete response for this indication [redacted] b(4)

AE/ET1: The pivotal goal of establishing a dose response is lost when the linear dose response analysis is reexamined by Dr. Siddiqui (FDA statistical reviewer) with proportional dose recoding and placebo excluded. A secondary outcome measure, seizure frequency ratio of response at each dose is reported by the sponsor to be significant at 400mg, 800mg and 1600mg, however when the analysis is refined by multiplicity testing, only the 800mg dose is statistically significant. In another secondary efficacy measure, the logistic regression analysis on the 25% and 50% responder rate, none of the doses is significant after adjusting for multiplicity. The significance of the logistic regression analysis of the GATE (Global Assessment of Therapeutic Effect) scale is only significant at 1600mg after multiplicity adjustment. The Poisson regression analysis on seizure frequency retains only 1600mg of rufinamide significant after multiplicity adjustment. In addition when the model is refitted without the 200mg dose the 400mg and 800mg subsequently lose significance. Dr. Siddiqui notes that each dose should independently have power to demonstrate significant efficacy. The ANCOVA on rank of total seizure frequency was repeated without transformation and with country as covariate. Again after multiplicity testing none of the doses was statistically significant.

In the initial review it was also seen that the percent reduction in seizure frequency for the rufinamide group over placebo was non linear. There was less reduction in at the 1600mg dose then at 800mg.

There is no clear dose response when placebo is removed from the dose response analysis; this implies that the significant slope in the dose response analysis is created by the placebo and the cluster of dose points which behave as a single point rather than an array of points with progressive increase in effect. The review also reveals a weak medication effect with significance oscillating between the 800mg a day and 1600mg a day dosage. This study does not define a usable range of medication dose. In order to define a clear effective dose range for this product a new dose ranging study is needed.

021A: The efficacy of rufinamide is modest and when analysis is limited to the US population only, significance is lost. A secondary analysis of efficacy measures was performed by the FDA statistical reviewer, using an ANCOVA model of rank of total partial seizure frequency / 28 days during baseline phase with treatment, country, age and sex as covariates there was no significance. An additional consideration by the FDA statistical reviewer pointed out the primary efficacy variable of

percent change in seizure frequency may have an advantage over change in total seizure frequency when there are a predominance of subjects with low baseline seizure frequency. In those circumstances a small reduction during treatment may translate into a large percent change in seizure frequency. These features indicate that the anticonvulsant effect is not robust.

In this second submission for approval of rufinamide in treatment of LGS (Lennox-Gastaut syndrome) the re-evaluation reveals that 022 is a positive study. It is also acknowledged that although studies AE/ET1 and 021A [redacted] do provide support for study 022 in approval of rufinamide for LGS treatment. Based on this evidence this reviewer recommends approval of rufinamide for treatment of Lennox-Gastaut syndrome. b(4)

1.2 Recommendation on Postmarketing Actions

Rufinamide has the novel adverse effect of dose related QT shortening. Data already collected during the rufinamide development program may be informative on the interaction of rufinamide with other drugs thought to shorten the QT interval or act to block sodium channels. The sponsor will be requested to examine the effect of concomitant medications on rufinamide treatment and shortening of the QT interval for clinical trials where QAT data was collected.

1.2.1 Risk Management Activity

none

1.2.2 Required Phase 4 Commitments

1. The sponsor will be asked to provide the following analysis on existing clinical study data:

a. The baseline (pre-treatment) mean QT interval (as measured by all three correction methods) in rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (see appendix 10.5) and in patients without such concomitant medications.

b. The mean on-treatment QT interval (again by all three correction methods) for rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (appendix 10.5) and in patients without such concomitant medications.

c. the same analysis for sodium channel blocking drugs (appendix 10.5).

2. Conduct an in vitro metabolism study to characterize the potential serious safety risk of the inhibitory effect of rufinamide on P-gp.

3. Conduct a juvenile dog toxicology study to identify the unexpected serious risk of adverse effects on postnatal growth and development.

1.2.3 Other Phase 4 Requests

None recommended

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Rufinamide is a new molecular entity with properties that show potential for use as an adjunctive antiepileptic drug for treatment of partial seizures and seizures associated with Lennox-Gastaut syndrome (LGS). The mechanism of action has not been fully elucidated but has been shown to limit the frequency of sodium dependent neuronal action potentials. The earliest elements of the development program began in 1989 with a PK study. Safety and efficacy trials in the initial submission span the interval from 1997 to year 2000. These studies have yielded three pivotal trials which are the focus of this submission, studies AE/ET1 and 021A for partial seizures in adults and study 022 in LGS .

- Study AE/ET1 is a multicenter, multinational, double blind, randomized, placebo-controlled, 5 arm parallel trial in patients with partial seizures on up to three concomitant antiepileptic drugs to investigate efficacy and tolerability in doses of 200mg/day,400mg/day,800mg/day, 1600mg/day. There was no dose titration. The trial period spanned November 1992 to December 1994. 647 patients were randomized to double blind treatment phase and 554 completed double blind treatment.

- Study 0021A is a multicenter, multinational, double-blind, placebo-controlled, randomized, stratified, parallel-group trial of rufinamide as adjunctive therapy in children and adults with inadequately controlled partial seizures. Primary objective to evaluate the safety and efficacy of rufinamide as adjunctive therapy, relative to placebo, in patients with inadequately controlled partial seizures. Dosing started at 800 mg/day and was titrated to 3200 mg/day over a 1 to 2 week period beginning at 400mg twice a day then advancing 800mg a day to achieve 3200mg a day. The rate of dose escalation may be reduced but the dose attained at the end of the two week titration will remain the patient dose during the maintenance period. Study interval spanned November 1997 to May 1999. A total of 274 adult patients were planned for analysis. A total of 313 adult patients were randomized with 156 randomized to rufinamide and 157 randomized to placebo.

- Study 0022 is a Multicenter, multinational, randomized, double-blind, placebo-controlled, parallel trial comparing the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut Syndrome. The study objective was to evaluate the safety and efficacy of rufinamide relative to placebo as adjunctive therapy in patients with inadequately controlled seizures associated with Lennox-Gastaut syndrome (LGS). Dosage was administered based on patient weight starting at 10mg/kg/day and titrated to a target of 45mg/kg/day over 1 to 2 weeks. The study interval spanned March 1998 to September 2000. 138 patients received

double blind treatment. 74 received rufinamide of which 64 completed the study. 64 patients received placebo, 59 completed the study.

Completed clinical trial exposure

In the population of all rufinamide-treated patients in completed clinical studies, 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.

In all double – blind study participants median doses were 2400 to 3200mg/day for 291 (23.5%) of patients and more than 3200mg/day for only 1 (0.1%) patient. More than half of the patients who received median doses of 2400 to 3200 mg/day were treated for at least 3 months.

In combined double blind and open label studies combined 1156 patients have had greater than six months exposure to a dose range 2400 to ≤3200mg. 705 subjects have had 12 months or greater exposure to the dose range 2400 to ≤3200mg. 141 patients have had 6 months or greater exposure to >3200mg daily dose. 88 patients were exposed for >12 months to >3200mg.

Ongoing clinical trials

In addition to the exposure in completed clinical studies there is further exposure in ongoing study E2080-A001-301 and extension phase E2080-A001-302. 223 patients were randomized into study A001-301 with 141 subsequently entering open label extension. The total exposure to study drug (rufinamide or placebo) in the double-blind portion of study E2080-A001-301 per cut-off date is 33,084 patient-days; total exposure to rufinamide either during the transition phase of study E2080- A001-301 or during open-label extension study E2080-A01-302 (all patients on rufinamide) is 21,632-days.

Post Marketing Exposure

Rufinamide has been approved for treatment of Lennox-Gastaut syndrome in the European Union since January of 2007. Using the available data from factory sales data on the number of tablets sold and with the defined daily dose for rufinamide considered to be 1600 mg with maximum dose 3200mg a day, it is estimated that there have been over [redacted] patient-days of exposure from product launch to 15 January 2008. The available post-marketing exposure data indicates approximately 73% of the exposure is estimated to be in the pediatric population (age 0-18 years) and 50% of the exposure is estimated to be in females. In the absence of highly valid data, these estimates are based on local affiliate market research data, key opinion leader interviews, and qualitative feedback from prescribers.

b(4)

Rufinamide will be supplied as 100mg, 200mg and 400mg. For Lennox-Gastaut syndrome the recommended dosage is 45mg/kg/day to a maximum of 3200mg total daily dose divided into two doses daily.

1.3.2 Efficacy

1.3.2.1 Adult partial seizures

The second submission is presented with no additional studies. The sponsor again presents analysis of the adult pivotal trials AE/ET1, and 21A. In the EOR meeting of December 18, 2006 the FDA agrees that these are two positive trials. The statistical analysis of AE/ET1 reveals a therapeutic effect but inadequate differentiation between 800mg / day and 1600mg a day. Study 016 (a double blind, randomized, parallel group monotherapy study of 112 days which enrolled 142 patients) compounds this observation with no difference identified between the 300mg and 3200mg a day dose. In this submission the sponsor presents pooled data pharmacometric analysis showing a concentration response curve in adults and to a lesser extent in children. b(4)

The sponsor also presents an argument based on effect size. This is presented in response to the implication of low effect size in the approvable letter. They note the 20.4% effect size in the highest study dose of 21A is within the range of effect size noted for several currently approved anticonvulsants. The magnitude of this effect size is generally within the lower range of the approved agents. This does not contradict FDA conclusion that rufinamide is effective but the effect is modest. b(4)

1.3.2.2 Lennox-Gastaut Syndrome (LGS)

In agreement with the initial submission, study 022 is strongly positive, p=0.0015 (Wilcoxon rank-sum test) based on primary efficacy endpoint of the percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase. The secondary efficacy measure of 50% responder rate for tonic-atonic seizure frequency relative to baseline was also highly positive with a 42.5% reduction in the rufinamide group compared to 16.7% in placebo, p=0.0020.

There is a large divergence in baseline seizure frequency between the rufinamide and placebo groups. The median baseline total seizure frequency in the rufinamide group is 290 seizures per 28 days and 205 seizures per 28 days in the placebo group. The median seizure rate during double blind treatment phase for the rufinamide group was 204.1 and 205.1 in the placebo group. Both treatment and placebo had numerically very close medians during treatment phase the resultant percent change in seizure frequency for rufinamide was -32.7%, where the source of significance in the study lies in the baseline seizure frequency. If there was a randomization bias resulting in the baseline difference then the significance of this value falls into question.

The sponsor was requested to re-evaluate the randomization procedure for systematic bias. There were three patients with a randomization error; two of those could not have any influence on the study. Examination of the distribution of 11 baseline variables with rufinamide and placebo treatment as covariates revealed p values ranging from 0.127 to 1.0, indicating no evidence of a systematic randomization bias see appendix 10.3.

Reviewer comment: Study 022 is a positive study, this in conjunction with two additional, although not robust, positive studies of efficacy in adult partial seizures are sufficient evidence that rufinamide is effective at the tested dose of 3200mg daily or 45mg/kg daily for the treatment of Lennox-Gastaut syndrome and approval is recommended

1.3.2.3 Efficacy related to concomitant anti-epileptic drugs.

In response to the concern in approvable letter that effectiveness may be associated with other AED's due to specific pharmacodynamic interactions the sponsor provides tables of efficacy for subgroups of patients taking 1-3 concomitant AED's as well as specific individual AED's. There are no systematic improvements in efficacy associated with AED subgroups in this analysis. See section 6.1.4.3.

1.3.3 Safety

For comprehensive review see Dr. Ramon initial safety review.

In this submission safety review was guided by issues expressed in the approvable letter of September 2006 and the end of review meeting of December 2006. These issues included:

1. clinically notable final laboratory values without follow up
2. hypothyroid response
3. status epilepticus
4. QT interval shortening
5. new safety data- ongoing clinical trials, dropouts and discontinuations
6. vomiting at higher doses

In preparation for labeling, the initial safety review was again reviewed, several residual issues were identified:

1. hyperthermia
2. hyponatremia
3. hypersensitivity
4. leukopenia

1.3.3.1 clinically notable final laboratory values

In summary the sponsor provided the tabular and narrative reports for the final clinically notable laboratory values pertaining to hepatobiliary function, renal laboratory values, hematology parameters and chemistry laboratory parameters. In the all of the four categories inclusive there were 217 final laboratory values that were clinically notable. These were

primarily isolated events preceded by normal laboratory values on study drug generally for several months before the final parameter was obtained at end of study or exit from open label treatment. In only 7 of these were follow up values obtained. This small number was insufficient to draw any new conclusions. In all seven cases the values normalized at follow up of which 6 of 7 were off medication at recheck. In one case medication status was unknown. This implies a dechallenge effect, however a six patient dechallenge across three areas of physiologic function are insufficient to conclude study drug causality. However each of the follow up values will be discussed in the specific laboratory area of section 8.

1.3.3.2 hypothyroid response

The approvable letter requested re-evaluation of the clinically notable thyroid studies with emphasis on those with elevated TSH and reduction in thyroxine values. The sponsor identified five patients with this profile. Upon analysis a confounding possible alternate cause of a hypothyroid response was identified, medication in 4 cases and abnormal baseline in one. The reviewer then returned to the clinically notable entries from the original submission ISS (integrated summary of safety). All clinically notable thyroid values were reviewed. Out of 263 entries 12 had the profile of elevated TSH and decrease in serum thyroxine. The sponsor submitted an additional case not present in the clinically notable data table raising the total to 13 cases. As a result of this review the thyroid data was found to be flawed due to unexplained changes in free thyroxine values seen in many cases. The best explanation for this observation is inconsistency in units expressing the thyroid values.

Review of the sponsor tables of clinically notable thyroid abnormalities reveals 39 cases of free thyroxine measurement that change units from ng/dl to pmole/liter part way through the study data. The ng/dl measures are all low relative to the SI unit measure of pmole/liter. These are marked abnormal in the table indicating the sponsor analysis has integrated these values into their analysis as abnormal and low. Four of these errors occur in study 027, 35 occur in study AE/ET1. 11 cases of a similar type of error are seen in the total thyroxine laboratory values.

On November 5, 2008 a teleconference with the sponsor took place to inform the sponsor of the broad profile of thyroid laboratory errors and the logical conclusion that these will incorrectly deflect the values of the statistical summary tables (shift table, table of central tendency and clinically notable table) which incorporate these erroneous values.

On November 10, 2008 the sponsor submits the corrected tables for studies 016, 018, 021A, 021P, 022, and 038. In addition separate tables are submitted for studies AE/ET1 and AE/PT2. The sponsor indicates that several isolated incorrect data entries as well as unit conversion errors were corrected in AE/ET1 and the tables recalculated.

The values of abnormal TSH and free thyroxine found in the corrected tables are in opposite physiologic direction in both the recent studies and older (AE/ET1,AE/PT2) studies. The expected direction of abnormality based on the preclinical features that resulted in this laboratory monitoring were values representing hypothyroidism. These changes do not reach a threshold either together or independently that indicated a thyroid safety signal.

1.3.3.3 status epilepticus

Status epilepticus did not occur in any patient who received placebo in any of the double-blind studies in the rufinamide clinical development program. Status epilepticus was an adverse event in 0.9% of all patients who received at least 1 dose of rufinamide, a serious adverse event in 0.3%, and an event that led to discontinuation of treatment in 0.1%. None of the affected subjects had a previous history of status epilepticus.

1.3.3.4 QT interval shortening

This has been thoroughly evaluated by the QT consult team and the office of surveillance and epidemiology (OSE). Rufinamide was observed at the time of initial review to cause QT shortening. The approvable letter the sponsor was asked to parse the QT observations into specific intervals for better analysis of this effect. Dr. Jones again identified that a dose related QT shortening effect occurs 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. However no patients had a decrease in QT interval below 300msec. There is no signal for unexpected malignant cardiac dysrhythmia present. The consensus of the safety and cardiology consultants is that there is no identifiable threat in the population with baseline normal QT interval, however there is a potential threat for the very rare patients with short QT syndrome rufinamide should not be used in that population. It is unknown if there is synergy between rufinamide and other drugs that shorten the QT interval.

1.3.3.5 ongoing clinical trials

There is an ongoing double blind trial conducted in North America. As of 15 February 2008 there have been 223 patients randomized (study drug status currently blinded) in the E2080-A001-301 clinical trial; of these, 141 patients have rolled over into the open-label extension study E2080-A001-302. This trial has yielded additional safety data since the initial NDA submission. Review of discontinuations and serious adverse events do not reveal a profile that is different from the studies in the initial submission. The most common adverse event leading to discontinuation was dizziness in 9 / 15 patients. There were no discontinuations due to bone marrow suppression, status epilepticus or hypersensitivity response. No deaths are reported in the annual report of study interval September 30,2006 to September 29,2007. The ISS update of February 28, 2008 is silent on deaths related to the new study so it cannot be ascertained if any death occurred from end of annual report in September 2007 until February 2008.

1.3.3.6 vomiting

At the end of review meeting on December 18, 2006 a concern about the safety and tolerance of rufinamide at high dose emerged. This concern noted in approvable letter, was prompted by the lack of clear dose direction in the treatment of partial seizures. If a higher than needed dose is selected the adverse event profile will likely increase. Vomiting is a common adverse event in anticonvulsant treatment and is present in rufinamide also. A discussion was requested of the sponsor to provide insight into the relation of high dose range rufinamide and vomiting. The sponsor notes the incidence of vomiting has a weak dose response relationship and is comparable

to several currently marketed anticonvulsants. They also indicate that much of the adverse event vomiting is confined to the pediatric population with LGS.

Review of the initial ISS, July 2006 reveals a dose response trend for vomiting that increases to the 1600 to 2400mg dose interval then levels off. Dose <400mg 6%, 400mg to 1600mg 10.9%, 1600 to 2400mg 17.3%, 2400 to ≤3200mg 16.2%, >3200mg 16.7%.

1.3.3.7 hyponatremia

This adverse effect is reviewed for the new submission because it was a residual issue indicated in the initial safety review. The case reports were examined for the possible hyponatremia cases. The case report reviews did not substantiate a hyponatremia response unique to rufinamide. The 4 cases were confounded by the presence of alternate medications or processes that could result in hyponatremia. There was no signal present in the summary statistics of the initial ISS.

1.3.3.8 hyperthermia

This adverse effect is reviewed for the new submission because it was a residual issue indicated in the initial safety review. The case reports were examined and found to contain processes that could produce hyperthermia or the clinical course was not consisted with a drug related hyperthermia. No unique signal for hyperthermia related to rufinamide was identified.

1.3.3.9 hypersensitivity

Several cases with features of hypersensitivity were identified. One case was consistent with a drug induced hypersensitivity syndrome with multiorgan involvement. There were no serious skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme) in the development program. The observed cases with multiorgan features was of sufficient concern that an addition of Multi-organ hypersensitivity reactions is added to the label.

1.3.3.10 leukopenia

This adverse effect is reviewed for the new submission because it was a residual issue indicated in the initial safety review. Review of clinically notable summary statistics reveals a 2.5% difference in WBC decrease between rufinamide and placebo. There is also 1 case reports with a dechallenge response to WBC suppression. This leaves a suspicion for leukocyte suppression, however placement of this observation in the adverse events labeling is appropriate

1.3.3.11 hepatobiliary response

There were no reports of serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system. Descriptive statistics, shift table analysis and summary clinically notable values between rufinamide treatment and placebo for all double blind study participants reveals no difference between treatment and placebo groups.

There are three individual cases of clinically notable hepatobiliary abnormality. One with an isolated increase in bilirubin to 10 times ULN with no other abnormal hepatobiliary laboratory parameter. This prompted a call to the sponsor for further investigation which revealed this to be

a transcription error from the case report form. The entry on the case report form indicated a value of less than 17, indicated as <17 which apparently was transcribed as 217umol/L. The second case with hepatobiliary abnormality revealed bilirubin elevated to 2 times ULN, SGOT elevated to 13 times ULN, SGPT elevated to 20 times ULN, alkaline phosphatase normal based on the laboratory established normal range. These abnormalities occurred on a background of a multiorgan hypersensitivity response. There was only one unconfounded clinically notable case with a transaminase elevation related to the study medication with dechallenge resolution. In this case the liver function abnormality was mild and otherwise asymptomatic, bilirubin was not elevated .

Conclusion: The primary safety concerns with this agent are the QT shortening, which almost only theoretical in threat is an issue of emerging understanding in cardiac electrophysiology, thus modification in labeling may be needed over time. Potentially intrusive but non - life threatening effects of somnolence and vomiting are anticipated at high dose range. Further data on this issue will be available from the ongoing open label study which has an option to advance dose to 4800mg daily. The safety profile is favorable compared to early generation anticonvulsant agents based on several counts, there have been no serious skin reactions, life threatening hepatitis, or serious bone marrow suppression. There is some indication of potential for hypersensitivity. In light of the significant efficacy for LGS, the safety profile is balanced.

1.3.4 Dosing Regimen and Administration

Rufinamide is indicated as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in adults and children age 4 years and older.

Rufinamide should be given with food.

b(4)

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 target dose of 45 mg/kg/day or 3200 mg/day whichever is less, administered in two equally divided doses. It is not known if doses lower than the target doses are effective.

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. It is not known if doses lower than the target doses are effective.

Drug-Drug Interactions

In vitro studies

Rufinamide shows no inhibition of most cytochrome P450 enzymes, and weak inhibition of CYP2E1. Drugs that are substrates of CYP2E1 (e.g. chlorzoxazone) may have increased plasma levels in the presence of rufinamide.

Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Broad-spectrum inducers such as carbamazepine and phenobarbital may have minor effects on rufinamide metabolism via this mechanism. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide.

Antiepileptic Drugs

The most notable interaction is between rufinamide and valproate in children where valproate at high dose may increase rufinamide concentration up to 70%. Phenobarbital, primidone and phenytoin may decrease rufinamide concentration up to 46%, carbamazepine may decrease rufinamide concentration up to 26%. Lamotrigine has no effect on rufinamide concentration.

Rufinamide may decrease carbamazepine and lamotrigine concentration by up to 13% and increase phenobarbital concentration up to 13%. Rufinamide may increase phenytoin concentration up to 21%.

(> b(4)

Special Populations

No new studies are submitted for review, the conclusions of the initial safety reviewer (Dr. Ramon) will be summarized.

Influence of sex was assessed only in the population PK analyses. A small difference between male and female patients was estimated, women showing a slightly lower apparent clearance. No specific study of ethnic differences in pharmacokinetics was conducted. The effect of ethnic origin was evaluated by population PK modeling using a pooled database in a study of healthy subjects. In the pooled dataset only the Black and White populations were sufficiently represented for an analysis, which showed no difference in clearance or volume of distribution after controlling for body size. In the pediatric age range no significant differences in plasma pharmacokinetic parameters as a function of age were observed. The only factor affecting both the apparent clearance and apparent volume of distribution was body size described either by weight or surface area. Geriatric pharmacokinetics were evaluated in 8 health elderly subjects compared to 7 young subjects. There were no significant differences found in the plasma and urine pharmacokinetic parameters of rufinamide between the younger and elderly subjects. In renal impairment pharmacokinetic evaluation showed that rufinamide pharmacokinetics were not affected by renal function impairment. There are no specific studies addressing the effect of hepatic impairment. There are also no adequate well controlled studies in pregnant women.

Based on the findings of embryo-fetal toxicity at doses associated with maternal toxicity, the sponsor proposed label classifies the drug as Pregnancy Category C.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.2 Currently Available Treatment for Indications

None in the United States. The first approval of rufinamide for marketing worldwide was the European Union plus Norway and Iceland via the centralized procedure on the 16 January 2007 (International Birthdate (IBD)). The requested indication in the application was for adjunctive therapy in the treatment of seizures associated with the Lennox-Gastaut Syndrome (LGS) in patients 4 years and older.

2.3 Availability of Proposed Active Ingredient in the United States

Not available in the United States

2.4 Important Issues With Pharmacologically Related Products

Anticonvulsant agents as a class have central nervous system adverse effects due to site of action. Several have significant risk of severe hypersensitivity response. Hepatobiliary adverse effects are also seen as an important issue in some of this class.

2.5 Presubmission Regulatory Activity

Dr. Hershkowitz initial efficacy review informs on the details of early rufinamide development.

"The IND for this product (#35,534) was originally filed on September 26, 1990 by Ciba-Geigy. Ciba-Geigy later merged with Sandoz to become Novartis. Novartis met with DNDP for an end of phase 2 meeting on April 23, 1998. At that meeting the proposed adjunctive study program was thought to generally be adequate. At that time, the proposed [redacted] not thought as adequate. Moreover, at that time, the division's statistical consultant made suggestions for [redacted] in the Lennox-Gastaut study. Novartis discontinued development of this product for "business reasons" in 2001. Eisai and Novartis met with DNDP in December 10, 2003 as part of a pre-NDA meeting. With minor exceptions the research program was considered adequate for filing an NDA for adjunctive treatment of partial seizure and seizures associated with Lennox-Gastaut syndrome. The Sponsor was, however, told that the final decisions on approval will be an issue of review. Latter in 2004 Eisai licensed rufinamide from Novartis. The Sponsor was granted Orphan status for rufinamide in the treatment of Lennox-Gastaut syndrome on October 8, 2004. A final pre-NDA meeting with Eisai occurred on November 15, 2004, during which the Sponsor was given advice on the format of the future submission as well as other specific information about analyses and data that will be required. "

b(4)

An initial NDA submission was filed on November 17, 2005. The submission was supported by 3 pivotal trials and several supporting trials. 2 of the pivotal trials were in adults, one in the pediatric population and one in Lennox-Gastaut syndrome. Following review an approvable letter was issued in September 2006. The concerns of the division were questionable efficacy of the agent with b(4) . There were also safety concerns. The studies had final study laboratory values that were abnormal with no follow up, the sponsor was requested to obtain follow up on outcome of these values. A possible hypothyroid response was present and further characterization of this response was requested. The potential for precipitation of status epilepticus was a concern with a .9% occurrence in the rufinamide group and none in the placebo group. The sponsor was asked to identify the proportion of these patients that had a history of status epilepticus. A dose related shortening of QT interval was identified therefore the division requested a representation of the QT data by absolute QT duration and also by reduction from baseline.

The adult trials consisted of a dose ranging trial of 200mg, 400mg, 800mg, 1600mg, and a fixed dose trial at 3200mg. The dose ranging trial established a minimal efficacy but did not distinguish any gradient of effect between 400mg and 1600mg. The fixed dose trial established efficacy based on the primary efficacy variable, however when a reanalysis is performed on log transformed 28 day seizure frequency with baseline frequency and country as covariates the study does not retain statistical significance.

The pediatric trial fails to establish significance at a fixed dose of 3200mg. The Lennox-Gastaut trial was highly significant at a fixed dose of 45mg/kg/day or maximum dose of 3200mg a day. The Lennox-Gastaut trial, although positive stood alone which was insufficient to support approval.

An end of review meeting occurred on December 18, 2006. The significant conclusions from this meeting were that studies AE/ET1 and 21A would be considered to meet the standard for two adequate and well controlled trials to demonstrate a seizure reducing effect of rufinamide as add on treatment for adults with partial seizures. The agency continued to hold the position that although the drug is effective. b(4)

The sponsor initiated an additional trial in May of 2006 using a fixed dose of 3200mg a day for adjunctive treatment of partial onset seizures in adults. This is a North American trial only. In the present submission of this NDA the sponsor is seeking approval of rufinamide for adjunctive treatment of partial seizures in adults and adolescents greater than 12 years old. In addition the submission is seeking approval for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults.

2.6 Other Relevant Background Information

Ongoing Clinical Trials-

In May of 2006 the sponsor initiated a double-blind, placebo-controlled, parallel study of rufinamide given as adjunctive therapy in patients with refractory partial seizures in patients 12 to 80 years old (E2080-A001-301). The study will recruit 408 patients from 80 North American centers. As of 15 February 2008 there have been 223 patients randomized (study drug status currently blinded) in the clinical trial; of these, 141 patients have rolled over into the open-label extension study E2080-A001-302. The total exposure to study drug (rufinamide or placebo) in the double-blind portion of the study by February 2008 is 33,084 patient-days; total exposure to rufinamide either during the transition phase of the double blind study or during open-label extension study (all patients on rufinamide) is 21,632-days.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.4 Data Quality and Integrity

The clinically notable thyroid data is of poor quality. There were 263 patient entries for clinically notable thyroid values in table 8.6-9 of the initial ISS. Those included on this table may have an abnormality in TSH **or** abnormal free thyroxine **or** abnormal thyroxine, and have abnormality in one or more of the thyroid parameters at any of the study visits. Review of the table reveals 39 cases (14.8% of entries) where a portion of the free thyroxine levels are reported in ng/dL then change to SI units (pmol/L). In most cases the baseline and early study visits are reported in ng/dL then change to SI units in the study visits that are in the interval from April 1995 to June 1996. The values in ng/dL are marked by an asterisk indicating a clinically notable result.

In addition to the unit variability in the free thyroxine values there are also recording errors in the total thyroxine data. Eleven cases (4.1% of entries) are found with sudden appearance of a very large value. As a example, one case begins with a correct thyroxine value of 82.6 nmol/L and at the subsequent visit the value jumps to a meaningless value of 61900000. The sponsor indicates that the second value had been entered as millimole/L and was subsequently converted from millimole to nanomole. Ten addition instances of this type were found in the data table. These large values are marked as abnormal on the data table.

In a teleconference November 5, the sponsor was advised of these anomalies and they submitted corrected tables of summary statistics (mean/median change in value from baseline to termination between rufinamide and placebo, shift tables for the interval from baseline to final thyroid laboratory result, and clinically notable thyroid laboratory values, low or high, placebo and rufinamide treatment) these are reviewed in section 8.1.3.1.3.

6 INTEGRATED REVIEW OF EFFICACY

This is a second submission for this product. This has created a sequence of initial presentation by sponsor, then review by FDA with issuance of an approvable letter. There was a subsequent end of review meeting with further clarification of the positions stated in the approvable letter.

It is noted in Dr. Hershkowitz initial efficacy review -the primary endpoint result revealed a median time of 4.8 days for the rufinamide group and 2.4 days for the placebo group. This barely met statistical significance (p=0.0499). A worst case scenario of the percent of patients exiting, where dropouts (i.e. from adverse events, withdrawal of consent, or protocol violations) are considered to have met exit criteria in drug but are considered completers placebo, found no numerical difference between drug and placebo groups (67.3% Vs 69.2%, respectively). This study acts as week supportive evidence for the Sponsor's intended use.

6.1.1.3.3 **0016**- This was a multicenter, double-blind, randomized, parallel-group monotherapy study of rufinamide in patients with inadequately-controlled partial seizures. Patients were randomized to receive either 300 or 3200 mg/day rufinamide for 112 days. A total of 142 patients were randomized: 70 patients to 300 mg/day rufinamide and 72 patients to 3200 mg/day rufinamide. No difference between doses was identified.

6.1.1.3.4 **0018**- This was a multicenter, multinational, double-blind, placebo-controlled, randomized, parallel-group study of rufinamide (800 mg/day versus placebo) as adjunctive therapy in patients with inadequately controlled PGTC seizures. The study consisted of a 56-day Baseline Phase and a 140-day Double-blind Phase during which patients were randomized to receive either rufinamide or placebo. A total of 155 patients were randomized: 80 to rufinamide 800 mg/day (78 treated) and 75 to placebo (75 treated). Although a greater median reduction in PGTC seizures was seen in the rufinamide group compared to the placebo group, the difference between the groups was not statistically significant.

Reviewer comment- [redacted] b(4)

6.1.2 General Discussion of Endpoints

6.1.2.1 Partial Epilepsy

Two studies were performed examining partial epilepsy.

6.1.2.1.1 Study AE/ET1:

6.1.2.1.1.1 Primary efficacy variable- A linear trend in dose response for seizure frequency per 28 days, constructed using all four doses of rufinamide and placebo for log-transformed seizure frequency during the double blind phase.

The initial study primary endpoint was set to time from randomization to fourth seizure. Sample size was set to this analysis. Prior to the unblinding of the trial, at a decision based on discussion of Working group 2 on August 30th, 1994 it was determined that this was not the best choice of endpoints as primary variable for evaluating seizure frequency in the traditional add on design. A decision was subsequently made to change the primary efficacy variable to the seizure frequency per 28 days in the double blind treatment phase.

The sponsor has initiated a second submission in response to the points in the approvable letter and end of review meeting which in turn has generated follow up statistical review of the pivotal trials.

In order to achieve improved understanding of this multi-tiered submission, the efficacy review format will be structured to provide a brief summary of the initial clinical trial review, followed by the specific analysis in the approvable letter and subsequent modifications in the end of review meeting. Next the sponsor response to each approvable letter and end of review point will be given followed by updated review of efficacy.

6.1 Indication

The sponsor seeks the following indications:
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.

6.1.1 Methods

6.1.1.1 Partial epilepsy

Discussed in 1.3.1, Brief overview of clinical program

6.1.1.2 Seizures associated with Lennox-Gastaut Syndrome

Discussed in 1.3.1, Brief overview of clinical program

6.1.1.3 Additional Supportive Studies

6.1.1.3.1 **AE/PT2**- Multicentre, multinational, double-blind, randomized, 2-armed parallel weekly rising dose trial in patients with epilepsy on up to 2 concomitant antiepileptic drugs (AED's) to investigate pharmacokinetics and tolerability in single (open design) and multiple dose (double-blind; 400/800/1200/1600mg/day). 25 subjects were recruited for treatment arm (rufinamide) and 25 to placebo. This study was not designed to carefully examine therapeutic efficacy. It was of short duration, small in size and did not have a pre-established primary endpoint. When the primary statistical analysis was performed with an intention to treat cohort, the result was not statistically significant.

6.1.1.3.2 **0038**- This was a multicenter, US, double-blind, placebo-controlled, randomized, parallel-group study of rufinamide as monotherapy in patients age 12 years or older with refractory partial seizures who had completed an inpatient presurgical diagnostic examination. The primary efficacy variable was the time to meeting one or more of four exit criteria. The primary objective of this study was to evaluate the safety and efficacy of rufinamide versus placebo as monotherapy in patients with refractory partial seizures. A total of 104 patients were randomized: 52 to rufinamide and 52 to placebo.

The initial efficacy review Dr. Hershkowitz indicated the primary endpoint in the study was somewhat atypical in using a regression analysis for the slope of a dose response curve of the absolute seizure frequency during the treatment period. He indicates "In studies with multiple doses this division usually depends upon a primary analysis of simple drug dose to placebo comparison with methods to maintain type 1 error: e.g. sequential high to low dose analysis is commonly used." The sponsor did perform such an analysis as a secondary endpoint but used a non-parametric analysis that did not allow correction for pertinent covariates.
6.1.2.1.1.2 Secondary efficacy variables

6.1.2.1.1.2.1 Analysis of seizure frequency treatment/baseline per 28 days (seizure frequency ratio) in double blind treatment phase divided by that in baseline phase, analyzed using Wilcoxon rank-sum tests

6.1.2.1.1.2.2 Responder rates, 25% and 50% reduction in seizure frequency analyzed by logistic regression.

6.1.2.1.1.2.3 Global Assessment of Therapeutic Effect (GATE), a 4 level ordered categorical scale completed by the investigator for the patient.

6.1.2.1.2 Study 021A. The second study used a typical ANCOVA analysis of the percent change from baseline of seizure frequency.

6.1.2.1.2.1 Primary efficacy- the primary efficacy was evaluated by determining the percent change in partial seizure frequency of the double blind phase relative to the baseline phase. Rufinamide was considered effective if the percentage reduction was statistically significantly greater ($p<0.05$) than placebo.

6.1.2.1.2.2 Secondary efficacy results

6.1.2.1.2.2.1 Total partial seizure frequency per 28 days during the double blind phase.

6.1.2.1.2.2.2 Responder rates, 25% and 50% reduction in partial seizure frequency relative to baseline.

6.1.2.2 Seizures Associated with Lennox-Gastaut Syndrome

6.1.2.2.1 Primary Efficacy variables 1) the percent change in total seizure frequency per 28 days; 2) the percent change in tonic-atonic (the sum of tonic and atonic seizures) seizure frequency per 28 days; and 3) the seizure severity rating from the Global Evaluation of the patient's condition.

The protocol specified that rufinamide would be considered effective if
1. The percent reduction in total seizure frequency per 28 days in the Double-blind Phase relative to the Baseline Phase was significantly greater ($p < 0.025$; two-sided) for rufinamide than placebo and/or

2. Both of the following were true
• The percent reduction in tonic-atonic seizure frequency per 28 days in the Double-blind Phase relative to the Baseline Phase was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo.
• The seizure severity rating from the Global Evaluation of the patient's condition was significantly greater ($p < 0.025$, two-sided) for rufinamide than placebo

6.1.2.2.2 Secondary efficacy variables- 1) response to treatment (i.e., experiencing at least a 50% reduction in tonic-atonic seizure frequency during the Double-blind Phase relative to the Baseline Phase); 2) percent change in the frequency per 28 days for seizure subtypes other than tonic-atonic; and 3) the composite score for the Global Evaluation of the patient's condition.

From Dr. Hershkowitz initial NDA review –"The analysis of this data was performed so that efficacy was concluded under one of two conditions: 1) the percent reduction in total seizures frequency was greater for the rufinamide then the placebo group at an alpha of 0.025, and/or 2) Superiority for the rufinamide group over placebo in the global and percent reduction in tonic and atonic seizures (both must be significant at an alpha of 0.025). The normal then lower alpha was added at the FDA's request to correct for multiple comparisons. Similar endpoints have been accepted by the FDA for anticonvulsant labeling in Lennox-Gastaut in the past. Thus topiramate was labeled based upon the dual endpoints of the global severity scale and percent change in drop attacks and lamotrigine was labeled based upon the percent change in "major motor" seizures (e.g. major myoclonic, tonic, atonic, myoclonic, tonic-clonic). The global is added because of the subtlety of some seizures and the difficulty in counting some. It adds additional face value to the endpoint. In conclusion, the present primary endpoints are acceptable and similar to those previously accepted for other drugs approved for this indication."

6.1.3 Study Design

For full study design see the initial NDA efficacy review by Dr. Hershkowitz

6.1.4 Efficacy Findings

6.1.4.1 Partial Seizures

6.1.4.1.1 Study AE/ET1
6.1.4.1.1.1 Sponsor initial submission- A positive slope of the dose-response relationship for seizure frequency per 28 days in the Double-blind Treatment Phase was statistically significant ($p=0.003$), and associated with a general decrease in seizure frequency per 28 days in the Double-blind Treatment Phase as the dose of rufinamide increased from placebo. This result was reproduced by demonstration of a statistically significant dose-response relationship in 25%

responder rate (p=0.0035). Furthermore, analysis of *AUC* plasma concentrations of rufinamide clearly demonstrated a dose-response relationship between reduction in seizure frequency and increasing *AUC* (p=0.0077).

Having confirmed that rufinamide was effective in the primary analysis, the seizure frequency ratio of individual doses of rufinamide was compared to placebo. This was done using pairwise Wilcoxon rank-sum tests to avoid dependence on distributional assumptions and the effects of outliers. The three higher doses, 400,800, and 1600 mg/day, produced a significant reduction in median seizure frequency compared with placebo of 11% (p=0.0274), 16% (p=0.0123), and 17% (p=0.0163), respectively. Rufinamide 200 mg/day was shown to be indistinguishable from placebo (reduction compared with placebo of 4%; p=0.8116). Thus, the minimum clinically effective dose in this trial was 400 mg/day in adults. This result was confirmed in the analysis of 25% responder rate; rufinamide 200 mg/day had a similar response to treatment (22.8%) as placebo (24.1 %) but as the rufinamide dose increased the 25% responder rate also increased to a rate of 37.6% for patients who received rufinamide 1600 mg/day. The percentage of patients with at least a 50% reduction in seizure frequency per 28 days was considerably less than the 25%responder rate, but was higher for patients who received rufinamide 400,800, 1600 mg/day than placebo (16%,11.6%, 14.3% vs. 9% respectively).

6.1.4.1.1.2 Initial Review analysis-

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

The percent reductions in seizure frequency for the rufinamide groups over placebo group were not linear (see Table 6.1.4.1-1). For the 1600 mg, the reduction was lower than the reduction for the 800 mg. Although the slope was statistically significant, the slope is very difficult to interpret if the trend is not linear. Only 800 mg dose showed some efficacy of rufinamide. Hence the study results were inconclusive to demonstrate the efficacy of rufinamide.

Table 6.1.4.1-1 Median seizure frequency per 28 days in the Baseline and Double-blind Phases, Study AE/ET1

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

[$] The sponsor used the same model to estimate regression slope.
[$$]% Reduction over placebo = 100 x [1-exp (LSMEAN rufinamide- LSMEAN placebo)]
LSMEAN: Least Square Mean.

Dr. Siddiqui, FDA Statistical Review

Medical Reviewer analysis, Dr. Hershkowitz- The reviewer was troubled by the very different distribution of placebo group as compared to all rufinamide dose groups. Thus, while all median frequencies amongst the placebo and dose groups are similar, the mean for the placebo is >30% that of all dose groups. While the logarithmic transformation presumably corrects for this, this difference still concerned the reviewer. The, review, would also depend upon other analysis performed as secondary endpoints.

6.1.4.1.1.3 Approvable letter- "Study ET1 compared 4 doses of rufinamide (200, 400, 800, 1600 mg/day) and placebo as adjunctive therapy in patients with partial seizures. Your primary outcome analysis (the linear trend test) was positive and we believe that the study does, overall, provide evidence of an effect, even though the results were not linear, with 800 mg having the largest effect. The results of the dose-finding aspect of the study, however, are hard to interpret. The reductions in seizure frequency compared to baseline were very modest, barely one to 1.5 seizure per month and the percent reductions compared to placebo were -3% 11%, 17% and 12% for the 200, 400, 800 and 1600 mg doses, respectively. We also note that your amended statistical plan for this study called for an analysis of the individual doses using a Poisson regression. The results of this analysis are not presented in your application; we request that you provide these results.

Although we acknowledge that the results of the Wilcoxon analysis that you did present yielded nominal statistical significance for all doses above 200 mg/day, in this reasonably large study (about 125-130 per group) only the 800 mg group attained a nominally statistically significant result when analyzed with a more traditional ANCOVA that included country as a covariate. Thus, the study suggests (but again, with an extremely small effect on seizure frequency), that 800 mg is at least as effective as a larger dose."

6.1.4.1.1.4 End of Review Meeting- further discussion developed on study AE/ET1 at the December 18, 2006 EOR. The minutes reflect that Eisai believes that study AE/ET1 and 21A were positive trials by test of their protocol specified primary endpoints and asked if the Agency did concur that the two trials meet the standard for two adequate and well controlled trials to demonstrate a seizure- reducing effect of rufinamide as add on treatment for adults with partial seizures. The Agency responded "yes"

The sponsor also reiterated that for rufinamide 400mg, 800mg, and 1600mg were all positive doses and that 3200mg was positive in one trial concluding there may be a gradual dose response. In response the division agreed that the drug is effective, however they will not approve a dose of 3200mg if 800mg is just as good but they are not yet convinced as to the efficacy of 800mg or lower doses. They (FDA), does not want to unnecessarily dose patients four times too high.

6.1.4.1.1.5 On February 28, 2008- In their second submission the sponsor continues the claim that the primary outcome, linear trend of dose-response for seizure frequency per 28 days, had significance (p=0.003). The sponsor also indicates that there were seven sensitivity analyses of dose-response performed showing consistent results (all $p \leq 0.0271$). A further exploratory analysis to examine the AUC for rufinamide plasma concentration and seizure frequency per 28 days was performed using a linear regression model. This also confirmed that seizure frequency per 28 days in the double-blind phase decreased significantly (p=0.008).

In the second submission the sponsor also looks to secondary outcome measures for confirmations. These included seizure frequency ratio of each treatment group compared to placebo which showed a statistically significant reduction of seizure frequency for the doses of 400mg/day, 800mg/day and 1600 mg/day (all $P \leq 0.0274$). Relative to placebo, these significant differences corresponded to a reduction in median seizure frequency of 11%, 16% and 17%, respectively. 200mg was not significant. The linear trend of dose response in terms of the 25% and 50% responder rates were statistically significant (P=0.0035 and P=0.0319) The sponsor again notes the significance of the GATE scale (see 6.1.2.1.1.2.3), notes that time to 4th seizure was also significant at doses of 800mg and 1600mg.

A Poisson regression which was not included in the first submission was provided in this submission. The Poisson regression was performed on the double-blind phase. The results of the analysis on the primary outcome measure are presented in Table 6.1.4.1-3 (below). These results are in agreement with the primary and secondary analysis presented in the CSR of linear trend of dose-response and pair-wise comparisons using the Wilcoxon rank sum test, respectively.

The sponsor notes that when tested, using the Pearson chi-square statistic, the assumption of proportionality of the mean and variance is not sustained. Therefore an analysis performed on seizure data using ANCOVA on ranks is most appropriate. The sponsor presents this data which shows significance at 400mg (p=0.0273), 800mg (p=0.0131) and 1600mg (p=0.0113). The sponsor also dissents from the Agency opinion that a traditional ANCOVA with country, sex and age as covariates is most appropriate and supports with several arguments that ANCOVA on

ranks is the correct approach. The sponsor concludes that AE/ET1 is a positive dose ranging study which establishes a minimum effective dose, [redacted] b(4)

6.1.4.1.1.6 Exposure response relationship

The sponsor creates an exposure response relationship based on pharmacokinetic data available from studies 027,018,016,21A,021P, AE/ET1, AE/PT2, and 022. The sponsor calls on this PK-PD model to add support to the conclusion that there is a dose response increase between 400mg and 3200mg a day. The sponsor notes that because of the difficulty in conducting and interpreting concentration-controlled trials, especially when exposure is not linearly related to dose level as in rufinamide, a pooled study approach was chosen. Figure 6.1.4.1-1 presents the model predictions for the exposure response for rufinamide in adult partial seizures from pooled PK-PD analysis of AE/ET1, AE/PT2 and study 21A. Study 022 is presented separately in figure 6.1.4.1-2

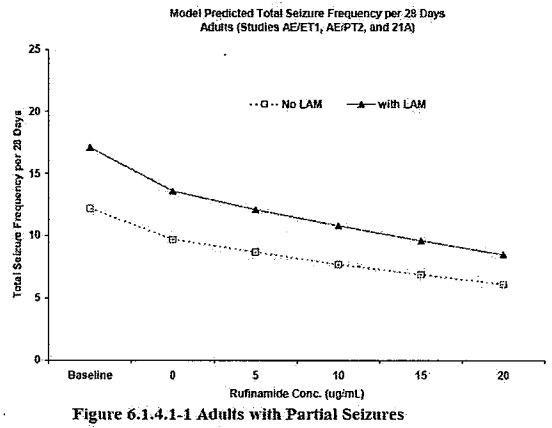


Figure 6.1.4.1-1 Adults with Partial Seizures

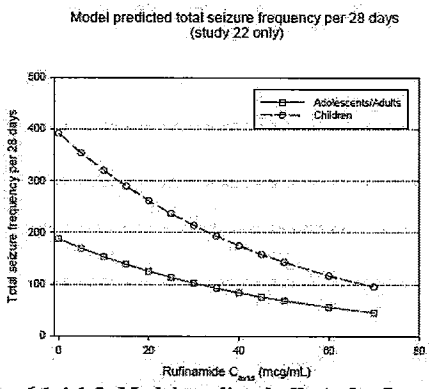


Figure 6.1.4.1-2 Model predicted effect of rufinamide on total seizure frequency

The sponsor presents several additional concentration response analyses to support a dose range from [redacted] to 3200mg. In addition a similar analysis is performed for children (study 21P) where the sponsor finds a significant rufinamide concentration response relationship but the slope is less steep (-0.011 mL/μg, Figure 6.1.4.1-3) than observed for the pooled analysis in adults (-0.023 mL/μg, figure 6.1.4.1-3). This compares to -0.021 mL/μg for the study 022 and -0.020 mL/μg for the pooled model. b(4)

6.1.4.1.1.6 FDA response to second submission

6.1.4.1.1.6.1 Statistical review, Dr. Siddiqui- The reviewer points out that the statistically significant dose response analysis might be due to either (i) there was a linear dose-response trend or (ii) there was no linear trend but a difference in responses between Placebo vs. all doses together (in presence of plateau dose response of the selected doses).
Dr. Siddiqui reports that in the dose response analysis the sponsor reassigned a numerical order to the 200mg,400mg,800mg, 1600mg as 0,1,2,3,4. He indicates that the numerical reassignment should maintain the proportionality of the dose and reassigned values of 2,4,8, and 16 instead of 1,2,3, and 4. The analysis is repeated with and without placebo arm using both the simple 1 to 4

assignment and the proportional assignment. Upon this subsequent reanalysis there is no significance (p=0.086) when the placebo is dropped and the dose values are coded proportionately at 2,4,8,16, (see table 6.1.4.1-2 below, FDA four modes of regression analysis). The insignificant slope indicates the efficacy of the four doses, 200mg, 400mg, 800mg, and 1600mg were similar. When the placebo group remains in the slope analysis, the value of the slope is significant (p =0.015), this finding indicates that the statistical significance of the slope is derived from the difference between placebo and treatment. However the non-significant slope obtained from treatment without placebo, indicates that there is no significant gradient of effect between the individual dosages between 200mg and 1600mg.

Table 6.1.4.1-2 FDA, four modes of regression analysis for dose response

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

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

Dr. Siddiqui, Statistical review, 2nd submission

Poisson Regression analysis (Table 6.1.4.1-3) – FDA reviewer, Dr. Siddiqui repeated the Poisson analysis with multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment). Following this adjustment only 1600mg of rufinamide remains significantly different from the placebo group.

Table 6.1.4.1-3 Sponsor Poisson Regression Analysis on Seizure Frequency during the administration double blind phase, prior to multiplicity adjustment

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

Note: Results are based on a generalized linear model with ordinal dose, country, sex, age, and log (baseline counts) as covariates and adjusted for over-dispersion using Pearson Chi-square as a scale factor.
Source: clinical overview of the submission dated Feb 29, 2008

In another modification of the Poisson regression model, Dr. Siddiqui dropped the 200mg dose and refitted the model. Table 6.1.4.1-4 below lists the findings of the analysis. In absence of the

200mg dose in the model, the 400mg and 800mg failed to retain the significance levels seen in table 6.1.4.1-4. Each dose group should have independent capability to demonstrate significant efficacy. The sponsor included log-transformed baseline seizure count as a covariate in the Poisson model. Since the seizure frequency data of post-baseline was modeled as count data, it is more appropriate to include the baseline seizure frequency data as a covariate without any transformation. Dr. Siddiqui then included baseline seizure frequency data as a covariate in the model without any transformation, and found that none of the doses were statistically significantly (p-values ≥0.245) different from placebo.

Table 6.1.4.1-4 Poisson Regression Analysis on Seizure Frequency during the administration double blind phase (exclude 200mg)

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

Dr. Siddiqui, Statistical review, 2nd submission

ANCOVA on Rank of percent change vs. Rank on total seizure frequency

The sponsor performed an ANCOVA on the rank of percent change in total seizure frequency per 28 days to compare the efficacy of the individual doses vs. placebo. Dr. Siddiqui repeated the analysis with multiplicity testing (either using Hochberg's method or Bonferroni adjustment), and found only 1600mg rufinamide had statistically significant difference from the placebo group. Dr. Siddiqui subsequently performed an ANCOVA analysis on the rank of total seizure frequency per 28 days at post-baseline, rather than rank of percent change in seizure frequency. In the analysis, the rank of baseline total seizure frequency per 28 days and country were included as covariates. Table 6.1.4.1-5 lists the p values of the analysis before multiplicity testing. After multiplicity adjustment (either using Hochberg's method or Bonferroni adjustment) none of the doses were statistically significantly different from placebo in the rank of total seizure frequency based on ANCOVA analysis.

Table 6.1.4.1-5 ANCOVA on Ranks of Total Seizure Frequency per 28 days at Post-baseline

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

¥ P-value based on ANCOVA model with ranked baseline Seizure and country as covariates

Dr. Siddiqui, Statistical review, 2nd submission

Secondary endpoints

In Table 6.1.4.1-6, the sponsor performed Wilcoxon rank-sum test was used to compare the seizure frequency ratio (a secondary measure) of each individual dose vs. placebo. Multiplicity adjustment is performed by Dr. Siddiqui (either using Hochberg's method or Bonferroni adjustment), subsequently only 800 mg of rufinamide was statistically significantly different from the placebo group. The sponsor did not consider any multiplicity adjustment in stating the significance of the dose vs. placebo comparisons.

Table 6.1.4.1-6 Secondary endpoints for AE/ET1

	Seizure frequency ratio [1]		Percentage of patients with a 25% reduction in seizure frequency [2]		Percentage of patients with a 50% reduction in seizure frequency [3]		Estimated odds-ratio for GATE [4]	
	Median	P value		P value		P value		P value
Placebo	1.05		14		9			
200 mg/day	1.01	0.8116	22.8	0.7847	4.7	0.1822	1.452	0.1164
400 mg/day	0.93	0.0274	32.8	0.1198	16	0.0875	1.744	0.0197
800 mg/day	0.88	0.0123	34.1	0.0803	11.6	0.4812	1.781	0.0143
1600 mg/day	0.87	0.0163	37.6	0.0238	14.3	0.1978	2.238	0.0005

[1] The seizure frequency ratio for each patient was the number of seizures that occurred during the Double-blind Phase divided by the number of seizures that occurred during the Baseline Phase. This was expressed per 28-day intervals. Wilcoxon rank-sum test was used to compare the seizure frequency ratio.
[2, 3, 4] Based on Logistic Regression
Source: clinical overview of the submission dated Feb 29, 2008

Reviewers comment: *As the statistical review proceeds through the sponsor's analysis the points of significance fall away. The pivotal goal of establishing a dose response is lost when the linear dose response analysis is reexamined by Dr. Siddiqui (FDA statistical reviewer) with proportional dose recoding and placebo excluded. A secondary outcome measure, seizure frequency ratio of response at each dose is reported by the sponsor to be significant at 400mg, 800mg and 1600mg, however when the analysis is refined by multiplicity testing, only the 800mg dose is statistically significant. In another secondary efficacy measure, the logistic regression analysis on the 25% and 50% responder rate, none of the doses is significant after adjusting for multiplicity. The significance of the logistic regression analysis of the GATE (Global Assessment of Therapeutic Effect) scale is only significant at 1600mg after multiplicity adjustment. The Poisson regression analysis on seizure frequency retains only 1600mg of rufinamide significant after multiplicity adjustment. In addition when the model is refitted without the 200mg dose the 400mg and 800mg subsequently lose significance. Dr. Siddiqui notes that each dose should independently have power to demonstrate significant efficacy. The ANCOVA on rank of total seizure frequency was repeated without transformation and with country as covariate. Again after multiplicity testing none of the doses was statistically significant.*

In the initial review it was also seen that the percent reduction in seizure frequency for the rufinamide group over placebo was non linear. There was less reduction in at the 1600mg dose then at 800mg.

There is no clear dose response when placebo is removed from the dose response analysis, this implies that the significant slope is created by the placebo and the cluster of dose points that

behave as a single point rather than an array of points with progressive increase in effect. The review also reveals a weak medication effect with significance oscillating between the 800mg a day and 1600mg a day dosage. This study does not define a usable range of medication dose. In order to define a clear effective dose range for this product a new dose ranging study with adequate power is needed.

6.1.4.1.2 Study 21A

6.1.4.1.2.1 Sponsor Initial Submission- The primary efficacy variable, percentage change in partial seizure frequency per 28 days of the Double-blind Phase from the Baseline Phase, was significant in favor of the rufinamide treatment group relative to the placebo treatment group (Wilcoxon rank-sum test, p=0.0158). Rufinamide-treated patients experienced a 20.4% median reduction in partial seizure frequency per 28 days from the Baseline Phase compared to a 1.6% median increase for placebo-treated patients. Table 6.1.4.1.2-1.

Table 6.1.4.1.2-1 Summary of percentage change in partial seizure frequency per 28 days from Baseline Phase (Intent-to-treat patients)

	Rufinamide (N=156)		Placebo (N=156)	
	Median	**Range**	**Median**	**Range**
Baseline partial seizure frequency per 28 days	8.5	(3.0, 275.0)	8.0	(2.5, 578.5)
Double-blind partial seizure frequency per 28 days	7.6	(0.0, 552.2)	8.7	(0.0, 416.3)
Percentage change in partial seizure frequency per 28 days from baseline	-20.4[a]	(-100.0, 987.5)	1.6	(-100.0, 6837.8)

Cross-reference: Post-text Table 9.1-1; Appendix 8.1, Table 9.1-1, Appendix 7.1, Selected Patient Listing 9.1-1.

[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0158.

The sponsor also finds that patients in the rufinamide treatment group demonstrated a consistent reduction in seizure frequency for each of the three partial seizure subtypes with median reduction ranging between 27.0% and 37.8%. In contrast the placebo treatment group showed wide variability in its reduction of the various partial seizure subtypes with median reduction ranging between 2.6% and 37.8%. Table 6.1.4.1.2-2.

Table 6.1.4.1.2-2 **Summary of percentage change in partial seizure frequency per 28 days from Baseline Phase by seizure type (Intent-to-treat patients)**

	Rufinamide (N=156)			Placebo (N=156)		
Seizure type	N	Median	Range	N	Median	Range
Simple partial seizures	60	-37.1	(-100.0, 1154.8)	67	-2.6	(-100.0, 11526.7)
Complex partial seizures	136	-27.0	(-100.0, 1125.0)	130	-12.0	(-100.0, 647.3)
Secondarily generalized seizures	47	-37.8	(-100.0, 335.6)	54	-37.8	(-100.0, 304.4)

Cross-reference: Post-text Tables 9.1-2, 9.2-3, Appendix 7.1, Selected Patient Listing 9.1-1.

The sponsor also performs an analysis of the percent change in partial seizure frequency per 28 days of the Double-blind Phase relative to the Baseline Phase that included only those patients who completed the Double-blind Phase (rufinamide N=120, placebo N=137). Results of this analysis confirmed the statistical superiority of rufinamide over placebo with respect to the reduction in partial seizure frequency (p=0.0019) and demonstrated the robustness of the results provided by the intent-to-treat patient population.

An additional analysis of the percent change in partial seizure frequency per 28 days was performed using the first 274 randomized patients in the intent-to-treat patient population. This analysis was performed to evaluate the consistency of the results obtained had the original planned sample size discussed in Section 6.2 been utilized. Results of the analysis on the first 274 enrolled patients (p=0.0036), confirmed the results of the analysis of the primary efficacy variable in the intent-to-treat population (n=312). Over-enrollment occurred because late in the conduct of the study, centers enrolled at a rate faster than anticipated

Secondary Efficacy Results

The sponsor performed an analysis of the total seizure frequency per 28 days during the double blind phase which demonstrated a trend towards significance (p=0.092). The sponsor attributes this lack of statistical significance to the lack of normality in this variable despite the $\log_e$ transformation. To confirm this conclusion a post-hoc, analysis of variance model, was fitted with treatment and country as factors relative to the ranks of the change in seizure frequency relative to baseline (double blind minus baseline seizure frequency). This model produced a result similar to what was seen for the primary efficacy variable (p=0.008).

50% responder rate: Significantly more patients receiving rufinamide treatment experienced a 50% reduction in partial seizure frequency relative to baseline during double-blind therapy compared with patients receiving placebo (p=0.0381, logistic regression model). The observed odds ratio of 1.76 indicates that patients who received rufinamide were 1.76 times more likely to experience at least a 50% reduction in partial seizure frequency relative to baseline compared with those receiving placebo.

25% responder rate: Significantly more patients receiving rufinamide treatment experienced a 25% reduction in partial seizure frequency relative to baseline during double-blind therapy compared with patients receiving placebo (p=0.0013, logistic regression model). The observed odds ratio of 2.18 indicates that patients who received rufinamide were 2.18 times more likely to experience at least a 25% reduction in partial seizure frequency relative to baseline compared with those receiving placebo.

6.1.4.1.2.2 Initial Medical Reviewer Analysis- This reviewer feels that this study has potentially demonstrated a therapeutic effect of rufinamide at 3200 mg/day. The magnitude of this effect appears to be of a moderate magnitude. Because of the uncertainty of the effect of rufinamide in the second pivotal study, performed at lower doses, the non-pivotal trials will need to be examined to determine reproducibility of this finding.

6.1.4.1.2.3 Approvable letter- "Study 21A compared rufinamide 3200 mg/day to placebo in a population similar to study ET1, showed a significant effect on the protocol-specified Wilcoxon rank sums test, but in a study with substantial geographic distribution it is desirable to examine effects of country and other covariates. Our ANCOVA analysis on log transformed 28 day seizure frequency, with baseline frequency and country as covariates, gave a p-value of 0.09. The study thus provides some, but not strong, evidence of an effect and again, the median change compared to baseline is just 20% (15% in US patients), a reduction compared to placebo of about one seizure per month. The dose, moreover, is fully 4 times that of the dose with the greatest treatment effect in study ET1."

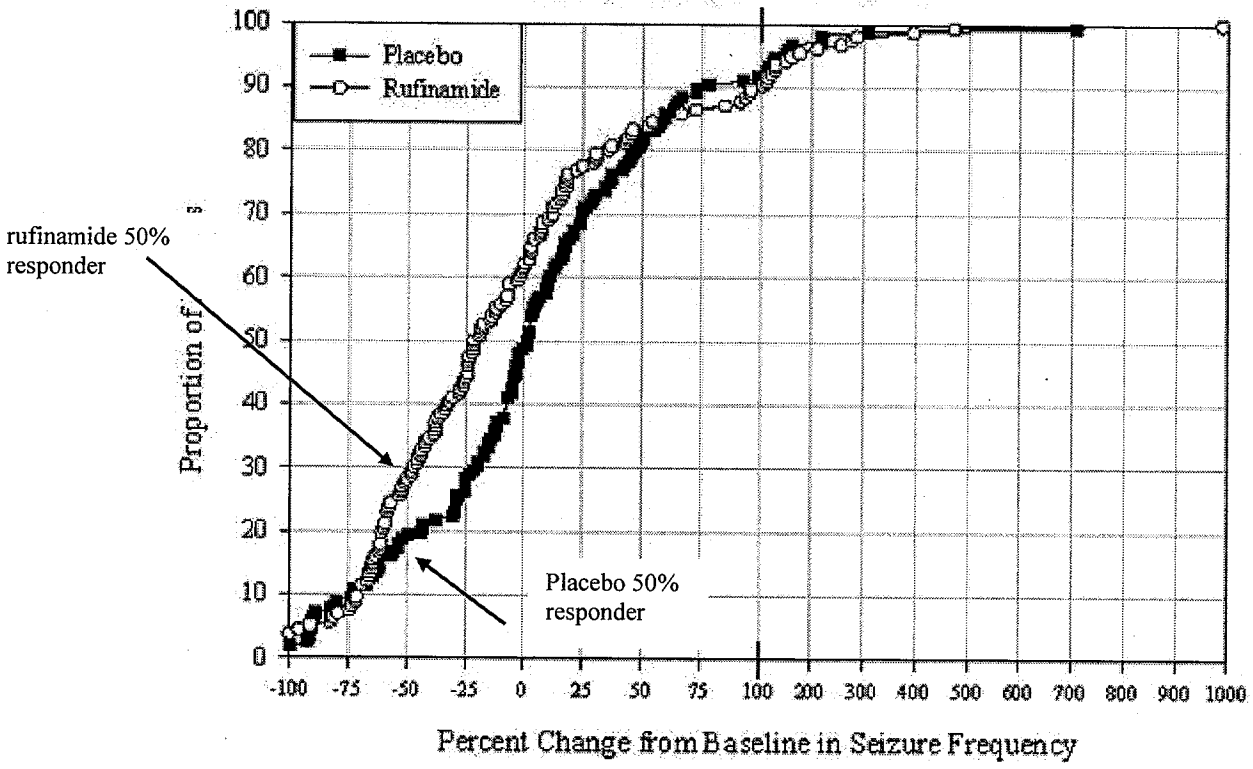
6.1.4.1.2.4 End of Review Meeting- further discussion developed on study AE/ET1 at the December 18, 2006 EOR. The minutes reflect that Eisai believes that study AE/ET1 and 21A were positive trials by test of their protocol specified primary endpoints and asked if the Agency did concur that the two trials meet the standard for two adequate and well controlled trials to demonstrate a seizure- reducing effect of rufinamide as add on treatment for adults with partial seizures. The Agency responded "yes"

The sponsor again quires if the agency considers 21A a positive trial although the secondary endpoint of ANCOVA on log transformed 28 day seizure frequency during double blind phase did not demonstrate statistical significance (p=0.09). The agency response was "yes"

6.1.4.1.2.5 Second submission February 28, 2008- The sponsor reiterates that study 21A is a positive study based on the primary efficacy endpoint of percent change in seizure frequency per 28 days from baseline phase. They indicate concern that the secondary analysis of change in seizure frequency per 28 days from baseline in the double blind phase turns out non-significant until the analysis is performed using a non-parametric method (ANCOVA on ranks including baseline and country as covariates). They report the results from this method as highly significant (p=0.008) and supportive of the primary efficacy measure. Eisai believes that the lack of significance of the log transformed 28-day seizure frequency is a reflection of the inadequacy of the log transformation of the seizure frequency. This due a non normal distribution of the transformed data.

The sponsor counters the FDA reviewer statement that 21A provides "some, but not strong evidence of an effect" by stating "that in order to more accurately evaluate the clinical benefit on a population, individual subject responses and not the change in the median number of seizures is the more appropriate analysis." In support of this statement the sponsor generated a cumulative distribution function (CDF) for % change from baseline in seizure frequency. Figure 6.1.4.1.2-1 below.

Figure 6.1.4.1.2-1 Study 21A (add-on partial seizures): Empirical Cumulative Distribution Function for percent change from baseline in seizure frequency by treatment group



Following extreme value is not included in this graph:
Subject ID: CRUF3310021_1284_05059, % Change = 6837.77778 , Treatment Group: Placebo

Based on this analysis the sponsor indicates that rufinamide demonstrates a consistent superiority over the range corresponding to larger seizure rate reductions.

6.1.4.1.2.5.1 Effect size

In the approvable letter FDA is concerned about the minimal effect size (median rufinamide seizure reduction – placebo median seizure reduction) in the positive studies. The sponsor counters by stating the study observed effect size does not have a clear correlate in clinical

practice or in the drug effect in an individual patient. Sponsor also proposes that the clinical trial population is more refractory to treatment than patients in normal clinical practice. The sponsor proposes that the cumulative distribution functions (CDF) are a more informative summary of individual patient response to treatment. In the CDF of study 21A the 50% responder rate can be seen, which was statistically significant. A CDF for study AE/ET1 expressed by individual doses and a CDF on the pooled population response of study AE/ET1 and 21A are shown below (see table 6.1.4.1.2-2 and 6.1.4.1.2-3).

Figure 6.1.4.1.2-2 **Study AE/ET1 (add-on partial seizures): Empirical Cumulative Distribution Function for percent change from baseline in seizure frequency by treatment group**

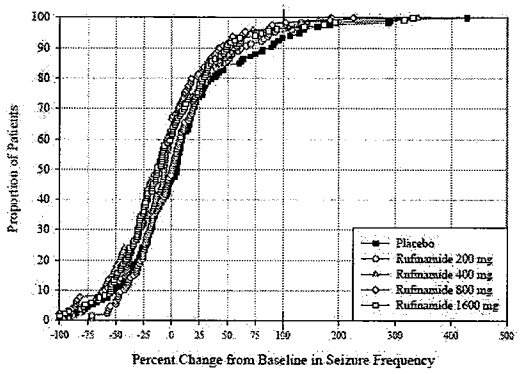
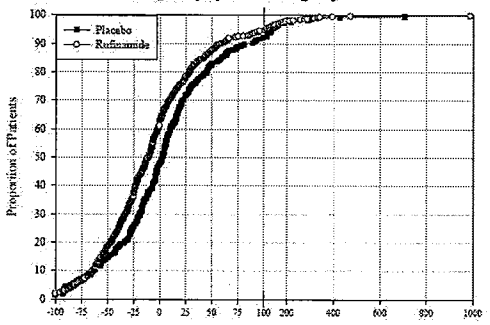


Figure 6.1.4.1.2-3 **Pooled data from studies AE/ET1 and 21A (add-on partial seizures): Empirical Cumulative Distribution Function for percent change from baseline in seizure frequency by treatment group**



Note: This plot is on the pooled population that consists of all patients from Study 21A and Study AE/ET1 (excluding patients from the Rufinamide 200mg treatment group)

Following extreme value is not included in this graph.
Subject ID: CRUF3310021_1284_05059, % Change = 6837.77778 ; Treatment Group: Placebo

6.1.4.1.2.6 FDA Response to Second Submission

6.1.4.1.2.6.1 Statistical Review- Dr. Siddiqui was able to reproduce the sponsor's reported primary and secondary efficacy results. Since about 50% patients were randomized from USA, it was important to evaluate the efficacy of rufinamide for the USA patients. Therefore, the efficacy of rufinamide was evaluated for the USA and non-USA patients separately using Wilcoxon Rank Sums test. Table 4 lists the efficacy findings by USA vs. non-USA patients. For the USA and Non-USA randomized patients, the median percentage changes in seizure frequency relative to baseline of the two treatment groups were very similar. However, for the USA patients (with 77 placebo patients and 80 Ruf patients), the rufinamide group was not statistically significantly (p-value=0.106, Wilcoxon Rank Sums test) different from placebo.

Dr. Siddiqui did a secondary analysis on the efficacy data of the study 21A. Table 6.1.4.1.2-3 lists the p-values for the comparison of rufinamide 3200mg vs. placebo for the secondary analyses. According to the sponsor, the lack of statistical significance in the ANCOVA analysis (i.e., Model#1) was due to the lack of normality in this variable despite the log transformation. The sponsor stated that an ANCOVA rank analysis is more appropriate in analyzing seizure frequency data. Therefore, as a remedy for the lack of normality, one can use an ANCOVA model (Model#2) on rank data of total partial seizure frequency per 28 days during the Double blind Phase including rank of total partial seizure frequency per 28 days during the baseline with

age, treatment, Country, and gender as covariates factors in the model. The model provided a p-value of 0.118. So, rufinamide was not statistically significantly different from placebo based on ANCOVA model on rank data of post-baseline seizure frequency.

Table 6.1.4.1.2-3 Study 21A- Comparison of Rufinamide 3200mg vs Placebo

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

Dr. Siddiqui, Statistical review, 2nd submission

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

Table 6.1.4.1.2-4 lists the mean and median seizure frequency per 28 days in the baseline and double-blind phases for the studies AE/ET1 and 21A. The changes in median seizure frequency from baseline to double-blind period were in the range of -1.16 to -0.95 for the doses of 400mg to 3200mg. The changes in median seizure frequency from baseline to double-blind period did not support any evidence of efficacy trend of the dose range 400mg to 3200mg. The same was true for the mean changes in seizure frequency.

Table 6.1.4.1.2-4 Median and Mean seizure frequency per 28 days in the Baseline and Double-blind Phases, Studies AE/ET1 and 21A

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

Dr. Siddiqui, Statistical review, 2nd submission

6.1.4.1.2.6.2 Pharmacometrics Review

Dr. Bhattaram analyzed the data as submitted by the sponsor and was able to confirm the sponsor's findings. He concluded there is evidence of effectiveness based on concentration-response analysis in adults however the effectiveness of rufinamide in children and adolescents based on reduction in seizure frequency was not clearly demonstrated.

6.1.4.1.2.6.3 Medical Reviewer comment: *Based on primary efficacy endpoint study 21A is positive. The efficacy however is modest and when analysis is limited to the US population only, significance is lost. On analysis of secondary efficacy measures by the FDA statistical reviewer, using an ANCOVA model of rank of total partial seizure frequency during baseline phase with Treatment, country, age and sex as covariates there is no significance. The primary efficacy variable of percent change in seizure frequency may have an advantage over change in total seizure frequency when there are a predominance of subjects with low baseline seizure frequency. In those circumstances a small reduction during treatment may translate into a large percent change. These features indicate that the anticonvulsant effect is not robust.*

6.1.4.2 Lennox Gastaut Syndrome (LGS)

6.1.4.2.1 Study 022

6.1.4.2.1.1 Sponsor initial submission

6.1.4.2.1.1.1 Primary efficacy variables. The sponsor examined three primary efficacy variables, percent change in total seizure frequency per 28 days relative to baseline (intent to treat patients), percent change in tonic-atonic seizure frequency per 28 days relative to baseline (intent to treat patients), and seizure severity rating of the global evaluation of the patient condition (intent to treat patients).

Primary efficacy variable 1, the percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p = 0.0015$). Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency (Table 6.1.4.2.1-1). Exploratory analysis using an ANCOVA model on ranks with treatment and region as factors and baseline total seizure frequency as a covariate verified these results ($p = 0.0026$). No significant treatment-by-region interaction was observed ($p = 0.7373$). Rufinamide remained significantly superior to placebo after adjusting for the number of AED's used at baseline ($p = 0.0021$)

Table 6.1.4.2.1-1 Summary of percent change in total seizure frequency per 28 days relative to baseline (intent to treat patients)

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

Cross-reference: Post-text Table 9.1-1; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.
[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0015

Primary efficacy variable 2, the percent change in tonic-atonic seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p < 0.0001$). Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic-atonic seizure frequency per 28 days. A brief summary of the results is presented in Table 6.1.4.2.1-2. Exploratory analysis using an ANCOVA model on ranks with treatment and region as factors and baseline tonic-atonic seizure frequency as a covariate verified these results ($p < 0.0001$). No significant treatment-by-region interaction was observed ($p = 0.3864$). Rufinamide remained significantly superior to placebo after adjusting for the number of AED's used at baseline ($p < 0.0001$)

Table 6.1.4.2.1-2 Summary of percent change in tonic-atonic seizure frequency per 28 days relative to baseline (intent to treat patients)

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

Cross reference: Post-text Table 9.1-2; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.
[a] 5 patients (1 rufinamide, 4 placebo) did not experience tonic-atonic seizures during the Baseline Phase.
[b] Between-group comparison using Wilcoxon rank-sum test p-value < 0.0001.

Primary efficacy variable 3, the seizure severity rating at the end of the Double-blind Phase, showed a significant difference between the two treatment groups in favor of rufinamide ($p = 0.0041$). An improvement in seizure severity was observed in 39 (53.4%) of the 73 rufinamide-treated patients compared to 19 (30.6%) of the 62 placebo-treated patients. A brief summary of the results is presented in Table 6.1.4.2.1-3. Exploratory analysis using a Cochran-Mantel-Haenszel test with region as strata confirmed these results ($p = 0.0029$)

Table 6.1.4.2.1-3 Summary of seizure severity rating of the Global Evaluation of the patient's condition (intent to treat patients)

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

Cross reference: Post-text Table 9.1-3; Appendix 7.1, Selected Patient Listing 9.1-3.
Wilcoxon rank-sum test p-value = 0.0041
[a] 3 patients (1 rufinamide, 2 placebo) did not have a seizure severity evaluation.

6.1.4.2.1.1.2 Secondary Efficacy Variables

Responder rate, tonic-atonic seizures- As shown in Table 6.1.4.2.1-4, the percent of patients who experienced at least a 50% reduction in tonic-atonic seizure frequency per 28 days, relative to baseline, was significantly higher in the rufinamide group (42.5%) than in the placebo group (16.7%) (p = 0.0020). The observed odds ratio of 3.81 indicates that patients who received rufinamide were approximately four times more likely to experience at least a 50% reduction in tonic-atonic seizure frequency, compared with those receiving placebo.

Table 6.1.4.2.1-4 Summary statistics of patients wih responded to treatment with at least a 50% reduction in tonic-atonic seizure frequency relative to baseline (intent to treat patients)

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

Cross reference: Post-text Table 9.2-1; Appendix 7.1, Selected Patient Listing 9.1-2.
[a] The odds of a rufinamide-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days relative to the odds of a placebo-treated patient experiencing at least a 50% reduction in tonic-atonic seizure frequency per 28 days.
[b] P-value based on logistic regression model with treatment, region, sex, and age as explanatory variables.

6.1.4.2.1.2 Initial Reviewer analysis

The initial medical review concluded that all primary endpoints of the protocol were satisfied at the required p value even when correcting for multiple endpoints. The secondary endpoint data also strongly supported the conclusion derived from the primary endpoint of a therapeutic benefit in the treatment of seizures associated with Lennox-Gastaut. Although not all endpoints exhibited a statistical significance there was a consistent therapeutic trend.

6.1.4.2.1.3 Approvable letter

"We also do not consider the data adequate to support an indication for use of rufinamide in LGS. While study 22 is clearly positive and there is at least some other evidence of activity from the adult studies, we do not at this time consider the evidence sufficient to support approval based on the single study. In the past, approvals based on single studies in LGS have been supported by clear evidence of an effect on partial seizures in adults, generally at least 2 clearly positive studies. We do not find that support here."

6.1.4.2.1.3 End of review meeting- no further discussion

6.1.4.2.1.4 Second Submission

The sponsor supports approval of rufinamide for Lennox-Gastaut syndrome based on 1998 Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products. The guidance reviews the approval of lamotrigine for treatment of Lennox-Gastaut syndrome which was based on a single adequate and well controlled trial and due in part to related data showing efficacy of the drug in partial onset seizures in adults. The sponsor cites a parallel between study 022 as the single well controlled trial and studies 21A and AE/ET1 as the supportive data showing efficacy in adult partial seizures. At the end of review meeting FDA agreed that studies AE/ET1 and 21A were 2 positive add on trials in adults with partial seizures.

6.1.4.2.1.5 FDA Response to Second Submission

6.1.4.2.1.5.1 Statistical Review

Primary variable 1: Total seizure frequency per 28 days Rufinamide was effective (p-value=0.0015) in reducing the percent change in total seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase. However, the median total seizure frequency per 28 days at double-blind period was almost same for the two groups (Table 6.1.4.2.1-5). Therefore, the statistical significance of the difference of the two groups might be due to the imbalance baseline seizure frequency per 28 days for the two groups at baseline.

Table 6.1.4.2.1-5 **Summary of percent change in total seizure frequency per 28 days relative to baseline (intent to treat patients)**

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

Cross-reference: Post-text Table 9.1-1; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.
[a] Between-group comparison using Wilcoxon rank-sum test p-value = 0.0015

Primary efficacy variable 2: Tonic-atonic seizure frequency per 28 days In comparison to placebo, rufinamide was effective (p-value<0.0001) in reducing the percent change in tonic-atonic seizure frequency per 28 days during the Double-blind Phase relative to the Baseline Phase

Primary efficacy variable 3: Seizure severity subscale of Global Evaluation of patient's Condition. Rufinamide was also effective (p-value=0.0041) compared to placebo with respect to the changes in seizure severity rating at the end of the Double-blind Phase.

Secondary efficacy measures.

Table 6.1.4.2.1-6 lists the median number of atypical absence, tonic, myoclonic, partial, and absence seizures that occurred during the Baseline Phase were higher in the rufinamide group than in the placebo group. That is, the two groups were imbalanced at baseline with respect to the subtypes seizure frequency.

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

Table 6.1.4.2.1-6 Summary of percent change in frequency of other seizure types per 28 days relative to baseline (intent to treat patients)

	Rufinamide			Placebo			
	n[a]	Median	Range	n[a]	Median	Range	p-Value[b]
Absence & atypical absence seizures							
Baseline frequency/ 28 days	66	63.5	(1, 2171)	56	53.0	(1, 4009)	
Double-blind frequency/ 28 days	66	39.1	(0, 2793.7)	56	43.0	(0, 5628.3)	
% change in frequency/ 28 days	66	-50.6	(-100, 1729.2)	56	-29.8	(-100, 584.3)	0.0222
Tonic seizures							
Baseline frequency/ 28 days	52	66.3	(1, 14304)	43	49.0	(1, 1066)	
Double-blind frequency/ 28 days	52	47.0	(0, 12036.1)	43	55.3	(0, 1228.6)	
% change in frequency/ 28 days	52	-27.8	(-100, 3003.6)	43	1.6	(-100, 300)	0.0821
Atonic seizures							
Baseline frequency/ 28 days	45	56.0	(1, 4037)	33	49.0	(2, 13122)	
Double-blind frequency/ 28 days	45	24.6	(0, 5450.2)	33	60.3	(0, 16946.7)	
% change in frequency/ 28 days	45	-44.8	(-100, 13660)	33	-21.0	(-100, 709.6)	0.0125
Myoclonic seizures							
Baseline frequency/ 28 days	37	80.0	(1, 38928)	31	50.8	(1, 92583)	
Double-blind frequency/ 28 days	37	52.3	(0.3, 30352.8)	31	39.3	(0, 90350.7)	
% change in frequency/ 28 days	37	-30.4	(-98.7, 338.6)	31	-13.6	(-100, 184.7)	0.5711
Tonic-clonic seizures							
Baseline frequency/ 28 days	37	18.0	(1, 336)	27	15.0	(1, 788)	
Double-blind frequency/ 28 days	37	9.8	(0, 714)	27	14.7	(0, 200)	
% change in frequency/ 28 days	37	-45.6	(-100, 789.2)	27	-18.1	(-100, 729.6)	0.3306
Partial seizures							
Baseline frequency/ 28 days	11	49.0	(1, 4195)	9	41.0	(3, 723)	
Double-blind frequency/ 28 days	11	14.3	(0, 7862)	9	23.6	(0, 600.7)	
% change in frequency/ 28 days	11	-71.9	(-100, 126.1)	9	-11.1	(-100, 43.4)	---[c]

Cross reference: Post-text Tables 9.2-2 to 9.2-11; Appendix 7.1, Selected Patient Listings 9.1-1 and 9.1-2.
[a] Number of patients who experienced a given type of seizure during the Baseline Phase.
[b] Wilcoxon rank-sum test.
[c] No p-value reported because this type of seizure occurred in <20% of the patients.

Dr. Siddiqui (the statistical reviewer) is concerned about the imbalanced baseline seizure frequency. Median seizure frequency in the rufinamide treated group is 290 at baseline while the median seizure frequency for the placebo group is 205 seizures / 28 days. The statistical significance between the groups may be due to this imbalance. The statistical reviewer believes that this indicates that the patients who had a greater disease severity were more likely to be randomized into the rufinamide group.

Key to the validity of the study is reliable randomization. In response to this unexpected divergence in distribution of baseline seizure frequency the sponsor was asked to reaffirm that the patient randomization performed by the study 022 investigators conformed to the randomization process described in the study protocol. In response the sponsor identifies three errors during the randomization process. One patient did not receive study drug although he was entered into the study under number 2101. The patient was allowed to enter the extension study thereafter. The second patient was re-randomized at visit 4, effectively he was double entered into the study. The patient was subsequently withdrawn from the study. In the third case one patient was given two bottles of medication belonging to a different participant, however both of the participants were randomized to rufinamide therefore there was no net effect on study. Full

narratives are in appendix 2. These three randomization errors could not contribute significantly to the large baseline difference between treatment and placebo groups.

In addition the sponsor provides the centers and the subject randomization sequence for each center.. The study population was drawn from 36 centers in Europe, South America (Brazil) and the United States. Brazil and Europe contributed 20 centers which entered in total 75 patients, the largest contributor was a German center which recruited 15 subjects. The United States had 16 centers which entered a total of 63 patients. The largest US center contributed 14 patients. The two largest center contributions were the German and US, contributing 15 and 14 patients respectively. The next largest center contributions were three contributing 8 subjects each. The average subject recruitment per center was 3.8. The center recruitment sequences are examined by the reviewer and there is no appearance of systematic non-randomness.

In the initial submission the intent to treat population of rufinamide and placebo cohorts was tested for evidence of significant difference in each of 11 baseline variables. These variables include sex, race, age, weight and baseline frequency of total, tonic- atonic, absence, myoclonic, tonic, tonic-clonic, and atonic seizures. Sex and race were tested for significant difference using Fisher's exact test. The remaining variables were tested using a Wilcoxon Rank-sum method. No significant difference was identified between rufinamide and placebo groups for any of the variables examined. The absence of difference in any of 11 variables acts as an index of the random quality of baseline group assignment. This provides evidence against a systematic bias in treatment assignment. (see table 6.1.4.2.1-7 below).

Table 6.1.4.2.1-7

Appendix 5.1, Table 1 (Page 1 of 1)
Baseline comparability of treatment groups
for demographic and baseline variables
(Intent-to-treat patients)

Variable	Test	Test statistic	P-value
Sex	Fisher's Exact		1.000
Race	Fisher's Exact		0.757
Age	Wilcoxon Rank-Sum	-0.802	0.423
Weight at randomization	Wilcoxon Rank-Sum	-0.730	0.465
Baseline total seizure freq. per 28 days	Wilcoxon Rank-Sum	-1.526	0.127
Baseline tonic-atonic seizure freq. per 28 days	Wilcoxon Rank-Sum	-0.946	0.344
Baseline atyp. absence seizure freq. per 28 days	Wilcoxon Rank-Sum	0.580	0.562
Baseline myoclonic seizure freq. per 28 days	Wilcoxon Rank-Sum	-0.842	0.400
Baseline tonic seizure freq. per 28 days	Wilcoxon Rank-Sum	-0.473	0.637
Baseline tonic-clonic seizure freq. per 28 days	Wilcoxon Rank-Sum	-1.142	0.253
Baseline atonic seizure freq. per 28 days	Wilcoxon Rank-Sum	-0.862	0.388

*: Indicates statistical significance at the 0.05 level

Baseline comparisons were performed for seizure subtypes experienced by at least 20% of the patients during the Baseline Phase

6.1.4.3 Efficacy related to concomitant anti-epileptic drugs (AED's)

It is possible that rufinamide may be effective only due to synergistic interaction with a concomitantly administered anticonvulsant agent. This issue was raised in the approvable letter. The sponsor was asked to provide subgroup analysis of rufinamide efficacy according to concomitant administered AED's . This was requested for all controlled trials including the 21P. The sponsor provided the analysis for 5 studies but not for study 022 the pivotal Lennox- Gastaut study.

6.1.4.3.1 study 018

Subgroup analysis reveals no difference in efficacy when comparing 1 concomitantly administered AED to two concomitantly administered AED's. There is no difference in efficacy identified between 4 named AED's, lamotrigine, carbamazepine, phenytoin, and valproate. See appendix 10.4, table 6.1.4.3.1.

6.1.4.3.2 study 021A

In the adult partial seizure study there is an increase in significance in the 2 AED subgroup analysis. This is the only significance identified. There is no difference in effectiveness among concurrent use of the specific anticonvulsants lamotrigine, phenytoin, or carbamazepine. See appendix 10.4, table 6.1.4.3.2.

6.1.4.3.3 study 21P

In this pediatric partial seizure study there is no difference in efficacy noted based on number of prescribed AED's or the specific anticonvulsants lamotrigine, carbamazepine or valproate. See appendix 10.4, table 6.1.4.3.3

6.1.4.3.4 study AE/ET1

This dose ranging study provides subgroup analysis of efficacy for 1, 2 and 3 concomitant AED's in addition to the specific named AED's vigabatrin, carbamazepine, phenytoin and valproate. There is significant efficacy in analysis of 1 concomitant AED at the 400mg / day and 800mg / day dose of rufinamide. There is no significance noted at 2 or 3 concomitant AED's or with concomitant use of vigabatrin, carbamazepine, phenytoin, or valproate. See appendix 10.4, table 6.1.4.3.4.

6.1.4.3.5 study AE/PT2.

In this adult partial seizure trial there is no significant difference in effectiveness upon examination of subgroups on 1 or 2 concomitant AED's or with examination of carbamazepine, phenytoin, or valproate. See appendix 10.4, table 6.1.4.3.5.

Reviewer comment: t*he subgroup analysis of study 21A reveals significance with two AED's that is not present with 1 AED or lamotrigine, phenytoin or carbamazepine. In study AE/ET1 there is significant efficacy at the 400 and 800mg dose on 1 AED with no significant difference in efficacy at any dose or with 2 or 3 concomitant AED's or with vigabatrin carbamazepine, phenytoin, or valproic acid. There is limited difference in efficacy in the aforementioned subgroup analysis, at only two doses in AE/ET1 and with one AED in study 21a.*

Carbamazepine was a concomitant AED in subgroup analysis with each of the 5 studies. Lamotrigine in 3 of 5 studies, phenytoin in 4 of the five studies valproate in 4 of 5 studies and vigabatrin in one of five studies. No difference in efficacy was seen across studies for any of these anticonvulsants and there was no systematic improved efficacy with increasing numbers of AED's.

There is no evidence of synergy between rufinamide and concomitant AED's to account for rufinamide efficacy.

6.1.5 Efficacy Conclusions

Reviewer comment: *Study 022 of epilepsy control in Lennox-Gastaut syndrome. The current study reveals statistically significant endpoints for study 022A in percent change in total seizure per 28 days relative to baseline for intent to treat patients. In addition there is a significant reduction in tonic-atonic seizure frequency per 28 days in rufinamide treatment patients relative to placebo. A secondary efficacy variable of percent change in seizure frequency over baseline for absence / atypical absence and atonic seizures was also positive.*

The difference in baseline seizure frequency between placebo and treatment is unexpectedly large, however there does not appear to be a breach in study protocol randomization to account for the divergence. Therefore the sponsor has fulfilled evidence that rufinamide is effective at the tested dose of 3200mg / 45mg/kg daily for the treatment of Lennox-Gastaut syndrome and approval is recommended.

7 INTEGRATED REVIEW OF SAFETY ONGOING TRIALS

7.1 Methods and Findings

New safety data from ongoing studies was reviewed to update the safety analysis for the second cycle of this NDA submission. Ongoing study safety data was presented in the ISS addendum of February 27, 2008 and used to populate the appropriate subheadings of the review template section 7.

7.1.1 Deaths

The ISS addendum of February 27, 2008 is silent on the issue of deaths in ongoing clinical rufinamide trials under IND 35534, although there is not an explicit statement that no deaths have taken place. This reviewer assumes that the absence of a statement indicates that there have been no deaths. The sponsor reports no deaths in their annual report on IND 35534 of September 29, 2007.

7.1.2 Other Serious Adverse Events

There are 15 serious adverse events (Table 7.1.2-1) in ongoing trials E2080-A0001-301 and open label extension E2080-A0012-302. These studies contain 223 unique patients. One serious adverse event occurred in ongoing study 2301 an ongoing compassionate use open label extension of study 022 the Lennox-Gastaut clinical trial (LGS).

Fifteen patients of study E2080-A0001-301 and E2080-A0012-302 are analyzed. Eight of fifteen were in double blind treatment, 4 of these withdrew from the study. Seven were in open label treatment, one withdrew due the adverse effect, one disposition is unknown and five remained in the study. The mean age of subjects with an adverse effect was 35.2 years old, with a median of 32 years and a range of 1 4 to 61 years. The mean time to onset of adverse effect after initiating treatment (Double blind) was 41.5 days, the median 26 days with a range of 3 to 111 days. The mean time to onset for subjects in the double blind group was 46.6 days, mean time to onset in the open label group was 36.1 days.

Table 7.1.2-1

Serious adverse effect in ongoing studies under IND 35534 (rufinamide)

Patient number	Event	DB/OL	Age	Onset days	Intervention	Withdraw/cont
508-001/ [redacted]	Prolonged seizure	OL	32	(7 years)		
10825002	Increased CP seizure	DB	56	24	Dose reduction	
10075021	Adenomyosis	DB	45	23	NA	Continued
10365003	Seizure	DB	61	111	Dose reduction	Withdraw
10575002	Decreased WBC	OL	39	56	Hospital , no change rufinamide	Continued
10465003	Increase seizures	DB	14	53		Continued
10095003	Fall from seizure	OL	51	?	Unknown	Unknown
10095010	No benefit,	DB	31	54	Pht toxic after	Withdraw

b(6)

	phenytoin toxic				study withdraw	
10555004	Weight loss, chg seizure	OL	20	46	Discontinued	Withdraw
10205009	Ataxia, lethargy, nausea, vomiting	DB	19	14	Dose reduction	Continue
10185002	Fall- shoes caught on stairs	OL	32	17		Continues
10725003	Flurry of seizures	DB	35	83		Withdraw
10075003	Asthmatic bronchitis	OL	30	67		Continues
10725007	Seizure flurry	DB	22	3		Withdraw
10135003	Seizure flurry	OL	28	3		Continue
10155004	Pneumonia	OL	45	28		continue

Reviewer comment: Sixteen serious adverse events are noted, the most frequent are seizures, 2 in open label, 4 in double blind. There are two falls, one from seizure, the second apparently a trip and fall on steps. The remaining 7 events are stand alone event with no pattern emerging. The 4 seizures that occur in double blind treatment raise the possibility of an increase seizure activity but blinding prevents association with medication. One case of leucopenia is present. The narrative report does not disclose the lowest value, only reporting that the patient was hospitalized on [redacted] for decreased WBC count. The low WBC count later resolved after discontinuation of trimethoprim/sulfamethoxazole. b(6)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In study E2080-A001-301 there were fifteen patients with 26 adverse events and resultant discontinuation from the study (Table 7.1.3-1 & 7.1.3-2). The most common adverse event leading to discontinuation was dizziness in 9 patients. There has been 1 report each of dizziness, unsteadiness, visual blurring, drowsiness, anxiety attacks, and difficulty speaking. An additional three patients dropped out due to adverse effects of increased seizure frequency, partial motor seizure and tongue numbness respectively.

Table 7.1.3-1 discontinuation by symptom

Patient #	Symptom / problem
10555004	CHANGE IN SEIZURE TYPE
10205006	DIPLOPIA
10055001	DIZZINESS
10055002	DIZZINESS
10125001	DIZZINESS
10135002	DIZZINESS
10205006	DIZZINESS
10215006	DIZZINESS
10335003	DIZZINESS
10575006	DIZZINESS
10595001	DIZZINESS
10575006	DOUBLE VISION
10755001	DOUBLE VISION
10065006	ELEVATED DILANTIN LEVEL
10205006	FATIGUE
10215006	FOGGINESS
10755001	INABILITY TO CONCENTRATE
10825002	INCREASE COMPLEX PARTIAL SEIZURES
10255001	INCREASED SLEEPINESS
10335003	LIGHTHEADEDNESS
10575006	NAUSEA
10725003	SEIZURE FLURRY
10575006	SLURRED SPEECH
10335003	SYNCOPE
10555004	WEIGHT LOSS
10575001	WEIGHT LOSS
10495003	INCREASE SEIZURE FREQUENCY
10595002	PARTIAL MOTOR SEIZURE
10105005	TONGUE NUMBNESS

Table 7.1.3-2 discontiuation by patient number

Patient #	Symptom / problem
10105005	TONGUE NUMBNESS
10495003	INCREASE SEIZURE FREQUENCY
10595002	PARTIAL MOTOR SEIZURE
10055001	DIZZINESS
10055002	DIZZINESS
10065006	ELEVATED DILANTIN LEVEL
10125001	DIZZINESS
10135002	DIZZINESS
10205006	DIPLOPIA
10205006	DIZZINESS
10205006	FATIGUE
10215006	DIZZINESS
10215006	FOGGINESS
10255001	INCREASED SLEEPINESS
10335003	DIZZINESS
10335003	LIGHTHEADEDNESS
10335003	SYNCOPE
10555004	CHANGE IN SEIZURE TYPE
10555004	WEIGHT LOSS
10575001	WEIGHT LOSS
10575006	DIZZINESS
10575006	DOUBLE VISION
10575006	NAUSEA
10575006	SLURRED SPEECH
10595001	DIZZINESS
10725003	SEIZURE FLURRY
10755001	DOUBLE VISION
10755001	INABILITY TO CONCENTRATE
10825002	INCREASE COMPLEX PARTIAL SEIZURES

A total of six patients dropped out of open label study E2080-A001-302.

7.1.3.2 Adverse events associated with dropouts

In study E2080-A001-301 the adverse event most prominently associated with dropout was dizziness. The next most common cause of dropout was seizure related. Three had an increase in seizure frequency noted as an increase in seizure in two and seizure flurry in one. One noted a change in seizure type and one noted partial motor seizure but did not indicate if this was a change in seizure type. An elevation in phenytoin level occurred in one instance. This event may have been precipitated by rufinamide which may increase phenytoin level by 7 to 21%. There were two symptoms of double vision, two of fatigue, one each of fogginess and inability to concentrate, one of nausea, one syncope, one of tongue numbness, and two of weight loss.

A total of six patients dropped out of open label study E2080-A001-302 due to adverse effects. One for each of the following symptoms. Dizziness, unsteadiness, visual blurring, drowsiness, anxiety attacks, and difficulty speaking.

7.1.4 Other Search Strategies-

Annual report September 2006 to September 2007 reviewed

7.1.5 Common Adverse Events

Common adverse events in ongoing studies E2080-A001-301 and E2080-A001-302 are reviewed in 7.1.5.1 -7.1.5.2

7.1.5.1 Incidence of common adverse events

A total of 469 adverse event (placebo or rufinamide) were reported in 211 patients in ongoing clinical trial E2080-A001-301. The most common SOC (system organ class) were the nervous system, the gastrointestinal system, general disorders and administration site conditions.

Table 7.5.1-1 (below) provides the number of adverse events in Study E2080-A001-301 that occurred in frequency greater than 5 events, with the exception of confusional state and gait disturbance. Confusional state and gait disturbance although with only 4 and 3 occurrences respectively are likely to be central nervous system side effects and provide insight into the overall frequency of potential central nervous system adverse effect.

Reviewers comment: *The adverse event profile for study E2080-A001-301 (currently blinded) is generally typical for anticonvulsant, centrally nervous system active agents. There is a preponderance of central nervous system adverse effects with dizziness most frequent occurring 45 out of 460 events, somnolence 20 occurrences, fatigue 15 occurrences, convulsion 8 occurrences, balance and gait disorder totaling to 9 occurrences, blurred vision 6 occurrences, tremor 6 occurrences and confusion 4 occurrences. The adverse event profile reveals headache is the second most common event behind dizziness. In the available data from adult double blind studies from the initial NDA submission, headache was modestly more common than placebo by 3%.*

7.1.5.2 Common adverse event tables

Table 7.1.5.-1
Study E2080-A001-301 Adverse events >5 events of 460 occurrences (remains blinded),

dizziness	45
Headache	41

Somnolence	20
Nausea	18
Fatigue	15
Diplopia	14
Upper respirator tract infection	11
Contusion	10
Nasopharyngitis	9
Convulsion	8
Constipation	7
Diarrhea	7
Urinary Tract infection	6
Skin laceration	6
Coordination, Abnormal	6
Balance Disorder	6
Vomiting	6
Tremor	6
Blurred vision	6
pyrexia	6
Confusional state	4
Gait Disturbance	3

The sponsor reports a total of 60 adverse events were reported in 101 patients in clinical trial E2080-A001-302. The most common SOC's were the nervous system, general disorders and administrative site conditions. There were 75 adverse events identified in sponsor's listing 1.2, p 59 ISS addendum (February 2008). Adverse events occurring in a frequency greater than or equal to two are noted in Table 7.1.5-2. Dizziness is the most frequent of adverse events occurring 13 of 75 events with the next most frequent event of skin laceration occurring in 3 of 75 events. This is not an unexpected finding in a centrally acting agent and was also prominent in the data from all double blind treated patients from the initial NDA submission. In that data the occurrence of dizziness was 15.5% in the rufinamide treated group compared with 9.4% of the placebo group.

Table 7.1.5-2 Study E2080-A001-302 Adverse event ≥ 2 of 75	
dizziness	13
skin laceration	3
decreased appetite	3
Asthenia	3
somnolence	2
nausea	2
muscle spasm	2
irritability	2
insomnia	2
headache	2
feeling abnormal	2

Balance disorder	2
Back pain	2
Ataxia	2

7.1.5.3 Identifying common and drug-related adverse events

The clearly drug associated events are central nervous system (CNS) and gastrointestinal. The central nervous system events are dizziness, somnolence, fatigue, and diplopia. This category of adverse effect is common in the anticonvulsant class of medication due to their inherent CNS site of action. The gastrointestinal effects is nausea, for rufinamide this is dose related with a notable increase in the 3200mg dose.

7.1.6 Less Common Adverse Events

The review of ongoing studies does not allow analysis of less common adverse events due to the limited database.

7.1.7 Laboratory Findings

A full ISS with laboratory findings is not yet generated for the ongoing studies.

7.1.8 Vital Signs

Vital sign data is not provided in the submission for the studies which are ongoing.

7.1.9 Electrocardiograms (ECGs)

Vital sign data is not provided in the submission for the studies which are ongoing.

7.2 Adequacy of Patient Exposure and Safety Assessments

See section 8.2

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See section 8.2

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies- full development program has been evaluated in the initial submission by Dr. Ramon.

7.2.2.3 Literature

8 INTEGRATED REVIEW OF SAFETY SECOND CYCLE SUBMISSION

8.1 Methods and Findings

Source documents reviewed to address these concerns were the ISS (Integrated Summary of Safety) addendum submitted by sponsor February 27, 2008, Dr. Ramesh Raman Medical Officer Safety review from September 8, 2006, the sponsor's clinical overview submitted February 27, 2008, ISS submitted July 26,2005.

The primary guidance for this second submission safety review was directed by the approvable letter issued by FDA in September 2006. The issues of concern were

1. The final outcome or disposition of patients noted in the initial safety review to have clinically notable changes in laboratory parameters at final visit.
2. a potential signal for hypothyroid response
3. a potential signal for an increase in status epilepticus
4. synergy with a concomitantly administered AED to produce efficacy
5. QT interval shortening
6. subject death and discontinuation.

New safety data from ongoing studies was reviewed to update the safety analysis. Ongoing study safety data was presented in the ISS addendum of February 27, 2008 and used to populate the appropriate subheadings of the review template section 7.

Method of review was to address the questions and concerns of the approvable letter by review of data in the ISS of February 27, 2008. Further depth of investigation required some review of the initial ISS, insight and analysis was provided by the Medical Officer Safety review of Dr. Raman. The review template was modified by adding a section 8, identical in outline structure to the standard section 7 "Integrated Review of Safety" , in this case to place the issues related to the second cycle submission distinct from review of the ongoing clinical trial which is placed in section 7 "Integrated Review of Safety".

8.1.1 Deaths

These have been reviewed by Dr. Ramon section 7.1.1 in the initial submission, medical safety review.

8.1.2 Other Serious Adverse Events

These have been reviewed by Dr. Ramon section 7.1.2 in the initial submission, medical safety review.

8.1.3 Dropouts and Other Significant Adverse Events (abnormalities *related to initial NDA submission safety review, including Thyroid abnormalities 8.1.3.1.3)*

These have been reviewed by Dr. Ramon section 7.1.3 in the initial submission, medical safety review.

8.1.3.1 Other significant adverse events- *related to initial NDA, safety review*

8.1.3.1.1 Hyponatremia

The safety review for the initial submission of November 17, 2005 revealed a concern for hyponatremia. Four cases were identified.

Patient 1276-05044 in study 021A a 39 year old female was on 2400mg of rufinamide which had been initiated 6 years earlier. The patient discontinued rufinamide on her own volition, one day after discontinuation she was hospitalized for loss of interest in her environment and constipation. On admission serum Na+ was found to be 129mEq/L with mild anemia. The patient was on concurrent carbamazepine 600mg a day and lamotrigine 500mg a day.

Patient 1284-5033, a 54 year old female with incomplete data reveals an interval of hyponatremia for 5 days. The baseline sodium is noted to be 143mmol/L with a decrease noted after patient was hospitalized for nausea, vomiting and sleepiness two days after beginning oxcarbazepine. The patient had a rapid titration beginning 300mg BID advanced the following day to 450mg BID. On this second day it is reported that the serum sodium was low but the numerical value is not provided. Concurrent medications included hydrochlorothiazide (HCTZ). The HCTZ and oxcarbazepine were discontinued with normalization of serum sodium along with mental status and resolution of nausea and vomiting.

Patient D/0008/1168 study AE/ET1e. Subject a 61 year old male on concurrent carbamazepine found to have hyponatremia during double blind phase of study on 800mg of rufinamide 800mg a day persisting into open label treatment also at 800mg a day. A fluctuating sodium level is noted over an interval from 5-31-1994 to 8-1-1994. The narrative report indicates the patient was in double blind treatment until 6-18-1994 when he entered open label treatment with rufinamide at 800mg a day. Sodium values are noted in table 8.1.3.1-1

Table 8.1.3-1, Na+ values aligned with study mode		
Date	Sodium	Treatment
5/31/1994	126 mmol/L	Double blind
6/3/1994	143 mmol/L	Double blind
6/14/1994	124 mmol/L	Double blind
8/1/1994	140 mmol/L	Open label 800mg daily

Patient B/0001/1631 study AE/ET1e. Subject a 30 year old female began open label rufinamide treatment on 7/4/94. On ——— day ~~ ——of rufinamide therapy) the patient was receiving 1200mg a day of rufinamide, the patient was hospitalized for dizziness, confusion and health deterioration for three days. Laboratory study revealed hyponatremia (value unavailable). b(6)

The patient was on concurrent therapy with carbamazepine which had reached an overdose level due to patient non compliance, this apparently occurred in the same interval as the hyponatremia. Carbamazepine levels are not provided. Carbamazepine was reduced and rufinamide discontinued due to the adverse event.

Four hyponatremia serious adverse events are noted in the initial safety review by Dr. Raman. In 3 of these cases identification of the cause of hyponatremia is seriously confounded by ongoing treatment in each of the patients with carbamazepine.. In the first case there was six years of preceding treatment using rufinamide with no report of hyponatremia. The patient was also on carbamazepine 600mg a day. The second case was confounded by concurrent use of oxcarbazepine and hydrochlorothiazide, the fourth case had been on rufinamide for 4 years without report of hyponatremia but developed hyponatremia after her carbamazepine dose had been elevated through non-compliance. In the third case as noted in table 7.1.3.3-1 the patient was not only on confounding carbamazepine but sodium normalized when on open label rufinamide 800mg a day 8 weeks after the first noted hyponatremia.

Reviewers comment: *Review of data from all completed double blind studies reveals only a 0.1 of 140.0 mmol/L decrease in mean sodium in rufinamide treated cohort between baseline and termination of treatment compared to 0.0 change in the placebo group between baseline and treatment termination. This is a negligible change. Shift table analysis of sodium values reveals a 2.1 percent shift from normal to low in rufinamide treatment group compared to a 1.7% shift from normal to low in the placebo group. This is a minor 0.4% change between the groups. When this data is taken in review of the identified clinically notable cases of hyponatremia above, there is not sufficient evidence to implicate rufinamide as a hyponatremic agent.*

8.1.3.1.2 Hyperthermia

The safety review for the initial submission of November 17, 2005 revealed a concern for hyperthermia. Two cases were identified.

Subject 3054/2071 in study 022e. Patient is a 4 year old female in open label extension trial of rufinamide. The patient developed a fever of 107 degrees F, no further data given but this did

follow a hospitalization for pneumonia which preceded the fever admission by approximately one month.

The patient again developed a fever approximately 10 weeks after the first fever hospitalization. A numerical temperature reading is not provided but the clinical report is an uncontrollable fever. Patient had agitation and was inconsolable. Hospital admission diagnosis is malignant hyperthermia and dehydration. Video EEG revealed agitation was not seizure activity. Fever was considered neurogenic and not associated with infection. Recovery was complete and patient discharged approximately 10 days following admission. Approximately six months later the patient was found expired in bed. Rufinamide was continued throughout the course.

Subject 0003-6419 in study 0021A. Patient is a 26 year old male who was admitted to the hospital for five episodes of complex partial seizures. Patient on rufinamide 3200mg a day. In 24 hours the flurry of seizures was controlled with diazepam both po and intramuscular. Subsequently the patient required an additional 100mg of IV diazepam and had hexobarbital 1000mg im. An additional 80mg of IM diazepam was given the following day. On the second day of treatment, corresponding to the day of seizure resolution, the patient developed abdominal pain, peritoneal signs and one episode of vomiting. He subsequently had a diagnostic laparotomy and was found to have acute hemorrhagic pancreatitis and peritonitis.

Four days after the initial breakthrough of seizure the patient developed a body temperature of 107.2 F (41.8 C), tachycardia, tachypnea and decreased level of consciousness. A lumbar puncture was performed demonstrating increased intracranial pressure but analysis of protein, glucose, RBC's and WBC's was within normal limits. Total peripheral WBC count was within normal limits but had increased bands at 33%. The patient subsequently expired, autopsy confirmed cerebral edema and herniation. There was also pulmonary edema, dystelectases in posterobasal parts of lungs, dynamic intestinal ileus with focal intramural hemorrhages in the small intestine and venous congestion in all visceral organs.

The patient's significant medical history included CT-confirmed hydrocephalus, excision of right temporal cystic lesion for the treatment of therapy resistant seizures in 1989, meningeal adhesions in areas of convex and right temporal lobe, and a syndrome of intracranial hypertension. The intracranial hypertension was diagnosed by echoencephalography at 8 years of age following an influenza infection. Symptoms of the intracranial hypertension were intermittent headaches, nausea and vomiting. The patient was treated with biannual 3-week courses of acetazolamide (Diacarb) and potassium/magnesium aspartate (Panangin) for the previous 5 years as prophylactic treatment of the intracranial hypertension.

Reviewer comment: *Case 2071 had two episodes of fever in the range of hyperpyrexia. These episodes were separated in time by approximately 8 weeks with no report of fever in the intervening interval. There is a report of agitation but no indication of any variety of muscle rigidity. The patient continued on rufinamide 1000 mg a day through both episodes. The episodic occurrence of hyperpyrexia while rufinamide treatment is maintained point away from a mechanism of fever that is driven by rufinamide. It is highly unlikely that the both febrile episodes would resolve with the inciting agent present. The scenario for case 6419 is most consistent with severely elevated temperature associated with the diffuse cerebral destruction of*

cerebral edema and herniation. The underlying inflammatory effect of the pancreatitis and peritonitis also provide some pyretic influence. Neither of these cases support a hypothesis that rufinamide is a generator of malignant hyperthermia syndrome.

8.1.3.1.3 Thyroid Abnormalities

The structure of the thyroid abnormalities section is base on a concern of the primary review of initial NDA submission November, 2005. This section begins with the approvable letter then provides the sponsor response and then moves into reviewer analysis.

Approvable letter: The FDA commented that " ... a clinically more meaningful evaluation of thyroid function tests suggesting a hypothyroid function response should be submitted. For the different subgroups of patients in the safety database, please submit re-analyses of the proportions of patients who simultaneously experienced an increase in serum TSH and a decrease in serum thyroxine (T_3, T_4 free and bound) or vice versa by treatment."

Sponsor response: 36 patients who had an increase in TSH and 5 of these 36 patients had a decrease in serum thyroxine. For all of these patients, high TSH/low thyroxine values occurred as the last measured value. However, abnormal values occurred at baseline (pre-treatment) for 3 of the 5 patients; 1 patient had a high TSH, another had a low free thyroxine, and a third had a low thyroxine (Table 8.1.3.3-2). In addition, another patient (Patient 0002 01608 in AE/ET1) had a medical history of hypothyroidism.

8.1.3-2 Patients with Increased TSH and Decreased T3 and T4 (Free and Bound)

Study	Patient Number	Medical History	Abnormal Baseline	Concomitant Medication
018	1142_00030			Valproate
022	0019_02099		High TSH	Valproate
AE/ET1	0002_1608	Hypothyroidism		
AE/ET1	0002_07508		Low free thyroxine	Carbamazepine
AE/ET1	0007_07078		Low thyroxine	Carbamazepine and valproate

Cross-reference: Patient profile (medical history); patient CRFs (concomitant medications)

Table, increase TSH -decrease thyroxine, from ISS amendment

Review analysis: The sponsor provides a narrative indicating 11 patients had a decrease in TSH, none of these had and increase in thyroxine. 36 patients had an increase TSH but only 5 of the 36 had the profile of greatest concern, a concurrent elevation of TSH and depression of thyroxine values. Of these five subjects there were baseline hypothyroid abnormalities in 3 of the five. A fourth patient had a medical history of hypothyroidism. A fifth patient remains with a combination of elevated TSH and depressed thyroxine value consisted with hypothyroidism. In this case the patient is on valproic acid which may be associated with hypothyroidism. Although the concomitant use of valproic acid is a mitigating circumstance there remains the possibility that case 00030 is a true hypothyroid response. Although the sponsor accounts for 4 the 5 patients with the combination of increase in TSH and decrease in thyroxine value, the remaining 31 case of elevated TSH may represent a state of early, compensated hypothyroidism.

The features of the overall thyroid laboratory dataset via a shift table, a table of central tendency and a table identifying clinically notable changes are examined. This approach can inform on the impact of the above identified case of TSH elevation and thyroxine decrease have on the overall safety analysis. In addition the role of the 31 cases of elevated TSH alone need to be evaluated in the prospective of TSH changes seen in the placebo group.

The tables in their original form from the sponsor are contaminated by errors in units of measurement. Review of the sponsor tables of clinically notable thyroid abnormalities reveals 39 cases of free thyroxine measurement that change units from ng/dl to pmole/liter part way through the study data. The ng/dl measures are all low relative to the SI unit measure of pmole/liter. These are marked abnormal in the table indicating the sponsor analysis has integrated these values into their analysis as abnormal and low. Four of these errors occur in study 027, 35 occur in study AE/ET1.

11 cases of a similar type of error are seen in the total thyroxine laboratory values. In these cases the unit of nmol/L is amplified by a factor of 10^6. 10 of these errors were found in study 021, and one in study 018. The initially submitted tables of thyroid laboratory value are rendered unusable by these errors. These errors result in artifactual designation of low to normal transitions during study treatment in many of the free thyroxine values of study AE/ET1. All 11 of the total thyroxine errors result in a designation of normal to high thyroxine transition. 12 of these errors are initially brought to the attention of the sponsor on September 17, 2008. These are individually corrected but reflection on the overall impact of these errors made it clear that the mix of accurate and inaccurate laboratory values in both free and total thyroxine was obscuring conclusions on thyroid safety. Correction of patient data focused in one category such as those with the combined elevation of TSH with depression of thyroxine would not elucidate the overall picture of safety for which accurate shift, clinically notable and comparison of means tables are needed.

On November 5, 2008 a teleconference with the sponsor took place to inform the sponsor of the broad profile of thyroid laboratory errors and the logical conclusion that these will incorrectly deflect the values of the statistical summary tables (shift table, table of central tendency and clinically notable table) which incorporate these erroneous values.

The sponsor reported that data from studies AE/ET1 and AE/PT2 could not be reliably corrected due to the remote age of the studies, trial completion December 1994 and January 1992 respectively. Sponsor reports that part way through trial completion there was a change in study laboratory. The sponsor is then requested to provide a corrected series of tables for the more recent studies where reliable laboratory data can be obtained for correction and a separate series of thyroid laboratory tables for pooled studies AE/ET1 and AE/PT2.

On November 10, 2008 the sponsor submits the corrected tables for studies 016, 018, 021A, 021P, 022, and 038. In addition separate tables are submitted for studies AE/ET1 and AE/PT2. The sponsor indicates that several isolated incorrect data entries as well as unit conversion errors were corrected in AE/ET1 and the tables recalculated. All of these tables are presented below.

To provide the corrected tables 8.1.3-3 to 8.1.3-5 the sponsor identified any thyroid laboratory values that were 10% greater than or equal to the upper limit of the normal reference range or 10% less than or equal to the lower limit of the normal reference range. If the plausibility of the value was in question the raw database and when possible the case report forms were reviewed and errors were corrected.

For studies (CRUF3310016, CRUF3310018, CRUF3310021A, CRUF3310021P, CRUF3310022, and CRUF3310038):

1. Unit conversion errors (between µg/dL and nmol/L) in total thyroxine values were corrected for:
    a. CRUF3310016, centers 1844, 1902, and 1903
    b. CRUF3310018 centers 0001, 0002, 0003, 0005, 0006, 0035,0036, and 0037
    c. CRUF3310022_0019_02098, CRUF3310022_0019_02099, and CRUF3310022_2863_02089 on dates 2000-09-06, 2000-09-07, 2000-09-14
2. 18 subjects with total thyroxine values greater or equal to 61,000,000 were identified. These values resulted from incorrect multiplication of the correct value by 10^6 and are corrected in the revised tables.
3. No systematic errors were identified for any TSH values

Change in termination for thyroid laboratory parameter values from baseline by laboratory test and treatment
(All treated patients with epilepsy during double-blind only)
(Studies: CRUF3310016, CRUF3310018, CRUF3310021A, CRUF3310021P, CRUF3310022, CRUF3310038)

Table 8.1.3-3

Laboratory Test (SI units) Summary Statistics	Statistics	Treatment: Rufinamide (N=638) Baseline	Rufinamide (N=638) Termination	Rufinamide (N=638) Difference	Placebo (N=480) Baseline	Placebo (N=480) Termination	Placebo (N=480) Difference
Thyroxine (nmol/L)	N	499	499	499	368	368	368
	Mean	76.6	86.5	9.8	78.8	79.0	0.7
	Std. Dev.	18.72	21.72	18.89	21.60	22.94	14.67
	Median	74.6	86.2	7.7	76.0	74.8	0.0
	Min	34.7	36.0	-42.6	30.9	32.2	-54.2
	Max	148.0	169.2	82.6	175.0	179.3	75.9
TSH (mU/L)	N	467	467	467	330	330	330
	Mean	2.2	2.3	0.1	2.3	2.5	0.2
	Std. Dev.	2.08	2.43	2.02	1.62	3.34	3.31
	Median	1.7	1.8	0.0	1.9	1.9	0.0
	Min	0.0	0.1	-25.5	0.1	0.2	-8.1
	Max	32.6	41.9	23.2	14.2	52.0	51.4

- Baseline = The last laboratory test obtained prior to the start of study drug.
- Termination = The last laboratory test taken during treatment.
- For each laboratory test, only patients with a value at both baseline and termination are included.
- There were no Free Thyroxine (FT4) measurement during Double-Blind
- 08NOV08:17:47 * [By: sofiat]

Table 8.1.3-3, Δ baseline to final, means/medians, treatment/placebo, corrected-pooled studies 016, 018, 021A, 021P, 022, 038.

Summary of changes from the baseline thyroid laboratory result to the final thyroid laboratory result
(All treated patients with epilepsy during double-blind only)

Table 8.1.3-4 (Studies: CRUF3310016, CRUF3310018, CRUF3310021A, CRUF3310021P, CRUF3310022, CRUF3310038)

	Final laboratory									
	Rufinamide(N=638)					Placebo(N=480)				
Lab Baseline	Low	Normal	High	Not Available	Total	Low	Normal	High	Not Available	Total
Thyroxine										
Low	65(10.20)	80(12.50)	0(0.00)	15(2.40)	160(25.10)	74(15.40)	34(7.10)	0(0.00)	10(2.10)	118(24.60)
Normal	24(3.80)	326(51.10)	4(0.60)	38(6.00)	392(61.40)	29(6.00)	228(47.50)	2(0.40)	24(5.00)	283(59.00)
High	0(0.00)	0(0.00)	0(0.00)	1(0.20)	1(0.20)	0(0.00)	0(0.00)	1(0.20)	0(0.00)	1(0.20)
NA *	7(1.10)	18(2.80)	0(0.00)	0(0.00)	25(3.90)	5(1.00)	17(3.50)	0(0.00)	0(0.00)	22(4.60)
Total	96(15.00)	424(66.50)	4(0.60)	54(8.50)	578(90.60)	108(22.50)	279(58.10)	3(0.60)	34(7.10)	424(88.30)
TSH (mU/L)										
Low	1(0.20)	3(0.50)	0(0.00)	1(0.20)	5(0.80)	0(0.00)	2(0.40)	1(0.20)	1(0.20)	4(0.80)
Normal	4(0.60)	421(66.00)	20(3.10)	112(17.60)	557(87.30)	2(0.40)	295(61.50)	10(2.10)	96(20.00)	403(84.00)
High	0(0.00)	10(1.60)	8(1.30)	6(0.90)	24(3.80)	0(0.00)	10(2.10)	10(2.10)	6(1.30)	26(5.40)
NA *	0(0.00)	22(3.40)	2(0.30)	0(0.00)	24(3.80)	1(0.20)	22(4.60)	2(0.40)	0(0.00)	25(5.20)
Total	5(0.80)	456(71.50)	30(4.70)	119(18.70)	610(95.60)	3(0.60)	329(68.50)	23(4.80)	103(21.50)	458(95.40)

- Baseline = The last laboratory test obtained prior to the start of study drug.
- Termination = The last laboratory test taken during treatment.
- * NA=Not available, data was not collected.
- There were no Free Thyroxine (FT4) measurement during Double-Blind
- 08NOV08:17:53 * [By: sofiat]

Table 8.1.3-4 shift, baseline to final, low-normal-high, corrected-pooled studies 016, 018, 021A, 021P, 022, 038.

Table 8.1.3-5 Treatment-emergent clinically notable laboratory values for thyroid laboratory tests by laboratory test and treatment
(All treated patients with epilepsy during double-blind only)
CRUF3310016, CRUF3310018, CRUF3310021A, CRUF3310021P, CRUF3310022, CRUF3310038)

		Treatment	
		Rufinamide	Placebo
Lab Test	Criteria	n(%)	n(%)
Thyroxine (nmol/L)	Total Patients	499	368
	Decrease *	5 (1.0)	15 (4.1)
	Increase *	2 (0.4)	1 (0.3)
	Total	7 (1.4)	16 (4.3)
TSH (mU/L)	Total Patients	467	330
	Decrease *	4 (0.9)	2 (0.6)
	Increase *	6 (1.3)	4 (1.2)
	Total	10 (2.1)	6 (1.8)

- * = Patients are counted only if the baseline value was normal.
- Patients who had measurement at both baseline and post baseline are included.
- There were no Free Thyroxine (FT4) measurement during Double-Blind

Table 8.1.3-5 clinically notable, ↑ or ↓ in value, corrected-pooled studies 016, 018, 021A, 021P, 022, 038.

Tentatively Corrected Tables for studies AE/ET1 & AE/PT2. For these studies the sponsor performed the following interventions.

1. Unit conversion errors were corrected for free thyroxine (ng%, ng/100 ml, ng/dL and pg/ml to pmol/L) for identified subjects in CRU331AEET1.
2. For USUBJID "CRUF331AEET1_0003_05036" for visit 14 dated 1994-04-13 the original and standard result was changed from 180 to 1.8 based on CRF review.
3. For subjects CRUF331AEET1_0001_01625 and CRUF331AEET1_0001_01622 the total thyroxine values at visits 13 and 15, respectively, were incorrectly entered into the database as free thyroxine values. Values were correct assigned to as total thyroxine with appropriate reference range. There were no recorded free thyroxine values for these visits.
4. No changes were made to values for study CRU331 AEPT2.

Note that the Triiodothyronine values for the two older studies (CRUF331AEET1 and CRUF331AEPT2) were left unchanged compared to the original NDA submission.

Change in termination for thyroid laboratory parameter values from baseline by laboratory test and treatment
(All treated patients with epilepsy during double-blind only)
(Studies: CRUF331AEET1, CRUF331AEPT2)

Table 8.1.3-6

Laboratory Test (SI units) Summary Statistics	Statistics	Treatment: Rufinamide (N=564) Baseline	Rufinamide (N=564) Termination	Rufinamide (N=564) Difference	Placebo (N=133) Baseline	Placebo (N=133) Termination	Placebo (N=133) Difference
Free Thyroxine (pmol/L)	N	475	475	475	121	121	121
	Mean	12.5	12.6	0.1	12.4	12.3	-0.1
	Std. Dev.	4.01	4.32	3.07	3.73	4.15	2.57
	Median	11.8	12.0	0.0	12.1	12.2	-0.1
	Min	0.9	0.8	-9.0	1.1	1.0	-10.7
	Max	33.0	41.2	25.2	25.7	22.8	10.3
Triiodothyronine (nmol/L)	N	49	49	49	---	---	---
	Mean	2.5	2.4	-0.0	---	---	---
	Std. Dev.	1.34	1.49	0.52	---	---	---
	Median	1.9	1.9	-0.1	---	---	---
	Min	1.4	1.1	-1.6	---	---	---
	Max	6.3	6.8	1.4	---	---	---

Laboratory Test (SI units) Summary Statistics	Statistics	Treatment: Rufinamide (N=564) Baseline	Rufinamide (N=564) Termination	Rufinamide (N=564) Difference	Placebo (N=133) Baseline	Placebo (N=133) Termination	Placebo (N=133) Difference
Thyroxine (nmol/L)	N	550	550	550	129	129	129
	Mean	68.7	68.5	-0.2	72.7	72.6	-0.1
	Std. Dev.	21.74	22.59	18.89	16.10	16.31	15.66
	Median	69.5	70.0	0.0	69.5	72.0	0.0
	Min	0.0	0.0	-84.0	45.2	34.8	-79.8
	Max	120.0	147.0	43.8	122.3	131.6	47.1
TSH (mU/L)	N	563	563	563	132	132	132
	Mean	2.0	1.9	-0.1	1.9	1.8	-0.1
	Std. Dev.	1.81	1.49	1.47	1.27	1.15	0.78
	Median	1.6	1.6	-0.1	1.6	1.5	-0.0
	Min	0.0	0.0	-18.9	0.0	0.0	-4.1
	Max	22.0	15.5	14.5	8.9	8.6	1.9

- Baseline = The last laboratory test obtained prior to the start of study drug.
- Termination = The last laboratory test taken during treatment.
- For each laboratory test, only patients with a value at both baseline and termination are included.

Table 8.1.3-6 Δ baseline to final, means/medians, treatment/placebo, corrected studies AE/ET1-AE/PT2.

Table 8.1.3-7

Summary of Changes from the Baseline Thyroid Laboratory Result to the Final Thyroid Laboratory Result
(All treated patients with epilepsy during double-blind only)
(Studies: CAUF331AEET1, CRUF331AEPT2)

Final laboratory

Lab Baseline	Rufinamide(N=564) Low	Normal	High	Not Available	Total	Placebo(N=133) Low	Normal	High	Not Available	Total
Free thyroxine (FT4)										
Low	79(14.00)	52(9.20)	0(0.00)	0(0.00)	131(23.20)	20(15.00)	6(4.50)	0(0.00)	0(0.00)	26(19.50)
Normal	36(6.40)	296(52.50)	9(1.60)	1(0.20)	342(60.60)	18(13.50)	76(57.10)	0(0.00)	1(0.80)	95(71.40)
High	0(0.00)	1(0.20)	2(0.40)	0(0.00)	3(0.50)	0(0.00)	1(0.80)	0(0.00)	0(0.00)	1(0.80)
NA *	0(0.00)	5(0.90)	0(0.00)	0(0.00)	5(0.90)	0(0.00)	1(0.80)	0(0.00)	0(0.00)	1(0.80)
Total	115(20.40)	354(62.80)	11(2.00)	1(0.20)	481(85.30)	38(28.60)	84(63.20)	0(0.00)	1(0.80)	123(92.50)
Triiodothyronine										
Low	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Normal	2(0.40)	34(6.00)	1(0.20)	0(0.00)	37(6.60)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
High	0(0.00)	1(0.20)	11(2.00)	0(0.00)	12(2.10)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
NA *	0(0.00)	0(0.00)	1(0.20)	0(0.00)	1(0.20)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Total	2(0.40)	35(6.20)	13(2.30)	0(0.00)	50(8.90)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Final laboratory

Lab Baseline	Rufinamide(N=564) Low	Normal	High	Not Available	Total	Placebo(N=133) Low	Normal	High	Not Available	Total
Thyroxine										
Low	143(25.40)	71(12.60)	0(0.00)	0(0.00)	214(37.90)	25(18.80)	18(13.50)	0(0.00)	1(0.80)	44(33.10)
Normal	53(9.40)	283(50.20)	0(0.00)	0(0.00)	336(59.60)	16(12.00)	70(52.60)	0(0.00)	0(0.00)	86(64.70)
High	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
NA *	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Total	196(34.80)	354(62.80)	0(0.00)	0(0.00)	550(97.50)	41(30.80)	88(66.20)	0(0.00)	1(0.80)	130(97.70)
TSH (mU/L)										
Low	2(0.40)	4(0.70)	0(0.00)	0(0.00)	6(1.10)	1(0.80)	1(0.80)	0(0.00)	0(0.00)	2(1.50)
Normal	7(1.20)	514(91.10)	13(2.30)	0(0.00)	534(94.70)	0(0.00)	124(93.20)	1(0.80)	1(0.80)	126(94.70)
High	0(0.00)	15(2.70)	8(1.40)	0(0.00)	23(4.10)	0(0.00)	4(3.00)	1(0.80)	0(0.00)	5(3.80)
NA *	0(0.00)	1(0.20)	0(0.00)	0(0.00)	1(0.20)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Total	9(1.60)	534(94.70)	21(3.70)	0(0.00)	564(100.0)	1(0.80)	129(97.00)	2(1.50)	1(0.80)	133(100.0)

- Baseline = The last laboratory test obtained prior to the start of study drug.
- Termination = The last laboratory test taken during treatment.
- * NA=Not available, data was not collected.
- 08NOV08:17:53 * [By: soriat]

Table 8.1.3-7 shift, baseline to final value, low-normal-high, corrected studies AE/ET1-AE/PT2

Appears This Way
On Original

Treatment-emergent clinically notable laboratory values for thyroid laboratory tests
by laboratory test and treatment
(All treated patients with epilepsy during double-blind only)
(Studies: CRUF331AEET1, CRUF331AEPT2)

Table 8.1.3-8

		Treatment	
		Rufinamide	Placebo
Lab Test	Criteria	n(%)	n(%)
Free thyroxine (pmol/L)	Total Patients	475	121
	Decrease *	114 (24.0)	36 (29.8)
	Increase *	17 (3.6)	2 (1.7)
	Total	131 (27.6)	38 (31.4)
Triiodothyronine (nmol/L)	Total Patients	49	0
	Decrease *	1 (2.0)	0
	Increase *	5 (10.2)	0
	Total	6 (12.2)	0
Thyroxine (nmol/L)	Total Patients	550	129
	Decrease *	56 (10.2)	12 (9.3)
	Increase *	0	0
	Total	56 (10.2)	12 (9.3)
TSH (mU/L)	Total Patients	563	132
	Decrease *	17 (3.0)	5 (3.8)
	Increase *	11 (2.0)	3 (2.3)
	Total	28 (5.0)	8 (6.1)

- * = Patients are counted only if the baseline value was normal.
- Patients who had measurement at both baseline and post baseline are included.
- 08NOV08:17:50 * [By: sofiat]

Table 8.1.3-8 clinically notable, ↑ or ↓in value, corrected studies AE/ET1-AE/PT2

Tables 8.1.3-3 to 8.1.3-5 are taken as the most reliable representation of thyroid function laboratory values. These more recent studies did not capture a free thyroxine value as did study AE/PT1. The largest placebo to treatment gradient occurs in the table of mean differences between baseline and termination value for total thyroxine. In this case there is a difference of 9.1% between placebo and rufinamide treatment. This represents a relative increase in total thyroxine at termination value for rufinamide treatment. There is no meaningful difference in TSH termination values between placebo and treatment groups.

The shift table analysis for total thyroxine reveals a shift from normal to low in 3.8% of rufinamide treated patients and 6% of placebo patients. There is a shift from normal to high in .6% of the rufinamide treatment patients and .4% of placebo patients.

The shift table analysis for TSH reveals a shift from normal to low in .6% of rufinamide treated patients and .4% of placebo patients. There is a shift from normal to high in 3.1% of rufinamide treatment patients and 2.1% of placebo treatment patients, a positive gradient of 1.0% toward rufinamide treatment.

The table of treatment emergent clinically notable values does not reveal any difference between treatment group and placebo that is unfavorable to the rufinamide treatment group.

Tables 8.1.3-6 to 8.1.3-8 represent the mean differences of thyroid values between baseline and study termination, shift tables and table comparing clinically notable values for studies AE/PT1 & AE/PT2. The reliability of the data corrections is questioned. The sponsor reports limitations obtaining confirmation of the nature of the errors from the source laboratory for these studies with last patient entry in 1994. The tables are presented for review but are not considered adequate for the thyroid function safety analysis.

In the table of mean differences between baseline and termination visit the differences between treatment group and placebo do not exceed .1% for means or medians. The shift table revealed a 1.5% difference between rufinamide treatment and placebo in the examination of patients who shift TSH value from normal at baseline to high at final thyroid laboratory study, where the rufinamide group has the greater incidence of shift from normal to high. There is a 1.6% difference between rufinamide treatment and placebo in the examination of patients who shift free Thyroxine value from normal baseline to high at final study visit, where the rufinamide group has the greater incidence of shift from normal to high. There are no other shift changes of a magnitude that may indicate a thyroid safety concern for rufinamide. The table of clinically notable values for free thyroxine reveals 3.6% of rufinamide treated patients has an increase in value whereas 1.7% of placebo treated patient has an increase in free thyroxine. This represents a 1.9% positive gradient between the placebo and rufinamide treatment group.

Reviewer comment: The values of TSH and free thyroxine are in opposite physiologic direction in both the recent studies and more remote studies AE/ET1 & AE/PT2. The expected direction of abnormality based on the preclinical features that resulted in this laboratory monitoring were values representing hypothyroidism. These changes do not reach a threshold either together or independently that indicated a thyroid safety signal.

8.1.3.1.4 Hematologic Abnormalities

In section 7.1.7.5 the related clinically notable final hematology laboratory parameters are covered. It is noted that there is follow up in only 3 of 121 clinically notable final laboratory values.

In the initial NDA by Dr. Raman identifies several cases of clinically notable hematologic alteration. Upon reexamination 2 of 9 cases remain as possibly indicating a hematopoietic signal. In the first case 0003-06026 described below there was a clinically notable drop in WBC count

that resolved with dechallenge. The second case is less compelling with minimum WBC count and absolute neutrophil count not reaching clinically notable.

Patient 0003-06026 in study AE/ET1 an 18 year old female on a stable dose of carbamazepine had a steady decline in WBC count after beginning rufinamide 400mg daily. At baseline the WBC = 4.6×10^9 . Three days after beginning rufinamide the WBC = 3.4×10^9, approximately 4 weeks later the WBC count declined to 2.7×10^9 . Rufinamide was discontinued and five days later the WBC count was 6.5×10^9.

Patient 0003-04265 in study AE/ET1 a 36 year old female developed a mild depression of WBC count which developed slowly after beginning rufinamide. Patient was on concomitant carbamazepine and phenytoin. On day 3 of treatment her total WBC count was 5.7×10^9 with 56% neutrophils. Day 13, WBC= 4.2, with 5 8% neutrophils, Day 28, WBC = 7.3 with 61% neutrophils, Day 55, WBC = 3.5, with 43% neutrophils. On day 29 the patient developed furuncles. The investigator wonder if the furuncles were the result of neutropenia (1505). Patient was discontinued prematurely from the trial.

Descriptive statistics are reviewed from the initial ISS of July 26, 2005 for hematology laboratory parameters, for all double blind study participants. These reveal a WBC change of 0.1 x 10^9 L between baseline and final study visit for patients treated with rufinamide and a change of 0.0 between baseline and final study visit for patients treated with placebo. Hemoglobin reveals a change of 0.0 between baseline and final visit for patients treated with rufinamide and -0.1g/L between baseline and final visit in patients treated with placebo. Platelet count reveals a change of 3.6×10^9 /L between baseline and final visit (3.6 out of baseline 233.4) for patients treated with rufinamide and a change of 1.7×10^9 between baseline and final visit for patients treated with placebo (1.7 out of 238.0 baseline). The neutrophil percent increased by 2.0% from baseline to final study visit (2.0% out of 55.4% at baseline) in rufinamide treated patients, increased by 0.4% between baseline and final study visit (0.4% out of 53.5% at baseline) in placebo treated patients.

Shift table analysis of WBC for all double blind patient participants reveals a change from normal to low in 3.7% of rufinamide treated patients and 2.4% of placebo treated patients. For hemoglobin there is a change from normal to low in 8.3% of rufinamide treated patients compared to a change from normal to low in 7.4% of placebo treated patients. Platelet count reveals a change from normal to low in 2.5% of rufinamide treated patients and a change from normal to low in 2.7% of placebo treated patients. Neutrophil counts changed from normal to low in 2.6% of rufinamide treated patients and from normal to low in 4.1% of placebo treated patients.

Statistics for clinically notable values were reviewed for all double blind patient participants. WBC count reveals a 3.7% decrease for rufinamide treated patients and a 1.2% decrease in placebo treated patients. Platelet count decreases in 1.9% of rufinamide treated patients compared to 1.1% of placebo treated patients. Hemoglobin decreases in 0.9% of rufinamide treated patients compared to 0.7% of placebo treated patients.

Reviewer comment: *Group statistics reveal a suspect hematopoietic signal. Evaluation of group clinically notable decrease in WBC count reveals a decrease of WBC in 3.7% and 1.2% in the placebo group . No compelling change is seen in clinically notable group values in platelet count, neutrophils or hemoglobin. The clinically notable change in group WBC is correlated with the individual cases from the initial safety review (0003-06026 study AE/ET1) and the observation of a dechallenge response in the final abnormal lab (3087-02073 in Study 022). An entry in labeling adverse events for leukopenia should be added.*

8.1.4 Other Search Strategies

8.1.5 Common Adverse Events

Common adverse events in ongoing studies E2080-A001-301 and E2080-A001-302 are reviewed in 7.1.5. Common adverse events are reviewed for the full development program by Dr. Ramon in the medical safety review 7.1.5.

8.1.6 Less Common Adverse Events

full development program see Dr. Ramon medical safety review, initial submission 7.1.6

8.1.7 Laboratory Findings-as addressed in approvable letter: clinically notable changes in final visit laboratory values.

8.1.7.1 Special assessments

In the approvable letter of September 2006 it was noted " There were a number of patient with clinically notable changes in some laboratory parameters noted at the final visit. The final disposition of such patient was not clear to us. Pleas re-examine the records for these patients 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 final outcome if known"

In response to the agency's request, Eisai has assessed and written narratives for each patient with clinically notable changes in hepatobiliary, renal, hematology, and chemistry laboratory parameters. Each narrative specifically addresses the elevated value, follow-up if any, and final disposition of the patient. The summary responses to these questions are given in each of the above noted categories.

8.1.7.1.1 Clinically Notable Hepatobiliary abnormalities

In response to the request in the approvable letter the sponsor provides narratives for 24 patients with abnormal, final hepatobiliary parameters. Only two patients were found to have complete laboratory follow up parameters. In both of these the studies normalized and patients were not on rufinamide at follow up laboratory study. In case 0002_08019 study AE/ET1 the patient had a

severe secondarily generalized seizure and developed a muscle entrapment syndrome as a result of the seizure. The abnormal hepatobiliary studies were obtained at the time of this severe medical event. These included SGOT of 1314 U/L, SGPT of 1056 U/L and bilirubin 32umol/L (1.6X ULN). The blood parameters returned to normal after rufinamide was discontinued creating a dechallenge association. Alternatively the medical extremis caused by the severe seizure and subsequent compartment syndrome may have caused or contributed to the laboratory abnormalities.

Subject 0513-00151 in study 38 had an approximately 3.5 x ULN elevation of ALT, with all other hepatobiliary parameters normal. The ALT elevation resolved after the patient completed rufinamide treatment. This dechallenge supports association between treatment and the mild liver function abnormality.

Subject 0003-07035 in study AE/ET1 was treated with rufinamide for 1 year and 6 months without clinically significant laboratory parameters when an elevated bilirubin of 217 umol/L was identified at final study visit. No other hepatobiliary parameters were abnormal at the same study. A three month follow up laboratory panel was obtained revealing no abnormal hepatobiliary parameters, however bilirubin value was not obtained at that study. On November 6, 2008 the sponsor was asked to participate in a teleconference to further explore this substantial elevation on bilirubin. Later the same day the sponsor reported that the elevation never occurred but was a transcription error from a case report form. The sponsor sent a tiff image of the case report form for the record.

Subject 0005-04408 in study 021p had severe elevation in AST, ALT, and LDH as well as bilirubin without corresponding elevation of alkaline phosphatase. However this occurred in the context of a severe hypersensitivity reaction involving skin, lung and a mild increase in eosinophils. The entire syndrome resolved after rufinamide discontinued. This case was addressed by Dr. Raman in the initial NDA safety review, however in response to the current review the sponsor was asked to review the subject database for additional cases that could fulfill criteria for a multiorgan hypersensitivity response.

Reviewer comment: *only one case stands out as a possible unconfounded hepatotoxic response to the study medication based on ALT elevation with dechallenge resolution. In this case the liver function abnormality was mild and otherwise asymptomatic. The review of final laboratory values for hepatobiliary parameters is congruent with the findings from the ISS summary statistic tables for hepatobiliary parameters where there is no increase of transaminases or bilirubin greater than seen in placebo in change from baseline, shift table or clinically notable values. The potential for liver function abnormality is indicated in the current draft labeling* b(4)

8.1.7.1.2 Clinically Notable Renal Laboratory tests

There were a total of 10 subjects with renal laboratory abnormalities at final visit across all of the epilepsy studies. One of the 10 had simultaneous elevation of BUN and creatinine. Most were

elevations in BUN. None had follow up evaluation. Review of the initial NDA ISS for all patients from double blind studies reveals no change in BUN for rufinamide treated patient between baseline and last study visit and no change between baseline and termination in placebo treated patients. Summary statistics for creatinine reveal an increase of 2.7 umol/L between baseline and termination visit for rufinamide treated patients and an increase of 0.9 between baseline and termination visit for placebo treated patients. These values are changes over a baseline of 78.9 umol/L and 78.8umol/L respectively.

Shift table analysis for BUN reveals a change from normal to high in 1.9% of rufinamide treated patients and 2.4% of placebo treated patients. Creatinine reveals change from normal to high in 3% of rufinamide treated patients and 3.3% of placebo treated patients.

Reviewer Comment: *There is no follow up study to determine outcome of final abnormal laboratory studies but no extreme values identified. Review of summary statistics reveals no signal for renal damage.*

8.1.7.1.3 Clinically Notable Hematology Laboratory Parameters

Under this category, data for all patients with clinically notable hematology lab test results at the final/termination visit was examined in detail. The hematology parameters included platelets, RBC, hematocrit, hemoglobin, WBC, basophils, eosinphils, lymphocytes, monocytes, and neutrophils. There were a total of 121 patients in this category across all of the epilepsy studies, some of whom had clinically notable values for multiple parameters.

In only 3 of 121 cases was the laboratory parameter in question clearly repeated to investigate a response to discontinuation of medication. In each of these cases the abnormal laboratory value returned to normal range. This occurred when the abnormal hemoglobin of subject 1747-02023 (Study 022) was rechecked approximately 2 months after finding severely reduced hemoglobin. A return to normal was also found for subject 3087-02073 (Study 022) who had significant leukopenia which returned to normal range when rechecked 43 days after the last dose of rufinamide. Subject 0501-00004 (Study 101) had mild thrombocytopenia which returned to normal when the value was repeated 20 days after last dose of rufinamide.

Reviewer comment: *These three dechallenge cases are suggestive of a potential for bone marrow suppression. There was one case each of anemia, leukopenia and thrombocytopenia.*

8.1.7.1.4 Clinically notable Chemistry Laboratory Parameters

Approvable letter: There were a number of patients with clinically notable changes in some laboratory parameters noted at the final visit. The final disposition of such patients was not clear to us. Please re-examine the records for these patients 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.

There are 62 clinically notable abnormalities in chemistry parameters. Follow up evaluation is only available for 2 of the 62 abnormalities. In a case of hyperuricemia, the abnormality resolved on follow up. The second, a case of hypercholesterolemia resolved at a 4 day recheck. Table 8.1.7-1 provides a numerical listing of the clinically notable chemistry abnormalities.

Table 8.1.7-1 Numerical listing of clinically notable chemistry parameters

	Number	
Hyperkalemia	23	7 studies obtained >1 month after medication discontinued, lab handling highly probable in 2 cases
Hypoglycemia	12	
Hyperuricemia	12	
Hyponatremia	6	
Hypercalcemia	3	
Hyperglycemia	3	
Increased bicarbonate	1	
Hypercholesterolemia	2	

Reviewer comment: Based on the nature of the question in the approvable letter these laboratory values were final laboratory values predominantly isolated events without preceding abnormality. *Hyperkalemia, the most frequent abnormality was very unlikely to be related to rufinamide. In 7 of 23 cases treatment cessation was more than a month before the laboratory study. In two cases the hyperkalemia is due to laboratory mishandling. In the remaining 14 cases the cause is unknown and no follow up available. Hyperuricemia was present in 12 subjects and was mild based on upper limit of male normal. Hypoglycemia was identified in 11 cases, in all cases the finding was a single event, etiology is uncertain without follow up. Hyponatremia was reported in 6 cases, 2 of these patients were on oxcarbazepine and one on carbamazepine which are confounding agents because of their ability to cause hyponatremia. The three remaining cases are of uncertain significance and had no follow up study. Three final results of hypercalcemia were identified, one case was lab error. Two were of uncertain significance. One case of hypochloremia was identified, of uncertain significance. Three cases of hyperglycemia were identified of which one occurred in the same case of hypercalcemia. There was hyperglycemia in one case and hypercholesterolemia in two. One of the hypercholesterolemia cases had follow up and was found to be resolved when rechecked 4 days later.*

Overall there is no compelling safety signal in the final abnormal chemistry parameters.

Reviewer summary comment on sponsor response to approvable letter.: *In this section follow up of abnormal final laboratory values is extremely limited and the dechallenge data that might be revealing is lost. There were a total of 227 clinically notable final laboratory parameters with only 8 available follow up laboratory values.*

8.1.8 Special Safety Studies

8.1.8.1 Status Epilepticus

Status Epilepticus: Approvable letter: "... across controlled trials, 1% of rufinamide-treated patients experienced status epilepticus while none of the placebo-treated patients experienced SE. We ask that you further address this finding.

"Status Epilepticus
Estimates of the incidence of treatment emergent status epilepticus among patients treated with rufinamide are difficult because standard definitions were not employed. In controlled Lennox Gastaut trials 3 of 74 (4.1 %) patients had episodes that could be described as status epilepticus in the rufinamide treated patients compared with none of 64 patients in the placebo-treated patients. In all controlled trials, that examined different epilepsies, 11 of 1,240 (0.9%) patients had episodes that could be described as status epilepticus in the rufinamide-treated patients compared with none of 635 patients in the placebo-treated patients."

Table 8.1.8-1 Overview of Status Epilepticus Adverse Event in All Epilepsy Patients During Double-Blind Trials

	Rufinamide		Placebo	
	N	n (%)	N	n (%)
Incidence of Status Epilepticus				
All AEs	1240	11 (0.9)	635	0 (0.0)
Related AEs	1240	2 (0.2)	635	0 (0.0)
Severity				
Moderate	1240	7 (0.6)	635	0 (0.0)
Severe	1240	4 (0.3)	635	0 (0.0)
Gender				
Male	620	4 (0.6)	338	0 (0.0)
Female	620	7 (1.1)	297	0 (0.0)
Age				
<12	119	1 (0.8)	112	0 (0.0)
12-16	93	3 (3.2)	84	0 (0.0)
17-64	1019	7 (0.7)	433	0 (0.0)
Discontinued				
All AEs	1240	1 (0.1)	635	0 (0.0)
Related AEs	1240	0 (0.0)	635	0 (0.0)
Serious Adverse Event				
All AEs	1240	4 (0.3)	635	0 (0.0)
Related AEs	1240	0 (0.0)	635	0 (0.0)

Table 3 from Sponsor ISS p15

As noted, status epilepticus did not occur in any patient who received placebo in any of the double-blind studies in the rufinamide clinical development program. As shown in table 8.1.8-1, status epilepticus was an adverse event in 0.9% of all patients who received at least 1 dose of rufinamide, a serious adverse event in 0.3%, and an event that led to discontinuation of treatment in 0.1%. Of the 1240 epilepsy patients who were in the double blind studies, 4 rufinamide-treated patients and 1 placebo-treated patient had a history of status epilepticus prior to entering the trials. However, none of these patients with a previous history of status epilepticus experienced the event during the double-blind rufinamide trial (table 8.1.8-2 below).

Table 8.1.8-2 Patients with Status Epilepticus

Study Number/ID	Age/sex	History of status epilepticus/ Triggering factors	Dose of rufinamide (mg/day)	Duration of rufinamide treatment (days)	Relatedness by investigator	Outcome	Rufinamide discontinued
Patients who had status epilepticus as SAE not leading to discontinuation							
CRUF3310016/1245_00581	35/F	None known	3200	73	Not Suspected	Completely Resolved	No
CRUF3310021/0001_04223	15/M	None known	1800	93	Not Suspected	Completely Resolved	No
CRUF3310021/1266_03037	15/F	None known	2400	46	Not Suspected	Completely Resolved	No
CRUF3310038/0518_00110	45/F	Presurgical withdrawal of AEDs	3200	2	Not Suspected		No
Patients who had status epilepticus as non-SAE leading to discontinuation							
CRUF3310021/1273_05151	30/F	Hypoglycemia	800	7	Not Suspected	Completely Recovered	Yes
Patients who had status epilepticus as non-SAE not leading to discontinuation							
CRUF3310021/0011_06231	31/F	Pneumonia, vomiting, severe dehydration	2400	84	Not Suspected	Complete Recovery	No
CRUF3310021/1266_03066	13/M	None known	1000 800	52 1028	Not Suspected	Complete Recovery	No
CRUF3310022/0001_02923	11/F	None known	1400	25	Not Suspected	Complete Recovery	No
CRUF3310022/0002_02539	25/M	None known	1400	19	Suspected	Complete Recovery	No
CRUF3310022/1553_02083	17/M	None known	1800 200 200 200	12 88 98 126	Not Suspected	Complete Recovery	No
CRUF331AEET1/0004_05001	22/F	None known	800	74	Not Suspected	Complete Recovery	No

Table 5 from Sponsor ISS p17

Reviewer comment: *The occurrence of status epilepticus in the treatment group and none in placebo is of concern. These were also first time cases of Status epilepticus. This risk has been addressed in the label under precautions.*

8.1.8.2 QT interval Shortening

From team leader review initial NDA submission:

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

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

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

From Approvable Letter, initial submission the agency commented "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 patients 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".

The reformatted data set has been submitted by the sponsor and Dr. Lisa Jones of the DNP safety team has reevaluated. In this review Dr. Jones has included tables using only the Fridericia correction of QT interval (QTcF). FDA table 8.1.8-3 below from Dr. Jones review provides a view of the relationship between the corrected QT duration and the dose of rufinamide. FDA table 8.1.8-4 from the same review illustrates the relationship between rufinamide dose and the magnitude of QTcF shortening.

FDA Table 8.1.8-3: 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)

FDA Table 8.1.8-4: 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

	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)

The review indicates that following a 3200mg dose 92% of subjects recorded a QT interval decrease of >20 msec, and 100% of subjects given a dose of 7200mg recorded a QT interval decrease of >20 msec. None of the subjects reduce their QTcF duration to less than 300 msec which is the threshold of concern based on data from familial short QT syndrome.

Dr. Jones reiterates the conclusion of her first review and that of the QT team review that "there is no algorithm for risk assessment" regarding QT reduction. As noted above the 9 events of sudden death in the development program are comparable to sudden death in other AED's, NDA's approved by the division. In his review Dr. Raman also concludes that of the 9 sudden deaths 5 fit SUDEP criteria, and the remaining 4 meet probable criteria. However, these conclusions do not provide full assurance that QT shorting has not precipitated a malignant

ventricular rhythm. Dr. Jones points out in her review " In fact, the ICH E14 guidance to industry on QT studies notes that arrhythmic events may be mistaken for seizures."

There is additional patient data since the initial review from ongoing clinical trials of rufinamide. In this data no additional deaths have been reported in the IND annual report between September 29, 2006 and September 29, 2007. No cardiac or hemodynamic type adverse events have appeared in 15 day AE reports. There have been 17 reports of dizziness, however this is not an unexpected occurrence in a central nervous system active agent. There are no deaths reported over the interval September 29, 2006 to September 29, 2007. One syncope and resultant study withdraw has occurred in study E2080-A001-301. This is not entirely unexpected and as a single event cannot be taken as a safety signal related to QT shortening. In the data from all double blind patients in the initial submission ISS, there were a higher proportion of syncope in the placebo than in the rufinamide treated groups, 0.5% vs. 0.2% respectively.

The remaining approach to monitor for QT shortening related events is continued monitoring for unexpected increase in sudden death or events that may be related to QT shorting which are postulated to be ventricular arrhythmias or spontaneous atrial fibrillation or syncope.

Dr. Jones has recommended a phase 4 commitment to evaluate the QT interval in rufinamide treated patients with and without concomitant medications that may shorten QT interval and in those patients treated with and without other agents that are considered sodium channel blockers. She has also recommended that labeling for rufinamide "include a summary of the QT data, a statement that the clinical effects of this degree of shortening is unknown and a recommendation that patients with known short QT not be treated with rufinamide." This has been captured in the following draft labeling:

CONTRAINDICATIONS: TRADENAME (rufinamide) is contraindicated in patients with Short QT syndrome.

PRECAUTIONS: QT Shortening
Formal cardiac EKG studies demonstrated shortening of the QT interval (up to 20 msec) with rufinamide treatment. In a placebo-controlled study of the QT interval, a higher percentage of rufinamide-treated subjects (46% at 2400 mg, 46% at 3200 mg, and 65% at 4800 mg) had a QT shortening of greater than 20 msec at Tmax compared to placebo (5 – 10%).

Reductions of the QT interval below 300 msec were not observed in the formal QT studies with doses up to 7,200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias.

The degree of QT shortening induced by rufinamide is without any known clinical risk. Familial syndromes of shortened QT interval are associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in these syndromes are believed to occur primarily when the corrected QT interval falls [redacted] 300 msec. b(4)
Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation.

Patients with short QT syndromes should not be treated with TRADENAME (rufinamide) (see Contraindications). Caution should be used when administering TRADENAME (rufinamide) with other drugs that shorten the QT interval.

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

ISS July 26, 2005, Clinical overview and ISS amendment February 28, 2008

8.2.2 Adequacy of Overall Clinical Experience

Completed clinical trial exposure

In the population of all rufinamide-treated patients in completed clinical studies, 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.

In all double – blind study participants median doses were 2400 to 3200mg/day for 291 (23.5%) of patients and more than 3200mg/day for only 1 (0.1%) patient. More than half of the patients who received median doses of 2400 to 3200 mg/day were treated for at least 3 months.

In combined double blind and open label studies combined 1156 patients have had greater than six months exposure to a dose range 2400 to ≤3200mg. 705 subjects have had 12 months or greater exposure to the dose range 2400 to ≤3200mg. 141 patients have had 6 months or greater exposure to >3200mg daily dose. 88 patients were exposed for >12 months to >3200mg.

Ongoing clinical trials

In addition to the exposure in completed clinical studies there is further exposure in ongoing study E2080-A001-301 and extension phase E2080-A001-302. 223 patients were randomized into study A001-301 with 141 subsequently entering open label extension. The total exposure to study drug (rufinamide or placebo) in the double-blind portion of study E2080-A001-301 per cut-off date is 33,084 patient-days; total exposure to rufinamide either during the transition phase

of study E2080- A001-301 or during open-label extension study E2080-A01-302 (all patients on rufinamide) is 21,632-days.

Post Marketing Exposure

Rufinamide has been approved for treatment of Lennox-Gastaut syndrome in the European Union since January of 2007. Using the available data from factory sales data on the number of tablets sold and with the defined daily dose for rufinamide considered to be 1600 mg with maximum dose 3200mg a day, it is estimated that there have been over——— patient-days of exposure from product launch to 15 January 2008. The available post-marketing exposure data indicates approximately 73% of the exposure is estimated to be in the pediatric population (age 0-18 years) and 50% of the exposure is estimated to be in females. In the absence of highly valid data, these estimates are based on local affiliate market research data, key opinion leader interviews, and qualitative feedback from prescribers. b(4)

Reviewer Comment: *rufinamide exposure has been adequate to ICH E1A "Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety".*

9 OVERALL ASSESSMENT

9.1 Conclusions

Partial Seizures

The sponsor seeks approval for rufinamide use in partial seizures for adults and adolescents 12 years of age and older b(4)

In this second submission the sponsor presents additional argument and analysis in support of rufinamide for adjunctive treatment of partial seizures. These include a proposal that there is precedent in the approval process for other anticonvulsants where there has been variability in efficacy between studies and review of the statistical analysis of study AE/ET1. In addition they present a PK/PD analysis of rufinamide concentration response based on pooled data from multiple trials. This reveals a decreasing seizure rate with increase in rufinamide dose; however it is supplemental to the statistical analysis but does not supersede the individual study statistical analysis. No additional clinical study to establish dose ranging study is performed.

The FDA statistical review reveals that there is no gradient of medication efficacy noted between 400mg and 800mg a day in study AE/ET1. When some multiplicity testing is performed on the ANCOVA of rank of percent change only the 1600mg a day retains significance. When an ANCOVA on rank of change in total seizure frequency between baseline and treatment,

comparing rufinamide to placebo, no dose remains significant when certain multiplicity testing is performed. The sponsor examines seizure frequency ratio between rufinamide and placebo using a Wilcoxon rank sum test without multiplicity testing. When the FDA statistical reviewer imposes multiplicity testing only the 800mg a day dose retains significance.

Study 21A is positive but not robust. The rufinamide dose was 3200mg. The primary endpoint is positive but when secondary efficacy measures are examined with more complete covariates there is no significance. The combined view of study 21A and AE/ET1 inform the reviewer that rufinamide has a modest anticonvulsant effect [redacted] of appropriate dose for partial onset seizures, from the range of 400mg to 3200mg is not clarified in this submission. b(4)

LGS

Rufinamide is studied for effectiveness at 45mg/kg/day or a maximum of 3200mg a day in Lennox-Gastaut syndrome. The study is strongly positive for percent change in total seizure per 28 days relative to baseline. There is a concern that baseline seizure frequency is unequally distributed but reevaluation by the sponsor does not reveal a breach in the randomization process. The agent is additionally supported by the evidence from the partial seizure trials which indicate anticonvulsant activity [redacted] b(4)

Safety

The safety profile is free of the most threatening skin reactions of Steven-Johnsons syndrome and toxic epidermal necrolysis. There were however significant hypersensitivity reactions in the pediatric age range including a case of multiorgan hypersensitivity which is reflected in labeling. There was also a modest signal for leukocyte suppression which is reflected in the adverse events sectionin labeling. There was no hepatobiliary safety signal.

A hypothyroid response was suggested by several clinically notable cases of elevated TSH with depression of total T4. These clinically notable cases were reviewed. During the review process errors in the clinically notable thyroid dataset were identified. These consisted of units mixed between international standard (SI units) and alternate measurment systems. It was concluded that the summary tables for change between baseline and final visit comparing placebo to treatment group, were unreliable. These tables allow differences between placebo and treatment group to be identified. Recalculation and correction of the tables was problematic because the abnormal values could not be confirmed as unit changes in the studies AE/ET1 and AE/PT2. The more recent trials (CRUF3310016, CRUF3310018, CRUF3310021A, CRUF3310021P, CRUF3310022, CRUF3310038) however were able to undergo accurate recalculation .

The sponsor provided recalculated tables. On examination there were some differences between placebo and rufinamide treatment but these were not of sufficient magnitude to indicate a safety signal. In addition changes were in opposite directions physiologically. In the recalculation of the recent trials TSH had a 1% greater shift from normal to high than placebo. In the recalculation of the mean difference between baseline and termination thyroxine had an increase that was 9.1 nmol/L greater than the placebo group mean change from baseline to termination value. This

increase is of small magnitude compared to the upper limit of normal for total thyroxine which is 155nmol/L. It is an even smaller portion of the study designated clinically notable upper limit of 173.3 nmol/L. This rise in thyroxine is contrary to the 1% greater shift to elevation in the TSH result noted above. Such a change in TSH would forecast a mean decrease in thyroxine rather than an increase.

The more recent trial group did not have free thyroxine obtained which shifted the analysis to TSH and total thyroxine. Total thyroxine is subjected to variability due to underlying patient medical status. Although not of confirmed accuracy, the recalculated tables for studies AE/PT1 and AE/PT2 are reviewed. In these studies a free thyroxine was performed. The differences seen between treatment and placebo groups were small and like the results in the other group of more recent studies the deviations of thyroxine and TSH were in opposite directions. A significant concern for a hypothyroid safety signal was not substantiated by the descriptive statistics, shift table analysis or clinically notable values form double blind studies.

9.2 Recommendation on Regulatory Action

"Approval" response for treatment of Lennox-Gastaut syndrome ages 4 to adult at adose up to 45mg/kg/day up or a maximum of 3200mg a day whichever is less.

b(4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

1. The sponsor will be asked to provide the following analysis on existing clinical study data:

a. The baseline (pre-treatment) mean QT interval (as measured by all three correction methods) in rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (appendix 10.5) and in patients without such concomitant medications.

b. The mean on-treatment QT interval (again by all three correction methods) for rufinamide-treated patients receiving concomitant drugs believed to shorten the QT interval (appendix 10.5) and in patients without such concomitant medications.

c. the same analysis for sodium channel blocking drugs (appendix 10.5).

2. Conduct an in vitro metabolism study to characterize the potential serious safety risk of the inhibitory effect of rufinamide on P-gp.

3. Conduct a juvenile dog toxicology study to identify the unexpected serious risk of adverse effects on postnatal growth and development.

9.3.3 Other Phase 4 Requests

none

9.4 Labeling Review

The sponsor proposed label has been modified to remove [redacted] b(4)
Short QT syndrome has been added as a contraindication. Central nervous systems adverse reactions of somnolence and motor coordination abnormalities. QT shortening has been added to precautions with a statement that caution should be used when administering rufinamide with other drugs that shorten the QT interval. Multiorgan hypersensitivity response and leukopenia have been added to precautions.

Drug interactions: specific rufinamide- phenytoin, valproic acid-phenytoin, and interaction with ethinyl estradiol and norethindrone have been added to the label.

The sponsor was asked to generate a list of the most commonly observed adverse reactions in patients participating in double blind studies. These reactions are stratified according to observed frequency. The list will be generated for events ≥ 10% and ≥5%, at all doses studied, also events ≥5% at 45mg/kg/day in children and at 3200mg a day in adults. The sponsor is also requested to provide the percent of discontinuations according to adverse effect.

9.5 Comments to Applicant

1. [redacted] b(4)

10 APPENDICES

10.1 Review of Individual Study Reports

To perform second submission review the sponsor February 28, clinical overview and ISS amendment as well as the initial Efficacy review by Dr. Hershkowitz and initial safety report by Dr. Ramon served as initial data source. Referral to the individual study AE/ET1, 21A, and 022 was made on an as needed basis and are indicated in the efficacy review headings " initial sponsor submission"

10.2 Line-by-Line Labeling Review

Performed at team meetings.

10.3 Randomization errors- case narrative

Randomized Patient USA/3054/2101 did not receive double-blind study drug due to an administrative error. The patient number (2101) was arbitrarily assigned. He was allowed to enter the Extension Phase directly after completing Visit 1. For the sole purpose of identification, information about this patient was placed in the rufinamide treatment group. This patient was not included in the double-blind analysis because he did not receive study medication and had no post-baseline efficacy or safety assessments in Study 0022.

• Patient USA/2863/2058 in the placebo group was mistakenly re-randomized by the investigator after completing Visit 4 and was assigned Patient number SA/2863/2060. The error was discovered in approximately 3 days and the patient was withdrawn from the study due to administrative problems. All data for this patient are included under Patient number 2058. Seizure information through Visit 4 was included. Efficacy data up to Visit 4 were included in the analyses.

• Patient USA/19/2097 was inadvertently given two bottles of study medication for Patient USA/19/2099 at Visit 5. Both these patient numbers were randomly assigned to receive rufinamide, so this error did not affect any of the data collected for Patient USA/19/2097. This patient was included in all efficacy and safety analyses.

10.4 Efficacy subgroup analysis for interaction with concomitant AED's

Table 6.1.4.3.1 **Summary of percent change in PGTC seizure frequency per 28 days relative to baseline by number and type of AEDs (Intent-to-treat patients) in Study 18**

	Rufinamide			Placebo			
	N	Median	Range	N	Median	Range	p-Value[a]
1 AED							
Baseline frequency/ 28 days	25	3.5	1.5, 52.5	26	2.8	1.5, 9.5	
Double-blind frequency/ 28 days	25	1.2	0.0, 27.8	26	1.2	0.0, 11.0	
% change in frequency/ 28 days	25	-60.0	-100.0, 270.0	26	-54.9	-100, 340.0	0.6729
2 AEDs							
Baseline frequency/ 28 days	49	3.5	1.5, 84.0	48	6.3	1.5, 74.0	
Double-blind frequency/ 28 days	49	3.2	0.0, 61.2	48	4.3	0.0, 148.0	
% change in frequency/ 28 days	49	-23.4	-100.0, 233.3	48	-11.0	-100.0, 1380.0	0.9923
Lamotrigine							
Baseline frequency/ 28 days	14	2.5	1.5, 84.0	22	4.0	1.5, 31.5	
Double-blind frequency/ 28 days	14	4.5	0.0, 50.6	22	3.1	0.4, 36.6	
% change in frequency/ 28 days	14	-8.1	-100.0, 233.3	22	-27.6	-95.5, 45.0	0.3634
Carbamazepine							
Baseline frequency/ 28 days	16	3.5	1.5, 84.0	22	3.0	1.5, 35.0	
Double-blind frequency/ 28 days	16	2.5	0.0, 50.6	22	1.8	0.0, 44.2	
% change in frequency/ 28 days	16	-21.7	-100.0, 60.0	22	-33.9	-100.0, 222.9	0.9627
Phenytoin							
Baseline frequency/ 28 days	13	4.0	1.5, 56.5	18	4.0	1.5, 74.0	
Double-blind frequency/ 28 days	13	4.0	0.0, 61.2	18	2.8	0.0, 73.6	
% change in frequency/ 28 days	13	-37.3	-100.0, 178.2	18	-25.5	-100.0, 340.0	0.5158
Valproate							
Baseline frequency/ 28 days	42	2.8	1.5, 64.0	34	4.0	1.5, 57.5	
Double-blind frequency/ 28 days	42	2.4	0.0, 44.8	34	3.5	0.0, 69.0	
% change in frequency/ 28 days	42	-36.1	-100.0, 233.3	34	-25.4	-100.0, 76.0	0.9778

[a] Based on the ANCOVA analysis on the rank of percent change in total seizure frequency per 28 days with treatment and region as factors and rank of baseline total seizure frequency as a covariates.

Table 10.6-1

Table 6.1.4.3.2 **Summary of percent change in Total seizure frequency per 28 days relative to baseline by number and type of AEDs (Intent-to-treat patients) in Study 21A**

	Rufinamide			Placebo			
	N	Median	Range	N	Median	Range	p-Value[a]
1 AED							
Baseline frequency/ 28 days	47	7.5	3.0, 241.5	50	7.0	3.0, 578.5	
Double-blind frequency/ 28 days	47	7.2	0.0, 552.2	50	7.5	0.0, 416.3	
% change in frequency/ 28 days	47	-8.0	-100.0, 987.5	50	3.1	-100.0, 6837.8	0.4263
2 AEDs							
Baseline frequency/ 28 days	109	10.5	3.0, 275.0	106	8.5	2.5, 135.5	
Double-blind frequency/ 28 days	109	7.7	0.0, 153.1	106	8.7	0.0, 129.7	
% change in frequency/ 28 days	109	-24.3	-100.0, 471.4	106	-2.5	-100.0, 706.1	0.0126
Lamotrigine							
Baseline frequency/ 28 days	34	12.5	3.0, 82.5	28	8.0	3.0, 90.0	
Double-blind frequency/ 28 days	34	13.9	1.8, 106.7	28	7.5	0.0, 156.0	
% change in frequency/ 28 days	34	6.7	-72.0, 471.4	28	5.5	-100.0, 99.1	0.8175
Phenytoin							
Baseline frequency/ 28 days	20	10.8	3.0, 121.5	30	6.5	3.0, 135.5	
Double-blind frequency/ 28 days	20	8.2	0.0, 124.7	30	7.0	0.0, 416.3	
% change in frequency/ 28 days	20	-26.9	-100.1, 112.1	30	-9.1	-100.0, 6837.8	0.4234
Carbamazepine							
Baseline frequency/ 28 days	94	8.3	3.0, 275.0	89	8.5	2.5, 578.5	
Double-blind frequency/ 28 days	94	7.3	0.0, 153.1	89	8.7	0.6, 129.7	
% change in frequency/ 28 days	94	-13.2	-100.0, 987.5	89	1.8	-91.2, 706.1	0.0509

[a] Based on the ANCOVA analysis on the rank of percent change in total seizure frequency per 28 days with treatment and region as factors and rank of baseline total seizure frequency as a covariates.

Table 10.6-2

Table 6.1.4.3.3 **Summary of percent change in Total seizure frequency per 28 days relative to baseline by number and type of AEDs (Intent-to-treat patients) in Study 021P**

	Rufinamide			Placebo			
	N	Median	Range	N	Median	Range	p-Value[a]
1 AED							
Baseline frequency/ 28 days	47	11.5	3.0, 774.0	35	10.0	2.0, 127.0	
Double-blind frequency/ 28 days	47	9.3	0.0, 1436.8	35	6.5	0.3, 222.5	
% change in frequency/ 28 days	47	-19.6	-100.0, 392.1	35	-21.6	-97.2, 646.7	0.3899
2 AEDs							
Baseline frequency/ 28 days	88	17.5	3.0, 910.0	96	15.0	3.0, 243.0	
Double-blind frequency/ 28 days	88	16.2	0.0, 945.5	96	14.6	0.6, 307.7	
% change in frequency/ 28 days	88	-7.0	-100.0, 758.1	96	-6.9	-89.7, 1293.0	0.3073
Lamotrigine							
Baseline frequency/ 28 days	23	11.5	3.0, 774.0	27	10.5	4.0, 132.0	
Double-blind frequency/ 28 days	23	15.6	0.6, 1436.8	27	10.6	1.2, 182.6	
% change in frequency/ 28 days	23	10.3	-88.7, 464.7	27	-17.0	-76.7, 121.1	0.2438
Carbamazepine							
Baseline frequency/ 28 days	70	13.3	3.0, 451.0	67	12.0	2.0, 243.0	
Double-blind frequency/ 28 days	70	10.6	0.0, 335.1	67	14.0	0.3, 281.9	
% change in frequency/ 28 days	70	-6.8	-100.0, 254.4	67	-4.5	-97.2, 1293.0	0.8100
Valproate							
Baseline frequency/ 28 days	42	15.5	3.0, 910.0	43	14.0	3.5, 205.0	
Double-blind frequency/ 28 days	42	12.0	0.0, 945.5	43	14.3	0.9, 307.7	
% change in frequency/ 28 days	42	-17.1	-100.0, 758.1	43	-10.1	-89.7, 1293.0	0.2205

[a] Based on the ANCOVA analysis on the rank of percent change in total seizure frequency per 28 days with treatment and region as factors and rank of baseline total seizure frequency as a covariates.

Table 10.6-3

Table 6.1.4.3.4 Adjusted Mean Seizure Frequency and Seizure Frequency ratio by Number and Type of AED in Study AE/ET1

	N	Seizure Frequency Adjusted Mean [a]	Seizure Frequency Ratio Comparison to Placebo Ratio	95%CI	p-value [a]
1 AED					
200mg	38	12.3	0.81	0.66, 1.01	0.0600
400mg	29	10.7	0.71	0.57, 0.89	0.0030
800mg	39	10.8	0.72	0.58, 0.89	0.0027
1600mg	31	12.4	0.82	0.66, 1.03	0.0829
Placebo	26	15.2			
2 AEDs					
200mg	57	14.7	1.16	0.93, 1.47	0.1945
400mg	68	11.4	0.91	0.73, 1.14	0.4248
800mg	57	10.9	0.87	0.69, 1.10	0.2415
1600mg	73	11.9	0.95	0.76, 1.18	0.6233
Placebo	69	12.5			
3 AEDs					
200mg	29	16.3	0.92	0.67, 1.27	0.6111
400mg	33	16.7	0.94	0.68, 1.31	0.7221
800mg	32	13.9	0.79	0.58, 1.08	0.1390
1600mg	28	12.1	0.69	0.49, 0.95	0.0246
Placebo	38	17.7			
Vigabatrin					
200mg	26	12.0	1.03	0.71, 1.48	0.8957
400mg	29	11.1	0.94	0.66, 1.36	0.7534
800mg	22	9.5	0.82	0.56, 1.20	0.2955
1600mg	28	9.8	0.84	0.59, 1.20	0.3385
Placebo	37	11.7			
Carbamazepine					
200mg	93	15.1	1.08	0.92, 1.25	0.3549
400mg	91	12.9	0.92	0.79, 1.07	0.2674
800mg	84	12.2	0.87	0.75, 1.02	0.0908
1600mg	93	12.4	0.89	0.76, 1.03	0.1182
Placebo	95	14.1			
Phenytoin					
200mg	24	15.2	1.07	0.66, 1.74	0.7726
400mg	27	13.2	0.93	0.59, 1.48	0.7582
800mg	32	12.6	0.89	0.57, 1.41	0.6222
1600mg	36	12.6	0.89	0.57, 1.38	0.5930
Placebo	23	14.2			
Valproate					
200mg	33	15.4	0.97	0.75,1.25	0.8042
400mg	25	15.2	0.96	0.72, 1.26	0.7510
800mg	30	12.7	0.80	0.62, 1.05	0.1021
1600mg	36	13.7	0.86	0.66, 1.12	0.2533
Placebo	38	16.0			

[a] Derived from an ANCOVA model with baseline, country, sex, age and treatment as covariates.

Table 10.6-4