CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-911

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 14, 2008
From	Norman Hershkowitz
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-911 0
Applicant	Eisai Inc.
Date of Submission	2/29/08
PDUFA Goal Date	9/3/08
Proprietary Name / Established (USAN) names	Banzel/rufinamide
Dosage forms / Strength	Tablets 100 mg, 200 mg, 400 mg and 300 mg
Proposed Indication(s)	1)Adjunctive treatment of partial onset seizures in adults 2) Adjunctive treatment of seizures associated with Lennox Gastaut syndrome in children ≥ 4 years and adults.
Recommended:	Complete Response in Partial onset seizures. Approval for seizures associated with Lennox Gastaut (see CDTL review).

Regulatory Background

The original application for rufinamide was received on November 17, 2005. At that time the Sponsor provided 3 pivotal double-blinded placebo-controlled trials: 2 in support of labeling for the treatment of adult partial epilepsy and 1 in support of labeling for the treatment of seizures associated with pediatric and adult Lennox Gastaut syndrome. Five supportive double-blinded placebo-controlled trials were also included. Following review an approvable letter was provided to the Sponsor on September 15, 2006. The principal reason for this actions was the absence of sufficient proof of efficacy. The letter noted that:

> < > The potential exception to this conclusion is the clearly favorable single study, study 22, in Lennox-Gastaut Syndrome (LGS), but, as will be explained below, we do not believe the remaining data adequately support the single study."

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Other comments were provided to the Sponsor in this action letter. Included among these was a request for additional informtion on specific clinical safety data, clinical pharmacology, animal toxicology, trade name and carton/container labeling.

Later post-action meeting was held on December 18, 2006, during which the principal topic of discussion was the issue of efficacy, although some pharm/tox issues were also discussed.

The Sponsor submitted a response to the approvable action on September, 15 2006. The below sections describes salient aspects of this submission and this and other reviewer's response to this submission.

Clinical Review for Efficacy

Pre-submission actions and meetings

The two pivotal studies provided by the Sponsor to support substantial evidence of efficacy in adjunctive treatment of partial seizures included a dose ranging study AE/ET1 (200 mg to 1600 mg) and a single dose study 21A (3200 mg).

Study AE/ET1 was designed as a dose ranging study with a primary endpoint that used a regression analysis to determine the existence of a positive slope when points including 0 (placebo), 200, 400 800 and 1600 mg/day were analyzed. This is an unconventional primary endpoints, which would generally not be found acceptable using today's standards. It does not allow for individual dose comparison to provide specific dosing recommendations. To offset this failure the Sponsor used a secondary endpoint, the Wilcoxin-Rank sum, to compare individual doses to placebo and found that all doses 400 mg/day and above exhibited statistical significance. The Sponsor failed to provide a Poisson analysis in the final study report which may also been used for this determination and was another secondary endpoint included in the original protocol. The median changes in the baseline were noted to be small in comparison to placebo and when different doses are examined, with the exclusion of placebo, no obvious dose response is apparent.

The primary endpoint analysis on percent change in seizure frequency using Wilcoxin rank sum in study 21A did prove to be statistically significant. When the FDA statistician performed an alternative sensitivity analysis using log transformed frequency and correction for baseline and country covariates no significance was observed. This rev test may not have been the optimal test because that the data was not normally distributed. In general the division conceded that this study represented a positive study.

The modest effects and lack of a definitive sloop in doses of 200 to 1600 mg/day led this division to express concern. This concern was supported by ambiguous effects observed in other studies. Thus, a study (21P) of nearly identical design to 21A, in pediatric patients failed to exhibit a statistically significant effect or even a trend inspite of the fact that drug exposures were nearly identical. Indeed this study was once a part of a larger study, combined with 21A, but studies were divided before unblinding and presented as separate studies. One monotherapy, low-high dose comparison showed no statistical

significance and another, pre-surgical study was positive, but showed no effect on certain sensitivity analyses.

One study, which examined the effect of 3200 mg/day of rufinamaide on seizures associated with Lennox Gastuat Syndrome (LGS) in children and adults, however, revealed a clearly positive statistically significant effect.

In its approvable letter the Division concluded:

> "In sum, there is a single study showing a clear effect in Lennox-Gastaut
>
> and great uncertainty as to the dose needed for the modest effect seen, with the two supportive studies suggesting 800 and 3200 mg/day (the latter study examined no other dose).

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Moreover the Division concluded:

> "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 the support here."

At the post-action meeting the division agreed that the two trials "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." But, the division also noted that "The division agreed that the drug is effective; however, they will not approve a dose of 3200mg if 800mg is just as good but that they are not yet convinced as to the efficacy of 800mg or lower doses. The division added that we would not want to unnecessarily dose patients at a dose that is four times higher than the necessary dose. It is possible the effect of the drug has a plateau. With this in mind the Division expressed concern that there was an absence of true dose response within this range. The Sponsor expressed a belief that dose-response relationship looks less steep than anticipated but continues to rise over the range of examined doses. At this meeting the Sponsor inquired whether they had adequate data to allow for approval without additional data.

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As the latter may not be possible that the division would consider approval for LG alone the Sponsor should provide an argument:

- That they do not need an additional dose response studies for this population of patients.
- That the safety profile at the higher doses was not unreasonable (particularly with regard to the high percentage of vomiting noted).

Present Submission: Partial Onset Seizures

Study 21A

The Sponsor argues that the fact that 21A was a positive according to the protocol specified primary endpoint at the dose of 3200 mg/day is undisputed by the division (Wilcoxin Rank sum test on the percent change in seizure frequency). The Sponsor, however, argues the contention that the effect was of small is incorrect. This reviewer would note that while median changes are not markedly less than the smallest effect of other drugs at thier lowest doses , it is less than the maximal effects of many drugs at thier higher does (e.g. Oxcarbazepine, Topiramate, Keppra and Lamictal) as a high dose it on the lower side of such effects observed effects.

The Sponsor noted that the secondary analysis performed by our statistical reviewer, to correct for covariates (an ANCOVA on the log transformed data), was inappropriate because of the lack of normality of the population. To correct for this the Sponsor performed an ANCOVA on rank of percent change from baseline in seizure frequency including baseline (rank of seizure freq) and country as covariates. This analysis was statistically significant. In response Dr Siddiqui, the FDA statistical reviewer, performed an alternative analysis of ANCOVA model on rank data of total partial seizure frequency per 28 days during the Double-blind Phase including rank of total partial seizure frequency per 28 days during the baseline and age as covariates, and treatment and found to statistical significance. This reviewer concludes that that while the study protocol specified primary endpoint analysis is highly suggestive of an effect, the contradictory sensitivity analysis, performed by the FDA statistical reviewer, is worrisome.

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AE/ET2

The Sponsor notes in their submission that they concur with the division's conclusion that study AE/ET1 shows a positive outcome per protocol. The Sponsors primary endpoint was a simple regression to determine if there was a positive dose/response

slope. The FDA statistical reviewer notes in his review that there a number of problems with the primary analysis of the primary endpoint:

- Upon performing the analysis the Sponsor recoded doses inappropriately (i.e. doses of placebo, 200, 400, 800 and 1600 mg/day were recoded as 0, 1, 2, 3 and 4 respectively instead of 0, 2,4 ,8 and 16).
- The Sponsor failed to examine slope when placebo was dropped, so as to determine whether there was a true intrinsic dose response for the doses studied : i.e. difference between placebo cold potentially drive the statistical significance of the slope finding.

When the first bulleted maneuver is performed result were still found to be statistically significant, but removal of the placebo group eliminated all statistical significance. This indicated that there was no obvious dose response amongst the different drug dosages. The Sponsors determination of a positive slope was solely dependent on the single placebo response. This is unexpected. This reviwer feels that this observation undermines the conclusion of effectiveness based upon slope analysis and suggests that replication at these lower doses would be needed to confirm such an observation.

The Sponsor depended on secondary endpoints for determining which doses differed form placebo [redacted] In the original submission they used the secondary endpoint analysis of Wilcoxin rank-sum the Sponsor and noted that all values are statistically significantly different from placebo except 200 mg/day. Dr Siduque notes that when corrected for multiplicity, using either using the Hochberg's or the Bonferroni method, only the 800 mg dose is significant. This reviewer would add, that had a typical sequential analysis been performed (high to low dose) significance would have been concluded. Another secondary endpoint, a Poisson analysis, while included in the original protocol was not included in the final study report. This was requested. The Sponsor apologized for this exclusion and included it in the present submission. A statically significant dose response was noted with all but the 200 mg dose differing form placebo. Dr Siduque notes that the sponsor included log-transformed baseline seizure count as a covariate in the Poisson model, but since the seizure frequency data of post-baseline was modeled as count data, it was more meaningful to include the baseline seizure frequency data as a covariate without any transformation. When he performed a reanalysis, with the baseline seizure frequency data as a covariate the model without any transformation, he found that none of the doses were statistically significantly (p-values $\geq$0.245) different from placebo.

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While some small effect is suggested by these data this reviewer does not feel adequately assured that such an effect is clinically significant for the following reasons:

- No actual dose response is obvious when placebo is not included in the regression analysis.
- Sensitivity analysis using different means of correcting for multiple comparisons gives different results.
- The use of another secondary endpoint when analyzed using the correct covariate

failed to demonstrate a statistically significant effect.

- The effect observed in this study is rather small compared to those observed with other drugs.
- There is no replication at these low doses.
- Treatment response at these low doses are small as compared to other anticonvulsants.

Pharmacometric Analysis

Of interest the Sponsor and FDA pharmacometric group performed an analysis across the 2 adult pivotal partial epilepsy trials. This analysis demonstrated a concentration response relation, which did not appear to plateau. This analysis suggests efficacy, but is unable to assist in the determination of a recommended dose. The fact that the concentration response curve fails to plateau suggests to this reviewer that the full range of the therapeutic curve has not been explored. This is consistent with the small magnitude of effect observed in these studies. Efficacy is generally limited in anticonvulsant treatment by drug tolerability. Dropouts due to adverse events at the highest dose studied were moderate, but it should be noted that titration rate in study 21A was over one week and no titration was used in the lower dose study. Titration for this class of agent is usually performed over a period of at least 2 weeks, to mitigate drug intolerance and to reduce dropouts. The titration rate may have been too rapid for this exploration.

The Sponsor performed a pharmacomeatric analysis from data in the pediatric (21P), which suggested a slope, but one that was markedly less than that observed in the "adolescent/adult."

In general this reviewer believes that such pharmacometric analysis can be used only as supportive data, once a conclusion is reached with more rigorous statistical testing that are protocol driven and corrects for covariates. Also, the Sponsor's analysis appears to use "total seizure frequency" and not change in seizure frequency. The latter would be a more appropriate measure. Moreover, while a pharmacometric analysis can provide data to "suggest" an effect, it cannot provide us with accurate dosing information.

In conclusion, such an analysis does not lead to a better understanding as to why the pediatric study was negative and provide no information as to what would constitutes appropriate dosing recommendation in a label .

Cumulative Distribution. Functions plots

In the Sponsors response to approval, they have provided Cumulative Distribution. Functions (CDF) plots. This information does not provide any additional information that could not be gleaned from the statistical analysis described above.

Inconsistent Results in Supportive Studies

The Sponsor argues that in the past the division has made decisions which resulted Iin approval of other drugs with inconsistent results. Examples included Topamax for LGS, Neurontin in partial seizures, Gabatril in partial seizures, and Depakote . The argument s made by the Sponsor is not rigorous. For example there is no discussion of the power of studies. Moreover two of the studies cited, were labeling supplements that were already marketed (Topamax and Depakote). In no case does the Sponsor note that any single large study trended in the wrong direction, as does 21P in the present application.

Conclusions

In conclusion, [redacted] b(4)

The single dose ranging study is the only study that provides data on low doses that the Sponsor intends to label. The interpretation of this study is complicated by a number of factors including (see above). This reviwer believes it can be considered a public health problem if an incorrectly low dose is recommended. This is particularly the case considering the fact that the only way to determine whether a patent is receiving an optimal dose is to wait and watch. Such a strategy can lead to additional risk to the patient, if the division recommends an initial dose that may be to low. Moreover, as there seems to be little differnce between all doses in this study, and only a small differnce with study 21A (see below), it would be inappropriate to recommend high doses when a low dose may suffice and result in fewer adverse events.

Study 21A suggests an effect at doses of 3200 mg/day, albeit the effect can not be considered robust in magnitude and is only slightly greater than that observed with 1600 mg/day dose in study AE/ET1. As previously noted in the initial review, it is worrisome that the pediatric study, 21P (a study that was once combined with 21A as a single protocol), indicated no trend in children at similar exposures. Moreover, although a trend was observed in a monotherapy trial presumably with adequate power, no statistical differnce was observed.

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As noted in this medical officer's prior review, study 22 which examined seizures associated with Lennox Gastaut were positive, exhibiting a robust effect. Thus, two alternative primary endpoints were used with one consisting of a dual co-primary endpoint. Not only did the study win on one of the alternative endpoints, but it won on all endpoints. Because the analysis was corrected for multiple comparison, the required p value (0.025) was far more stringent than most studies. Moreover, supporting the robustness of an effect, there was a trend toward a therapeutic effect in many seizure subtypes, with statistical significance in some. In this medical officer's previous review, it was recommended that the Sponsor provide the division with a second Lennox Gastaut study or adequate data for approval for partial seizures. This was not provided. An argument may be made for approval based on the fact that: 1) such studies may be difficult to perform as this is an orphan indication, 2) the effect observed is a robust effect and, 3) the disorder is rather serious. Mitigating this is the fact that there are a number of medications that are labeled for the treatment of seizures associated with Lennox Gastaut (i.e. Felbatol, Topamax, Lamictal and Klonopin). Moreover, there is an absence of dose ranging data. This reviwer would recommend approval, but acknowledges that this is a "close call" and that a more traditional proof of efficacy (with dose ranging informtion if possible) would have been helpful. It should be noted that many of the alternative medications used for the treatment of seizures associated Lennox Gastruat are not without problems. Rufinamide is presently approved in Europe, but only for Lennox Gastaut.

Examination of baselines revealed some disparity with a median frequency of total seizure frequency of 290/28 days in the rufinamide and a frequency of 205/28 days for placebo. This disparity may bias toward not finding an effect, with the more severe cases existing in the drug treated group. It however raises the issue as to whether there was a randomization bias. The Sponsor was asked to examine this, Three patients were observed with such and error, these cases were not believed capable of influencing the results. Moreover, to support the lack of a randomization error, demographic features of both populations where observed to be relatively similar between both treatment groups.

Clinical Review for Safety

Interim analysis

Interim analysis since the prior review revealed 15 new serious cases from a total of 223 unique patients. Most were a result of seizure related events (e.g., seizure flurry, increase seizure etc). However, there was one case leucopenia. Leucopenia will be included in the label (see below). Accordingly, Dr Dinsmore notes that values are not provided, but according to him, patient was continued on drug. There did not appear to be any new deaths.

Examination of interim reporting on adverse events and common adverse events did not lead to a change from previous reviews in potential risks.

Reanalysis of prior data

A number of issues were identified in the initial Medical Officer review (Dr. Ramon) for which he thought may be significant signals. Although these were not noted in the letter to the Sponsor Dr Dinsmore and I reexamined some of these data. What follows is a brief review of such issues.

Hyponatremia

Review of 4 serious cases of hyponatremia was noted revealed that all had confounding factors. All cases had concomitant treatment with drugs known to case hyponatremia. One case was noted to resolve with continued treatment. Central analysis and shift analysis also failed to indicate any significant differences between placebo and drug treatment groups in the control database. No recomendations are made with regard these findings.

Hyperthermia

Two serious cases of hypothermia were identified by Dr Ramon. Dr Ramon suggested these may represent cases of malignant hyperthermia. One case was noted in a 4 year old who presented with a fever of 107 F during an episode of pneumonia, followed 10 weeks later by another high fever (no value given) with agitation which completely resolved and was thought to be neurogenic. Drug was continued, despite no further reports of hyperthermia. The second case was a 26 years old who was admitted with a rather complex medical presentation including an initial presentation of flurries of seizures and the discovery of hemorrhagic pancreatitis and peritonitis. The patient was noted to have tachycardia, tachypnea and a temperature of 107 with a decrease level of consciousness. The patient had a lumbar puncture performed and soon died of herniation. This patient had a prior history intracranial hypertension. Dr. Dinsmore notes that both cases were not typical for malignant hypertension. Of note, this CDTL would mention there was no mention of rigidity. Dr. Dinsmore also adds that the first case is unusual in that two episodes where observed weeks apart and that and the second case had other potentials causes of hypothermia and pathological processes which may explain the presentation (peritonitis and elevated intracranial pressure with imminent herniation). No action is thought to be necessary at this point.

Status epilepticus

The prior review notes a number of cases of status epilepticus in drug group but none in the placebo group in the Lennox Gastaut controlled trial. Becasue of this, it is recommended that status epilepticus be noted in the Precautions section. This is similar to prior recommendations.

Multi-organ Hypersensitivity Reactions

The previous review noted one patient experienced rash, urticaria, facial edema, fever, eosinophilia, stuperous state, and severe hepatitis, beginning day 29 of rufinamide of therapy with resolution 11 days after discontinuation. Additional possible cases that presented with rash and in addition to other symptonms (e.g. fever, elevated liver function studies, hematuria, and/or lymphadenopathy) were observed. Because of this multi-organ hypersenitivity will be noted in the precautions section.

Analysis of Additional requested Informtion fro the approvable letter

Thyroid Function

Thyroid function abnormalities were monitored in the developmental program becasue of an animal signal indicating an increase risk of thyroid adenomas. Because of inadequacies of presentation of thyroid function abnormalities the Sponsor was requested, in the approvable letter to provide:

> "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."

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 an abnormal baseline in one.

The thyroid data was confounded by the mixing of units (standard and international) in evaluations of central analysis, shift tables and outlier. This was discussed with the Sponsor who noted some of the data could not be corrected because it was derived from studies which were many years old. This reviewer requested that the Sponsor provide tables for only newer studies were the proper analysis of units can be assured. This constituted a majority of the data. Analysis of these tables did not indicate a thyroid function signal.

Hematology

Dr Ramon identified 9 potential cases with a hematological abnormalities for which narratives were provided. On reexamination Dr Dinsmore notes that only 2 can be considered a potential signal. One case involved a WBC shift from 4.6×10^9 to 2.7×10^9 55 days after treatment and a return to 6.5×10^9. The other was an even more modest change from 5.7×10^9 at baseline to 3.5×10^9 on day 28 after treatment was initiated. No mention of a dechallenge was made. These cahnges are minor. There were 121 clinically notable labs on termination for which follow up was requested. Only 3 follow-ups were available and therefore provided. One was for reduced hemoglobin, one for

reduced platelets and one for reduced WBCs. All three returned to normal with drug discontinuation. Examining clinically notable tables in placebo control studies for WBCs revealed 3.7% patients on rufinamide and 1.2% patients on placebo exhibited potentially significant clinical reductions in WBC (3.0 X 10^9/L). Shift tables for reductions and central tendencies were unremarkable. Examination of outlier, shift and central tendency tables for hemoglobin and hematocrit was unremarkable. There was a very slight disparity of outliers for reduction in platelets with 1.9% in drug and 1.2% for placebo. From this Dr. Dinsmore noted that potential for "leucopenia" should be noted in the adverse events section. This reviewer agrees.

Hepatobiliary Abnormalities

The prior approvable letter requested clarifiaction, in the form of narratives, for 24 patients with identified abnormalities in LFTs at last visit. Complete follow up was not available nor received from all patients. Upon examination of the available data Dr Dinsome described 4 cases. Two cases had elevation of LFTs, on drug which was >3.5 times the upper limit of normal, but which returned to normal on dechalange. One of these cases was associated with elevated billirbubin just less then 2X normal but appeared to be complicated by a number of medical issues. Thus this event appeared to follow a serious seizure and muscle entrapment syndrome that likely confounded a determination of causality. Another case described bilirubin elevation by greater than 10 fold but without other liver function abnormalities. Because of he unusual nature of this case the Sponsor was asked to provide additional informtion at a teleconference. The result was found to be an error of transcription and no elvetion of bilirubin was experienced. The last case, exhibited a increase transaminase associated with increases in alkaline phosphatase and bilirubin. It was concluded that this represents multiorgan sensitivity, which will be labeled in the Precautions section. Dr Dinsmore concludes "*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.*" Shift tables, central tendency tables and outlier tables did not indicate any differences in transaminase levels. In conclusion, no signal is appreciated except that associated with hypersensitivity, which will be labeled.

Follow Up on Clinically Notable Laboratories

The prior approvable letter requested follow up on a number of other clinically notable values for Hypoglycemia, Hyperglycemia, Hyperuricemia, Hyponatremia, Hypercalcemia , Increased bicarbonate , Hypercholesterolemia. The Sponsor could only locate follow up on 2 of 62 requested. Both provided follow-ups (hyperuricemia and hypercholesterolemia) abnormalities resolved spontaneously. Dr. Dinsmore examined all the remaining cases of lab abnormalities, which included cases of Hypoglycemia, Hyperglycemia, Hyperuricemia, Hyponatremia, Hypercalcemia , Increased bicarbonate , Hypercholesterolemia, and found no reason to believe these represented a signal. These values were all last value examined after patients was on the medication for a long period of time. They were not reasons for discontinuation and changes tended to be mild in

magnitude and therefore may have been spurious. Some were noted to occur well after treatment was discontinued, appeared to be lab errors, or there were other alternative causes.

QT interval changes

Initial review of the thorough QT study indicated no QT lengthening, but a QT interval shortening. Thus, at the dose of 2400 mg QTcF was shortening ranged from -9.6 msec to -16.7. Most studies concentrate on QT prolongation becasue of the risk of the fatal Torsades arrhythmia. But, there remains a theoretical risk that shortened QT may lead to ventricular arrhythmias. These data are principally derived form the familial short QT syndrome, for which there exists a high risk for ventricular arrhythmias and sudden death. There is no direct data regarding pharmacological shortening, but it remains a theoretical possibility that such shorting may lead to similar arrhythmias. Becasue the original study was designed to examine QT prolongation, there was no analysis by the Sponsor of shorting.

The Sponsor was requested to provide such informtion. Thus, when examined approximately 46 % of patients showed >200 msec of shorting at the 2400 mg dose whereas 65% showed similar shorting at the dose of 4800 mg (all in QTcF). No patients, however, showed an absolute QTcF of less then 300 msec. There is no algorithm to indicate the risk significance of this. Dr Jones, safety reviewer suggests that in the familial syndrome that absolute QTc values of 280 to 300 msec may be associated with increased sudden death and it is reassuring that no such shorting was observed in the formal QT study. Other, less definitive studies suggested higher cut offs (i.e. >300 msec absolute QT interval). Examination of adverse events associated with rufinamide failed to identify an obvious signal that suggested that QT shorting was contributing to mortality or morbidity. This reviewer concludes that the QT shorting remains a theoretical problem which should be described n the Precautions or Warnings sections and the drug should be contraindicated in patient with underlying familial short QT syndrome. Dr Jones, the safety reviewer, concurs.

Because of this issue Dr. Jones, safety reviewer, has recommended a phase 4 commitment (see below).

Clinical Pharmacology

No issues were identified except for a phase 4 commitment, which is requested (see below).

Chemistry

No issues were identified.

Phram/Tox

No issues were identified except for a phase 4 commitment, which is requested (see below).

Recommended Action

- Complete Response in Partial onset seizures.
- Approval for seizures associated with Lennox Gastaut (see CDTL review).

Phase 4 Commitments

1. Conduct additional analyses to further examine the effect of Banzel (rufinamide) on the QT interval, specifically studying its effect in patients receiving concomitant medications that may also shorten the QT interval. For clinical trials AE/ET1 and CRUF331-0022 (and any other trials in which patients were treated with medications other than rufinamide and in which QT data was collected), please provide the following:
    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 (listed below) 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 and in patients without such concomitant medications.

    Conduct the same analysis for sodium channel blocking drugs.

2. Conduct an *in vitro* metabolism study to characterize the potential serious safety risk of the inhibitory effect of Banzel (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.

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/s/

Norman Hershkowitz
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