CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201367
Priority or Standard	Priority
Submit Date(s)	8/12/14
Received Date(s)	8/12/14
PDUFA Goal Date	2/12/15
Division / Office	DNP
Reviewer Name(s)	Steven T Dinsmore, DO
Review Completion Date	January 18, 2015
Established Name	Rufinamide
(Proposed) Trade Name	BANZEL™
Therapeutic Class	Antiepilepsy drug
Applicant	EISAI
Formulation(s)	Suspension
Dosing Regimen	Twice Daily
Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS)
Intended Population(s)	children 1 year of age and older and adults

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

As provided in 21CFR314.55(a) the division concluded that the course of LGS and treatment with rufinamide are sufficiently similar in the ≥4 year old pediatric age group to the < 4 year old pediatric patients that a controlled trail to establish effectiveness in the age range ≥1 year to <4 year age range was not necessary. The effectiveness demonstrated in the original trial in the older pediatric population 4 to 12 years old can be extrapolated to the younger patients because LGS is physiologically similar in the younger group.

A pediatric written request (PWR) was fashioned to obtain pharmacokinetic and safety data in the range ≥1 year to <4 year population. The PWR may be seen in 10.0 Written Request, revised 2/26/14, Key Elements. The primary mission of the PWR is shown in the following bullet points:

- To evaluate the overall safety and tolerability of rufinamide in the target population
- to evaluate the age group specific pharmacokinetics of rufinamide
- to establish a tolerable dosage regimen that will produce plasma levels in this population similar to that in the population in whom rufinamide is currently recommended.

Review of safety and tolerability data presented in this NDA supplement supports the approval of BANZEL for treatment of LGS in the population band from age ≥1 to <4 years old.

1.2 Risk Benefit Assessment

This clinical review examined the adverse event profile of the 25 patients, age >1 year to < 4 years of age who received rufinamide in the safety population of study E2080-G000-303 (henceforth “303”). Clinical review of the application does not reveal evidence of a new safety signal or worsening of known safety issues from the prior (b) (4) development program.

Established safety concerns in current BANZEL labeling, section 5 include central nervous system reactions; somnolence and fatigue and coordination abnormalities. Also

in section 5 are QT shortening, status epileptics, multi-organ hypersensitivity reactions and leukopenia. Additional focus was directed at these issues in the review of this application. One patient had an episode of status epilepticus but was discharged after one hospital day (an SAE), no patient had an AE entry from the “Blood and Lymphatic disorders” SOC, there was no exacerbation of the signal for CNS reactions, one patient had an SAE of rash but continued on rufinamide with resolution of the finding, there were no adverse events in the “Cardiac disorders” SOC. An extensive analysis of the QT characteristics of study 303 ECGs was performed and the QTcF reductions from baseline were less prominent than seen in the BANZEL development TQT study (E2080-A001-002). The frequency of patients with QTcF values below defined thresholds of <400, <390, <350 and <300 were greater than the frequency seen in the TQT study; however, this observation was found to be commensurate with the high proportion of study 303 patients with low baseline QTcF values, see QT analysis. Overall there was no evidence of a worsening of established BANZEL safety signals in the younger pediatric population.

The pediatric written request identified pancreatitis as an issue for monitoring. There were no instances of a pancreatitis adverse event or abdominal pain.

Examination for new or novel safety signals in the >1 to <4 year old population was also a focus of the review. A focused seizure frequency analysis performed on the seizure frequency (ADSZF.xpt) dataset did not reveal evidence of seizure worsening in the rufinamide treated patients, see Seizure Worsening. A mean decline in bicarbonate in rufinamide treated patients was observed in the review as well as a high proportion of low bicarbonate outliers. There were an underlying high proportion of patients with baseline low bicarbonate as well as confounding by concomitant topiramate treatment which resulted in a sum of evidence with no support for a low bicarbonate safety signal, see, Bicarbonate (mmol/L). Weight analysis was also an area of special interest because of the know signal for nausea, vomiting and loss of appetite in BANZEL treatment seen in clinical trials, (current BANZEL label, section 6.1). A meticulous examination of the weight data from study 303 with comparison to the prior LGS study in patients ≥4 years of age revealed a small group mean percentile weight loss at weeks 4, 16 and 40 and a single outlier patient with persistent weight loss. This patient had weight loss preceded by vomiting at week 8, with additional persistent weight loss at week 40, and 56 before improvement was noted, see Figure 10. The overall evidence does not indicate a worsening vulnerability to weight loss compared to the population ≥ 4 years of age although continued pharmacovigilance of this issue should be maintained. The entry for weigh loss in proposed labeling section 6.1 “weight decreased 8%” as well as “decreased appetite 12%” should be retained. Together, these entries are adequate strength in labeling for the observations of weight loss identified in the Weight Analysis of this review.

In summary, there are no safety signals identified that are of sufficient magnitude to alter the established risk benefit assessment of BANZEL.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

none

1.4 Recommendations for Postmarket Requirements and Commitments

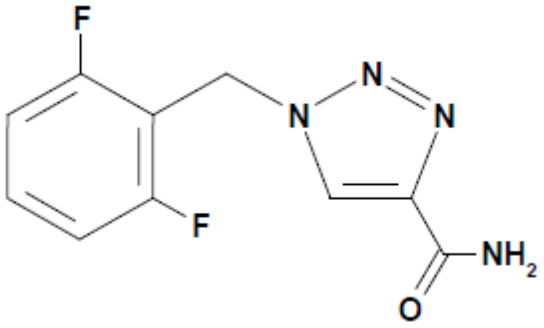
none

2 Introduction and Regulatory Background

2.1 Product Information

BANZEL (rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1H1,2,3-triazole-4 carboxamide. It has an empirical formula of C10H8F2N4O and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile.

Figure 1 Chemical Structure of BANZEL (rufinamide)



Rufinamide tablets (100, 200, and 400 mg) were approved under New Drug Application (NDA) 021911 on 14 Nov 2008 for adjunctive therapy of seizures associated with LGS in children 4 years and older and adults. Rufinamide, oral suspension (40 mg/mL), was approved under NDA 201367 on 03 Mar 2011 for the same indication.

The effectiveness of rufinamide as adjunctive treatment for the seizures associated with LGS was established in a single, pivotal, multicenter, double-blind, placebo-controlled, randomized, parallel-group study (study 022). Male and female patients (n=138, between 4 and 30 years of age) were included if they had a diagnosis of inadequately

controlled seizures associated with LGS (including both atypical absence seizures and drop attacks) and were being treated with 1 to 3 fixed-dose concomitant AEDs.

BANZEL is available for oral administration in film-coated tablets, scored on both sides, containing 200 and 400 mg of rufinamide. BANZEL is also available for oral administration as a liquid containing rufinamide at a concentration of 40 mg/mL.

2.2 Tables of Currently Available Treatments for Proposed Indications

Drug	Basis for use
Felbatol (felbamate)	Approved Labeling: as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.
Depakote (divalproex sodium) Depakene (valproic acid)	Clinical Experience and conventional medical accepted practice
Lamictal (lamotrigine)	Approved labeling: generalized seizures of Lennox-Gastaut syndrome
Onfi (clobazam)	Approved Labeling: adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older
Topamax (topiramate)	Approved Labeling: in patients age with seizures associated with Lennox-Gastaut syndrome (LGS)

2.3 Availability of Proposed Active Ingredient in the United States

Rufinamide, was approved as BANZEL on November 14th, 2008.

2.4 Important Safety Issues with Consideration to Related Drugs

Rufinamide is not structurally related to any other antiepilepsy drug although it does modulate the action of sodium channels as do several other antiepilepsy drugs. In general, other anticonvulsant agents as an overarching class have central nervous system adverse effects due to sodium channel action. Several have significant risk of severe hypersensitivity response. Hepatobiliary adverse effects are also seen as an important issue in some antiepilepsy drugs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

BANZEL® (rufinamide) tablets (100, 200, and 400 mg) were approved under New Drug

Application (NDA) 021911 on 14 Nov 2008 for adjunctive therapy of seizures associated with LGS in children 4 years and older and adults. Rufinamide, oral suspension (40 mg/mL), was approved under NDA 201367 on 03 Mar 2011 for the same indication.

The effectiveness of rufinamide as adjunctive treatment for the seizures associated with LGS was established for initial market approval by study CRUF331 0022 (Study 022), a single, pivotal, multicenter, double-blind, placebo-controlled, randomized, parallel-group study. Male and female patients (n=138, between 4 and 30 years of age) were included if they had a diagnosis of inadequately controlled seizures associated with LGS (including both atypical absence seizures and drop attacks) and were being treated with 1 to 3 concomitant AEDs.

On 05 Aug 2011, FDA issued a Pediatric Written Request (WR) to NDA 021911 (Amendment 1 issued 26 Feb 2014) requesting a pharmacokinetic (PK) and safety trial to support approval of rufinamide in children ages ≥1 to <4 years. An additional trial to establish effectiveness of rufinamide in this age group was not deemed necessary, as the effectiveness demonstrated in the original trial (Study 022) in the older pediatric population can be extrapolated to the younger patients because this disorder is physiologically similar in the younger group. Study E2080-G000-303 (Study 303) “A Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to less than 4 years of age with Inadequately Controlled Lennox-Gastaut Syndrome” is being conducted to fulfill the WR as well as a Paediatric Investigational Plan (PIP) requirement from the European Medicines Agency (EMA) to evaluate the long-term effect of rufinamide on cognitive development. Study 303 remains ongoing to fulfill the long-term efficacy objectives required in the PIP. An interim full clinical study report (CSR) of Study 303 has been prepared and is the basis of this supplemental NDA (sNDA).

Key Elements of Written Request: see Appendix 10.0 Written Request, revised 2/26/14, Key Elements

2.6 Other Relevant Background Information

none

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Not all laboratory reference values of potential clinical concern could be unambiguously identified from the CTCAE criteria. Urinalysis samples variables without explanation were present.

3.2 Compliance with Good Clinical Practices

The sponsor attests the following on page 1 of the E2080-G000-303 study report: “This study was performed in full compliance with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation is archived as required by regulatory authorities”

3.3 Financial Disclosures

The PK and safety study E2080-G000-303 is not a “covered study” based on 21 CFR §. 54.2(e). However; the sponsor provides form 3453 with signed attestation that all listed clinical investigators had no disclosable financial interests. No investigators were identified as having financial interests and no investigators are reports as “unable to contact”

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No DARRTS entry at time of Review completion

4.2 Clinical Microbiology

none

4.3 Preclinical Pharmacology/Toxicology

There are no new studies to support this submission

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As noted in currently approved labeling:

"The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. The results of in vitro studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide (≥ 1 μM) significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive firing of sodium-dependent action potentials (EC50 of 3.8 μM)."

4.4.2 Pharmacodynamics

An exposure response analysis of was not performed on the PK data of this package on the following basis:

- Comparable exposures to patients 4+ years
- Sample size is small (n=25 on RUF)
- Efficacy: Study was not designed to assess efficacy
- Safety: TEAE rate was comparable in rufinamide and control arm

4.4.3 Pharmacokinetics

Clinical pharmacology review of the current NDA supplement has revealed that rufinamide exposures in the 1 to 4 year age group are comparable to exposures achieved in patients greater than 4 years of age identified in the initial BANZEL approval.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

E2080-G000-303

Type of Study	Study Identifier	objective	Study Design and type of control	Test Product, Dose Regimen and Route	Number of Subjects	Healthy Subjects or Diagnosis	Duration	Study status
Phase 3 Safety	E2080-G000-303	A Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to Less than 4 Years of Age with Inadequately Controlled Lennox-Gastaut Syndrome	Randomized, Controlled, Open-label, Multicenter Control: Any other AED added as adjunctive therap	Test Product: Rufinamide 40 mg/mL Dosing Regimen: starting dose as 10 mg/kg/day and increased every 3 days to 40 mg/kg/day then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. Dose administered in 2 equally divided doses per day. Route of Administration: Oral	Randomized: 37 (n=25 on rufinamide; n=12 on any other AED).	LGS	2 years	Ongoing, Interim full study report

5.2 Review Strategy

The review strategy is directed at safety only. Efficacy is demonstrated by extrapolation from the 4 to 12 year old population.

As noted in section 5.3 this NDA labeling supplement contains a single study, E2080-G000-303, of 25 rufinamide treated patients aged 1 to <4 years to provide safety and Pk information in this population. The safety data from this study will be reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

Study E2080-G000-303 (303) is the study designed to fulfill the BANZEL pediatric written request. An additional study E2007-J081-304, a controlled study using BANZEL for the treatment of LGS in Japan was identified at the Pre-NDA meeting of June 24, 2014. This study was performed to support approval in Japan and enrolled only Japanese patients. There were 58 patients enrolled with 28 in the rufinamide arm. A brief descriptive presentation, discussion, and analysis of the safety findings of study 304 was requested for inclusion into the summary of clinical safety, as well as submissions of narratives of patients that died, had an SAE, or had an AE leading to study withdrawal.

Study 303

Study 303 is being conducted to fulfill the FDA written request (WR) as well as a PIP requirement from the EMA to evaluate the long-term effect of rufinamide on cognitive development. The outcome elements for the EMA component of the study are the Childhood Behavioral Checklist (CBCL), Language Development Survey (LDS) score and the Quality of Life in Childhood Epilepsy (QoLCE) total and subscores. The duration of the study for examination of the cognitive outcomes is two years and the study is ongoing

Sponsor Background Statement:

This study (E2080-G000-303) was conducted to fulfill the United States Food and Drug Administration (FDA) Written Request (WR) and the European Medicines Agency (EMA) Paediatric Investigation Plan (PIP). FDA requested a 6-month study to evaluate pharmacokinetic (PK) and safety objectives in this age population, while the EMA requested a 2-year study for the primary evaluation of cognitive development and behavioral effects in a pediatric population 1 to less than 4 years of age. This study remains ongoing to fulfill long-term efficacy objectives required in the PIP; this interim CSR has been prepared to evaluate the PK, safety, and tolerability objectives of the FDA WR, using a data cutoff date of 28 Feb 2014.

The objectives listed below are those presented in the study protocol and will be fully evaluated at the end of the 2-year duration of the study. An additional objective, added as per the FDA WR, was to establish a tolerable dosage regimen that would produce plasma levels in this population similar to that in the population in whom rufinamide is currently recommended. Details of the analysis and results based on this objective are provided in a separate population PK report.

Title of Study: A Multicenter, Multinational, Randomized, Controlled, Open-label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of

Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to less than 4 years of age with Inadequately Controlled Lennox-Gastaut Syndrome

Study Period: 16 Jun 2011 to 28 Feb 2014 (interim clinical study report [CSR] database cutoff date)

Study Centers: There were 20 study sites from among 6 countries. There were 43 patients screened and 37 patients enrolled at the time of the application submission. The number of patient and proportions may be seen in Table 1. Forty three (43%) percent of patients were from US sites, Table 1.

Table 1 Study 303 Patient Enrollment by Country

COUNTRY	Number of patients	% of Patients
CAN	1	3
FRA	1	3
GRC	4	11
ITA	6	16
POL	9	24
USA	16	43

Primary Objectives:

• To compare the effect of 2 drug regimens (EMA consideration) consisting of either rufinamide or any other approved AED of the investigator's choice as an add-on to the subject's existing regimen of 1-3 AEDs on the overall safety and tolerability of rufinamide in subjects aged 1 to less than 4 years of age with inadequately controlled LGS.

Note- the written request states: An open-label design, multicenter study to evaluate the safety and pharmacokinetics of adjunctive rufinamide treatment over a six-month period in pediatric patients >1 to <4 years of age with inadequately controlled Lennox-Gastaut syndrome (LGS). This study may have multiple arms, but this written request is directed toward the safety data in patients in the rufinamide treated group.

• To characterize the age group specific pharmacokinetics of rufinamide in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS, using the population approach.

• (EMA) To evaluate the effect of rufinamide as adjunctive treatment on the cognitive development and behavioral effects in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS.

Study Design:

This study is a 2-year evaluation of the safety, pharmacokinetics and cognitive/behavioral effects of rufinamide as add-on treatment for control of seizures associated with LGS in subjects 1 to less than 4 years of age. The study will consist of 2 phases: a Pre-randomization Phase and a Randomization Phase.

Pre-randomization Phase

Screening Period: During this period subjects will be screened to verify that study requirements are met. Subjects will be on a fixed dose of 1-3 concomitant AEDs for a minimum of 4 weeks; diaries to confirm consistent seizures and recording of AED treatment will be maintained.

Baseline: This visit will be done within 8 weeks from the Screening visit. Adherence to study requirements will be confirmed and seizure diary will be collected to assess baseline seizure frequency.

Randomization Phase

Titration Period: Subjects will be randomized to receive rufinamide or any other approved add-on AED of the investigator's choice in a 2:1 ratio, added to their existing regimen of 1-3 AEDs. Rufinamide will be administered at 10 mg/kg/day (with all daily treatments administered in 2 divided doses) and increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, rufinamide will be allowed to be titrated more slowly or titrated to a lower dose at the investigator's discretion. The approved add-on AED of the investigator's choice will be administered according to the investigator's usual practice.

Maintenance Period: The dose reached at the end of the Titration Period will be the starting dose of the Maintenance Period. Subsequently, the dose can be adjusted according to the investigator's discretion. All subjects will be observed for worsening of seizures (increase in seizure frequency overall or increase in frequency of major seizures or occurrence of new seizure type) and treatment will be adjusted or withdrawn as clinically appropriate. Subjects who withdraw from treatment will continue to be followed for safety and cognitive evaluations to the end of the core study (end of Maintenance Period). At the end of the 2 year Maintenance Period, study treatment (rufinamide or add-on AED) will no longer be supplied or reimbursed by the Sponsor except for those subjects that require taper. The subject should be transitioned to other standard of care treatment according to the investigator's usual practice.

Taper Period: Study treatments will be discontinued as recommended for rufinamide or according to the investigator's usual practice for add-on AED.

Number of Subjects:
Planned: 75 subjects (50 subjects rufinamide, 25 subjects any-other-AED). As per the amended FDA WR (dated 26 Feb 2014), the planned number of subjects was revised to allow a minimum of 21 rufinamide-treated subjects.
Enrolled: 43 subjects
Randomized: 37 subjects (25 subjects rufinamide, 12 subjects any-other-AED).
Treated: 36 subjects (25 subjects rufinamide, 11 subjects any-other-AED).

Diagnosis and Main Criteria for Inclusion

• Age 1 to less than 4 years
• Clinical diagnosis of LGS at screening, which might have included the presence of a slow background electroencephalogram rhythm, slow spikes-waves pattern (less than 3 Hz), the presence of polyspikes; care should have been taken not to include benign myoclonic epilepsy of infancy, subjects with a diagnosis of atypical benign partial epilepsy (pseudo-Lennox syndrome), or continuous spike-waves of slow sleep
• On a fixed and documented dose of 1 to 3 concomitant regionally approved AEDs for a minimum of 4 weeks prior to randomization with an inadequate response to treatment
• Consistent seizure documentation (ie, no uncertainty of the presence of seizures) during the Prerandomization Phase

Exclusion Criteria:

• Familial short QT syndrome
• Prior treatment with rufinamide within 30 days of Baseline Visit or discontinuation of rufinamide treatment due to safety issues related to rufinamide

Test Treatment, Dose, Mode of Administration

Rufinamide up to 45 mg/kg/day, in 2 divided doses, administered as oral suspension (40 mg/mL)

Figure 2 Study Diagram (303)

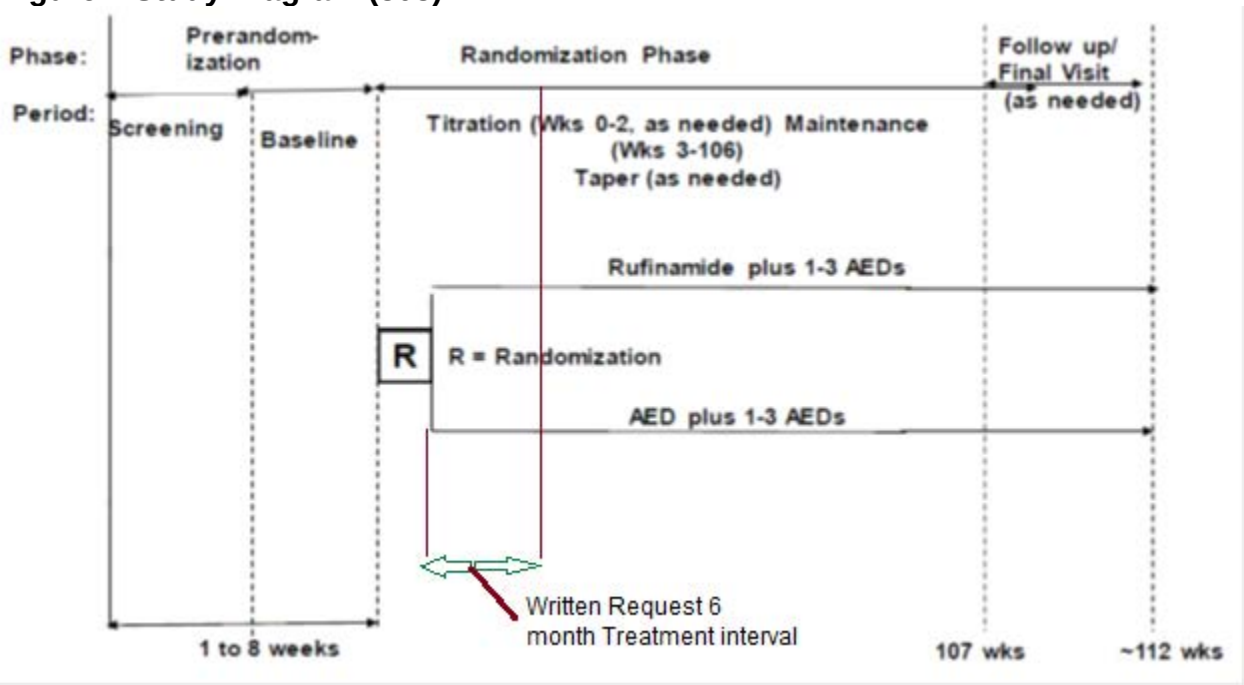


Table 2 Schedule of Key Procedures and Assessments (303)

Phase	Prerandomization		Randomization Phase														
Period	Screening	Baseline	Titration	Maintenance										Taper	Follow-up /Final Visit	Un-scheduled Visit	Early Dis-continuation Visit
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13				
Week	-8 to -1	0	1	2	4	8	16	24	40	56	72	88	106				
ECG	X	X			X	X	X										
Lab tests	X	X		X	X	X	X	X					X		X		x

6 Review of Efficacy

Efficacy Summary

The effectiveness demonstrated in the original trial in the older pediatric population 4 to 12 years old can be extrapolated to the younger patients because LGS is physiologically similar in the younger group. In addition, as stated in the pediatric written request, the clinical pharmacology review of the application has revealed that rufinamide exposures in the 1 to 4 year age group are comparable to exposures

achieved in patients greater than 4 years of age identified in the initial BANZEL approval.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study E2080-G000-303 is the only source of data in the application to directly evaluate safety in the population of interest for the proposed labeling change.

There is a source of new pediatric data available from a study conducted for registry of rufinamide in Japan. There were 16 rufinamide treated patients in the age range ≥4 years to <17 years old with 19 placebo treated patients. At the pre-NDA meeting of June 24, 2014 the division requested a brief descriptive presentation, discussion, and analysis of the safety findings of study 304 as well as submissions of narratives of patients that died, had an SAE, or had an AE leading to study withdrawal. Discussions of exposure and demographics and direct examination of datasets will only be provided for study 303, the written request based study.

7.1.2 Categorization of Adverse Events

Adverse events are coded using MedDRA ver 17.0. There were 234 TEAE recorded in the study from 22 rufinamide treated patients and 11 patients treated with “any other AED”.

Events of interest due to potential for morbidity with rufinamide treatment include nausea, vomiting, loss of appetite, upper respiratory infections. Verbatim terms are examined to identify related events and determine if there is appropriate and consistent coding of these events to preferred terms. There is no evidence of inappropriate lumping or splitting of physiologically related adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There is a single study of the population relevant to the proposed change in labeling.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 25 subjects were exposed to rufinamide in the determined therapeutic range (10 to 40 mg/kg/day) and 11 subjects were exposed to any other add-on AED. As of the data cutoff date, 21 (84%) subjects randomized to rufinamide had at least 16 weeks of exposure in the study, 18 (72%) subjects had at least 24 weeks of exposure, and 12 (48%) subjects reached over 1 year of exposure, see Table 3.

The median average daily dose of rufinamide was 328.6 mg during the Titration Period, 511.3 mg during the Maintenance Period, and 240.4 mg during the Taper Period During the Maintenance Period, the majority of subjects (75%) received rufinamide at a dose of greater than or equal to 40 mg/kg/day.

Table 3 Rufinamide vs comparator "any other AED"

Extent of Exposure	Rufinamide (N=25) n (%)	Any-Other-AED (N=11) n (%)
Any exposure	25 (100.0)	11 (100.0)
>1 day	25 (100.0)	11 (100.0)
>1 week	25 (100.0)	11 (100.0)
>2 weeks	25 (100.0)	11 (100.0)
>4 weeks	24 (96.0)	10 (90.9)
>8 weeks	22 (88.0)	9 (81.8)
>16 weeks	21 (84.0)	9 (81.8)
>24 weeks	18 (72.0)	6 (54.5)
>40 weeks	16 (64.0)	4 (36.4)
>56 weeks	12 (48.0)	3 (27.3)
>72 weeks	8 (32.0)	2 (18.2)
>88 weeks	6 (24.0)	2 (18.2)
>106 weeks	2 (8.0)	1 (9.1)
Duration of exposure (weeks)		
n	25	11
Mean (SD)	56.3 (36.8)	41.1 (38.4)
Median	53.1	28.0
Min, Max	3.7, 121.1	3.1, 118.4

Number of subject-weeksc	1407.4	452.1

Exposure by subject is shown in Table 4. These data reveal that 18 patients achieved greater than 24 weeks exposure while 9 of these patients achieved a mean dose greater than 45mg/kg/day during the entire maintenance interval. All 18 patients with greater than 24 weeks of exposure achieved a maximum dose of at least 44mg/kg/day. The overall study mean treatment duration for all patients was 394 days (13.1months) with a mean dose of 40.9 mg/kg/day.

Table 4 Study Interval Rufinamide Exposure parameters by subject ID. Mean, Maximum, and longest duration treatment.

Subject ID	MEAN DOSE MG/KG	MAX DAILY DOSE MG/KG	LONGEST DURATION MG/KG	Treatment Duration Days*	Treatment Duration Weeks	Treatment Duration Months (30 day)
E2080-G000-303-5002-1001	30.3	45.4	45.4	26	3.7	0.9
E2080-G000-303-1001-1001	27.5	44.2	44.2	32	4.6	1.1
E2080-G000-303-4001-1002	18.7	40.9	12.6	37	5.3	1.2
E2080-G000-303-1006-1002	34.7	44.4	44.4	94	13.4	3.1
E2080-G000-303-4008-1001	26.4	38.8	30.6	121	17.3	4.0
E2080-G000-303-4006-1001	48.6	55.6	55.6	122	17.4	4.1
E2080-G000-303-1005-1005	39.7	41.6	41.6	162	23.1	5.4
E2080-G000-303-4004-1002	45.1	52.7	47.9	170	24.3	5.7
E2080-G000-303-8002-1001	40.9	45.3	42.1	276	39.4	9.2
E2080-G000-303-7002-1002	53.3	57.7	54.1	344	49.1	11.5
E2080-G000-303-1005-1003	46.6	49.4	49.4	352	50.3	11.7
E2080-G000-303-5005-1004	46.3	51.4	45.7	362	51.7	12.1
E2080-G000-303-7002-1001	43.4	44	44	372	53.1	12.4
E2080-G000-303-5003-1003	44.4	45.8	45.8	409	58.4	13.6
E2080-G000-303-5003-1002	42.8	48.7	45.2	423	60.4	14.1
E2080-G000-303-1010-1002	42.7	44.4	44.4	425	60.7	14.2
E2080-G000-303-5002-1002	44.8	45.3	45.3	479	68.4	16.0
E2080-G000-303-1016-1003	33.4	46.7	33.3	598	85.4	19.9
E2080-G000-303-5005-1002	48.5	50	50	614	87.7	20.5
E2080-G000-303-1007-1001	54.4	73.6	55.2	656	93.7	21.9
E2080-G000-303-5003-1001	45.8	49.5	45.7	702	100.3	23.4
E2080-G000-303-4004-1001	36.6	44.7	32.9	740	105.7	24.7
E2080-G000-303-5005-1001	32.2	45	25	740	105.7	24.7
E2080-G000-303-1017-1002	49	63.8	59.6	748	106.9	24.9
E2080-G000-303-1016-1001	47.6	51.4	47.7	848	121.1	28.3
Mean of Dose Parameters	40.9	48.8	43.5	394.1	56.3	13.1
* From TRTDUR variable, ADEX dataset (ADAM)						
Shaded rows achieved > 24 weeks of exposure, green shaded subject ID achieved a mean dose ≥45mg/kg.						

Subject ID	MEAN DOSE MG/KG	MAX DAILY DOSE MG/KG	LONGEST DURATION MG/KG	Treatment Duration Days*	Treatment Duration Weeks	Treatment Duration Months (30 day)
All patients with greater than 24 weeks exposure achieved a maximum dose within 1mg/kg of target dose.						

Reviewer Comment: Eighteen of 21 enrolled patients reached target duration of treatment and all of these achieved a maximum dose within 1 mg/kg/day of the target dose. A majority of these 18 patients maintained treatment for notably longer than six months to result in a mean treatment duration for all study patients of 13.1 months. This duration of exposure is sufficient to reveal worsening of known safety signals or emergence of new safety signals.

Demographics

The rufinamide treatment population has 25 patients in the safety population. A minimum of 35% of 21 patients in the less than 3 year old age range was specified in the written request. The composition of the safety population by increments of 1 year of age and by age band 1 to <3 years is shown in Table 5. There were 17 patients in the age range 1 to <3 years and eight (8) patients in the range 3 to <4 years. This composition fulfils the parameters of the written request.

There distribution of male and females in the safety population was 56% and 44% respectively, shown in Table 6. Due to the small total sample size recruited for the study these proportions are acceptable. The population was overwhelmingly caucasian with only 8% black patients, shown in Table 7. The distribution by geographic region is divided into North American and Europe- rest of world with 40% and 60% from each region respectively, also shown in Table 8. The distribution by country is shown in Table 9.

Table 5 Distribution of rufinamide treatment patients by age in years

Percent of Total rufinamide treatment group by 1 year age increments			Percent of total rufinamide treatment group by written request strata, ages 1 to < 3	
Age band, years	Total patients in age band	% Patients	Age band years	% Patients
1 to <2	10	40	1 to <3	68
2 to <3	7	28		
3 to <4	8	32	3 to <4	32

Table 6 distribution of rufinamide treatment patients by sex

SEX	Number of patients	%
F	11	44
M	14	56

Table 7 rufinamide treatment patients distribution by race

RACE	Number of patients	% patients
Black or African American	2	8
White	23	92

Table 8 rufinamide treatment patients' distribution by geographic region

REGION	# patients	% Patients
EU/ROW	15	60
North America	10	40

Table 9 rufinamide treatment patients distribution by country

COUNTRY	Number of patients	% patients
CAN	1	4
GRC	2	8
ITA	5	20
POL	8	32
USA	9	36

Reviewer Comment: The study population provides a robust experience with the youngest age patients. Forty percent of patients were between 1 and 2 years of age and 68% between 1 and 3. The ratio of male to female patients is acceptable. US patients comprise the largest national subset at 36%. The racial diversity is very limited with 92% caucasian patients potentially limiting generalizability of the study to other racial groups. This was also a limitation of the pivotal LGS trial supporting (study 022) the current BANZEL label where 82% of patients were caucasian and 9.3% black.

7.2.2 Explorations for Dose Response

In study 022, infections, vomiting, nausea, and decreased appetite have been observed more frequently in rufinamide treatment than placebo treatment. These items were examined in study 303 to determine if a dose response was present. The rufinamide treated patients from study 303 are divided into two treatment strata based on the last dose before taper. There were 25 rufinamide treated patients. Six of these patients did not reach a dose greater than 40mg/kg while the remaining 19 patients attained a target dose greater than 40mg/kg, Table 10.

Table 10 Rufinamide Treated Patients by Dose Strata at Last Dose Before Taper

<40mg/kg		**≥40mg/kg**	
Subject ID	Dosage mg/kg	Subject ID	Dosage mg/kg
E2080-G000-303-4001-1002	13	E2080-G000-303-8002-1001	40
E2080-G000-303-1001-1001	16	E2080-G000-303-5002-1001	41
E2080-G000-303-5005-1001	25	E2080-G000-303-1005-1005	42
E2080-G000-303-4008-1001	31	E2080-G000-303-7002-1001	44
E2080-G000-303-1016-1003	33	E2080-G000-303-1006-1002	44
E2080-G000-303-4004-1001	35	E2080-G000-303-1010-1002	44
Mean dose	25.5 mg /kg	E2080-G000-303-5002-1002	45
median	28 mg/kg	E2080-G000-303-5003-1003	46
		E2080-G000-303-1016-1001	48
		E2080-G000-303-5003-1002	49
		E2080-G000-303-1005-1003	49
		E2080-G000-303-5003-1001	50
		E2080-G000-303-5005-1002	50
		E2080-G000-303-5005-1004	51
		E2080-G000-303-4004-1002	53
		E2080-G000-303-1007-1001	55
		E2080-G000-303-4006-1001	56
		E2080-G000-303-7002-1002	58
		E2080-G000-303-1017-1002	64
		Mean dose	48.9 mg/kg
		median	49 mg/kg

The frequency of adverse events of interest is shown by dose strata in Figure 3 & Figure 4.

Figure 3 Rufinamide Treatment Patients, SOC of Concern by Dose Stratum

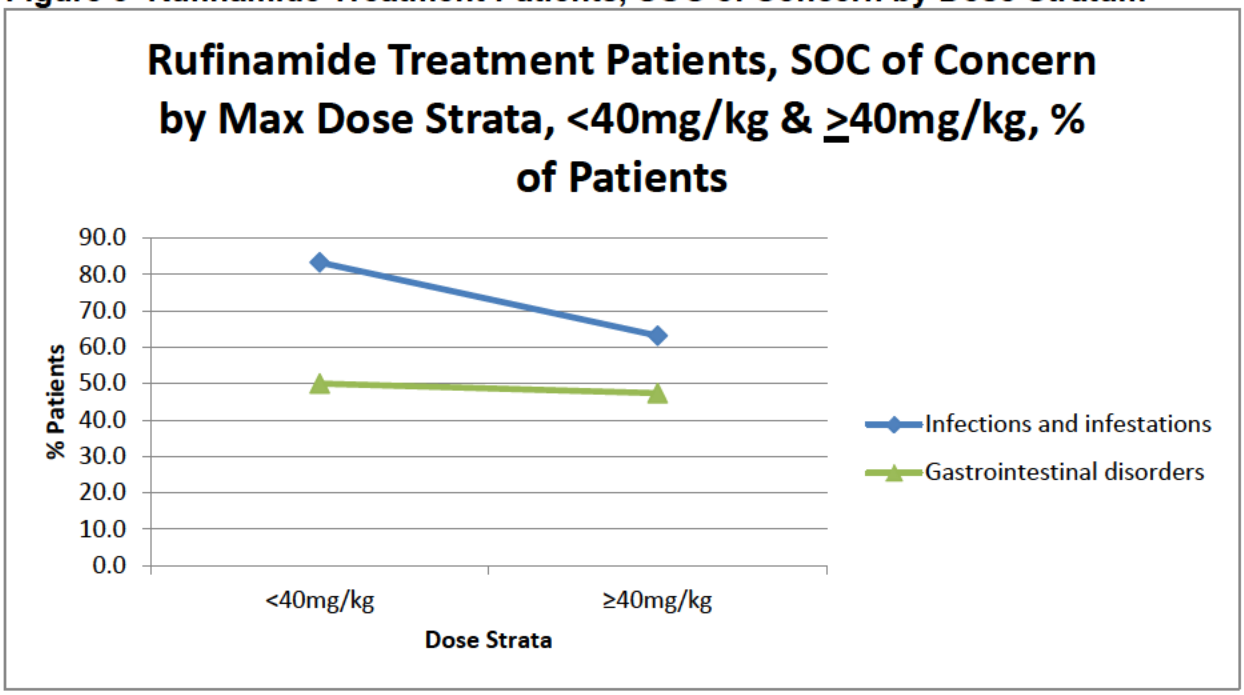
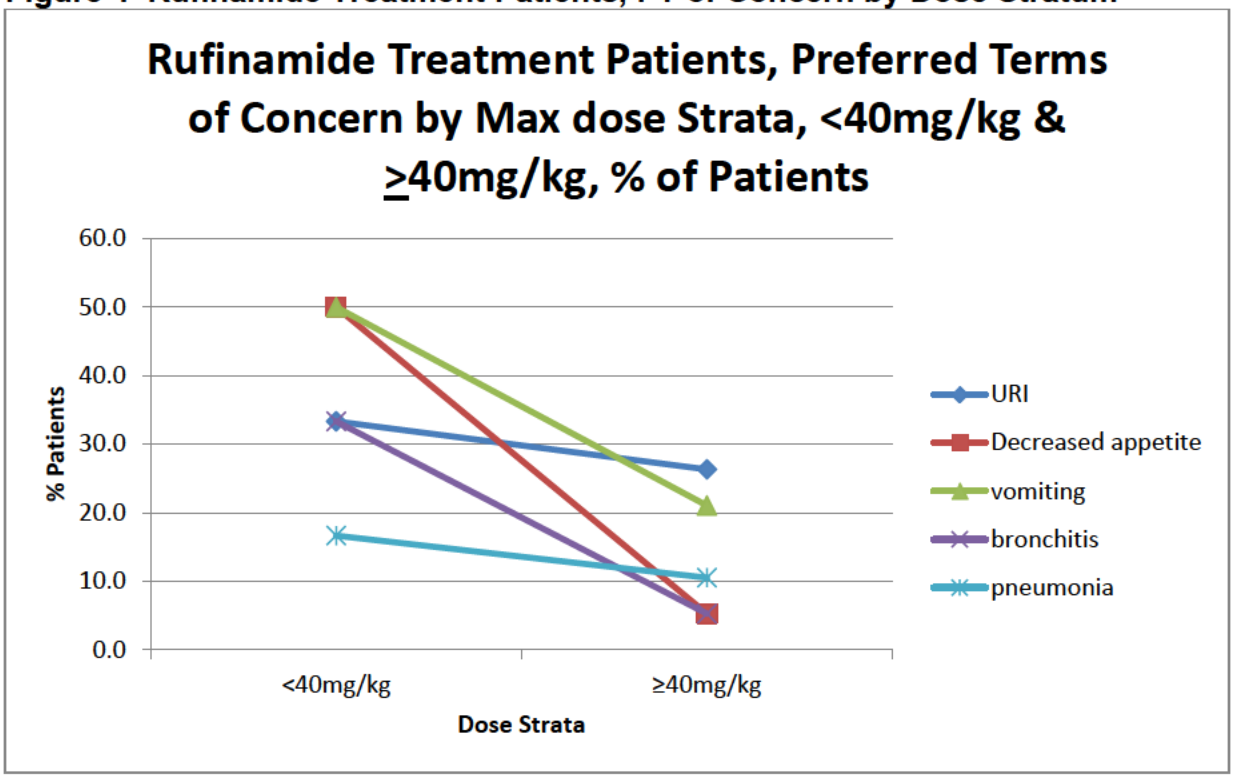


Figure 4 Rufinamide Treatment Patients, PT of Concern by Dose Stratum



Reviewer Comment: Although the number of patient comprising the lower dose strata is small, based on this analysis there is no trend of dose response for adverse effect of concern.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

This sNDA for revised labeling is supported by a single PK and safety study 303, see section 5.3 Discussion of Individual Studies/Clinical Trials. Safety assessments consisted of monitoring and recording all adverse events and serious adverse events; monitoring of laboratory parameters including hematology, blood chemistry and urine studies, Table 11. There was also periodic monitoring of vital signs and performance of physical examination. ECG was also performed. The schedule of evaluations during the course of the study is shown in Table 12. The spacing between clinical laboratory evaluations during the initial two months of the study, where more frequent evaluations are needed to assess any potential new subacute toxicities, was every two weeks for the first month followed by an interval of one month to the end of month number 2. ECG is obtained at baseline and weeks 4, 8 and 16. Following baseline a physical exam and brief neurologic exam is obtained at all visits except at week 72. The safety assessments are of appropriate content and frequency.

Table 11 Clinical Laboratory Studies

Category	**Parameters**
Hematology	RBC, Hgb, Hct, platelets, and WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	Sodium, potassium, chloride, bicarbonate
Liver function tests	Alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin
Renal function parameters	Blood urea/ BUN, creatinine
Other	Amylase, lipase, glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, LDH, total protein, globulin, uric acid
Urinalysis	pH, protein, glucose, ketones, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity

Table 12 Schedule of Safety Studies

Phase	Pre- Randomization		Post Randomization / Treatment												
Period	Screening	Baseline	Titration	Maintenance										Taper	Follow up / Final Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		
Week	**-8 to -1**	**0**	**1**	**2**	**4**	**8**	**16**	**24**	**40**	**56**	**72**	**88**	**106**		
ECG	X	X[a]			X[a]	X[a]	X[a]								
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Phase	Pre- Randomization		Post Randomization / Treatment											
Period	Screening	Baseline	Titration	Maintenance									Taper	Follow up / Final Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	
Height	X	X											X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical/ Neurologic exam[c]	X	X	X	X	X		X	X		X		X	X	X	X
Laboratory tests	X	X		X	X	X	X	X					X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Twelve-lead, duplicate, consecutive, ECGs to be performed prior to dosing at Visit 2 and approximately 4 to 6 hours after study drug administration at Visits 5, 6, and 7.
[b]Vital signs include sitting (or in a sitting like position) systolic and diastolic blood pressure, radial pulse, respiration and body temperature
[c]Perform a comprehensive physical exam. A complete neurological exam (if possible) to be performed at Screening and Baseline visits only. Subsequent neurological exams will be an abbreviated exam. Changes from the baseline examination will be recorded as AEs on the CRF.

Reviewer Comment: Routine clinical testing performed in study 303 was adequate for safety review.

7.2.5 Metabolic, Clearance, and Interaction Workup

These parameters have been characterized for initial approval; see section 12 of BANZEL label.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Rufinamide is a triazole derivative that is structurally unrelated to other AEDs[1].

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in studies 303 or 304.

7.3.2 Nonfatal Serious Adverse Events

Study 303: There were 7 (28%) patients who experienced 15 (SAE's in the rufinamide treatment group and 3 (27%) patients who experienced 7 SAE's in the "any other AED" group. The table of SAE's occurring in each group is shown in Table 13 and Table 14.

[1] Cross HJ, Kluger G, Lagae L. Advancing the management of childhood epilepsies. European Journal of Paediatric Neurology. 2013;17(4):334-347

Table 13 Rufinamide Treatment Group, SAEs with Severity rating and relatedness*

Patient count	USUBJID	SOC	Preferred Term	Severity classification	AEACN	Related to treatment
1	E2080-G000-303-1007-1001	Infections and infestations	Bronchitis	SEVERE	Dose Not Changed	Not Related
	E2080-G000-303-1007-1001	Respiratory, thoracic and mediastinal disorders	Pneumonia Aspiration	SEVERE	Dose Not Changed	Possibly Related
2	E2080-G000-303-1016-1001	Skin and subcutaneous tissue disorders	Rash	MODERATE	Dose Not Changed	Not Related
3	E2080-G000-303-1016-1003	Respiratory, thoracic and mediastinal disorders	Respiratory Distress	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-1016-1003	Respiratory, thoracic and mediastinal disorders	Respiratory Distress	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-1016-1003	Respiratory, thoracic and mediastinal disorders	Respiratory Distress	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-1016-1003	Respiratory, thoracic and mediastinal disorders	Respiratory Distress	MILD	Dose Not Changed	Not Related
	E2080-G000-303-1016-1003	Infections and infestations	Respiratory Syncytial Virus Bronchiolitis	MODERATE	Dose Not Changed	Not Related
4	E2080-G000-303-1017-1002	Infections and infestations	Bronchitis Viral	MODERATE	Not Applicable	Not Related
	E2080-G000-303-1017-1002	Nervous system disorders	Status Epilepticus	MODERATE	Dose Increased	Possibly Related
5	E2080-G000-303-4004-1002	Infections and infestations	Bronchopneumonia	MILD	Dose Not Changed	Not Related
6	E2080-G000-303-7002-1001	Infections and infestations	Respiratory Tract Infection	MODERATE	Dose Not Changed	Not Related
7	E2080-G000-303-8002-1001	Infections and infestations	Gastroenteritis	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-8002-1001	Nervous system disorders	Grand Mal Convulsion	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-8002-1001	Infections and infestations	Pneumonia Influenzal	SEVERE	Dose Not Changed	Not Related
	*One shaded set of rows is a single patient					

The SAEs in the rufinamide treatment group included respiratory infection preferred terms. These were bronchitis, bronchitis viral, bronchopneumonia, pneumonia influenza, respiratory syncytial virus (RSV) and respiratory tract infection. The episode of RSV was associated with three instances of an SAE "respiratory distress". There was also 1 episode of an SAE due to status epilepticus, one grand mal convulsion, one gastroenteritis and a rash. The predominance of respiratory term SAEs causes some concern for a respiratory infection safety signal. A full analysis of the frequency of SOC "infection and infestation" terms and more specifically the respiratory tract infections with the SOC found in studies 303 and LGS study 022 does not reveal evidence of a respiratory infection safety signal. The full analysis is presented in section 7.3.5.

submission specific safety concerns in Respiratory Tract Infections. A brief outline presentation of the findings is also provided in 10.1 Infection Adverse Event Analysis, Brief Outline Presentation

The overall profile of adverse events is consistent with the known safety profile of rufinamide as established in study 022.

The single SAE that occurred in the rufinamide treatment group of study 304 (Japanese study) was a drug eruption. This patient continued study drug (rufinamide) after a rechallenge that resulted in reoccurrence of a less severe rash.

Table 14 "any other AED" group SAEs with severity rating and relatedness*

Patient Count	USUBJID	SOC	Preferred term	Severity classification	AEACN	Related to treatment
1	E2080-G000-303-1005-1001	Nervous system disorders	Convulsion	SEVERE	Dose Increased	Not Related
2	E2080-G000-303-1006-1001	Metabolism and nutrition disorders	Dehydration	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-1006-1001	Injury, poisoning and procedural complications	Joint Dislocation	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-1006-1001	Nervous system disorders	Lethargy	MODERATE	Drug Interrupted	Possibly Related
	E2080-G000-303-1006-1001	Musculoskeletal and connective tissue disorders	Muscular Weakness	MILD	Dose Not Changed	Not Related
3	E2080-G000-303-4001-1003	Infections and infestations	Bronchopneumonia	MODERATE	Dose Not Changed	Not Related
	E2080-G000-303-4001-1003	Nervous system disorders	Convulsion	MODERATE	Drug Interrupted	Probably Related
	* One shaded set of rows is a single patient					
	33% of those with an SAE had an event in the SOC "infections and infestations"					

7.3.3 Dropouts and/or Discontinuations

In Study 303, two (2) of 25 (8.0%) subjects in the rufinamide group and 1 of 11 (9.1%) subjects in the any-other-AED group had TEAEs that resulted in discontinuation from study drug.

In the rufinamide group, Subject 40011002 discontinued treatment during the Maintenance Phase due to TEAEs of vomiting and decreased appetite and Subject 50021001 discontinued treatment during the Titration Phase due to a TEAE of vomiting. In the any-other-AED group, Subject 40011003 discontinued treatment during the Titration Phase due to a TEAE of rash.

In the Japanese study 304 there were 4 treatment emergent adverse effects resulting in discontinuation among the rufinamide treatment group (14%).

Reviewer comment: gastrointestinal adverse effects were seen in study 022 entered as nausea and vomiting and are present in the BANZEL label. The frequency of vomiting was 17% with rufinamide treatment compared to 7% in the placebo group while the frequency of nausea was 7% with rufinamide treatment and 3% in the placebo group. The two patients who discontinued due to vomiting in study 303 represents a frequency of 8% which is not notable divergent from the frequency of this AE in study 022.

7.3.4 Significant Adverse Events

Four (16%) of patients in the rufinamide treatment group had 6 adverse events identified as severe, Table 15, while 2 (18%) patients in the "any other AED" group had 3 adverse events identified as severe. From among the six adverse events in the rufinamide group identified as "severe" there were 3 (50%) which were related to infections and 3 (50%) related to gastrointestinal dysfunction. Two patients experienced 3 infection related events which were also identified as an SAEs while the remaining two patients had gastrointestinal related events which were not concurrently identified as SAEs. One patient, 4001-1002, who experienced "loss of appetite" and "vomiting" had study drug withdrawn[2]. Two events, "bronchitis" and "H1N1 pneumonia" from one patient each were considered unrelated to the study drug while the remaining 4 events were considered possibly related. Patient 1007-1001 experienced bronchitis and aspiration pneumonia, patient 4001-1002 experience an event of "loss of appetite" and "vomiting", these events resulted in study discontinuation but were not entered as SAE. Patient 4004-1001 experienced an event of "weight loss" which was not an SAE. Patient 8002-1001 experienced an event of "H1N1 pneumonia" which was entered as an SAE. This profile of adverse events with severity identified as "severe" is consistent with the known safety profile of rufinamide as established in study 022.

Table 15 Significant Adverse Events (events with severity variable of "severe" in the ADAE dataset)

Subject	SOC	Preferred term	Verbatim term	SAE	Action taken	Drug related
E2080-G000-303-1007-1001	Infections and infestations	Bronchitis	Bronchitis	Y	Dose Not Changed	Not Related
E2080-G000-303-1007-1001	Respiratory, thoracic and mediastinal disorders	Pneumonia Aspiration	Aspiration Pneumonia	Y	Dose Not Changed	Possibly Related
E2080-G000-303-4001-1002	Metabolism and nutrition disorders	Decreased Appetite	loss of appetite	N	Drug Withdrawn	Possibly Related
E2080-G000-303-	Gastrointestinal	Vomiting	vomiting	N	Drug	Possibly

[2] In this paragraph the verbatim term for the event is in quotation marks.

4001-1002	disorders				Withdrawn	Related
E2080-G000-303-4004-1001	Investigations	Weight Decreased	Weight loss	N	Dose Not Changed	Possibly Related
E2080-G000-303-8002-1001	Infections and infestations	Pneumonia Influenzal	H1N1 Pneumonia	Y	Dose Not Changed	Not Related

7.3.5 Submission Specific Primary Safety Concerns

Weight

In study 022 the most prominent adverse reactions, with a frequency in ≥ 5% of patients, were “somnolence”, “vomiting”, “headache”, “fatigue”, “dizziness”, “nausea”, “Nasopharyngitis”, and “decreased appetite”. The largest separation from placebo in study 022 was also seen for “vomiting”, “nausea”, and “decreased appetite”. These latter three adverse reactions may have a greater impact in the current study (303) population of 1 to 4 year old patients due to smaller body mass and volume. This possibility is a focus of the safety review and is investigated by analysis of the adverse event data as well as patient weight from the vital sign dataset examined over the course of study 303, see Weight Analysis.

QT interval

During the review of rufinamide earlier in the development program (2005) a novel adverse event of dose related QT shortening was identified. The risk associated with QT shortening among outliers in the general population is uncertain. A focused examination of the QT interval derived from study 303 derived ECGs is performed to determine if there is any differential sensitivity of the younger group (age >1 year to <4 years) to the QT shortening effect of BANZEL. See QT analysis.

Seizure Worsening

Adverse Event Examination

Epilepsy worsening is a concern in anticonvulsant development programs, there is a known potential for some antiepilepsy drugs at high levels to lower seizure threshold. A signal for seizure worsening is therefore a consideration in evaluation of treatment of a new epilepsy population. In addition to the adverse event data, the study 303 ADSZF seizure frequency dataset was examined for evidenced of a “seizure worsening” signal.

Examination of the adverse event dataset reveals 8 epilepsy related preferred term events form among 6 patients. Two of these were SAEs and none resulted in discontinuation of treatment. One patient had three events, two of “grand mal convulsion” and one “atonic seizures”. One patient each had events of “convulsion”,

"myoclonic epilepsy", "status epilepticus", "epilepsy" and "tonic convulsion". These 6 patients represent 24% of the rufinamide treatment population, see Table 16.

Table 16 Seizure related Adverse event preferred terms

Subject ID	Preferred Term	Day of Study
E2080-G000-303-8002-1001	Atonic Seizures	81
E2080-G000-303-1010-1002	Convulsion	43
E2080-G000-303-8002-1001	Grand Mal Convulsion	89
E2080-G000-303-8002-1001	Grand Mal Convulsion	113
E2080-G000-303-4001-1002	Epilepsy	10
E2080-G000-303-4004-1001	Tonic Convulsion	0
E2080-G000-303-1016-1003	Myoclonic Epilepsy	112
E2080-G000-303-1017-1002	Status Epilepticus	189

Seizure Frequency Audit: seizure frequency of select seizure types at 4 months and 6 months.

In addition to an analysis of adverse events for evidence of seizure worsening an examination of the study 303 ADSZF.xpt dataset is performed. A spot audit of the frequency of 3 seizure types at 4 and 6 months compared to baseline is performed. Only rufinamide treated patients are examined. The seizure types examined are *total seizures*, *partial seizures* and *tonic-atonic seizures*.

The 4 month examination of *total seizures* reveals that 16 of 19 patients with entries at this time point had a reduction in seizure frequency from baseline while 3 patients had an increase. The mean and median percent changes from baseline were -38 and -55 percent respectively, Figure 66. The same analysis of partial seizures revealed that all 10 patients with an entry for this seizure type at the 4 month time point had a reduction in seizure frequency from the baseline value. The mean and median percent change from baseline was -74 and -87 percent respectively, Figure 67. The tonic-atonic seizure analysis at 4 months revealed that 11 of 13 patients with an entry for this seizure type at this time point had a reduction in seizure frequency compared to baseline with a mean and median of 39 and -60 percent change respectively. There was a single outlier patient with a 1251 percent increase from baseline. This patient had 6.5 tonic-atonic seizures per 28 days at baseline which increased to 87 per 28 days at 4 months, Figure 68. *Myoclonic seizures* are a frequent component of LGS syndrome, this seizure type is also examined at four months. There were 12 patients with an entry for this seizure type at 4 months. Ten of these 12 patients had a reduction in seizure frequency. The group had a mean and median percent change from baseline seizure frequency of -46 and -48 percent respectively, Figure 70.

Examination of *total seizure* frequency at 6 months reveals that 14 of 16 patients with an entry for this seizure group at this time point had a reduction in seizure frequency with a mean and median percent reduction of -44 and -59 percent respectively, Figure

71. All 9 patients with an entry for *partial seizures* at six months had a reduction in seizure frequency from baseline with a mean and median of -71 and -74 percent reduction respectively, Figure 72. There were 10 patients with an entry for *tonic-atonic seizures* at 6 months, all had a reduction in seizure frequency from baseline with a mean and median of -70 and -70 percent respectively, Figure 73. All distributions may be seen in 9.8 Seizure Frequency Analysis.

Reviewer Comment: the analysis of epilepsy related adverse events in rufinamide treated patients reveals that (6) 24% of patients experienced an AE in this category while (2) 18% in the any other AED group experience an epilepsy related AE. While high compared to the double blind phase of study 022 from the LGS study of the initial NDA, a signal for seizure worsening is not supported by the finding of overall seizure reduction in the audit of percent change in seizure frequency from baseline at 4 months and 6 months. The small sample size and severity of the underlying epilepsy syndrome also mitigate the interpretation of the epilepsy related adverse events. The overall evidence does not support a signal of seizure worsening.

Respiratory Tract Infections

In study 303 there was a high frequency of adverse effect entries in the SOC “infections and infestations” which were primarily respiratory tract infections. This observation prompted a more focused examination of the issue of respiratory tract infections which is provided in the following presentation. Also see Appendix 10.1 Infection Adverse Event Analysis, Brief Outline Presentation.

There is no double blind treatment period or blinded placebo in study 303. Study 303 is an open labeled study of rufinamide treatment and an active “any other AED” treatment arm. This second treatment arm is referred to as AO in the following analysis. The pediatric written request was directed at the acquisition of 6 months of safety data. The adverse events during a 24 week observation interval are examined as the primary treatment interval. This interval is 2 weeks shorter than a full six months, however this interval corresponds to the available laboratory and vital sign safety examination capture points designed into study 303. There are 25 patients in the rufinamide and 11 patients in the “any other AED” (AO) safety datasets of study 303. These numbers will be the denominators to examine percent occurrence of adverse events.

Examination of frequency of adverse events in the “Infection and infestation” system organ class (SOC) in study 303 is compared between rufinamide and the AO group. There were 13 (52%) patients in the rufinamide group and 7 (63%) patients in the AO group with adverse events in this SOC.

The events were then further examined to identify “any respiratory tract infection”, including upper and lower respiratory tract. Non-respiratory tract infections were eliminated from the analysis. This analysis reveals there were 10 (40%) patients in the

rufinamide group, Table 17, with a respiratory infection adverse event and 7 (63%) patients in the AO group, Table 18.

Table 17 Study 303, Rufinamide treatment group, respiratory tract infections during 24 week treatment interval

Respiratory Tract Preferred Terms, RUF, 24 week observation, treatment interval.				
Patient count	USUBJID	Preferred term	instances of event	SAE
1	E2080-G000-303-1005-1003	Upper Respiratory Tract Infection	2	N
2	E2080-G000-303-1005-1005	Sinusitis	1	N
	E2080-G000-303-1005-1005	Upper Respiratory Tract Infection	3	N
3	E2080-G000-303-1007-1001	Bronchitis	1	Y
4	E2080-G000-303-1010-1002	Pharyngitis	1	N
	E2080-G000-303-1010-1002	Upper Respiratory Tract Infection	1	N
5	E2080-G000-303-1016-1003	Bronchitis	1	N
	E2080-G000-303-1016-1003	Upper Respiratory Tract Infection	2	N
6	E2080-G000-303-4004-1002	Bronchopneumonia	1	Y
	E2080-G000-303-4004-1002	Nasopharyngitis	1	N
	E2080-G000-303-4004-1002	Rhinitis	1	N
7	E2080-G000-303-5002-1002	Upper Respiratory Tract Infection	2	N
8	E2080-G000-303-5005-1001	Upper Respiratory Tract Infection	1	N
9	E2080-G000-303-7002-1001	Upper Respiratory Tract Infection	1	N
10	E2080-G000-303-8002-1001	Nasopharyngitis	1	N

Table 18 Study 303, AO group, respiratory tract infections during 24 week treatment interval.

Respiratory Tract Preferred Terms, AO , 24 week observation , treatment interval				
Patient count	USUBJID	Preferred term	Instances of event	SAE
1	E2080-G000-303-1005-1001	Upper Respiratory Tract Infection	1	N
2	E2080-G000-303-1005-1006	Pharyngitis	1	N
	E2080-G000-303-1005-1006	Upper Respiratory Tract Infection	2	N
3	E2080-G000-303-1005-1007	Pharyngitis Streptococcal	1	N
	E2080-G000-303-1005-1007	Upper Respiratory Tract Infection	1	N
4	E2080-G000-303-1006-1001	Sinusitis	1	N
5	E2080-G000-303-1010-1001	Nasopharyngitis	2	N
6	E2080-G000-303-1016-1002	Upper Respiratory Tract Infection	1	N
7	E2080-G000-303-4001-1003	Bronchopneumonia	1	Y

To gain an understanding of respiratory infections that occurred during the entire course of study 303 the adverse event dataset was examined for the occurrence of respiratory tract infections captured at any time during the study. In the rufinamide treatment group there were 13 (52%) patients identified with any respiratory tract infection and 6 (24%) patients from among these had a serious adverse event (SAE), see Table 19. The median study day of occurrence of the 13 respiratory infections in study 303 occurring at any point in the study was 138 with a range from 4 to 544 days. Two of the six SAEs

occurred in the 24 week observation interval while 4 occurred thereafter. From among the 4 SAEs that occurred beyond 24 weeks the mean occurrence was day 296 with a median of 265 days.

The preferred term for one of those with an SAE was “pneumonia influenzal” and a second patient experienced an SAE of the preferred term “bronchopneumonia”. Due to the more generally serious nature of “pneumonia” and “bronchopneumonia” these terms will be pooled and compared separately to occurrence of pneumonia in study 022. The residual respiratory infection terms not included are “bronchitis”, “bronchitis viral”, “respiratory syncytial virus”, and “respiratory tract infection” because they less commonly have the same clinical gravity as “pneumonia” and “bronchopneumonia” The terms “bronchopneumonia” and “Pneumonia” treated as terms with near equivalent seriousness. This assignment of weight (seriousness) results in 2 (6%) patients in the rufinamide treatment group with SAE terms of “pneumonia” seriousness identified at any point in the study.

Table 19 Study 303, Rufinamide treatment group, Respiratory tract infection Serious Adverse Events (SAE) at any time during study. Study day of event included.

RUF treatment Respiratory tract preferred terms, total study interval, **SAEs***			
Patient count	USUBJID	Preferred term	Study day of event (weeks)
1	E2080-G000-303-1007-1001	Bronchitis	50 (7.1)
2	E2080-G000-303-1017-1002	Bronchitis Viral	442 (63.1)
3	E2080-G000-303-4004-1002	Bronchopneumonia	41 (5.9)
	E2080-G000-303-4004-1002	Bronchopneumonia	265 (37.9)
4	E2080-G000-303-8002-1001	Pneumonia Influenzal	258 (36.9)
5	E2080-G000-303-1016-1003	Respiratory Syncytial Virus Bronchiolitis	169 (24.1)
6	E2080-G000-303-7002-1001	Respiratory Tract Infection	346 (49.4)
AO treatment Respiratory tract preferred terms, total study interval, SAEs			
1	E2080-G000-303-4001-1003	Bronchopneumonia	29 (4.1)
* Summary of Case Narratives is presented in Table 23			

There were 7 (63%) patients in the AO group with any respiratory tract infection and 1(9%) among these was an SAE. The SAE term in this event was “bronchopneumonia”, thus there was 1 (9%) patient in the AO group with an SAE of pneumonia.

Examination of the frequency of respiratory tract SAEs in the 24 week observation interval reveals there were 2 (8%) patients in the rufinamide treatment group and 1 (9%) patient in the AO group with an SAE, see Table 19.

Respiratory infections are common in young children, thus a high background rate of respiratory infection is expected. The influence of the rate of background respiratory tract infection may be obtained by an examination of the baseline frequency of respiratory tract infection in the rufinamide and AO treatment groups. There were 2 (8%) patients in the rufinamide group at baseline with respiratory tract infection and 5 (45%) patients in the AO group with baseline respiratory tract infection. During the 24 week maintenance period 10 (40%) patients in the rufinamide group and 7 (63%) patients in the AO group who developed respiratory tract infection.

A cross study comparison is made to the LGS study (022) which was the basis for initial BANZEL approval. This was a double blind, randomized placebo controlled trial with a 12 week (84 day) maintenance interval of patients in the age range 4 to 35 years old. The younger subset of this study from ages 4 to 12 is examined. This subset includes 72 patients. There were 36 patients each in the rufinamide and placebo treatment groups. As in the analysis of study 303 the frequency of adverse events in the "infection and infestation" SOC is examined followed by an analysis of a subset of this SOC which are those patients with any respiratory tract infection (upper or lower tract). Events in the double blind treatment interval are examined to allow for treatment placebo comparison. There were 16 (44%) patients in the rufinamide group and 17 (47%) in the placebo group with any preferred term from the "infection and infestation" SOC. Exam of the respiratory tract infection AE subset reveals there were 11 (31%) patients in the rufinamide group and 12 (33%) patients in the placebo group with a respiratory tract infection see Table 20 and Table 21. From among the 11 rufinamide treatment patients 1 (4%) experienced a respiratory tract infection related SAE. From among the 12 placebo treatment patients with a respiratory tract infection AE there was 1 (4%) who experienced an SAE.

Table 20 Study 022, Rufinamide treatment group, DB treatment period, any respiratory tract infection.

Rufinamide treatment , respiratory tract preferred terms, DB treatment interval, age 4 to 12				
Patient count	USUBJID of ARM-AGE from DM 022 RUF	AEDECOD	AESER	AGE
1	CRUF3310022 0001 02802	Nasopharyngitis	N	5
2	CRUF3310022 0001 02922	Influenza	N	8
3	CRUF3310022 0001 02923	Influenza	N	11
	CRUF3310022 0001 02923	Influenza	N	11
4	CRUF3310022 0002 02811	Nasopharyngitis	N	4
5	CRUF3310022 0002 02812	Pneumonia NOS	N	7
6	CRUF3310022 0004 02513	Nasopharyngitis	N	11
7	CRUF3310022_0005_02520	Upper respiratory tract infection NOS	Y	4
	CRUF3310022_0005_02520	Upper respiratory tract infection NOS	Y	4
8	CRUF3310022_1557_02010	Upper respiratory tract infection NOS	N	10

	CRUF3310022_1557_02010	Upper respiratory tract infection NOS	N	10
9	CRUF3310022_1558_02041	Sinusitis NOS	N	8
	CRUF3310022_1558_02041	Sinusitis NOS	N	8
10	CRUF3310022_3054_02072	Nasopharyngitis	N	4
	CRUF3310022_3054_02072	Nasopharyngitis	N	4
	CRUF3310022_3054_02072	Nasopharyngitis	N	4
11	CRUF3310022_3054_02086	Nasopharyngitis	N	7
	CRUF3310022_3054_02086	Nasopharyngitis	N	7
	CRUF3310022_3054_02086	Upper respiratory tract infection NOS	N	7
	CRUF3310022_3054_02086	Nasopharyngitis	N	7

Table 21 Study 022, Placebo group, DB treatment period, any respiratory tract infection.

Placebo , , respiratory tract preferred terms, DB treatment interval, age 4 to 12				
Patient count	USUBJID of ARM-AGE from DM 022	AEDECOD	AESER	AGE
1	CRUF3310022_0001_02502	Upper respiratory tract infection NOS	N	12
2	CRUF3310022_0002_02810	Nasopharyngitis	N	7
3	CRUF3310022_0002_02910	Pharyngitis	N	5
	CRUF3310022_0002_02910	Pharyngitis	N	5
	CRUF3310022_0002_02910	Pharyngitis	N	5
	CRUF3310022_0002_02910	Pharyngitis	N	5
4	CRUF3310022_0002_02911	Sinusitis NOS	Y	7
	CRUF3310022_0002_02911	Sinusitis NOS	N	7
5	CRUF3310022_0019_02098	Upper respiratory tract infection NOS	N	10
	CRUF3310022_0019_02098	Upper respiratory tract infection NOS	N	10
	CRUF3310022_0019_02098	Upper respiratory tract infection NOS	N	10
	CRUF3310022_0019_02098	Upper respiratory tract infection NOS	N	10
6	CRUF3310022_1551_02013	Upper respiratory tract infection NOS	N	9
	CRUF3310022_1551_02013	Upper respiratory tract infection NOS	N	9
7	CRUF3310022_1552_02006	Respiratory tract infection NOS	N	4
8	CRUF3310022_1553_02025	Pharyngitis	N	8
9	CRUF3310022_1553_02027	Upper respiratory tract infection NOS	N	10
10	CRUF3310022_1747_02022	Upper respiratory tract infection NOS	N	12
	CRUF3310022_1747_02022	Upper respiratory tract infection NOS	N	12
	CRUF3310022_1747_02022	Upper respiratory tract infection NOS	N	12
	CRUF3310022_1747_02022	Upper respiratory tract infection NOS	N	12
	CRUF3310022_1747_02022	Upper respiratory tract infection viral NOS	N	12
	CRUF3310022_1747_02022	Upper respiratory tract infection NOS	N	12
11	CRUF3310022_3053_02061	Nasopharyngitis	N	9
12	CRUF3310022_3054_02069	Upper respiratory tract infection NOS	N	9
	CRUF3310022_3054_02069	Upper respiratory tract infection NOS	N	9
	CRUF3310022_3054_02069	Upper respiratory tract infection NOS	N	9

From within study 022 the summation of double blind treatment interval, open label and post study taper period are next examined for the frequency of respiratory tract infection adverse events. There were 23 (63%) patients in the rufinamide treatment group with respiratory tract infection adverse events and from among these there were 4 (11%) SAEs. Three (8%) of these 4 SAEs were the preferred term pneumonia. The mean study day of occurrence of respiratory tract infections was 260 days with a median of 157 days. There were 23 (63%) patients in the placebo treatment group with respiratory tract infection adverse events and from among these there were 2 (6%) patients that experience an SAE. Both of these 2 (6%) SAEs were the preferred term pneumonia. Pneumonia is the most serious of the respiratory infection terms and as noted in the discussion above on study 303 will be considered separately from the remaining respiratory infection terms. These residual terms include “bronchitis”, “croup infections” (identified as moderate intensity in the adverse event dataset), “influenza”, “nasopharngytis”, “respiratory tract infection”, “rhinitis”, “sinusitis”, “sinusitis NOS”, “tonsillitis”, “upper respiratory tract infection”, and “upper respiratory tract infection NOS”.

The pneumonia terms are given additional focus in the examination of study 303 (“pneumonia” and “bronchopneumonia) and study 022. It is found that in study 303 there were 2 (6%) pneumonia SAEs in the rufinamide group and 1 (9%) in the AO group. In study 022 there were 3 (8%) pneumonia SAEs in the rufinamide group and 2 (6%) in the placebo group. There was a lower frequency of pneumonia SAEs in the rufinamide treatment group of study 303 compared to the both the AO group of study 303 and the rufinamide treatment arm of study 022, see Table 22.

Table 22 Pneumonia term serious adverse events (SAE) in Studies 303 and 022.

Pneumonia SAE assessment	
Study 303 Pneumonia term SAEs	
Rufinamide treatment	2 (6%)
AO group	1 (9%)
Study 022 pneumonia term SAEs (age 4 to 12 year subset)	
Rufinamide treatment	3 (8%)
Placebo	2 (6%)

The differential in respiratory tract SAEs between the rufinamide and AO treatment groups of study 303 may in part be due to the difference in cumulative exposure between the groups. There were 9852 patient days of exposure in the rufinamide treatment group and 3165 patient days of exposure in the AO group. The exposure ratio was 3.1, rufinamide to AO thus a greater number of rufinamide treatment patients had longer exposure than in the AO group. This accounts for a portion of the difference in frequency of respiratory related SAEs. These data are show graphically in Figure 5 and Figure 6.

Figure 5 Study 303 Study Timeline, Rufinamide Cumulative Exposure, Respiratory SAE and Patients remaining in study.

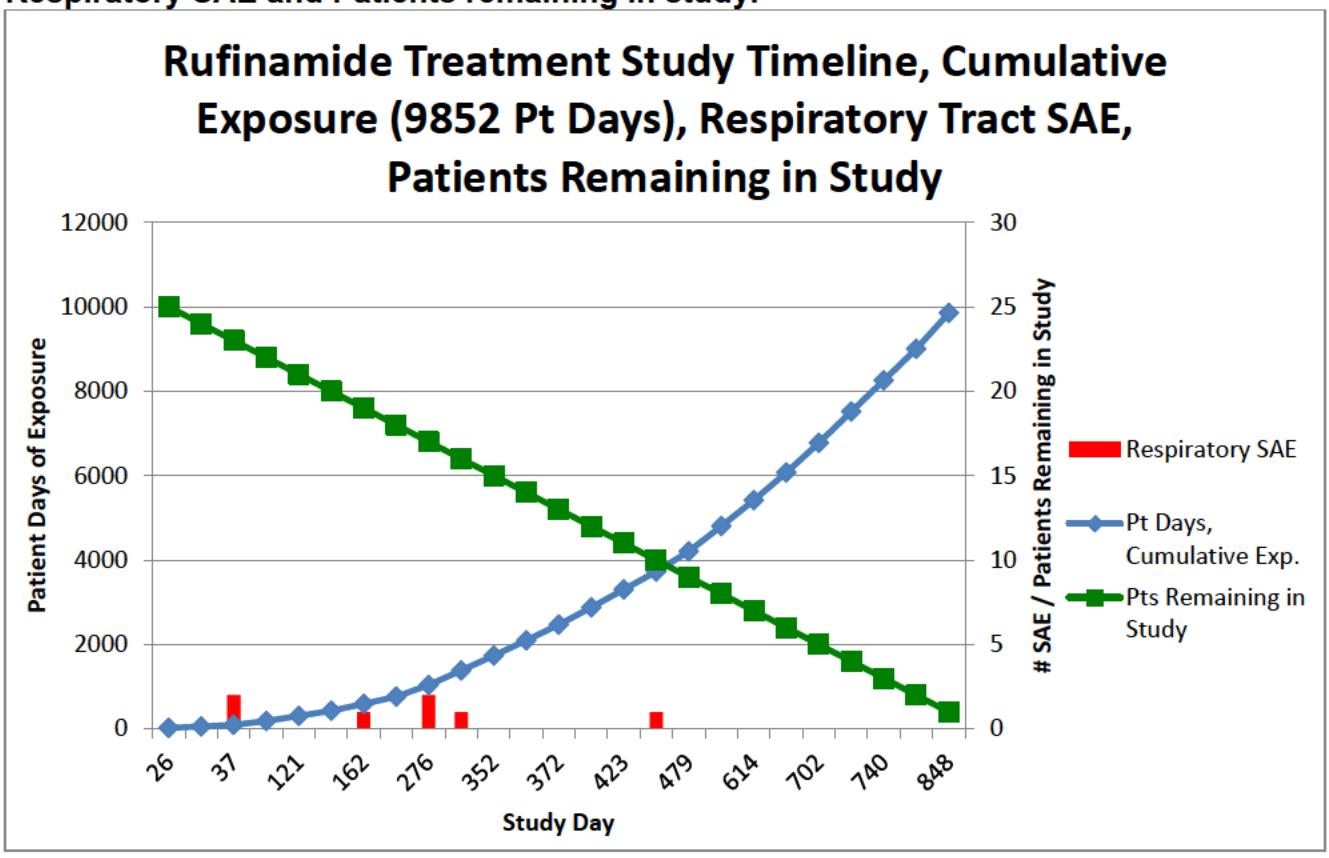
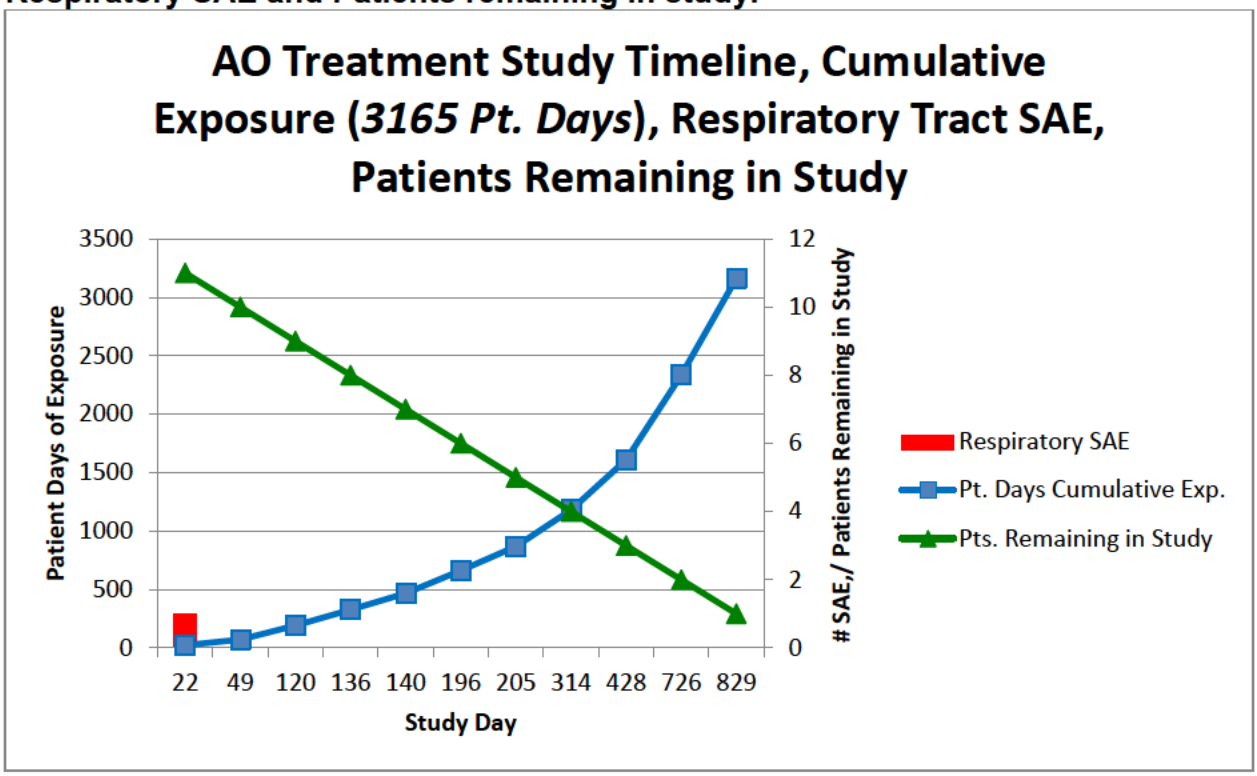


Figure 6 Study 303 Study Timeline, AO group treatment Cumulative Exposure, Respiratory SAE and Patients remaining in study.



As noted above there were six respiratory tract SAEs in the rufinamide treatment group of study 303. The case narratives from these events are examined to determine the nature of the illness, determine if there were predisposing features, whether the patients were selectively vulnerable or should have been expected to have resistance to respiratory illness. If this later expectation is the case then a concern for a specific rufinamide safety signal may be postulated. The six cases are presented in Table 23 with brief core features of each case and a reviewer comment. These six patients are found to have significant background neurologic illness as well as confounding concomitant medication treatment rendering them susceptible to infection. The occurrence of a respiratory infection during a prolonged observation interval allows a greater probability of challenge from a respiratory pathogen. The characteristics of the respiratory infection case reports reveal a group with notable vulnerability to respiratory infection and do not provide supporting evidence for a new safety signal clearly attributable to study drug treatment.

Table 23 Study 303, Rufinamide treatment group, Respiratory Tract Serious Adverse Events during full Study Course. Synopsis of Case Narratives

USUBJID	Clinical Characteristics	Comment
E2080-G000-303-1007-1001	Age 16 months, female, PMH: infantile spasms, developmental delay, GE reflux disease, hearing impaired, hypotonia, cortical blindness, and developmental hip	The record indicates very severe underlying neurodevelopmental disability

	dysplasia. Concomitant medications: topiramate, vigabatrin, omeprazole, clobazam, salbutamol. The patient developed bronchitis on day 50, onset with fever, vomiting and congestion. Patient was admitted to the hospital on study day (b) (6), discharge date is not provided although resolution is entered as study day (b) (6).	which places the patient at higher risk for infection. The causative picture is also confounded by concomitant AEDs
E2080-G000-303-1017-1002	21 month old female. PMH: micorcephaly, cerebral palsy, muscle spasticity, dysphagia, bronchospasm, GE reflux. Concomitant medications at time of adverse event are reported as oxcarbazepine, lansoprazole, levosalbutamol, lamotrigine, and clonazepam. At onset of bronchitis the patient had low oxygen saturation with fever and exposure to a sibling with influenza. The patient was subsequently found to be positive for influenza b. The record indicates resolution of the viral bronchitis 6 days after diagnosis.	the record indicates severe underlying neurodevelopmental disability and history consistent with reactive airway disease which places the patient at higher risk for respiratory infection. The causative picture is also confounded by concomitant AEDs.
E2080-G000-303-4004-1002	37 month old male, PMH of developmental delay, visual impairment, dysmyelination, dyskinesia. Concomitant medications were valproic acid and nitrazepam. The patient was hospitalized on study day (b) (6) with radiologic and clinical diagnosis of bronchopneumonia. The subject was treated with amoxicillin / clavulanic acid, clarithromycin and cefuroxime. Respiratory status improved on the 5th day. No additional SAE entry of bronchopneumonia is present.	the record indicates severe underlying neurodevelopmental disability which places the patient at higher risk for infection
E2080-G000-303-8002-1001	34 month old white female, PMH: infantile spasms, developmental delay, encephalopathy. On study day (b) (6) the patient had fever and later experienced 2 episodes of tonic – atonic seizure. Following these seizures the patient was unresponsive. There was a subsequently a diagnosis of H1N1. Concomitant AEDs at the time included phenobarbital and sabril. The patient continued to have a depressed level of consciousness but was showing improvement on day 272.	the record indicates severe underlying neurodevelopmental disability which places the patient at higher risk for infection
E2080-G000-303-1016-1003	28 month old white female, PMH: herpes simplex encephalitis with hemiparesis and epilepsy. On study day (b) (6) the patient experienced labored breathing with retractions, the patient was hospitalized and a diagnosis of respiratory syncytial virus was made by PCR. The patient had persistent dyspnea and hypoxia. Concomitant medications at the time of onset were topiramate, acyclovir, vigabatrin, clobazam, and ranitidine, The event of RSV was noted to be resolved on study day 174.	The record indicates the patient suffered prior severe viral encephalitis with severe sequelae. The patient then was infected with a common and contagious childhood viral infection. A more aggressive course may be expected in a patient with a severe underlying illness.
E2080-G000-303-7002-1001	26 month old white male. PMH: cerebral palsy, feeding disorder, aspiration. On study day (b) (6) the patient experienced fever and respiratory distress and was hospitalized. The patient was treated with ceftriaxone for 3 days and the infection resolved on study day 350. Concomitant medications: lansoprazole, levocarnitine, montelukast, iron, valproic acid, and clobazam.	The record indicates severe underlying neurodevelopmental disability and history consistent with reactive airway disease which places the patient at higher risk for respiratory infection.

Reviewer Comment: ***No evidence of a new safety signal related to respiratory infection is identified.*** Examination of the 24 week observation interval of study 303 reveals a lower percentage of events from the "infection and infestation" SOC in the rufinamide treatment group compared to the AO group. Likewise when the infection events are limited to upper and lower respiratory tract there is a larger gradient between the rufinamide (40%) and AO (63%) group percent of patients with AEs. When the observation interval is extended to the entire study course there remains a lower percent of rufinamide patients with respiratory tract infection compared to the percent of these infections in the AO group, 53% compared to 63% respectively. When the proportion of SAEs due to respiratory tract infection is examined in the full study interval there is a higher percent of SAE events in the rufinamide group compared to the AO group. There were 6 (24%) patients from the rufinamide group and 1 (9%) patient in the AO group with respiratory tract SAEs. The separation in respiratory SAE frequency is due to the greater exposure in the rufinamide group, unpredictable distribution of more severely affected LGS patients between groups, a high frequency of infections in this young (and compromised) population and a small sample size. These individual issues are briefly summarized below.

Examination of the most severe respiratory infection SAEs, pneumonia or bronchopneumonia, that occurred at any time during studies 303 and 022 reveal a very similar frequency in the two studies as noted in Table 22. The importance of this observation is the absence of a clear divergence between the rufinamide treatment groups of the two studies and a modestly lower frequency in study 303.

The narrative reports from the rufinamide respiratory tract infection SAEs reveal that all of these patients have significantly compromised underlying neurologic status. In addition they are in an age range of known to have a high frequency of respiratory infection even in the healthy population.

An additional consideration in the analysis when comparing the overall respiratory infection frequency and those respiratory infections categorized as SAEs is the baseline level of cognitive and motor compromise. LGS is a heterogeneous syndrome and the level of severity among study participants may not be distributed evenly between the rufinamide and AO treatment groups due to the small sample sizes. More severely compromised patients may be more susceptible to respiratory infection.

The examination of study 022 when compared to study 303 reveals a somewhat lower frequency of infection related AEs and an even lower frequency of SAEs. This may reflect the older age and increased resistance study 022 age range of 4 to 12 years in this analysis group. The proportion of respiratory tract AEs is more similar in the treatment and placebo in study 022 while in study 303 the AO group has a higher

percent of “infection and infestation” AEs and respiratory tract AEs than is seen in the rufinamide group of study 303. This may be due to chance disproportion in the small study 303 group but offers some reassurance that a respiratory infection safety signal is not present.

The baseline frequency of infection was examined in the rufinamide and AO groups. It was found that 2 (8%) patients in the rufinamide group had infection at baseline while 5 (45%) patients in the AO group had baseline respiratory infection. This may suggest that rufinamide promotes a shift toward respiratory tract infection but more likely demonstrates there is a high frequency of infection in this population at this age and chance distribution resulted in a greater occurrence in the AO baseline.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 303

Any adverse event in the rufinamide group occurred in 22 (88%) patients. In the rufinamide treatment group 8 (32%) patients experienced an adverse event of upper respiratory infection, 6 (24%) vomiting, 5 (20%) somnolence 4 (16%) diarrhea, and 3 (12%) occurrences each of bronchitis, constipation, cough, decreased appetite, Nasopharyngitis, otitis media, pneumonia and rash, the corresponding frequencies in the “any other AED” group are show as comparators see Table 24.

Any adverse event in the “any other AED” group occurred in 11 (100%) patients. In the “any other “AED group” there were 4 (36%) patients who experienced an AE of diarrhea, 3 (36%) patients who experienced an event of pyrexia, and 2 (18%) patients each who experience and event of convulsion, dermatitis diaper, Nasopharyngitis, and vomiting, Table 24.

Table 24 Common Adverse Events, number and percent of patients in rufinamide treatment and “any other AED” treatment

Preferred term	Rufinamide		Any other AED		
AEDECOD	Number of patients	% patients	Number of patients	% patients	delta RUF-“any other AED”
Upper Respiratory Tract Infection	8	32	4	36	-4.4
Vomiting	6	24	2	18	5.8
Somnolence	5	20	0		20.0
Diarrhoea	4	16	4	36	-20.4
Bronchitis	3	12	0		12.0
Constipation	3	12	1	9	2.9

Cough	3	12	1	9	3.0
Decreased Appetite	3	12	1	9	3.0
Nasopharyngitis	3	12	2	18	-6.2
Otitis Media	3	12	2	18	-6.2
Pneumonia	3	12	1	9	3.0
Rash	3	12	1	9	3.0
Blood Bicarbonate Decreased	2	8	1	9	-1.1
Gait Disturbance	2	8	1	9	-1.1
Gastroenteritis	2	8	0	0	8.0
Irritability	2	8	1	9	-1.0
Nasal Congestion	2	8	1	9	-1.0
Pharyngitis	2	8	0	0	8.0
Pneumonia Aspiration	2	8	0	0	8.0
Pyrexia	2	8	3	27	-19.0
Respiratory Tract Congestion	2	8	1	9	-1.0
Weight Decreased	2	8	0	0	8.0

The sponsor provides the frequency of common adverse events for studies 022 and 304 as entered in the following paragraphs.

Of subjects 4 to less than 12 years of age in Study 022, 28 of 31 (90.3%) subjects in the rufinamide group and 30 of 33 (90.9%) in the placebo group reported at least 1 TEAE. Common TEAEs (occurring in ≥10% of subjects in any treatment group) are summarized by MedDRA PT. The most frequently reported TEAEs in the rufinamide treatment groups were pyrexia (25.8%), vomiting (22.6%), somnolence (16.1%), and diarrhea (12.9%).

For Study 304, the incidence of AEs was 93.1% (27 of 29 subjects) in the rufinamide group and 70.0% (21 of 30) in the placebo group. Frequent AEs that occurred in the rufinamide group were nasopharyngitis (9 of 29 [31.0%] subjects), status epilepticus (8 of 29 [27.6%] subjects), decreased appetite (6 of 29 [20.7%] subjects), somnolence (6 of 29 [20.7%] subjects), and vomiting (5 of 29 [17.2%] subjects)

In study 303, adverse event data was provided for up to 741 days as shown in Figure 7. There was one event which occurred at 741 days and 39 events were captured at >6 months duration of treatment. The number of patients present over the study timeline is shown in Figure 8

Figure 7 Treatment duration at Start of Any Adverse Event

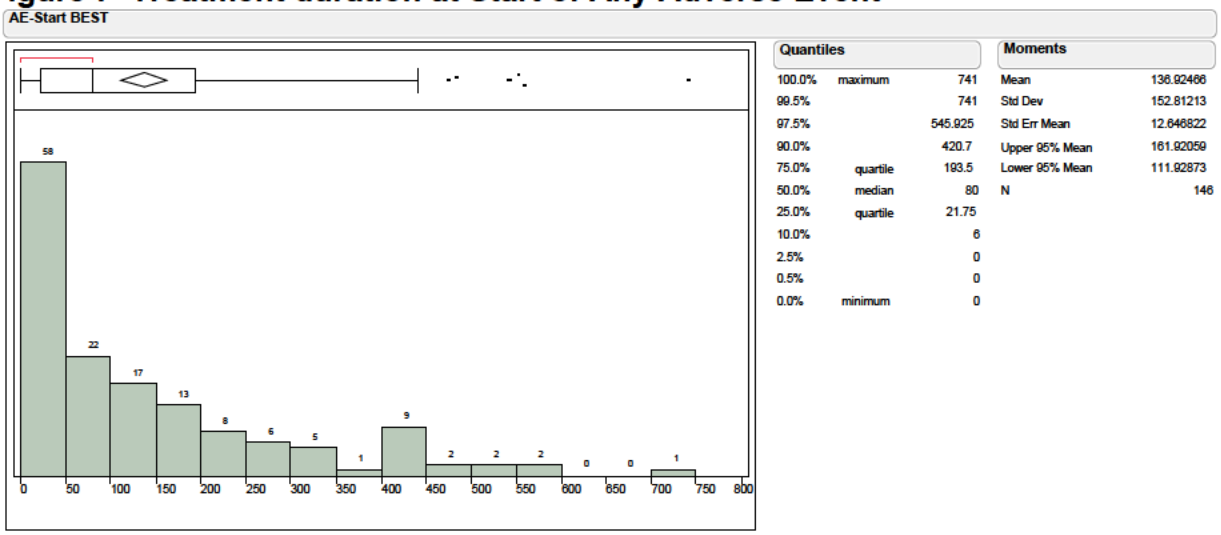
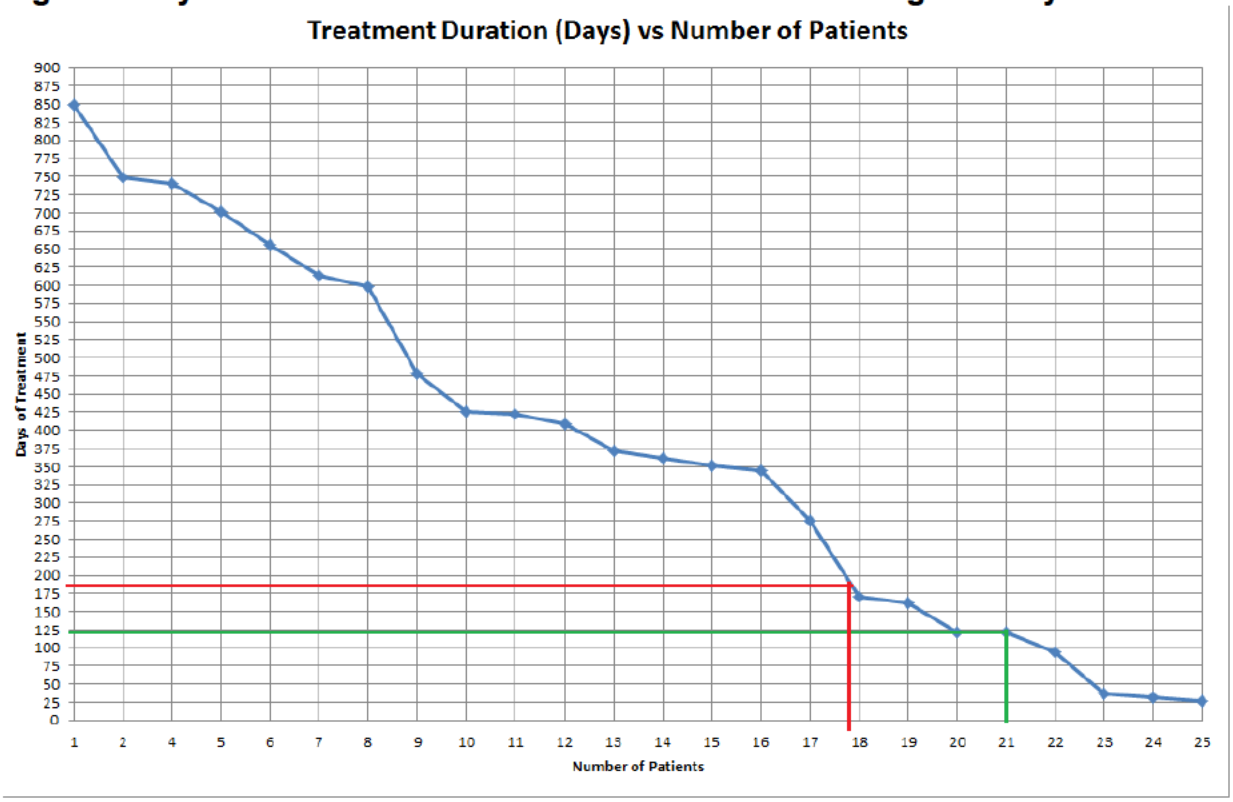


Figure 8 Days of treatment vs Number of Patients Remaining in Study



Reviewer Comment: The overall frequency of any adverse event in study 303 is comparable to the rufinamide treatment groups in studies 022 and 304. The frequency of vomiting, somnolence and diarrhea in study 022 are very similar to study 303.

Study 303 has an upper respiratory tract infection frequency of 32% while this adverse event is not included in the list of frequent events in study 022. Study 304 (Japanese study) has 31% frequency of nasopharyngitis. This preferred term may be considered a subset of the upper respiratory infection. The finding of a high frequency of upper respiratory infection in study 303 is not likely a safety signal. Study 304 reveals a similar frequency of a similar adverse event which may be considered a subset of “upper respiratory tract infection”. In addition the population in study 303 is younger than study 022 and is more susceptible to upper respiratory tract infection.

Overall there is no new safety signal based on examination of common adverse events.

7.4.2 Laboratory Findings

The written request parameters were to examine safety and Pk for an interval of 6 months (24 weeks), however study 303 was conducted to fulfill the United States Food and Drug Administration (FDA) Written Request (WR) and the European Medicines Agency (EMA) Pediatric Investigation Plan (PIP). As previously noted, the FDA requested a 6-month study to evaluate pharmacokinetic (PK) and safety objectives in this age population, while the EMA requested a 2-year study for the primary evaluation of cognitive development and behavioral effects in a pediatric population 1 to less than 4 years of age. This study remains ongoing to fulfill long-term efficacy objectives required in the PIP; the following laboratory data is derived from the interim CSR that has been prepared to evaluate the PK, safety, and tolerability objectives of the FDA WR, using a data cutoff date of 28 Feb 2014.

The widow of laboratory measurements evaluated in this section encompasses the 24 week interval of the written request. The schedule of clinical laboratory assessments is shown in Table 25. Studies in the analysis are shown in Table 26.

Table 25 Schedule of Clinical Laboratory Assessments

Period	Screening	Baseline	Titration	Maintenance										Taper	Follow up	Unscheduled	Early discontinuation
Week	-8 to -1	0	1	2	4	8	16	24	40	56	72	88	106				
Laboratory tests	X	X		X	X	X	X	X					X		X		X

Table 26 Hematology and Chemistry Parameters for Analysis

Category	Parameter
Hematology	RBC, Hgb, Hct, platelets, and WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	ALT, AST, ALP, Total Bilirubin, Direct Bilirubin, LDH, Na+, K+, Cl^-, HCO_3, PO_4, Albumin, Amylase, Triacylglycerol lipase, Ca^{++}, BUN, Creatinine, serum protein, uric acid, Urine ph, serum glucose, triglycerides.

Although there is a randomized, parallel control group it does not represent a blinded control. In the analysis of clinical laboratory parameters the reviewer does not perform direct comparison to this parallel comparator except in instances where means, outliers or shifts indicate a potential safety signal, see 9.4 Laboratory Analysis Appendix.

The sponsor indicates there were no changes of clinical importance in mean hematology or clinical chemistry values over time, for any parameter. The sponsor also reports the shift analysis also revealed no shifts of clinical concern for hematology or clinical chemistry parameters. The outlier examination by the sponsor revealed notably low values for bicarbonate in 5 of 25 [20.0%] of subjects in the rufinamide group and 4 of 11 [36.4%] subjects in the any-other-AED group).

Due to the decline in bicarbonate seen in the sponsor's outlier examination the bicarbonate laboratory dataset is examined in detail by the reviewer. There is a mean and median decline in bicarbonate values noted at week 16 but not week 24. There are also 4 (20%) subjects who have a shift from normal to low at week 16 and 2 (10 %) subjects with a shift from normal baseline to low value at week 24. The comparator group is examined and reveals a similar mean change from baseline over the course of the study. Chloride values are examined to determine if there is a parallel increase in chloride values, a reciprocal change in these laboratory parameters which may be seen in metabolic acidosis. No notable increase in chloride is identified.

The reviewer examination of hemoglobin revealed negative mean change from baseline at weeks 4, 8, 15 and 24. These changes were small, not exceeding 2% but due to the consistency of the mean negative change additional expanded examinations were performed on hemoglobin and hematocrit. This analysis is also examined in the "any other AED" group and there is no notable difference between the two treatment groups. Outlier and shift analysis are also performed which reveal one low hemoglobin outlier in the rufinamide treatment group at weeks 16 and 24 each. There is also one shift from normal to low hemoglobin at weeks 16 and 24. The minimum hemoglobin values in these shifts is 10.3 g/dl. The observation of a small negative mean change from baseline, a single patient with a CTCAE category I outlier value and a single patient at 16 and 24 weeks with shift from normal baseline to low value do not sum to significant evidence of a safety signal for hemoglobin decline, see Hemoglobin.

Urinalysis

The sponsor indicates no changes of clinical importance in mean urinalysis values over the course of the study. The reviewer spot checked leukocytes, occult blood and patient E2080-G000-303-5005-1004, a 15 month old, is identified with TNTC leukocytes in urine at weeks 2 and 8 with an AE of “Escherichia Urinary Tract Infection” at approximately week 10. . There are urine occult blood measurements available for 17 of the rufinamide patients with one positive result at week 8 in the same patient, E2080-G000-303-5005-1004, who experienced “Escherichia Urinary Tract Infection”. Another two patients are identified with single incidents of 4 to 12 leukocytes / HPF on week 4. The AE dataset is examined and no urinary tract infection is identified in these subjects.

Any crystals are identified in 5/11 (45%) of the “any other AED” group and 9/24 (38%) in rufinamide treatment group. Bacteria are identified in the urine of 12/24 (50%) in rufinamide treatment group and 6/11 (54%) in the “any other AED” group. Hyaline casts are identified in 2/24 (8%) of the rufinamide treatment group and 1/11 (9%) of the “any other AED” group.

Examination of the urinalysis results supports the sponsor conclusion that there are no changes indicating a safety signal in the urinalysis results.

Reviewer Comment, Laboratory Findings: The review directs additional focus on bicarbonate due to the mean negative change and 20% shift to low at week 16 with no shift to high. The AE dataset reveals there are 2 (20%) patients in the 1 to <2 year group with an AE preferred term of “blood bicarbonate decreased”. A comparison to the older LGS patient group from study 022 cannot be performed because bicarbonate was not measured in that study. Examination of the study 303 comparator “any other AED” group reveals there is also 1 patient (33%) in the 1 to <2 year group with “blood bicarbonate decreased”. A post marketing search of preferred terms related to low bicarbonate or acidosis reveals no EB05 signal, see section 8 Postmarket Experience. Overall examination of the clinical laboratory findings supports the sponsor’s conclusion that “there were no changes of clinical importance in mean hematology or clinical chemistry values over time, for any parameter”.

7.4.3 Vital Signs

Blood Pressure

Examination of the mean and median change from baseline systolic blood pressure reveals values of 0.32mmhg and -3.57mmhg respectively at week 16 and a mean of 2.65mmhg and median of -0.96mmhg at week 24 with a range at both weeks 16 and 24 that has a near equal distribution around zero. Examination of the change from baseline mean and median diastolic values at week 16 is 0.25mmhg and 0 respectively with a

range of -27 to 40. The mean and median at week 24 are 8.2 and 3.3 respectively with a range of -15 to 67mmhg.

Systolic and diastolic blood pressure outliers are examined. The sponsors' clinically notable flag is utilized to mark outliers. Patients in the systolic outlier flag group had a blood pressure at visit that was less than 90mmhg with a decline from baseline greater than 20mmhg. Patients with the diastolic low blood pressure flag had a value, less than 50mmhg with a decline from baseline ≥15mmhg.

There was one systolic low outlier at week 16 and 24 each as well as one diastolic blood pressure outlier at week 16. *There were no high systolic or diastolic blood pressure outliers*.

Shift analysis was performed using low or high shift criteria of ±20mmhg for both systolic and diastolic blood pressure. Weeks 4, 16 and 24 were examined. Examination of systolic blood pressure at week 4 and 16 revealed equal numbers of patients with high and low shifts. At week 24 there was one patient with a low shift and 2 with high shift. Diastolic blood pressure revealed no low shift at week 4 and 2 high shifts while at week 16 there were no patients with a change greater than ±20mmhg from baseline. At week 24 there were no patients with low shift and one patient with high shift, Table 27.

Patients with the two largest negative changes from baseline were examined for overall trend during the study. The patients sustained a large negative change from baseline during the study; however, examination of the adverse events reveals these patients did not have adverse events associated with a decline in blood pressure. Both these patients were approximately 2 years of age. All patients with a decline in systolic blood pressure greater than 20mmhg at any time during the study had an examination of their blood pressure values during the entire study timeline. This exam did not reveal a trend of sustain declining blood pressure in any patient. Blood pressure values were seen to decline then stabilize or decline and return toward baseline, Figure 63 .

Examinations of measures of central tendency, outliers and shifts from baseline in the "any other AED" comparator reveal blood pressure features similar to the rufinamide treatment group, Table 28.

A graphic display of the systolic and diastolic blood pressure mean and median change from baseline from weeks 1 to 24 in rufinamide and "any other AED" treatment may be seen in 9.7 Blood Pressure Analysis.

Table 27 Rufinamide Treatment, Means, Medians, Outliers and Shifts at Week 16 and 24

Rufinamide treatment
Systolic BP, Percent (%) change from Baseline to Week 16 and 24. Means and Medians, 0-24 weeks

Statistic	Week 16	Week 24
Mean	0.32	2.65
Median	-3.57	-0.96
Range	-32 to 28	-30 to 42

Diastolic BP, Percent (%) change from Baseline to Week 16 and 24. Means and Medians, % change 0-24 weeks

Statistic	Week 16	Week 24
Mean	0.25	8.2
Median	0	3.33
Range	-27 to 40	-15 to 66.7

Outliers (normal at baseline, based on sponsor clinically significant low – high flags: Systolic BP <90mmhg at visit with decline from baseline ≥20mmhg, Diastolic BP low <50mmhg and decline from baseline ≥15mmhg

	Week 16	Week 24
Systolic # Patients Low	1 (5%)	1 (6%)
Min value	86	84
Diastolic , # Patients low	1 (5%)	0
Min value	44	
Systolic # Patients high	0	0
Diastolic , # Patients high	0	0

Systolic BP, ± 20mmHg Shifts from Baseline at Weeks 4, 16 and 24

	Shift from baseline to week 4, all (n=21)		Shift from baseline to week 16, all (n=19)		Shift from baseline to week 24, (n=18)	
	<(-20)	>20	<(-20)	>20	<(-20)	>20
# patients	2	2	1	1	1	2
high value		113		124		118
Low value	92		86		84	

diastolic BP Shifts from Normal to high or low at Weeks 4, 16 and 24

	Shift from baseline to week 4, all (n=21)		Shift from baseline to week 16, all (n=19)		Shift from baseline to week 24, (n=18)	
	<(-20)	>20	<(-20)	>20	<(-20)	>20
# patients	0	2	0	0	0	1
high value		86				70
Low value						

Among the six outliers values (2 patients) with the largest negative change from baseline at any point in the study there are no adverse events associated with a decline in blood pressure. There are no instances of syncope or dizziness, postural dizziness, or orthostatic hypotension.

USUBJID	WEEK of Treatment	CHANGE FROM BASELINE
E2080-G000-303-1016-1003	8	-46

E2080-G000-303-1016-1003	16	-40	
E2080-G000-303-1016-1003	40	-48	
E2080-G000-303-7002-1001	1	-60	
E2080-G000-303-7002-1001	2	-39	
E2080-G000-303-7002-1001	24	-36	

Table 28 "any other AED" Comparator, Means, Medians, Outliers and Shifts at Week 16 and 24

"any other AED" treatment						
Systolic BP, Change from Baseline to Week 16 and 24. Means and Medians, % change 0-24 weeks						
Statistic			Week 16		Week 24	
Mean			3.7		-4.7	
Median			2.86		-7.77	
Range			-26 to 27.5		-11 to 7.5	
Diastolic BP, Change from Baseline to Week 16 and 24. Means and Medians, % change 0-24 weeks						
Statistic			Week 16		Week 24	
Mean			1.25		-6.9	
Median			3.9		-8.5	
Range			-37 to 41		-23 to 8.8	
Outliers (normal at baseline, based on sponsor clinically significant low – high flag						
			Week 16		Week 24	
Systolic # Patients Low			1		0	
Min value			87			
Diastolic , # Patients low			1		0	
Min value			50			
Systolic # Patients high			0		0	
Diastolic , # Patients high			0		0	
Systolic BP, ± 20mmHg Shifts from Baseline at Weeks 4, 16 and 24						
	Shift from baseline to week 4, all (n=9)		Shift from baseline to week 16, all (n=6)		Shift from baseline to week 24, (n=5)	
	<(-20)	>20	<(-20)	>20	<(-20)	>20
# patients	0	2	1	1	0	0
high value		115		102		
Low value			80			
diastolic BP Shifts from Normal to high or low at Weeks 4, 16 and 24						
	Shift from baseline to week 4, all (n=9)		Shift from baseline to week 16, all (n=6)		Shift from baseline to week 24, (n=5)	
	<(-20)	>20	<(-20)	>20	<(-20)	>20
# patients	0	0	1	0	0	0

high value						
Low value			79			

Reviewer Comment: Analysis of blood pressure in rufinamide treated patients during the course of the study does not reveal clinically notable sustained changed from baseline. This conclusion is further supported by similar findings in examination of the "any other AED" comparator.

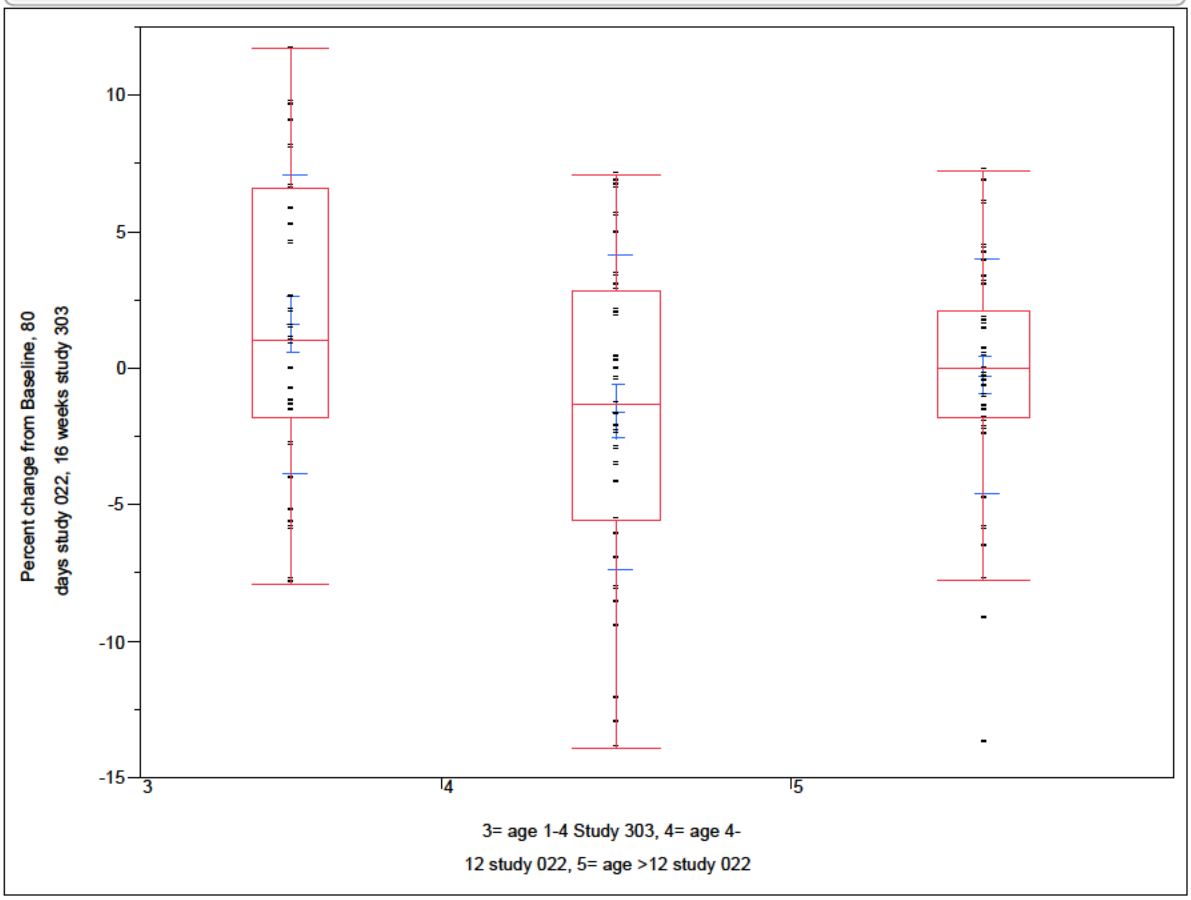
Weight Analysis

Rufinamide may cause nausea, vomiting and loss of appetite. Decreased weight has also been observed in post marketing use. The younger population with less physiologic reserve due to smaller body mass may be susceptible to adverse effects of weight decrease if there is gastrointestinal intolerance. Weight is evaluated in several ways in the subsequent analysis. Absolute weight change over time is not a reliable metric in young children, unlike adults. Due to the growth and development trajectory that is superimposed over the time course of the study patient weight will be expected to increase in a predictable relationship to their age; however, absolute weight nonetheless contains some information. If weight remains static over time or declines in the 1 to 4 year old population it may be considered an undesirable effect, it is counter to expected growth trajectory. In both these cases (static or declining weight) the absence of weight gain indicates a suppression of expected development. A metric which integrates the expected developmental increase in weight based on age group is needed for assessment. This metric is the weight percentile for age.

An initial analysis based on direct weight measurement in rufinamide treated patients is performed to examine the change from baseline weight across several age ranges, including age strata not contained in study 303. To perform this analysis the mean and median change from baseline weight at week 16 in study 303 and at day 80 in study 022 are examined. The age composition of study 022 ranges from 4 years to 35 years of age. Patients from the rufinamide treated arm are divided into two groups, one containing ages 4 to <12 and the second containing ages 12 and older. These two age strata are compared to all patients (age 1-<4) from study 303. This analysis is shown below in Figure 9. This examination reveals a mean and median gain in weight at week 16 of study 303 while there was a mean and median decline in weight in both the young and older age strata of study 022. This tendency was greater in study 022 age ranges 4 to 12. The sample size of each age strata was similar, shown in Table 29. The observation that weight in the younger population of study 303 remains stable when compared to the two age strata of study 022 provide some assurance that this young population does not have an selective vulnerability to the weight reduction properties of rufinamide.

Figure 9 Percent Change from Baseline at 16 weeks in Study 303 and 80 days in study 022. X axis Code: 3= Study 303 all pts (age 1-4), 4= Study 022 ages 4-12, 5= Study 022 ages <12. Rufinamide treatment

Oneway Analysis of Percent change from Baseline, 80 days study 022, 16 weeks study 303 By 3= age 1-4 Study 303, 4= age 4-12 study 022, 5= age >12 study 022



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
3	-7 89474	-5.86016	-1.86632	1 008105	6.606786	9 58379	11.66667
4	-13.8776	-10.488	-5.55556	-1.29032	2.880658	6.710675	7.096774
5	-13.6919	-6.62942	-1.8198	0	2.140975	4.598667	7.220217

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
3	30	1.6036	5.48477	1.0014	-0.444	3.6517
4	35	-1.6017	5.78883	0.9785	-3.590	0.3868
5	38	-0 2778	4.31311	0.6997	-1.696	1.1399

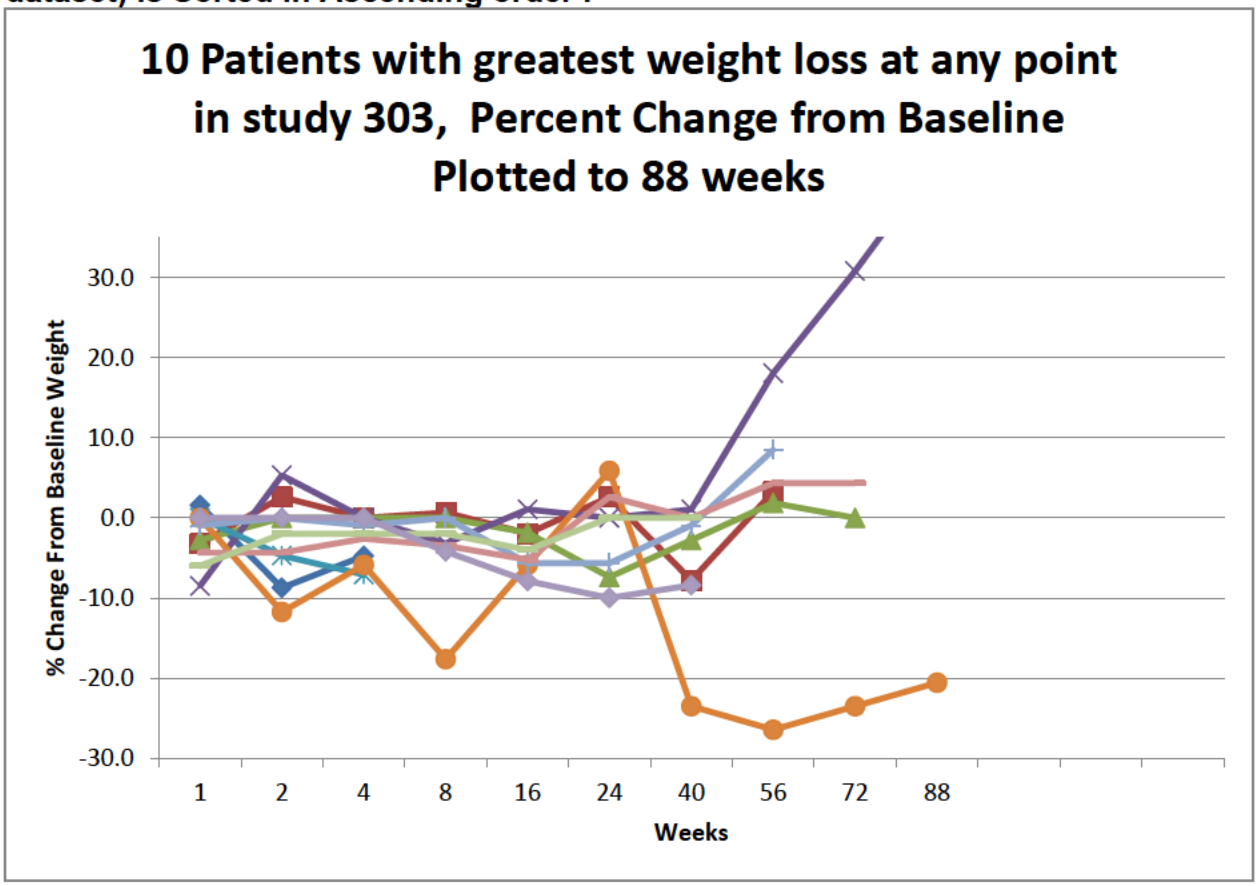
Table 29 Sample size (n) of age groups from percent change from baseline analysis shown in Figure 9.

Study and ages of rufinamide treatment patients	Sample time (weeks)	N
Study 303, ages 1 to ≤4 years	16	31
Study 022 ages 4 to ≤ 12 years	11.5	35
Study 022, ages >4 years	11.5	38

The next approach in weigh evaluation of study 303 is an examination of outliers. The 10 rufinamide treated patients with the largest declines in weight at any point in the study are captured from the vital signs dataset. One of these patients 4004-1001 a 37 month old female had a sustained downward trend through the course of the study to 56 weeks, see Figure 10. This trend was interrupted by a single increase from baseline at week 24. This patient had an adverse event of weight decrease that was considered severe but was not an SAE. This patient also had several AE entries of bronchitis, in addition to a single entry each for tonic convulsion, gastroenteritis, and vomiting. Rufinamide was not discontinued. There was a second patient with an adverse event of weight decrease, subject 4001-1002 a 13 month old male, also in the group of top 10 weight loss patients. This patient also had several AE entries, none SAEs. The AE entries included three entries of decreased appetite, one “epilepsy”, one entry of varicella, three entries of vomiting as well as the weight loss. In this case it is possible that superimposed illness contributed to weight loss. The timeline of the weight decrease entry is subsequent to the entry for varicella.

These 10 patients are those who have an entry of largest magnitude weight decrease at any point on the study timeline. Each of these patients has weight measurements from all study visits captured to create a weight vs time trend, see Figure 10. As noted above, only patient 4004-1001 had a sustained decrease in weight. This graph reveals weight stabilizes without dropping below a 10% reduction from baseline in 9 of the 10 patients, but does not appear to keep up with expected developmental weight increase.

Figure 10 Percent Change from Baseline Plotted to 88 Weeks. 10 Patients with Highest Magnitude Weight Loss When Change from Baseline Weight (ADVS.xpt dataset) is Sorted in Ascending order .



Percentile weight for age is examined at weeks 24 and 40. These longer time intervals are chosen to capture weight change that are more likely due to a sustained treatment effect. The weight percentile based on age and weight is calculated using the Medscape medical calculator where percentile values are provided by the CDC[3]. The baseline weight percentile is calculated as well as the week 40 and 24 weight percentiles. The percentile calculation for weeks 24 and 40 are adjusted for the addition of (growth) time elapsed from baseline. Twenty four weeks is added to baseline age to give age at 24 weeks, the percentile weight is then calculated based on the resultant age (24 weeks + baseline age). The same approach is used to calculate week 40 percentile.

The 40 week analysis of rufinamide treated patients reveals a mean and median change from baseline percentile of 3.7 (percentile units) and 1 (percentile unit) respectively. The range of percentile change ranges from -87 to 45, Figure 11 . An

[3] http://reference.medscape.com/calculator/infant-weight-age-percentile
Supplied by WEBMD LLC, 825 8th Ave. 11th Floor, New York, NY 10019.

analysis of bivariate fit of the percentile reduction by age is performed to determine if there is a notable correlation between the percentile reduction and patient age, Figure 12. This analysis revealed no correlation.

Figure 11 Distribution of the Change in Weight Percentile from Baseline to Week 40 among rufinamide treated patients. N=17

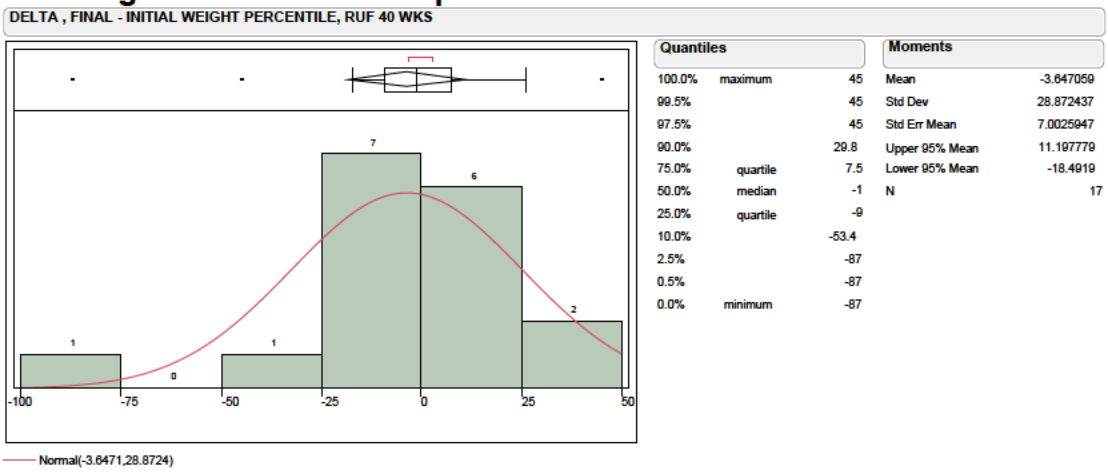
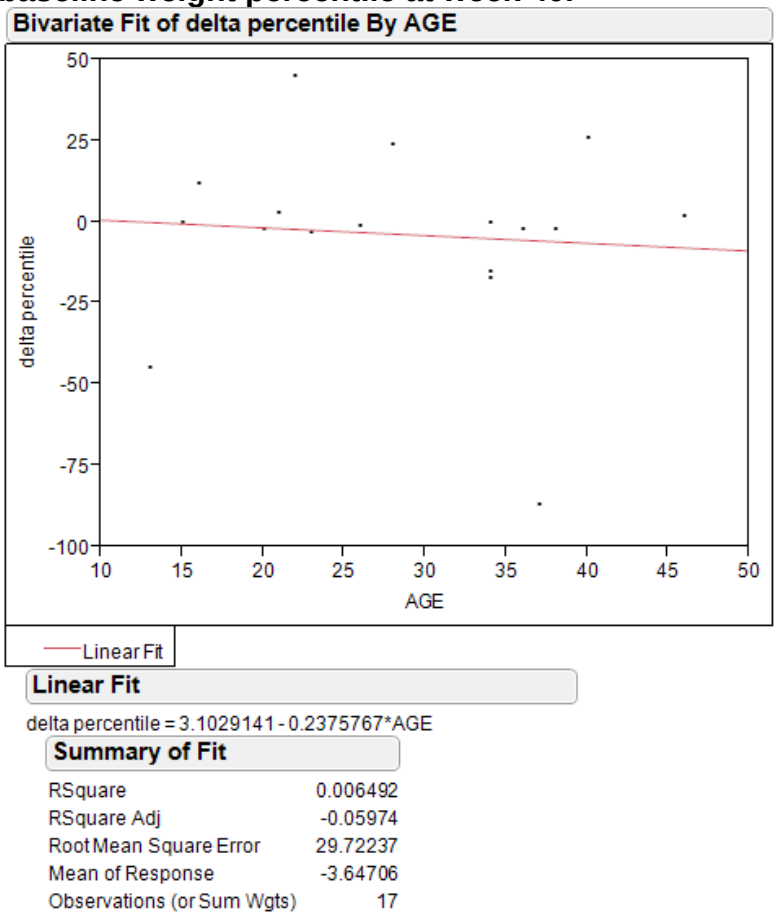


Figure 12 analysis of correlation between age in months and change from baseline weight percentile at week 40.



A 24 week analysis is also performed to examine the same parameters as in the 40 week analysis. The 24 week analysis reveals a mean and median reduction from baseline weight percentile of 0.7 and 1.5 percent respectively. The range of percentile change is from -30 to 28, Figure 13. An analysis of bivariate fit of the percentile reduction by age is performed to determine if there is a notable correlation between the percentile reduction and patient age, Figure 14. This analysis revealed no correlation.

Figure 13 Distribution of the Change in Weight Percentile from Baseline to Week 24 among rufinamide treated patients. N=20

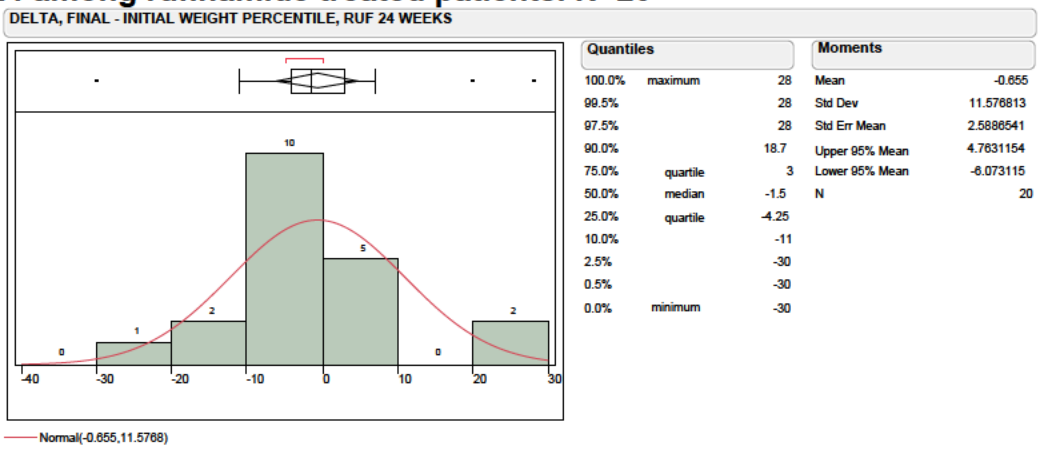
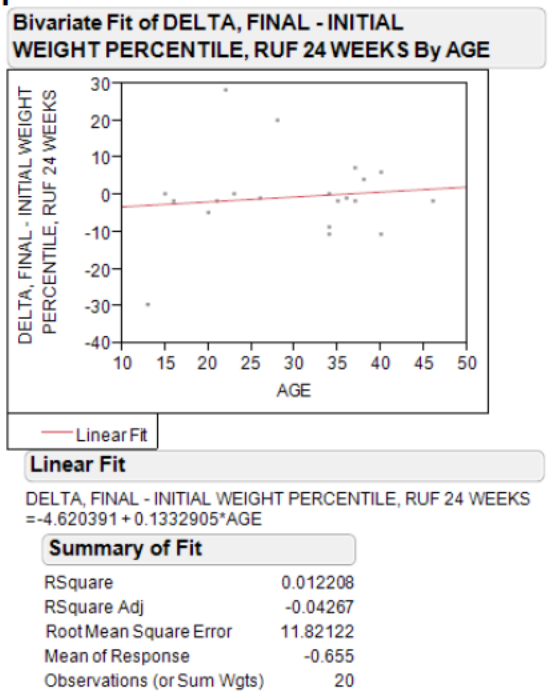


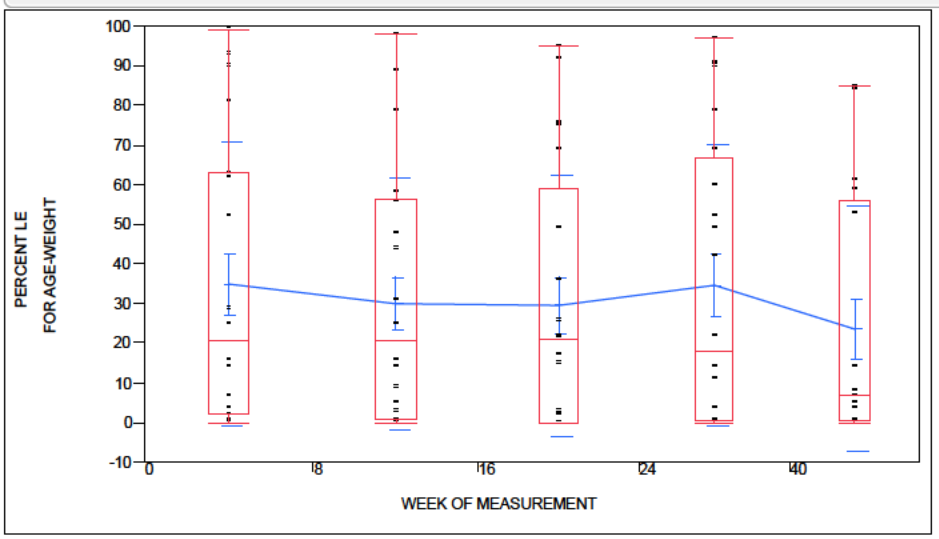
Figure 14 analysis of correlation between age and change from baseline weight percentile at week 24



In order to examine the trend in percentile weight through the course of study 303 among rufinamide treated patients, the mean and median percentile values at baseline, and weeks 8, 16, 24 and 40 are plotted in Figure 15. This analysis reveals a small mean reduction is weight percentile at weeks 8 and 16 with a larger decline at week 40. The median values reveal a small median increase at week 16 with a larger median decrease at week 40.

Figure 15 Mean and Median Patient Weight Percentile by Study Week, rufinamide treatment study 303 (n=17).

Oneway Analysis of PERCENTILE FOR AGE-WEIGHT By WEEK OF MEASUREMENT



Quantiles

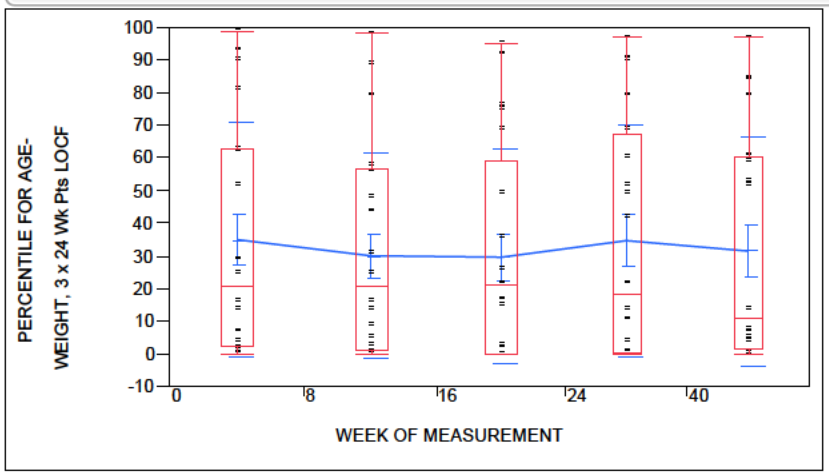
Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	0	0.03	2	20.5	63	92.1	99
8	0	0	0.75	20.5	56.5	86	98
16	0	0	0	21	59	88.8	95
24	0	0	0.25	18	66.75	90.9	97
40	0	0	0.5	7	56	84.2	85

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
0	22	34.9136	35.6870	7.6085	19.091	50.736
8	22	29.9545	31 5542	6.7274	15.964	43.945
16	21	29.5238	32.9053	7.1805	14.545	44.502
24	20	34.6000	35.7306	7.9896	17.878	51.322
40	17	23.5294	31.0768	7.5372	7.551	39.508

Figure 16 Mean and Median Patient Weight Percentile by Study Week with 3 of the post 24 week missing values included at week 40 as LOCF, rufinamide treatment study 303 (n=20).

Oneway Analysis of PERCENTILE FOR AGE-WEIGHT,
3 x 24 Wk Pts LOCF By WEEK OF MEASUREMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	0	0.03	2	20.5	63	92.1	99
8	0	0	0.75	20.5	56.5	86	98
16	0	0	0	21	59	88.8	95
24	0	0	0.25	18	66.75	90.9	97
40	0	0	1.75	11	60.5	84.9	97

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
0	22	34.9136	35.6870	7.6085	19.091	50.736
8	22	29 9545	31.5542	6.7274	15.964	43.945
16	21	29 5238	32.9053	7.1805	14.545	44.502
24	20	34.6000	35.7306	7 9896	17.878	51.322
40	20	31.4000	35.1679	7 8638	14.941	47.859

Reviewer Comment: Multiple analyses of weight during the course of study 303 are performed due the concern about the impact of nausea, vomiting and loss of appetite observed in the development program. These adverse effects will have a disproportionately greater effect on young children who have small body volume and mass.

A cross study examination of weight to compare the mean change from baseline to week 16 in study 303 and day 80 in LGS study 022 was performed. There was a mean increase of 1.6 kg in study 303 composed of patients ages 1 to <4 years. In the subset of patients ages 4 to <12 in study 022 there was a mean decline of 1.6 kg. The subset

of patients in study 022 greater than or equal to 12 years of age had a mean decline of .23 kg. The change in weight in these groups is in part driven by the growth and development curve which spans the age 1 to >12 age range. The slope of this curve is not uniform across this span, thus analysis of absolute weight across these age groups lacks precision. The general conclusion which may be established is the youngest age group of study 303 continued to have mean positive weight during the treatment interval while the 4 to 12 age group of study 022 had movement that was counter to the expected direction. This offers some assurance that younger patients treated with rufinamide do not have a selective vulnerability to weight loss during treatment. This conclusion is further supported by the analysis of the slope of percentile weight change examined by age. There was no correlation between weight change at weeks 24 or 40 and age.

Examination of percentile weight change from baseline at weeks 24 and 40 reveals a small mean decline. Additional analysis of patient weight percentile at baseline and weeks 8, 16, 24, and 40 also reveals a consistent mean decline that becomes suddenly steeper at week 40. Further scrutiny of the week 40 patient group reveals the absence of 3 patients who contributed to the week 24 group analysis. These patients collectively contribute an average weight percentile of 76%. The remaining 17 patients who contribute to the week 40 sample are examined to determine their percentile weight change from week 24. Seven of these patients have an increase in percentile weight, three patients have no change and 7 have a decline in percentile weight. One of those with a decline is an extreme outlier with a week 24 to week 40 difference in weight percentile of -86 (patient E2080-G000-303-4004-1001). This patient is also seen in Figure 10 as an outlier with the steepest negative decline in weight from week 24 to 40.

An examination is performed which retains the 3 patients from week 24 group analysis who did not contribute to initial week 40 analysis. The percentile weights of these three patients are carried forward (LOCF) to 40 weeks. In this scenario the mean percentile at week 40 is 31.4 percentile. This value is lower than week 24 but greater than at weeks 8 and 16, see Figure 16. This carry forward analysis also yields a mean change in percentile points between weeks 24 and 40 of -3.2. This examination does not capture the true behavior of the three patient discontinuations where there may have been some weight loss; however, it provides a more accurate balance to the extreme outlier which results in the marked decline in mean weight percentile of the 17 patient 40 week analysis.

An analysis of the weight percentile by study week in “any other AE”group is performed as a comparator. There is a notably higher baseline mean percentile weight in the 11 entering patients compared to the rufinamide treatment arm. Between week 8 and week 40 there is also a continued decline in weight although the number of patients at each week also declines notably. The small numbers as the study progresses confound a meaningful comparison to the rufinamide arm.

In summary, weight loss is seen over the study interval. In those with the largest weight loss at any point in the study the weight is seen to stabilize in all but one of these outlier patients, see Figure 10. The weight loss in this young population is not more prominent than seen in the older pediatric population of study 022. The decline in weight is dramatic in only a single outlier patient who developed a confounding illness during the study. The entry for weigh loss in proposed labeling section 6.1 “weight decreased 8%” as well as “decreased appetite 12%” should be retained. Together, these entries are adequate strength in labeling for the observations of weight loss identified in the foregoing analyses.

7.4.4 Electrocardiograms (ECGs)

QT analysis

Background

During the initial review of in 2005 it was found that Rufinamide has the novel adverse effect of dose related QT shortening. The risk associated with QT shortening among outliers in the general population is uncertain. There is risk identified in patients with short QT syndrome. The short QT syndrome (SQTS), a rare familial disorder characterized by an abnormally shortened cardiac repolarization and a propensity for cardiac arrest (CA) was recognized approximately 14 years ago[4]. Mutations in genes encoding potassium and L-type cardiac calcium channels have been identified that explain the disease in a small proportion of SQTS patients. Detailed genotype-phenotype information is limited by the rare nature of this disorder. The natural history of the disease is incompletely understood, and uncertainties exist about all aspects of SQTS, from diagnosis to risk stratification and management. Diagnostic criteria for SQTS are debated and the cutoff value of the QT interval required to consider a diagnosis of the disease is not established.[5] QTc values of 350 ms for men and 360 ms for women are derived considering a cutoff value of 2 SDs from the mean value obtained in a normal population. It is unclear if there is a strict partitioning between patients at risk from short QT who have an underlying channelopathy and those who may develop a short QT interval due to drug induced shortening. However, a longitudinal study of healthy individuals with a QTc <340 ms revealed no documented evidence of arrhythmias over an average follow-up of 29 years.[6]

In a cohort of SQTS defined as a QTc interval <340 ms or QTc interval between 341 ms and 360 ms and 1 or more of the following: history of CA or syncope, a family history of

[4] Gussak I, Brugada P, Brugada J, et al. Idiopathic short QT interval: a new clinical syndrome? Cardiology 2000;94:99–102
[5] Mazzanti A, Kanthan A, Monteforte N, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol 2014;63: 1300–8.
[6] Anttonen O, Junttila MJ, Rissanen H, Reunanen A, Viitasalo M, Huikuri HV. Prevalence and prognostic significance of short QT interval in a middle-aged Finnish population. Circulation 2007;116: 714–20.

unexplained CA at a young age (40 years of age or younger), or a family history of SQTS. In this study the rate of CA was 4% in the first year of life and 1.3% per year between 20 and 40 years; the probability of a first occurrence of CA by 40 years of age was 41%. The annual rate of a first cardiac arrest was 0.9% over a mean observation period of 31 years. A history of CA was the only predictor of recurrences at follow-up.[7]

These studies do not firmly clarify the risk to patient on a QT shortening drug. The definition of a short QTc is also not firmly established and there is inconsistency in the method used for heart rate related QTc correction. Bazett's method was utilized in the population study by Anttonen et al., as well as the recent SQTS cohort study by Mazzanti et al. The use of Bazett's correction for diagnosis of short QT syndrome has been criticized in the medical literature[8] and is not the recommended method by the E14 Guidance. The guidance states "In general, however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute (bpm) and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates."[9]

Based on the threshold for short QTcB applied by Mazzanti et al. no rufinamide treatment patients fulfil criteria for SQTS at any post baseline measurement in study 303. Examination using QTcF reveals 15 patients who have short QT syndrome at any scheduled post baseline measurement. Subsequent analysis will be performed using QTcF based on the E14 guidance (QTcF); however this does not allow comparison with values identified by the reviewer from recent cardiology literature (due to the use of QTcB in the literature). An alternate strategy will be to compare QTcF data from study 303 to the data provided for the second cycle review of rufinamide in the ISS Amendment[10].

Source of QTcF measurements

ECG data from Study E2080-G000-303: ECG parameters are sorted and QTcF values for baseline and weeks 4, 8, and 16 are captured for analysis from the ADEG.xpt dataset.

QTcF data from the EIASI Complete Response to FDA September 15, 2006 Approvable letter, ISS amendment (amendment to original submission 9/8/2005) is examined. The derivation of the source of the ISS tables is not identified in the document but is likely from the TQT study (E2080-A001-002). Subsequent examination of the ISS tables and

[7] Mazzanti A, Kanthan A, Monteforte N, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol 2014;63: 1300–8.
[8] Bjerregarrd P. Proposed Diagnostic Criteria for Short QT Syndrome Are Badly Founded. J Am Coll Cardiol 2011;58:548-551.
[9] E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. P14
[10] Response Document to FDA Approvable Letter, Rufinamide, ISS Addendum. February 28, 2008.

comparison to the study E2080-A001-002 dataset, as described in greater detail below, confirms the tables are derived from the TQT study. These tables provide the basis for comparison to study 303.

Division Request for Analysis of QT Shortening

The basis of QTcF parameters from the prior submission is uncertain on initial inspection. The approvable action letter of September 15, 2006 requests: "The results of Study E2080-A001-002, which examined QT intervals, found rufinamide to be associated with reduction of the QT interval ranging from approximately 2 to 20 msec. For this study (E2080-A001-002) and for the ECG data collected in the clinical trials, please provide outlier tables summarizing the number and percent of subjects with QT intervals in each of the following categories….. We ask that you provide this table for each dose level and stratify by heart rate correction method."

Identity of ISS Amendment QT Analysis

In the ISS tables which are provided[11] the sponsor does not denote the study sources of the outlier patients. It is not stated if the patients are exclusively from study E2080-A001-002 or a larger pool of patients. The numbers of patients in the rufinamide and placebo groupings approximate the expectations of the numbers from treatment and placebo groups of the "definitive QTc" study where there were 117 patients enrolled with 56 patients receiving rufinamide and 45 subjects given moxifloxacin active control. In addition, entries for rufinamide dose and the timing of ECG procurement match those specified in the protocol for study E2080-A001-002. The PKATMOX dataset, an analysis dataset submitted with study E2080-A001-002, submitted on 3/17/2006 is examined. Day 12 data are extracted and analyzed. The analysis reveals an exact match between the ISS amendment tables and the PKATMOX dataset for both the total number of patients at the 3200mg dose with QTcF <400ms at all time collections and for the number of patients at 5.417 hrs post dose with a QTcF<400ms. These observations allow the conclusion that the QTc data tables in the 2008 ISS amendment are completely derived from the "definitive QT", "TQT" study E2080-A001-002 and may serve as comparators to study 303 of this application. This comparison will be developed in subsequent paragraphs.

Comparability of Study 303 and the 2008 ISS Amendment (containing tables from definitive QT study E2080-A001-002)

In order to be comparable the dose and timing of the ECG (QTcF) measurements must both be captured at the steady state of a given dose and at Tmax. The study 303 protocol indicates that ECG's were captured on the following schedule: "Twelve-lead, duplicate and consecutive, ECGs will be obtained at baseline (Visit 2), and Visits 5, 6,

[11] Response Document to FDA Approvable Letter, Rufinamide, ISS Addendum. February 28, 2008.

and 7. Visit 2 should be collected prior to dosing and Visits 5, 6, and 7 approximately 4 to 6 hours (where Tmax is 5.4 hr) after study drug administration..." Visit 2, 5, 6, and 7 correspond to weeks 0, 4, 8, and 16 respectively while the capture interval of 4 to 6 hours is approximately concordant with Tmax.

The QTc tables in the 2008 ISS amendment contain entries for the daily dosage of 2400mg, 3200mg, 4800mg, and 7200mg with ECGs obtained at 0 through 12 hours post dose. There is an entry at 5.4 hours which corresponds to the Tmax of rufinamide.

Dose comparison: the mean dose in study 303 during maintenance was 39mg/kg/day while the mean maximum achieved dose during the maintenance phase was 50 mg/kg/day. This dose is compared to "definitive QT" study dose of 3200 mg administered day 12. The mean dose delivered to patients who received rufinamide 5.4 hours after 1st rufinamide dose on day 12 of study E2080-A001-002 was 43.4 mg/kg. This is the dose strata of study E2080-A001-002 which best approximates the dose delivered to study 303 patients during maintenance.

Exposure: the exposure between study 303 and Study E2080-A001-002 is not comparable. The QTcF datapoints in study 303 are acquired in duplicate, between 4 and 6 hours post dose at baseline, weeks 4, 8, and 16. The QTcF values from the 3200mg dose in study E2080-A001-002 are acquired following the 1st dose on day 12 of rufinamide treatment. This is approximately 53 hours following the transition from 2400mg to 3200mg. The half-life of rufinamide is between 6 and 10 hours so both sampling points (study 303 and E2080-A001-002) are expected to be at steady state. However, it is uncertain if the additional (*much longer*) sustained exposure in study 303 affects QT properties.

Analysis of QTcF; study 303 compared to study E2080-A001-002

A QTcF shortening from baseline to weeks 4 through 16 is identified. There is a mean (median) QTcF reduction in duration from baseline of -9.9ms (-12), -14.2ms (-16), and -10.6ms (-13) at weeks 4, 8, and 16 respectively. In the "any other AED" active control comparator group there is a mean (median) increase in duration from baseline of 3.7ms (5), 8.9ms (6.5), and 12.5ms (10) at weeks 4, 8, and 16 respectively, see **9.5 Analysis of QTcF**.

Comparison of the frequency of patients at selected QTcF duration thresholds between study 303 and the TQT study E2080-A001-002 is shown in Table 30. This comparison reveals a notably greater proportion of patients in study 303 with QTcF durations shorter than those in the TQT study at successively each of the selected QTcF thresholds. This observation is noted beginning with QTcF intervals less than 400ms where 98% of study 303 patients have a QTcF <400ms and 83% of patients in the TQT study have a QTcF of shorter duration. At the <390ms threshold 95% of patients in study 303 have a shorter QTcF while in the TQT study there are 62% of patients with a shorter QTcF. At

the <350ms threshold it is seen that 43% of study 303 patients have a shorter QTcF while 4% of the TQT patients have a QTcF below this threshold.

In Table 30 one patient is seen to have QTcF duration below 300ms. Examination of this patients QTcF values at treatment weeks 4 to 16 reveals the lowest value occurred at week 4 with a value of 346ms at week 8 and 307 at week 16. There is no trend of declining QTcF with continued rufinamide exposure.

Examination of QTcF shift from baseline values reveal similarity in the shift profile between study 303 and the TQT study. There were 63% of patients in study 303 with a decrease of greater than 10ms from baseline to maintenance interval while in the TQT study 77% of patients had a decline in duration from baseline greater than 10ms. Forty five percent (45%) of patients in study 303 had a decline from baseline to any maintenance measurement greater than 20ms while in the TQT study 46% of patients had a decline from baseline to 3200mg /day that was greater than 20ms, Table 31.

The analysis to this point reveals there is a divergence between the proportions of patients during rufinamide treatment at progressively shorter QTcF thresholds in study 303 compared to the TQT study. This divergence is notable beginning at 400ms. In contrast, the proportion of patients during rufinamide treatment who have a reduction from baseline to treatment where QTcF values are reduced more than 10ms and reduced more than 20ms is similar between the two studies, Table 31.

The divergence between absolute QTcF intervals and change from baseline values between study 303 and the TQT study is further evaluated by comparing baseline QTcF values between the two studies. This examination reveals that baseline QTcF values in study 303 are consistently shorter than in the TQT study. It is shown in Table 32 that 95% of patients in study 303 had a baseline QTcF less than 400ms while in the TQT study 50% of patients had a shorter QTcF. Eighty one percent (81%) of patients in study 303 have a baseline QTcF less than 390ms compared to 33% in the TQT study. Continuing to QTcF duration less than 350ms it is seen that 19% of patients in study 303 have a shorter QTcF while in none of the patients in the TQT study have a baseline value less than 350ms.

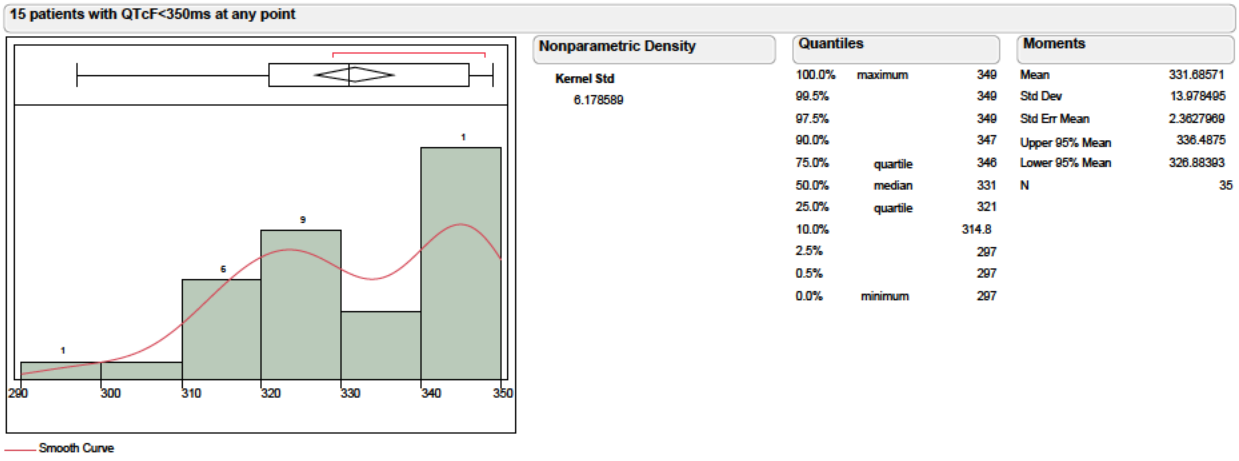
There are several differences between the subjects in study 303 and those in the TQT study. These differences include age of the sample group. The mean age of rufinamide treated patients in study 303 is 28 months (2.3 years) while the mean age of patients in the 3200mg rufinamide treatment group in the TQT study is 32.5 years. The medical status of the two groups is clearly different. Study 303 is comprised of Lennox-Gastaut syndrome patients treated with one to three concomitant antiepilepsy (AED) drugs while the TQT study patients are *healthy volunteers* on no prescription drugs with the exception of oral contraceptives. An additional difference is duration of exposure to rufinamide. At the time of ECG sampling in the TQT study at the 3200mg dose level, subjects have been receiving rufinamide for approximately 12 days while in study 303 at

the week 4 ECG measurements the mean rufinamide treatment duration is 31 days. These are substantial differences although none is clearly causative of the divergence in baseline ECG between the samples.

Table 30 Magnitude of QTcF shortening in study 303 compared to the TQT study group based on examination of the proportion of rufinamide treated patients in the range of QTcF strata from <400ms to <300ms.

Comparison of Study 303 frequency of Patient at Selected QTcF Thresholds to BANZEL Development							
WEEK OF ECG Study 303	**N Rows**	**n measure ments**	**% of measure ments**	**total patients**	**Patients less than**	**% patients less than**	**"definitive QT" data % patients (n) <QTcF value at 3200mg* (days of total exposure =12, days at 3200mg ≈ 2.5)***
<410							
4	35	36	97	20	20	100	
8	35	35	100	20	20	100	
16	33	33	100	20	20	100	
Mean study 303 % patients over weeks 4-16			99			**100**	**94 (49)**
<400							
4	34	36	94	20	19	95	
8	35	35	100	20	20	100	
16	32	33	97	20	20	100	
Mean study 303 % patients over weeks 4-16			97			**98**	**83 (43)**
<390							
4	31	36	86	20	19	95	
8	33	35	94	20	19	95	
16	31	33	94	20	19	95	
mean wks 4-16			91			**95**	**62 (32)**
<350**							
4	12	36	33	20	9	45	
8	13	35	37	20	9	45	
16	10	33	30	20	8	40	
Mean study 303 % patients over weeks 4-16			34			**43**	**4 (2)**
<300							
4	1	36	3	20	1†	5	
8	35	35		20	0		
16	33	33		20	0		
Mean study 303 % patients over weeks 4-16			1			**2**	**0 (0)**
*EIASI Complete Response to FDA September 15, 2006 Approvable letter. Amendment to a pending application. m 5.3.5.3 ISS amendment Table 2.1, p 642 ,Table 3.1 p 648, Table 4.1 p 654, Table 5.1 p 660, Table 6.1 p 666.							

** In total there were 15 patients with QTcF <350 at ECG 1, 2 or both in week 4, 8, or 16. The mean QTcF of 35 measurements was 332 msec with a median of 331.



† Patient E2080-G000-303-5002-1002 had QTcF of 346 msec on week 8 and 307 at week 16.

† Patient E2080-G000-303-5002-1002 who had a QTcF value of 297ms at week 4 was seen to have an increase in QTcF duration at weeks 8 and 16 as shown below-

Subject ID	STUDY WEEK OF ECG, RUF, (DUPLICATE RECORDINGS 1 & 2)	QTcF Value
E2080-G000-303-5002-1002	4	297
E2080-G000-303-5002-1002	8	346
E2080-G000-303-5002-1002	16	307

Table 31 Proportion of patients with reduction from baseline QTcF greater than -10 or greater than -20 milliseconds (ms) during rufinamide treatment in study 303 and TQT

Study 303 frequency of shifts, <-10 and <-20 msec from baseline compared to TQT study, QTcF							
Study 303							"definitive QT" data % patients (n) <QTcF value at 3200mg* (days of total exposure =12, days at 3200mg ≈ 2.5)*
WEEK	N Rows	# SAMPLES	% SHIFT	n patients	patients <-10	% patients	
<-10							
4	19	36	53	20	13	65	
8	20	35	57	20	12	60	
16	19	33	58	20	13	65	
						63	**77 (40)**
<-20							
WEEK	N Rows				patients <-20		
4	9	36	25	20	8	40	
8	15	35	43	20	11	55	
16	11	33	33	20	8	40	
						45	**46 (24)**

*EIASI Complete Response to FDA September 15, 2006 Approvable letter. Amendment to a pending application. m 5.3.5.3 ISS amendment, table 8.1, page 678 and table 10.2 page 692.

Table 32 Comparison of Study 303 Baseline QTcF values with rufinamide TQT study Placebo Group

Comparison of Study 303 Baseline QTcF values with TQT Placebo Group QTcF					
STUDY 303					"definitive QT" data % patients (n) <QTcF value at 3200mg* (days of total exposure =12, days at 3200mg ≈ 2.5)*
N Rows	% samples	total patients with measurements available	# Patients < QTcF value	study 303 % patients < QTcF value	
<410					
33	94	21	20	95	83 (n=43)
<400					
32	91	21	20	95	50 (n= 26)
<390					
29	83	21	17	81	33 (n= 17)
<350					
6	17	21	4	19	0 (n=0)
<300					
35	0	21	0	0	0 (n=0)
*EIASI Complete Response to FDA September 15, 2006 Approvable letter. Amendment to a pending application. m 5.3.5.3 ISS amendment Table 2.1, p 642 ,Table 3.1 p 648, Table 4.1 p 654, Table 5.1 p 660, Table 6.1 p 666.					

Reviewer Comment: There is a notable increase in the magnitude of QTcF shortening in study 303 compared to the TQT group based on examination of the proportion of rufinamide treated patients in the range of QTcF strata from <400ms to <300ms. Further examination of the proportion of patients with shift from baseline to shortened QTcF values during treatment reveals a larger percentage of TQT study patients have a greater than 10ms reduction in QTcF than patients in study 303. The proportion of subjects in each of these studies who have a QTcF value greater than 20ms reduction from baseline to treatment is approximately equal. The disparity between proportions of patients with specific QTcF post treatment threshold values and post treatment *change from baseline* (baseline to treatment delta) is due to lower baseline QTcF values among the study 303 cohort. The basis of the baseline QTcF difference is uncertain but is likely based in the difference in characteristics between the study groups as discussed above. The overall impact of rufinamide on the QTcF based on examination of change from baseline is approximately the same in this 1 to 4 year old LGS cohort and the TQT (healthy) cohort. There is no evidence of a differential QT effect in the study 303 cohort compared to the cohort of subjects who participated in the TQT study for initial LGS approval

7.4.5 Special Safety Studies/Clinical Trials

none

7.4.6 Immunogenicity

Rufinamide is a small molecule drug and thus less likely than a therapeutic protein to elicit an antibody response, immunogenic action of this type has not been established. Current rufinamide (BANZEL®) labeling has a warning for Multi-Organ hypersensitivity Reactions, section5.4. The mechanism of this reaction is uncertain. In section 6.1, table 2 there is a 3% frequency of pruritus.

In study 303 there were no serious skin reactions. There were three patients who experienced rash, one an SAE although study drug was not discontinued. One patient experienced an AE “drug eruption” though to be due to treatment with amoxicillin, rufinamide was not discontinued. In total, there were 4 patients had an event of potential immunologic basis. There were no other adverse events of a clearly immunogenic nature in the AE dataset.

Reviewer Comment: There is no new signal for immunogenicity in the study 303 dataset.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The adverse event dataset is examined for rufinamide dose at time of any AE. The dose is divided into 10mg/kg epochs. The peak frequency of adverse events occurs at the target dose epoch. This is likely due to the higher exposure at this dose as well a longer sustained period of exposure at this dose level. At lower dose patients are moving through titration to the target does of 45mg/kg. Titration is 10mg/kg every three days. If tolerated, by day 13 patients have reached target dose.

Table 33 Number of Patients with any AE by 10 mg/kg Dose Epochs.

dose epoch mg/kg	# pts
0-10	6
10-20	5
20-30	6
30-40	8
40-50	18
50-60	3

7.5.2 Time Dependency for Adverse Events

Time to adverse events in study 303 by 4 week epochs was examined from week number 4 to week 24. This method captures events that occur within the 4 week interval between the displayed time points of weeks 4, 8, 12, 16, 20 and 24. In the examination of any adverse event the analysis reveals that 15 (60%) of patients have an adverse event within the first four weeks followed by 12 patients with an adverse event from week 4 to week 8. A patient may have more than one adverse event, thus may contribute an adverse event to more than one epoch.

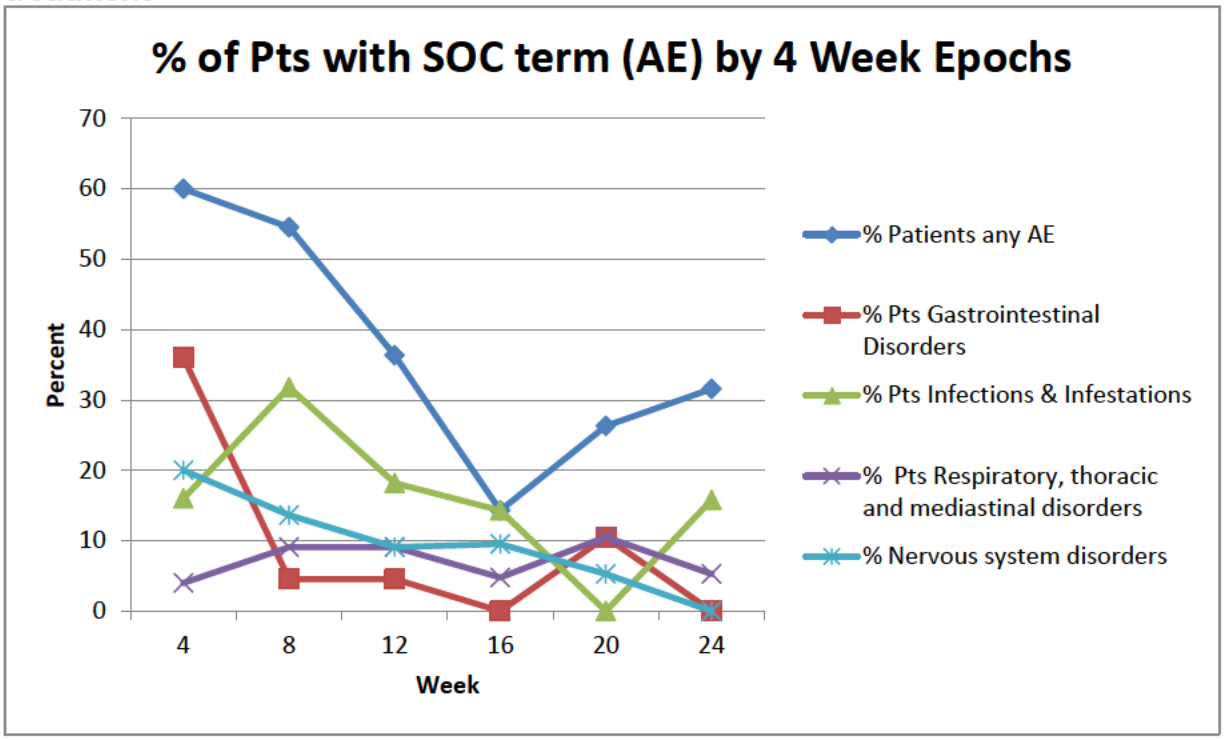
The time to any adverse event analysis reveals the highest frequency of adverse event occurs between weeks 0 and 8 with a notable decline thereafter. This methodology is applied to the SOC categories with the 4 highest occurrences of adverse events. These SOCs are in decreasing order; "Infections and infestations" (45 instances), "Respiratory, thoracic and mediastinal disorders" (21 instances), "Gastrointestinal disorders" (19 instances), and "Nervous system disorders" (18 instances).

The analysis of the SOC frequencies reveals that "Gastrointestinal disorders" has the highest frequency of occurrence in the first 4 weeks followed by a steep decline. "Respiratory, thoracic and mediastinal disorders" have a level occurrence throughout the 24 week analysis interval. "Infections and infestations" occur irregularly with a peak between week 4 and 8 followed by a level occurrence to week 24 with a zero frequency between week 16 and 20. "Nervous system disorders" like "Gastrointestinal disorders" have a peak between week 1 and 4 followed by a decline. These findings are shown in tabular and graphic form in Table 34 and Figure 17 respectively.

Table 34 Frequency of Any AE and Top 4 SOC terms (by number of instances) by % of Patients by 4 Week Epochs, Weeks 0 to 24. Study 303 rufinamide treatment

Week	# pts in study	# pts with any AE in 4 week band	% Pts any AE	Pts with Gastrointestinal Disorders SOC	% Pts Gastrointestinal Disorders	Pts with Infections and infestations	% Pts Infections & Infestations	Pts with Respiratory, thoracic and mediastinal disorders SOC	% Pts Respiratory, thoracic and mediastinal disorders	Pts with nervous system disorders	% Nervous system disorders
4	25	15	60	9	36	4	16	1	4	5	20
8	22	12	55	1	5	7	32	2	9	3	14
12	22	8	36	1	5	4	18	2	9	2	9
16	21	3	14	0	0	3	14	1	5	2	10
20	19	5	26	2	11	0	0	2	11	1	5
24	19	6	32	0	0	3	16	1	5	0	0

Figure 17 Frequency of Any AE and Top 4 SOC terms (by number of instances) by % of Patients by 4 Week Epochs, Weeks 0 to 24.Study 303 rufinamide treatment



Reviewer Comment: The analysis of time dependence for adverse events reveals the highest percent of any AE occurs in the early phase of rufinamide treatment. This pattern is also observed for events in the gastrointestinal disorders SOC suggesting there is adaptation to the gastrointestinal tolerance of rufinamide. There is a similar but less prominent tendency for decline in the "Nervous System disorders" SOC as the study progresses. This may be due to the development of tolerance to the CNS depressant AEs which may be seen in this SOC. Exam of the "Infections and infestations" and "Respiratory, thoracic and mediastinal disorders" reveals a more persistent occurrence of adverse events in these SOCs as the study progresses along with a less pronounced tendency for an early peak of these events. This profile does not reveal a new safety condition.

7.5.3 Drug-Demographic Interactions

The frequency of any adverse event by age strata reveals a declining proportion of adverse event as age increases from 1 to < 4 years of age, Table 35. Examination of adverse events by sex reveals a larger proportion of males had any AE. The difference between the groups is 8%. In this small sample size this does not indicate a sex specific safety signal, Table 36. The rufinamide treatment group is composed of 92 caucasian patients therefore the distribution of adverse events by race is too small for meaningful

analysis, Table 37. Examination by geographic region reveals that 100% of patients in the North American group had any adverse event while 80% in the Europe-rest of world group had any AE, Table 38.

The composition of adverse events by SOC is similar between the less than 4 years age group from study 303 and the 4 year and older group in study 022 of the initial BANZEL NDA application. This may be seen Table 39 to Table 40. From among SOCs with a frequency of 20% (*occurrence in ≥20% of patients*) or greater, 7 of 8 SOC terms from study 303 are concordant with 7 of the 9 SOC terms in study 022. However, examination of the frequency of SOC terms with a frequency of 20% or greater reveals a gradient of decreasing frequency with increasing age. This is observed in both study 303 and 022. The decline in frequency in study 303 appear disproportionate in the age 3 to <4 year strata which may be due to the small numbers in each sample, see Table 39.

Adverse events that occurred in more than one patient are compared across one year age intervals in study 303. The 1 to <2 year age group had the greatest number of novel terms not present in the 2 to <3 year and 3 to <4 year groups. These terms are "diarrhoea", "blood bicarbonate decreased", "constipation", "decreased appetite", "nasal congestion", and "pneumonia". The 2 to <3 year group had only one novel term, "gait disturbance". "Somnolence is common to the 1 to <2 year and 2 to <3 year group while "upper respiratory tract infection" is common to the 2 to <3 year and 3 to < 4 year groups. "Vomiting" is the only term common to all three age strata, also similar in frequency in all age strata, Table 41. The complete table of AEs by preferred term may be seen in 9.6 Adverse Events by Age Group Analysis. A comparative examination of the "any other AED" group is performed for the two novel preferred terms "diarrhoea" and "blood bicarbonate decreased" due to the potential related and physiologically threatening characteristic of these terms. In the "any other AED" group age 1 to <2 one patient (33%) had an adverse event of "blood bicarbonate decreased" and 1 (33%) patients had an AE of diarrhea. Although the small "any other AED" 1 to <2 year group provides only a small sample (n=3) of 3 patients the comparison suggests these adverse events are common to the younger age group in both rufinamide and comparator treatment.

Table 35 study 303 rufinamide treatment, total AE, by 1 year age increments, any AE

Age band, years	# patients with AE	Total patients in age band	% with any AE
1 to <2	10	10	100.0
2 to <3	6	7	85.7
3 to <4	6	8	75.0

Table 36 study 303, rufinamide treatment, Total AE by Sex, Any AE

SEX	Number of patients	% of total	% with any AE
F	11	44	40
M	14	56	48

Table 37 study 303, rufinamide treatment, Total AE by Race, Any AE

RACE	Number of patients	% patients	% with any AE
Black or African American	2	8	100
White	23	92	87

Table 38 study 303, rufinamide treatment, Total AE by Geographic Region

REGION	# patients	% patients in region with AE
EU/ROW (n=15)	12	80
North America (n= 10)	10	100

Table 39 AE, SOC by Age Strata, number and percent of patients, study 303, rufinamide treatment.

Age Group	1 to <2 (n=10)		2 to <3 (n=7)		3 to <4 (n=8)	
SOC	Number of patients	% pts	Number of patients	% pts	Number of patients	% pts
Infections and infestations	6	60	6	86	5	63
Gastrointestinal disorders	6	60	4	57	2	25
Nervous system disorders	5	50	3	43	2	25
Respiratory, thoracic and mediastinal disorders	3	30	2	29	2	25
Skin and subcutaneous tissue disorders	3	30	2	29	1	13
Psychiatric disorders	2	20	2	29	1	13
Metabolism and nutrition disorders	2	20	2	29	0	0
Investigations	2	20	1	14	1	13
General disorders and administration site conditions	1	10	2	29	0	0
Renal and urinary disorders	1	10	1	14	0	0
Musculoskeletal and connective tissue disorders	0	0	1	14	0	0
Injury, poisoning and procedural complications	0	0	1	14	0	0

Table 40 AEs by SOC in Study 022, rufinamide treatment

Adverse event frequency by Number and % of Patients, Rufinamide treatment study 022, LGS (n=75)		
Adverse event SOC	Number of Patients	% patients
Infections and infestations	50	67
Nervous system disorders	43	57
Gastrointestinal disorders	38	51
General disorders and administration site conditions	31	41
Respiratory, thoracic and mediastinal disorders	29	39
Metabolism and nutrition disorders	23	31
Psychiatric disorders	22	29
Skin and subcutaneous tissue disorders	22	29
Injury, poisoning and procedural complications	16	21
Musculoskeletal and connective tissue disorders	8	11
Investigations	7	9
Renal and urinary disorders	5	7
Vascular disorders	5	7
Endocrine disorders	4	5
Eye disorders	4	5
Blood and lymphatic system disorders	3	4
Cardiac disorders	3	4
Immune system disorders	3	4
Reproductive system and breast disorders	3	4
Ear and labyrinth disorders	1	1

Table 41 Study 022 rufinamide treatment, Frequency of SOC terms in patients <12 years and ≥ 12. (Restricted to terms with frequency ≥ 20%)

Study 022, LGS	**<12 (n= 31)**		**≥ 12 (n=44)**	
SOC	**N Rows**	**% PATIENTS**	**N Rows**	**% PATIENTS**
Infections and infestations	23	74	27	61
Nervous system disorders	19	61	24	55
Gastrointestinal disorders	18	58	20	45
General disorders and administration site conditions	14	45	17	39
Respiratory, thoracic and mediastinal disorders	14	45	15	34
Skin and subcutaneous tissue disorders	12	39	10	23
Metabolism and nutrition disorders	10	32	13	30
Injury, poisoning and procedural complications	7	23	9	20

Psychiatric disorders	6	19	16	36

Table 42 AE in Greater than 1 patient by Preferred Term and Age Strata, study 303, rufinamide treatment.

1 to <2 years (n=10)			2 to <3 years (n=7)			3 to <4 years (n=8)		
Preferred term	# patients	% patients	Preferred term	# patients	% patients	Preferred Term	# patients	% patients
Diarrhoea	3	30	Upper Respiratory Tract Infection	4	57	Upper Respiratory Tract Infection	3	38
Blood Bicarbonate Decreased	2	20	Gait Disturbance	2	29	Vomiting	2	25
Constipation	2	20	Somnolence	2	29			
Decreased Appetite	2	20	Vomiting	2	29			
Nasal Congestion	2	20						
Pneumonia	2	20						
Somnolence	2	20						
Vomiting	2	20						

Reviewer Comment: One of the primary missions of this application is to determine if there is any difference in the safety and tolerability characteristics of rufinamide in the 1 to <4 year old population compared to the older pediatric population that participated in LGS study 022. The approach in this section was to compare the adverse event content (specific SOC and Preferred terms) and frequency of events across the age strata in study 303 and to the pediatric population in study 022. There is no clear difference in the SOC or Preferred term content found in the adverse event data nor the overall frequency of these adverse events. There is a trend toward an increase in adverse event frequency in the youngest age strata; however, the small sample size does not allow a definite conclusion. Comparison of AE preferred terms in the rufinamide treatment group and "any other AED" of study 303 does not reveal clear differentiation of the content or frequency of the AE terms.

7.5.4 Drug-Disease Interactions

The small sample size and absence of a blinded placebo arm did not allow sufficient data for a suitable analysis of drug-disease interaction.

7.5.5 Drug-Drug Interactions

The primary study included in this supplemental NDA, study 303, was performed to compare exposure to rufinamide in pediatric population aged 1 to less than 4 years in

Study 303 to that in subjects aged 4 years and older in Studies 0022 and E2080-J081-304 (Study 304). No new drug interaction studies were performed.

Key adverse event preferred terms were examined for association with concomitant medications. No interaction is identified when the concomitant medication dataset is examined for association with the preferred terms “status epilepticus” and “upper respiratory tract infection”. From among concomitant medications associated with the preferred term “somnolence” the AEDs topiramate, clobazam, vigabatrin, and diazepam occurred with the greatest frequency. Valproic acid appeared in the highest frequency when testing the association of concomitant medication and vomiting. Infection related preferred terms were tested for association with concomitant medications. The only concomitant medications observed to have a high frequency association were medications of the antibiotic class.

7.6 Additional Safety Evaluations

none

7.6.1 Human Carcinogenicity

Carcinogenicity studies are not performed for this application.

7.6.2 Human Reproduction and Pregnancy Data

Human reproduction and pregnancy studies are not performed for this application

7.6.3 Pediatrics and Assessment of Effects on Growth

Assessed via weight analysis

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor indicates safety analysis for drug abuse was not assessed for Study 303. There were no adverse event preferred terms related to overdose, abuse, withdrawal or rebound.

7.7 Additional Submissions / Safety Issues

120 Day Safety Update

This submission is a priority review which places the 120 day safety update in close proximity to the completion of the primary review. The addition to each safety dataset is

small. There are 2 new patients added to the week 106 laboratory analyses, 3 new patients added to the week 106 weight measurements and 8 patients contribute 20 new adverse events. Because this is a small additional layer of safety data it is not integrated into the adverse event, laboratory or vital sign datasets of the initial submission to create a pooled review. The existing datasets would not be expanded sufficiently to uncover a new safety signal. The late study entries of the 120 day update are examined for new or unexpected outliers. In addition the updated exposure data is provided.

Exposure:

Over the additional duration of exposure in this update, there was no change from the sNDA in the number of subjects who received at least 1 dose of study drug or remained ongoing in the study. The percentage of subjects in the rufinamide group who discontinued from the study increased from 16% (4/25) to 20% (5/25). This was attributable to the loss of Subject 40061001 to follow-up. The number of rufinamide-treated subjects who completed the study increased from 1 to 3.

Duration of Exposure

Over the additional duration of exposure in this update, there was no change from the sNDA in the number of subjects exposed to rufinamide in the determined therapeutic range (10 to 40 mg/kg/day) or exposed to any other add-on AED. The number of subjects with at least 16 weeks of exposure in the study increased by 1, from 21/25 (84%) to 22/25 (88%). The number of subjects with at least 24 weeks of exposure in the study increased by 3, from 18/25 (72%) to 21/25 (84%), and the number of subjects who reached over 1 year of exposure increased by 5, from 12/25 (48%) to 17/25 (68%). The maximum exposure to rufinamide increased, by 5.3 weeks, from 121.1 to 126.4 weeks and the total exposure to rufinamide increased, by 324.5 subject-weeks, from 1407.4 to 1731.9 subject-weeks.

Deaths: none

Serious Adverse Events (SAEs): There were 4 new SAEs during the 120 safety update interval from among 2 patients. These two patients had SAEs prior to the initial safety cutoff data leaving the overall number of patients with an SAE unchanged at 7 (28%). One subject had a second event of “Bronchopneumonia” at study day 268. A second patient (E2080-G000-303-8002-1001) had 3 additional SAES, one each of “blindness”, “encephalitis” and “status epilepticus”. This patient had an influenza pneumonia which was followed in time by these three SAEs, see Table 43. The patient recovered from events of encephalitis and blindness.

Table 43 Subject E2080-G000-303-8002-1001, all adverse events in Study 303. Serious Adverse Events are shaded

Subject E2080-G000-303-8002-1001, Adverse events during the course of study 303		
Preferred term	**Study Day**	**SAE**
Fatigue	15	N
Rash	26	N
Rash	26	N
Atonic Seizures	82	N
Vomiting	83	N
Grand Mal Convulsion	90	N
Nasopharyngitis	107	N
Grand Mal Convulsion	114	Y
Gait Disturbance	118	N
Toe Walking	118	N
Gastroenteritis	142	Y
Candida Nappy Rash	258	N
Pneumonia Influenzal	258	Y
Status Epilepticus	258	Y
Thrombocytopenia	259	N
Dermatitis Diaper	263	N
Blindness	268	Y
Encephalitis	268	Y
Rash	280	N

Discontinuations: There were no additional discontinuations from treatment due to treatment emergent adverse events during the 120 safety update interval.

Common Adverse events: Examination of the 120 day adverse event analysis dataset (ADAE) reveals 13 new rows for adverse event terms. This examination identifies 8 patients contributing 20 adverse events not present in the sNDA adverse event analysis dataset. There is an excess of 7 new events although there are only 13 new rows. These seven excess events are accounted for by 5 rows in the initial sNDA dataset where there was an entry for a subject ID but no entry for the adverse event terms. One term for urinary tract inflammation in the initial dataset appears as urinary tract infection in the 120 day safety update dataset. A final term in the initial sNDA dataset “aphagia” does not appear in the 120 day update dataset. This leaves room for an additional or new adverse event without the additional of an additional row. In summary there are 7 new preferred term entries without new rows in the dataset. This is allowed by the aforementioned accounting with a resultant safety interval total of 20 new terms and 4 new SAEs.

These twenty new adverse event terms are derived form 8 (32%) of rufinamide treated patients, see Table 44. One patient (E2080-G000-303-8002-1001) who suffered a severe H1N1 pneumonia accounts for 7 of these terms. From among the remaining 13 terms ten are related to infection and 8 of the ten infection related adverse events occur at 5.9 months or more after starting study treatment. This follows the trend of a high frequency of infection terms seen in the initial adverse event dataset and reflects the high frequency of infectious events seen in the pediatric population when followed over time.

Table 44 New Adverse Event Terms with SUBJID in the 120 day Safety Update

Preferred Term	USUBJID	SAE	Study day at Start of AE
Bronchiolitis	E2080-G000-303-1005-1003		360
Pneumonia	E2080-G000-303-1005-1003		360
Pyrexia	E2080-G000-303-1005-1003		359
Otitis Media	E2080-G000-303-1005-1005		208
Rhinitis Allergic	E2080-G000-303-1005-1005		151
Sinusitis	E2080-G000-303-1005-1005		165
Upper Respiratory Tract Infection	E2080-G000-303-1005-1005		190
Irritability	E2080-G000-303-1006-1002		120
Pyrexia	E2080-G000-303-1010-1002		518
Agitation	E2080-G000-303-1016-1003		673
Bronchopneumonia	E2080-G000-303-4004-1002	y	265
Urinary Tract Infection	E2080-G000-303-5002-1001		15
Urinary Tract Inflammation	E2080-G000-303-5002-1001		19
Blindness	E2080-G000-303-8002-1001	y	268
Candida Nappy Rash	E2080-G000-303-8002-1001		258
Dermatitis Diaper	E2080-G000-303-8002-1001		263
Encephalitis	E2080-G000-303-8002-1001	Y	268
Rash	E2080-G000-303-8002-1001		280
Status Epilepticus	E2080-G000-303-8002-1001	y	258
Thrombocytopenia	E2080-G000-303-8002-1001		259

Laboratory Studies

Examination of week 106 is performed for all laboratory parameters. At the 120 safety update there are 4 patients in this group. This represents addition of two patients during the 120 day safety interval. Values are screened for a shift from normal to low or normal to high. 8 entries from among the four patients are identified which fulfill these criteria. Three of the entries are for shifts that are not of physiologic concern (low shift for ALT,

bilirubin, and uric acid) while one is a minor increase out of normal reference range (PO4 .03mmol/L above normal). The remaining entries are for hematologic parameters. There were two entries for Lymphocytes/Leukocytes (%) shift to high. In both cases the shift was a modest increase over reference high normal. The adverse event profile of both these patients is examined. In the first case there are no adverse events within 180 days of the reported high lymphocytes. In the second case the patient had a left ear infection two days before the shift to high lymphocytes. The remaining shifts reported are a shift to high monocytes and a shift to low percent neutrophils in patient 40041001. This patient has four adverse event entries for bronchitis; however, the most proximate adverse event entry occurred 200 days prior to these shifts in hematologic parameters. Examination of these late study laboratory entries does not reveal a new safety signal.

Weight

Week 106 weight entries are examined. There are 3 new patients with a weight entry at week 106 with a resulting total of 5 patients. The percent change from baseline for these patients is examined. Four of five patients had an increase from baseline weight. Those patients with a positive change from baseline had a mean increase of 57% over baseline weight. The single patient with a decline had a 24 percent reduction from baseline. The patient with reduction from baseline was observed to have 2 of 11 weight measurements below baseline value during the course of the study as well as adverse events of vomiting at study day 11 and weight loss at study day 56.

Reviewer Comment: Examination of the 120 day safety update reveals there is a modest increase in exposure with no overall change in safety profile seen in the adverse event, laboratory or weight data.

8 Postmarket Experience

Post Marketing adverse events are examined for key review safety items. An examination of the FAERS database is performed for cardiac dysrhythmic events and cardiac death, low bicarbonate (metabolic acidosis) and any preferred term.

Cardiac Terms

The cardiac term analysis yields 2 entries of SUDEP with a resultant EB05 of 0.836. The two patient reports are examined.

Report 7085318 concerns a 36 year old US female with intractable epilepsy. The patient had a dental procedure under anesthesia. Following the procedure the patient is report to be “not doing well”. The patient subsequently fell and suffered a distal tibial fracture. Shortly thereafter BANZEL dose was increased to 600mg BID then 800mg Bid. Approximately (b) (6) weeks later the patient was found expired in bed early in the morning.

Report 8481853: Mar/28/2012: Initial Jun/6/2012: Correction made to previous version amending the NDA approval number This Physician report from USA describes a 17-Year-old Female who received BANZEL for the treatment of unknown indication. Date unknown: The patient began BANZEL 400 mg daily. [redacted] (b) (6): There was no witnessed convulsion. As per, the parent and police report she apparently died quietly overnight while sleeping in her bed. The patient experienced SUDDEN UNEXPLAINED DEATH IN SETTING OF EPILEPSY (SUDEP). No Autopsy was performed. Mar/28/2012: The Physician reports event to the company "Only recent medication change. Treatment of Depo-lupron was scheduled to be started. Despite advise to the contrary, her family discontinued maintenance of Ativan (not cosuspect) approximately 2 days prior to her death". Reporter's comment: I do not believed patient's death was related to BANZEL or to any interaction involving BANZEL. The seriousness and outcome of event was classified as follows: SUDDEN UNEXPLAINED DEATH IN SETTING OF EPILEPSY (SUDEP): Serious: Death.

Figure 18 FAERS Cardiac search Terms

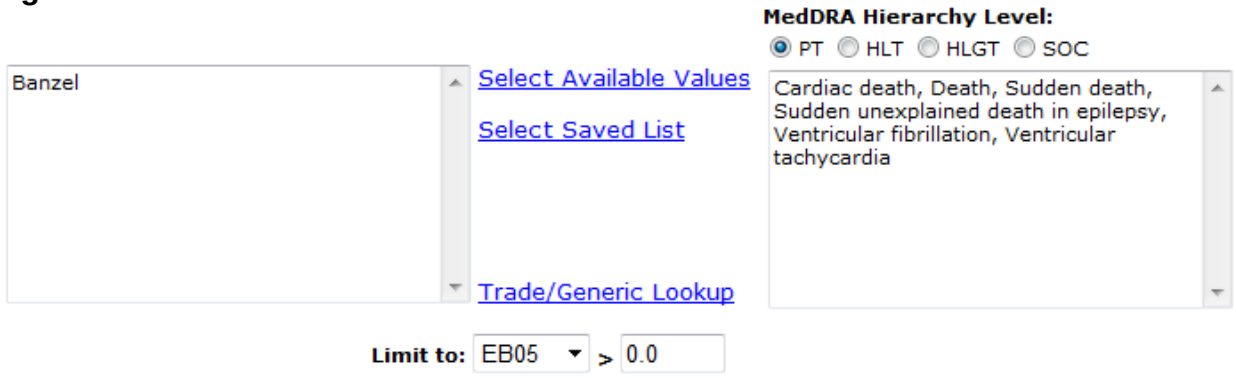


Figure 19 Results of FAERS Cardiac Search Term analysis

1 rows

	Trade name (Derived by LTI)	PT	N	EBGM	EB05	EB95
	Banzel	Sudden unexplained death in epilepsy	2	3.53	0.836	62.7

Low bicarbonate / acidosis

Examination of the FAERS database via Empirica signal reveals 1 report captured by low bicarbonate / metabolic acidosis search terms yielding an EB05 of 0.259. Salient components of the case report are provided below.

Report 7274366
Case Narrative:

Consumer report from USA describes an 18 Year old Male who received BANZEL for the treatment of Lennox-Gastaut syndrome. Mar//2009: The patient began BANZEL 400 mg BID. Nov//2009: The patient gradually began NOT EATING for approximately six days and was VOMITING (unclear of duration of vomiting).

Continued. Additional information received Feb/04/2010, Feb/05/2010, and Feb/08/2010 from the Physician to include patient demographics, past medical history, drug therapy, laboratory data, new serious events NAUSEA, ACUTE RENAL FAILURE, SEVERE LACTIC ACIDOSIS, METABOLIC ACIDOSIS. The event NOT EATING was not mentioned in follow-up. May/28/2009: The patient began BANZEL 800 mg daily (400 mg BID). //2009: Since starting BANZEL the patient's seizures declined. (b) (6): The patient was admitted to the hospital with low blood sugars (value of 30, not reported as an event), NAUSEA, VOMITING, and increased seizures (not reported as an event). A viral illness was suspected. NAUSEA and VOMITING were considered life threatening and probably related to BANZEL. The Physician reported "suggested increase in BANZEL to 600 mg BID, dosed with food given seizures at presentation were worse".

(b) (6): The patient developed SEVERE LACTIC ACIDOSIS and ACUTE RENAL FAILURE both considered possibly related to BANZEL. He was treated and then transferred to another hospital. (b) (6): The patient developed METABOLIC ACIDOSIS and septic like syndrome (not specified). (b) (6): The patient died. LACTIC ACIDOSIS, METABOLIC ACIDOSIS, ACUTE RENAL FAILURE were all reported with an outcome of death. The Physician reported that the patient had been hospitalized for similar circumstances (acidosis) in the past.

Medical History

Glycogen storage disease (Type 1A Von Gierke disease), epilepsy, frequent Grand mal seizures, numerous hospitalizations for acidosis and hyperglycemia, GERD, refractory nausea and vomiting, strokes. The patient received corn starch daily in his diet to avoid hyperglycemic events. He had poor seizure response to Tegretol, Felbamate, Valproic acid, Topamax, Lamictal, Phenobarbital, Clonazepam, Brivaracetam (study protocol), Neurontin, Ethosuxamide, Lorazepam.

Figure 20 FAERS, Low bicarbonate search terms

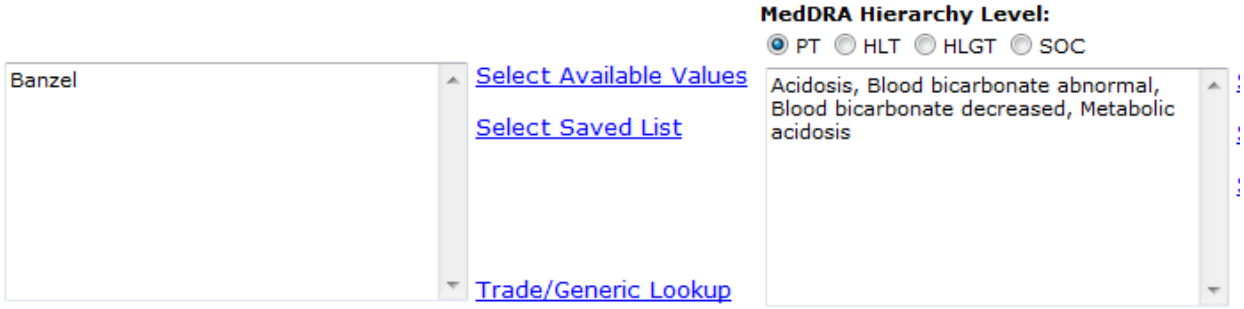


Figure 21 Results of FAERS Low bicarbonate search terms

1 rows Rows Per Page: 50

Trade name (Derived by LTI)	PT	N	EBGM	EB05	EB95
Banzel	Metabolic acidosis	1	1.28	0.259	4.35

Additional terms of Concern

The FAERS database is examined via Empirica Signal to explore the frequency of reports with EB05 threshold set to 0.0, for the following terms: pancreatitis, leukopenia, neutropenia, agranulocytosis, hypersensitivity, DRESS, SJS and TEN. The search identifies no reports for these terms.

Any Preferred term

An examination to identify any preferred term with an EB05 greater than 1.0 yielded 6 terms. The term with the largest EB05 was identified as convulsion with an EB05 of 5.3. The second in magnitude was abnormal behavior with an EB05 of 2.0. The remaining terms were lethargy, psychotic disorder, rash and vomiting. This array of adverse events is not divergent from the adverse reactions in section 6.1 in current BANZEL labeling. Aggression and psychomotor hyperactivity are abnormal behavioral characteristics which are similar in coding to abnormal behavior and psychotic disorder. Neither of the latter terms exceeds an EB05 of 2.0 thus do not appear to be a worsening signal.

6 rows

	Trade name (Derived by LTI)	PT	N	EBGM	EB05	EB95
	Banzel	Abnormal behaviour	6	4.03	2.00	7.46
	Banzel	Convulsion	18	8.10	5.30	12.5
	Banzel	Lethargy	3	2.82	1.05	6.43
	Banzel	Psychotic disorder	4	3.98	1.66	8.57
	Banzel	Rash	6	2.82	1.40	5.19
	Banzel	Vomiting	7	2.33	1.22	4.13

Weight

The FAERS database is examined via Empirica Signal to explore the frequency of reports related to weight loss with EB05 threshold set to 0.0. The following preferred terms are examined: Abnormal loss of weight, Underweight, Weight abnormal, Weight decreased Weight gain poor. There are two reports identified for only the term “weight decreased” which yields an EB05 of 0.418. The second report is found to be a duplicate, thus there is only a single post marketing report captured that is related to weight loss. In this report a 14 yo female on BANZEL was observed to have persistent weight loss and vomiting after replacement of a vagal nerve stimulator.

Reviewer Comment: assessment of the post marketing safety areas which are concordant with items given special focus in this review do not reveal compelling evidence of a new safety signal of metabolic acidosis. Preferred terms based on” known drug safety concerns and monitoring” cited in the pediatric written request are also examined. These include terms related to cardiac death or dysrhythmia (to capture QT shortening related AEs), multi-organ hypersensitivity reactions, leukopenia and pancreatitis. No reports are captured using preferred terms for hypersensitivity reactions, pancreatitis or bone marrow disorders. The cardiac assessment reveals 2 case reports of sudden cardiac death. Report 8481853 is confounded by an absence of temporal relationship between the SUDEP event and initiation of BANZEL. Report 7085318 indicate the patient is “doing poorly” without specifics but the serious fall and fracture raises the possibility of poor seizure control. In this context a SUDEP event is possible.

An assessment of preferred terms related to bicarbonate and metabolic acidosis was performed due to the frequency of low (although confounded) bicarbonate values observed in the review. There was a single case report that from a patient with a fragile metabolic state due to a glycogen storage disease (Type 1A Von Gierke disease) in addition to a severe epilepsy syndrome. Overall, the post marketing examination does not reveal a new or worsening safety signal.

9 Appendices

Table 45 APPENDIX TABLE MARKER

Appendix Table Marker

Figure 22 APPENDIX FIGURE MARKER

Appendix Figure Marker

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

1. Agree with proposed labeling to included “decreased weight 8%” in the new subheading *Pediatric Patients ages 1 to less than 4 years section*, of section 6.

9.3 Advisory Committee Meeting

N/A

9.4 Laboratory Analysis Appendix

Hematology Panel

Hemoglobin

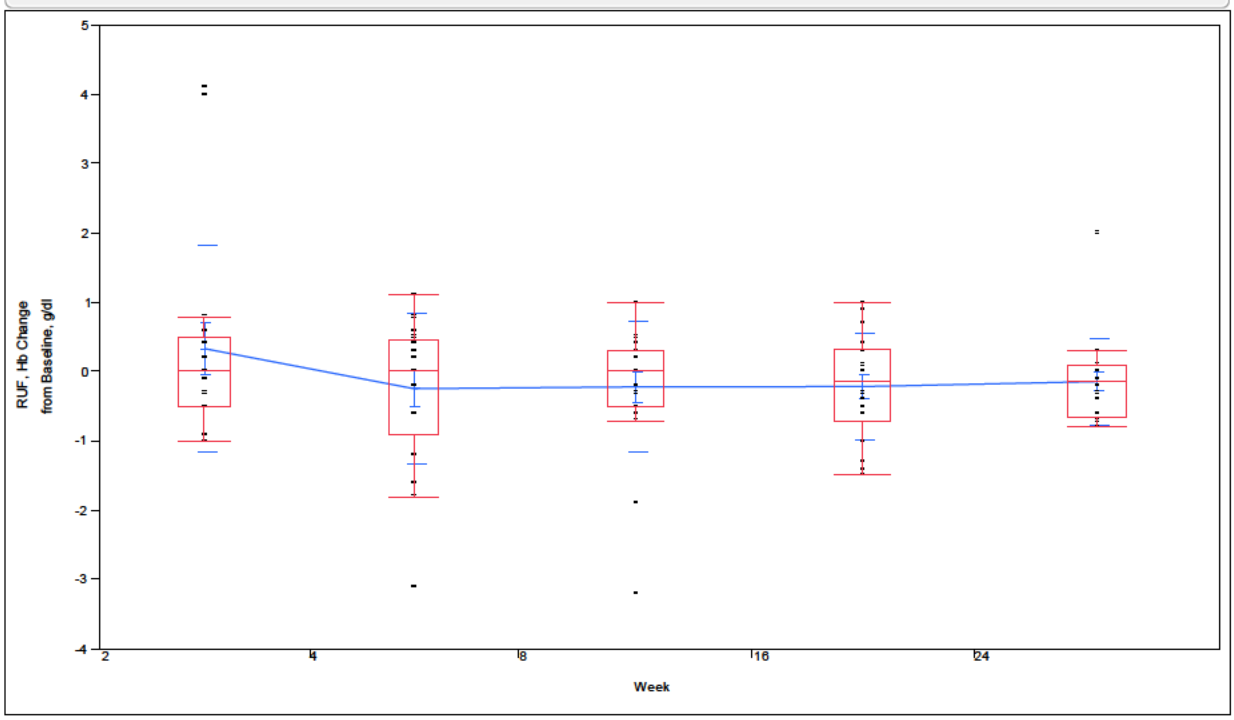
Table 46 Hemoglobin, means, medians, outliers, shift, rufinamide treatment

Hemoglobin (normal 10.5 to 14.5 g/dl)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.22		-0.15	
Median	-0.15		-0.15	
Range	-1.5 to 1		-0.8 to 2.0	
Outliers (normal at baseline), relative to potentially clinically significant values from				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	1 (6%)		1 (5%)	
Min value	10.3		10.4	
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=18)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	1 (6%)	0	1 (5%)	0
high value				
Low value	10.3			10.4
Patients with CTCAE toxicity grade >0 at any time during study				

treatment are examined. Six patients are identified. These patients experienced a total of 50 adverse events, however only 1 of these events was a preferred term related to low hemoglobin which was the preferred term “Haemoglobin Decreased”. This event was not an SAE. There were no terms for syncope. There were 3 events of somnolence. None of the 50 AE terms was an SAE. From among the “any other AED” group there is a small negative mean change in hemoglobin seen only at week 8.

Figure 23 Hemoglobin Change from baseline by week, rufinamide treatment

Oneway Analysis of RUF, Hb Change from Baseline, g/dl By Week



Quantiles

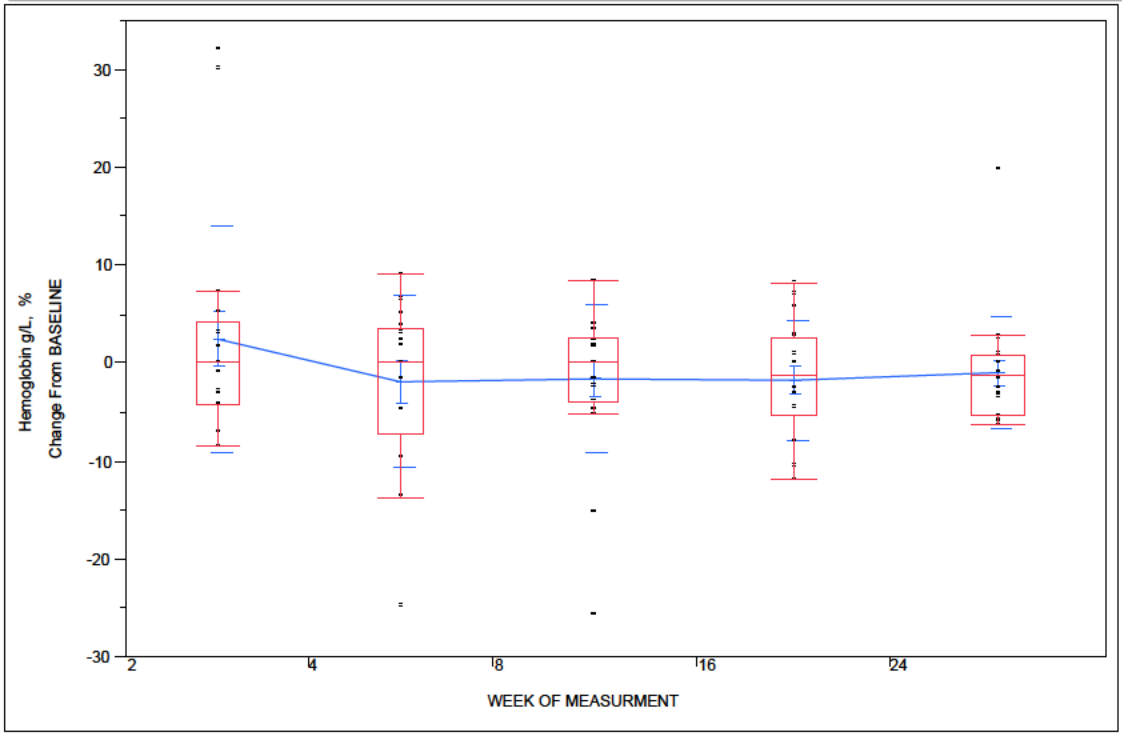
Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-1	-0.92	-0.5	0	0.5	4.02	4.1
4	-3.1	-2.06	-0.9	0	0.45	0.86	1.1
8	-3.2	-1.9	-0.5	0	0.3	0.5	1
16	-1.5	-1.41	-0.7	-0.15	0.325	0.91	1
24	-0.8	-0.79	-0.675	-0.15	0.1	0.3	2

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	0.32941	1.48903	0.36114	-0.4362	1.0950
4	17	-0.24706	1.09323	0.26515	-0.8091	0.3150
8	19	-0.22105	0.94315	0.21637	-0.6756	0.2335
16	18	-0.21667	0.75323	0.17754	-0.5912	0.1579
24	20	-0.14500	0.62279	0.13926	-0.4365	0.1465

Figure 24 hemoglobin percent change from baseline by week of treatment, rufinamide treatment

Oneway Analysis of Hemoglobin g/L, % Change From BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-8.40336	-7.39496	-4.22009	0	4.195997	30.4664	32.03125
4	-24.8	-15.9002	-7.12411	0	3.555806	7.12259	9.166667
8	-25.6	-15.0794	-3.93701	0	2.5	3 960396	8.403361
16	-11.9658	-11.8265	-5.44567	-1.25	2.658659	7 204399	8.264463
24	-6 34921	-6.25753	-5.43706	-1.22843	0.81584	2.801407	19 80198

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	2.4578	11.5815	2 8089	-3.497	8.4124
4	17	-1 9100	8.7918	2.1323	-6.430	2 6103
8	19	-1 6142	7.6011	1.7438	-5 278	2 0494
16	18	-1.7512	6.1170	1.4418	-4.793	1.2907
24	20	-0 9720	5.7333	1.2820	-3 655	1.7113

Figure 25 Hemoglobin low outlier values at any point during study, rufinamide treatment group

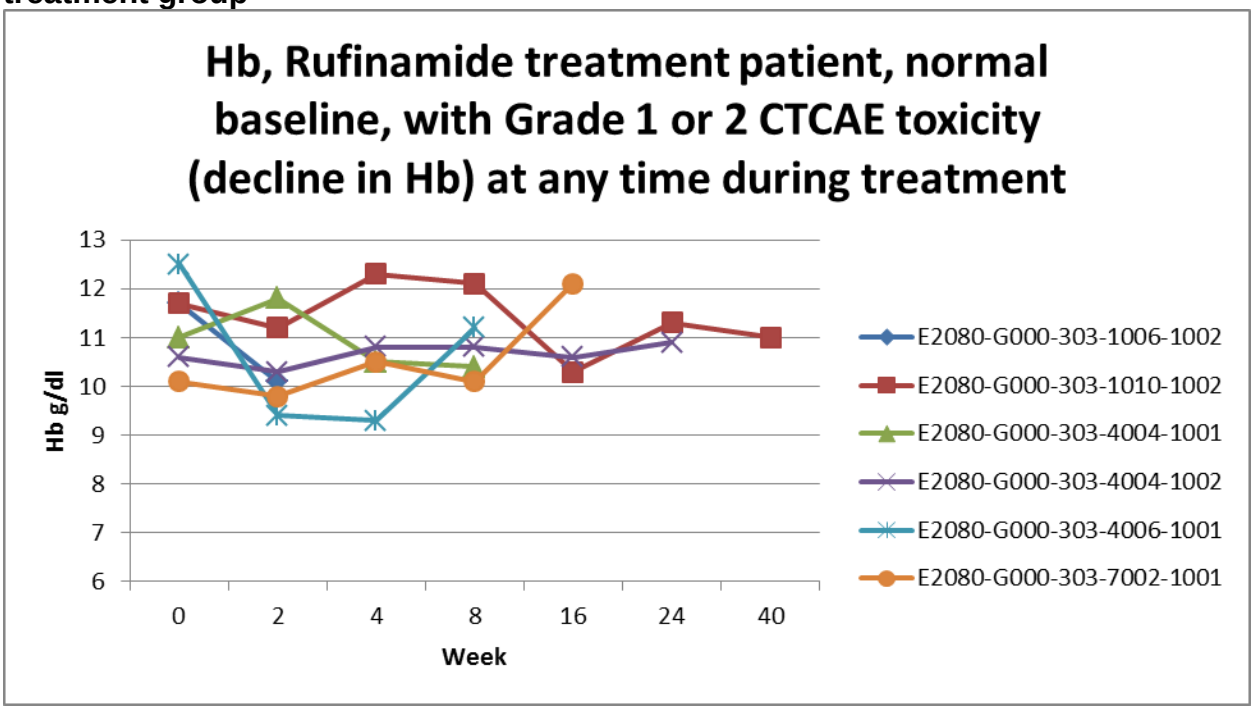
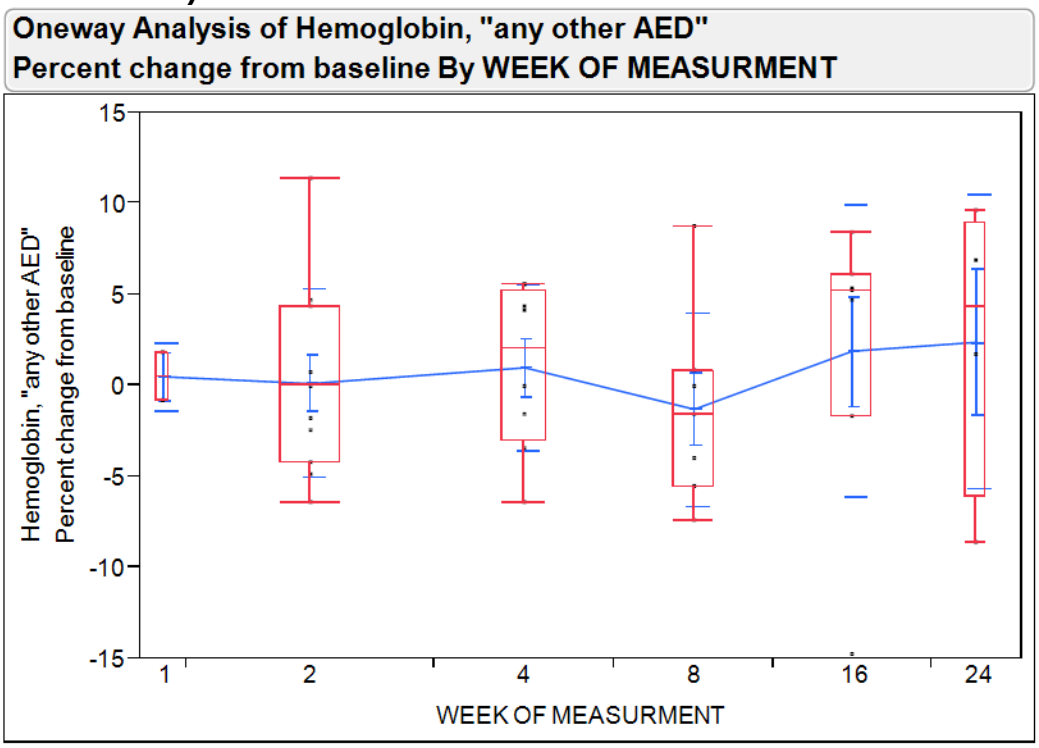


Figure 26 Any Other AED: Hb %Change from Baseline by week (mean in blue, median in red)



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-0.80645	-0.80645	-0.80645	0.514205	1.834862	1.834862	1.834862
2	-6.45161	-6.1449	-4.20168	0	4.385965	10.06769	11.40351
4	-6.45161	-6.45161	-3.02528	2.04918	5.224932	5.6	5.6
8	-7.37705	-7.37705	-5.51181	-1.63934	0.840336	8.77193	8.77193
16	-14.7541	-14.7541	-1.75439	5.263158	6.140351	8.403361	8.403361
24	-8.66142	-8.66142	-6.05747	4.338731	8.930769	9.6	9.6

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	2	0.5142	1.86769	1.3207	-16.27	17.295
2	11	0.1325	5.14470	1.5512	-3.32	3.589
4	8	1.0067	4.56697	1.6147	-2.81	4.825
8	7	-1.2783	5.32231	2.0116	-6.20	3.644
16	7	1.9153	7.98349	3.0175	-5.47	9.299
24	4	2.4040	8.06370	4.0319	-10.43	15.235

Summary: mean and median percent change from baseline at study weeks 2 to 24 are examined and reveal a small negative mean change from baseline. This analysis is also examined in the “any other AED” group and there is no notable difference between the treatment groups. Outlier and shift analysis are also performed which reveal one low

outlier at weeks 16 and 24 each. There is also one shift from normal to low at weeks 16 an 24. The minimum hemoglobin values in these shift is 10.3 g/dl. Overall there is no evidence of a notable decline in hemoglobin.

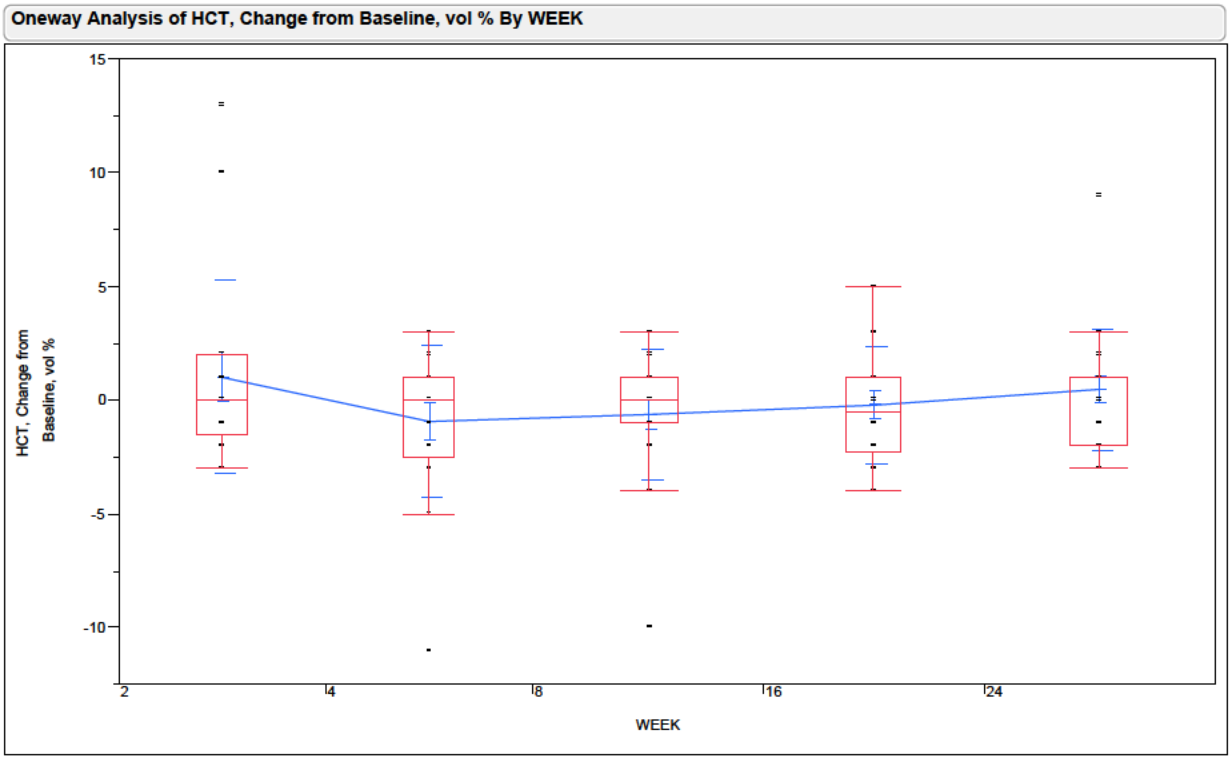
Conclusion: no notable change in Hb

Hematocrit

Table 47 Hematocrit, means, medians, outliers, shift, rufinamide treatment

Hematocrit (normal 28 to 42%)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.22		0.47	
Median	-0.5		1	
Range	-4 to 5		-3 to 9	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=18)		Shift from baseline to week 24, (n=19)	
	N to L	N to H	N to L	N to H
	0	1	0	0
high value		42.7		
Low value				

Figure 27 Hematocrit change from baseline by week, vol %, Rufinamide treated patients



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-3	-2.2	-1.5	0	2	10.6	13
4	-11	-6.2	-2.5	0	1	3	3
8	-10	-4	-1	0	1	3	3
16	-4	-3.1	-2.25	-0.5	1	5	5
24	-3	-2	-2	1	1	3	9

Means and Std Deviations

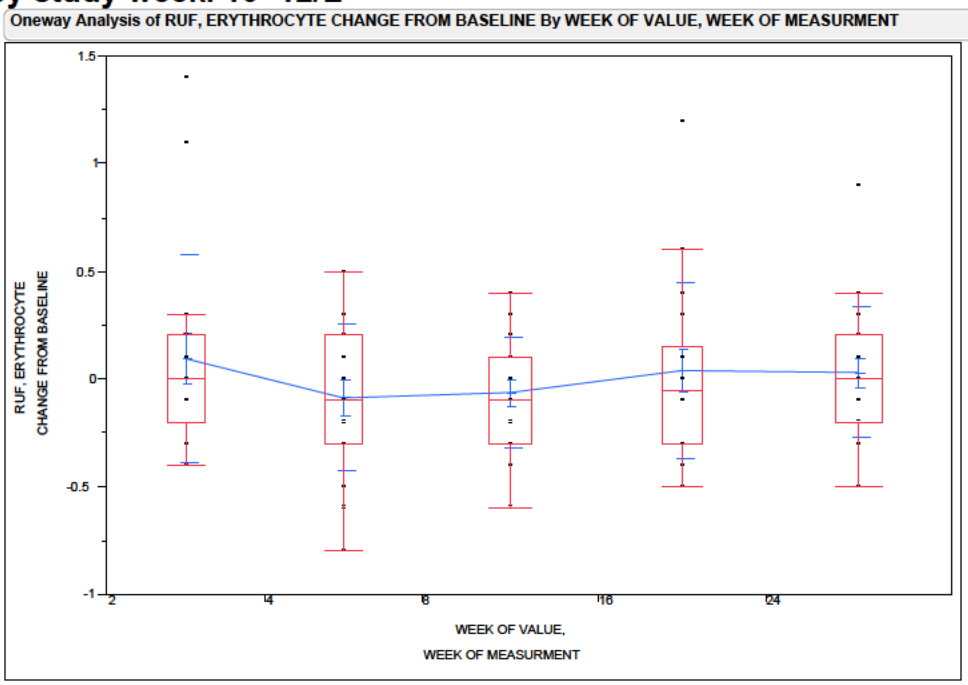
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	1.0000	4.25735	1.0326	-1.189	3.1889
4	17	-0 9412	3 36286	0 8156	-2.670	0.7878
8	19	-0 6316	2 87152	0 6588	-2.016	0.7524
16	18	-0 2222	2 55655	0 6026	-1.494	1.0491
24	19	0.4737	2 65348	0 6087	-0.805	1.7526

Conclusion: no notable change in HCT

Erythrocytes

No notable change from baseline

Figure 28 Rufinamide treatment group, Erythrocyte count change from baseline by study week. 10^12/L



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-0.4	-0.4	-0.2	0	0.2	1.16	1.4
4	-0.8	-0.64	-0.3	-0.1	0.2	0.34	0.5
8	-0.6	-0.4	-0.3	-0.1	0.1	0.3	0.4
16	-0.5	-0.41	-0.3	-0.05	0.15	0.66	1.2
24	-0.5	-0.29	-0.2	0	0.2	0.39	0.9

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	0.09412	0.484085	0.11741	-0.1548	0.34301
4	17	-0.08824	0.342568	0.08308	-0.2644	0.08790
8	19	-0.06316	0.260791	0.05983	-0.1889	0.06254
16	18	0.03889	0.404590	0.09536	-0.1623	0.24009
24	20	0.03000	0.306251	0.06848	-0.1133	0.17333

Platelets

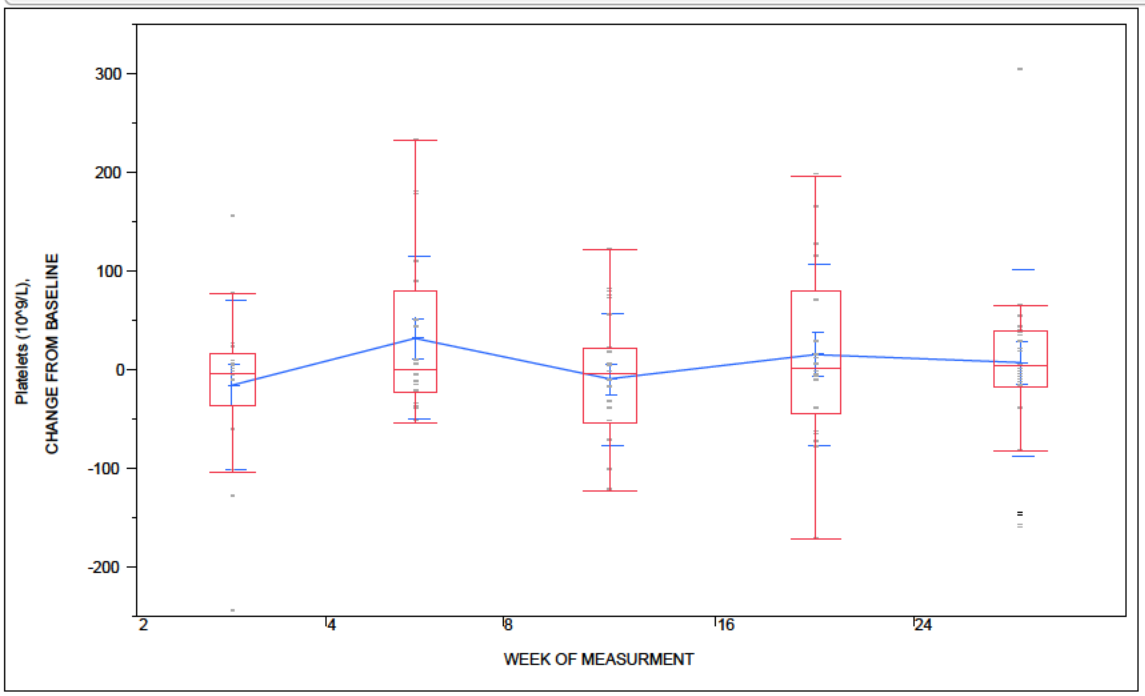
Table 48 Platelets, means, medians, outliers, shift, rufinamide treatment

Platelets (10^9/L)		
Change from Baseline to Week 16 and 24. Means and Medians		
Statistic	Week 16	Week 24
Mean	15.3	7.3
Median	1	4
Range	-171 to 197	-159 to 304
Outliers (normal at baseline), relative to potentially clinically significant		

values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		1	
Min value			107	
			Pt ID: E2080-G000-303-8002-1001	
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=18)		Shift from baseline to week 24, (n=18)	
	N to L	N to H	N to L	N to H
	0	1	1	
high value		491		
Low value			107	
Baseline mean 266 x10^9/L				
Reference range 140 to 450				
Patient E2080-G000-303-8002-1001 has 9 adverse reactions including those preferred terms which may be related to thrombocytopenia: “pneumonia influenza”- verbatim H1N1 pneumonia, PT “Rash”, “nasopharyngitis” and “gastroenteritis”.				

Figure 29 Platelet count, change from baseline by week, rufinamide treatment

Oneway Analysis of Platelets (10^9/L), CHANGE FROM BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-245	-151.4	-35	-4	16	91.8	155
4	-53	-43 9	-23 5	0	80	194.2	232
8	-124	-122	-53	-3	22	81	121
16	-171	-88 2	-45 25	1	80.25	167.3	197
24	-159	-147	-17	4	39	64	304

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	-15.765	85.8476	20 821	-59.90	28.374
4	16	31.813	81.9660	20.492	-11.86	75.489
8	19	-9.211	67.0800	15.389	-41.54	23.121
16	18	15.278	91.7008	21 614	-30.32	60.880
24	19	7 316	94.3357	21 642	-38.15	52.784

Conclusion: no notable change in platelets during the course of the study.

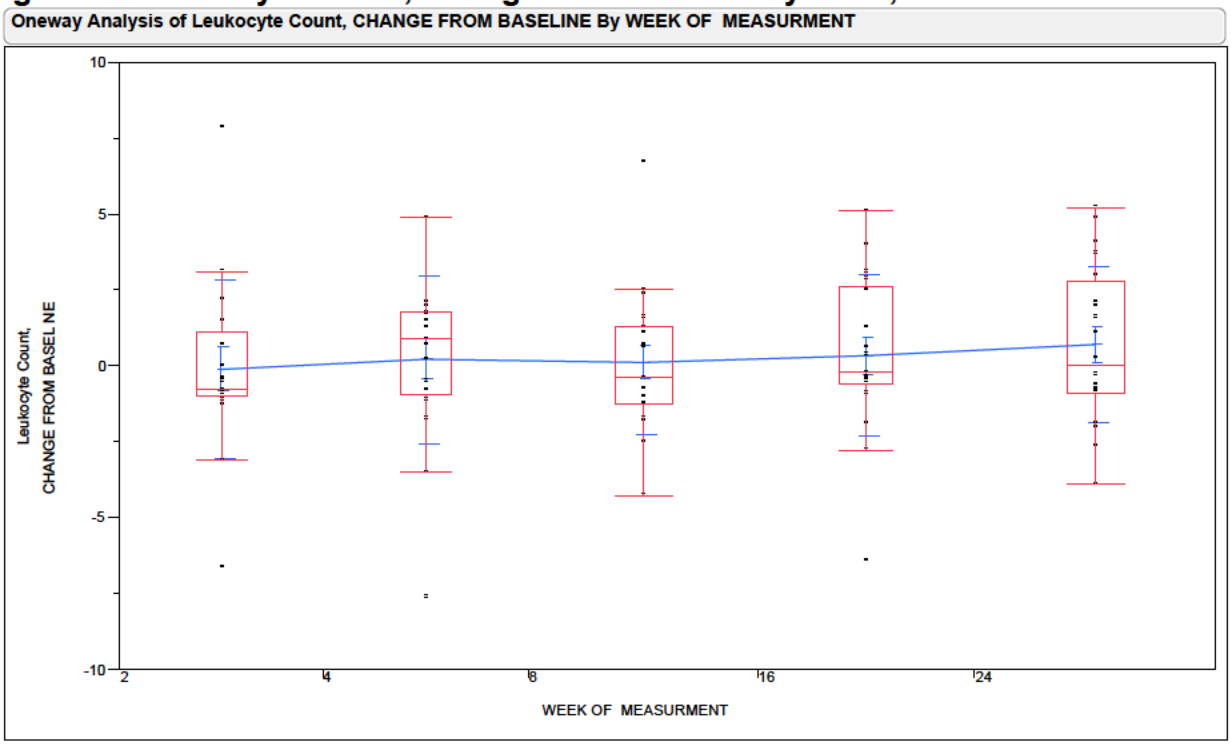
Leukocyte Count

Table 49 Leukocyte count, means, medians, outliers, shift, rufinamide treatment

Leukocytes (normal 6.3 to [13.7]14.8 10^9/L)

Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	0.33		0.70	
Median	-0.2		0	
Range	6.4 to 5.1		-3.9 to 5.2	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	1		0	
Min value	5.4			
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=16)		Shift from baseline to week 24, (n=17)	
	N to L	N to H	N to L	N to H
	1	2	0	2
high value		15.6		15.6
Low value	5.4			
The outlier low patient had an adverse event preferred term of “upper respiratory tract infection” not reported as an SAE.				

Figure 30 Leukocyte Count, Change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-6.6	-3.8	-1	-0 8	1.1	4.06	7.9
4	-7.6	-4.32	-0 95	0.9	1.788179	2 66	4 9
8	-4.3	-2.5	-1.3	-0.4	1 3	2 5	6.7
16	-6.4	-3.16	-0.6	-0 2	2.6	4.11	5.1
24	-3.9	-2.54	-0 875	0	2.775	4.82	5.2

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	-0.11765	2 95513	0.71672	-1.637	1.4017
4	17	0.21626	2.75216	0.66750	-1.199	1.6313
8	19	0.11053	2 36688	0.54300	-1.030	1.2513
16	18	0 33333	2 66105	0.62722	-0.990	1.6566
24	20	0.70000	2 56577	0.57372	-0.501	1.9008

Conclusion: no notable change in leukocyte count

Lymphocytes/Leukocytes (%)

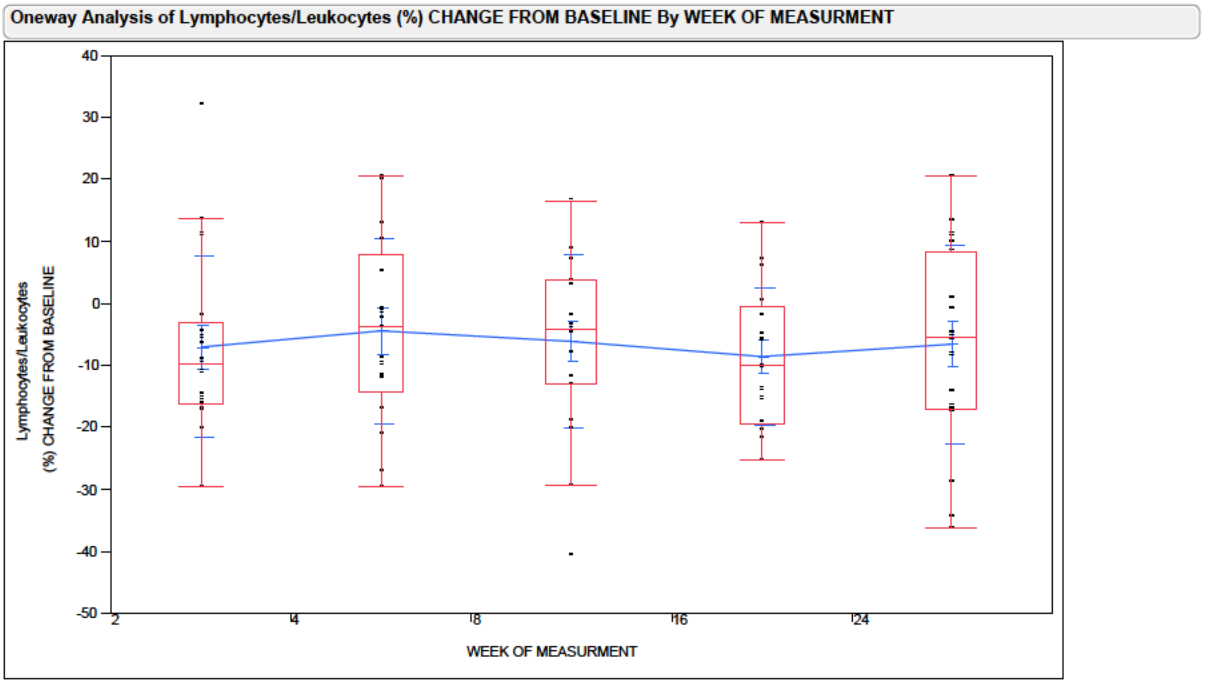
Table 50 Lymphocytes percent, means, medians, outliers, shift, rufinamide treatment

Lymphocytes/Leukocytes (%)

Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-8.6		-6.6	
Median	-9.9		-5.3	
Range	-25.3 to 13.1		-36.3 to 20.6	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	3		0	
Max value	54			
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=18)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	3	0	3
high value		54		68.9
Low value				
14 patients were high at baseline.				
The highest shift patient, E2080-G000-303-1017-1002, is noted to have preferred term AEs of “Bronchitis Viral”, “Ear infection” and “pneumonia”				
Normal ranges(%):				

Low	High
13.1	45.2
11	50.6

Figure 31 Lymphocytes percent, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-29.6	-22.08	-16.4	-9.6	-3.15	17.38	32.1
4	-29.6	-27.6	-14.4	-3.9	7.75	20.2	20.6
8	-40.5	-29.3	-13.1	-4.1	3.8	9	16.5
16	-25.3	-22.42	-19.3	-9.9	-0.55	8.22	13.1
24	-36.3	-34.5	-17	-5.3	8.5	13.5	20.6

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	-7.0647	14.6732	3.5588	-14.61	0.480
4	17	-4.4471	14.9852	3.6345	-12.15	3.258
8	19	-6.1474	13.9367	3.1973	-12.86	0.570
16	17	-8.6000	11.1418	2.7023	-14.33	-2.871
24	19	-6.6000	16.0381	3.6794	-14.33	1.130

Conclusion: no notable change in lymphocyte %. The highest outlier patient may have had lymphocyte count driven by a viral infection.

Monocytes/Leukocytes (%)

Table 51 Monocytes percent, mean, media, outliers, shift, rufinamide treatment

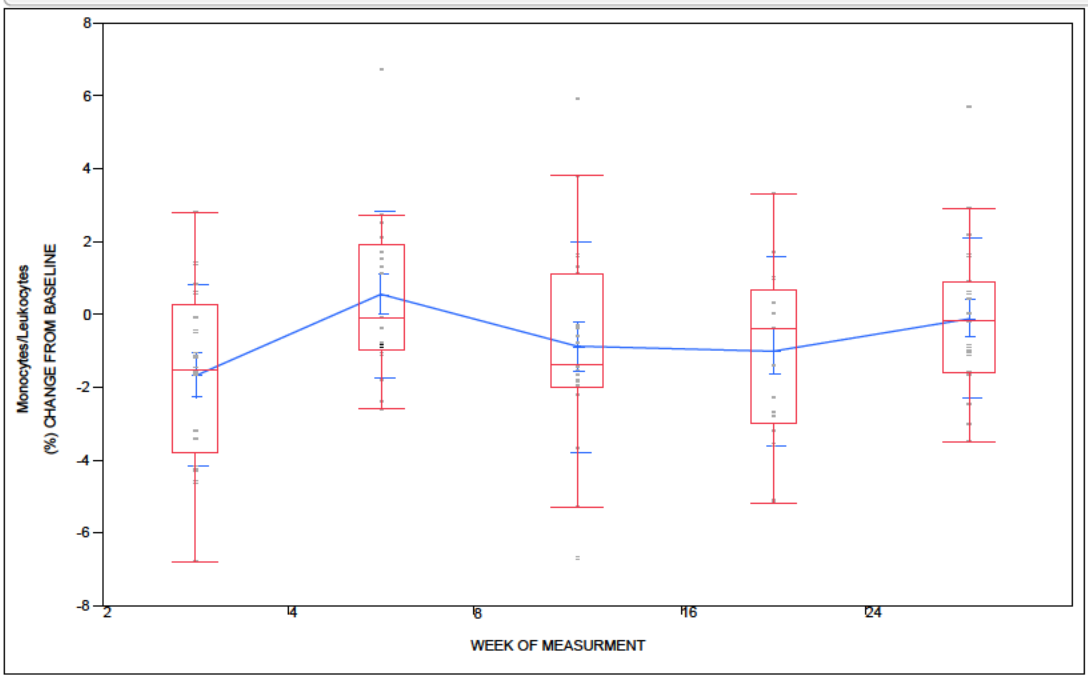
Monocytes/Leukocytes (%)

Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-1.01		-0.12	
Median	-0.4		-0.2	
Range	-5.2 to 3.3		-3.5 to 5.7	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=18)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	2	0	0	0
high value				
Low value	2.8			
Normal ranges %:				

Low	High
3.1	12.5
4.4	13.9

Figure 32 Monocytes percent, change from baseline by week, rufinamide treatment

Oneway Analysis of Monocytes/Leukocytes (%) CHANGE FROM BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-6.8	-5.04	-3.8	-1.5	0.25	1.68	2.8
4	-2.6	-2.44	-1	-0.1	1.9	3.5	6.7
8	-6.7	-5.3	-2	-1.4	1.1	3.8	5.9
16	-5.2	-5.12	-3	-0.4	0.65	3.3	3.3
24	-3.5	-3	-1.6	-0.2	0.9	2.9	5.7

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	-1.6824	2.48275	0.60216	-2.959	-0.406
4	17	0.5529	2.29514	0.55665	-0.627	1.733
8	19	-0.8737	2.89556	0.66429	-2.269	0.522
16	17	-1.0118	2.59082	0.62837	-2.344	0.320
24	19	-0.1211	2.19306	0.50312	-1.178	0.936

Conclusion: no notable change in monocyte percent

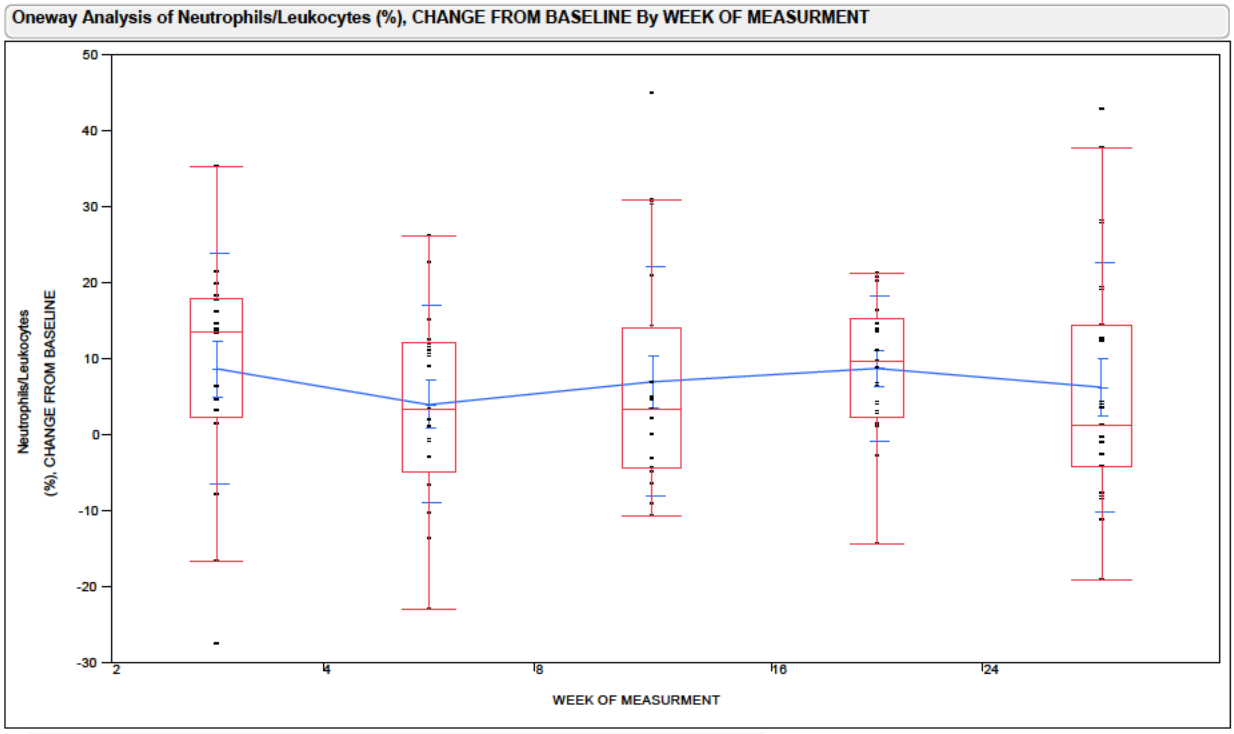
Neutrophils/Leukocytes (%)

Table 52 Neutrophils percent, mean, median, outliers, shift, rufinamide treatment

Neutrophils/Leukocytes (%)		
Change from Baseline to Week 16 and 24. Means and Medians		
Statistic	Week 16	Week 24

<table>
<tr><td>Mean</td><td colspan="2">8.68</td><td colspan="2">6.22</td></tr>
<tr><td>Median</td><td colspan="2">9.5</td><td colspan="2">1.3</td></tr>
<tr><td>Range</td><td colspan="2">-14.5 to 21.2</td><td colspan="2">-19.2 to 42.8</td></tr>
<tr><td colspan="5">Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)</td></tr>
<tr><td></td><td colspan="2">Week 16</td><td colspan="2">Week 24</td></tr>
<tr><td># Patients High*</td><td colspan="2">0</td><td colspan="2">0</td></tr>
<tr><td>Max value</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td># Patients low*</td><td colspan="2">0</td><td colspan="2">0</td></tr>
<tr><td>Min value</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td colspan="5">Shifts from Normal to high or low at Week 16 and 24</td></tr>
<tr><td></td><td colspan="2">Shift from baseline to week 16, all (n=14)</td><td colspan="2">Shift from baseline to week 24, (n=14)</td></tr>
<tr><td></td><td>N to L</td><td>N to H</td><td>N to L</td><td>N to H</td></tr>
<tr><td></td><td>1</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>high value</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Low value</td><td>31.6</td><td></td><td>25.2</td><td></td></tr>
<tr><td colspan="5">Normal ranges %:
<table>
<tr><td>Low</td><td>High</td></tr>
<tr><td>20.7</td><td>70.9</td></tr>
<tr><td>32.3</td><td>78.6</td></tr>
</table></td></tr>
<tr><td colspan="5">Baseline mean 34%</td></tr>
</table>

Figure 33 Neutrophils percent, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-27.6	-18.96	2.3	13.5	17.95	24.26	35.3
4	-23.1	-15.58	-4.9	3.2	12.05	23.38	26.1
8	-10.9	-9.1	-4.4	3.3	14	30.9	45
16	-14.5	-5.22	2.15	9.5	15.35	20.8	21.2
24	-19.2	-11.2	-4.3	1.3	14.3	37.8	42.8

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	8.64118	15.1547	3.6755	0.849	16.433
4	17	3.91765	12.9233	3.1344	-2.727	10.562
8	19	6.93158	15.0306	3.4483	-0.313	14.176
16	17	8.68824	9.4374	2.2889	3.836	13.541
24	19	6.22105	16.4661	3.7776	-1.715	14.157

Conclusion: no notable change in % neutrophils.

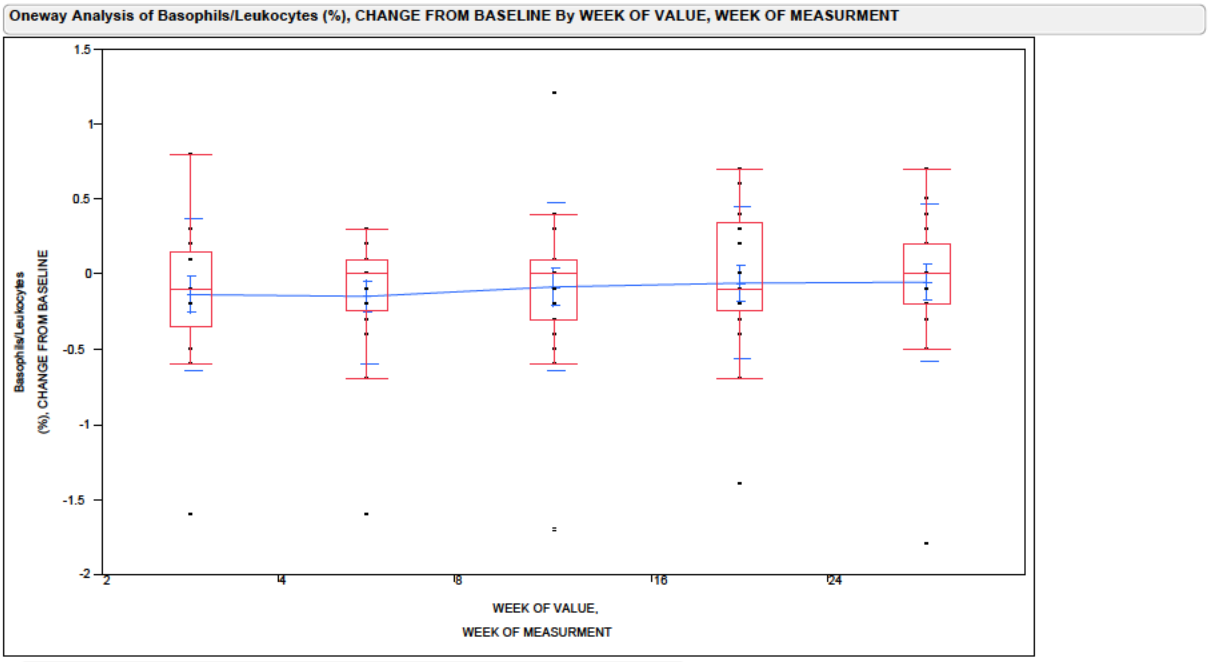
Basophils/Leukocytes (%)

Table 53 Basophils percent, mean, median, outliers, shift, rufinamide treatment

Basophils/Leukocytes (%)
Change from Baseline to Week 16 and 24. Means and Medians

Statistic	Week 16		Week 24	
Mean	-0.059		-0.053	
Median	-0.1		0	
Range	-1.4 to 0.7		-1.8 to 0.7	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean 0.525 %				
Normal range: 0 to 2.4%				

Figure 34 Basophils percent, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-1.6	-0.8	-0.35	-0.1	0.15	0.4	0.8
4	-1.6	-0.88	-0.25	0	0.1	0.22	0.3
8	-1.7	-0.6	-0.3	0	0.1	0.4	1.2
16	-1.4	-0.84	-0.25	-0.1	0.35	0.62	0.7
24	-1.8	-0.5	-0.2	0	0.2	0.5	0.7

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	-0.13529	0.506139	0.12276	-0.3955	0.12494
4	17	-0.14706	0.445979	0.10817	-0.3764	0.08224
8	19	-0.08421	0.557039	0.12779	-0.3527	0.18427
16	17	-0.05882	0.503809	0.12219	-0.3179	0.20021
24	19	-0.05263	0.521076	0.11954	-0.3038	0.19852

Conclusion: no notable change in % basophils

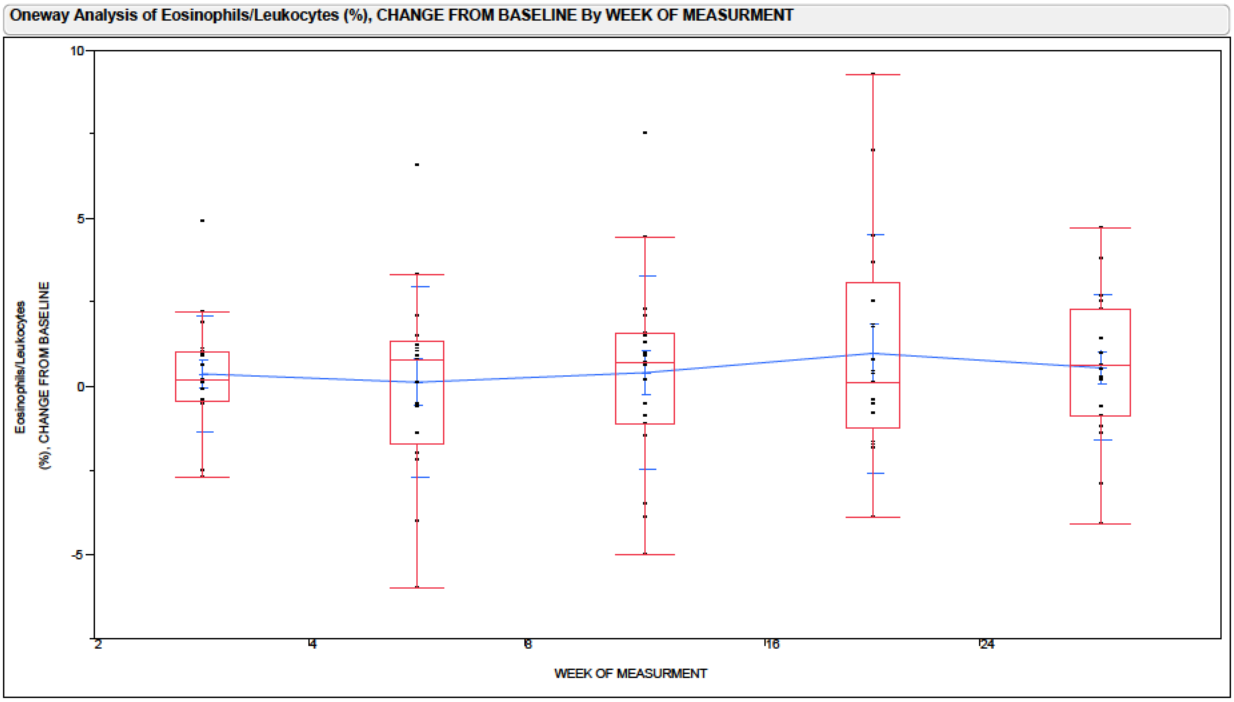
Eosinophils/Leukocytes (%)

Table 54 Eosinophils percent, mean, median, outliers, shift, rufinamide treatment

Eosinophils/Leukocytes (%)		
Change from Baseline to Week 16 and 24. Means and Medians		
Statistic	Week 16	Week 24
Mean	0.98	0.55
Median	0.1	0.6

Range	-3.9 to 9.3		-4.1 to 4.7	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=14)		Shift from baseline to week 24, (n=17)	
	N to L	N to H	N to L	N to H
	0	2	0	4
high value		6.4		6.8
Low value				
Baseline mean 3.16%				
Normal range 0 to 4.8%				
The adverse events of the 4 patient with a shift from normal baseline to high at week 24 were captured. There were 36 AEs, three were SAEs. The three SAE preferred terms were “bronchitis”, “pneumonia aspiration” and “respiratory tract infection”. There was one preferred term of “drug eruption” and two of “pyrexia” both associated with the same patient.				

Figure 35 Eosinophils percent, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-2.7	-2.54	-0.45	0.2	1.05	2.756357	4.9
4	-6	-4.4	-1.7	0.8	1.35	3.96	6.6
8	-5	-3.9	-1.1	0.7	1.6	4.440892	7.5
16	-3.9	-3.9	-1.25	0.1	3.1	7.46	9.3
24	-4.1	-2.9	-0.9	0.6	2.3	3.8	4.7

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	17	0.371791	1.73007	0.41960	-0.518	1.2613
4	17	0.123529	2.84836	0.69083	-1.341	1.5880
8	19	0.407415	2.87419	0.65939	-0.978	1.7927
16	17	0.982353	3.54511	0.85982	-0.840	2.8051
24	19	0.552632	2.16548	0.49679	-0.491	1.5964

Conclusion: no notable change in eosinophil percent. There was one drug eruption from among the group with a shift from normal baseline to high at 24 weeks. There is not sufficient evidence to consider a signal for hypereosinophilic events.

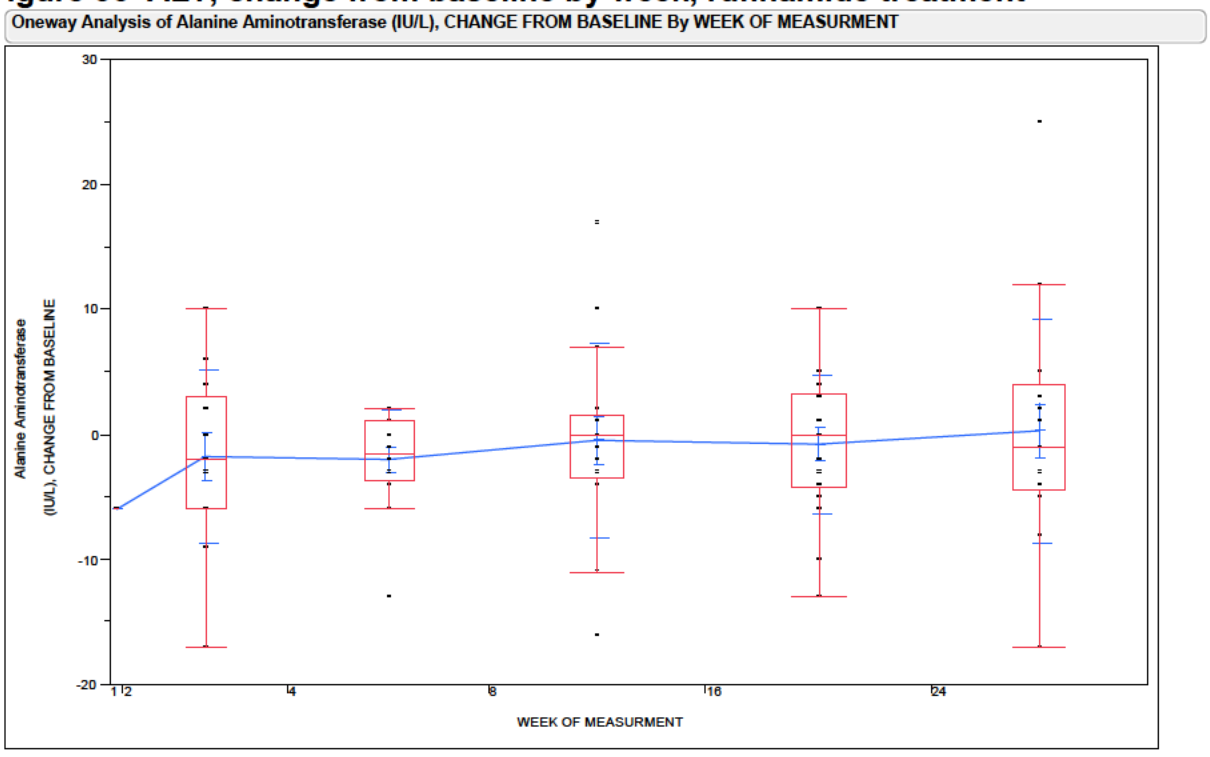
Clinical Chemistry

Alanine Aminotransferase (IU/L)

Table 55 ALT, mean, median, outliers, shift, rufinamide treatment

Alanine Aminotransferase (IU/L) (ALT)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.78		0.29	
Median	0		-1	
Range	-13 to 10		-17 to 25	
Outliers (baseline low not removed, no baseline high present), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
Shifts from Normal or Low to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	1	0	1	0
high value				
Low value	4		4	
Baseline mean 16.5 IU/L				
Normal range 5 to 45 IU/L				

Figure 36 ALT, change from baseline by week, rufinamide treatment



Missing Rows 14

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-6	-6	-6	-6	-6	-6	-6
2	-17	-13.8	-6	-2	3	8.4	10
4	-13	-8.1	-3.75	-1.5	1	2	2
8	-16	-12	-3.5	0	1.5	11.4	17
16	-13	-10.3	-4.25	0	3.25	5.5	10
24	-17	-9.8	-4.5	-1	4	14.6	25

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-6.0000	.	.	.	.
2	13	-1.7692	6.91802	1.9187	-5.950	2.4113
4	16	-2.0000	3.94968	0.9874	-4.105	0.1046
8	17	-0.4706	7.78715	1.8887	-4.474	3.5332
16	18	-0.7778	5.57891	1.3150	-3.552	1.9965
24	17	0.2941	8.91463	2.1621	-4.289	4.8776

Conclusion: no notable change in ALT

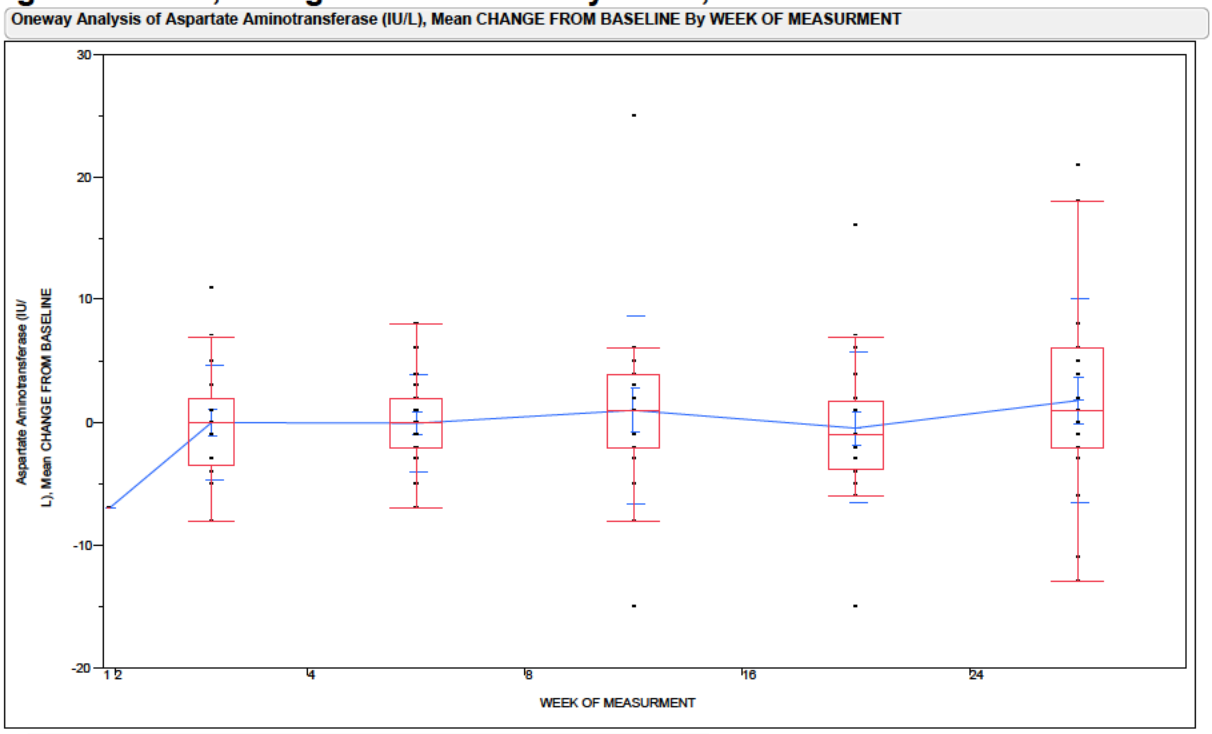
Aspartate Aminotransferase (IU/L)

Table 56 AST, mean, median, outliers, shift, rufinamide treatment

Aspartate Aminotransferase (IU/L) -AST

Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.45		1.8	
Median	-1		1	
Range	-16 to 16		-13 to 21	
Outliers (low at baseline not removed), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	2	0	1	0
high value				
Low value	19		19	
Normal range 20 to 60 IU/L				
Baseline mean: 29.8 IU/L				

Figure 37 AST, change from baseline by week , rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-7	-7	-7	-7	-7	-7	-7
2	-8	-5.6	-3.5	0	2	7.8	11
4	-7	-7	-2	0	2	6	8
8	-15	-8	-2	1	4	6	25
16	-15	-5.9	-3.75	-1	1.75	6.9	16
24	-13	-11	-2	1	6	18	21

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-7.0000	.	.	.	.
2	17	0.0000	4.66369	1.1311	-2.398	2.3978
4	19	-0.0526	3.97874	0.9128	-1.970	1.8651
8	19	1.0000	7.64490	1.7539	-2.685	4.6847
16	20	-0.4500	6.09983	1.3640	-3.305	2.4048
24	19	1.7895	8.28371	1.9004	-2.203	5.7821

Conclusion: no notable change in AST value during the study

Alkaline Phosphatase (IU/L)

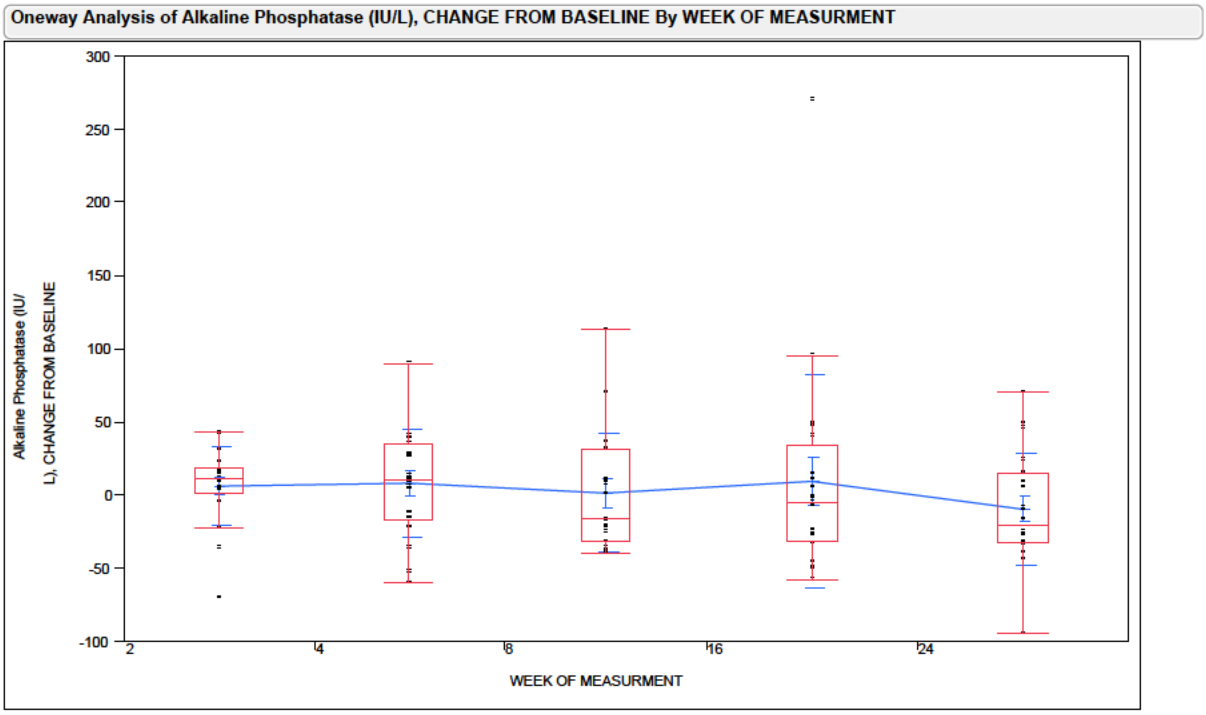
Table 57 Alkaline Phosphatase, mean, median, outliers, shift, rufinamide treatment

Alkaline Phosphatase (IU/L)
Change from Baseline to Week 16 and 24. Means and Medians

Statistic	Week 16		Week 24	
Mean	9.7		-9.4	
Median	-5		-20.5	
Range	-57 to 271		-95 to 71	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	1		0	
Max value	439			
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	1	0	0
high value		439		
Low value				
Baseline mean = 198 IU/L				
Patient E2080-G000-303-4008-1001 is removed from the analysis due to an abnormally high screening value of 1828 IU/L. This patient only contributed a week 1 and 8 value before study discontinuation. (?)				

E2080-G000-303-4008-1001			
Screening	-1		1828
Week 1	1	Y	855
Week 8	8	Y	223

Figure 38 Alkaline Phosphatase, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-69	-38.4	2	11.5	19.5	42.1	43
4	-60	-52.8	-16.5	10.5	36	45.9	90
8	-40	-39	-31	-16	31	70	113
16	-57	-49.9	-30.75	-5	34.5	91.4	271
24	-95	-42.6	-32.5	-20.5	14.25	49.6	71

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	18	6.4444	26.8662	6.332	-6.92	19.805
4	18	8.4444	36.8690	8.690	-9.89	26.779
8	19	1.6842	40.8358	9.368	-18.00	21.366
16	20	9.7000	73.0487	16.334	-24.49	43.888
24	20	-9.4000	38.0642	8.511	-27.21	8.415

Conclusion, no notable change in Alk phos

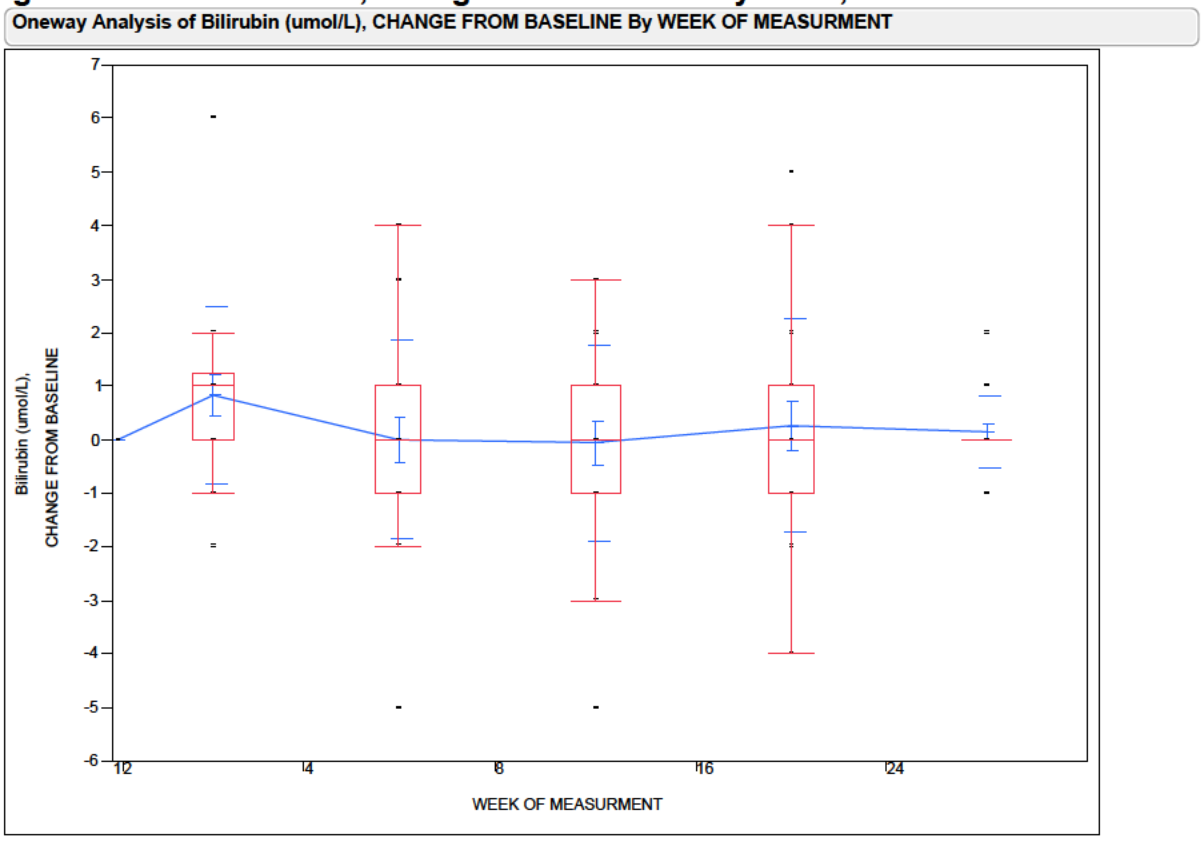
Total Bilirubin (umol/L)

Table 58 Total Bilirubin, mean, median, outliers, shift, rufinamide treatment

Total Bilirubin (umol/L)
Change from Baseline to Week 16 and 24. Means and Medians

Statistic	Week 16		Week 24	
Mean	0..26		0.15	
Median	0		0	
Range	-4 to 5		-1 to 2	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
		N to H		N to H
		0		0
high value				
Baseline mean 3.0				
Reference range 3 to 21 umol/L				

Figure 39 Total Bilirubin, change from baseline by week, rufinamide treatment



Missing Rows 1

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	0	0	0	0	0	0	0
2	-2	-1.1	0	1	1.25	2.4	6
4	-5	-2	-1	0	1	3	4
8	-5	-2.8	-1	0	1	2	3
16	-4	-2	-1	0	1	4	5
24	-1	-0.9	0	0	0	1	2

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	0.00000	.	.	.	.
2	18	0 83333	1.65387	0 38982	0.0109	1 6558
4	19	0.00000	1.85592	0.42578	-0 8945	0.8945
8	20	-0.05000	1.82021	0.40701	-0 9019	0.8019
16	19	0 26316	1.99561	0.45782	-0 6987	1 2250
24	20	0.15000	0 67082	0.15000	-0.1640	0.4640

Conclusion: no notable change in Bilirubin during the course of the study

Direct Bilirubin (umol/L)

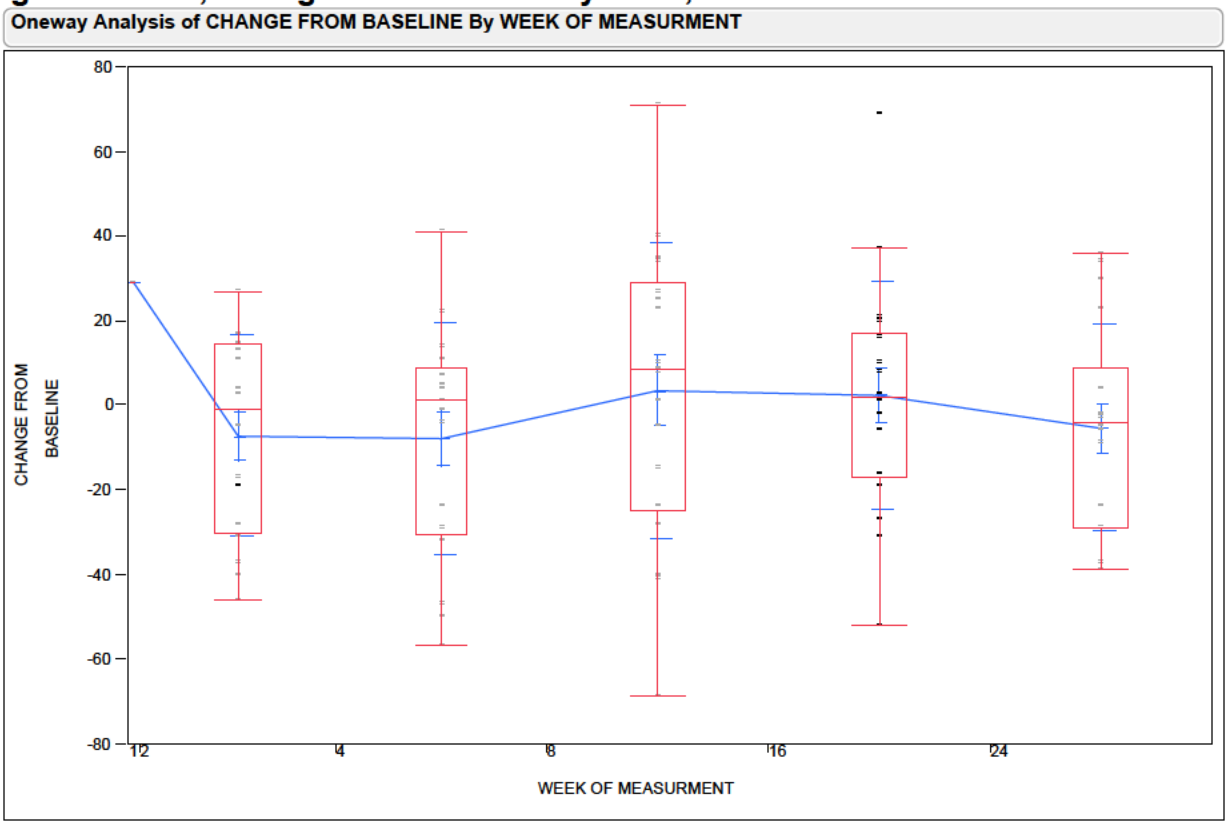
No abnormal levels

Lactate Dehydrogenase (IU/L)

Table 59 LDH, mean, median, outliers, shift, rufinamide treatment

Lactate Dehydrogenase (IU/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	2.28		-5.5	
Median	2		-4	
Range	-52 to 69		-39 to 36	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean 223				
Reference range 120 345 IU/L				

Figure 40 LDH, Change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	29	29	29	29	29	29	29
2	-46	-41.8	-30.25	-1	14.5	20	27
4	-57	-51.4	-30 5	1	9	25 8	41
8	-69	-43.8	-25	8.5	28.75	43.1	71
16	-52	-33.1	-16.75	2	17	40 2	69
24	-39	-39	-29	-4	8.75	34.2	36

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	29.000	.	.	.	.
2	16	-7.375	23.6893	5.9223	-20.00	5 248
4	17	-7.941	27.3095	6.6235	-21.98	6.100
8	18	3.389	34.8073	8.2042	-13.92	20.698
16	18	2.278	27.0333	6.3718	-11.17	15.721
24	18	-5.500	24.4763	5.7691	-17.67	6 672

Conclusion: There is no large change in value and no consistent change in direction of means or medians during the course of the study. No notable change in Lactate Dehydrogenase.

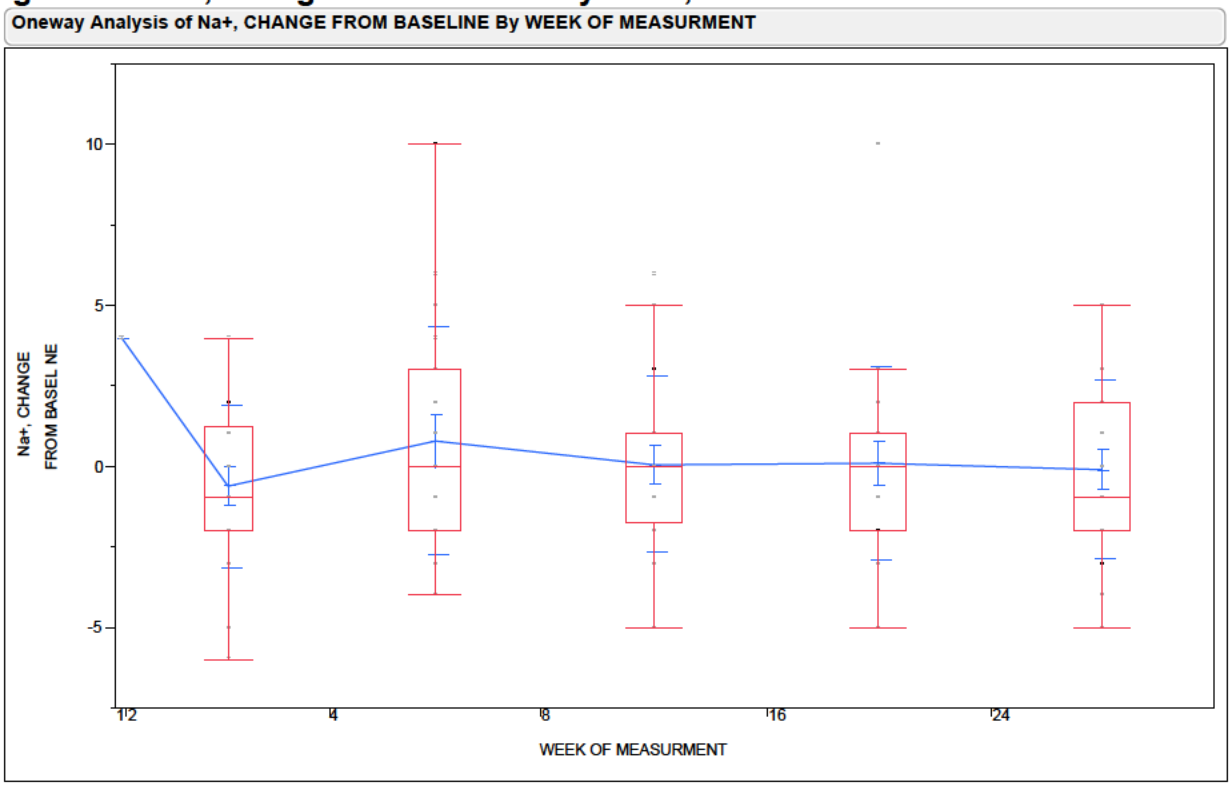
Electrolyte Panel

Sodium (mmol/L)

Table 60 Na+, mean, median, outliers, shift, rufinamide treatment

Sodium (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	0.1		-0.1	
Median	0		-1	
Range	-5 to 10		-5 to 5	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 141 umol/L				
Reference Range 132 to 147 umol/L				

Figure 41 Na+, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	4	4	4	4	4	4	4
2	-6	-5.1	-2	-1	1.25	2.2	4
4	-4	-3	-2	0	3	6	10
8	-5	-3	-1.75	0	1	4.8	6
16	-5	-3	-2	0	1	2.9	10
24	-5	-3.9	-2	-1	2	4.8	5

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	4.0000	.	.	.	.
2	18	-0 6111	2 50033	0.58933	-1.854	0 6323
4	19	0.7895	3 56805	0.81857	-0.930	2 5092
8	20	0.0500	2.72368	0.60903	-1.225	1.3247
16	20	0.1000	3 04181	0.68017	-1.324	1.5236
24	20	-0.1000	2.78908	0.62366	-1.405	1.2053

Potassium (mmol/L)

Table 61 K+, mean, median, outliers, shift, rufinamide treatment

Potassium (mmol/L)

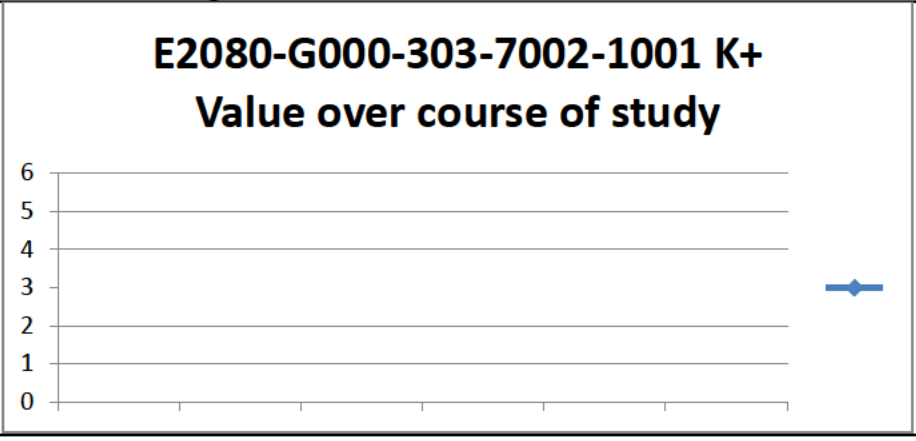
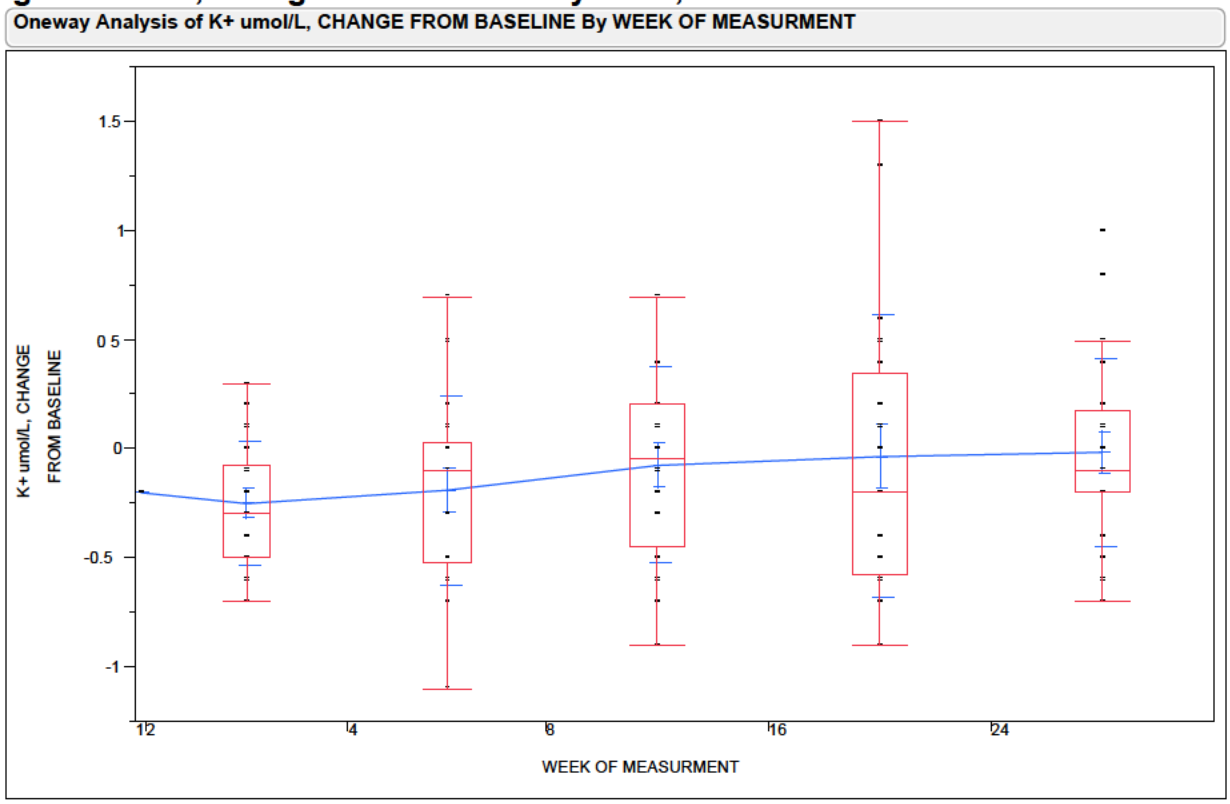
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.035		-0.015	
Median	-0.2		-0.1	
Range	-0.9 to 1.5		-0.7 to 1	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	1		0	
Max value	6.0			
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	1	0	0
high value		6.0		
Low value				
Baseline mean 4.52 umol/L				
Reference range 3.5 to 5.5 umol/L				
				
Patient E2080-G000-303-7002-1001 (age 26 mo) had nine adverse event entries, none related to renal, electrolye or cardiovascular events. 1 SAE, preferred term “respiratory tract infection”				

Figure 42 K+ , change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-0.2	-0.2	-0 2	-0.2	-0 2	-0.2	-0.2
2	-0.7	-0.61	-0 5	-0.3	-0.075	0.21	0 3
4	-1.1	-0.74	-0.525	-0.1	0.025	0.52	0.7
8	-0.9	-0.7	-0.45	-0.05	0.2	0.67	0.7
16	-0.9	-0.7	-0.575	-0.2	0.35	1.23	1.5
24	-0.7	-0.59	-0 2	-0.1	0.175	0.77	1

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-0 20000	.	.	.	.
2	18	-0 25000	0 285431	0.06728	-0 3919	-0.1081
4	18	-0.18889	0.437760	0.10318	-0.4066	0.0288
8	20	-0 07500	0.451751	0.10101	-0 2864	0.1364
16	20	-0 03500	0 646672	0.14460	-0 3377	0.2677
24	20	-0 01500	0.431978	0.09659	-0 2172	0.1872

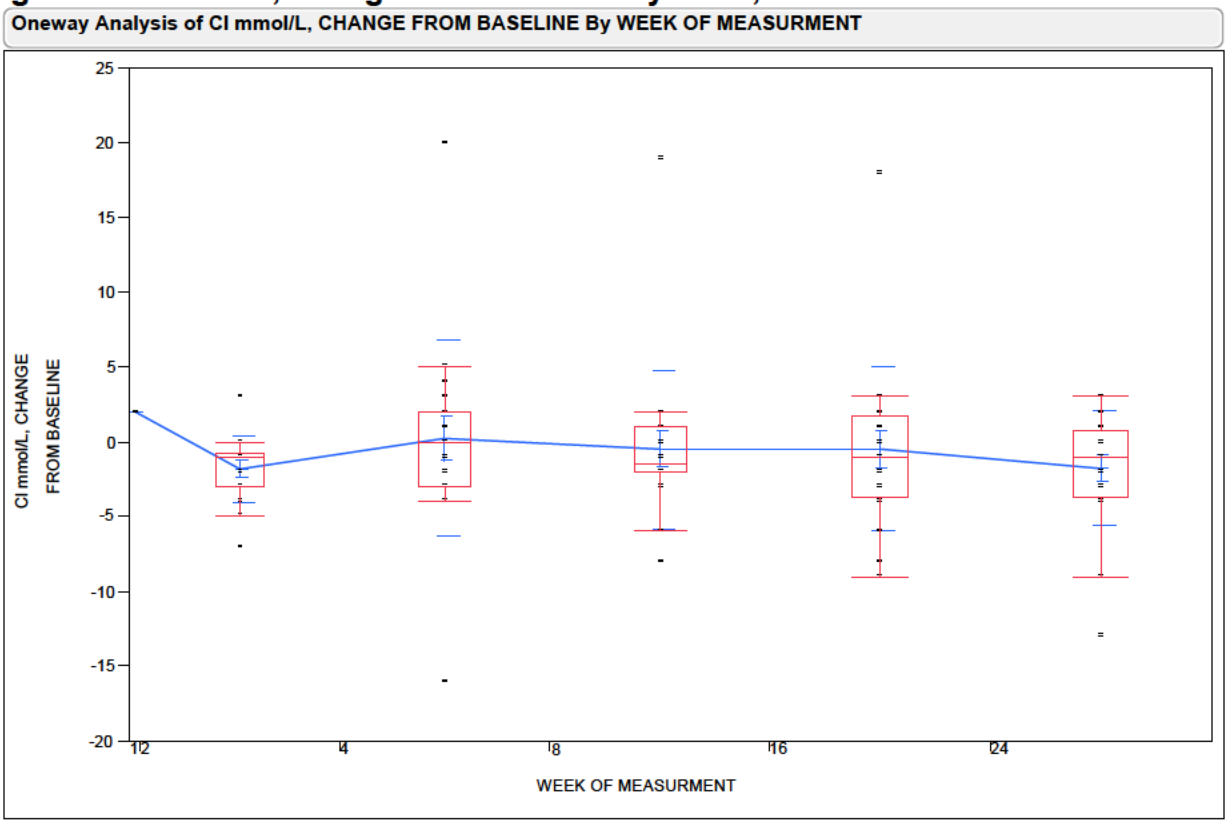
Conclusion: one patient had a 27% increase in K+ value between baseline and week 16. Value returned to normal limits at week 24. No adverse events related to renal, electrolyte or cardiac rhythm AE. Overall no notable change in potassium during the course of the study (no new safety signal)

Chloride (mmol/L)

Table 62 Chloride, mean, median, outliers, shift, rufinamide treatment

Chloride (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.5		-1.8	
Median	-1		-1	
Range	-9 to 18		-13 to 3	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 104 mmol/L				
Reference range = 94 to 111 mmol/L				

Figure 43 Chloride, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	2	2	2	2	2	2	2
2	-7	-5 2	-3	-1	-0.75	0.3	3
4	-16	-4	-3	0	2	5	20
8	-8	-6	-2	-1.5	1	2	19
16	-9	-7 8	-3.75	-1	1.75	2 9	18
24	-13	-8 5	-3.75	-1	0.75	2	3

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	2.0000	.	.	.	.
2	18	-1 8333	2.22948	0.5255	-2.942	-0.725
4	19	0.2105	6.57925	1.5094	-2.961	3.382
8	20	-0 5000	5.31631	1.1888	-2.988	1.988
16	20	-0 5000	5.49162	1.2280	-3.070	2.070
24	20	-1 8000	3.81962	0.8541	-3.588	-0.012

Conclusion: no notable change in chloride level during the course of the study

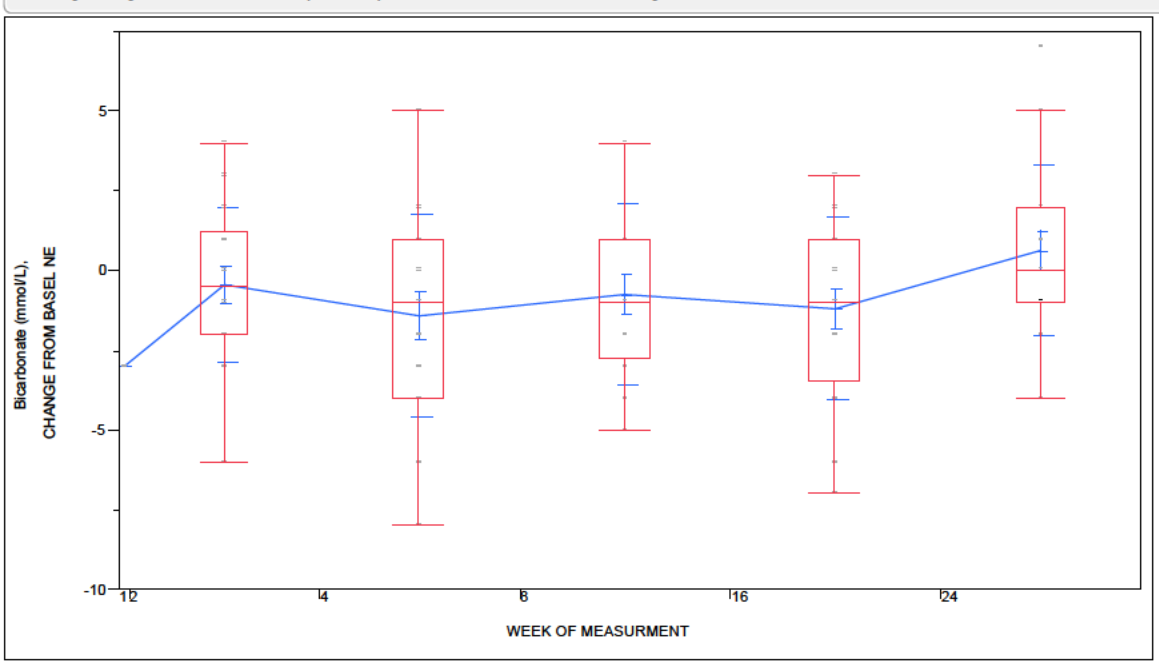
Bicarbonate (mmol/L)

Table 63 Bicarbonate, mean, median, outliers, shift, rufinamide treatment

Bicarbonate (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-1.2		0.63	
Median	-1		0	
Range	-7 to 3		-4 to 7	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	15 (11/15 low at baseline)		11 (9/11 low at baseline)	
Min value	15 (both lowest patients were low at baseline)		15 (single patient low at baseline)	
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	4	0	2	
high value				
Low value	17		20	
	E2080-G000-303-4006-1001 E2080-G000-303-1005-1005 E2080-G000-303-5003-1002 E2080-G000-303-5003-1003			
Baseline mean = 19.3				
Reference range = 21 to 33 mmol/L				
Note 17 of 24 (70%) baseline values were below reference range				

Figure 44 Bicarbonate, change from baseline by week, rufinamide treatment

Oneway Analysis of Bicarbonate (mmol/L), CHANGE FROM BASELINE By WEEK OF MEASURMENT



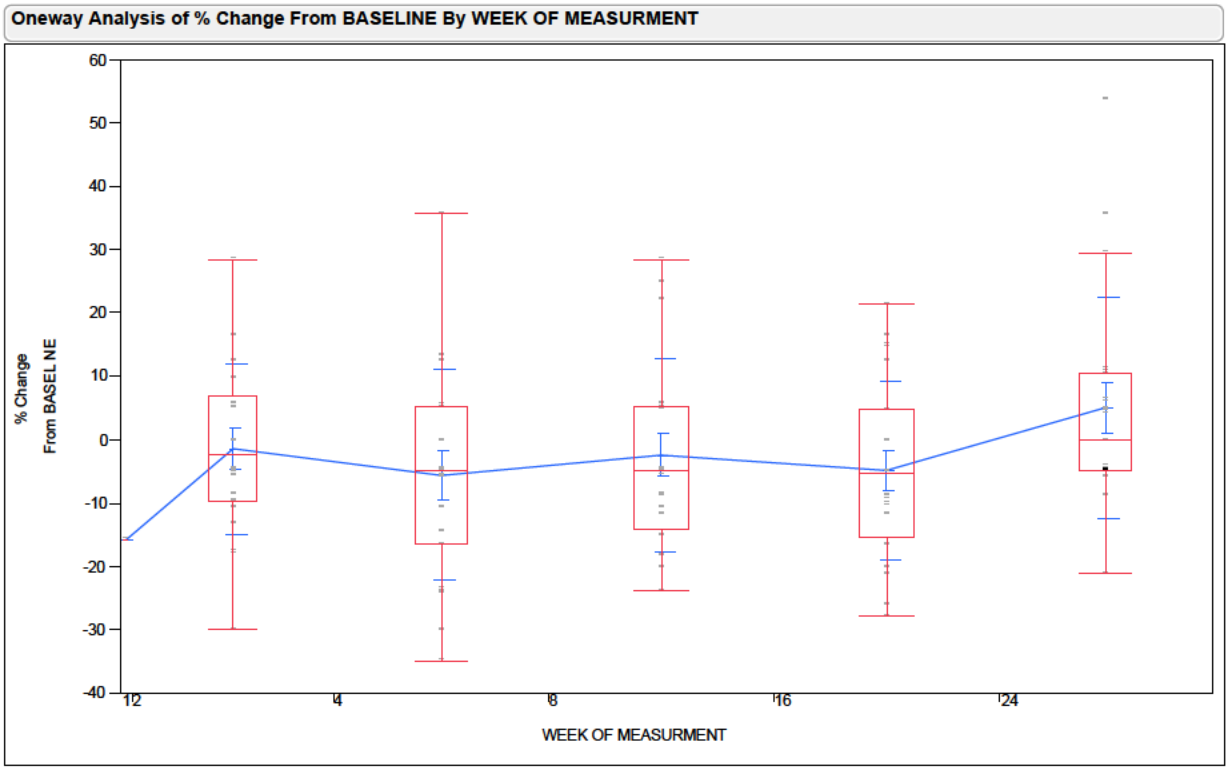
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-3	-3	-3	-3	-3	-3	-3
2	-6	-3 3	-2	-0.5	1.25	3.1	4
4	-8	-6	-4	-1	1	2	5
8	-5	-4 9	-2.75	-1	1	4	4
16	-7	-5 8	-3 5	-1	1	3	3
24	-4	-2	-1	0	2	5	7

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-3.0000	.	.	.	.
2	18	-0.4444	2.43074	0 57293	-1.653	0.7643
4	19	-1.4211	3.18531	0.73076	-2.956	0.1142
8	20	-0.7500	2.82610	0 63194	-2.073	0 5727
16	20	-1.2000	2.87640	0 64318	-2.546	0.1462
24	19	0.6316	2.67105	0.61278	-0.656	1.9190

Figure 45 Bicarbonate, percent change from baseline by week, rufinamide treatment



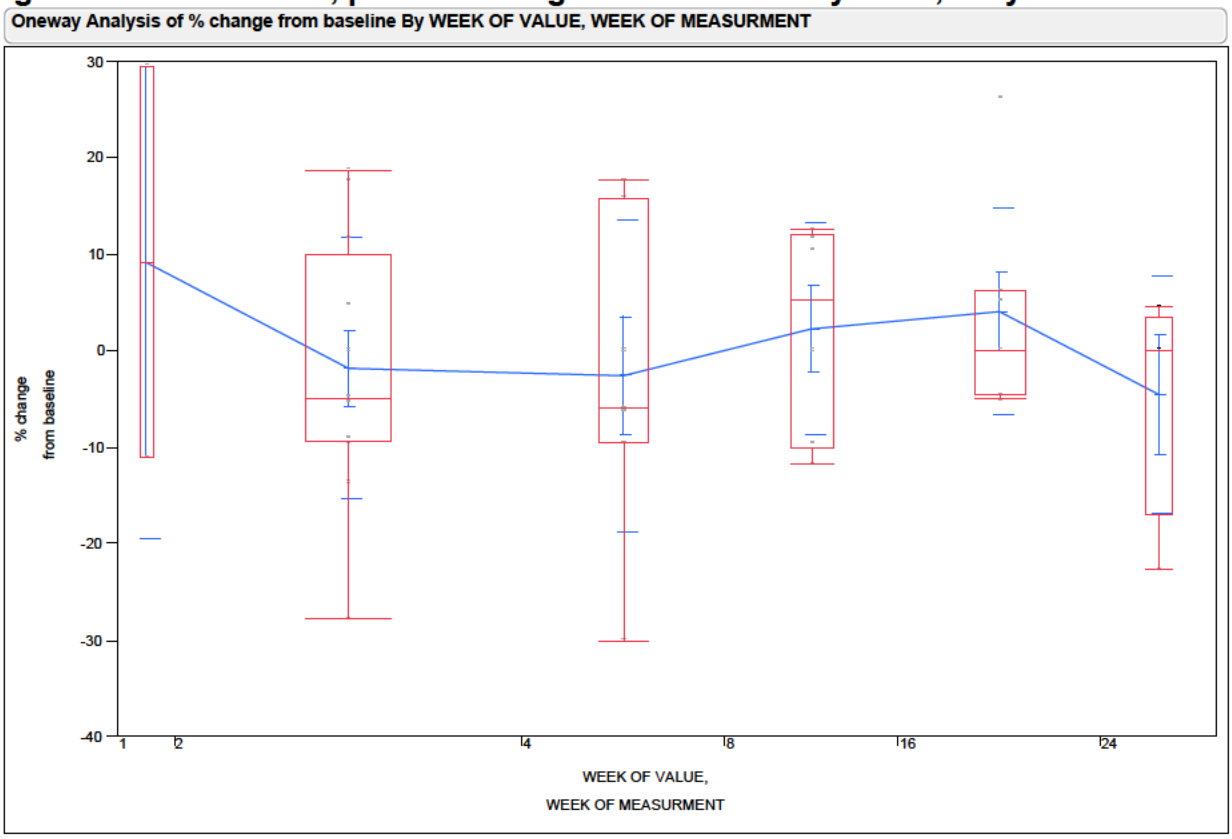
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-15.7895	-15.7895	-15.7895	-15.7895	-15.7895	-15.7895	-15.7895
2	-30	-18.8824	-9.77444	-2 27273	6.911765	17.85714	28 57143
4	-34.7826	-30	-16.6667	-5	5.263158	13.33333	35.71429
8	-23 8095	-20	-14.1912	-5 01253	5.263158	24.72222	28 57143
16	-28	-25.5835	-15.4412	-5 26316	4.761905	16 5	21.42857
24	-21 0526	-8.69565	-5	0	10 52632	35.71429	53 84615

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-15.789	.	.	.	.
2	18	-1.405	13.5172	3.1860	-8.13	5.317
4	19	-5 625	16.7160	3.8349	-13 68	2.432
8	20	-2.424	15.1200	3.3809	-9.50	4.652
16	20	-4 838	14.1104	3.1552	-11.44	1.766
24	19	5.099	17.5266	4 0209	-3.35	13 547

Figure 46 Bicarbonate, percent change from baseline by week, "any other AED"



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-11.1111	-11.1111	-11.1111	9.150327	29.41176	29.41176	29.41176
2	-27.7778	-23.5354	-9.41558	-4 88095	10.01401	18.41912	18.75
4	-30	-30	-9.52381	-5 88235	15.78947	17 64706	17.64706
8	-11.7647	-11.7647	-10.084	5 263158	11.94853	12 5	12.5
16	-5	-5	-4.54545	0	6 25	26.31579	26 31579
24	-22.7273	-22.7273	-17.0455	0	3.409091	4.545455	4 545455

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	2	9.1503	28.6540	20.261	-248.3	266.60
2	12	-1 8442	13.4487	3.882	-10.4	6.70
4	7	-2 6028	16 2156	6.129	-17.6	12 39
8	6	2.2504	10.9926	4.488	-9.3	13.79
16	7	4.0405	10.7290	4 055	-5.9	13 96
24	4	-4 5455	12.3091	6.155	-24.1	15 04

Summary analysis: the results of bicarbonate values are difficult to interpret due to the high proportion of patients with low baseline bicarbonate values. Fifteen of the 24 rufinamide treated patients were on concomitant topiramate. It is noted that 2 patients who were found to have a normal to low shift at 16 weeks were on concomitant topiramate. Ten (10) of the 17 (58%) patients with low baseline bicarbonate were found

to be on concomitant topiramate. Percent change from baseline bicarbonate over the course of the study is examined. There is one patient with a week 1 measurement who has a 16% decline in bicarbonate. This patient (E2080-G000-303-4008-1001) has a low value at baseline with only a week 1 and 8 measurement. The value is 16mmol/L at week 1 and 17 mmol/L at week 8.
The mean and median percent change from baseline in the remaining weeks 2 to 24 do not reveal a value greater than 6% change from baseline. The mean change from baseline is negative at weeks 2, 4, 8, and 16 but becomes positive at week 24. The percent change in baseline over the course of the study does not reveal a consistent trend. In addition, examination of chloride percent change from baseline does not reveal a parallel increase in chloride values.

Table 64 Chloride, percent change from baseline, means and medians by study week, rufinamide treatment

Chloride, percent change from baselinje, medians and means by study week

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	1.923077	1.923077	1.923077	1.923077	1.923077	1.923077	1.923077
2	-6.14035	-4.66809	-2.87101	-0.97563	-0.69444	0.3	3
4	-14.0351	-3.8835	-2.7027	0	1.960784	5	23.80952
8	-7.01754	-5.63488	-1.92308	-1.38472	0.96854	1.938049	22.61905
16	-8.10811	-6.89271	-3.52463	-0.94348	1.67129	2.896078	21.42857
24	-11.7117	-7.48988	-3.54447	-0.93491	0.728155	1.992308	2.912621

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	1.9231	.	.	.	.
2	18	-1.6945	2.04804	0.4827	-2.713	-0.676
4	19	0.5467	6.96813	1.5986	-2.812	3.905
8	20	-0.1919	5.90366	1.3201	-2.955	2.571
16	20	-0.1904	5.95274	1.3311	-2.976	2.596
24	20	-1.6310	3.48110	0.7784	-3.260	-0.0018

Any other AED;
6/11 have low baseline. 1 (25%) has a normal to low shift at 24 weeks.

The “any other AED” group also has a high frequency of low bicarbonate at baseline with a 25% shift to low at week 24. Examination of % change from baseline reveals a negative value at weeks 2, 4 and 24 with positive mean change from baseline at weeks 8 and 16. An inconsistent trend as seen in the rufinamide treatment group.

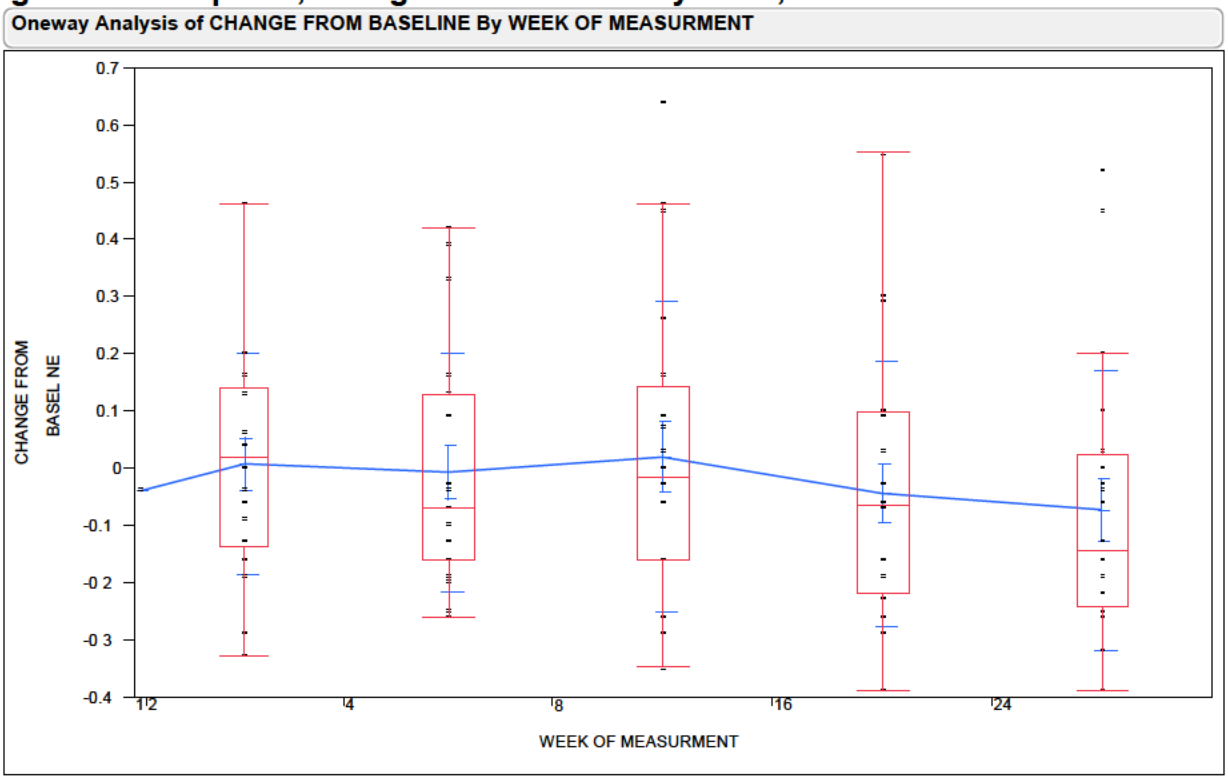
Conclusion: The frequency of low bicarbonate observed during treatment prompts concern that a new safety signal for metabolic acidosis may be present. The overall evidence does not support a conclusion that a safety signal is present due to confounding by concomitant treatment with topiramate in 58% of patients, a very high frequency of low baseline bicarbonate values among the rufinamide treatment patients (70%) and the inconsistent trend in percent change in baseline through the course of the study.

Phosphate (mmol/L)

Table 65 Phosphate, mean, median, outliers, shift, rufinamide treatment

Phosphate (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.045		-0.073	
Median	-0.065		-0.145	
Range	-0.39 to 0.55		-0.39 to 0.52	
Percent Change from Baseline to Week 16 and 24. Means and Medians				
Mean	-1.78		-3.5	
Median	-3.9		-8.5	
Range	-20.4 to 36		-23.6 to 39	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	2	0	1
high value		2.07		1.97
Low value				
Baseline mean 1.64				
Reference range 1 to 1.94 mmol/L				

Figure 47 Phosphate, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-0.04	-0.04	-0 04	-0 04	-0 04	-0.04	-0.04
2	-0.33	-0.294	-0.1375	0.02	0.1375	0.226	0.46
4	-0.26	-0.25	-0.16	-0 07	0.13	0.39	0.42
8	-0.35	-0.344	-0.16	-0.015	0.1425	0.459	0.64
16	-0.39	-0.29	-0 22	-0.065	0 0975	0.299	0.55
24	-0.39	-0.383	-0.2425	-0.145	0 0225	0.425	0.52

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-0 04000	.	.	.	.
2	18	0.00722	0.194295	0.04580	-0 0894	0.10384
4	19	-0 00737	0.207601	0.04763	-0.1074	0.09269
8	20	0.01900	0.272163	0.06086	-0.1084	0.14638
16	20	-0 04450	0.233136	0.05213	-0.1536	0.06461
24	20	-0 07300	0.244758	0.05473	-0.1876	0.04155

Conclusion: there is no notable change in phosphate level.

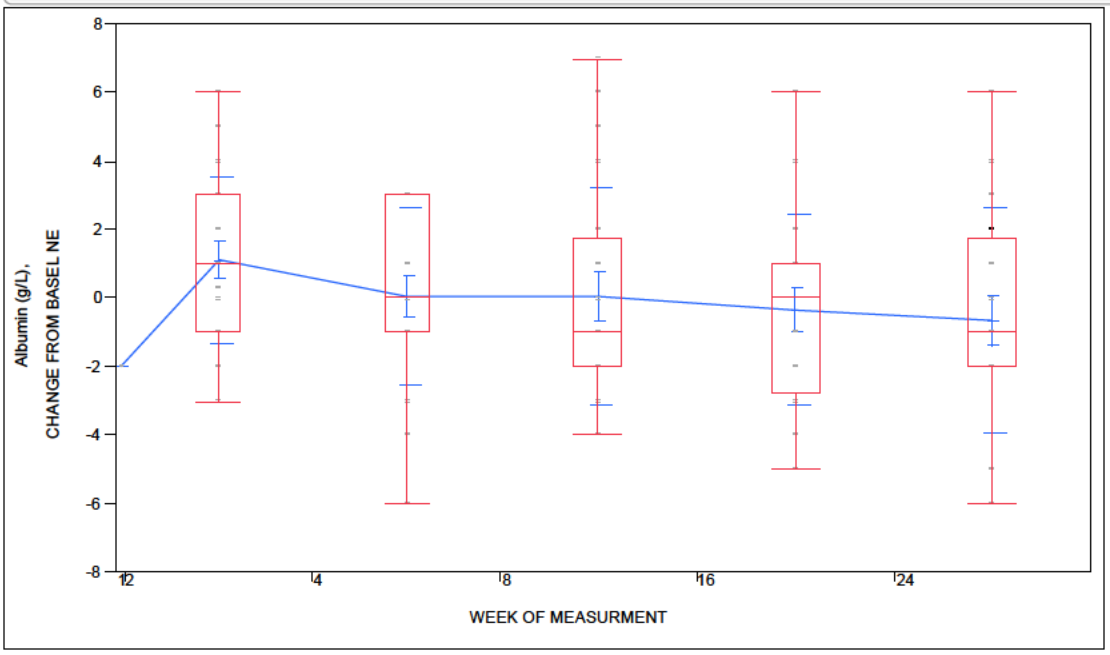
Albumin (g/L)

Table 66 Albumin, mean, median, outliers, shift, rufinamide treatment

Albumin (g/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.35		-0.65	
Median	0		-1	
Range	-5 to 6		-6 to 6	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	2	0	1
high value		50		49
Low value				
Baseline mean = 42.7				
Reference range = 29 to 47				

Figure 48 Albumin, change from baseline by week, rufinamide treatment

Oneway Analysis of Albumin (g/L), CHANGE FROM BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-2	-2	-2	-2	-2	-2	-2
2	-3	-2	-1	1	3	5	6
4	-6	-4	-1	0	3	3	3
8	-4	-3	-2	-1	1.75	5.9	7
16	-5	-3.9	-2.75	0	1	3.8	6
24	-6	-5	-2	-1	1.75	4	6

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-2.0000	.	.	.	.
2	19	1.1211	2.41766	0.55465	-0 044	2.2863
4	19	0 0526	2.59216	0.59468	-1.197	1 3020
8	20	0 0500	3.18673	0.71258	-1.441	1 5414
16	20	-0.3500	2.79614	0.62524	-1 659	0.9586
24	20	-0.6500	3.29713	0.73726	-2.193	0.8931

Conclusion: no notable change in albumin

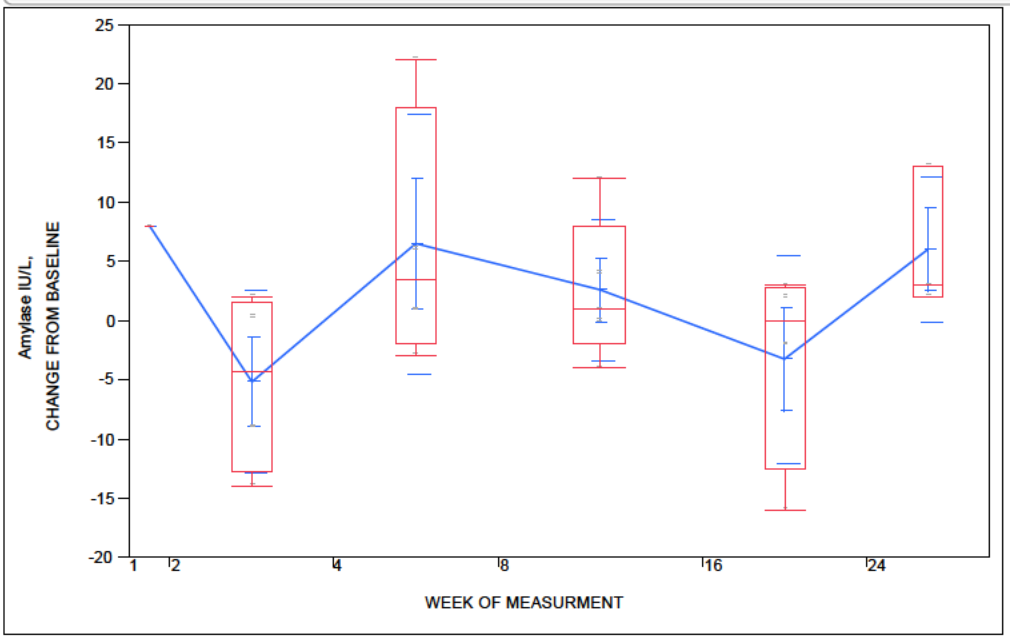
Amylase (IU/L)

Table 67 Amylase, mean, median, outliers, shift , rufinamide treatment

Amylase (IU/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16 (n=4)		Week 24 (n=3)	
Mean	-3.25		6	
Median	0		3	
Range				
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean (n=6) 42 IU/L				
Reference range = 20 to 112 IU/L				

Figure 49 Amylase, change from baseline by week, rufinamide treatment

Oneway Analysis of Amylase IU/L, CHANGE FROM BASELINE By WEEK OF MEASURMENT



Missing Rows 10

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	8	8	8	8	8	8	8
2	-14	-14	-12.75	-4 35	1.575	2	2
4	-3	-3	-2	3.5	18	22	22
8	-4	-4	-2	1	8	12	12
16	-16	-16	-12 5	0	2.75	3	3
24	2	2	2	3	13	13	13

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	8.0000	.	.	.	.
2	4	-5.1750	7 6151	3.8075	-17.29	6.942
4	4	6.5000	10 9697	5.4848	-10.96	23.955
8	5	2.6000	5 9833	2.6758	-4.83	10.029
16	4	-3.2500	8.7702	4.3851	-17.21	10.705
24	3	6.0000	6 0828	3.5119	-9.11	21.110

Conclusion: Available values are limited due to laboratory communication error reported by the sponsor. The small numbers of measurements do not reveal a notable change in serum amylase.

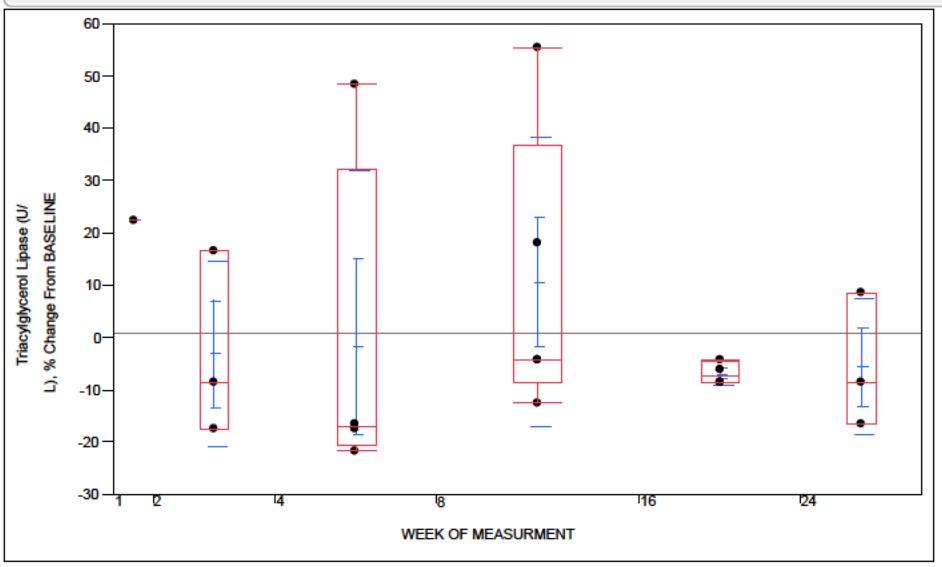
Triacylglycerol Lipase (U/L)

Table 68 Lipase, mean, median, outliers, shift, rufinamide treatment

Triacylglycerol Lipase (U/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-1.75 (n=4)		-1.33 (n=3)	
Median	-2		-2	
Range	-2 to -1		-4 to 2	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 24.2 (n=5)				
Reference range= 0 to 32				

Figure 50 Lipase, percent change from baseline by week, rufinamide treatment

Oneway Analysis of Triacylglycerol Lipase (U/L), % Change From BASELINE By WEEK OF MEASURMENT



Missing Rows 10

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	22.22222	22.22222	22.22222	22.22222	22.22222	22.22222	22.22222
2	-17.3913	-17.3913	-17.3913	-8.69565	16.66667	16.66667	16.66667
4	-21.7391	-21.7391	-20.6522	-17.029	32.19697	48.48485	48.48485
8	-12.5	-12.5	-8.42391	-4.34783	36.86869	55.55556	55.55556
16	-8.69565	-8.69565	-8.69565	-7.37813	-4.64015	-4.16667	-4.16667
24	-16.6667	-16.6667	-16.6667	-8.69565	8.695652	8.695652	8.695652

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	22.222	.	.	.	.
2	3	-3.140	17.6956	10.217	-47.10	40.82
4	4	-1.828	33.6167	16.808	-55.32	51.66
8	5	10.508	27.6538	12.367	-23.83	44.85
16	4	-6.905	2.2079	1.104	-10.42	-3.39
24	3	-5.556	12.9695	7.488	-37.77	26.66

Conclusion: One patient with an elevated baseline measurement has a continued rise of in lipase of an additional 48% at week 4. Available values are limited due to laboratory communication error reported by the sponsor. The small numbers of measurements do not reveal a notable change in serum amylase.

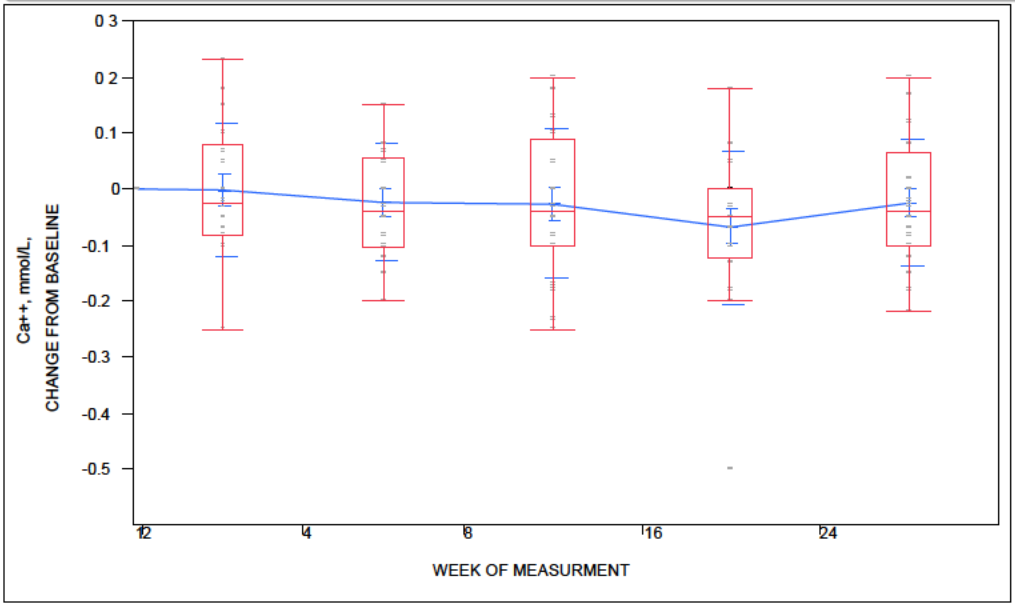
Calcium (mmol/L)

Table 69 Calcium, mean, median, outliers, shift, rufinamide treatment

Calcium (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.068		-0.025	
Median	-0.05		-0.04	
Range	-0.5 to 0.18		-0.22 to 0.2	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	1		0	
Max value	2.73			
# Patients low*	1		0	
Min value	2.08			
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	1	1	0	0
high value		2.73		
Low value	2.08			
Baseline mean = 2.49 mmol/L				
Reference range 2.2 to 2.7 mmol/L				

Figure 51 Calcium, change from baseline by week, rufinamide treatment

Oneway Analysis of Ca++, mmol/L, CHANGE FROM BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	0	0	0	0	0	0	0
2	-0.25	-0.115	-0.08	-0.025	0.0775	0.185	0.23
4	-0.2	-0.155	-0.105	-0.04	0.055	0.15	0.15
8	-0.25	-0.225	-0.1	-0.04	0.0875	0.18	0.2
16	-0.5	-0.198	-0.1225	-0.05	0	0.077	0.18
24	-0.22	-0.177	-0.1	-0.04	0.065	0.165	0.2

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	0.00000	.	.	.	.
2	18	-0.00167	0.118334	0.02789	-0.0605	0.0572
4	18	-0.02389	0.104383	0.02460	-0.0758	0.0280
8	20	-0.02700	0.133144	0.02977	-0.0893	0.0353
16	20	-0.06800	0.137596	0.03077	-0.1324	-0.0036
24	20	-0.02500	0.112226	0.02509	-0.0775	0.0275

Conclusion: there is no notable change in serum Ca++ values during the course of the study.

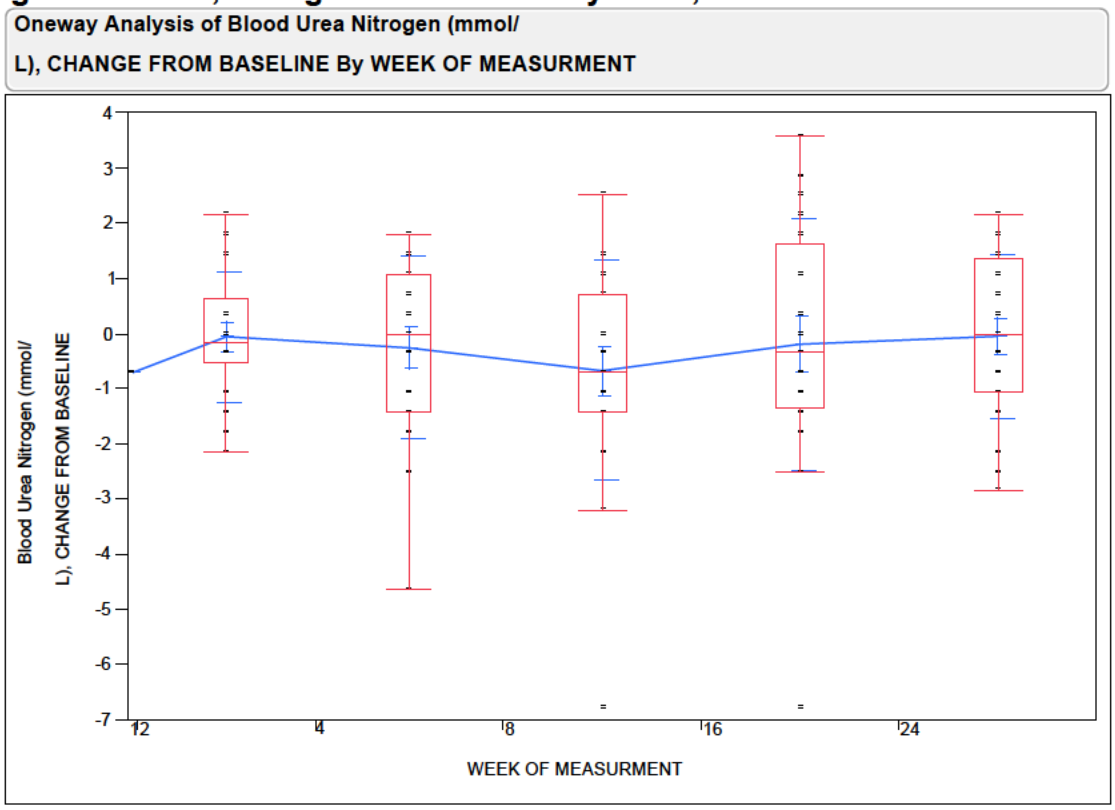
Renal Panel

Blood Urea Nitrogen (mmol/L)

Table 70 BUN, mean, median, outliers, shift, rufinamide treatment

Blood Urea Nitrogen (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.2		-0.05	
Median	-0.36		0	
Range	-6.78 to 3.57		-2.85 to 2.14	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 4.79				
Reference range = 4 to 24				

Figure 52 BUN, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-0.71	-0.71	-0.71	-0.71	-0.71	-0.71	-0.71
2	-2.14	-1.825	-0.5375	-0.175	0.6275	1.825	2.14
4	-4.64	-2.5	-1.43	0	1 07	1.78	1.79
8	-6.78	-3.103	-1.43	-0.71	0.72	1.43	2.5
16	-6.78	-2.429	-1.34	-0.36	1.61	2.815	3.57
24	-2.85	-2.464	-1.07	0	1.3425	1.79	2.14

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-0.71000	.	.	.	.
2	18	-0.05944	1.17708	0.27744	-0.645	0.52590
4	19	-0.26316	1.63985	0.37621	-1.054	0.52722
8	20	-0.67700	1.98566	0.44401	-1.606	0.25232
16	20	-0.19700	2.27078	0.50776	-1.260	0.86576
24	20	-0.05300	1.48886	0.33292	-0.750	0.64381

Conclusion: most changes in the value of BUN are negative. No notable change in BUN during the course of the study.

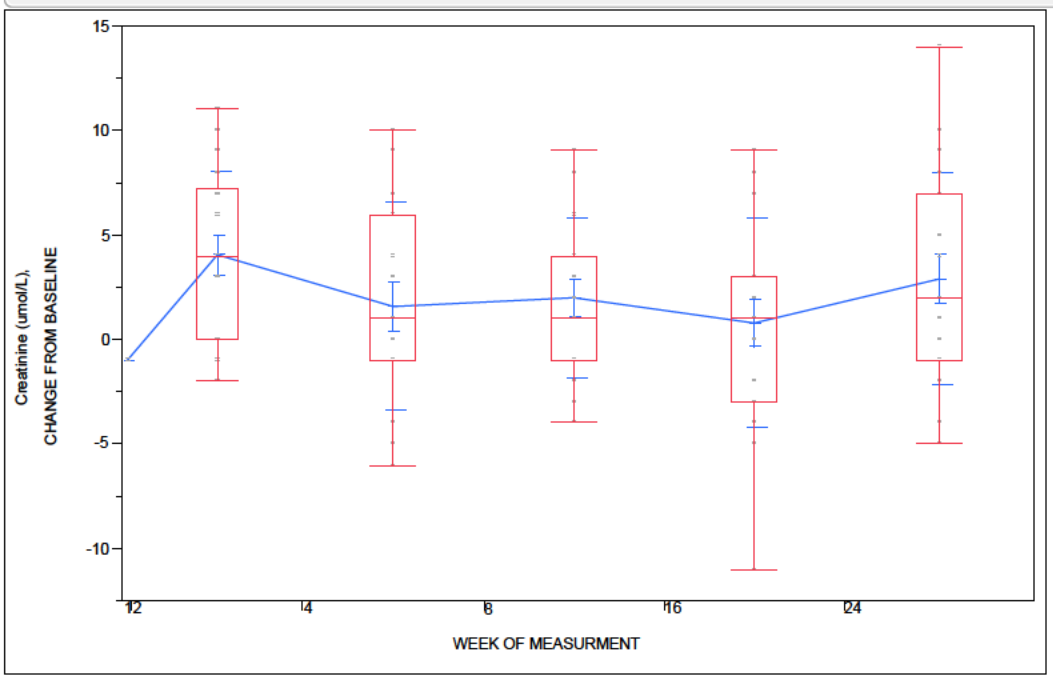
Creatinine (umol/L)

Table 71 Creatinine, mean, median, outliers, shift, rufinamide treatment

Creatinine (umol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	0.79		2.9	
Median	1		2	
Range	-11 to 9		-5 to 14	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		1	
Max value			47	
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	1	0	0	1
high value				47
Low value	<18			
Baseline mean= 27				
Reference range = 18 to 44				

Figure 53 Creatinine, change from baseline by week, rufinamide treatment

Oneway Analysis of Creatinine (umol/L), CHANGE FROM BASELINE By WEEK OF MEASURMENT



Missing Rows 2

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-1	-1	-1	-1	-1	-1	-1
2	-2	-2	0	4	7.25	10.1	11
4	-6	-5	-1	1	6	10	10
8	-4	-3	-1	1	4	9	9
16	-11	-5	-3	1	3	8	9
24	-5	-3.8	-1	2	7	9 9	14

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-1.0000	.	.	.	.
2	18	4 0556	4.02159	0.9479	2.056	6.0554
4	19	1.5789	4.95890	1.1376	-0.811	3.9691
8	19	2 0000	3.82971	0.8786	0.154	3.8459
16	19	0.7895	4.99532	1.1460	-1.618	3.1971
24	20	2 9000	5.06692	1.1330	0.529	5.2714

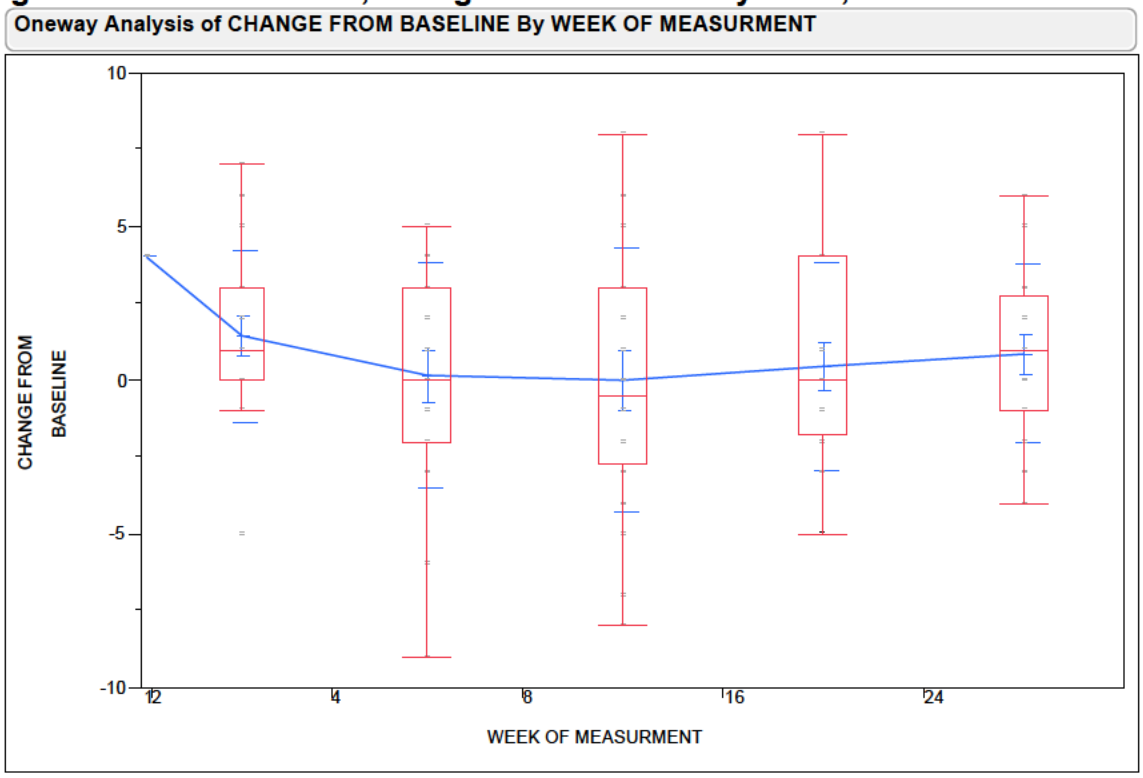
Conclusion: no notable change in serum creatinine.

Protein (g/L)

Table 72 Serum Protein, mean, median, outliers, shift, rufinamide treatment

Protein (g/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	0.45		0.85	
Median	0		1	
Range	-5 to 8		-4 to 6	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=20)	
	N to L	N to H	N to L	N to H
	1	0	0	0
high value				
Low value	55			
Baseline mean =66.3 g/L				
Reference range 57 to 80 g/L				

Figure 54 Serum Protein, change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	4	4	4	4	4	4	4
2	-5	-1.4	0	1	3	6.1	7
4	-9	-6	-2	0	3	5	5
8	-8	-6.8	-2.75	-0 5	3	5.9	8
16	-5	-4.8	-1.75	0	4	4	8
24	-4	-3	-1	1	2.75	5	6

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	4.00000	.	.	.	.
2	18	1.44444	2.79121	0.65789	0.056	2.8325
4	19	0.15789	3.67065	0.84211	-1.611	1.9271
8	20	0.00000	4.27970	0.95697	-2.003	2.0030
16	20	0.45000	3.37912	0.75559	-1.131	2.0315
24	20	0.85000	2.88873	0.64594	-0.502	2.2020

Conclusion: no notable change in serum protein during the course of the study.

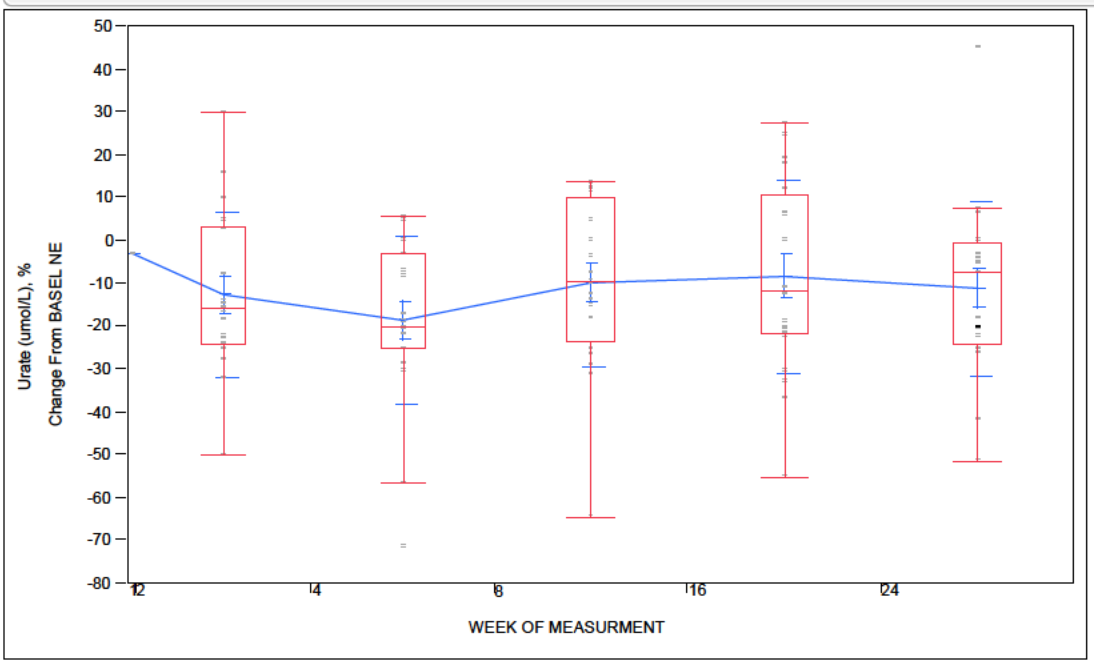
Urate (umol/L)

Table 73 Uric Acid, mean, median, outliers, shift, rufinamide treatment

Urate (umol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-23.4		-25.7	
Median	-27		-21	
Range	-244 to 65		-107 to 59	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	2	0	2	0
high value				
Low value	95		89	
Baseline mean = 221 umol/L				
Reference range 119 to 327 umol/L				

Figure 55 Uric Acid, change from baseline by week, rufinamide treatment

Oneway Analysis of Urate (umol/L), % Change From BASELINE By WEEK OF MEASURMENT



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-3.15789	-3.15789	-3.15789	-3.15789	-3.15789	-3.15789	-3.15789
2	-50 3497	-33.8921	-24.3859	-15.9404	3.090756	17.19372	29.83193
4	-71 5909	-56.8116	-25.4808	-20.1681	-3.15789	5.042017	5.454545
8	-64.7727	-31.0621	-23.6835	-9.84202	9.771429	13.53589	13.74046
16	-55.4545	-36.6363	-22.1012	-11.8581	10 57895	24.01091	27.31092
24	-51 6304	-40.2409	-24.4782	-7.59104	-0.78947	7.138683	45.03817

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-3.158	.	.	.	.
2	18	-12.810	19.1833	4.5215	-22.35	-3.270
4	19	-18.760	19.8457	4.5529	-28.33	-9.195
8	20	-10.020	19.7431	4.4147	-19.26	-0.780
16	20	-8.545	22.6124	5.0563	-19.13	2 038
24	20	-11.289	20.2917	4.5374	-20.79	-1.792

Conclusions: there is a reduction of serum uric acid post baseline of uncertain significance.

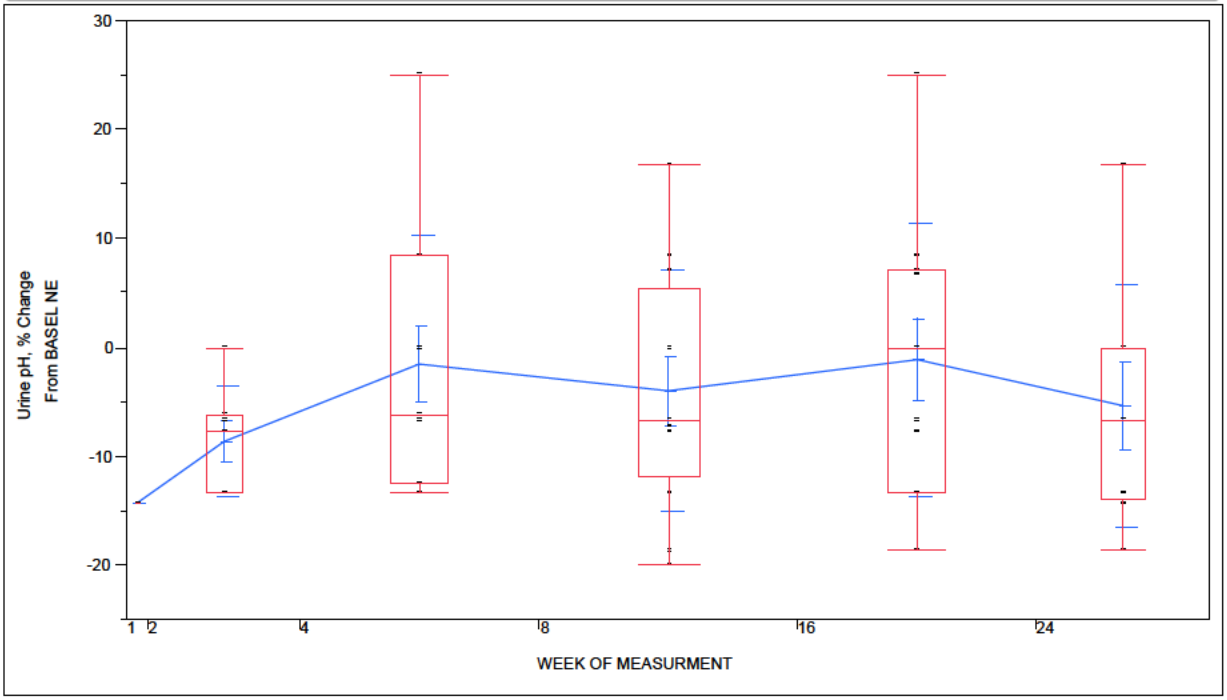
Urine pH

Table 74 Urine pH, mean, median, outliers, shift, rufinamide treatment

Urine pH				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	-0.136		-0.437	
Median	0		-0.5	
Range	-1.5 to 1.5		-1.5 to 1	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 7.16				
Reference range 5 to 8				

Figure 56 Urine pH, percent change from baseline by week, rufinamide treatment

Oneway Analysis of Urine pH, % Change From BASELINE By WEEK OF MEASURMENT



Missing Rows 5

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-14.2857	-14.2857	-14.2857	-14 2857	-14 2857	-14 2857	-14.2857
2	-13.3333	-13.3333	-13.3333	-7.69231	-6.25	0	0
4	-13.3333	-13.3333	-12.5	-6.25	8.333333	21.66667	25
8	-20	-19 625	-11.9231	-6.66667	5.357143	14.16667	16.66667
16	-18.75	-17.6667	-13.3333	0	7.142857	21.66667	25
24	-18.75	-18.75	-14.0476	-6.66667	0	16 66667	16.66667

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-14.286	.	.	.	.
2	7	-8 658	5.0205	1 8976	-13.30	-4 015
4	11	-1 553	11.7351	3.5383	-9.44	6.331
8	12	-4 009	11.0115	3.1788	-11.01	2.987
16	11	-1.148	12.5942	3.7973	-9.61	7.312
24	8	-5 379	11.1392	3.9383	-14.69	3.933

Conclusion: there is a small shift to lower urine pH during rufinamide treatment that is not clinical notable.

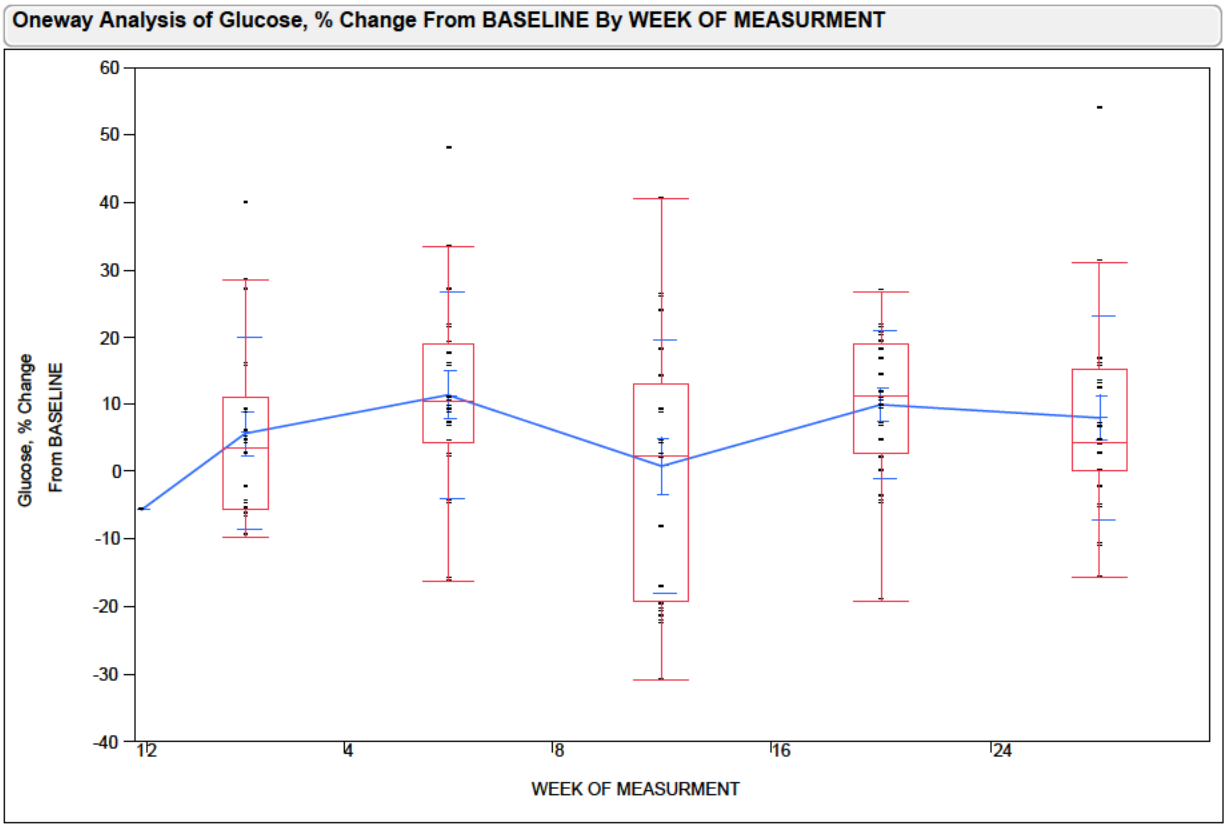
Other metabolic Panel

Glucose (mg/dl)

Table 75 Serum Glucose, mean, median, outliers, shift, rufinamide treatment

Glucose (mg/dl)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	7.8		5.9	
Median	8.1		3.6	
Range	-16 to 22		-14 to 36	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
	Week 16		Week 24	
# Patients High*	0		0	
Max value				
# Patients low*			1	
Min value			67	
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=)		Shift from baseline to week 24, (n=)	
	N to L	N to H	N to L	N to H
	0	0	0	0
high value				
Low value				
Baseline mean = 4.52				
Reference range = 3.8 to 6.5				

Figure 57 Serum Glucose, percent change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-5.66038	-5.66038	-5.66038	-5.66038	-5.66038	-5.66038	-5.66038
2	-9.52381	-9.32447	-5.54847	3.562802	10.95402	29.71429	40
4	-16.3265	-15.9091	4.444444	10.41667	19.04762	33.33333	47.82609
8	-30.9091	-22.1277	-18.9512	2.299154	13.03987	25.96273	40.54054
16	-19.1489	-4.45455	2.721088	11 21936	19.12879	21.73913	26.66667
24	-15.6863	-10.0745	0	4.499494	15.26515	29.52381	54.05405

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-5.660	.	.	.	.
2	18	5.714	14.1173	3.3275	-1.307	12.734
4	19	11.420	15.3118	3.5128	4.040	18.800
8	20	0.876	18.7721	4.1976	-7.910	9.662
16	20	9.983	11.0930	2.4805	4.791	15.174
24	20	8.029	15.0458	3.3643	0 988	15.071

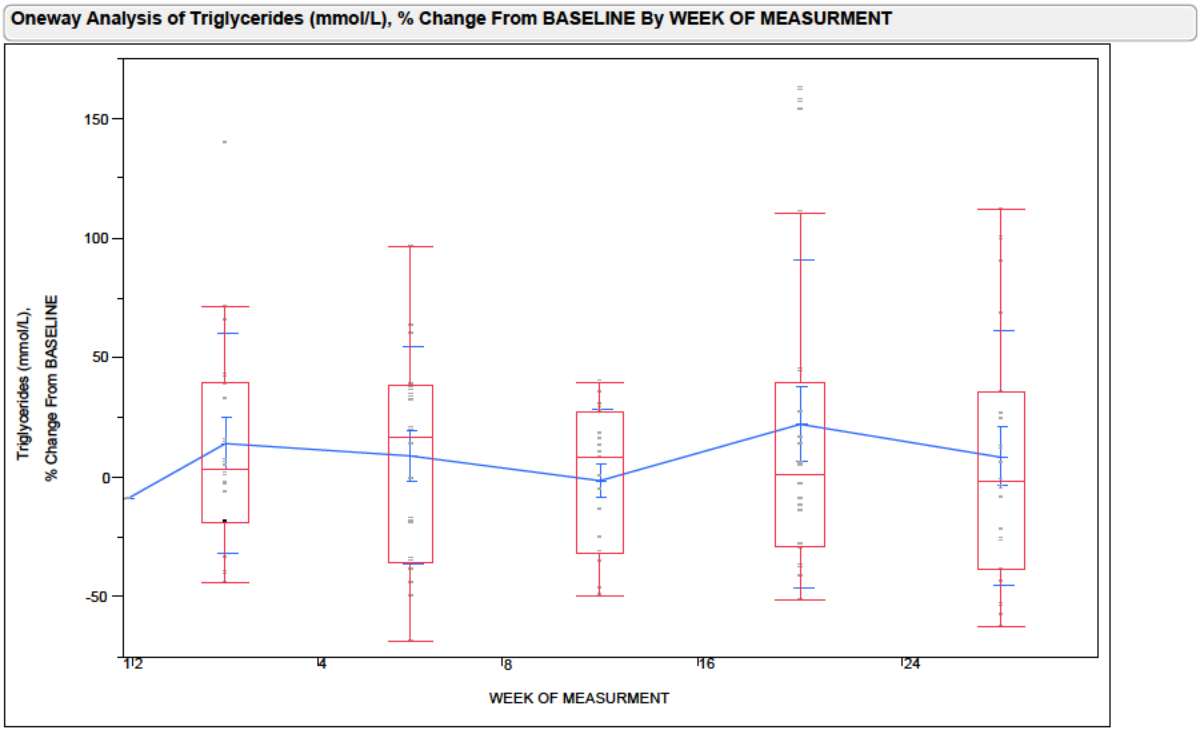
Conclusion: there is no notable change in glucose values during the course of the study

Triglycerides (mmol/L)

Table 76 Triglycerides, mean, median, outliers, shift, rufinamide treatment

Triglycerides (mmol/L)				
Change from Baseline to Week 16 and 24. Means and Medians				
Statistic	Week 16		Week 24	
Mean	0.042 (SD 0.59)		-0.02 (0.75)	
Median	-0.005		-0.01	
Range	-0.97 to 0.97		-1.29 to 1.31	
Outliers (normal at baseline), relative to potentially clinically significant values based on Common Terminology Criteria for Adverse Events (CTCAE)				
11 / 25 rufinamide treatment patients have an elevated baseline. These are removed from the high outlier analysis.	Week 16		Week 24	
# Patients High*	4		1	
Max value	1.6 (154% over baseline)		1.44 (35% over baseline)	
# Patients low*	0		0	
Min value				
Shifts from Normal to high or low at Week 16 and 24				
	Shift from baseline to week 16, all (n=20)		Shift from baseline to week 24, (n=19)	
	N to L	N to H	N to L	N to H
	0	4	0	1
high value		1.57		1.44
Low value				
Baseline mean 1.4 mmol/L, SD = 0.65				
Baseline mean of high (outlier values) n= 13 is 1.90 , SD= 0.42				
Reference range 0.31 to 1.25				

Figure 58 Triglycerides, percent change from baseline by week, rufinamide treatment



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-8.84956	-8.84956	-8.84956	-8 84956	-8 84956	-8 84956	-8 84956
2	-44.2529	-40.3446	-18.6794	3 327461	40.10618	78 0678	140
4	-68.3962	-51.8396	-35.4481	16.99482	38 32745	66 82318	96 61017
8	-50	-48.855	-31.746	8 653846	26 98413	35 39823	39 62264
16	-51.3228	-40.8354	-28.9462	1.268766	40.15519	157.0362	162.7119
24	-62.069	-57.5893	-38.4615	-1 28205	35 84906	100	111.8644

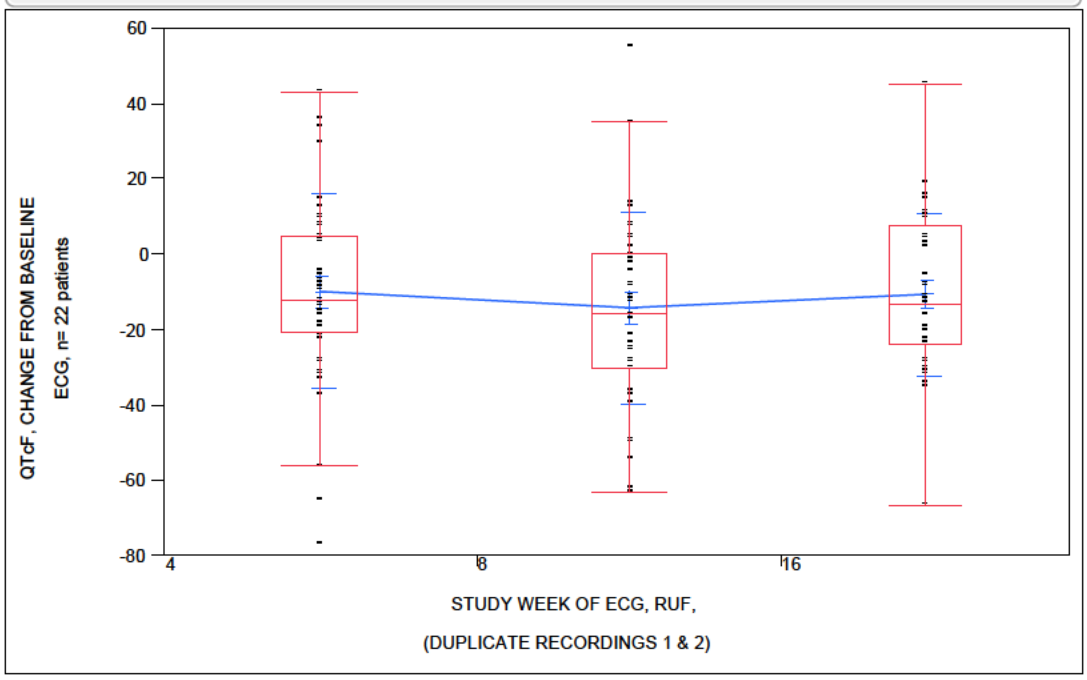
Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	1	-8 850	.	.	.	.
2	18	14.114	45.7963	10.794	-8 66	36.888
4	18	8.961	45.4507	10.713	-13.64	31.563
8	19	-1.414	30.1162	6.909	-15.93	13.101
16	20	22.180	68 5367	15.325	-9 90	54.256
24	19	8.423	53 3882	12.248	-17.31	34.155

Conclusion: There are 4 outliers, normal at baseline with post baseline triglyceride elevations at week 16. The large number of baseline high values confound conclusion concerning the effect of rufinamide. No clear safety signal for elevation of TG is present.

9.5 Analysis of QTcF

Figure 59 Rufinamide Treatment Group, QTcF Mean and Median Change from Baseline (ms) at Weeks 4, 8, and 16.



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
4	-77	-42.7	-20.5	-12	5	31.2	43
8	-63	-51	-30	-16	0	14	55
16	-67	-34	-24	-13	7.5	15.6	45

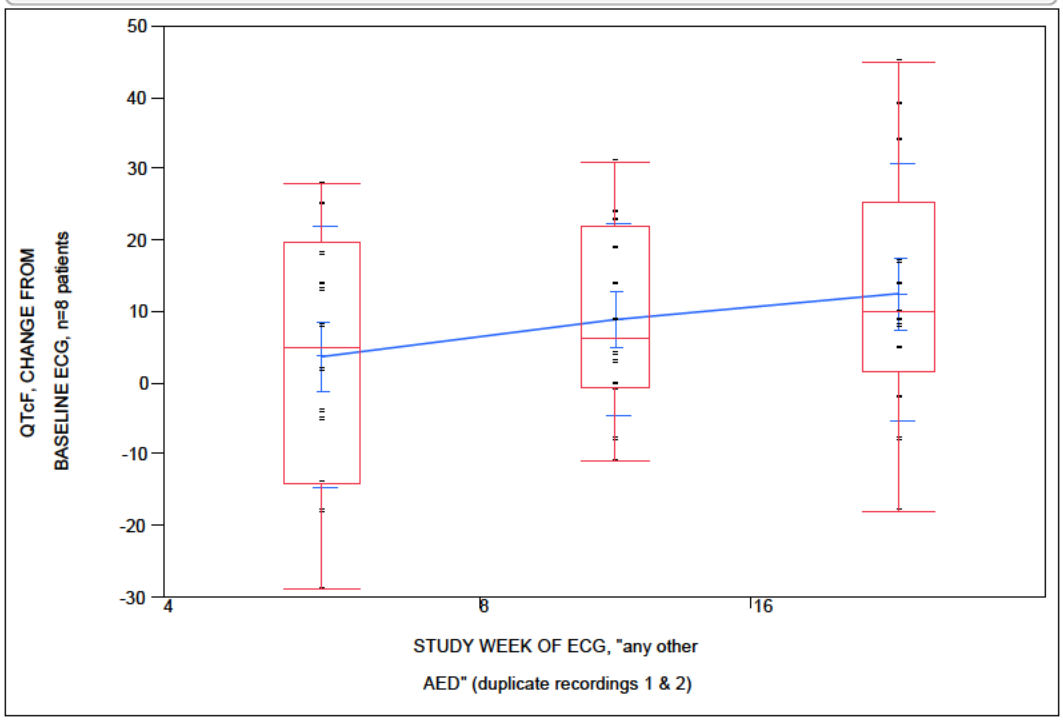
Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
4	36	-9.889	25.8034	4.3006	-18.62	-1.158
8	35	-14 200	25.3305	4.2816	-22.90	-5.499
16	33	-10.636	21.4269	3.7300	-18.23	-3.039

Figure 60 "any other AED" Group, QTcF Mean and Median Change from Baseline (ms) at Weeks 4, 8, and 16.

Oneway Analysis of QTcF, CHANGE FROM BASELINE ECG, n=8 patients

By STUDY WEEK OF ECG, "any other AED" (duplicate recordings 1 & 2)



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
4	-29	-23.5	-14	5	19.75	28	28
8	-11	-10.1	-0.75	6.5	22	28 9	31
16	-18	-14	1.5	10	25.5	42.6	45

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
4	14	3.7143	18 3027	4.8916	-6.853	14.282
8	12	8.9167	13 3516	3 8543	0.433	17.400
16	13	12.5385	18 0398	5 0034	1.637	23.440

9.6 Adverse Events by Age Group Analysis

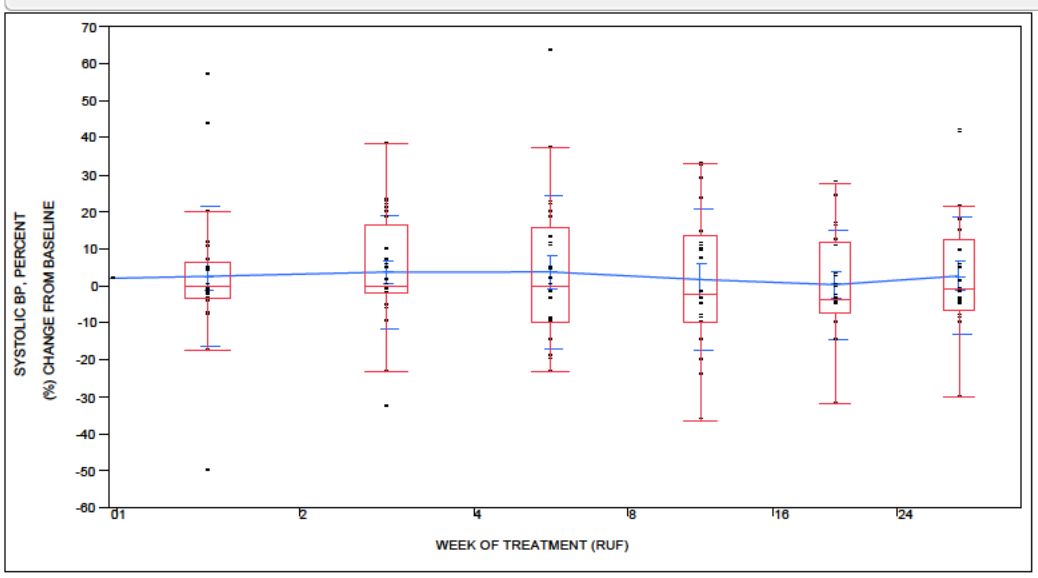
1 to <2			2 to <3			3 to <4		
Preferred term	# patients	% patients	Preferred term	# patients	% patients	Preferred Term	# patients	% patients
Diarrhoea	3	30	Upper Respiratory Tract Infection	4	57	Upper Respiratory Tract Infection	3	38

Blood Bicarbonate Decreased	2	20	Gait Disturbance	2	29	Vomiting	2	25
Constipation	2	20	Somnolence	2	29	Bronchitis	1	13
Decreased Appetite	2	20	Vomiting	2	29	Bronchopneumonia	1	13
Nasal Congestion	2	20	Aphagia	1	14	Constipation	1	13
Pneumonia	2	20	Atonic Seizures	1	14	Cough	1	13
Somnolence	2	20	Body Temperature Increased	1	14	Gastroenteritis	1	13
Vomiting	2	20	Bronchitis	1	14	Middle Insomnia	1	13
Aspiration	1	10	Chronic Respiratory Disease	1	14	Nasopharyngitis	1	13
Blood Triglycerides Increased	1	10	Cough	1	14	Nervousness	1	13
Bronchitis	1	10	Decreased Appetite	1	14	Otitis Media	1	13
Bronchitis Viral	1	10	Diarrhoea	1	14	Rash	1	13
Catheter Site Infection	1	10	Disturbance In Attention	1	14	Respiratory Tract Congestion	1	13
Convulsion	1	10	Eczema	1	14	Rhinitis	1	13
Cough	1	10	Fatigue	1	14	Somnolence	1	13
Drooling	1	10	Gastroenteritis	1	14	Tonic Convulsion	1	13
Drug Eruption	1	10	Grand Mal Convulsion	1	14	Weight Decreased	1	13
Ear Infection	1	10	Haemoglobin Decreased	1	14			
Epilepsy	1	10	Head Injury	1	14			
Erythema	1	10	Hypoglycaemia	1	14			
Escherichia Urinary Tract Infection	1	10	Irritability	1	14			
Hemiparesis	1	10	Myoclonic Epilepsy	1	14			
Insomnia	1	10	Nasopharyngitis	1	14			
Irritability	1	10	Otitis Media	1	14			
Nasopharyngitis	1	10	Pharyngitis	1	14			
Nausea	1	10	Pneumonia	1	14			
Oliguria	1	10	Pneumonia Aspiration	1	14			
Otitis Media	1	10	Pneumonia Influenzal	1	14			
Pharyngitis	1	10	Pyrexia	1	14			
Pneumonia Aspiration	1	10	Rash	1	14			
Pyrexia	1	10	Respiratory Distress	1	14			
Rash	1	10	Respiratory Syncytial Virus Bronchiolitis	1	14			
Respiratory Tract Congestion	1	10	Respiratory Tract Infection	1	14			
Rhinorrhoea	1	10	Salivary Hypersecretion	1	14			
Sneezing	1	10	Sinusitis	1	14			
Status Epilepticus	1	10	Sleep Disorder	1	14			
Upper Respiratory Tract Infection	1	10	Toe Walking	1	14			
Varicella	1	10	Urinary Tract Inflammation	1	14			

9.7 Blood Pressure Analysis

Figure 61 Rufinamide Treatment, Systolic Blood Pressure Percent Change From Baseline by Week of Treatment.

Oneway Analysis of SYSTOLIC BP, PERCENT (%) CHANGE FROM BASELINE By WEEK OF TREATMENT (RUF)



Missing Rows 23

Quantiles

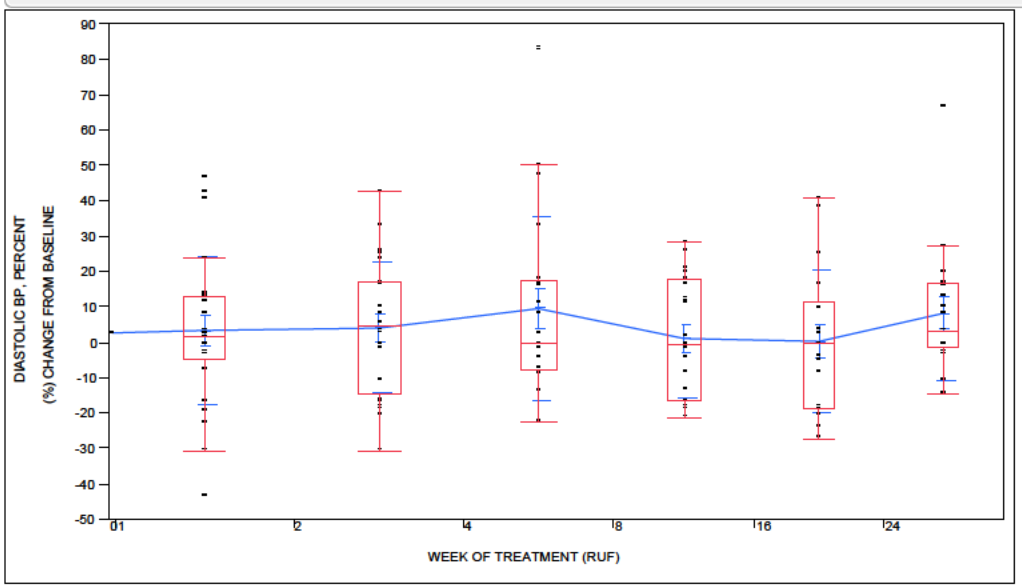
Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	2.040816	2.040816	2.040816	2.040816	2.040816	2.040816	2.040816
1	-50	-11.5119	-3.24334	0	6.108247	29.58242	57.14286
2	-32.5	-16.3998	-2.14482	0	16.51099	22.70531	38.57143
4	-23.3333	-19.3033	-10	0	15.88272	34.21429	63.76812
8	-36.5079	-23.7022	-10	-2.43925	13.61111	32.46862	33.33333
16	-31.746	-17.7778	-7.5	-3.57143	11.80556	25.27716	27.83505
24	-30	-14	-6.46259	-0.96154	12.33871	25.72538	42.02899

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
0	1	2.04082	.	.	.	.
1	25	2.57418	19.1063	3.8213	-5.313	10.461
2	24	3.71764	15.2587	3.1147	-2.726	10.161
4	21	3.74963	20.7573	4.5296	-5.699	13.198
8	20	1.70555	19.1348	4.2787	-7.250	10.661
16	17	0.31897	14.6985	3.5649	-7.238	7.876
24	17	2.65072	15.8687	3.8487	-5.508	10.810

Figure 62 Rufinamide Treatment, Diastolic Blood Pressure Percent Change From Baseline by Week of Treatment

Oneway Analysis of DIASTOLIC BP, PERCENT (%) CHANGE FROM BASELINE By WEEK OF TREATMENT (RUF)



Missing Rows 23

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	2.631579	2.631579	2.631579	2.631579	2.631579	2.631579	2.631579
1	-43.2432	-25.7222	-4.95215	1.612903	12.5	41.42857	46.42857
2	-30.6452	-19.2901	-14.5881	4.470046	16.93262	29.66667	42.85714
4	-22.3684	-20.4805	-7.7381	0	17.42424	49.52381	82.97872
8	-21.0526	-18.2844	-16.6667	-0.73529	17.80303	25.36866	28
16	-27.1429	-26.7143	-18.6092	0	11.42473	38.5157	40.47619
24	-14.8649	-14.5519	-1.38889	3.333333	16.48642	35.15152	66.66667

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
0	1	2.63158	.	.	.	.
1	25	3.34094	21.0985	4.2197	-5.368	12.050
2	24	3.99310	18.5620	3.7890	-3.845	11.831
4	21	9.49625	25.8285	5.6362	-2.261	21.253
8	20	1.04936	16.8068	3.7581	-6.816	8.915
16	18	0.24915	20.2793	4.7799	-9.836	10.334
24	17	8.18574	19.2074	4.6585	-1.690	18.061

Figure 63 Rufinamide Treatment Outliers. All Patients with 20mm Decline from Baseline Systolic Blood Pressure at Any Time During Study. Patients (6) Systolic BP Shown Over Study Timeline Week 1 to 40.

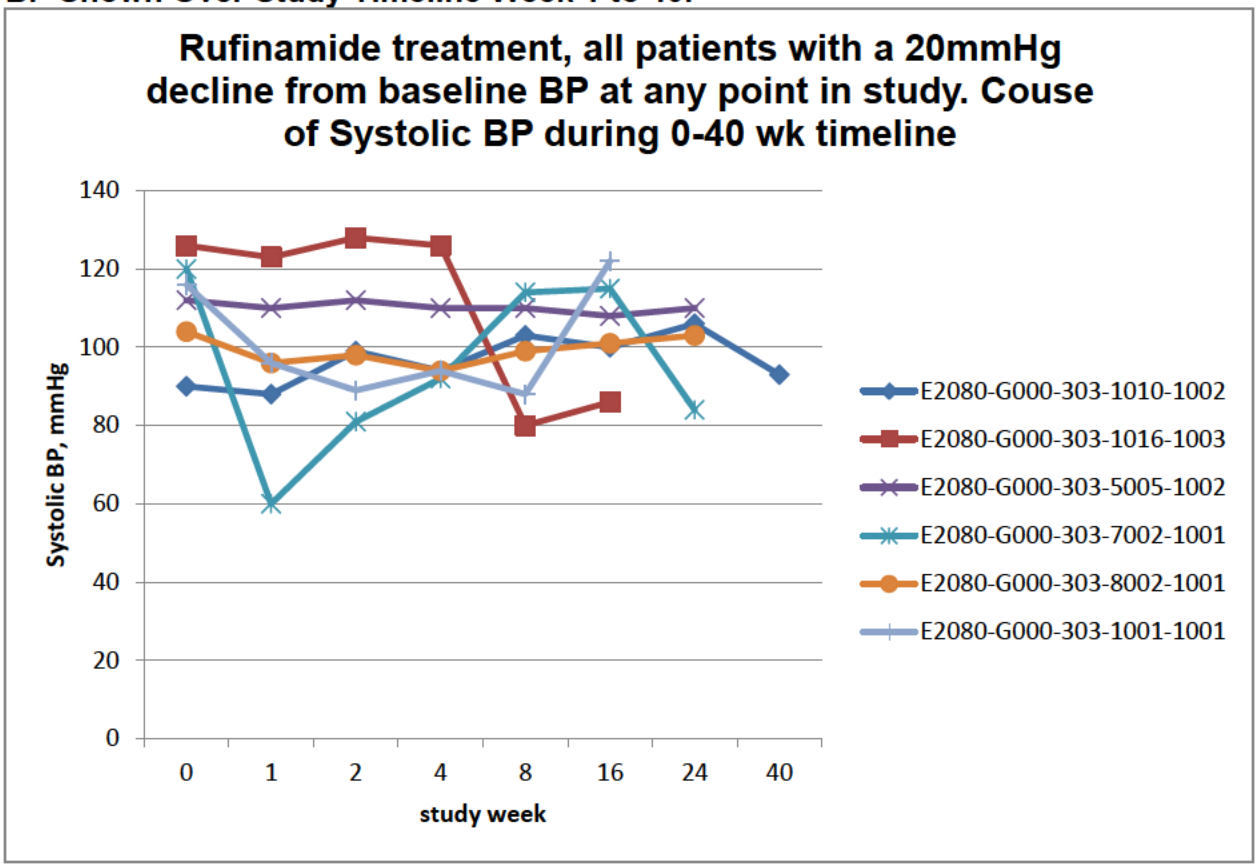
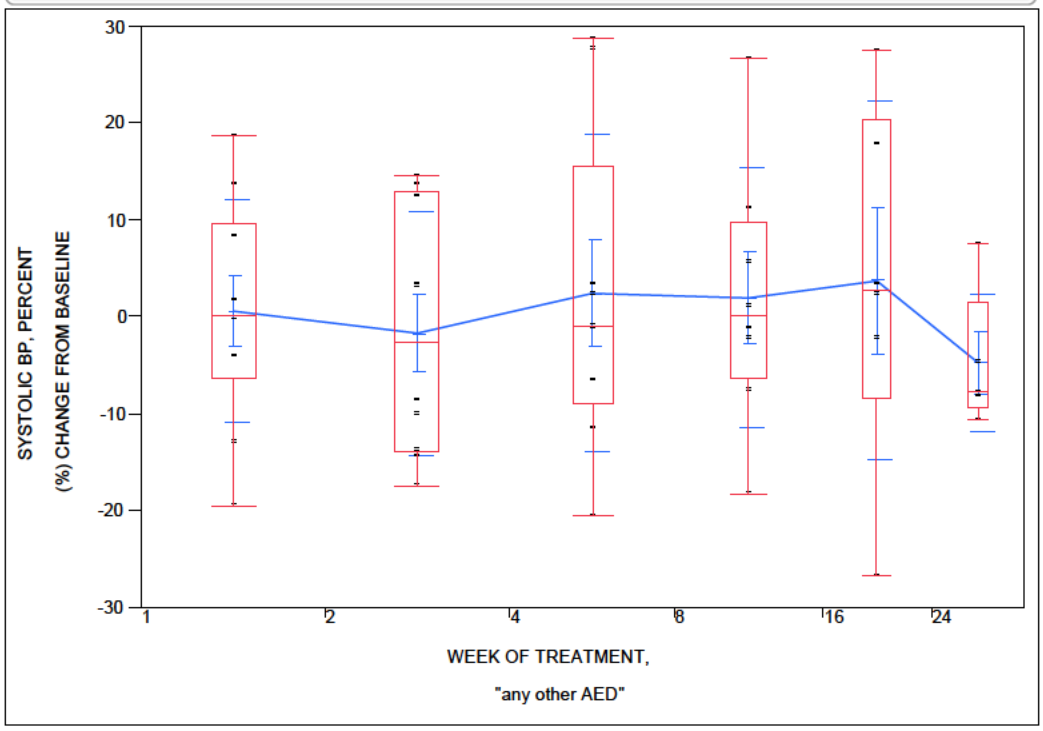


Figure 64 "any other AED" comparator treatment, Percent Change in Systolic BP from Baseline by Week of Treatment.

Oneway Analysis of SYSTOLIC BP, PERCENT (%) CHANGE FROM BASELINE By WEEK OF TREATMENT, "any other AED"



Missing Rows 12

Quantiles

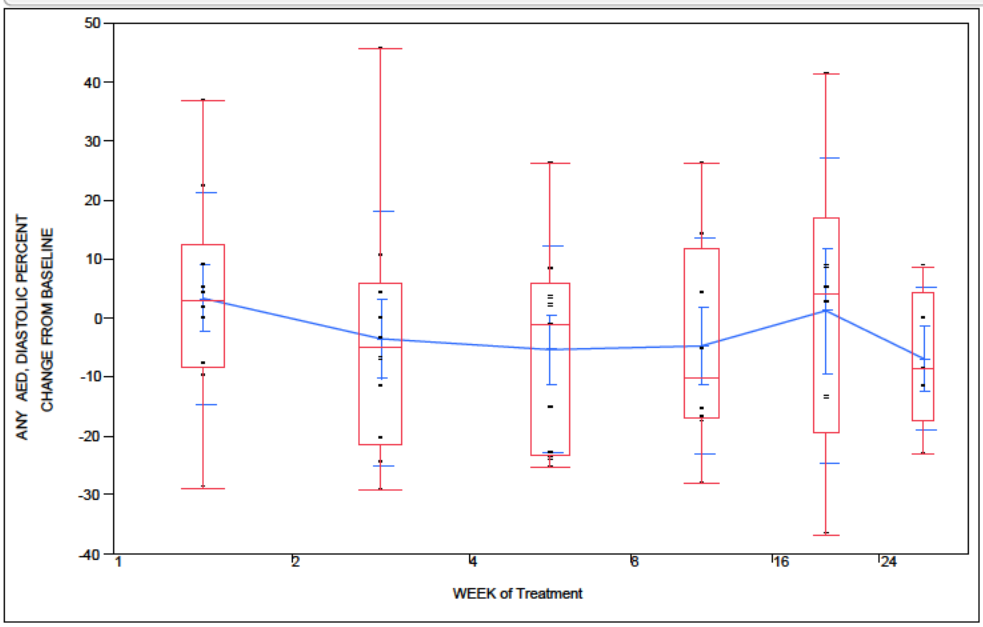
Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-19.5402	-18.8765	-6.22581	0	9.601751	18.23864	18.75
2	-17.4312	-17.1166	-13.9163	-2.67064	12.8125	14.375	14.44444
4	-20.4301	-20.4301	-8.95814	-0.89286	15.61303	28.75	28.75
8	-18.3486	-18.3486	-6.18864	0.019157	9 857955	26.78571	26.78571
16	-26.6055	-26.6055	-8.26428	2.860502	20.26786	27.5	27.5
24	-10.7143	-10.7143	-9.38013	-7.77778	1.46459	7.526882	7.526882

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	10	0.5986	11.3998	3.6049	-7.56	8.754
2	10	-1.6709	12.5642	3.9732	-10.66	7 317
4	9	2.4358	16.4109	5.4703	-10.18	15.050
8	8	1 9633	13.3422	4.7172	-9.19	13.118
16	6	3.7204	18.5559	7.5754	-15.75	23.194
24	5	-4.7218	7.1824	3.2120	-13.64	4.196

Figure 65 "any other AED" comparator treatment, Percent Change in Diastolic BP from Baseline by Week of Treatment.

Oneway Analysis of ANY AED, DIASTOLIC PERCENT CHANGE FROM BASELINE By WEEK of Treatment



Missing Rows 12

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-28.8136	-26.8999	-8.18859	3.004853	12.42163	35.50225	36.95652
2	-29.1139	-28.6384	-21.344	-5.06118	5.823068	42.13959	45.65217
4	-25.3165	-25.3165	-23.2679	-1.28205	5.890805	26.08696	26.08696
8	-27.8481	-27.8481	-17.0977	-10.2587	11.64075	26.08696	26.08696
16	-36.7089	-36.7089	-19.3467	3.91363	16.7916	41.30435	41.30435
24	-23.0769	-23.0769	-17.3718	-8.47458	4.385965	8.77193	8.77193

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	10	3.3351	17.8557	5.646	-9.44	16.108
2	10	-3.5167	21.4427	6.781	-18.86	11.822
4	9	-5.3487	17.5346	5.845	-18.83	8.130
8	8	-4.7286	18.2428	6.450	-19.98	10.523
16	6	1.2474	25.8329	10.546	-25.86	28.357
24	5	-6.8892	12.0428	5.386	-21.84	8.064

9.8 Seizure Frequency Analysis

Distribution of percent change from baseline at 4 and 6 months in rufinamide treated patients

Figure 66 Distribution, Total Seizure Frequency percent change form baseline per 28 days at 4 months, rufinamide treatment

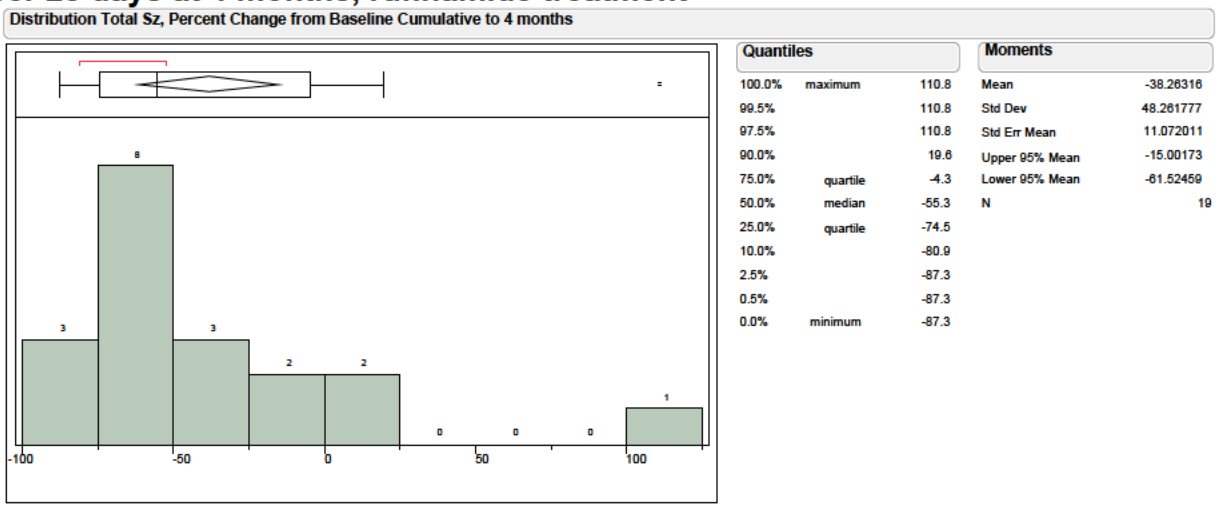


Figure 67 Distribution, Partial Seizure Frequency percent change from baseline per 28 days at 4 months, rufinamide treatment

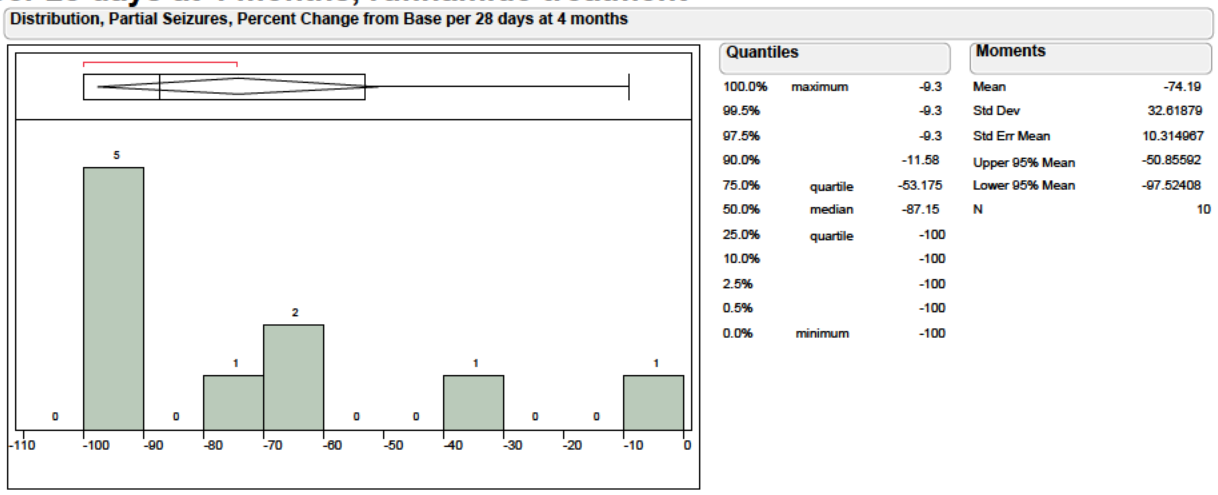
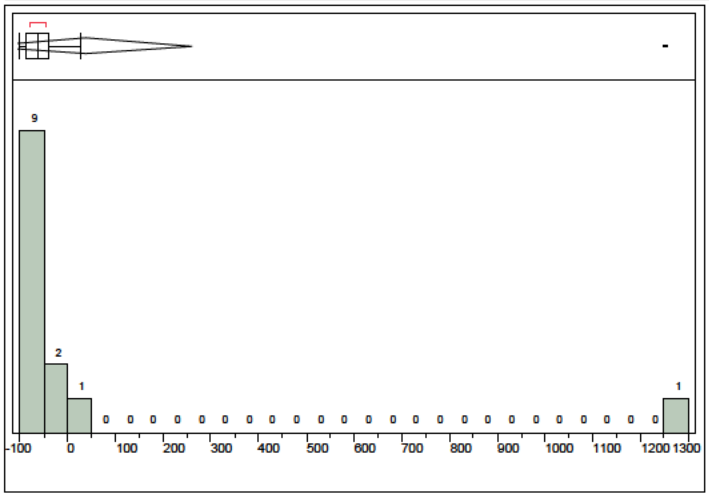


Figure 68 Distribution, Tonic-Atonic Seizure frequency percent change from baseline per 28 days at 4 months, rufinamide treatment

Distribution, Tonic-Atonic Seizures, Percent Change from Base per 28 days at 4 months

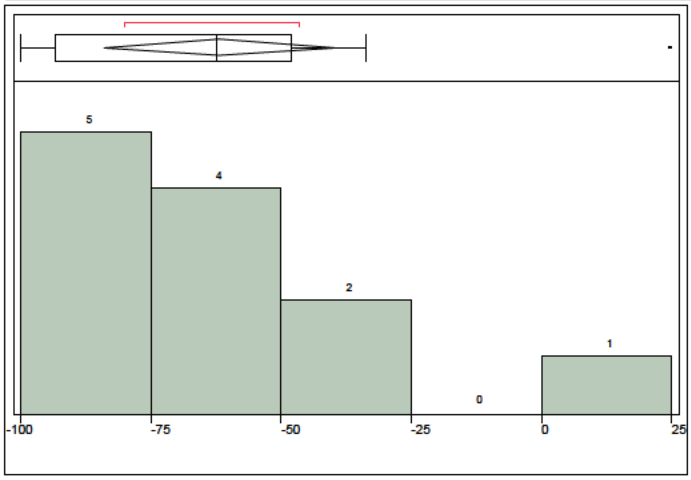


Quantiles		
100.0%	maximum	1250.6
99.5%		1250.6
97.5%		1250.6
90.0%		760.24
75.0%	quartile	-40.25
50.0%	median	-60.4
25.0%	quartile	-89
10.0%		-100
2.5%		-100
0.5%		-100
0.0%	minimum	-100

Moments	
Mean	39.069231
Std Dev	365.5635
Std Err Mean	101.38907
Upper 95% Mean	259.97704
Lower 95% Mean	-181.8386
N	13

Figure 69 Distribution, Tonic-Atonic Seizure frequency percent change from baseline per 28 days at 4 months, rufinamide treatment, Outlier filter of single patient with 1250 seizures (included in Figure 68).

Distribution, tonic-atonic sz percent change from baseline per 28 days at 4 months, RUF, 1 outlier filter

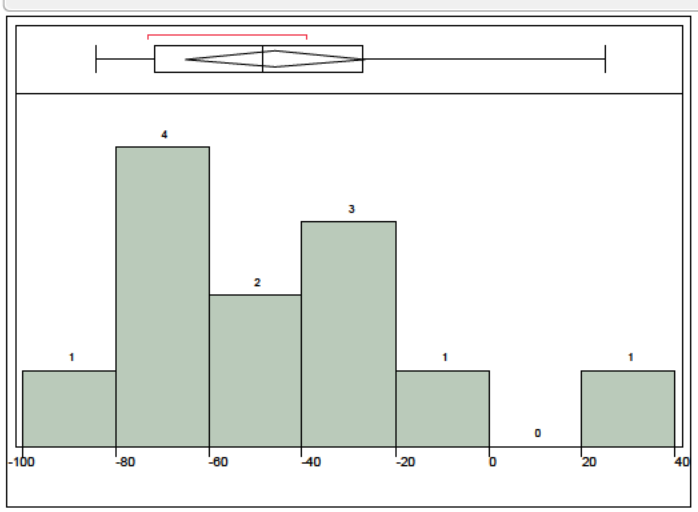


Quantiles		
100.0%	maximum	24.7
99.5%		24.7
97.5%		24.7
90.0%		7.15
75.0%	quartile	-47.975
50.0%	median	-62.45
25.0%	quartile	-93.4
10.0%		-100
2.5%		-100
0.5%		-100
0.0%	minimum	-100

Moments	
Mean	-61.89167
Std Dev	35.053218
Std Err Mean	10.118992
Upper 95% Mean	-39.61991
Lower 95% Mean	-84.16342
N	12

Figure 70 Distribution, Myoclonic Seizure frequency percent change from baseline per 28 days at 4 months. Rufinamide treatment

Distribution, Myoclonic Sz, Percent change from Baseline per 28 days at 4 months RUF

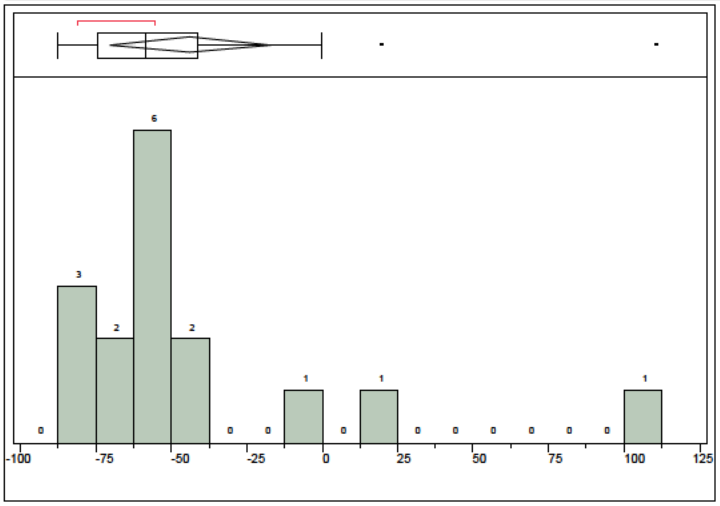


Quantiles		
100.0%	maximum	25
99.5%		25
97.5%		25
90.0%		12.91
75.0%	quartile	-27.3
50.0%	median	-48.25
25.0%	quartile	-71.7
10.0%		-81.4
2.5%		-84.1
0.5%		-84.1
0.0%	minimum	-84.1

Moments	
Mean	-45.85
Std Dev	30.629205
Std Err Mean	8.8418898
Upper 95% Mean	-26.38913
Lower 95% Mean	-65.31087
N	12

Figure 71 Distribution, Total Seizure frequency percent change from baseline per 28 days at 6 months. Rufinamide treatment

Distribution, Total Seizures percent change from baseline per 28 days at 6 months

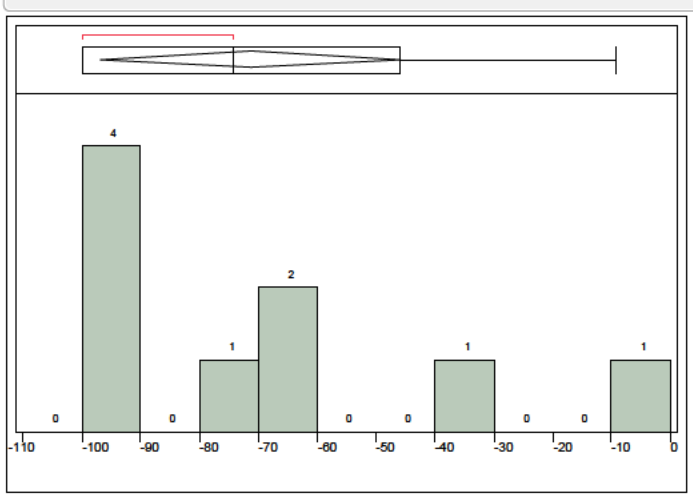


Quantiles		
100.0%	maximum	110.8
99.5%		110.8
97.5%		110.8
90.0%		46.96
75.0%	quartile	-41.275
50.0%	median	-58.45
25.0%	quartile	-74.575
10.0%		-82.82
2.5%		-87.3
0.5%		-87.3
0.0%	minimum	-87.3

Moments	
Mean	-43.675
Std Dev	49.970198
Std Err Mean	12.492549
Upper 95% Mean	-17.04776
Lower 95% Mean	-70.30224
N	16

Figure 72 Distribution, Partial Seizure Frequency percent change from baseline per 28 days at 6 months, rufinamide treatment

Distribution, Partial Seizures percent change from baseline per 28 days at 6 months

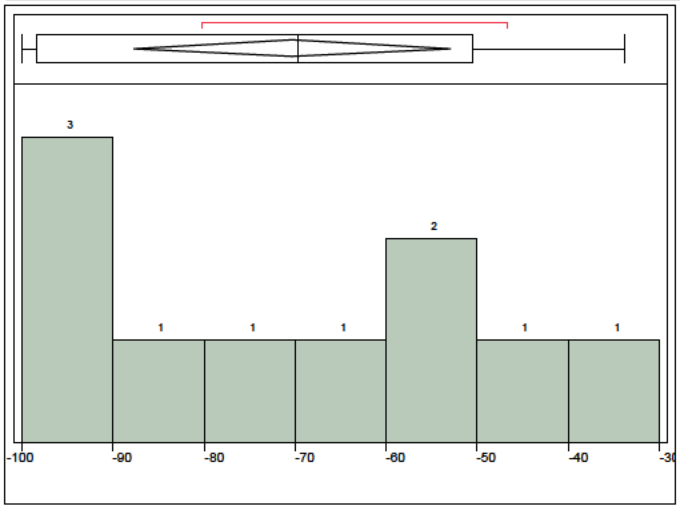


Quantiles		
100.0%	maximum	-9.3
99.5%		-9.3
97.5%		-9.3
90.0%		-9.3
75.0%	quartile	-46.15
50.0%	median	-74.3
25.0%	quartile	-100
10.0%		-100
2.5%		-100
0.5%		-100
0.0%	minimum	-100

Moments	
Mean	-71.32222
Std Dev	33.233446
Std Err Mean	11.077815
Upper 95% Mean	-45.77673
Lower 95% Mean	-96.86771
N	9

Figure 73 Distribution, Tonic-Atonic Seizure frequency percent change from baseline per 28 days at 6 months. Rufinamide treatment

Distribution, Tonic-Atonic Seizurs, Percent Change from Base per 28 days at 6 months



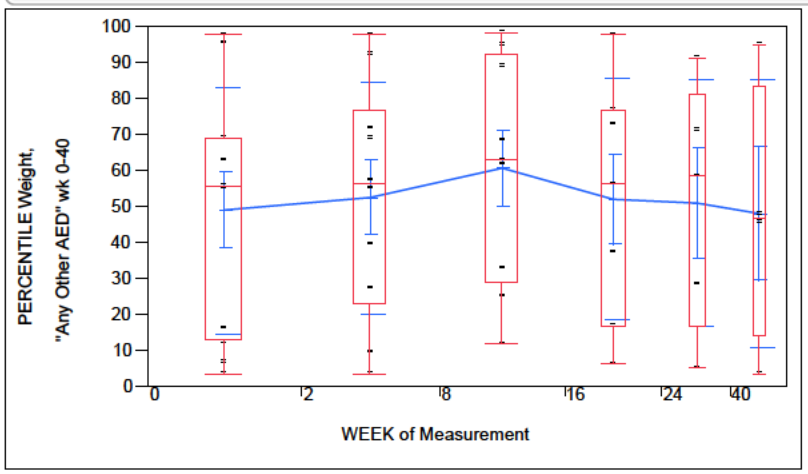
Quantiles		
100.0%	maximum	-33.8
99.5%		-33.8
97.5%		-33.8
90.0%		-35.09
75.0%	quartile	-50.525
50.0%	median	-69.6
25.0%	quartile	-98.35
10.0%		-100
2.5%		-100
0.5%		-100
0.0%	minimum	-100

Moments	
Mean	-70.29
Std Dev	24.280237
Std Err Mean	7.678085
Upper 95% Mean	-52.92097
Lower 95% Mean	-87.65903
N	10

9.9 Weight analysis

Figure 74 Percentile Weight, change from baseline weeks 0 to 40, "any other AED" treatment

Oneway Analysis of PERCENTILE Weight, "Any Other AED" wk 0-40 By WEEK of Measurement



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
0	3.6	4.26	12.5	55.6	69.1	97.3	97.7
2	3.6	4.19	22.7	56 35	76.775	97.43	98
8	11.7	11.7	29.05	62.6	92.05	98.5	98.5
16	6.2	6.2	16.4	56	76.4	97.7	97.7
24	5.2	5.2	16.8	58.3	81.1	91.2	91.2
40	3.5	3.5	14.025	46.6	83.075	94.9	94.9

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
0	11	48.8818	34.1731	10.304	25.92	71.84
2	10	52.3600	32.2765	10.207	29.27	75.45
8	9	60 5444	31.4431	10.481	36.38	84.71
16	7	51.8571	33.4531	12.644	20.92	82.80
24	5	50.8200	34.1964	15.293	8 36	93.28
40	4	47.9000	37.3530	18.677	-11.54	107.34

10.0 Written Request, revised 2/26/14, Key Elements

Clinical studies:

Study 1: An open-label design, multicenter study to evaluate the safety and pharmacokinetics of adjunctive rufinamide treatment over a six-month period in pediatric patients >1 to <4 years of age with inadequately controlled Lennox-Gastaut syndrome

(LGS). This study may have multiple arms, but this written request is directed toward the safety data in patients in the rufinamide treated group.

Objective of the study:

- to evaluate the overall safety and tolerability of rufinamide in the target population
- to evaluate the age group specific pharmacokinetics of rufinamide
- to establish a tolerable dosage regimen that will produce plasma levels in this population similar to that in the population in whom rufinamide is currently recommended

Patients to be Studied:

- Age group in the study to be performed: Patients >1 to <4 years old, with at least 35% of the rufinamide treated patients derived from the >1 to ≤ 3 years age range

- Number of patients to be studied: Enrollment of at least 21 or greater in rufinamide treated patients

- Safety: At least 21 patients with rufinamide exposures in the determined therapeutic range.

- Pharmacokinetics: PK data from this study will be combined with data from two other studies (CRUF331 0022 and E2080-J081-304) using a population modeling approach. Age as a continuous and categorical covariate (≤4 years vs >4 years) will be analyzed with the purpose to determine if PK data from 1-4 year old patients with LGS are consistent with those in older patients with the disorder.

- Representation of Ethnic and Racial Minorities: The study must include adequate (i.e., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, you must provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study Endpoints

- Pharmacokinetic Endpoints: Pharmacokinetic parameters such as CL, Vd, AUC, and Cavgss must be evaluated using sparse sampling. The pharmacokinetic parameters must be compared to previous data from patients >4 years of age. The timing of blood samples must be such that the effect of concomitant AEDS on rufinamide pharmacokinetics can be characterized.

- Safety Endpoints: Safety outcomes must include a standard evaluation of safety parameters, to include clinical chemistry, hematology parameters, amylase and lipase, performed on all treated subjects. ECG's must also be performed to monitor for QT shortening and other cardio-electrophysiological effects, one recording at baseline and 3 duplicate at a sampling point corresponding to Cmax after achieving steady state rufinamide levels. Treatment-emergent adverse events must be summarized by presenting incidence of adverse events. Height, weight and head circumference must also be monitored using standardized methodology at baseline and at the end of rufinamide treatment interval. Descriptive summary statistics (mean plus standard deviation, median, and range) of the laboratory, and vital signs, and changes from baseline must be evaluated.

Plasma concentrations of rufinamide should be checked at the time of significant undesirable effect.

Review of Adverse Events (AEs) must be performed at each visit (Baseline, week 2, 4, 8, 16, and 24); laboratory tests must be performed at Screening, Baseline, and weeks 2, 4, 8, 16 and 24.

While all adverse events must be reported, patients must be actively monitored for the following adverse events: pancreatitis, liver toxicity, blood dyscrasias, skin reactions, hypersensitivity reactions, EKG and cardiovascular events, neuropsychiatric effects, and significant changes in growth and development.

Known Drug Safety concerns and monitoring

- Somnolence, fatigue and coordination abnormalities
- QT shortening
- Multi-Organ Hypersensitivity Reactions
- Leukopenia
- Pancreatitis

Extraordinary results: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

10.1 Infection Adverse Event Analysis, Brief Outline Presentation

Study 303

1. All Infection and Infestation SOC, 24 week observation treatment period
    a. Rufinamide: 13 patients (52%)
    b. AO: 7 patients (63%)
2. Any Respiratory tract infection (sinusitis included) , 24 week observation treatment period
    a. Rufinamide: 10 patients (40%)
    b. AO: 7 patients (63%)
3. Any Respiratory tract infection (sinusitis included), total and SAE, full range of available post baseline observation interval
    a. Rufinamide treatment: median study day of event occurrence = 138, range 4 to 544 days
        i. 13 patients (52%), SAE 6 patients (24%).
        ii. Study day of SAEs that occurred after 24 week observation interval, mean 296 days, median 265 days.
    b. AO: median study day of event occurrence = 66, range 3 to 727
        i. 7 patients (63%), SAE 1 patient (9%)
4. Any Respiratory Tract infection SAE , 24 week observation treatment period
    a. Rufinamide: 2 patients (8%)
    b. AO: 1 patient (9%)
5. Baseline to treatment any respiratory tract infection
    a. Rufinamide: Baseline 2 patients (8%), 24 week observation 10 patients (40%)
    b. AO: baseline 5 patients (45%), 24 week observation 7 patients (63%)

Study 022, age 4 to 12 year strata. (rufinamide treatment n=36, PBO n= 36)

1. All Infection and Infestation SOC, DB treatment interval
    a. Rufinamide: 16 of 36 patients (44%)
    b. PBO: 17 of 36 patients (47%)
2. Any Respiratory tract infection , DB treatment interval
    a. Rufinamide: 11 patients (31%)
    b. PBO: 12 patients (33%)
3. Any Respiratory tract infection (includes sinusitis, herpangina excluded), total and SAE, full range of available post baseline observations (open label and post study taper period)
    a. Rufinamide treatment: median study day of event occurrence = 153, range 1 to 927 days
        i. 23 patients (63%), SAE 4 patients (11%).
        ii. Study day of SAEs that occurred after DB treatment interval, mean 260 days, median 157 days.

iii. The Preferred term and age of patients with SAEs were as follows: pneumonia 3 patients, ages 4 , 8 and 10 years. Upper respiratory tract infection, 1 patient age 4 years.

b. Placebo: median study day of event occurrence = 66, range 3 to 727
   i. 23 patients (63%), SAE 2 patient (6%)
   ii. Study day of SAEs that occurred after DB treatment interval were at 120 and 366 days
   iii. The Preferred term and age of patients with SAEs were as follows: pneumonia 2 patients ages 7 and 10 years.

4. Any Respiratory Tract infection SAE , DB interval
   a. Rufinamide: 1 patient (4%)

PBO: 1 patient (4%)

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

/s/

STEVEN T DINSMORE
02/08/2015

NORMAN HERSHKOWITZ
02/09/2015