Clinical Pharmacology Review

PRODUCT (Generic Name):	Rufinamide
sNDA:	201367 (0041) (Supplement 003)
PRODUCT (Brand Name):	Banzel™
DOSAGE FORM:	Liquid suspension
INDICATION:	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome in children 1 year of age and older and adults
NDA TYPE:	Efficacy supplement
SPONSOR:	Eisai Inc.
IND :	058463
REVIEWER:	Michael Bewernitz, Ph.D.
TEAM LEADERS:	Angela Men, M.D., Ph.D., Kevin Krudys, Ph.D.
OCP DIVISIONS:	Division 1 (DCP 1), Pharmacometrics (DPM)
OND DIVISION:	Neurology (DNP)

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1. EXECUTIVE SUMMARY

Banzel was approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in 2008. This sNDA was submitted to provide pediatric data for BANZEL® (rufinamide) oral suspension to fulfill the pediatric Written Request (PWR) and request pediatric exclusivity. Banzel was granted orphan designation for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in children 1 year and older and adults (designation number 14-1395).

In this submission, Sponsor submitted a pharmacokinetic study report (Study 303) of rufinamide in patients with LGS age 1 to less than 4 years. The Sponsor also submitted population pharmacokinetic report CPMS-E2080-002R-v1, which utilized PK data from study 303 as well as two other clinical trials in LGS patients of age 4 to 30 years.

Body weight and concomitant use of Valproic Acid (VPA) were covariates that were included in the final population PK model. There was no significant difference between the exposure of rufinamide in patients age 1 to < 4 years and pediatric patients age 4 years and older as well as adults at the recommended dose. Patients age 1 to < 4 years will undergo the same titration when initiating Banzel as is approved for children age 4 years and older (e.g. 10 mg/kg/day, bid, increasing 10 mg/kg increments every other day to a target dose of 45 mg/kg/day). In addition, as is the case for pediatric patients age 4 years and older, a starting titration dose lower than 10 mg/kg/day will be recommended for patients age 1 to < 4 years who receive concomitant VPA as this concomitant medication significantly reduces rufinamide clearance.

From a clinical pharmacology perspective, the Sponsor has fulfilled the requirements of the PWR.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 1 (DCP-1) has reviewed the NDA 201,367 and found the application is acceptable from a clinical pharmacology standpoint.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Rufinamide PK data were obtained from Study E2080-G000-303, a multicenter, randomized, controlled, open-label study to evaluate cognitive development effects and safety, and PK of adjunctive rufinamide treatment in pediatric subjects age 1 to less than 4 years of age with inadequately controlled Lennox-Gastaut Syndrome (LGS). PK data from previously completed studies in LGS patients age 4 to 30 years (CRUF331 0022 and study E2080-J081-304) were also used in the analyses.

Due to the sparse PK data from all 3 studies, a constant rate infusion model (was utilized. A similar modeling approach was utilized in the original rufinamide tablet submission (see the clinical pharmacology review of NDA 021911 signed on 09/11/2006 for additional details). The PWR included a request to assess the effects of age as a continuous as well as a

categorical covariate on rufinamide pharmacokinetics. Sponsor determined that continuous or categorical age was not a significant covariate for rufinamide PK after taking weight into account. The effects of concomitant carbamazepine, lamotrigine, phenytoin, and valproic acid (VPA) on rufinamide PK were assessed. Body weight and concomitant use of Valproic Acid (VPA) were covariates that were included in the final population PK model. As VPA concentration increases, rufinamide exposure also increases. There was no significant difference between the exposure of rufinamide in patients age 1 to < 4 years and pediatric patients age 4 years and older as well as adults at the recommended dose.

As a requirement for the development program in Europe, the Sponsor assessed Child Behavior Check List (CBCL) survey in study 303. There was no apparent relationship between rufinamide exposure and CBCL score.

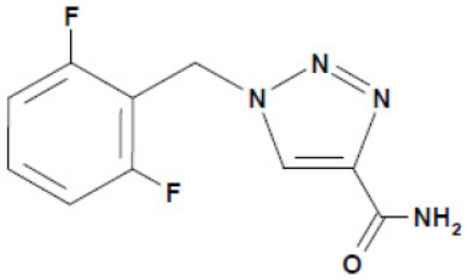
2. QUESTION BASED REVIEW

2.1 GENERAL ATRIBUTES

2.1.1. Drug/Drug Product Information

Rufinamide is a triazole derivative structurally unrelated to currently-marketed antiepileptic drugs (AEDs). The empirical formula is $C_{10}H_8F_2N_4O$ and the molecular weight is 238.2.

Figure 1: Chemical Structure of Rufinamide



2.1.2. Formulation

Banzel oral suspension is an orange-flavored liquid supplied in a (b) (4) bottle. The suspension contains 40 mg/mL banzel, (b) (4) sorbitol (b) (4) propylene glycol (b) (4) as well as other ingredients.

2.1.3. Mechanism of Action

The mechanism of action for the antiepileptic effect of rufinamide is unknown. The results of in-vitro studies suggest that the principal mechanism of action is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel.

2.1.4. Indication

BANZEL (rufinamide) is an antiepileptic drug indicated for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in children 1 year of age and older and adults.

2.1.5. Proposed dose and dosing regimen

The recommended starting daily dose of BANZEL in pediatric patients with Lennox-Gastaut Syndrome is approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day until a maximum daily dose of 45 mg/kg/day, not to exceed 3200 mg/day, administered in two equally divided doses, is reached.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1. What are the design features of the clinical pharmacology and efficacy studies used to support dosing or claims?

Sponsor conducted a single clinical trial which assessed safety, cognitive effects, and PK of rufinamide in LGS epilepsy patients age 1 to < 4 years. Sponsor submitted a report which contains results of population PK analyses and comparisons of exposures between patients age 1 to < 4 years and patients ≥ 4 years.

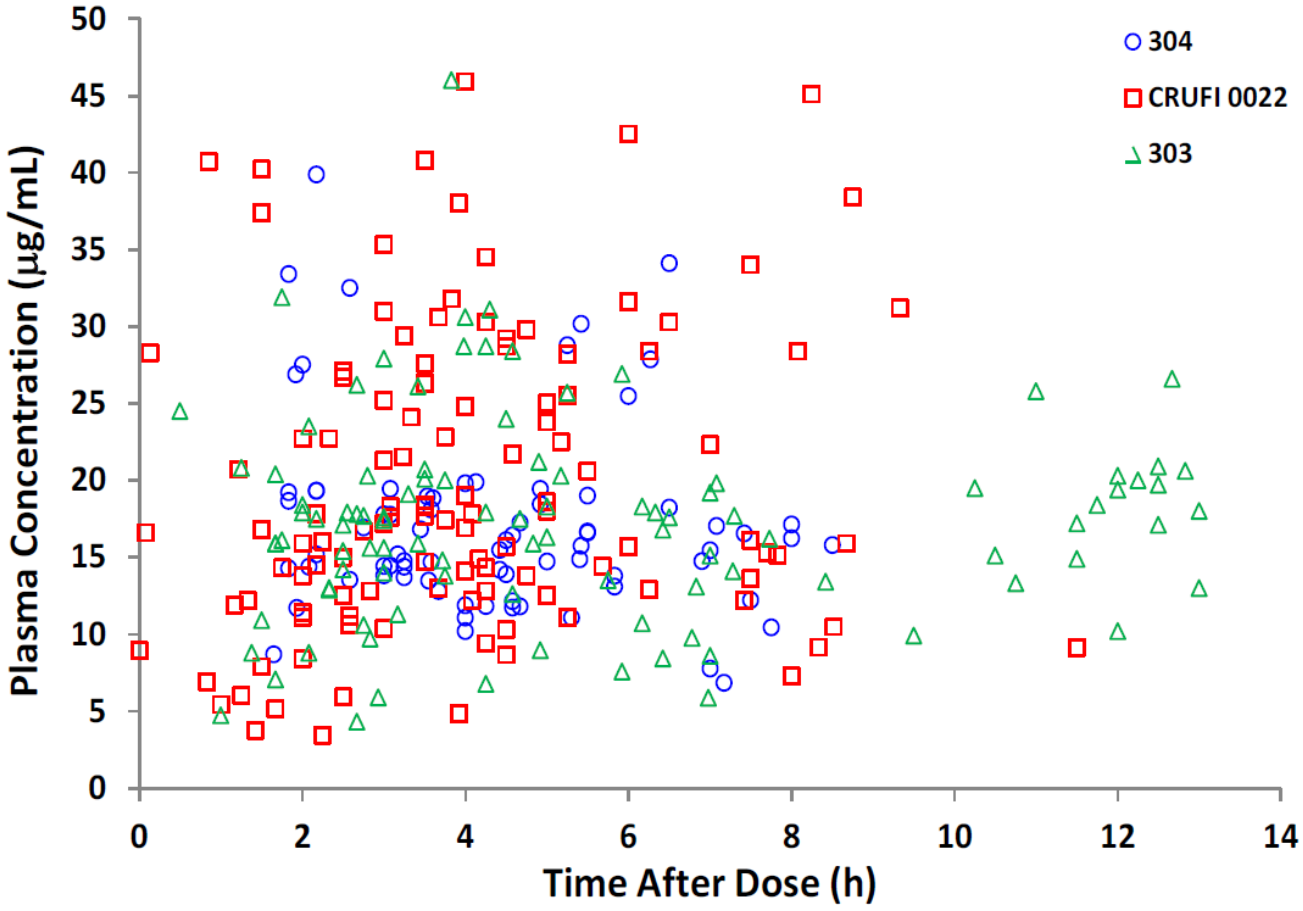
Table 1: Summary of Clinical Studies Where PK Data Were Collected or Analyzed

Type of Study and Study Identifier	Objective(s) of the Study	Study Design	Doses, Route, Regimen	n	Healthy or Patients
E2080-G000-303 (Clinical Trial)	To evaluate the cognitive development effects and safety and PK in pediatric subjects age 1 to less than 4 years	Randomized, Controlled, Open-Label, Multi-Center	10 mg/kg/day, increased every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to target maintenance level of 45 mg/kg/day. Dose orally administered in 2 equally divided doses per day.	37 (n=25 on rufinamide, n=12 on other AED)	LGS epilepsy patients age 1 to <4 years
CRUF331 0022	To evaluate the safety and efficacy of rufinamide as adjunctive therapy in patients with inadequately controlled seizures associated with Lennox-Gastaut syndrome.	Multicenter, randomized, double-blind, placebo controlled, parallel study	18.0 - 29.0 kg: 1000 mg/day 29.1 - 50.0 kg: 1800 mg/day 50.1 - 70.0 kg: 2400 mg/day ≥70.1 kg: 3200 mg/day Administered orally, bid. Baseline (28 days), double-blind (84 days: 14 days of titration followed by 70 days of maintenance) and long-term extension	139 (n=5 on oral rufinamide, n=64 on placebo)	LGS patients age 4-30 years
E2080-J081-304	To evaluate the safety and efficacy rufinamide as adjunctive therapy in Japanese subjects with inadequately controlled LGS.	A placebo-controlled, double-blind comparative study	15.0 - 30.0 kg: 1000 mg/day 30.1 - 50.0 kg: 1800 mg/day 50.1 - 70.0 kg: 2400 mg/day ≥70.1 kg: 3200 mg/day Administered orally, bid. Baseline (28 days), double-blind (84 days: 14 days of titration followed by 70 days of maintenance) and long-term extension	26 (PK data are available from n=26 subjects that received oral rufinamide)	LGS patients age 4-30 years (Japan)
CPMS-E2080-002R-v1 (PK Analysis Report)	To characterize the rufinamide PK in LGS epilepsy patients and compare rufinamide exposure in patients 1 ≤ age < 4 years to patients ≥ 4 years	n/a	n/a	N=115 (304 plasma concentration observations)	LGS patients age 1-35 years

2.2.2. What are the PK characteristics of the drug?

The following figure illustrates the individual PK profiles for all subjects that participated in all 3 clinical trials.

Figure 2: Individual Observed Rufinamide Plasma Concentrations from Studies 303, 304, and CRUFI 0022

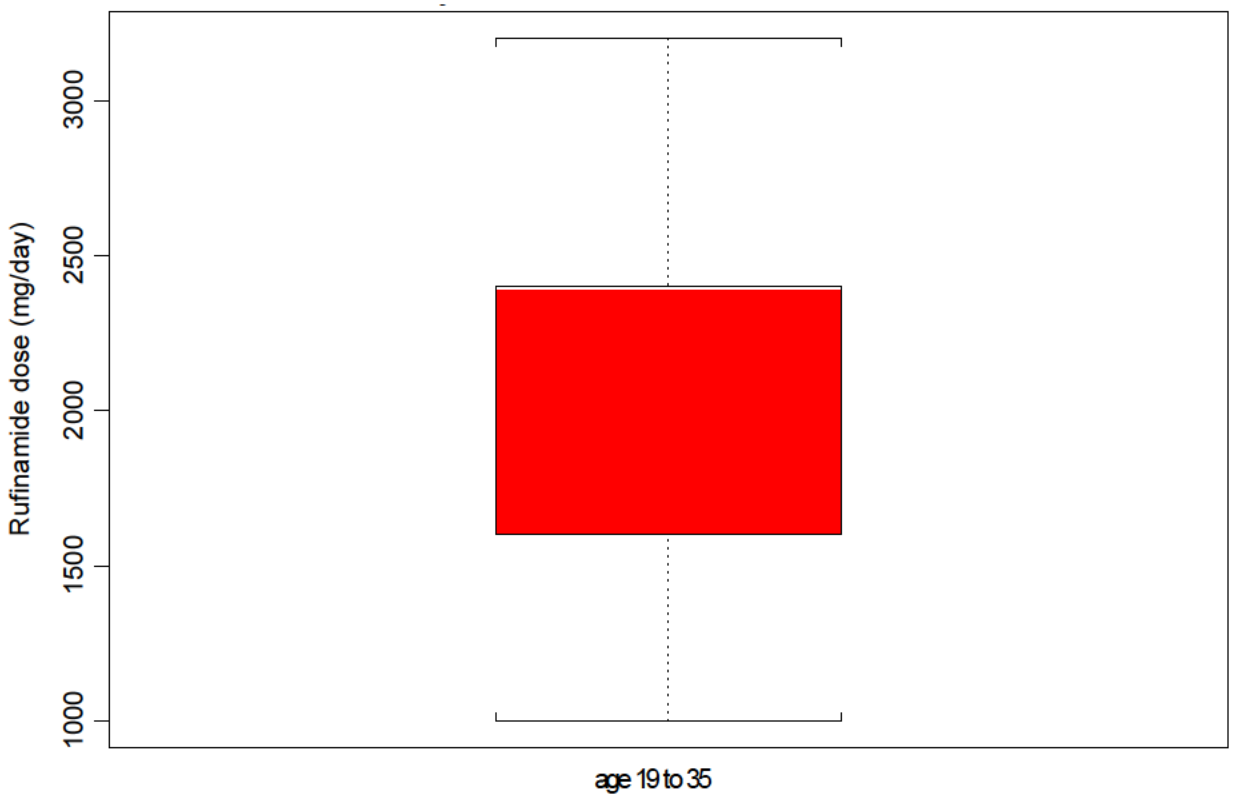


2.2.3. Are the Dose and Dose Regimen Acceptable?

Yes. Sponsor's rationale for selecting a 45 mg/kg/day dose (with titration) in study 303 was that this regimen was well-tolerated, effective, and approved in tablet form in the US, EU, and other countries based on the results from Study CRUF331 0022. Study CRUF331 0022 was the primary basis of approval for rufinamide using this dose regimen and patient population (LGS). The oral suspension was demonstrated to be bioequivalent to the tablet and well-tolerated in studies comparing tablet and suspension formulations.

Reviewer analyses: In study 303, 25 pediatric patients age 1 to < 4 years were randomized to the rufinamide arm and were titrated over a 2-week period toward a target dose of 45 mg/kg/day (administered b.i.d.). PK data were available for 24 of these 25 patients. In addition, PK data were available from n=40 subjects age 4-12 years, n=21 subjects age 13-18 years, and n=30 subjects age 19-35 years from studies 304 and CRUF331-0022. In studies 304 and CRUF331-0022, patients age 4 – 18 years were titrated over a 2-week period towards a target dose of 45 mg/kg/day and adults toward 3200 mg/day (administered bid). The final daily adult doses after titration ranged from 1000 to 3200 mg/day (median 2400 mg/day). The distribution of adult doses is shown in the figure below.

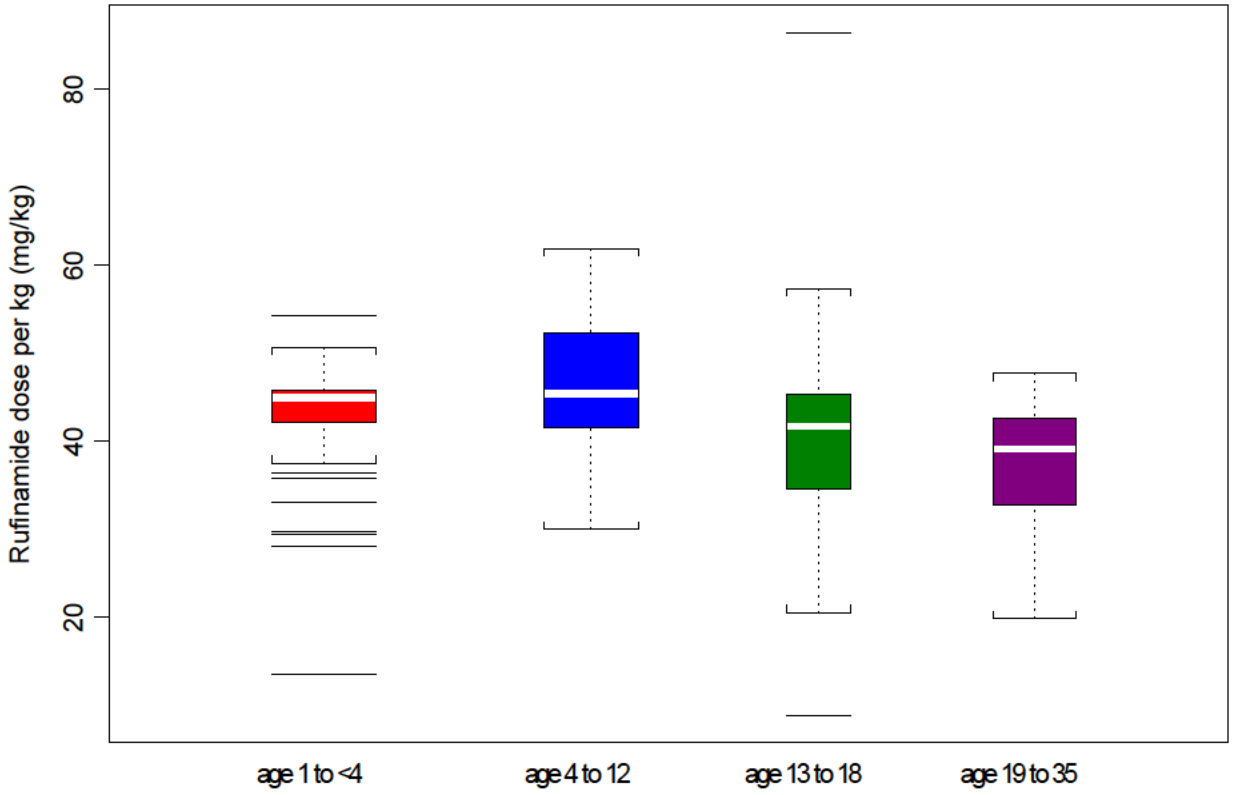
Figure 3: Actual Doses (mg/day) administered to Adults in Studies 304 and CRUF331-022



The median dose was 2400 mg.

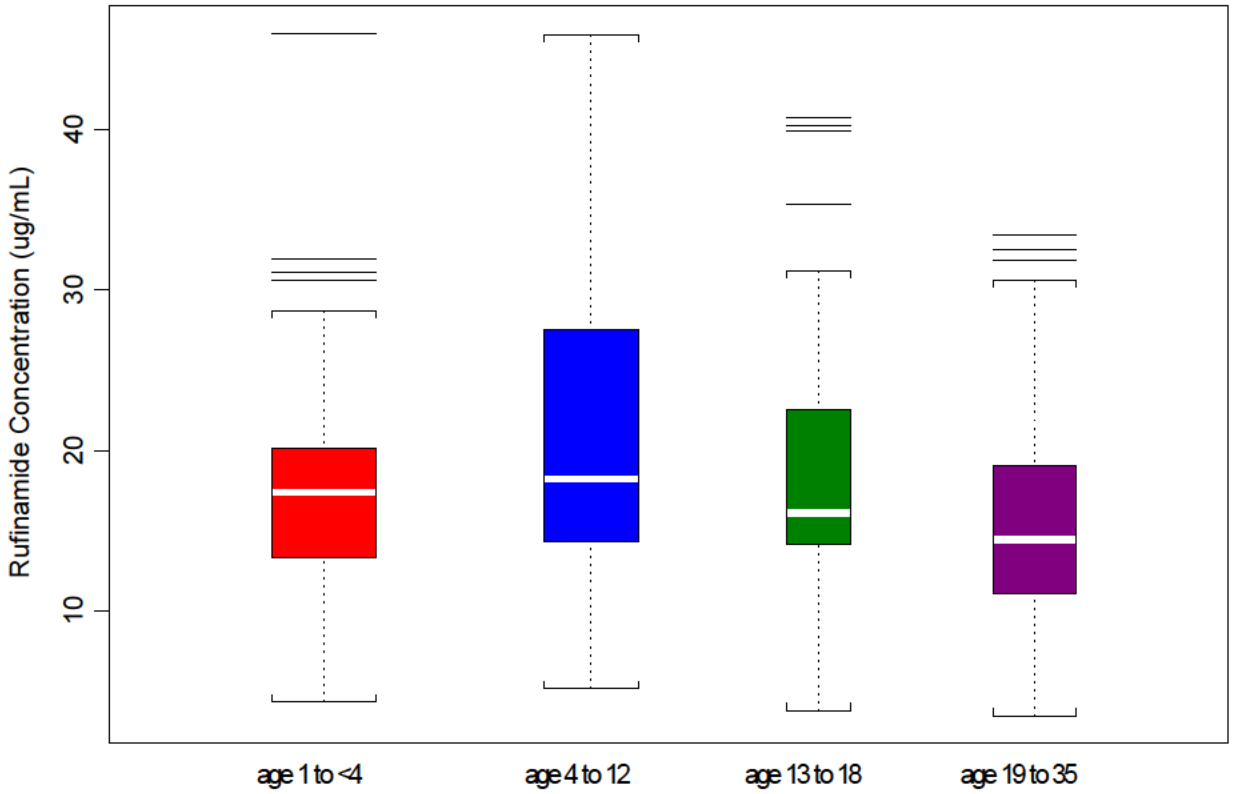
The following figure shows the actual dose, normalized to mg/kg, for all adult and pediatric patients included in the population PK analyses.

Figure 4: Actual Doses (mg/kg) Administered to Pediatric and Adult Patients in Studies 303, 304, and CRUF331-022



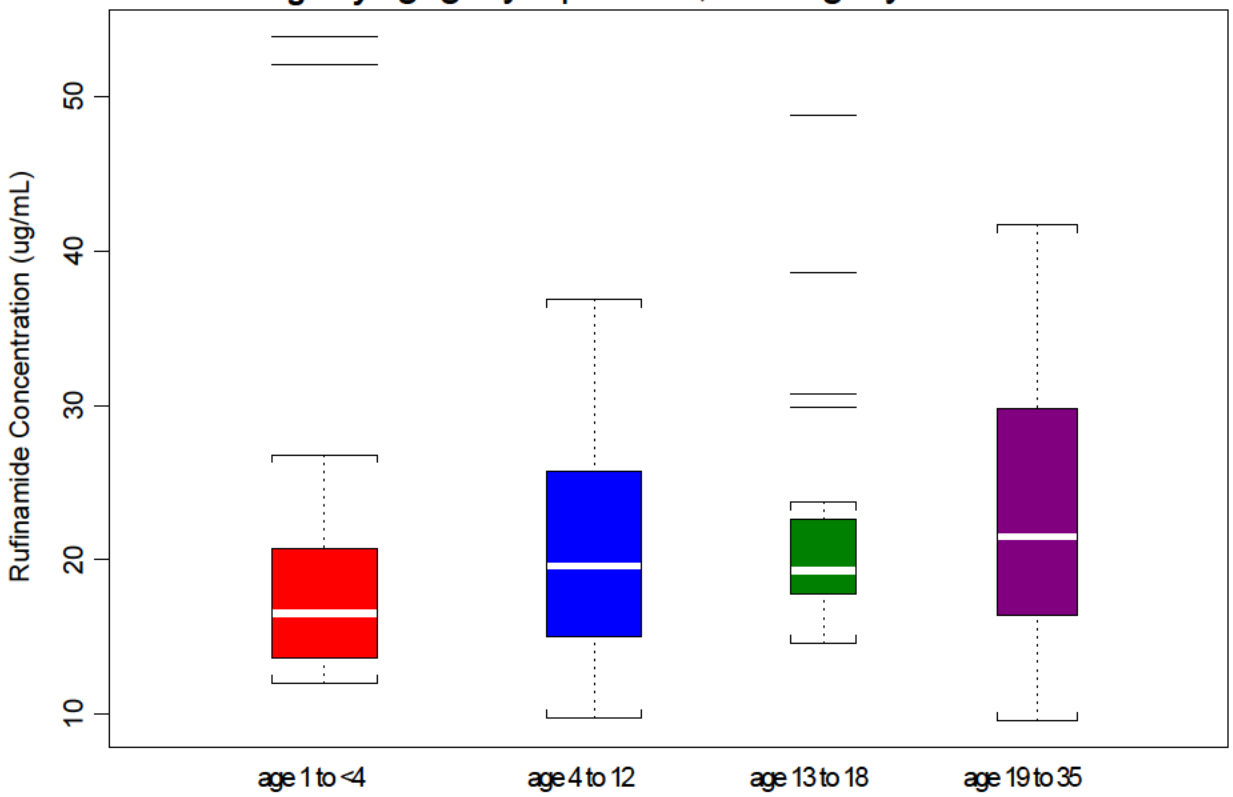
For patients receiving the doses in the figure above, the following figure shows the corresponding observed rufinamide concentrations.

Figure 5: Observed Steady-State Rufinamide Concentrations for Pediatric and Adult Patients in Studies 303, 304, and CRUF331-022



The figure above suggests that rufinamide concentrations in subjects age 1 to < 4 years are comparable to rufinamide concentrations in patients age 4 to 12 years, age 13 to 18 years, and age 19 to 35 years. However, the concentrations above are associated with the final titrated doses presented in Figure 4. Since the doses in Figure 4 vary, and the Sponsor is recommending a 45 mg/kg/day target dose in pediatrics (and a 3200 mg/day target dose is approved in adults), the exposures at the recommended dose levels were predicted. For details on the pharmacokinetic modeling and simulation procedure see section 4.1.1 .

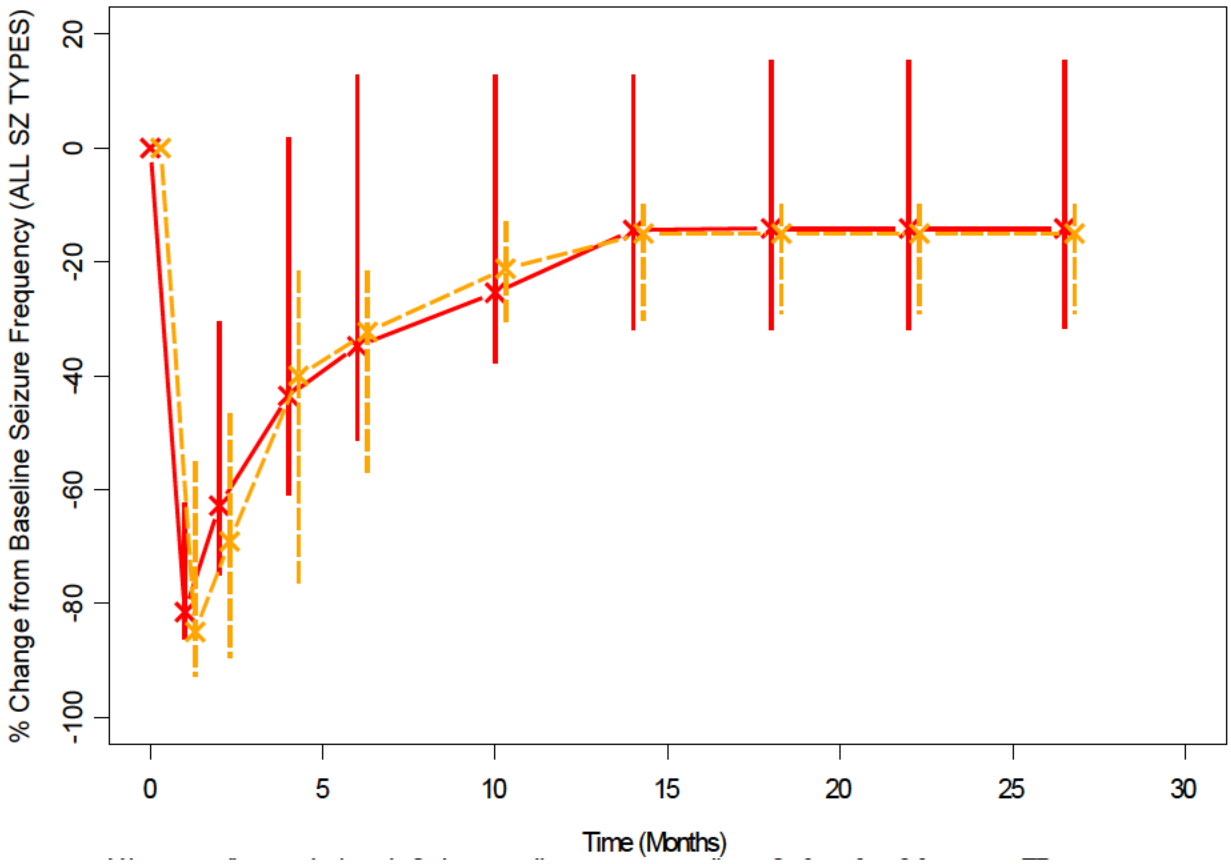
Figure 6: Predicted Rufinamide Concentrations Following 45 mg/kg/day in Pediatric Patients and 3200 mg/day in Adult Patients



If pediatric subjects and adults received the maximum dose (45 mg/kg/day for pediatric patients and 3200 mg/day for adult patients) then the median predicted rufinamide concentration in children age 1 to < 4 years would be 16, 14, and 23 % lower compared to older groups (16.5, 19.6, 19.3, and 21.5 µg/mL for age groups 1 to < 4, 4 to 12, 13 to 18, and 19 to 35, respectively). These concentration decreases of patients age 1 to < 4 ears compared to older patients represent a "worst-case" scenario.

Sponsor collected seizure information from trial 303. The following plot shows the percent change from baseline seizure frequency in patients that were assigned rufinamide compared to the patients that were assigned "other AEDs" in study 303.

Figure 7: Change from Baseline Seizure Frequency over Time for the Rufinamide Arm (n=25) and the "Other AED" Arm (n=9) in Study 303



The solid-red series (series offset slightly to the left for purposes of visualization) represents the rufinamide arm and the segmented-orange series (the series offset slightly to the right) represents the "Other AEDs" arm in study 303.The "X" points in the plot represent the median % change from baseline seizure frequency across all patients within the arm at the particular time point. The vertical bars request the 25th percentile to 75th percentile of the % change in seizure frequency across all patients within the arm at the particular time point. This plot includes all seizure types.

Though this study was not designed to assess rufinamide efficacy, the plot above suggests that the patients receiving rufinamide (solid-red series) experienced a comparable seizure reduction to the patients who received "Other AEDs".

Overall, the selection of the 45 mg/kg/day as the target dose, with a 2-week titration, for patients age 1 and older is acceptable.

2.3. Intrinsic Factors

Rufinamide clearance in patients age 1 to 35 increased with body weight as described by a power function with an exponent of 0.831. Once body weight was accounted for, age was not significant as either a categorical or continuous covariate.

Rufinamide PK was not significantly affected by sex, race (Caucasian versus non-Caucasian), hepatic function (in terms of alkaline phosphate or total bilirubin measures), or renal function (in terms of creatinine clearance). See section 4.1.1. for details.

Reviewer comment: These intrinsic factors effects on rufinamide PK are comparable with statements in the currently available label.

2.4 Extrinsic Factors

2.4.1 What is the potential for DDI?

2.4.1.1. Effect of Other Drugs on Rufinamide

Concomitant administration of valproic acid significantly reduced the rufinamide clearance in subjects 1 to 4 years old. The trend of decreasing rufinamide CL/F with increasing valproic acid concentration was described with a linear model with a slope of -0.496. Without valproic acid, median rufinamide C_{av} was 13.4, 17.2, 14.0, and 12.2 µg/mL for patients age 1 to <4 years, 4 to 12 years, 13 to 18 years, and 19 to 35 years in the population PK analysis dataset. With valproic acid, median rufinamide C_{av} was 17.8, 19.6, 16.9, and 16.2 µg/mL for patients age 1 to <4 years, 4 to 12 years, 13 to 18 years, and 19 to 35 years. When comparing rufinamide concentrations in patients who received concomitant valproic acid to patients who did not receive concomitant VPA, rufinamide concentrations were 33%, 14%, 21%, and 33% greater in patients age 1 to < 4 years, 4 to 12 years, 13 to 18 years, and 19 to 35 years.

Reviewer Comment: The data from study 303 suggest that the effect of concomitant VPA on rufinamide PK in children age 1 to < 4 years is comparable to older pediatric patients and adults. However, the 33% increase in rufinamide concentration associated with concomitant VPA use in trial 303 is the median increase for patients that received concomitant VPA. Using the Sponsor's population PK model, the reviewer predicted the effect of various VPA concentrations levels on rufinamide concentration in a patient at the median weight in the 1 to < 4 year age group.

In patients age 1 to < 4 years who received concomitant valproic acid, the median weight was 13 kg, median valproic acid concentration was 81 ng/mL, and the median rufinamide dose was 600 mg/day (300 mg bid). The effect of VPA on rufinamide concentrations in this situation is as follows:

For a patient of this mass not receiving VPA, the expected rufinamide CL/F is:

$CL/F = \Theta_{CL} * (WGT / 18.1)^{\Theta WGT} + \Theta_{CVPAC} * (CVPAC / 96)$

$= 2.19 * (13 / 18.1)^{0.831} + (-0.496) * (0 / 96) = 1.66$ L/h

, and the expected rufinamide C_{av} is:

C_{av} (µg/mL) = Dose $_{single\ administration}$ (mg) / Dosing Interval (12 h) / CL/F

= 300 mg / 12 h / 1.66 L/h = 20 mg/L = ***15 µg/mL***

For a patient of this mass receiving VPA, the expected rufinamide CL/F is:

$CL/F = \Theta_{CL} * (WGT / 18.1)^{\Theta WGT} + \Theta_{CVPAC} * (CVPAC / 96)$

$= 2.19 * (13 / 18.1)^{0.831} + (-0.496) * (81 / 96) = 1.24$ L/h

, and the expected rufinamide C_{av} is:

C_{av} (µg/mL) = Dose $_{single\ administration}$ (mg) / Dosing Interval (12 h) / CL/F

= 300 mg / 12 h / 1.24 L/h = 20 mg/L = ***20 µg/mL***

The maximum valproic acid concentration measured in study 303 was 160 ng/mL. For this scenario, the expected rufinamide CL/F is:

$CL/F = \Theta_{CL} * (WGT / 18.1)^{\Theta WGT} + \Theta_{CVPAC} * (CVPAC / 96)$

$= 2.19 * (13 / 18.1)^{0.831} + (-0.496) * (160 / 96) = 0.84$ L/h

, and the expected rufinamide C_{av} is:

C_{av} (µg/mL) = Dose $_{single\ administration}$ (mg) / Dosing Interval (12 h) / CL/F

= 300 mg / 12 h / 1.24 L/h = 20 mg/L = ***30 µg/mL***

As such, based on the population PK model predictions, concomitant valproic acid use could result in 30%-100% increased rufinamide C_{av}.

The current label recommendation, which is to initiate patients receiving concomitant VPA at a lower rufinamide dose, is acceptable for children ages 1 to < 4 years.

2.5. General Biopharmaceutics

Sponsor utilized the same oral suspension formulation in children age 1 to < 4 years of age as is approved for children ages 4 and above.

2.6. Analytical

2.6.1. Concentration Measurements

2.6.1.1. PK sample collection schedule

Study 303: Sponsor collected PK samples at Weeks 2, 4, 8, 16, and 24 (visits 4, 5, 6, 7, and 8), and at early discontinuation in study 303. Samples acquired during Weeks 2, 8, and 24 (visits 4, 6, and 8) are collected during the morning visit. Samples acquired during Weeks 4 and 16 (visits 5 and 7) are collected during an afternoon visit to the clinic.

2.6.1.2. What bioanalytical methods were used?

Study 303: Sponsor utilized an LC/MS/MS method to quantify rufinamide plasma concentration. In addition LC/MS/MS methods were utilized for the antiepileptic co-medications carbamazepine, lamotrigine, phenytoin, and valproic acid.

2.6.1.3. Were the analytical methods utilized in study 303 adequately validated?

Yes. The following table summarizes the Sponsor's analytical method validation data for rufinamide measured in study 303.

Table 2: Bioanalytical Validation Information for Rufinamide LC-MS/MS Method AM-034-R0 (Study 303)

Information Requested	Data
Analyte	Rufinamide
Internal standard (IS)	(b) (4)
Limit of quantitation	20 ng/mL
Average recovery of drug (%)	91.1%
Average recovery of IS (%)	88.0%
Standard curve concentration	20, 40, 100, 500, 5000, 10000, 15000, 20000 ng/mL
Standards accuracy range (%)	95.5%- 103.7%
Standards precision range (%)	1.2%-3.9%
QC range	50, 500, 4000, and 14000 ng/mL
QC accuracy range (%)	99.6%- 101.9%
QC precision range (%)	3.3%- 5.3%
Bench-top stability (hrs)	6 hours
Stock stability (days)	24 hours
Post-preparative stability (hrs)	24 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	34 days at -20°C
Dilution integrity	105.3% accuracy, 0.7% precision at 20-fold dilution
Selectivity	No significant interference from chromatographic peaks detected in blank plasma

The assay for rufinamide (method AM-034-R0) is acceptable.

Table 3: Bioanalytical Validation Information for Rufinamide LC-MS/MS Method AM-034-R1 (Study 303)

Information Requested	Data
Analyte	rufinamide
Internal standard (IS)	(b) (4)
Limit of quantitation	20 ng/mL
Average recovery of drug (%)	Not reported
Average recovery of IS (%)	Not reported
Standard curve concentration	20, 40, 100, 500, 5000, 10000, 15000, 20000 ng/mL
Standards accuracy range (%)	91.3 – 108.2%
Standards precision range (%)	1.2 – 3.4%
QC range	50, 500, 4000, and 14000 ng/mL
QC precision range (%)	0.7-4.8%
QC accuracy range (%)	89.9-106.2%
Bench-top stability (hrs)	At least 6 hours at room temperature
Stock stability (days)	At least 223 days at 4°C for rufinamide / (b) (4)
Post-preparative stability (hrs)	At least 41 hours at room temperature
Freeze-thaw stability (cycles)	Not reported
Long-term storage stability (days)	At least 143 days at -20 °C for rufinamide At least 756 days at -70 °C for rufinamide
Dilution integrity	100,000 ng/mL diluted 20-fold with blank human plasma
Interference test	No interference was detected from 14 AEDs at clinically relevant levels Interference test (Gabapentin, Carbamazepine, Clonazepam, Zonisanide, Topiramate, Valproic acid, Phenytoin, Phenobarbital, Primidone, Lamotrigine, Ethosuximide, Nitrazepam, Clobazam, Acetazolamide)
Selectivity	No interfering peaks were detected at the retention time of rufinamide or the IS in blank human plasma.

The difference between method R1 and R0 is that method R0 is designed to assay a Volume of 200 µL whereas method R1 is designed to assay a volume of 50 µL.

The assay for rufinamide (method AM-034-R1) is acceptable.

Table 4: Bioanalytical Validation Information for Valproic Acid LC-MS/MS Method AM-190-R1 (Study 303)

Information Requested	Data
Analyte	Valproic Acid
Internal standard (IS)	Valproic Acid-d_{15}
Limit of quantitation	1 µg/mL
Average recovery of drug (%)	101.7%
Average recovery of IS (%)	103.2%
Standard curve concentration	1, 2, 4, 40, 80, 120, 160, 200 µg/mL
Standards accuracy range (%)	95.7% to 102.5%
Standards precision range (%)	0.5% to 3%
QC range	3, 78, 156 µg/mL
QC precision range (%)	2.1 % to 4.3%
QC accuracy range (%)	93% to 94.2%
Bench-top stability (hrs)	≥ 24 hours @ room temperature
Stock stability (days)	223 days at -20 °C
Post-preparative stability (hrs)	≥ 45 hours at room temperature
Freeze-thaw stability (cycles)	3 freeze/thaw cycles
Long-term storage stability (days)	692 days at -20 °C 752 days at -70 °C
Dilution integrity	2000 µg/mL diluted 40 times
Interference	no interference from rufinamide on valproic acid determination in human plasma
Selectivity	No interfering peaks noted in blank human plasma samples

The assay for valproic acid is acceptable.

Table 5: Bioanalytical Validation Information for Carbamazepine LC-MS/MS Method AM-197 (Study 303)

Information Requested	Data
Analyte	Carbamazepine
Internal standard (IS)	Carbamazepine-d_{10}
Limit of quantitation	50 ng/mL
Average recovery of drug (%)	103.6
Average recovery of IS (%)	100.4
Standard curve concentration	50 80 100 1000 2000 3000 4000 5000 ng/mL
Standards accuracy range (%)	96.3 – 106.6%
Standards precision range (%)	3.0 – 11.3%
QC range	90,900,3800
QC precision range (%)	Intraday: 3.4 – 8.6% Interday: 3.6 – 7.8%
QC accuracy range (%)	Intraday: 104.4 – 114.6% Interday: 107.4 – 109.4%
Bench-top stability (hrs)	25 hour @ room temperature
Stock stability (days)	224 days at -20 °C
Processed stability (hrs)	98 hours @ room temperature
Freeze-thaw stability (cycles)	3 freeze/thaw cycles
Long-term storage stability (days)	-20 °C for a period of 355 days,
Dilution integrity	20000 ng/mL diluted 10 times
Selectivity	No interfering peaks found in blank human plasma samples

The assay for Carbamazepine is acceptable.

Table 6: Bioanalytical Validation Information for Lamotrigine
LC-MS/MS Method AM-197 (Study 303)

Information Requested	Data
Analyte	Lamotrigine
Internal standard (IS)	Lamotrigine-$^{13}C_3$
Limit of quantitation	50 ng/mL
Average recovery of drug (%)	100.9%
Average recovery of IS (%)	103.6%
Standard curve concentration	50 80 100 1000 2000 3000 4000 5000 ng/mL
Standards accuracy range (%)	92.9 – 108.4%
Standards precision range (%)	2.4 – 5.8%
QC range	90, 900, 3800 ng/mL
QC precision range (%)	Intraday: 2.1 – 8.8% Interday: 5.3 – 6.8%
QC accuracy range (%)	Intraday: 99.0 – 114.5 % Interday: 102.6 – 108.4 %
Bench-top stability (hrs)	25 hour @ room temperature
Stock stability (days)	224 days at -20 °C
Processed stability (hrs)	98 hours @ room temperature
Freeze-thaw stability (cycles)	3 freeze/thaw cycles
Long-term storage stability (days)	-20 °C for a period of 355 days
Dilution integrity	20,000 ng/mL diluted 10 times
Selectivity	No interfering peaks found in blank human plasma samples

The assay for Lamotrigine is acceptable.

Table 7: Bioanalytical Validation Information for Phenytoin LC-MS/MS Method AM-156 (Study 303)

Information Requested	Data
Analyte	Phenytoin
Internal standard (IS)	Phenytoin-d_{10}
Limit of quantitation	50 ng/mL
Average recovery of drug (%)	104 – 111.4%
Average recovery of IS (%)	110.5%
Standard curve concentration	50, 80, 100, 1000, 2000, 3000, 4000, 5000 ng/mL
Standards accuracy range (%)	95.4 – 104.3%
Standards precision range (%)	1.7 – 5.8%
QC range	90, 900, 3800 ng/mL
QC precision range (%)	Intraday: 1.9 – 4.7 % Interday: 3.0 – 5.5%
QC accuracy range (%)	Intraday: 93.2 – 104.4% Interday: 95.2 – 102.2%
Bench-top stability (hrs)	24 hours
Stock stability (days)	264 days for stock solutions at -20 °C in methanol and 209 days for spiking solutions at -20 °C in diluent
Processed sample integrity (hrs)	117 hours at room temperature
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	-20 °C for a period of 355 days,
Dilution integrity	50000 ng/mL, diluted 50 times
Selectivity	No interfering peaks found in blank human plasma samples

The assay for Phenytoin is acceptable.

3. Labeling Recommendations

7 DRUG INTERACTIONS

(b) (4)

[*Reviewer comment: The information previously located in section 7 was proposed for re-location to* (b) (4) .]

8 (b) (4) Renal Impairment

Rufinamide pharmacokinetics in patients with severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects. Dose adjustment in patients undergoing dialysis should be considered [*see* (b) (4) *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

(b) (4)

Use of BANZEL in patients with severe hepatic impairment (Child-Pugh score 10 to 15) is not recommended. Caution should be exercised in treating patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment (b) (4)

12.3 Pharmacokinetics

…

Special Populations

…

Pediatrics

Based on a population analysis in a total of (b) (4) -patients (b) (4) the pharmacokinetics of rufinamide (b) (4) similar (b) (4) .

Renal Impairment

Rufinamide pharmacokinetics in 9 patients with severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects. Patients undergoing dialysis 3 hours post rufinamide dosing showed a reduction in AUC and C_{max} by 29% and 16%, respectively. (b) (4)

(b) (4)

[*Reviewer comment:* (b) (4) .]

Drug Interactions

Based on *in vitro* studies, rufinamide shows little or no inhibition of most cytochrome P450 enzymes at clinically relevant concentrations, with weak inhibition of CYP 2E1. Drugs that are substrates of CYP 2E1 (e.g., chlorzoxazone) may have increased plasma levels in the presence of rufinamide, but this has not been studied.

Based on *in vivo* drug interaction studies with triazolam and oral contraceptives, rufinamide is a weak inducer of the CYP 3A4 enzyme and can decrease exposure of drugs that are substrates of CYP 3A4 [(b) (4)

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

[*Reviewer comment: Drug interaction information was moved from* (b) (4) *to section 12.3.*]

14 CLINICAL STUDIES

...

Pediatric Patients ages 1 to less than 4 years

(b) (4)

4. Appendices

4.1 Pharmacometric Review

The purpose of this review is to answer the following key questions:

4.1.1 Is the Sponsor's proposed dose acceptable?

Yes. Figure 5 (see section 2.2.3) demonstrates that patients age 1 to < 4 years after titration experienced rufinamide exposures comparable to children age 4 years and older as well as adults after titration. In addition, patients age 1 to < 4 years receiving rufinamide experienced a comparable reduction from baseline seizure frequency to patients age 1 to < 4 years receiving other AEDs in study 303.

Results of Sponsor's Analyses:

The Sponsor modeled steady state rufinamide PK using a model with constant rate infusion, describing the relationship between steady state rufinamide plasma concentrations and daily dosing. The constant infusion model approach was previously applied during the original approval of rufinamide tablets (see the clinical pharmacology review of NDA 021911 dated 09/11/2006). The final model for CL/F is as follows:

$$\frac{CL}{F}(L/h) = 2.19 * \left(\frac{WGT}{18.1}\right)^{0.831} - 0.496 * \left(\frac{CVPAC}{96}\right)$$

The Sponsor's modeling approach utilized CL/F estimates to calculate C_{avss} as follows:

$$C_{AVSS} = \frac{Amt/12}{Cl/F}$$

Where 2 x Amt is equal to total daily dose.

Sponsor investigated potential for CL/F covariates using forward addition. *Univariate* addition of the concentration of valproic acid (CVPAC), use of carbamazepine (CBZ), use of phenytoin (PHT), and total rufinamide daily dose (DDOS) as covariates resulted in statistically significant decreases in the objective function.

Figure 8: Base PK Model Box Plot of Eta for CL/F By Valproic Acid Use (Categorical)

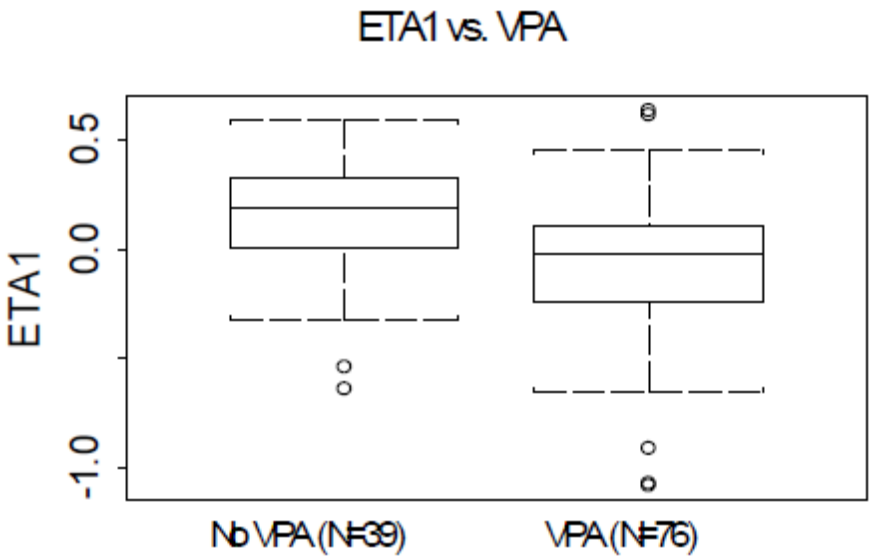


Figure 9: Base PK Model Box Plot of Eta for CL/F By Valproic Acid Concentration (Continuous)

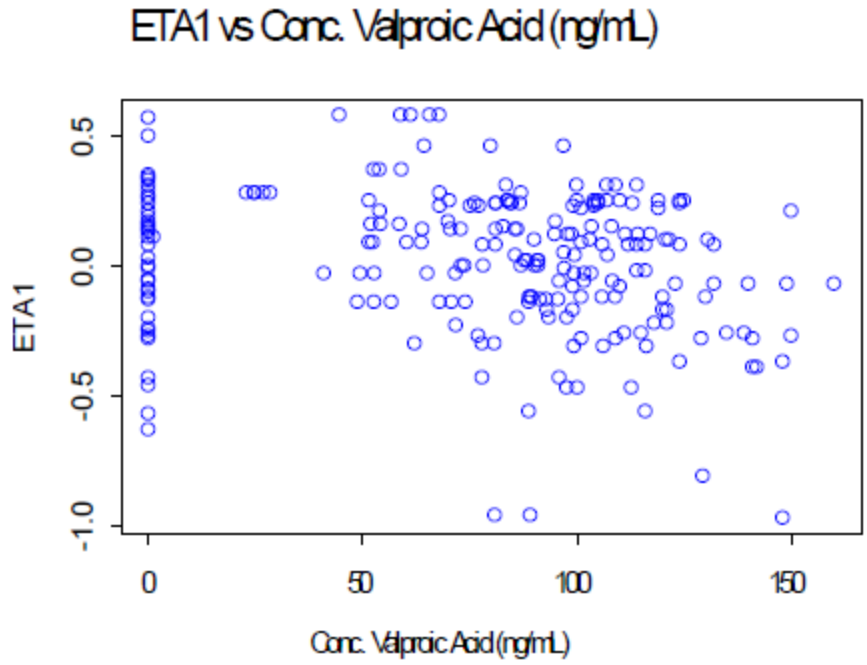


Figure 10: Base PK Model Box Plot of Eta for CL/F By Carbamazepine Use (Categorical)

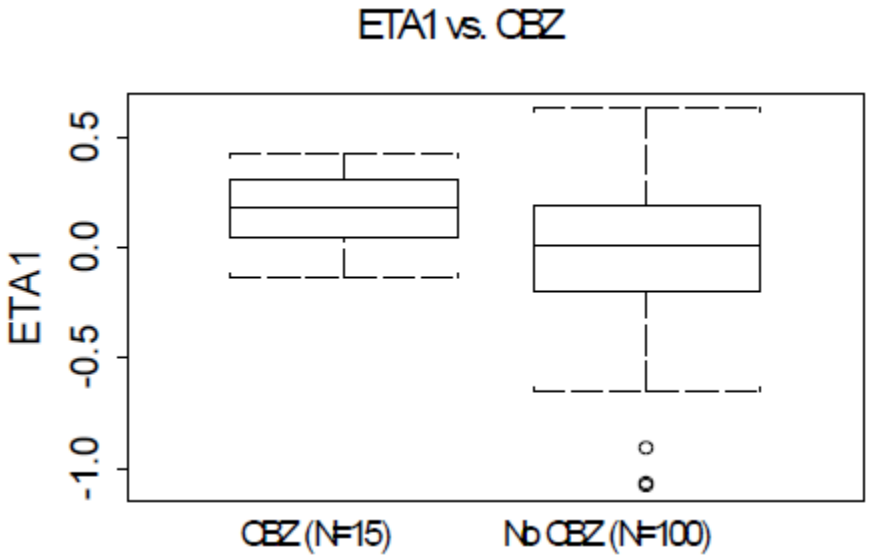


Figure 11: Base PK Model Box Plot of Eta for CL/F By Phenytoin Use (Categorical)

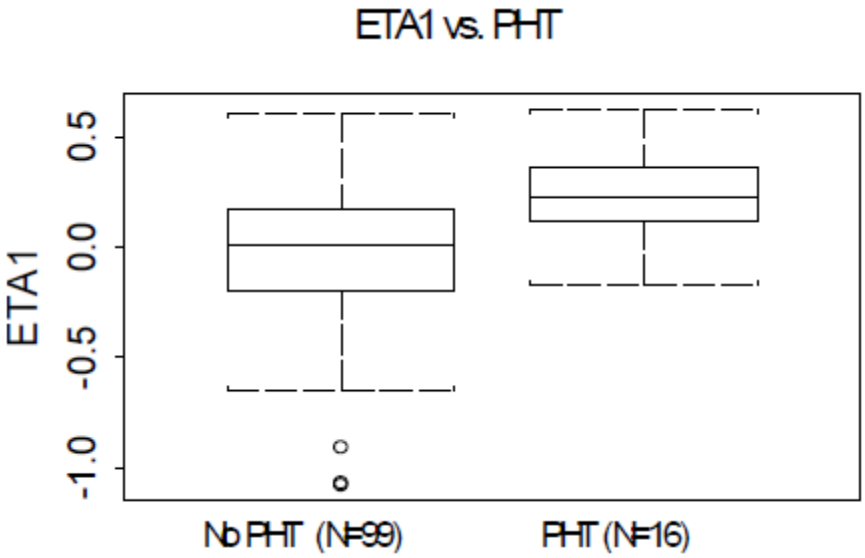


Figure 12: Base PK Model Box Plot of Eta for CL/F By Age Group (Categorical)

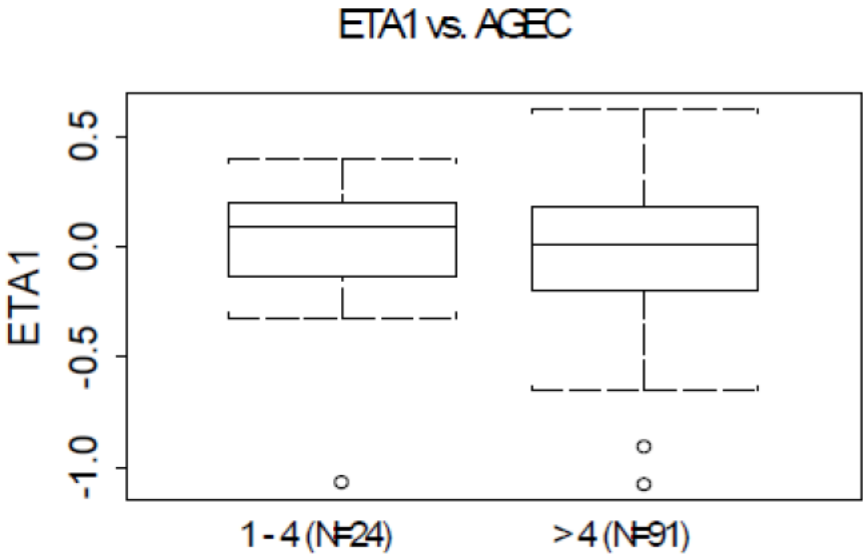


Figure 13: Base PK Model Scatter Plot of Eta for CL/F By Age (Continuous)

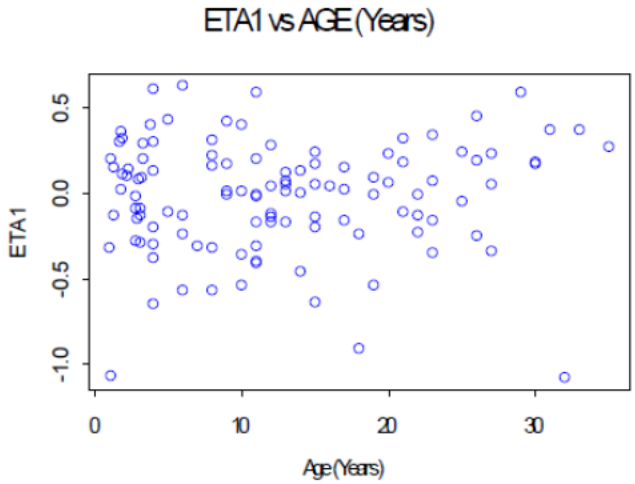
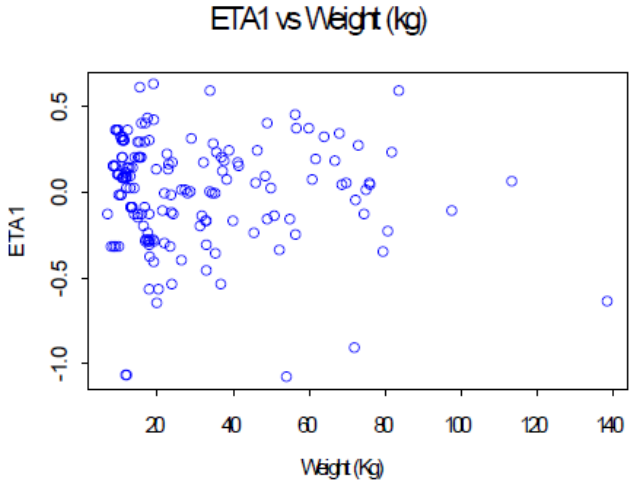


Figure 14: Base PK Model Scatter Plot of Eta for CL/F By Weight (Continuous)



Based on the forward addition results, the Sponsor combined WGT, CBZ, PHT, DDOS, and CVPAC as covariates on CL/F in the "full PK model". Sponsor utilized backward deletion at the 0.001 significance level (corresponding to an *increase* in the objective function of at least 10.828 when the covariate is removed) to further assess the inclusion of covariates in the full model. As a result, Sponsor removed total rufinamide daily dose in mg (DDOS), concomitant use of carbamazepine, and concomitant use of phenytoin as these covariates were no longer statistically significant when combined in the full model. The final model utilized weight and valproic acid concentration as covariates on CL/F.

Pharmacokinetic parameter estimates from the final population PK model are summarized in the following table.

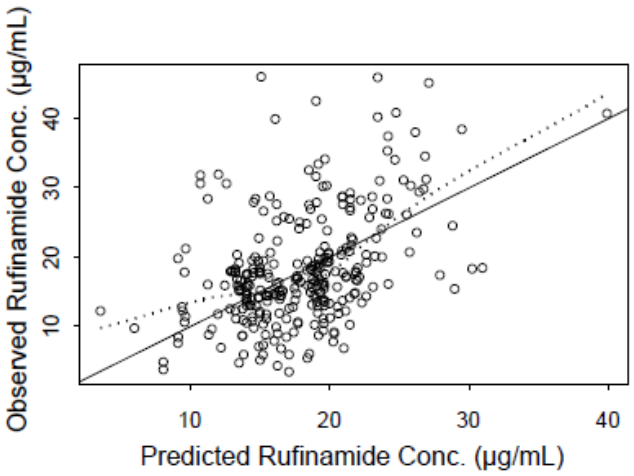
Table 8: Sponsor's Final Population PK Parameters Estimates for Rufinamide

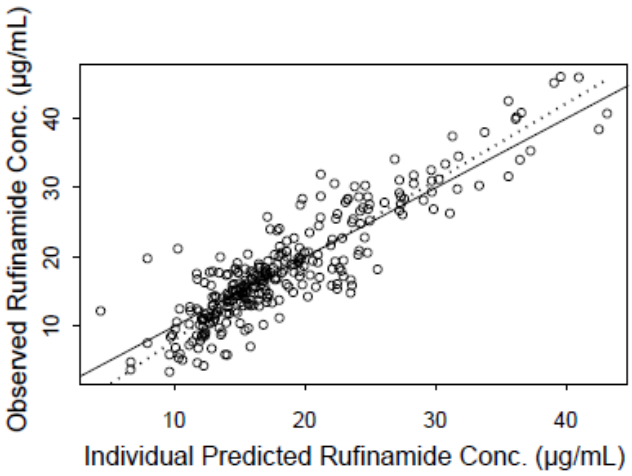
Parameter [Units]	Point Estimate	%RSE	95% CI
$CL = \Theta_{CL} * (WGT/18.1)^{\Theta WGT} + (\Theta_{CVPAC}/96) * CVPAC$			
Basal CL/F in L/h (Θ_{CL})	2.19	5.75	1.94 – 2.44
Exponent of weight effect on CL/F (Θ_{WGT})	0.831	7.77	0.704 – 0.958
Slope for effect of valproic acid on CL/F (Θ_{CVPAC})	- 0.496	21.4	-0.704 – -0.288
Inter-individual variability (%CV)			
CL/F	33.3	19.5	
Residual variability (µg/mL, SD)			
Additive (SD)	4.31	11.7	

*Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CI = confidence interval. CL/F = apparent clearance; WGT = body weights (kg); CVPAC = plasma concentration of valproic acid; %CV = percent coefficient of variation; SD = standard deviation; 18.1kg is median body weight; 96.1 ng/mL is median valproic acid concentration.*

The following diagnostic plots and visual predictive check were generated using the final population PK model.

Figure 15: Diagnostic Plots for the Final Population PK Model





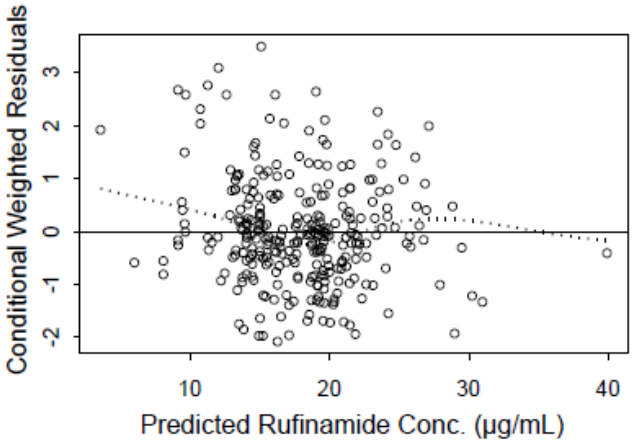
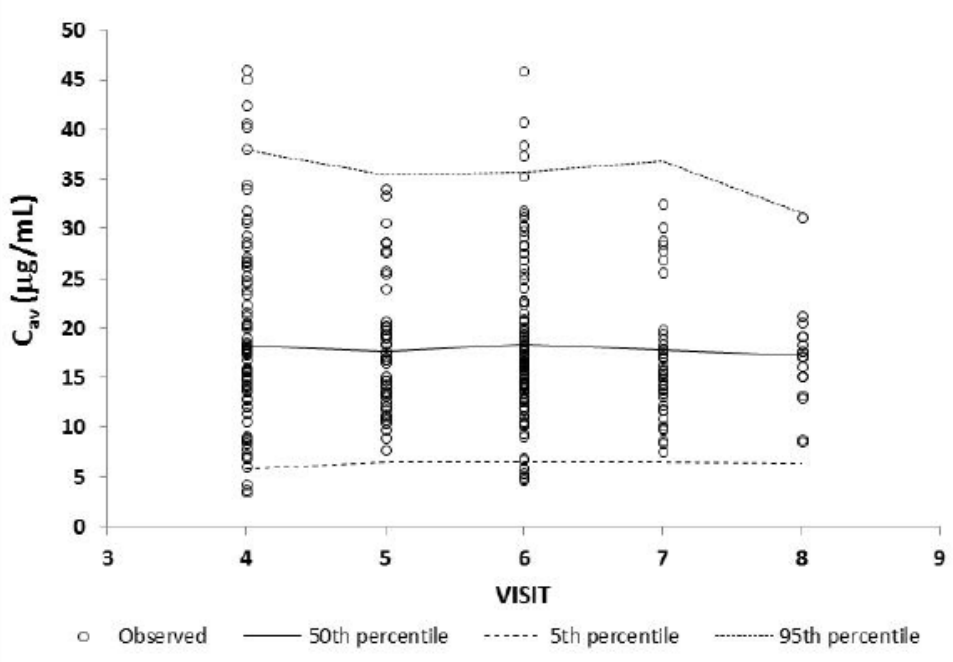


Figure 16: Visual Predictive Check of Rufinamide Average Concentrations



The Sponsor's model-building procedure and final model selection are acceptable.

4.1.2 Is there an Exposure-Response Relationship for the Child Behavior Check List Sub item Scales?

Sponsor performed assessments of Child Behavior Check List (CBCL) in an attempt to assess the effects of rufinamide use on cognition. The CBCL assessments included Emotionally Reactive, Anxious/Depression, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive behavior. Sponsor conducted CBCL assessments at visit 8/week 24, visit 10/week 56, visit 12/week 88 and visit 12/week 106.

Sponsor conducted a graphical assessment of the relationship between CBCL component scores with rufinamide concentrations stratified by valproic acid use (see the figures below).

Figure 17: % Change from Baseline In CBCL Components Versus Rufinamide Average Concentration

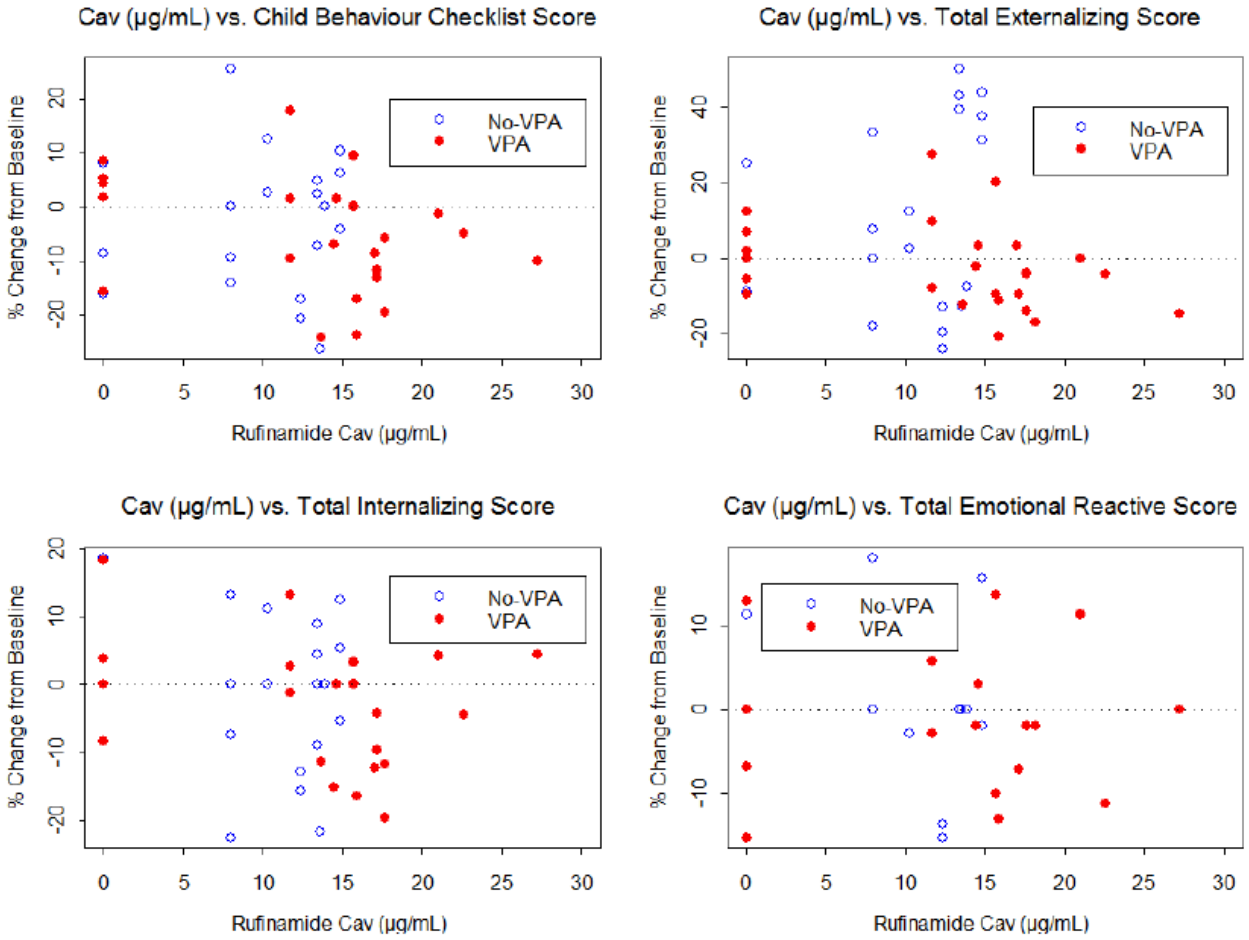
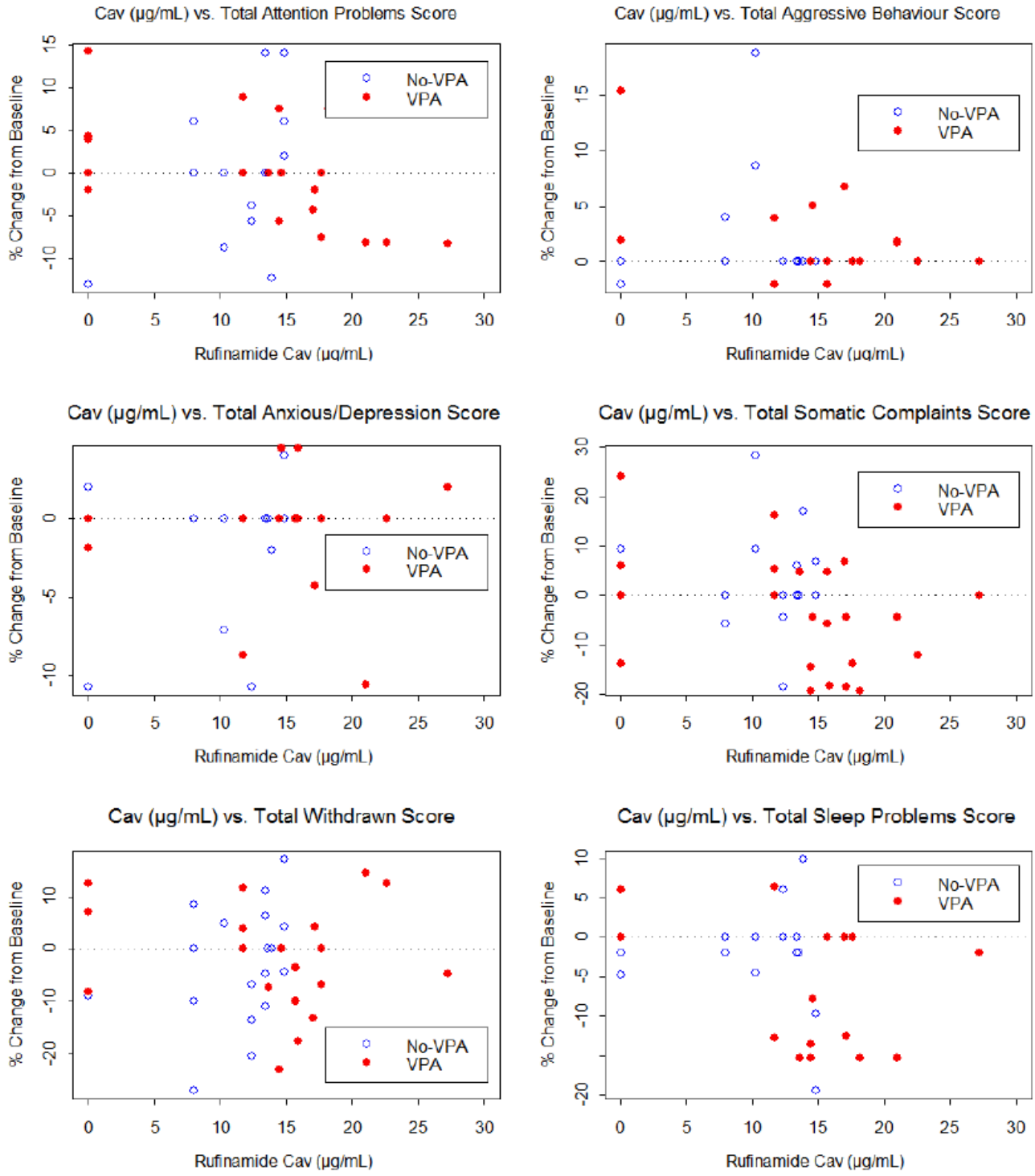


Figure 18: % Change from Baseline In CBCL Components Versus Rufinamide Average Concentration (Continued)



Sponsor concludes that in general, no clear relationship between increasing rufinamide C_{av} and any CBCL scores % change from baseline at visits 8, 10, 12, or 13 could be observed.

The plots above do not suggest a relationship between rufinamide concentration and any component of the CBCL survey.

4.2 Individual Study Review

4.2.1 E2080-G000-303: PK, Safety, and Cognitive Development effects of Adjunctive Rufinamide in LGS Patients 1 ≤ age < 4 years

Study Report#	*E2080-G000-303*
Title	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
Objectives	Primary: • Safety and tolerability • Age-group specific PK • Cognitive development and behavioral effects Exploratory: • Effects on language development • Effect on quality of life • Efficacy (seizure reduction) • Characterize relationship of average exposure and most frequent adverse event
Study Design	Randomized, controlled, parallel, open-label study
PK Assessment	PK samples were collected at Weeks 2, 4, 8, 16, and 24 (visits 4, 5, 6, 7, and 8), and at early discontinuation in study 303. Samples acquired during Weeks 2, 8, and 24 (visits 4, 6, and 8) are collected during the morning visit. Samples acquired during Weeks 4 and 16 (visits 5 and 7) are collected during an afternoon visit to the clinic.
Statistical Analysis	Sponsor conducted a population PK analysis. See Report CPMS-E2080-002R-v1 for details.
Bioanalytical Methods	HPLC-MS/MS (method AM-034-R1) Sample Volume: 50 µL Analyte: Rufinamide Internal standard (IS): (b) (4) Limit of quantitation: 20 ng/mL Average recovery of drug (%): Not reported Average recovery of IS (%); Not reported Standard curve concentration: 20 40 100 500 5000 10,000 15,000 20,000 ng/mL Standards accuracy range (%): -8.5 to 8.2% Standards precision range (%): 1.6 to 3.8 % QC range: 50 500 4000 14,000 100,000 ng/mL QC precision range (%): 3.1 to 12.4% QC accuracy range (%): -9.3 to 1.8% *Method AM-034-R1 (applied in pediatric study 303) utilizes a sample volume of 50 µL. Method AM-034-R0 (applied in the adult study 304 conducted in Japan) utilizes a sample volume of 200 µL. The assay is considered acceptable. See section 2.6 for details regarding method AM-034-R0.*
Population/ Demographics	N=36 LGS patients, 1 ≤ age < 4 years of age, on a fixed and documented dose of 1 to 3 regionally approved concomitant AEDs for a minimum of 4 weeks prior to randomization. There were 25 subjects in the rufinamide arm and 11

	subjects in the any-other-AED arm. The original plan was for n=75 subjects (50 subjects rufinamide, 25 subjects any-other-AED). As per the amended FDA WR (February 26th, 2014), the number was revised to allow a minimum of 21 rufinamide-treated subjects.
PK Results	The Sponsor submitted a separate report detailing the population pharmacokinetics of rufinamide. Briefly, the Sponsor reports that PK of rufinamide was not significantly affected by age either as a continuous covariate (1 to 35 years) or as a categorical covariate (age categories: 1 ≤ age < 4 years, ≥ 4 years) after factoring in body weight. Co-administration of valproic acid decreased rufinamide clearance in a concentration dependent manner. See the ISR for CPMS-E2080-002R-v1 for details.
Safety	The overall incidence of TEAEs was 88% (22 of 25 subjects) in the rufinamide group and 82% (9 of 11 subjects, 82%) in the any-other-AED group. The most common treatment-emergent adverse events (TEAEs) that occurred at a frequency ≥ 10% of the subjects were vomiting (24%), upper respiratory tract infection (20%), diarrhea and somnolence (both 16%) , as well as constipation, cough, bronchitis, rash, and decreased appetite (12.0% each). The TEAEs of special interest were weight loss (2 subjects), skin reactions (5 subjects), somnolence (4 subjects), and fatigue (1 subject).
Sponsor's Conclusions	Safety and efficacy in patients randomized to receive rufinamide were comparable to the patients randomized to receive add-on of any-other-AED arm. PK was dose-independent and not significant affected by age as a continuous or categorical covariate after factoring in body weight. Concomitant valproic acid decreases rufinamide clearance in a concentration-dependent manner (similar to that observed in subjects 4 years and above).
Reviewer Comment	*The PK is not dependent on dose over the dose range utilized in study 303. The use of body weight as a covariate (rather than age) is acceptable. The Sponsor's assessment of the effect of VPA on rufinamide PK is acceptable.* *Please refer to the clinical review by Dr. Steven Dinsmore for details regarding safety.*

4.2.2 Population Analysis Report (from Studies 303, 304, 0022)

Study Report #	CPMS-E2080-002R-v1
Title	Population Pharmacokinetics of Rufinamide in Subjects With Inadequately Controlled Lennox-Gastaut Syndrome (Studies E2080-G000-303, CRUF331 0022 and E2080-J081-304)
Objectives	Primary • Characterize rufinamide PK in LGS subjects and compare exposure in subjects ≥ 4 years old to exposure in subjects 1 ≤ age < 4 years by testing age as a continuous and categorical covariate • Identify intrinsic and extrinsic factors that explain between subject variability in rufinamide PK Exploratory objectives for study 303 data • Graphical exploration of the relationship between Cav and most frequent AEs • Graphical exploration of the relationship between Cav and cognitive development as well as behavioral effects
Study Design	Study 303 (n=24 with PK): Multicenter, Randomized, Controlled, Open-Label study of efficacy, safety, and PK in LGS patients age 1 to < 4 years Study 304 (n=26 with PK): A placebo-controlled, double-blind comparative efficacy study of E2080 in LGS Patients age 4 to 30 years Study CRUF331 0022 (n=65 with PK): Multicenter, randomized, double-blind, placebo controlled, parallel study of efficacy, safety, and PK study of adjunctive rufinamide in LGS patients age 4 to 30 years
PK Assessment	Study 303 (n=24): Sparse PK were collected during the Maintenance: *Visits 4, 6 and 8*: one sample during a morning visit to the clinic during Weeks 2, 8 and 24 *Visits 5 and 7*: one sample during an afternoon visit to the clinic during Weeks 4 and 16 Study 304 (n=26): One sparse PK sample per visit was collected at any time on Days 28, 56, and 84 of treatment during the maintenance period, or when a patient was terminated form the trial. Study 022 (n=65): One sparse PK sample per visit was collected at any time during visits 4 and 6 (i.e., after 28 and 84 days of treatment, respectively) or when a patient was terminated from the trial.
Statistical Analysis	Sponsor utilized the non-linear mixed effects approach using the NONMEM version 7.2 software package to model the population pharmacokinetics. Due to the Sparse nature of the PK data, a constant rate infusion model parameterized in terms of clearance (CL/F) was utilized to describe the concentration versus time profile of rufinamide. Univariate forward addition of covariates on CL/F was applied to identify candidate CL/F covariates for a "full PK model". Backwards deletion of covariates in the "full PK model" was conducted to determine which of the CL/F covariates in the "full PK model" should remain in the final model.
Bioanalytical Methods: Study 303	The assay method AM-034-R1 was utilized in study 303. Please see section 2.6.1.3 for details. *The assay is considered acceptable.*
Bioanalytical Methods: Study 304	LC-MS/MS (method AM-034-R0) Sample Volume: 200 µL Analyte: Rufinamide

<table>
<tr><td></td><td>Internal standard (IS) : [redacted] (b) (4)
Limit of quantitation: 20 ng/mL
Average recovery of drug (%): 82.9 – 92.4 %
Average recovery of IS (%); 88%
Standard curve concentration (ng/ml) :
20 40 100 500 5000 5,000 10,000 15,000 20,000 ng/mL
Standards accuracy range (%): 92.7 to 107.2 %
Standards precision range (%): 2.7 to 8.6 %
QC range: 50 500 4000 14,000 100,000 ng/mL
QC accuracy range (%): 91.8 to 107.1%
QC precision range (%): 4.2 to 6.7%
The assay is considered acceptable.</td></tr>
<tr><td>Bioanalytical Methods: Study 0022</td><td>The rufinamide assay utilized in study 022 was deemed acceptable by the Office of Clinical Pharmacology in the review of NDA 021911 by Dr. Veneeta Tandon (dated 09/11/2006). The LLOQ of the rufinamide assay in study 0022 ranged from 0.20 to 1.00 µg/mL (200 to 1000 ng/mL), which over 10-folder greater than the LLOQ for methods utilized in studies 304 and 303 (20 ng/mL).

The lowest PK data point from study 0022 (3.44 µg/mL) utilized in the population PK analyses is 3 times greater than the highest estimate of LLOQ in study 0022. Though the LLOQ in study 0022 is higher than the other two studies, the PK data from study 0022 are considered reliable for inclusion in the population PK analyses.
Though the LLOQ for the assay utilized in study 0022 is different from the LLOQ for the assays utilized in studies 303 and 304, this difference is not expected to significantly alter the population PK analysis results. Due to the sparse sampling schedule and the sample size, inclusion of a separate residual variability term (e.g. a separate epsilon in NONMEM terminology) based on the assay used in study 0022 does not appear reasonable. As such, it is acceptable to combine the PK data from study 0022, 303, and 304 and utilize a single residual variability term for all subjects in the NONMEM model.</td></tr>
<tr><td>Population/ Demographics</td><td>
<table>
<tr><th>Covariate (unit)</th><th>Mean (SD)</th><th>Median</th><th>Range (Min-Max)</th></tr>
<tr><td>Dose (mg per day)</td><td>1315 (845)</td><td>1000</td><td>160 - 4400</td></tr>
<tr><td>Age (years)</td><td>12.6 (8.8)</td><td>11</td><td>1 - 35</td></tr>
<tr><td>Weight (kg)</td><td>28.8 (23.2)</td><td>18.1</td><td>7 – 138.5</td></tr>
<tr><td>Alkaline phosphatase (U/L)</td><td>318.2 (227.2)</td><td>229</td><td>103 - 1828</td></tr>
<tr><td>Bilirubin (U/L)</td><td>0.3 (0.1)</td><td>0.3</td><td>0.1 – 1.0</td></tr>
<tr><td>Creatinine Clearance (mL/min)*</td><td>68.7 (41.5)</td><td>53.4</td><td>23.3 – 289.7</td></tr>
<tr><td>Age (categorical)</td><td colspan="3">1 to < 4 years = 24; ≥ 4 years = 91</td></tr>
<tr><td>Sex</td><td colspan="3">Females=47; Males=68</td></tr>
<tr><td>Race</td><td colspan="3">Caucasian=75; Non-Caucasian=40</td></tr>
<tr><td colspan="4">*Creatinine clearance was capped at 150 mL/min as a reasonable value.</td></tr>
</table>
</td></tr>
</table>

Results

Final population PK model estimated population clearance with covariates of weight and concentration of concomitant valproic acid on CL/F.

$$\frac{CL}{F}(L/h) = 2.19 * \left(\frac{WGT}{18.1}\right)^{0.831} - 0.496 * \left(\frac{CVPAC}{96}\right)$$

$$C_{AVSS} = \frac{Amt/12}{Cl/F}$$

Where 2 x Amt is equal to total daily dose.

Inter-individual variability was estimated for CL/F. Residual variability was additive.

NONMEM Estimates			
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**
$CL = \Theta_{CL} * (WGT/18.1)^{\Theta WGT} + (\Theta_{CVPAC}/96) * CVPAC$			
Basal CL/F in L/h (Θ_{CL})	2.19	5.75	1.94 – 2.44
Exponent of weight effect on CL/F (Θ_{WGT})	0.831	7.77	0.704 – 0.958
Slope for effect of valproic acid on CL/F (Θ_{CVPAC})	- 0.496	21.4	-0.704 – -0.288
Inter-individual variability (%CV)			
CL/F	33.3	19.5	
Residual variability (µg/mL, SD)			
Additive (SD)	4.31	11.7	

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CI = confidence interval. CL/F = apparent clearance; WGT = body weight (kg); CVPAC = plasma concentration of valproic acid; %CV = percent coefficient of variation; SD = standard deviation; 18.1 is median body weight and 96 in median valproic acid concentration in ng/mL.

Conclusions

- Rufinamide PK was described by a constant input model parameterized for CL/F
- CL/F increased with body weight as a power function.
- Rufinamide PK was independent of dose and was not significantly affected by age as a continuous or categorical covariate after body weight was taken into consideration.
- Rufinamide was not affected by sex, race (Caucasian vs. non-Caucasian), ALP levels of 103 to 1828 IU/L, BILI levels from 0.1 to 1.0 mg/dL, or CRCL from 23.3 to 298.7 mL/min.
- Rufinamide CL/F decreased as VPA concentration increased in a manner comparable to subjects age 4 years and above. There is no need for a dose adjustment for concomitant use of lamotrigine, carbamazepine, or phenytoin.
- No further dose adjustment is required based on age (after body weight is taken into consideration), and no further dose adjustment is required for patients age 1 to < 4 years.

Comment

The Sponsor's model-building procedure and final model selection are acceptable. The titration procedure for pediatric patients age 4 years and older in the approved label is appropriate for pediatric patients age 1 to < 4 years.

4.3 OCP Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	201,367-0041	Brand Name	Banzel
OCP Division (I, II, III)	DCP-I	Generic Name	Rufinamide
Medical Division	DNP	Drug Class	Triazole derivative
OCP Reviewer	Michael Bewernitz, Ph.D.	Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in children 1 year and older and adults
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Liquid suspension
Pharmacometrics Team Leader	Kevin Krudys, Ph.D.		
Date of Submission	08/12/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	01/19/2015	Sponsor	Eisai, Inc.
Division Due Date	01/26/2015	Priority Classification	S
PDUFA Due Date	02/12/2015		

Clin. Pharm. and Biopharm. Information

This is efficacy supplement for Banzel (rufinamide liquid suspension for oral administration) was submitted under section 505(b)(1) of the FFDCA. The proposed indication is "Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in children 1 year and older and adults". Banzel liquid suspension has received Orphan Drug Designation for this indication (#14-1935). Banzel was originally approved (NDA 021911) on November 14th 2008 (as oral tablets 200 mg, 400mg)

Sponsor submitted results from an on-going phase 3 trial and a population PK report to support approval.

Phase 3 Studies

E2007-G000-303 (PK and Safety Study, n=36): This study is titled "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".

Reports of PK Analyses

CPMS-E2080-002R-v1 (Population PK Report): This report contains results from population PK analyses of combined PK data from Study 303, Study 022, and Study 304 (as was requested in the WR). Exposures in patients ≥ 4 years are compared to exposures in patients 1 < age <4 years. In addition, age has also been included as a continuous covariate (as was described in the WR).

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Annotated and clean versions of the label are included.
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				
single dose:	-			
multiple dose:	-			
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	-			
fasting / non-fasting multiple dose:	-			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			Effects of concomitant medications are addressed in the population PK analyses

In-vitro:	-			
Subpopulation studies -				Various demographic attributes were assessed in the population PK analyses
ethnicity:				
gender:	-			
pediatrics:	-			
geriatrics:	-			
Renal impairment:	-			
Hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -	-			
solution as reference:	-			
alternate formulation as reference:	-			
Bioequivalence studies -	-			
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:				
Dissolution:	-			
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			

Pediatric development plan	-			
Literature References	-			
Total Number of Studies		2		- 1 PK (Phase-3) - 1 PK analysis report

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	-	
QBR questions (key issues to be considered)	1. Have the analytical methods been sufficiently validated? 2. Are the dose and dose regimen acceptable? 3. Are the label statements acceptable?	
Other comments or information not included above	---	
Primary reviewer Signature and Date	Michael Bewernitz	
Secondary reviewer Signature and Date	Angela Yuxin Men , Kevin Krudys	

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have	X			

	appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Sponsor conducted graphical exposure-response analyses for multiple items in the Child Behavior Check List
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan status was granted (#14-1935).
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

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

/s/

MICHAEL A BEWERNITZ
01/29/2015

KEVIN M KRUDYS
01/30/2015

YUXIN MEN
02/03/2015