Exposure–Response Analysis of Eslicarbazepine Acetate as Adjunctive Treatment of Patients With Partial-onset Seizures

Jahnavi Kharidia[1]; Julie Passarell[2]; Gary Maier[1], Jacqueline Zummo[1]; Elizabeth Ludwig[2], Ted Grasela[2], Jill Fiedler-Kelly[2]
[1]Sunovion Pharmaceuticals Inc, Marlborough, MA; [2]Cognigen Corporation, Buffalo, NY

Introduction

- Eslicarbazepine acetate (ESL) is a novel once-daily (QD) antiepileptic drug (AED) currently under clinical development in the US.[1]
- ESL is rapidly and extensively metabolized to its major active metabolite, eslicarbazepine, which blocks voltage-gated sodium channels.[1]
- In two phase 3 studies (Study -301 and -302) of patients with partial-onset seizures treated with 1 to 3 concomitant AEDs,[2,3] ESL 800 mg and 1200 mg QD was well tolerated and more effective than placebo.[2,3] Long-term safety was demonstrated in open-label extensions of these studies.[4]
- Examination of exposure-response relationships using efficacy endpoint data from these clinical trials, in conjunction with drug exposure measures generated from a previously developed population pharmacokinetic (PK) model, supported dose selection for ESL in the treatment of partial-onset seizures.
- Drug exposure measures were generated from a population PK model developed previously using the eslicarbazepine analyte concentrations.

Objective

- Develop pharmacokinetic/pharmacodynamic (PK/PD) models to explore the exposure-response relationships between patient-specific measures of eslicarbazepine exposure and seizure frequency, as well as responder rate.

Methods

Study Design and Data

- Data were pooled from adult patients enrolled in 2 multi-center, randomized, placebo-controlled Phase 3 studies of ESL as adjunct therapy for partial-onset seizures.
- Each study included an 8-week baseline period during which all patients received placebo. The baseline period was followed by a double-blind 2-week titration period and a 12-week maintenance treatment period. In one study there was a 4-week tapering-off period (Study -301). At the end of the baseline period, patients were randomly assigned to 1 of the 4 treatment groups: ESL 1200 mg QD, 800 mg QD, 400 mg QD, or placebo QD.
- Pertinent entry criteria: adult males and females with simple and complex partial seizures (with or without secondary generalization) for at least 12 months before screening who were receiving up to 3 concomitant AEDs in a stable dose regimen for at least 2 months before screening, and had at least 4 partial-onset seizures during each of the 4-week periods of the 8-week baseline period.
- The primary efficacy endpoint was seizure frequency, standardized to a frequency per 4 weeks. A secondary endpoint was responder rate (defined as ≥50% reduction in seizure frequency per 4-weeks from baseline during the maintenance period).
- Patients recorded all seizures by date and time of occurrence, and seizure type during the baseline and double-blind treatment phases in a written diary (with or without assistance). The frequency and types of seizures were determined based on the entries in these diaries.

Data Analysis

- Data preparation was performed using SAS, Version 9.1.3;[5] the population PK/PD analyses were performed using NONMEM, Version V, Level 1.1.[6] Both FO and FOCE estimation methods were used for the seizure frequency model development, and the laplacian estimation method was used for the responder rate model.
- Individual-predicted estimates of steady-state average eslicarbazepine concentration ($C_{av\text{-}ss}$) obtained using a previously developed population PK model were used in the exposure-response analyses.
- Seizure frequency data were log transformed (ln) prior to analysis. Because some patients experienced no seizures during the maintenance period, the seizure frequency was increased by 4 for all patients included in the analysis prior to transformation.
- Covariates evaluated were baseline weight, sex, and seizure frequency. Assessment was performed using forward selection with α=0.01.

Seizure Frequency Model Development

- The base structural model to predict seizure frequency was a function of a baseline (intercept), a placebo effect, and eslicarbazepine exposure (evaluated using linear, log-linear, and saturable (E_{max} model)) effects.
- Estimation of between-patient (inter individual) variability (IIV) in selected model parameters and within-patient (residual) variability (RV) in seizure frequencies was also included in the base structural model.
- Goodness-of-fit was assessed using scatter plots of measured versus predicted seizure frequency (derived as above) and weighted residuals versus the predicted seizure frequency (derived as above), %SEM of the parameter estimates, and changes in the estimates of IIV and RV.

Responder Rate Model Development

- Logistic regression analysis was used to describe the responder rate as the sum of a placebo effect and the effect of eslicarbazepine, which could be described by various functions (i.e., linear, saturable [E_{max} model]).
- The responder rate for a given patient and for a specified predicted ESL concentration was obtained using the equations in **Figure 1**.
- IIV and RV could not be estimated since each patient contributed only 1 value to define responder status.
- Since typical residual plots were not appropriate in this situation, the percentage of responders relative to the predicted steady-state average eslicarbazepine concentration was evaluated graphically.

Figure 1. Equations Used to Obtain Responder Rate

$$P(Y=1)=\frac{e^{Logit}}{\left(1+e^{Logit}\right)}$$

$$P(Y=0)=1-\left[\frac{e^{Logit}}{\left(1+e^{Logit}\right)}\right]$$

Results

Data Description

- 628 subjects and 1253 standardized seizure frequency measures were included in the analyses. The median subject age was 36.4 years, and median baseline seizure frequency was 7.6 seizures/28 days. Demographic characteristics are shown in **Table 1**.
- Summary statistics for eslicarbazepine $C_{av\text{-}ss}$ and for seizure frequency during the baseline and maintenance periods are shown in **Table 2**.

Table 1. Baseline Demographic Characteristics

Patient Characteristic		Study -301	Study -302	Pooled Data
Age (y)	Median	37.7	35.0	36.4
	Minimum, Maximum	18.0, 75.6	18.0, 69.3	18.0, 75.6
	n	322	306	628
Baseline standardized seizures (n/28 days)	Median	7.132	8.351	7.566
	Minimum, Maximum	2.00, 153.48	2.00, 87.93	2.00, 153.48
	n	322	306	628
Weight (kg)	Median	70.0	69.0	70.0
	Minimum, Maximum	40, 130	38, 138	38, 138
	n	322	306	628
Race, n (%)	Caucasian	322 (100)	270 (88.2)	592 (94.3)
	Black	0	17 (5.6)	17 (2.7)
	Asian	0	5 (1.6)	5 (0.8)
	Hispanic	0	14 (4.6)	14 (2.2)
Sex, n (%)	Male	169 (52.5)	163 (53.3)	332 (52.9)
	Female	153 (47.5)	143 (46.7)	296 (47.1)
Randomized treatment dose, n (%)	Placebo	102 (31.7)	99 (32.4)	201 (32.0)
	400 mg	78 (24.2)	70 (22.9)	148 (23.6)
	800 mg	76 (23.6)	76 (24.8)	152 (24.2)
	1200 mg	66 (20.5)	61 (19.9)	127 (20.2)

Table 2. Eslicarbazepine Steady-State Average Concentration ($C_{av\text{-}ss}$), and Seizure Frequencies During the Baseline and Maintenance Periods (Pooled Data)

		ESL QD Dose			
		Placebo (n=201)	400 mg (n=148)	800 mg (n=152)	1200 mg (n=127)
$C_{av\text{-}ss}$ (ng/mL)	Mean SD	0	3775.168 1604.141	7821.357 2567.008	12954.992 5375.058
	Median	0	3335.770	7340.821	11664.256
	Minimum, Maximum	0, 0	1636.07, 10222.44	2240.75, 18373.57	6572.55, 42992.26
Seizures per 28 days in baseline period[a]	Mean SD	12.592 15.697	12.288 10.364	13.650 14.069	13.618 16.867
	Median	6.877	8.073	7.368	8.145
	Minimum, Maximum	2.00, 153.48	2.50, 55.50	3.00, 78.69	2.00, 141.53
Seizures per 28 days in maintenance period[a]	Mean SD	12.016 16.165	9.622 9.998	9.924 15.018	9.365 15.004
	Median	6.959	5.929	5.228	4.667
	Minimum, Maximum	0, 122.33	0, 55.34	0, 144.31	0, 141.01
Natural log of seizures per 28 days + 4 in maintenance period	Mean SD	2.512 0.653	2.431 0.562	2.373 0.645	2.322 0.660
	Median	2.394	2.296	2.222	2.159
	Minimum, Maximum	1.39, 4.84	1.39, 4.08	1.39, 5.00	1.39, 4.98

[a]Fractional minimum and maximum values resulted when standardized per 4 weeks.

Seizure Frequency Model

- The final model (**Figure 2**) for the ln seizure frequency was the sum of a baseline seizure frequency, a constant placebo effect, and an eslicarbazepine drug effect that was best described by an E_{max} function of the predicted $C_{av\text{-}ss}$.
- All parameters in the final model were estimated precisely (%SEM <50%) with the exception of residual variability as shown in **Table 3**.
- E_{max} was related to baseline seizure frequency; a larger maximum effect is expected with higher baseline seizure frequencies.
- Additive IIV was estimated on baseline seizure frequency and the placebo effect, and proportional IIV was estimated on E_{max}. RV was modeled using an additive error model.
- Diagnostic plots (**Figure 3**) show reasonable goodness-of-fit.
- For patients receiving placebo, the predicted seizure frequency was 8.7 seizures/28 days.
- Based on the model, seizure frequencies per 28 days for the median $C_{av\text{-}ss}$ associated with QD ESL doses of 400 mg, 800 mg, and 1200 mg were: 7.3, 6.7, and 6.6, respectively.
- The shallow nature of the relationship between dose-related eslicarbazepine $C_{av\text{-}ss}$ and seizure frequency is shown in **Figure 4**.

Figure 2. Final Model for Seizure Frequency

$$\ln(\text{std SF}+4)_j = 2.64 - 0.0971 \times plac_j + \left(\eta - plac_j\right) \times \left[\frac{-0.337 \times \left(\frac{\ln\left(\eta_{seiz_j}\right)}{2.45}\right) \times C_{av\text{-}ss_j}}{1970 + C_{av\text{-}ss_j}}\right]$$

Where:

$plac_j$ = an indicator variable for treatment with placebo (1 = yes, 0 = no) in the jth patient

$C_{av\text{-}ss_j}$ = steady-state average ESL concentration in the jth patient

$\ln\left(\eta_{seiz_j}\right)$ = natural log of the baseline standardized seizure frequency in the jth patient

Table 3. Parameter Estimates From the Final Seizure Frequency Model

	Final Parameter Estimate		Magnitude of Interindividual Variability	
Parameter	Population Mean	%SEM	Final Estimate	%SEM
Baseline standardized seizures (N)	2.64	0.8	0.297[a]	7.7
Constant placebo effect	-0.0971	29.8	0.144[b]	18.1
E_{max} at the baseline standardized SF of 2.4	-0.337	12.3	1.52[c]	18.8
EC50 (ng/mL)	1970	43.6	NE	NA
Additive RV	0.0104[d]	66.6	NA	NA
Minimum value of the objective function = -712.517				

Abbreviations: EC50, value of ESL $C_{av\text{-}ss}$ leading to 50% of the maximum change in ln (standardized SF +4); E_{max}, maximum change in the ln (standardized SF +4) due to $C_{av\text{-}ss}$; NA, not applicable; NE, not estimated; RV, residual variability; %SEM, percent standard error of the mean.
[a]This estimate (0.297) is a variance term. The corresponding SD = 0.54 ln (standardized SF +4).
[b]This estimate (0.144) is a variance term. The corresponding SD = 0.38 ln (standardized SF +4).
[c]This estimate (1.52) is a variance term. The corresponding %CV = 123.29%.
[d]This estimate (0.0104) is a variance term. The corresponding SD = 0.10 ln (standardized SF +4).

Figure 3. Goodness-of-Fit Plots for the Seizure Frequency Model

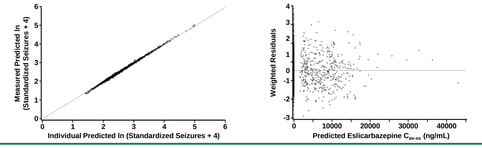
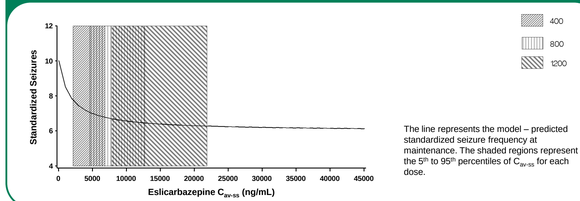


Figure 4. Relationship Between Predicted Standardized Seizure Frequency and Eslicarbazepine $C_{av\text{-}ss}$



The line represents the model – predicted standardized seizure frequency at maintenance. The shaded regions represent the 5th to 95th percentiles of $C_{av\text{-}ss}$ for each dose.

- The logit model for responder rate is the sum of an effect of placebo and the eslicarbazepine effect described by a linear function of the eslicarbazepine $C_{av\text{-}ss}$ as shown in **Figure 5**.
- All model parameters were estimated with good precision (%SEM ≤40%) as shown in **Table 4**.
- Eslicarbazepine $C_{av\text{-}ss}$ was shown to be statistically significantly related to the responder rate, with increasing likelihood of response as eslicarbazepine $C_{av\text{-}ss}$ increases.
- For patients receiving placebo, the predicted responder rate (probability of response) was of 0.19.
- Based on the model, the predicted responder rates (probability of response) for patients with the median eslicarbazepine $C_{av\text{-}ss}$ associated with QD ESL doses of 400 mg, 800 mg, and 1200 mg were 0.28, 0.33, and 0.38, respectively.
- The relationship between the predicted responder rate and eslicarbazepine $C_{av\text{-}ss}$ is shown in **Figure 6**, and shows that this exposure-response relationship is relatively shallow over this range of doses.

Figure 5. Logit Model for the Responder Rate

$$Logit_j = -1.46 \times plac_j + \left(\eta - plac_j\right) \times \left[1.09 + 0.000051 \times C_{av\text{-}ss_j}\right]$$

Where:

$plac_j$ = an indicator variable for treatment with placebo (1 = yes, 0 = no) in the jth patient

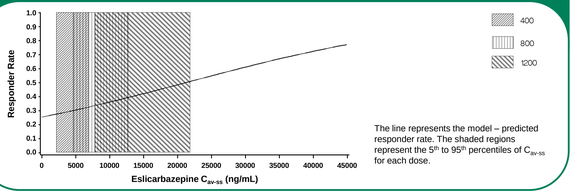
$C_{av\text{-}ss_j}$ = steady-state average ESL concentration in the jth patient

Table 4. Parameter Estimates for the Final Responder Rate Model

		Final Parameter Estimate
Parameter[a]	Population Mean	%SEM
Placebo effect	-1.46	12.3
Intercept for the ESL effect	-1.09	18.1
Slope for ESL effect	0.000051	40.2
Minimum value of the objective function = -734.353		

Abbreviation: %SEM, percent standard error of the mean.
[a]Parameter estimates on the logit scale.

Figure 6. Relationship Between Responder Rate and Eslicarbazepine $C_{av\text{-}ss}$



The line represents the model – predicted responder rate. The shaded regions represent the 5th to 95th percentiles of $C_{av\text{-}ss}$ for each dose.

Conclusion

- In this analysis, the exposure-response models demonstrated a statistically significant effect of eslicarbazepine exposure on seizure frequency-related responses, with a reduction in seizure frequency and an increase in responder rate expected as eslicarbazepine exposure increases over the clinical dose range of 400 mg to 1200 mg QD.
- When taken together with traditional statistical analyses of these endpoints, the exposure-response models support the recommended maintenance doses of eslicarbazepine acetate 800 mg to 1200 mg QD.
- Monitoring of eslicarbazepine plasma concentrations was not required to guide therapeutic dosing, given the relatively shallow exposure-response relationships and safety profile of eslicarbazepine acetate from the Phase 3 studies.

References

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