Population Pharmacokinetic Evaluation of Eslicarbazepine Acetate for Adjunctive Therapy in Refractory Partial Onset Seizures

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Abstract

Statement of Purpose, Innovation or Hypothesis: Eslicarbazepine acetate (ESL), a once-daily antiepileptic drug (AED), is converted to eslicarbazepine, the primary active metabolite of ESL, after oral administration. The population pharmacokinetics (PK) of eslicarbazepine were investigated, including assessment of covariates and concomitant antiepileptics.

Description of Methods and Materials: Multiple ESL doses (400-1200 mg) administered once-daily were studied. Modeling was performed with data from eleven Phase 1 (224 subjects/4240 concentrations) and three Phase 3 studies (815 subjects/1725 concentrations).

Data and Results: A 1-compartment model with first-order absorption and elimination reasonably fit these data. Estimated eslicarbazepine apparent clearance (CL/F) was 2.43 L/h, with lower (33.8%) area under the concentration-time curve at steady-state (AUC_{ss}) with concomitant administration of phenobarbital/phenobarbital-like metabolic inducers (phenytoin, primidone) or carbamazepine (range: 25.1% - 34.4% for carbamazepine doses of 200 mg twice daily to 400 mg three times daily). Eslicarbazepine CL/F increases with increasing creatinine clearance (CrCL); a hypothetical subject with an estimated CrCL of 80 or 50 mL/min, and body weight of 70 kg will have a higher (7.5% and 17.8%) eslicarbazepine AUC_{ss} as compared to a hypothetical subject with the median CrCL of 115.7 mL/min and body weight of 70 kg. Eslicarbazepine CL/F increases in proportion to body weight, with AUC_{ss} 24.3% higher and 27.5% lower for a hypothetical subject weighing 34 or 140 kg versus 70 kg, a CrCL of 115.7 mL/min, and not receiving concomitant AEDs. Concomitant administration of phenobarbital/phenobarbital-like metabolic inducers (phenytoin, primidone) resulted in higher (19.6%) eslicarbazepine apparent distribution volume (V/F). Females had lower (16.15%) eslicarbazepine V/F compared to males; a difference not expected to be clinically relevant. The V/F increases with increasing weight and is predicted to be 47.7, 51.4, and 56.2 L in a hypothetical female subject with a weight of 62, 70, or 81 kg, and 56.9, 61.3, and 67.1 L for a male subject with equivalent weight.

Interpretation, Conclusion or Significance: This modeling supported individual subject eslicarbazepine exposure estimation for Phase 3 PK/PD efficacy analyses.

Introduction

- Eslicarbazepine acetate is a novel single-enantiomer member of the carboxamide family of AEDs.[1]
- Following oral administration, eslicarbazepine acetate is rapidly and extensively metabolized to eslicarbazepine, which represents about 95% of total systemic drug exposure.[2]
- Although the precise mechanism of action is unknown, *in vitro* electrophysiological studies indicate that both eslicarbazepine acetate and eslicarbazepine competitively interact with Site 2 of the inactivated state of a voltage-gated sodium channel.[3,4]
- Maximum plasma concentration (Cmax) of eslicarbazepine is attained approximately 3 hours post dose, with steady state attained after 4 to 5 days of once-daily dosing.[2]
- Eslicarbazepine is eliminated from the systemic circulation, primarily by renal excretion, in the unchanged and glucuronide conjugate forms.[3,5]

Objective

- Develop a population PK model describing the influence of selected covariates and other AEDs on the PK of eslicarbazepine.

Methods

Study Design and Data

- Data were obtained from adult subjects enrolled in 11 densely sampled Phase 1 studies and 3 sparsely sampled Phase 3 studies; analysis included only multiple 400-mg to 1200-mg doses administered once daily.
- Subjects randomized to treatment in the Phase 3 trials had at least 4 partial-onset seizures per 4 weeks during the baseline period, were aged 16 years or more, and currently receiving treatment with 1 or 2 AEDs in a stable dose regimen.
- Part I: Each Phase 3 study included an 8-week placebo baseline period, followed by a double-blind 2-week dose titration period, a 12-week maintenance period, and a 4-week tapering off period (1 study only).
- Part II: 1-year open-label extension of two Phase 3 studies, starting with eslicarbazepine acetate 800 mg once daily for 1 month, then allowing for dose titration to 400 mg or 1200 mg once daily in 400-mg increments.
- Part III: An additional 1-year open-label extension in one Phase 3 study, with dose titration as above.
- Sparse PK sampling (trough concentrations) was performed during Part I prior to the baseline period, prior to the first treatment dose, week 8 (1 study only), at the end of maintenance therapy week 12, at the end of the tapering period (1 study only), and during Part II at 1, 6, and 12 months. Full-profile PK sampling was performed (n = 50) during a visit in Part III, and in all Phase 1 studies to 24 hours post dose.
- Plasma samples were analyzed for eslicarbazepine concentrations with chiral liquid chromatography coupled to mass spectrometry (LC-MS/MS) assay. The lower limit of quantitation was 50 ng/mL.

Data Analysis

- Data preparation was performed using SAS, Version 9.2;[6] the population PK analysis was performed using NONMEM, Version 6, Level 2.0,[7] using the first-order conditional estimation (FOCE) and FOCE with interaction methods.
- The base structural model included estimation of between-subject (interindividual) variability (IIV) in PK parameters and within-subject (residual) variability (RV) in drug concentrations.
- Goodness of fit was assessed using scatterplots of predicted versus measured concentrations and versus weighted residuals, %SEM of the parameter estimates, and changes in the estimates of IIV and RV.
- Model validation was performed using a visual predictive check (VPC) procedure (1000 replicate datasets were simulated with NONMEM using the final model).

Covariate Analysis

- Stationary covariates assessed were age, height, body weight, body mass index, race, and sex.
- Creatinine clearance[8] was tested as a time-varying covariate.
- Concomitant AEDs tested were carbamazepine, valproate, lamotrigine, topiramate, levetiracetam, phenobarbital, clonazepam, primidone, phenytoin, pregabalin, gabapentin, vigabatrin, zonisamide, clobazam, and tiagabine.
- The effect of concomitant AEDs was analyzed sequentially by presence/absence and, if significant, by the effect of AED dose and/or the effect of AED concentration.
- Bayesian estimates of parameters were generated for each individual subject using the base structural PK model, and were plotted versus each of the subject covariates to identify potential relationships between unexplained variability in PK parameters and covariates.

Results

Data Description

- 5965 concentrations from 1039 subjects were available for analysis.
- Demographic characteristics of the subjects are shown in **Table 1**.
- **Figure 1** shows dose-normalized eslicarbazepine concentrations versus time relative to dosing.
- Overall, the concurrent AEDs most commonly administered were carbamazepine (40.6%), lamotrigine (20.8%), and valproate (18.2%) as shown in **Table 2**.

Population PK Model Development

- A 1-compartment model with first-order absorption and elimination was found to be an appropriate fit to these data.
- The estimated basal eslicarbazepine CL/F was 2.43 L/h, V/F was 61.3 L, and first-order absorption t½ was 0.296 h.
- The final model parameters are listed in **Table 3**. All fixed and random effect parameters were estimated with good precision (%SEM ≤ 35%).
- The concomitant administration of phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) resulted in lower (33.8%) eslicarbazepine AUCss compared to subjects administered no other AEDs.

Table 1. Patient Demographics

		Phase 1	Phase 3	Overall
Patient Characteristic	**n[a]**	**224**	**815**	**1039**
Age (year)	Mean (SD[b])	36.17 (12.09)	37.99 (11.97)	37.60 (12.02)
	Median	35.00	37.00	36.00
	Minimum, Maximum	18.0, 80.0	16.0, 75.6	16.0, 80.0
Weight (kg)	Mean (SD)	72.62 (11.69)	72.70 (17.01)	72.69 (16.01)
	Median	72.00	71.00	71.00
	Minimum, Maximum	48.0, 106.0	34.0, 140.0	34.0, 140.0
Height (cm)	Mean (SD)	170.31 (9.35)	168.45 (9.70)	168.85 (9.66)
	Median	170.00	168.00	169.00
	Minimum, Maximum	149.0, 199.9	130.0, 205.0	130.0, 205.0
Body mss index (kg/m²)	Mean (SD)	24.77 (3.14)	25.57 (5.52)	25.40 (5.11)
	Median	25.00	24.90	24.90
	Minimum, Maximum	16.4, 30.0	15.2, 71.4	15.2, 71.4
Baseline creatinine clearance (mL/min)	Mean (SD)	112.65 (24.41)	118.13 (26.54)	116.95 (26.18)
	Median	111.56	116.60	115.51
	Minimum, Maximum	38.9, 160.0	41.1, 160.0	38.9, 160.0
Gender, n (%)	Male	144 (64.3)	433 (53.1)	577 (55.5)
	Female	80 (35.7)	382 (46.9)	462 (44.5)
Race, n (%)	Caucasian	166 (74.1)	683 (83.8)	849 (81.7)
	Black	29 (12.9)	24 (2.9)	53 (5.1)
	Asian/Pacific Islander	4 (1.8)	61 (7.5)	65 (6.3)
	Other	4 (1.8)	47 (5.8)	51 (4.9)
	Unknown	21 (9.4)	0 (0.0)	21 (2.0)
Renal function category, n (%)	Normal	185 (82.6)	685 (84.0)	870 (83.7)
	Mild impairment	36 (16.1)	124 (15.2)	160 (15.4)
	Moderate impairment	3 (1.3)	6 (0.7)	9 (0.9)

[a] n = number of subjects.
[b] SD = standard deviation.

Figure 1. Dose-Normalized Eslicarbazepine Concentrations Versus Time Relative to Dosing, by Study Phase

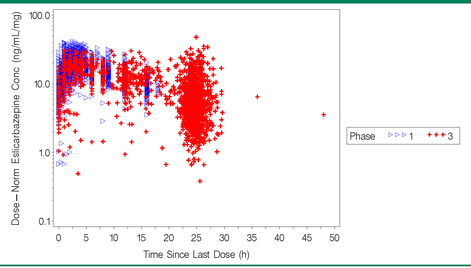

Table 2. Number and Percent of Subjects Taking Concomitant Antiepileptic Drugs

Concomitant Medications	Phase 1	Phase 3	Overall
Carbamazepine , n (%)	18 (8.0)	404 (49.6)	422 (40.6)
Clobazam , n (%)	0 (0.0)	117 (14.4)	117 (11.3)
Clonazepam , n (%)	0 (0.0)	51 (6.3)	51 (4.9)
Gabapentin , n (%)	0 (0.0)	23 (2.8)	23 (2.2)
Lamotrigine , n (%)	14 (6.3)	202 (24.8)	216 (20.8)
Levetiracetam , n (%)	0 (0.0)	145 (17.8)	145 (14.0)
Phenobarbital , n (%)	0 (0.0)	73 (9.0)	73 (7.0)
Phenobarbital-like , n (%)[a]	15 (6.7)	139 (17.1)	154 (14.8)
Phenytoin , n (%)	15 (6.7)	71 (8.7)	86 (8.3)
Pregabalin , n (%)	0 (0.0)	10 (1.2)	10 (1.0)
Primidone , n (%)	0 (0.0)	6 (0.7)	6 (0.6)
Tiagabine , n (%)	0 (0.0)	8 (1.0)	8 (0.8)
Topiramate , n (%)	13 (5.8)	105 (12.9)	118 (11.4)
Valproate , n (%)	0 (0.0)	189 (23.2)	189 (18.2)
Vigabatrin , n (%)	0 (0.0)	3 (0.4)	3 (0.3)
Zonisamide , n (%)	0 (0.0)	17 (2.1)	17 (1.6)

[a] phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone).
Note: Some subjects were on >1 concomitant AED.

Table 3. Parameter Estimates and Standard Errors From the Final Pharmacokinetic Model

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV[a])	
	Population Mean	%SEM[b]	Final Estimate	%SEM
k_a (h^{-1})	2.34	9.6	126.49	18.4
CL/F for no carbamazepine use (L/h)	2.43	1.3	27.04	10.5
Additive shift of concomitant phenobarbital or phenobarbital-like inducers (phenytoin, primidone) on CL/F (L/h)	1.24	6.7		
Slope term for effect of body weight on CL/F (L/h/kg)	0.0132	24.0		
Power Term for effect of creatinine clearance on CL/F	0.195	33.9		
Additional CL/F when carbamazepine dose = 800 mg (L/h)	1.08	5.4		
Power term for effect of carbamazepine dose on CL/F	0.411	35.8		
V/F (L)	61.3	2.0	17.69	15.6
Additive shift of female gender on V/F (L)	-9.9	18.2		
Additive shift of concomitant phenobarbital or phenobarbital-like inducers (phenytoin, primidone) on V/F (L)	12.0	30.3		
Power term for effect of body weight on V/F	0.617	15.0		
Ratio of additive/proportional RV components[c] (σ_2/σ_1), Phase 1	4520	18.4	NA	NA
Proportional RV component (σ_1), Phase 1	0.0124	7.8	NA	NA
Ratio of additive/proportional RV components[d] (σ_2/σ_1), Phase 3	0.0000632	31.6	NA	NA
Additive RV component (σ_2), Phase 3	5290000	17.1	NA	NA
Minimum value of the objective function = 99315.706				

[a] %CV = percent coefficient of variation.
[b] %SEM = percent standard error of the mean.
[c] Residual variability in the Phase 1 data was estimated to range from 23.74 %CV to 11.24 %CV at predicted eslicarbazepine concentrations ranging from 2400 ng/mL to 33000 ng/mL, respectively.
[d] Residual variability in the Phase 3 data was estimated to range from 311.15 %CV to 15.68 %CV at predicted eslicarbazepine concentrations ranging from 740 ng/mL to 39200 ng/mL, respectively.

- Subjects administered carbamazepine had a lower eslicarbazepine AUCss (range: 25.1% - 34.4% for carbamazepine doses ranging from 200 mg twice daily to 400 mg three times daily) compared to subjects administered no other AEDs.
- Apparent oral clearance of eslicarbazepine increases with increasing CrCL. A hypothetical subject with an estimated CrCL of 80 or 50 mL/min and a body weight of 70 kg will have a higher (7.5% and 17.8%, respectively) eslicarbazepine AUCss as compared to a hypothetical subject with the median CrCL of 115.7 mL/min and a body weight of 70 kg.
- Eslicarbazepine CL/F increases in proportion to body weight, with AUCss 24.3% higher and 27.5% lower for a hypothetical subject with a body weight of 34 or 140 kg, a CrCL of 115.7 mL/min, and not receiving concomitant AEDs relative to the same subject with a body weight of 70 kg.
- Eslicarbazepine V/F increases with increasing body weight. For a male subject with a body weight of 61, 70, or 79 kg, the V/F of eslicarbazepine is predicted to be 56.9, 61.3, or 67.1 L. These differences are not expected to be clinically relevant.
- The V/F was also increased in subjects treated with phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone) by 12.0 L. This increase in V/F is not expected to be clinically relevant.
- The V/F of eslicarbazepine was estimated to be 9.9 L lower in females as compared to males with the same body weight. This small gender difference in V/F is not expected to be clinically relevant.
- The equations to predict the typical CL/F and V/F of eslicarbazepine are shown in **Figure 2**.
- **Figure 3** displays goodness-of-fit plots for the final population PK model.

Figure 2. Population Pharmacokinetic Model Equations

$$CL/F_j = \left[2.43 + 1.08 \times \left(\frac{dose_{cbz\,j}}{800}\right)^{0.411} + 1.24 \times flag_{phb_j} + 0.0132 \times (wt_j - 70)\right] \times \left(\frac{CrCL_j}{115.7}\right)^{0.195}$$

$$V/F_j = \left(61.3 - 9.9 \times flag_{sexf\,j} + 12.0 \times flag_{phb_j}\right) \times \left(\frac{wt_j}{70}\right)^{0.617}$$

Where:

$CrCL_j$	is the creatinine clearance in the jth subject
$dose_{cbz\,j}$	is the daily carbamazepine dose in the jth subject
$flag_{phb\,j}$	is the flag variable for the presence of phenobarbital or phenobarbital-like metabolic inducers in the jth subject (0 for no; 1 for yes)
$flag_{sexf\,j}$	is the flag variable for gender of the jth subject (0 for male; 1 for female)
wt_j	is the body weight in the jth subject

References

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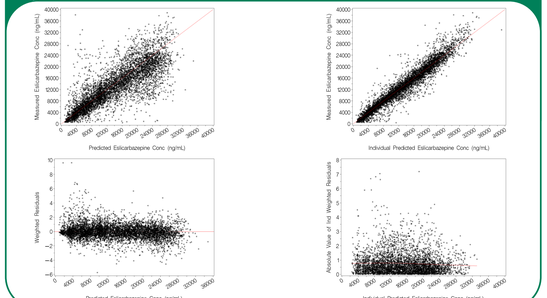
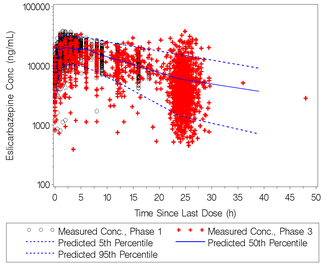
Figure 3. Goodness-of-Fit Plots



Model Validation

- The majority of the observed sparse data fall within the prediction interval as shown in **Figure 4**, as do all of the full-profile samples collected during the PK sub-study in Part III and the Phase 1 studies.
- The proportion of observed data points falling below and above the 5th and 95th percentile prediction interval bounds was 7.55% and 6.02%, respectively.
- Overall, no apparent bias in the model fit is evident in this comparison of the simulated data (based on the model) to the raw data.

Figure 4. Percentiles of Simulated Data From the Visual Predictive Check of the Final Model Overlaid on the Observed Eslicarbazepine Concentration Data



Conclusions

- The PK of eslicarbazepine are described by a 1-compartment model with first-order absorption and linear elimination. The estimated basal eslicarbazepine CL/F was 2.43 L/h, V/F was 61.3 L, and first-order absorption t½ was 0.296 h.
- Eslicarbazepine CL/F was higher in subjects administered concomitant carbamazepine, phenobarbital or phenobarbital-like metabolic inducing agents, and was also shown to increase with increasing body weight or creatinine clearance.
- The population PK model provided the basis to obtain individual steady-state concentration estimates for later exposure-response analyses of eslicarbazepine acetate efficacy in patients with refractory partial epilepsy.

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