Population Pharmacokinetics of Eslicarbazepine Acetate in Patients With Partial-onset Seizures

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Introduction

- Eslicarbazepine acetate (ESL) is a novel once-daily antiepileptic drug (AED) currently under clinical development in the US.[1]
- Following oral administration, ESL is rapidly and extensively metabolized to eslicarbazepine, which represents about 95% of total systemic drug exposure.[2]
- Maximum plasma concentration (C_{max}) of eslicarbazepine is attained approximately 3 hours post-dose, with steady state attained after 4 to 5 days of once-daily (QD) dosing.[2]
- Eslicarbazepine is eliminated from the systemic circulation, primarily by renal excretion, in the unchanged and glucuronide conjugate forms.[3,4]
- Population pharmacokinetic (PK) modeling was undertaken to describe the PK of the eslicarbazepine analyte in the clinically relevant patient population, and provide a means to support a later exposure-response evaluation of eslicarbazepine efficacy endpoints.

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 patients enrolled in 2 multi-center, randomized, placebo-controlled Phase 3 studies (-301 and -302) of ESL (400 mg, 800 mg, and 1200 mg QD) as adjunct therapy for partial-onset seizures.[5-7]
- Approximately 400 patients (100 per treatment group) with at least 4 partial-onset seizures per 4 weeks during the baseline period, and currently receiving treatment with 1 to 3 AEDs in a stable dose regimen were randomized to treatment in each trial.
- Part I: 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.
- Part II: 1-year open-label extension of each study, starting with eslicarbazepine acetate 800 mg QD for 1 month, then allowing for dose titration to 400 mg or 1200 mg QD in 400 mg increments.
- Part III: an additional 1-year open-label extension in one study, with dose titration as above.
- Sparse PK samples (trough concentrations) were collected in both studies during Part I prior to the baseline period, at the beginning and end of the maintenance treatment period, at the end of the tapering period (Study -301 only), and during Part II (open-label extension) at 1, 6, and 12 months.
- Full-profile PK sampling was performed in 50 patients during a visit in Part III at pre-dose, then at 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.
- Plasma samples were analyzed for eslicarbazepine concentrations with chiral liquid chromatography coupled to mass spectrometry (LC-MS/MS) assay. The LLOQ was 50 ng/mL.

Data Analysis

- Data preparation was performed using SAS, Version 9.1.3;[8] the population PK analysis was performed using NONMEM, Version V, Level 1.1,[9] with the first-order conditional estimation method with interaction.
- The base structural model included estimation of between-patient (inter individual) variability (IIV) in PK parameters and within-patient (residual) variability (RV) in drug concentrations.
- Goodness-of-fit was assessed using scatter plots 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 VPC procedure (500 replicate datasets were simulated with NONMEM using the final model).

Covariate Analysis

- Stationary covariates assessed: age, height, body weight, body mass index, race, and sex.
- Time-varying covariate assessed: creatinine clearance (CrCL).[10]
- Concomitant AEDs tested: carbamazepine, valproate, levetiracetam, phenobarbital and phenobarbital-like metabolic inducers (primidone, phenytoin), and gabapentin.
- 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.
- Covariates were evaluated using forward selection with α=0.01; backward elimination was performed using α=0.001.
- Bayesian estimates of parameters were generated for each individual patient using the base structural PK model, and were plotted versus each of the patient covariates to identify potential relationships between unexplained variability in PK parameters and covariates.

Results

Data Description

- 1484 concentrations from 517 subjects were available for analysis. Demographic characteristics are shown in **Table 1**.
- **Figure 1** shows eslicarbazepine concentrations versus time relative to dosing.
- The concurrent AEDs most commonly administered were carbamazepine (55.6%), valproate (25.3%), and phenobarbital and phenobarbital-like inducing agents (17.2%) 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.
- Allometric scaling[11,12] was used in the base structural model to adjust CL/F and V/F by body weight: $CL/F \times wt^{0.75}$ and $V/F \times wt^{1}$.
- Significant covariates included concomitant carbamazepine dose, co-administration of phenobarbital or a phenobarbital-like metabolic inducer, and serum concentration of concomitant valproate.
- The final model parameters are listed in **Table 3**. All fixed and random effect parameters were estimated with good precision (%SEM ≤ 41%).
- Estimated basal eslicarbazepine CL/F was 3.66 L/h, with an increase to 4.75 L/h with concurrent phenobarbital or phenobarbital- like metabolic inducers (phenytoin, primidone).

Table 1. Patient Demographics

Subject Characteristic		Study -301	Study -302	Pooled Data
Age (y)	Mean (SD)	38.03 (11.91)	37.23 (11.90)	37.71 (11.90)
	Median	37.50	34.70	36.20
	Min, Max	18.0, 75.6	18.3, 69.3	18.0, 75.6
	n	311	207	518[a]
Height (cm)	Mean (SD)	170.33 (8.74)	166.57 (10.21)	168.83 (9.53)
	Median	171.00	166.00	169.00
	Min, Max	130.0, 198.0	140.0, 205.0	130.0, 205.0
	n	311	207	518[a]
Weight (kg)	Mean (SD)	71.21 (15.03)	70.69 (15.76)	71.00 (15.31)
	Median	70.00	68.00	69.00
	Min, Max	40.0, 130.0	41.0, 135.0	40.0, 135.0
	n	311	207	518[a]
Race, n (%)	Caucasian	311 (100.0)	183 (88.4)	494 (95.4)
	Black	0 (0.0)	12 (5.8)	12 (2.3)
	Asian/Pacific Islander	0 (0.0)	5 (2.4)	5 (1.0)
	Other	0 (0.0)	7 (3.4)	7 (1.4)
Sex, n (%)	Male	163 (52.4)	111 (53.6)	274 (52.9)
	Female	148 (47.6)	96 (46.4)	244 (47.1)

[a]Includes one patient who was later excluded from PK analysis.

Figure 1. Eslicarbazepine Concentrations Versus Time Relative to Dosing, by Treatment Group

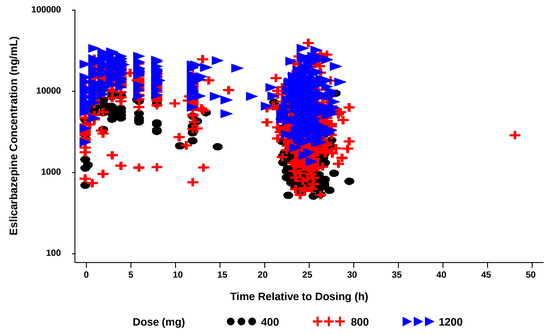


Table 2. Number and Percent of Patients Taking Concomitant Antiepileptic Drugs

Subject Characteristic		Study -301	Study -302	Pooled Data
Carbamazepine, n (%)	No	138 (44.4)	92 (44.4)	230 (44.4)
	Yes	173 (55.6)	115 (55.6)	288 (55.6)
Gabapentin, n (%)	No	294 (94.5)	202 (97.6)	496 (95.8)
	Yes	17 (5.5)	5 (2.4)	22 (4.2)
Levetiracetam, n (%)	No	304 (97.7)	172 (83.1)	476 (91.9)
	Yes	7 (2.3)	35 (16.9)	42 (8.1)
Phenobarbital and Phenobarbital-like metabolic inducers, n (%)	No	268 (86.2)	161 (77.8)	429 (82.8)
	Yes	43 (13.8)	46 (22.2)	89 (17.2)
Valproate, n (%)	No	224 (72.0)	163 (78.7)	387 (74.7)
	Yes	87 (28.0)	44 (21.3)	131 (25.3)

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

	Final Parameter Estimate		Magnitude of Interindividual Variability (%CV)	
Parameter	Population Mean	%SEM	Final Estimate	%SEM
CL/F (L/h)	3.66	3.9	35.9	18.9
V/F (L)	81.7	7.7	41.4	38.7
ka (h^{-1})	1.01	12.5	NE	NA
Effect of carbamazepine dose on CL/F (L/h)	0.821	12.4	NA	NA
Effect of valproate concentration on CL/F (L/h)	-0.251	41.0	NA	NA
Effect of phenobarbital-like metabolic inducers on CL/F (L/h)	1.09	16.2	NA	NA
Covariance term (IIV CL/F and IIV V/F)	0.121	30.4	NA	NA
RV (SD in log concentration units)	0.41	8.5	NA	NA
Minimum value of the objective function = -517.626				

Abbreviations: CL/F, apparent oral clearance; %CV, percent coefficient of variation; IIV, interindividual variability; ka, first-order absorption rate constant; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean; V/F, apparent volume of distribution

- Eslicarbazepine CL/F was higher in patients taking concomitant carbamazepine (11.2% to 33.7% at carbamazepine daily dosage of 200 mg twice daily to 400 mg three times daily) compared to patients receiving only ESL.
- Patients co-administered valproate had a lower [6.9% to 19.8% for 50 µg/mL (lower limit of desired range) to 143.7 µg/mL (maximum observed concentration) observed valproate concentration] eslicarbazepine CL/F compared to patients administered only ESL.
- Tissue distribution of eslicarbazepine is extensive, with the typical V/F estimated to be 81.7 L.
- The equation to predict the typical CL/F of eslicarbazepine is shown in **Figure 2.**
- **Figure 3** displays goodness-of-fit plots for the final population PK model.

Figure 2. Population PK Model Equation

$$CL/F_j = \left[3.66 + 0.821 \times \frac{dose_{carbamazepine_j}}{800} - 0.251 \times \frac{Cp_{valproate_j}}{49.8} + 1.09 \times flag_{phenobarbital\text{-}like_j}\right] \times \left(\frac{wt_j}{69}\right)^{0.75}$$

Where:

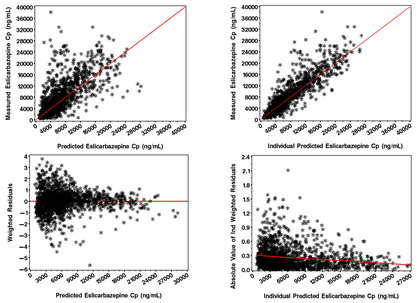
$dose_{carbamazepine_j}$ = the daily dose of carbamazepine in the jth patient where the median carbamazepine dose is 800 mg

$Cp_{valproate_j}$ = the pre-dose (steady-state) valproate concentration in the jth patient where the median valproate concentration is 49.8 µg/mL

$flag_{phenobarbital\text{-}like_j}$ = flag variable for the presence of phenobarbital or phenobarbital-like metabolic inducers in the jth patient (0 or 1 for absence or presence, respectively)

wt_j = weight in the jth patient where the median weight is 69 kg

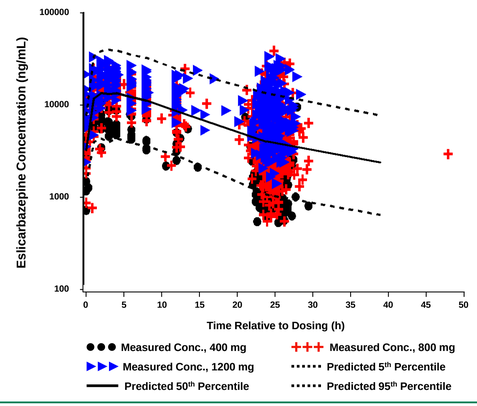
Figure 3. Population PK Model Equation



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 PK sub-study in Part III.
- Overall, no apparent biases in the model fit are 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



Conclusion

- 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 3.66 L/h, and V/F was 81.7 L.
- Eslicarbazepine CL/F was higher in patients administered concomitant carbamazepine, phenobarbital or phenobarbital-like metabolic inducing agents; however, eslicarbazepine CL/F was lower with concomitant valproate administration.
- 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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