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Eslicarbazepine acetate monotherapy: a population pharmacokinetic analysis

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED), approved by the US Food and Drug Administration for the treatment of partial-onset seizures (POS) as monotherapy or adjunctive therapy. ESL is approved by the European Medicines Agency as adjunctive therapy of POS in adults.
- ESL is rapidly and extensively metabolized to eslicarbazepine,[1] which is thought to act primarily by preferentially stabilizing the inactivated state of voltage-gated sodium channels.[2]
- The efficacy and safety of ESL monotherapy (1200 and 1600 mg QD) have been explored in two Phase III studies in patients with POS, which demonstrated superior efficacy to a historical control and a safety/tolerability profile consistent with that reported for adjunctive ESL.[3,4]
- Here we report the development of a population pharmacokinetic (PK) model for eslicarbazepine during ESL monotherapy.

OBJECTIVE

- To develop a population PK model and to characterize the disposition of eslicarbazepine during once-daily ESL monotherapy in adults.

METHODS

Study designs and populations

Phase III studies

- The design of the two Phase III conversion-to-monotherapy studies (093-045 and -046) has been reported previously.[3,4]
- **Population**: Patients were aged 16–70 years with POS (with or without secondary generalization) not adequately controlled by one to two AEDs. Inclusion criteria included:
  - ≥4 POS in the 8 weeks prior to screening
  - maximum of one concomitant sodium channel blocker
  - elderly patients (age 65–70 years) must have had no additional health concerns.
- **Titration period (Weeks 1–3)**: While maintaining stable doses of concomitant AEDs, ESL was initiated and titrated over 3 weeks to 1200 mg QD (Week 1: 400 mg QD; Week 2: 800 mg QD) or to 1600 mg (Week 1: 600 mg QD; Week 2: 1200 mg QD).
- **Conversion-to-monotherapy period (Weeks 3–9)**: Doses of concomitant baseline AEDs were tapered off.
- **Monotherapy period (10 weeks)**: Patients continued to receive the target dose of ESL as monotherapy.

Phase I studies

- Data from 10 Phase I studies of ESL monotherapy (with conditions that matched those of the Phase III clinical trials) were included in the analysis: BIA-2093-105, -110, -111, -115, -116, -119, -120, -121, -127, and -129.
  - Multiple-dose studies in healthy volunteers (male and female); ESL 600, 800, 900, and 1200 mg QD, with collection of plasma samples during the 24-hour interval following dosing.

Measurement of eslicarbazepine in plasma samples

- Plasma samples were collected and eslicarbazepine concentrations determined by validated chiral liquid chromatography with tandem mass spectrometry. The lower limit of quantitation for eslicarbazepine was 0.05 µg/mL.
- In Phase III studies, during the ESL monotherapy period, 1–5 plasma samples were collected per patient (4 for most patients), in the 24-hour period after each dose.
- In Phase I studies, 12–21 plasma samples were collected per subject during the 24-hour period after each dose.

Exploratory data analysis

- Exploratory analyses and visualization were used to understand the dataset, search for outliers, assess possible trends and relationships, verify model assumptions, and identify any errors in dataset creation or manipulation.

Pharmacokinetic modeling

- The dataset comprised eslicarbazepine plasma concentrations from all 12 studies (10 Phase I and two Phase III studies).
- A previously developed population PK structural model for eslicarbazepine was applied to the dataset and further refined.
- An exponential error model was used to explore the inter-individual variability (IIV) in:
  - absorption rate constant (k_a; Phase I data only)
  - apparent oral clearance (CL/F; CL: clearance; F: bioavailability)
  - apparent volume of distribution (V/F).
- Two separate, additive plus constant, coefficient of variation error models were used to describe residual error.
- Statistically significant predictors of PK variability were identified using a univariate forward selection–backward elimination method, assessing a number of covariates:
  - age, weight, body mass index (BMI), race, gender, and creatinine clearance (CrCl).
- Concordance between simulated data (using the finalized model) and observed data was validated using a visual predictive check.

RESULTS

Dataset

- In total, 4620 estimates of plasma eslicarbazepine concentration from 558 individuals were evaluated.
- After exclusions, 3869 estimates from 493 individuals were analyzed.
- Concomitant carbamazepine was taken by 26% of subjects, and phenytoin by 10% of subjects in the Phase III monotherapy trials PK population. Other enzyme-inducing AEDs (barbiturates) were excluded from analysis.

Exploratory data analysis

- Concentration-time profiles for the pooled dataset showed linear kinetics within the dose range explored.
- Dose-normalized eslicarbazepine concentrations overlapped between subjects in the Phase I and Phase III studies.
- During the monotherapy phase, variability between patients in plasma eslicarbazepine concentrations (and the change in concentrations over time) was similar for subjects who had taken carbamazepine, phenytoin and other AEDs during the baseline period.
  - Thus, effects of other AEDs on eslicarbazepine PK (mediated via effects on cytochrome P450 enzymes) were not evident during the monotherapy phase.

Model-predicted population pharmacokinetic parameters

- The final population PK model was a one-compartment model with first-order absorption and first-order elimination.
- The population PK parameters predicted by the final model (plus the related estimates of precision [%SE] and variability) are shown in **Table 1**.
- The estimated first-order absorption half-life was 0.654 hours.
- The estimated elimination half-life in subjects of median body weight was approximately 16 hours in females and 17 hours in males.

Table 1. Population mean PK parameter estimates for the final PK model of eslicarbazepine during ESL monotherapy

Parameter	Final population mean (%SE)	IIV %CV (%SE)
k_a, h^{-1}	1.06 (6.15)	75.5 (14.9)
CL/F, L/h	2.56 (1.71)	22.8 (10.6)
Power term for effect of body weight on CL/F	0.291 (21.9)	
Additive shift in CL/F for female gender, L/h	–0.240 (26.6)	
V/F, L	62.6 (2.30)	18.6 (18.8)
Power term for effect of body weight on V/F	0.718 (15.9)	
Additive shift in V/F for female gender, L	–7.76 (26.8)	

%CV: percentage coefficient of variation; %SE: percentage standard error of the mean; CL/F: apparent oral clearance; ESL: eslicarbazepine acetate; IIV: inter-individual variability; k_a: absorption rate constant; PK: pharmacokinetic; V/F: apparent volume of distribution.

- The estimated V/F was 62.6 L. At the median body weight of 74.4 kg, eslicarbazepine V/F is predicted to be 0.84 L/kg for a male subject and 0.74 L/kg for a female subject, while eslicarbazepine CL/F is predicted to be 2.56 L/h (0.034 L/h/kg) for a male subject and 2.32 L/h (0.031 L/h/kg) for a female subject.
  - These parameters are consistent with the results of a population PK analysis for adjunctive ESL (studies 2093-301, -302, -304); CL/F was 2.43 L/h and V/F was 61.3 L in subjects not using carbamazepine.[5]
- The inter-individual variability was high for k_a and moderate for CL/F and V/F.
- The residual variability of the Phase III data was moderate (30.2 percentage coefficient of variation [%CV]), while the residual variability of the Phase I data was higher at the lower concentration (25.5 %CV at 3.5 µg/mL) than at the higher concentration (11.7 %CV at 39 µg/mL).

Predictors of pharmacokinetic variability, and effects on pharmacokinetic parameters

- Body weight and gender were found to be statistically significant predictors of both CL/F and V/F (**Table 1**).
- Neither age nor race had a statistically significant impact on CL/F or V/F.
- The effects of BMI on CL/F and V/F were highly correlated with body weight. Similarly, the effects of CrCl on CL/F were highly correlated with body weight.

Apparent volume of distribution

- Eslicarbazepine V/F was predicted to increase in proportion to body weight (**Table 2**).
- Predicted V/F was lower in females than males of the same body weight; at the median body weight (74.4 kg), V/F was predicted to be 12.4% lower in females than in males.

Table 2. Predicted impact of body weight on V/F of eslicarbazepine during ESL monotherapy

	Effect on V/F[a]	
Body weight percentile	Male	Female
1st percentile (48 kg)	27.0% lower	30.8% lower
99th percentile (145.6 kg)	61.9% higher	70.7% higher

[a]Compared with V/F for a subject of the same sex with median body weight (74.4 kg).
ESL: eslicarbazepine acetate; V/F: apparent volume of distribution.

Elimination half-life

- The predicted variability in CL/F and V/F with body weight and gender showed minimal differences. The variability in elimination half-life is predicted to result in, at most, a difference of 2 days in time to steady state, between the lowest and highest weight percentiles.

Exposure

- The effects of body weight and gender on eslicarbazepine exposure (area under the curve at steady state; AUC_{ss}) were evaluated, initially using the typical population PK parameters from the final model.
- AUC_{ss} was predicted to be inversely related to body weight (**Table 3**).
- For subjects of the same body weight (median 74.4 kg), AUC_{ss} was predicted to be 10.3% higher in females than males.

Table 3. Predicted impact of body weight on eslicarbazepine exposure (AUC_{ss}) during ESL monotherapy

	Effect on AUC_{ss}[a]	
Body weight percentile	Male	Female
1st percentile (48 kg)	13.6% higher	15.2% higher
99th percentile (145.6 kg)	17.7% lower	19.2% lower

[a]Compared with AUC_{ss} for a subject of the same sex with median body weight (74.4 kg).
AUC_{ss}: area under the curve at steady state; ESL: eslicarbazepine acetate.

CONCLUSIONS

- During ESL monotherapy, plasma eslicarbazepine concentrations were described by a one-compartment model with first-order absorption and linear elimination.
- The doses of ESL used in the monotherapy trials (1200 mg, 1600 mg QD) were higher than those in previous studies of adjunctive ESL. Despite this difference, estimates of CL/F and V/F were very similar to those reported for ESL when used as adjunctive therapy.[5]
  - For subjects not using carbamazepine, CL/F was 2.43 L/h and V/F was 61.3 L.
- Neither age nor race had a significant effect on eslicarbazepine PK parameters.
- Although the effects of body weight and gender on CL/F and V/F were statistically significant, the consequential impact on exposure was not clinically relevant. Accordingly, during ESL monotherapy, no dose adjustments are required to account for differences in body weight and gender.

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ACKNOWLEDGMENTS

Medical writing support was provided by Michael Simpson of FireKite, an Ashfield company, and was funded by Sunovion Pharmaceuticals Inc.