Modeling and simulation to support clinical development of eslicarbazepine acetate in partial-onset epilepsy

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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.
- In Phase III studies in patients with POS not adequately controlled by previous AED therapy, ESL has demonstrated efficacy, both as adjunctive therapy[1–3] and monotherapy.[4,5]
- ESL is administered orally, and is rapidly metabolized to the primary active metabolite, eslicarbazepine.[6]
- A model-based drug development paradigm was employed for the ESL adjunctive therapy and monotherapy development programs, to evaluate eslicarbazepine pharmacokinetics (PK) and relationships between eslicarbazepine and efficacy and safety outcomes, and to inform decisions on dose selection.

OBJECTIVE

- To evaluate the PK of eslicarbazepine and assess the exposure–response relationships for drug safety and efficacy.

METHODS

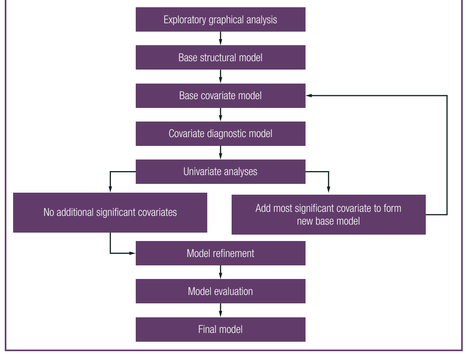
Development of population PK models for eslicarbazepine during ESL adjunctive therapy and monotherapy

- Population PK models for eslicarbazepine during administration of ESL (adjunctive therapy and monotherapy) were developed using combined data from 11 Phase I clinical studies, and three Phase III adjunctive therapy studies (BIA-2093-301, -302, -304), and separately using data from two Phase III monotherapy studies (093-045 and -046).
- A previously developed structural PK model was initially applied, and then refined using an exponential error model to describe inter-individual variability; two additive plus proportional error models were used to account for differences in residual variability between Phase I and Phase III data.

Development of PK/pharmacodynamic (PD) models to describe the relationship between eslicarbazepine exposure and ESL efficacy/safety outcomes

- The following measures of eslicarbazepine exposure were calculated for each patient, using the population PK models for ESL monotherapy and adjunctive therapy:
  - average eslicarbazepine plasma concentration (C_{av})
  - minimum and maximum eslicarbazepine plasma concentration (C_{min}, C_{max})
  - area under the plasma concentration–time curve (AUC_{0-24}).
- For ESL adjunctive therapy, relationships between eslicarbazepine exposure and the following outcomes were evaluated using non-linear mixed-effects modeling, logistic regression or Poisson regression:
  - standardized seizure frequency (SSF)
  - probability of response
  - weekly seizure frequency
  - probability of selected treatment-emergent adverse events (TEAEs).
- For ESL monotherapy, PK/PD models were developed to describe the relationship between eslicarbazepine exposure and the following safety and efficacy outcomes, using logistic regression or survival analysis:
  - time to study exit
  - time to third or sixth seizure (during the 10-week ESL monotherapy period and the 16-week double-blind period, respectively)
  - probability of being seizure-free (during the 10-week ESL monotherapy period and the last 4 weeks of ESL monotherapy)
  - time to first occurrence of selected TEAEs.
- The relationship between eslicarbazepine exposure and serum sodium levels was also analyzed.
- The influence of selected covariates (including concurrent AEDs) on eslicarbazepine PK was assessed.
- Simulation-based model evaluation or appropriate alternatives were performed.
- The overall process for developing the predictive models is shown in **Figure 1.**

Figure 1. Flow chart showing the model development process

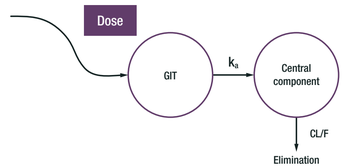


RESULTS

Population PK models

- The PK of eslicarbazepine during ESL treatment (both adjunctive therapy and monotherapy) was described by a one-compartment model with first-order absorption/elimination (**Figure 2**).
- Eslicarbazepine clearance (CL/F), distribution volume (V/F), and absorption rate constant (k_a) were found to be similar between ESL adjunctive and monotherapy.

Figure 2. Schematic of the eslicarbazepine PK model used for both adjunctive ESL therapy and ESL monotherapy



CL: clearance; GIT: gastrointestinal tract; k_a: absorption rate constant; PK: pharmacokinetic.

ESL adjunctive therapy: population PK analysis

- Metabolic inducers and creatinine CL/F <50 mL/minute had clinically relevant effects on eslicarbazepine PK.
  - The apparent oral CL/F of eslicarbazepine increased with increasing creatinine CL/F according to a power function (**Table 1**).
  - Co-administration of phenobarbital or enzyme-inducing AEDs (EIAEDs) with ESL increased eslicarbazepine V/F by 19.6% versus ESL used alone (**Table 1**). This increase was not predicted to be clinically relevant.
  - When ESL was administered with concomitant phenobarbital/EIAEDs, eslicarbazepine exposure (AUC at steady-state; AUC_{ss}) was 33.8% lower than for ESL given alone. Consequently, when ESL is taken with concomitant phenobarbital or similar EIAEDs, a higher dose may be necessary to achieve eslicarbazepine exposure equivalent to that achieved when ESL is taken alone.
- Eslicarbazepine AUC_{ss} during concomitant carbamazepine (CBZ) administration was also lower than for ESL given alone (reductions of 25.1–34.4% occurred with doses from 200 mg twice daily to 400 mg three times a day). ESL dose adjustment may be warranted, given the potential for an increase in AEs; when ESL and CBZ are taken concomitantly, the dose of ESL or CBZ may need to be adjusted based on efficacy and tolerability.
- Body weight was a statistically significant predictor of eslicarbazepine CL/F and V/F during adjunctive ESL therapy, and gender was a significant predictor of V/F, but the impact on predicted eslicarbazepine exposure was not clinically significant.

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

Parameter	Final population mean (%SE)	IIV %CV (%SE)
Absorption rate constant (k_a), h^{-1}	2.34 (9.6)	126.49% (18.4)
Apparent oral clearance (CL/F), L/h		
No concomitant medication use	2.43 (1.3)	27.04% (10.5)
Δ CL/F with phenobarbital or other EIAEDs	+ 1.24 (6.7)	
Power term for effect of creatinine clearance	0.195 (33.9)	
Δ CL/F with concomitant CBZ 800 mg	+ 1.08 (5.4)	
Power term for effect of CBZ	0.411 (35.8)	
Apparent volume of distribution (V/F), L		
No concomitant AEDs	61.3 (2.0)	17.69% (15.6)
Δ V/F with phenobarbital or other EIAEDs	+ 12.0 (30.3)	

AED: antiepileptic drug; CBZ: carbamazepine; C/F: eslicarbazepine clearance; CV: coefficient of variation
EIAED: enzyme-inducing AED; ESL: eslicarbazepine acetate; IIV: inter-individual variability; PK: pharmacokinetic; SE: standard error
V/F: volume of distribution.

ESL monotherapy: population PK analysis

- The population PK parameters predicted by the final model for ESL monotherapy are shown in **Table 2**.
- Effects of gender and body weight on eslicarbazepine CL/F and V/F were statistically significant during ESL monotherapy but, as for adjunctive therapy, the impact of these characteristics on predicted eslicarbazepine exposure was not clinically significant.

Table 2. Population mean PK parameter estimates for the final 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)	
Power term for effect of body weight on CL/F	0.291 (21.9)	22.8 (10.6)
Additive shift in CL/F for female gender, L/h	–0.240 (26.6)	
V/F, L	62.6 (2.30)	
Power term for effect of body weight on V/F	0.718 (15.9)	18.6 (18.8)
Additive shift in V/F for female gender, L	–7.76 (26.8)	

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

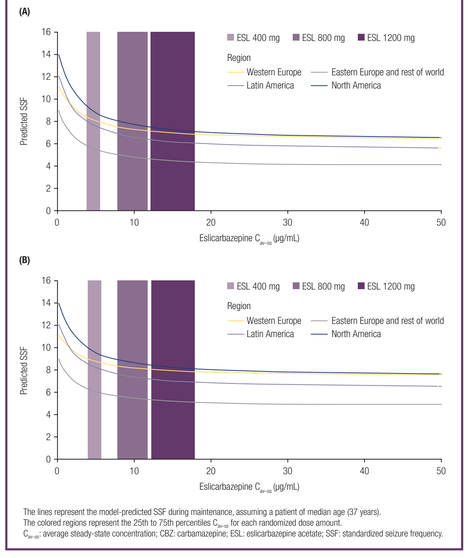
Adjunctive ESL therapy: relationship between eslicarbazepine exposure and efficacy outcomes

- Analyses of SSF, response status, and weekly seizure frequency suggested a shallow relationship with exposure, e.g., only slight improvements in seizure control occurred with higher concentrations of eslicarbazepine (**Figure 3**).
- The model predicted a maximum reduction from baseline in weekly seizure frequency of 56% during treatment with ESL, and indicated that this effect was related to time and average steady-state concentration (C_{av-ss}).
- The reduction in SSF was predicted to be less in Western European patients than those from other regions (**Figure 3**).
- Patients taking CBZ at baseline were predicted to have smaller reductions in SSF.

Adjunctive ESL therapy: relationship between eslicarbazepine exposure and safety outcomes

- The starting ESL dose (400 mg or 800 mg QD during Week 1) was a strong predictor of TEAEs.
  - The probability of a TEAE (dizziness, somnolence, or headache) for a starting dose of 800 mg QD was approximately twice that for a starting dose of 400 mg QD.
- When the starting dose was included in the exposure–response models, eslicarbazepine AUC_{0-24} was a statistically significant predictor of the probability of dizziness and headache, while C_{max} was a statistically significant predictor of somnolence.
  - C_{max} was not a significant predictor of dizziness or headache.

Figure 3. Predicted SSF versus eslicarbazepine C_{av-ss}, by region and baseline CBZ use: (A) no baseline CBZ use; (B) baseline CBZ use

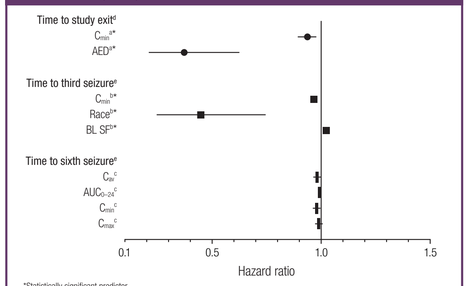


The lines represent the model-predicted SSF during maintenance, assuming a patient of median age (37 years).
The colored regions represent the 25th to 75th percentiles C_{av-ss} for each randomized dose amount.
C_{av-ss}: average steady-state concentration; CBZ: carbamazepine; ESL: eslicarbazepine acetate; SSF: standardized seizure frequency.

ESL monotherapy: relationship between eslicarbazepine exposure and efficacy outcomes

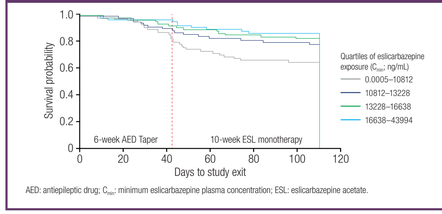
- Higher eslicarbazepine C_{min} and use of one versus two AEDs during the baseline period were significantly associated with lower risk of study exit (**Figure 4**).
- Higher C_{min} was a predictor of increased time to third seizure during the 10-week ESL monotherapy period, and freedom from seizures during the last 4 weeks of monotherapy.
- Other significant predictors of time to third seizure were black or African–American race and lower baseline seizure frequency.
- A relationship was apparent between measures of eslicarbazepine exposure and time to sixth seizure (**Figure 5**), but no single exposure measure was a statistically significant predictor.

Figure 4. Significant predictors of time to study exit and time to third seizure, and relationship between eslicarbazepine exposure measures and time to sixth seizure



*Statistically significant predictor.
[a]n = 296; [b]n = 263; [c]n = 296; [d]16-week ESL monotherapy period; [e]10-week ESL monotherapy period.
AED: antiepileptic drug; AUC_{0-24}: area under the concentration–time curve/1000 ng*h/mL; BL: baseline; C_{av}: average eslicarbazepine plasma concentration/1000 ng/mL; C_{min}/C_{max}: minimum/maximum eslicarbazepine plasma concentration/1000 ng/mL; SF: seizure frequency.

Figure 5. Kaplan-Meier survival probability (no study exit) versus time by quartiles of eslicarbazepine exposure

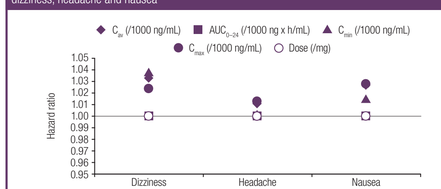


AED: antiepileptic drug; C_{min}: minimum eslicarbazepine plasma concentration; ESL: eslicarbazepine acetate.

ESL monotherapy: relationship between eslicarbazepine exposure and safety outcomes

- No significant relationship was identified between eslicarbazepine exposure and time to first occurrence of dizziness, headache, or nausea (**Figure 6**).
  - A possible reason for this finding is that these AEs tended to occur during the first 2 weeks of the study, when ESL dose and eslicarbazepine exposure would have been low.
  - Alternatively, the AEs could have been caused by AEDs being taken before the transition to ESL monotherapy was completed.

Figure 6. Relationship between predicted eslicarbazepine exposure and time to first occurrence of dizziness, headache and nausea



Note: none of the eslicarbazepine exposure measures were statistically significant predictors of time to first occurrence of dizziness, headache, or nausea; all p-values were greater than 0.22.
AUC_{0-24}: area under the concentration–time curve; C_{av}: average concentration; C_{max}: predicted maximum drug concentration
C_{min}: predicted minimum drug concentration.

- Serum sodium levels appeared to decrease (but only slightly) with increasing eslicarbazepine exposure.
  - At the highest eslicarbazepine C_{max}, linear regression predicted a <3 mEq/L decrease in serum sodium concentration from baseline.

CONCLUSIONS

- The results of the exposure-response analyses support the indicated dosing for adjunctive ESL in the treatment of POS; doses of 800 and 1200 mg QD were found to be efficacious and to have acceptable safety profiles.
- The exposure-response findings do not support routine monitoring of eslicarbazepine plasma concentrations for making decisions regarding potential tolerability issues and hyponatremia.
- The population PK analysis indicates that ESL dose should be increased by 50% when used with phenobarbital, phenytoin and primidone.
- ESL dose adjustment may be warranted during concomitant use of carbamazepine, based on efficacy and tolerability.
- No dose adjustments are required for other AEDs when used with ESL.

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