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Relationship between exposure and efficacy of eslicarbazepine acetate monotherapy

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily, 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.
- After oral administration, ESL is rapidly hydrolyzed to eslicarbazepine (the primary active metabolite) by hydrolytic first-pass metabolism.[1]
- Two multicenter, Phase III studies (093-045 and -046) demonstrated ESL monotherapy to be effective and well tolerated in patients with POS uncontrolled by 1–2 AEDs, compared with a historical control.[2,3]
- In a pooled analysis of the data from studies -045 and -046, there was a difference in exit rates between the ESL 1600 mg (20.6%, 95% confidence interval [CI]: 15.6–26.8%) and ESL 1200 mg doses (30.8%, CI: 23.0–40.5%; p=0.062).[4]
- In addition, higher ESL doses lead to greater eslicarbazepine exposure.[5]
- This analysis examines the relationship between eslicarbazepine exposure and the efficacy of ESL monotherapy, using data from studies -045 and -046, to assess whether monitoring plasma eslicarbazepine concentrations could be useful to physicians when making decisions regarding ESL dosing.
- ESL is not approved for monotherapy use.

OBJECTIVE

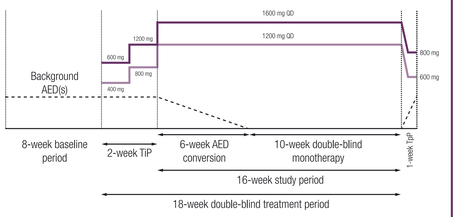
- To use statistical models to evaluate whether measures of eslicarbazepine exposure may be used as predictors for the efficacy of ESL monotherapy.

METHODS

Study design (studies -045 and -046)

- Data from two Phase III studies (-045 and -046) were pooled for this analysis. Both were 18-week, double-blind, multicenter, randomized, conversion-to-monotherapy studies, which evaluated the efficacy and safety of ESL 1600 mg and 1200 mg once-daily as monotherapy, compared with a historical control.
- Both studies utilized the same design (**Figure 1**). Following an 8-week baseline period, patients with POS not well controlled by 1–2 AEDs were randomized (2:1) to receive ESL 1600 mg or 1200 mg QD.
  - Patients entered an 18-week double-blind treatment period, which consisted of a 2-week titration period, a 6-week conversion-to-monotherapy period (with gradual withdrawal of baseline AEDs), and a 10-week monotherapy period. Patients then had the option to either continue into an open-label extension study or enter a 1-week tapering-off period.
- Major inclusion and exclusion criteria have been previously reported.[2,3]

Figure 1. Study design



AEDs: antiepileptic drugs; QD: once daily; TIP: titration period; TpP: taper period.

Assessments and endpoints

- Patients used a seizure diary to record seizures throughout the study.
- Patients exited the study if they met one of the five exit criteria (indicating worsening seizure control) post-titration (**Table 1**).

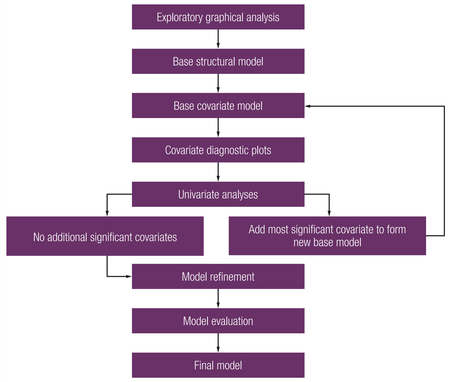
Table 1. Five exit criteria signifying worsening seizure control

Exit criteria
One episode of status epilepticus
One secondary generalized partial seizure (in patients who did not have generalized seizures during the 6 months prior to screening)
A two-fold increase in any consecutive 28-day seizure rate compared with the highest consecutive 28-day seizure rate during the 8-week baseline period
A two-fold increase in any consecutive 2-day seizure rate compared with the highest consecutive 2-day seizure rate during the 8-week baseline period. If the highest number of seizures in any consecutive 2-day period during the 8-week baseline was one, then three seizures in a consecutive 2-day period were required to exit
Worsening of seizures or increase in seizure frequency considered serious or requiring intervention as judged by the investigator

Population pharmacokinetic/pharmacodynamic analysis methodology

- The following measures of eslicarbazepine exposure were calculated for each patient, using a previously developed population pharmacokinetics model.
  - Average eslicarbazepine plasma concentration (C_{av}).
  - Minimum/maximum eslicarbazepine plasma concentration (C_{min}/C_{max}).
  - Area under the plasma concentration-time curve (AUC_{0-24}).
- Predictive models, developed through the process shown in **Figure 2**, were used to describe the relationship between eslicarbazepine exposure and:
  - time to study exit
  - time to sixth seizure during the 16-week double-blind treatment period (monotherapy conversion and ESL monotherapy periods)
  - time to third seizure during the 10-week ESL monotherapy period
  - probability of being seizure-free (during the 10-week ESL monotherapy period and during the last 4 weeks of ESL monotherapy).

Figure 2. Flow chart of the predictive model development process



- The following covariates were evaluated: age, race, gender, body weight, number of AEDs at baseline, baseline carbamazepine use, baseline valproic acid use, baseline levetiracetam use, seizure frequency during the 8-week baseline period, and time to study exit (time to study exit model only).
- The predictive models were validated for concordance between simulated and observed data, using either a simulation-based visual predictive check methodology (models for time to study exit, and time to third and sixth seizure), or the Hosmer-Lemeshow statistic and the receiver operating characteristic curve (models for probability of being seizure-free).

RESULTS

Analysis dataset

- A total of 28,018 records from 296 patients were included in this analysis; not all patients contributed to all endpoints.

Patients

- The patient demographics and baseline characteristics are reported in **Table 2**.

Table 2. Patient demographics and baseline characteristics

	Study population (n = 296)
Age, years; median (range)	38.0 (16–67)
Male; n (%)	150 (50.7)
Race; n (%)	
Caucasian	245 (82.8)
Black (or African-American)	24 (8.1)
Asian	5 (1.7)
Other[a]	22 (7.4)
Ethnicity; n (%)	
Hispanic or Latino	32 (10.8)
Weight, kg; median (range)	79.1 (39–188)
Seizure frequency (per 8 weeks); median (range)	15.0 (4–91)
Number of AEDs during the baseline period; n (%)	
1	199 (67.2)
2	97 (32.8)
AEDs used during the baseline period by ≥20% of patients, n (%)	
Carbamazepine	78 (26.4)
Levetiracetam	71 (24.0)
Valproic acid	62 (20.9)

[a]Includes American Indian/Alaskan Native and multiple races.
AEDs: antiepileptic drugs.

Time to study exit

- The following parameters were significantly associated with a lower risk of study exit (**Table 3**):
  - higher eslicarbazepine C_{min} (hazard ratio [HR]=0.905)
  - use of one AED, versus two AEDs during the baseline period (HR=0.380).
- For each 1000 ng/mL increase in C_{min}, the risk of study exit appeared to decrease by 9.5%.
- At the median C_{min} for each ESL dose, patients taking ESL 1600 mg were ~13% less likely than those taking ESL 1200 mg to exit the study (not tested statistically).

Table 3. Significant predictors of time to study exit[a] (n = 296)

	HR	95% CI	p value
Effect of C_{min} (/1000 ng/mL)	0.905	0.850–0.963	0.0018
Effect of one AED versus two AEDs at baseline	0.380	0.232–0.624	0.0001

[a]During the 16-week double-blind ESL treatment period.
AED: antiepileptic drug; CI: confidence interval; C_{min}: minimum eslicarbazepine plasma concentration; HR: hazard ratio.

Time to first, third and sixth seizure during the 16-week ESL treatment period

- During the 16-week double-blind ESL treatment period (6-week AED conversion and 10-week ESL monotherapy periods), 94% of patients had one or more seizures, 85% had three or more seizures, and 76% of patients had six or more seizures.
- A relationship was apparent between eslicarbazepine exposure and time to sixth seizure (but not to first or third seizure). However, no single exposure measure was a significant predictor of the time to sixth seizure during this time period (**Table 4**).

Table 4. Relationship between measures of eslicarbazepine exposure and time to sixth seizure[a] (n = 296)

Eslicarbazepine exposure parameter	HR	95% CI	p value
C_{av} (/1000 ng/mL)	0.983	0.961–1.006	0.1461
AUC_{0-24} (/1000 ng x h/mL)	0.999	0.998–1.000	0.1205
C_{min} (/1000 ng/mL)	0.973	0.945–1.002	0.0633
C_{max} (/1000 ng/mL)	0.991	0.973–1.009	0.3396

[a]During the 16-week double-blind ESL treatment period.
AUC_{0-24}: area under the concentration-time curve; C_{av}: average eslicarbazepine plasma concentration; CI: confidence interval; C_{min}/C_{max}: minimum/maximum eslicarbazepine plasma concentration; HR, hazard ratio.

Time to first, third and sixth seizure during the 10-week ESL monotherapy period

- During the 10-week ESL monotherapy period, 88.6% of patients had one or more seizures, 76.4% had three or more seizures, and 59.3% of patients had six or more seizures.
- When eslicarbazepine exposure measures were analyzed by quartiles, a relationship was apparent between exposure quartile and time to first, third and sixth seizures.
- A model was developed for time to third seizure, as this endpoint demonstrated the most consistent relationship with eslicarbazepine exposure.
- The following parameters were significantly associated with a lower risk of third seizure (**Table 5**):
  - higher eslicarbazepine C_{min} (HR=0.952)
  - black or African-American race (HR=0.431)
  - lower baseline seizure frequency (HR=1.038).
- For each 1000 ng/mL increase in eslicarbazepine C_{min}, the risk of a third seizure appeared to decrease by 4.8%.
- Assuming the median C_{min} for each ESL dose, the risk of a third seizure was ~10% less for patients receiving ESL 1600 mg than for patients receiving ESL 1200 mg (not tested statistically).
- For each additional seizure during the baseline period, the risk of a third seizure increased by 3.8%.

Table 5. Significant predictors of time to third seizure during the 10-week ESL monotherapy period (n = 263)

	HR	95% CI	p value
Effect of C_{min} (/1000 ng/mL)	0.952	0.920–0.984	0.0039
Effect of race[a]	0.431	0.243–0.765	0.0040
Effect of baseline seizure frequency	1.038	1.028–1.047	<0.0001

[a]Black (or African-American) versus non-black.
CI: confidence interval; C_{min}: minimum eslicarbazepine plasma concentration; ESL: eslicarbazepine acetate; HR, hazard ratio.

Probability of seizure freedom

- During the 10-week ESL monotherapy period, 27 patients were seizure-free (10% of patients in each dose group, and overall).
- No measures of eslicarbazepine exposure were significant predictors of seizure freedom during the 10-week ESL monotherapy period.
- During the last 4 weeks of the ESL monotherapy period, 50 patients were seizure-free (19% of patients in each dose group, and overall).
  - Higher eslicarbazepine C_{min} was associated with a statistically significant increase in the probability of seizure freedom during this period.
  - Assuming median C_{min} for each ESL dose, the predicted probability of seizure freedom during the last 4 weeks of ESL monotherapy was 0.21 for patients taking ESL 1600 mg and 0.16 for patients taking ESL 1200 mg.

CONCLUSIONS

- Plasma eslicarbazepine C_{min} was a weak predictor of time to study exit, time to third seizure during the 10-week ESL monotherapy period, and probability of seizure freedom during the last 4 weeks of monotherapy, and was not a predictor of overall seizure freedom during the 10-week monotherapy period.
- The following factors were also weak predictors of the efficacy of ESL: number of baseline AEDs (time to study exit); race and baseline seizure frequency (time to third seizure during the 10-week ESL monotherapy period).
- As previously reported for the Phase III ESL monotherapy trials,[2,3] this study demonstrates a dose-response relationship between ESL and efficacy, with a weak association to eslicarbazepine concentration.
- Dose and duration of ESL use were stronger predictors of seizure reduction and seizure freedom than eslicarbazepine levels.

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ACKNOWLEDGMENTS

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