Relationship between eslicarbazepine exposure and efficacy of eslicarbazepine acetate adjunctive therapy

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Jay H Harvey,[1] Eva Andermann,[2,3] Steve Chung,[4] Eugen Trinka,[5] Fernando Cendes,[6] Julie Passarell,[7] Jill Fiedler-Kelly,[7] Elizabeth Ludwig,[7] Soujanya Sunkaraneni,[8] Rui Sousa,[9] Francisco Rocha,[9] David Blum[8]

[1]Texas Epilepsy Group, Dallas, TX, USA; [2]Neurogenetics Unit, Montreal Neurological Institute and Hospital, Montreal, QC, Canada; [3]Departments of Neurology and Neurosurgery, and Human Genetics, McGill University, Montreal, QC, Canada; [4]Barrow Neurological Institute/St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA; [5]Department of Neurology, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria; [6]UNICAMP – Universidade Estadual de Campinas, Campinas, Brazil; [7]Cognigen Corp, a subsidiary of Simulations Plus, Buffalo, NY, USA; [8]Sunovion Pharmaceuticals Inc., Marlborough, MA, USA; [9]BIAL – Portela & Cª., S.A., S. Mamede do Coronado, Portugal

INTRODUCTION

- Eslicarbazepine acetate (ESL; Aptiom®) is a novel once-daily (QD) oral antiepileptic drug, approved in the US, Canada and the EU as adjunctive treatment of partial-onset seizures (POS).
- ESL is extensively and rapidly converted to eslicarbazepine after oral administration.[1]
- Data from three randomized, controlled, Phase III trials (Studies 301, 302, and 304) demonstrated that ESL was effective as adjunctive therapy for POS.[2]
  - ESL led to dose-related improvements in most efficacy outcomes, with an effective dose range of 800–1200 mg QD.
- Data from the above studies were used to examine the relationship between eslicarbazepine exposure and selected efficacy endpoints.

OBJECTIVE

- To develop statistical models describing the relationships between eslicarbazepine exposure and selected efficacy outcome measures (standardized seizure frequency [SSF], probability of response [PR], and weekly seizure frequency over time) in patients with POS.

METHODS

Study design

- The design of the three randomized trials included in this analysis has been reported previously.[2]
- Each trial included an 8-week baseline period and a 14-week double-blind period (2 weeks titration; 12 weeks maintenance).
- ESL doses: 400 mg (Studies 301 and 302 only), 800 mg, and 1200 mg QD.

Patients

- Key inclusion criteria:
  - age ≥16 years (Study 304) or ≥18 years (Studies 301 and 302)
  - ≥12 months' history of simple or complex POS ± secondary generalization
  - ≥4 POS during baseline, with no seizure-free period >21 consecutive days (Studies 301 and 302), or
  - ≥8 POS during baseline, with ≥3 seizures in each 4-week period of the baseline, and no seizure-free period >28 consecutive days (Study 304).
- Key exclusion criteria:
  - oxcarbazepine use
  - felbamate use (Studies 301 and 302; allowed if stable in Study 304).

Development of predictive models

- Data for the whole 14-week double-blind treatment period were analyzed.
- Eslicarbazepine exposures in individual patients were calculated using a population pharmacokinetic (PK) model.
- Predictive models were developed to describe the relationship between eslicarbazepine exposure and:
  - standardized seizure frequency (SSF)
  - probability of response (PR): response being defined as ≥50% reduction in SSF from baseline
  - weekly seizure frequency over time.
- Predictive models describing the relationship between eslicarbazepine exposure and SSF or weekly seizure frequency over time were developed via exploratory data analysis, followed by development of a base structural model with evaluation of covariate effects, and final refinement and evaluation of the model.
  - For SSF, the final model was validated using a visual predictive check, to assess concordance between observed and simulated data.
  - For weekly seizure frequency over time, the final Poisson regression model was validated using a posterior predictive check, to assess concordance between simulated distribution of the percentage of responders per dose group versus the observed percentages.
- The predictive model for PR was developed via exploratory data analysis, development of a base logistic regression model with forward selection of covariates, followed by model refinement and finalization.
  - The final logistic regression model was validated using the Hosmer-Lemeshow statistic (estimate of goodness of fit), and the receiver operating characteristic curve (estimate of predictive capacity of the model).

RESULTS

Patients

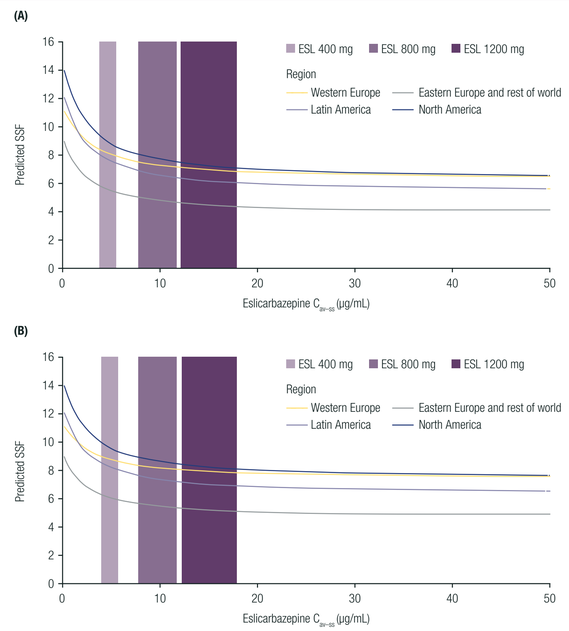
- The exposure–efficacy analyses included 2300 exposure estimates (calculated using the population PK model), based on 1150 patients (80% Caucasian, 53% male; median age 37 years [range, 16–75 years]).
- At baseline, 48.3% of patients were receiving concomitant carbamazepine.
- SSF during the baseline period showed a high level of variability (from 2 to 412 seizures per 28 days).

Relationship between exposure and measures of efficacy

Predictive model for standardized seizure frequency

- The model predicted a decrease in SSF with increasing ESL dose (ESL 400 mg, 5.4 seizures/28 days; ESL 800 mg, 4.6 seizures/28 days; ESL 1200 mg, 4.3 seizures/28 days; placebo, 6.5 seizures/28 days).
- The reduction in SSF with ESL (maximum pharmacologic effect [E_{max}]; **Table 1**) was predicted to be less in patients who were taking carbamazepine at baseline, and in those from Western Europe (WE; **Figure 1**).

Figure 1. Predicted standardized seizure frequency versus eslicarbazepine C_{av-ss}* by region and baseline carbamazepine use: (A) no baseline carbamazepine use; (B) baseline carbamazepine use



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

Table 1. Parameter estimates and standard errors for the final predictive model for standardized seizure frequency

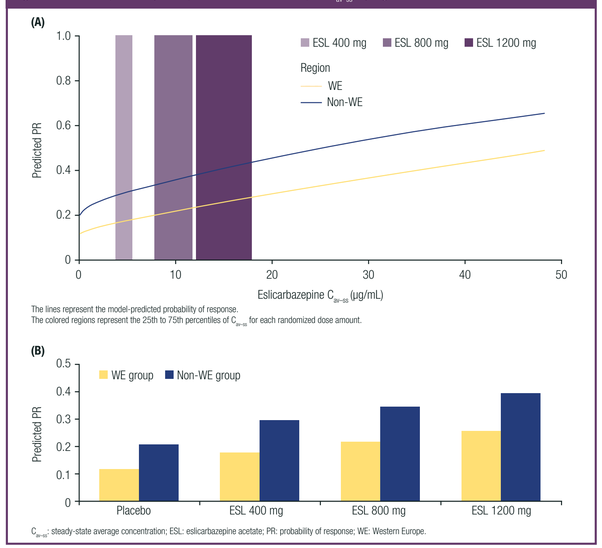
	Final parameter estimate Population mean (% SEM)
Baseline standardized seizures	2.19 (1.3)
Effect of Western European region	0.228 (30.6)
Effect of Latin American region	0.310 (18.4)
Effect of North American region	0.46 (15.3)
Age effect (slope)	–0.00922 (18.3)
Constant placebo effect	–0.276 (13.1)
E_{max} at baseline SSF of 2.4	–0.822 (13.9)
Effect of baseline carbamazepine use on E_{max}	0.150 (37.5)
Effect of Western European region on E_{max}	0.242 (27.9)
EC_{50} (ng/mL)	3530 (51.0)
Additive residual variability	0.0255 (58.0)

EC_{50}: half maximal effective concentration; E_{max}: maximum pharmacologic effect; SEM: standard error of the mean.

Predictive model for probability of response

- A lower PR was predicted for patients from WE than for non-WE patients* (**Figure 2**).
  - For the WE group, predicted PR was 0.12 for placebo, 0.18 for ESL 400 mg, 0.22 for ESL 800 mg, and 0.26 for ESL 1200 mg.
  - For the non-WE group, predicted PR was 0.21 for placebo, 0.30 for ESL 400 mg, 0.35 for ESL 800 mg, and 0.40 for ESL 1200 mg.

Figure 2. Predicted probability of response versus eslicarbazepine C_{av-ss}, by region



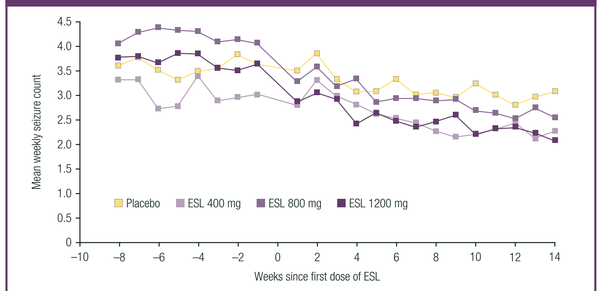
The lines represent the model-predicted probability of response.
The colored regions represent the 25th to 75th percentiles of C_{av-ss} for each randomized dose amount.
C_{av-ss}: steady-state average concentration; ESL: eslicarbazepine acetate; PR: probability of response; WE: Western Europe.

Predictive model for weekly seizure frequency

- The model predicted a maximum reduction in weekly seizure frequency from baseline of 56% during treatment with ESL.
- The model indicated that this effect was related to both time (i.e., a placebo effect; 39%; see **Figure 3**) and eslicarbazepine average steady-state concentration (C_{av-ss}; 61%; see **Figure 4**).
- The estimated eslicarbazepine EC_{50} (half maximal effective concentration) was 9450 ng/mL; this is similar to the median C_{av-ss} with ESL 800 mg QD, indicating that ~50% of the maximal response could be expected with an 800 mg dose of ESL.

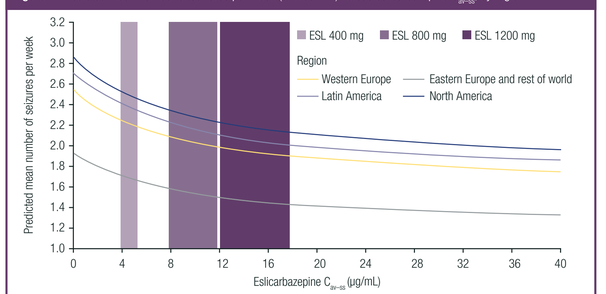
*The PR estimates for the Latin America, North America and rest of world regions were poor. Consequently, patients were regrouped into WE versus non-WE regions.

Figure 3. Mean weekly seizure count versus weeks since first dose, by dose



ESL: eslicarbazepine acetate.

Figure 4. Predicted mean number of seizures per week (at Week 14) versus eslicarbazepine C_{av-ss}, by region



The lines represent the model-predicted mean weekly seizure count at Week 14, assuming a patient of median age (37 years).
The colored regions represent the 25th to 75th percentiles of C_{av-ss} for each randomized dose amount.
C_{av-ss}: steady-state average concentration; ESL: eslicarbazepine acetate.

CONCLUSIONS

- The predictive model developed for standardized seizure frequency (SSF) agreed closely with that developed for probability of response (PR).
  - Both models predicted a better outcome with higher eslicarbazepine exposure (C_{av-SS}) and a worse outcome in patients from WE.
  - The SSF model predicted a worse outcome for patients who were taking carbamazepine at baseline.
- The predicted relationship between exposure and SSF was shallow over the studied concentration range; only slight improvements in seizure control are expected at higher concentrations of eslicarbazepine. Therefore, these findings do not necessarily support the use of eslicarbazepine plasma concentration monitoring to inform dose adjustments of ESL.
- Together with a related analysis of key safety endpoints,[3] this analysis supports the ESL dosing recommendations; the optimal risk–benefit profile is associated with a starting dose of 400 mg and titration to 800 mg or 1200 mg QD; the 1200 mg dose (and concomitant carbamazepine use) may increase the frequency of side effects.[4]

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