Relationship between eslicarbazepine exposure and safety endpoints for eslicarbazepine acetate adjunctive therapy

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED), approved in the US, Canada and the EU as adjunctive treatment of partial-onset seizures (POS).
- After oral administration, ESL is extensively and rapidly converted to its major active metabolite, eslicarbazepine.[1]
- Data from three randomized controlled Phase III trials (studies 2093-301, -302 and -304) showed that adjunctive ESL (400–1200 mg QD) was generally well tolerated by patients with POS.[2]
- The current analysis uses data from the above studies to examine the relationship between eslicarbazepine exposure and the incidence of the most frequently occurring treatment-emergent adverse events (TEAEs) during adjunctive use of ESL.

OBJECTIVES

- To develop statistical models describing the relationship between eslicarbazepine exposure and the incidence of (a) selected TEAEs (b) serum sodium levels, in patients with POS using data from three Phase III studies.
- To characterize the influence of selected covariates on the probability of occurrence of TEAEs.

METHODS

Study design

- The design of the three randomized trials included in this analysis was 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 were 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 month history of simple or complex POS ± secondary generalization
  - ≥4 POS during baseline, with no seizure-free period >21 consecutive days (studies -301, -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).

Data collection and blood sampling

- Adverse events (AEs) were recorded during study visits on Day 1 and at Weeks 2, 8 and 14 (and also at Week 18 in study -301), and by telephone at Week 4. Blood samples for measurement of serum sodium concentrations were taken at –8 weeks (start of baseline period), Day 1, and Weeks 8 and 14.

Development of predictive models

- A previously developed population pharmacokinetic (PK) model for eslicarbazepine was applied to data from the 14-week double-blind treatment period, to determine PK parameter estimates for each patient, which were then used to calculate patient-specific measures of eslicarbazepine exposure, for use in model development as follows: average steady-state concentration ($C_{av,ss}$); area under the concentration time curve (AUC); maximum concentration (C_{max}).
- Predictive models for the probability of selected TEAEs according to eslicarbazepine exposure were developed (for TEAEs occurring in >10% of patients), via exploratory data analysis followed by development of a base logistic regression model with forward selection of covariates, and further refinement of the final model.
  - The final logistic regression model was validated using the Hosmer–Lemeshow statistic (goodness-of-fit), and the receiver operating characteristic curve (predictive capacity of the model).
- A predictive model relating serum sodium concentration to eslicarbazepine exposure was developed via exploratory data analysis, followed by development of a base structural model, evaluation of the effects of covariates, and refinement and evaluation of the final model.
  - The final model was validated using a visual predictive check to assess concordance between the observed and simulated data.
- Potential effects of the following covariates were also evaluated: age; race; gender; body weight; geographic region; use of carbamazepine during baseline; baseline serum sodium concentration.
- The effect of concomitant AED use (and its variation over time) was also evaluated; see **Table 1** for a list of AEDs that were considered for evaluation of influence on model parameters.

Table 1. Concomitant AEDs considered for evaluation of possible influence on model parameters

Carbamazepine	Clobazam	Clonazepam
Gabapentin	Lamotrigine	Levetiracetam
Phenobarbital	Phenytoin	Pregabalin
Primidone	Tiagabine	Topiramate
Valproic acid	Vigabatrin	Zonisamide

RESULTS

Analysis datasets

TEAEs

- The dataset for analysis of TEAEs comprised 9216 TEAE records, based on 1152 patients (306 from study -301, 307 from study -302, and 539 from study -304).
- 80% of patients were Caucasian and 52% were male.
- Patients were between 16 and 75 years old (median 37 years).
- Body weight was 34–135 kg; median 70 kg (females 63 kg; males 75 kg).
  - Mean body mass index (BMI) was 25 kg/m^2 (range 15–54 kg/m^2); <20% of patients were obese (BMI >30 kg/m^2).
- 47% of patients were from Europe, 22% Latin America (LA), 17% North America (NA), and 14% 'rest of the world' (ROW).
- 48% of patients were taking carbamazepine during the baseline period.

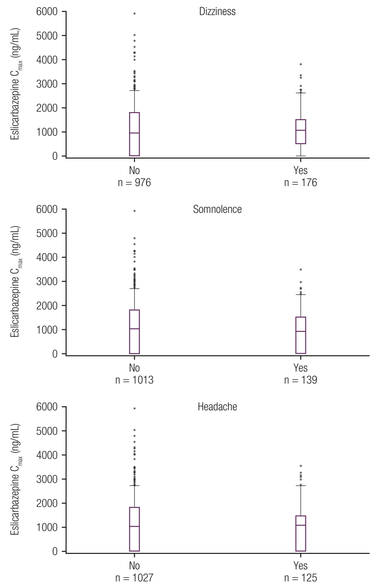
Serum sodium concentrations

- The dataset for analysis of serum sodium concentrations consisted of 3354 measurements from 1128 patients.
- The median serum sodium concentration at baseline was 141 mEq/L (range 121–156 mEq/L). The lowest concentration (121 mEq/L) was found in a patient taking ESL 400 mg QD (the lowest dose studied).
- There was no apparent trend in serum sodium concentrations over time in the placebo group, while some patients in each of the ESL groups (particularly the higher dose groups) showed a slight trend for decreasing serum sodium concentrations over time.
- 29 patients had a decrease in serum sodium concentration >10 mEq/L versus baseline.
- Discontinuation rates due to hyponatremia (serum sodium <125 mEq/L) in the ESL treatment groups were: ESL 400 mg, 0%; ESL 800 mg, 0.2%; ESL 1200 mg, 0.7% (safety population, i.e. all patients who received at least one dose of study medication).
  - Patients with hyponatremia were required to discontinue by the study protocol (no other treatments or investigations were specified).
- Overall, 1.4% of patients who took ESL plus concomitant carbamazepine had serum sodium concentrations ≤125 mEq/L, compared with 0.8% of those who did not take concomitant carbamazepine.

Predictive models for the relationship between exposure and probability of selected TEAEs

- Predictive models were developed for TEAEs reported in >10% of patients, i.e. dizziness, somnolence, and headache.
- Comparisons of C_{max} for patients who did, and did not develop dizziness, somnolence, and headache are shown in **Figure 1**. The distribution of exposure was similar between patients with and without these TEAEs.

Figure 1. Predicted eslicarbazepine exposure (C_{max}) in patients with and without dizziness, somnolence, and headache



Boxes are 25th, 50th and 75th percentiles; whiskers are 5th to 95th percentiles; *are data points outside this range.
C_{max}: maximum concentration.

- The effect of eslicarbazepine exposure (AUC from 0–24 hours [AUC_{0-24}] and C_{max}) on the probability of dizziness, somnolence, and headache was evaluated using both linear and power models.
  - The starting dose for the first week (400 mg or 800 mg) was a strong predictor of the risk of each of these TEAEs.
  - Once the starting dose was included in the models, eslicarbazepine AUC_{0-24} was found to be a statistically significant predictor of the probability of dizziness and headache, while C_{max} was a statistically significant predictor of the probability of somnolence. C_{max} was not a significant predictor of dizziness or headache.
- In the final predictive models for dizziness and headache, the probability of a TEAE was described as a decreasing linear function of eslicarbazepine AUC_{0-24}, with additive shifts for initial doses of 400 mg and 800 mg ESL.
- In the final model for somnolence, the probability of a TEAE was described as a decreasing function of eslicarbazepine C_{max}, with additive shifts for initial doses of 400 mg and 800 mg ESL, compared with placebo.
- Based on the models, the probability of a TEAE (dizziness, somnolence, and headache) for a starting dose of ESL 800 mg QD was approximately twice that for a starting dose of 400 mg QD.
- Higher eslicarbazepine exposure was associated with a lower probability of each of the TEAEs analyzed.
  - This may be explained by the fact that the models were based on incidence data (reflecting only the first occurrence of TEAEs).
  - In each study, the onset of the TEAEs dizziness, somnolence, and headache tended to be during the first 2 weeks of therapy (i.e. during the titration period), when most patients were receiving ESL 400 or 800 mg, and eslicarbazepine exposure was relatively low. In later weeks, when patients were receiving higher doses of ESL, and eslicarbazepine exposure was generally higher, new onset of dizziness, somnolence, and headache was less frequent.

Influence of covariates on the probability of TEAEs

Gender

- The risk of dizziness and somnolence during use of adjunctive ESL was predicted to be greater in females than in males ($p<0.05$).

Body weight

- Patients with higher body weight were predicted to be at less risk of developing dizziness, headache, and somnolence than those with lower body weight ($p<0.001$).

Geographic region

- The risk of dizziness was predicted to be higher among patients from NA, LA and ROW than those from Europe, whereas the risk of somnolence was predicted to be higher in patients from LA than those from Europe, NA and ROW ($p<0.05$).

Use of other AEDs

- Patients who took carbamazepine during the baseline period were predicted to have a higher risk of dizziness and a lower risk of somnolence than those who took other AEDs ($p<0.05$).
- Concomitant use of lamotrigine was predicted to increase the risk of dizziness ($p<0.01$), but not that of somnolence. Although concomitant lamotrigine use was initially identified as a significant predictor of headache, this covariate was not included in the final model due to poor precision of the parameter estimate.
- Concomitant use of levetiracetam and valproic acid were not statistically significant predictors of the probability of the analyzed TEAEs.

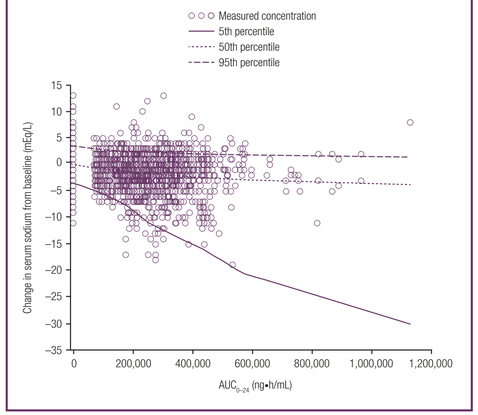
Other covariates

- Other covariates did not significantly affect the probability of dizziness, somnolence, and headache.

Predictive model for the relationship between exposure and serum sodium concentration

- The effect of eslicarbazepine exposure on the change from baseline in serum sodium concentration was evaluated using a number of different structural models (including linear, power, and exponential models).
- The different exposure measurements were found to be highly correlated ($r = 0.97$), and the preliminary models using AUC_{0-24} or C_{max} had nearly identical fits. Therefore, AUC_{0-24} was chosen for use in model development and refinement.
- The relationship between change in serum sodium concentration and eslicarbazepine AUC_{0-24} was best described by a linear model, with reductions in serum sodium levels being proportional to eslicarbazepine exposure (**Figure 2**).
  - A 165,000 ng•h/mL increase in AUC_{0-24} (equivalent to a 400 mg increase in ESL dose) is predicted to lead to a reduction in serum sodium concentration of 0.68 mEq/L.

Figure 2. Median and 90% prediction interval derived from the simulated datasets, overlaid on the observed change from baseline serum sodium values



CONCLUSIONS

- For each of the TEAEs analyzed, the most significant predictor was the initial dose of ESL; the probability of an event was higher for an initial dose of 800 mg QD than for an initial dose of 400 mg QD.
- Based on the serum sodium model, an increase in ESL dose of 400 mg would be predicted to cause a reduction in serum sodium levels of 0.68 mEq/L. This finding is difficult to reconcile with the observations that the proportion of patients with hyponatremia[3] (decrease in sodium ≥10 mEq/L from baseline), and the frequency of hyponatremia reported as a TEAE[2] both showed evidence of dose dependency.
- Together with efficacy modeling data,[4] these results indicate that an optimal risk–benefit profile is achieved by using an initial dose of 400 mg ESL, followed by titration to 800 or 1200 mg; use of an initial dose of 800 mg carries a greater risk of TEAEs.
- After accounting for the initial dose of ESL, there was no significant ascending relationship between eslicarbazepine exposure and the incidence of three of the most frequently occurring TEAEs. Consequently, routine monitoring of eslicarbazepine plasma concentrations does not appear to be useful for predicting potential tolerability issues.

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