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Exposure-safety and efficacy response relationships and population pharmacokinetics of eslicarbazepine acetate

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Objectives: Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED) for focal-onset seizures (FOS). Pharmacokinetic (PK) and pharmacodynamic (PD) models were developed to assess dose selection, identify significant AED drug interactions, and quantitate relationships between exposure and safety and efficacy outcomes from Phase 3 trials of adjunctive ESL.

Methods: Eslicarbazepine (the primary active metabolite of ESL) population PK was evaluated using data from 1351 subjects enrolled in 14 studies (11 Phase 1 and three Phase 3 studies) after multiple oral doses ranging from 400 to 1200 mg. Population PK and PD models related individual eslicarbazepine exposures to safety outcomes and efficacy responses.

Results: Eslicarbazepine PK was described by a one-compartment model with linear absorption and elimination. The probability of a treatment-emergent adverse event (TEAE; dizziness, headache, or somnolence) was higher with an initial dose of ESL 800 mg than with an initial dose of ESL 400 mg QD. Body weight, sex, region, and baseline use of carbamazepine (CBZ) or lamotrigine were also found to influence the probability of TEAEs. Eslicarbazepine exposure influenced serum sodium concentration, standardized seizure frequency, and probability of response; better efficacy outcomes were predicted in patients not from Western Europe (WE; vs WE patients) and those not taking CBZ (vs taking CBZ) at baseline.

Conclusions: Pharmacokinetic and PK/PD modeling were implemented during the development of ESL for adjunctive treatment of FOS in adults. This quantitative approach supported decision-making during the development of ESL, and contributed to dosing recommendations and labeling information related to drug interactions.

KEYWORDS
antiepileptic, epilepsy, eslicarbazepine, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Despite availability of a broad array of therapeutic agents, substantial numbers of patients with epilepsy experience recurrent seizures during antiepileptic drug (AED) therapy and require an alternative monotherapy or add-on treatment.[1] Eslicarbazepine acetate (ESL) is a once-daily (QD) oral AED for focal-onset seizures (FOS). ESL is a member of the dibenzazepine carboxamide family of AEDs, with structural and metabolic differences to the other members of this family, carbamazepine (CBZ) and oxcarbazepine.[2-5] Following oral administration, ESL undergoes rapid first-pass hydrolysis to the primary active metabolite eslicarbazepine.[4,6] Eslicarbazepine and its glucuronide metabolites account for 94% of oral systemic exposure[7]; the minor active metabolites, R-licarbazepine and oxcarbazepine, account for 5% and 1% of systemic exposure, respectively.[8] Eslicarbazepine inhibits sodium currents by binding to voltage-gated sodium channels and preferentially stabilizing the inactivated state of the channel.[9] The apparent half-life of eslicarbazepine is 13-20 hours in plasma and ~20-24 hours in cerebrospinal fluid.[7,8]

Integration of pharmacokinetic (PK) and pharmacokinetic/pharmacodynamic (PK/PD) modeling during clinical drug development provides a quantitative approach to support decision-making for dose selection related to concomitant medication use and other patient- or disease-related factors. Drug exposure (eg area under the plasma concentration–time curve [AUC]) can be predicted for individual patients from a population PK model developed based on plasma drug concentrations from one or more studies. Population PK/PD models can be used to evaluate relationships between drug exposure and relevant efficacy and safety responses. Many examples of the successful application of pharmacometric modeling in clinical drug development have been described and include pharmacologic agents used in treatment of epilepsy.[10-12] PK/PD models have previously been developed for ESL using data from three Phase 3 studies in Europe, but have not included patient data from North America.[13]

This study describes the development of PK and PD models using data from two European studies, a North American study, and 11 Phase 1 studies, to support dose selection, identify significant AED drug interactions, and quantify relationships between exposure and safety and efficacy outcomes in Phase 3 trials. Exposure-response relationships for safety have not been reported previously. The results of these analyses were submitted as part of the US Food and Drug Administration New Drug Application for ESL and contribute to our further understanding of the clinical pharmacology of ESL in the treatment of FOS.

2 | MATERIALS AND METHODS

2.1 | Study design and populations

Data from three Phase 3 and 11 Phase 1 studies of ESL were included in this analysis. The three ESL Phase 3 studies (2093-301 [NCT00957684], 2093-302 [NCT00957047], and 2093-304 [NCT00988429], hereafter defined as Studies 301, 302, and 304; registered at ClinicalTrials.gov) were randomized, double-blind, placebo–controlled, multicenter studies assessing the efficacy and tolerability of oral QD adjunctive ESL 400 mg (Studies 301 and 302 only), 800 mg, and 1200 mg.[14-16] One thousand four hundred and 47 adult patients with at least four FOS within the 4-week period prior to screening despite treatment with 1-3 concomitant AEDs were randomized to treatment. These studies consisted of an 8-week baseline period, a 2-week titration period, and a 12-week maintenance period. All marketed AEDs except oxcarbazepine (due to metabolic similarities with ESL) and felbamate (Studies 301 and 302 only, due to safety reasons) were allowed as concomitant AEDs and dosage was kept stable during the study. A fourth randomized, double-blind, placebo-controlled Phase 3 study was also performed (Study 2093-303)[17] but was not included in the analysis due to Good Clinical Practice deficiencies found during a sponsor audit. The 11 Phase 1 studies (224 subjects included for PK analyses only) were designed based on the specific study objective (eg drug interaction, QTc assessment); these studies included ESL doses ranging from 400 mg to 1200 mg in healthy subjects or special populations.

All participants met the inclusion criteria for the study in which they were enrolled and provided written informed consent prior to participation. Approval was received from the Independent Ethics Committee or Institutional Review Board of each study center.

Details of blood sampling and analysis, and collection of efficacy and safety data, are provided in Appendix S1.

2.2 | Pharmacokinetic modeling

A population PK model for eslicarbazepine was previously developed[13] using data from Phase 3 Studies 301, 302, and 303[14,15,17] and was later refined using data from 11 Phase 1 studies and three Phase 3 studies (Studies 301, 302, and 304). Data from 500/1039 of the subjects included in the current model were also included in the previously developed model.

Covariate analysis was performed to investigate the effects of demographic and clinical covariates (including individual baseline AEDs) on eslicarbazepine PK parameters, and the effects of ESL use on PK parameters of other AEDs; further methodological details are provided in Appendix S1.

2.3 | Exposure-response modeling

Exposure-response analyses (including covariate analyses) were performed using data from patients with available safety and seizure frequency information. Detailed descriptions of the models used to predict the relationship between eslicarbazepine exposure and safety (ie treatment-emergent adverse event [TEAE] incidences and serum sodium levels) and efficacy (ie weekly seizure frequency and likelihood of response) are reported in Appendix S1.

3 | RESULTS

3.1 | Subjects and data

The eslicarbazepine PK model was developed using 5965 plasma eslicarbazepine concentrations from 1039 subjects. Demographic characteristics of subjects from Phase 1 and 3 studies were generally similar at baseline as shown in Table S1, except for the proportion of subjects using specific AEDs. The majority (81.7%) of subjects included were Caucasian and 97.7% were <65 years of age (median age [range]: 36 [16-80] years). AEDs used by >15% of the pooled Phase 3 population included CBZ, lamotrigine, levetiracetam, phenobarbital-like enzyme-inducing AEDs [EIAEDs] (phenobarbital, primidone, or phenytoin), and valproate.

3.2 | Pharmacokinetic modeling of eslicarbazepine

The final population PK model was a one-compartment model with first-order absorption and elimination, with all parameters estimated with good precision (<36% SEM [standard error of the mean]). Further details of the model, and the results generated by the model, are reported in Appendix S1. In summary, eslicarbazepine apparent oral clearance (CL/F) increased with increasing body weight, increasing dose of concomitant CBZ, and with concomitant use of phenobarbital or phenobarbital-like EIAEDs; eslicarbazepine CL/F decreased with worsening renal function (creatinine clearance [CrCL]). Furthermore, the apparent volume of distribution (V/F) of eslicarbazepine was lower in women vs men (of the same body weight), and increased with increasing body weight and with concomitant use of phenobarbital or phenobarbital-like EIAEDs. The effects of concomitant AEDs on eslicarbazepine exposure (AUC at steady-state [AUC_{ss}]) are summarized in Figure 1A. Use of CBZ and phenobarbital-like AEDs reduced eslicarbazepine exposure, such that dose adjustments of ESL may be warranted. The effects of ESL use on exposure to concomitant AEDs are shown in Figure 1B. Use of ESL had a small effect on exposure to CBZ and phenytoin, such that dose adjustments of these AEDs may be required when used in combination with ESL (see Figure 1B). See Appendix S1 for further discussion of Figure 1A,B.

3.3 | Exposure-response relationships for select adverse events

Data for the safety analysis were available from 1152 patients (306 from Study 301, 307 from Study 302, and 539 from Study 304). Eighty percent of the patients were Caucasian, with a median age

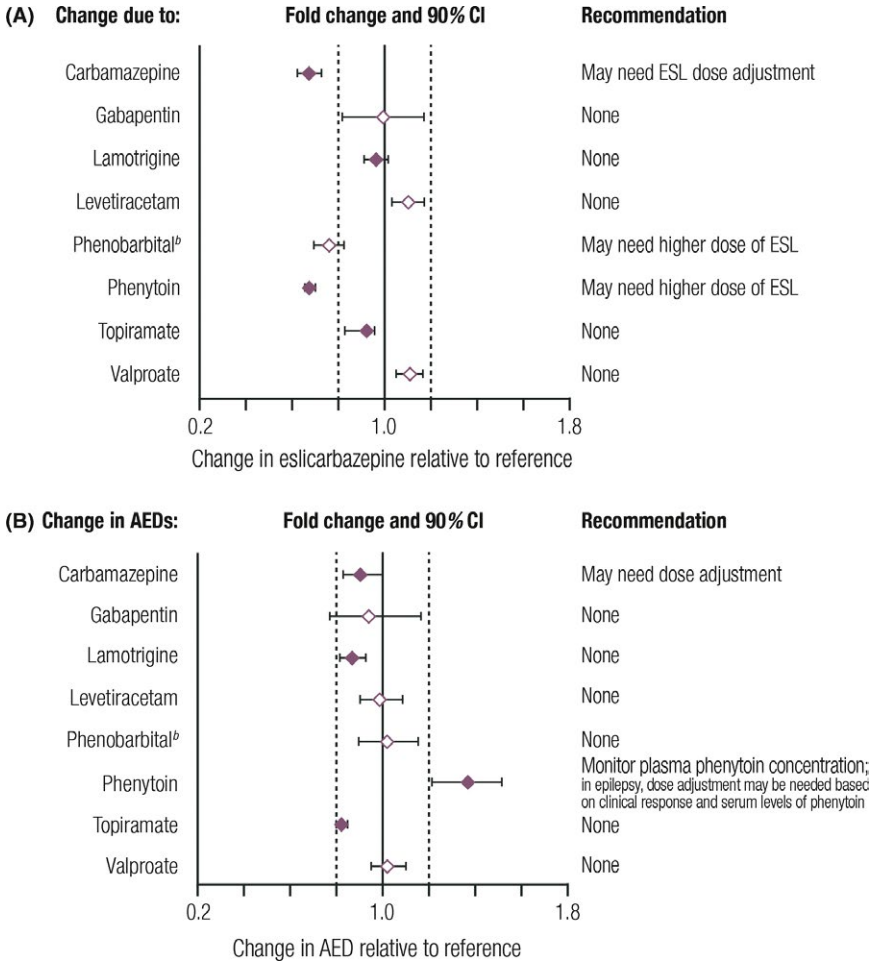

FIGURE 1 A, Potential effects of concomitant AED use on eslicarbazepine exposure.[a] B, Potential effects of ESL on exposure[a] to concomitantly used AEDs.

[a]Based on AUC. [b]Phenobarbital and/or phenobarbital-like AEDs (eg primidone).
Open markers: population PK data; solid markers: Phase 1 study.
AED, antiepileptic drug; AUC, area under the plasma concentration-time curve; CI, confidence interval; ESL, eslicarbazepine acetate; INR, international normalization ratio; PK, pharmacokinetic

of 37 years. Of this patient group, 48% were receiving CBZ therapy during the baseline period.

Predictive models were developed using logistic regression for the TEAEs reported in >10% of patients (dizziness, somnolence, and headache). Comparisons of maximum concentration (C_{max}) for patients who did, and who did not, develop dizziness, somnolence, and headache are shown in Figure 2. The distributions of exposure were similar between patients with and without these TEAEs.

The effect of eslicarbazepine exposure (AUC from 0-24 hours [AUC_{0-24}] and C_{max}) on the probabilities 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.

In the final predictive models for dizziness, headache, and somnolence, the probability of a TEAE was described as a decreasing linear function of eslicarbazepine AUC_{0-24} (dizziness and headache) or C_{max} (somnolence) after accounting for higher probability of occurrence with initial ESL doses of 400 mg and 800 mg, compared to placebo. Based on the models, the probability of a TEAE (dizziness, headache, or somnolence) for a starting dose of ESL 800 mg QD was twice that for a starting dose of ESL 400 mg QD.

Higher eslicarbazepine exposure was associated with a lower probability of each of the TEAEs analyzed. This finding was unexpected and is discussed later. A number of covariates were found to influence the probability of TEAEs. Patients with higher body weight were predicted to be at less risk of developing dizziness, headache, and somnolence than those with lower body weight ($P < .001$). The risk of dizziness and somnolence during use of adjunctive ESL was predicted to be greater in women than in men ($P < .05$), and may potentially be related to the lower body weight in women. The risk of dizziness was predicted to be higher among patients from North America, Latin America, and Rest of World than those from Europe, whereas the risk of somnolence was predicted to be higher in patients from Latin America than those from Europe, North America, and Rest of World ($P < .05$). Patients who took CBZ 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 ($P < .05$). Region and concomitant use of CBZ were not statistically significant predictors of the probability of headache. Concomitant use of lamotrigine was predicted to increase the risk of dizziness ($P < .01$) and headache ($P < .05$), but not that of somnolence. Concomitant use of levetiracetam and valproate were not statistically significant predictors of the probability of the TEAEs evaluated.

3.4 | Exposure-response relationships for serum sodium

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 highest dose group) showed a trend for decreasing serum sodium concentrations over time (data not shown); these patients were considered outliers. When serum sodium levels decreased after initiation of ESL, they appeared to stabilize, or recover, after approximately 8 weeks of exposure to eslicarbazepine (data not shown).

A predictive model relating serum sodium concentration to eslicarbazepine exposure was developed using 3354 serum sodium measurements from 1128 patients. The median serum sodium concentration at baseline was 141 mEq/L (range 121-156 mEq/L), with the lowest pretreatment concentration (121 mEq/L) being in a patient randomized to take ESL 400 mg QD. Overall, the model predicted a weak relationship between change in serum sodium concentration and eslicarbazepine AUC_{0-24}; this is demonstrated by Figure 3, which shows curves (median and 90% prediction interval)

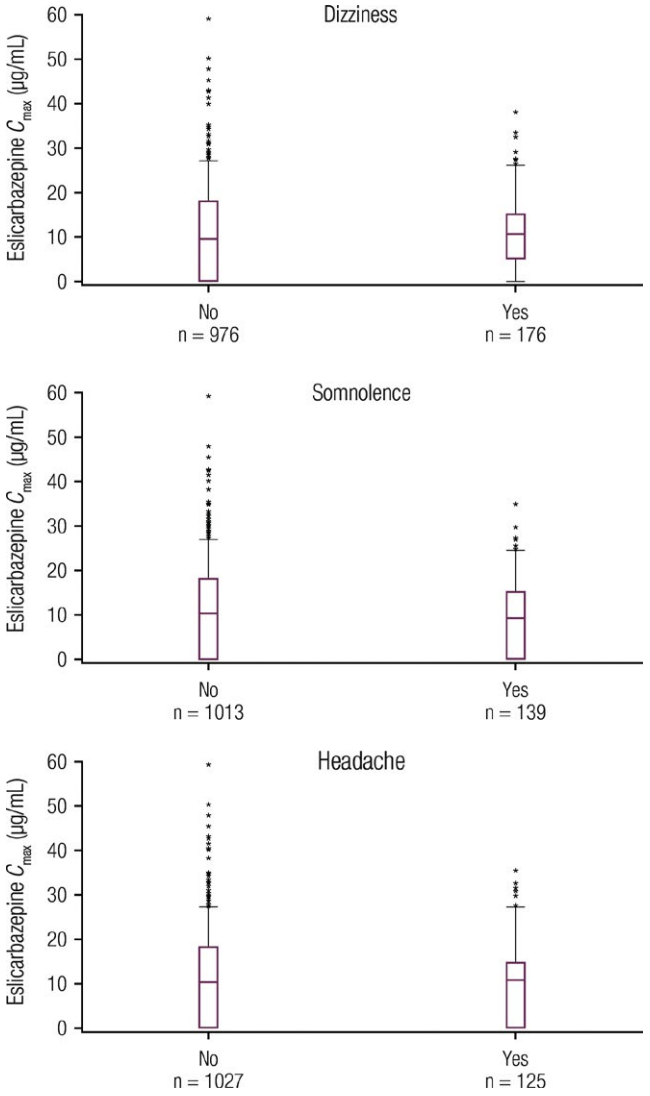

FIGURE 2 Predicted eslicarbazepine exposure (C_{max}) in patients with and without dizziness, somnolence, and headache.

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

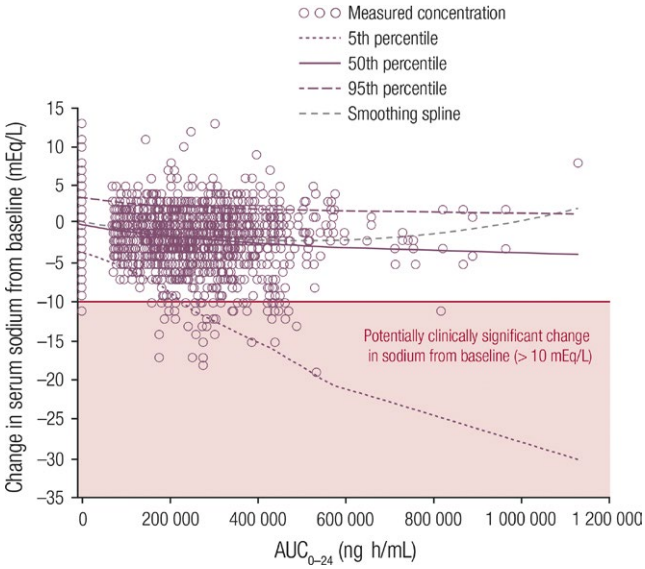

FIGURE 3 Median and 90% prediction interval derived from the simulated datasets, and smoothing spline derived from the observed values, overlaid on the observed values of change from baseline in serum sodium values.

AUC_{0-24}, area under the plasma concentration–time curve from 0-24 hours at steady-state

describing the relationship between the model-predicted change in serum sodium concentration from baseline and eslicarbazepine exposure (AUC_{024}), together with the observed data for patients in the Phase 3 trials of ESL. The shallow slope of the smoothing spline in the same figure (Figure 3) confirms the weak relationship between changes in serum sodium concentration and eslicarbazepine AUC_{0-24} in the observed (non-simulated) data. Although the simulated exposure-response relationship was weak, it was best described by a linear model, where reductions in serum sodium levels were proportional to eslicarbazepine exposure. According to the model, the increase in exposure produced by a 400-mg increase in ESL dose (165 μg h/mL increase in AUC_{0-24}) would be predicted to lead to a reduction in serum sodium concentration of 0.68 mEq/L. A visual predictive check assessment, using simulation of 1000 datasets, supported the predictive capability of the model.

3.5 | Exposure-response relationships for efficacy

High variability in standardized seizure frequency (seizures per 4 weeks [SSF]) was observed during the baseline period (2-412 seizures per 28 days); a substantial percentage of patients (~49%) were receiving concomitant CBZ. The best model for the SSF was the sum of a baseline, a constant placebo effect, and the ESL drug effect which was characterized by a maximum pharmacologic effect (E_{max}) function of the predicted steady-state average eslicarbazepine concentration in plasma. The model predicted a decrease in SSF with increasing ESL dose (placebo, 6.5 seizures/28 days; ESL 400 mg, 5.4 seizures/28 days; ESL 800 mg, 4.6 seizures/28 days; ESL 1200 mg, 4.3 seizures/28 days). The reduction in SSF with ESL E_{max} was predicted to be less in patients who were taking CBZ at baseline, and in those from Western Europe (WE) as shown in Figure 4.

The model for the probability of response was the sum of a placebo effect (corresponding to an effect associated with no exposure to eslicarbazepine), the eslicarbazepine exposure effect described by a power function of the eslicarbazepine average steady-state concentration ($C_{av\text{-}ss}$), and an additive shift for WE. A lower probability of response was predicted for patients from WE than for non-WE patients as shown in Figure 5A. For the WE group, predicted probability of response 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 probability of response was 0.21 for placebo, 0.30 for ESL 400 mg, 0.35 for ESL 800 mg, and 0.40 for ESL 1200 mg.

The weekly seizure frequency model predicted a maximum reduction from baseline of 56% during treatment with ESL. Based on the model, this effect was related to both time (that is, a placebo effect accounted for 39% of the maximum reduction) and eslicarbazepine $C_{av\text{-}ss}$ (accounted for the remaining 61% of the maximum reduction). The predicted mean number of seizures vs $C_{av\text{-}ss}$, by region is displayed in Figure 5B. The estimated eslicarbazepine EC_{50} (half maximal effective concentration) was 9.5 μg/mL; this value is similar to the median $C_{av\text{-}ss}$ with ESL 800 mg QD, indicating that approximately 50% of the maximal response could be expected with an 800 mg dose of ESL.

4 | DISCUSSION

This report describes the development of PK and PK/PD models to support dose selection, understanding of potential drug interactions, and relationships between eslicarbazepine exposure and safety and efficacy outcomes in patients taking adjunctive ESL. This exposure-effect analysis did not account for the minor active metabolites of ESL, R-licarbazepine and oxcarbazepine, due to the minimal level of exposure to these metabolites. The PK model was a one-compartment model for eslicarbazepine with first-order absorption and first-order elimination that adequately described the pooled plasma concentration data from 11 Phase 1 studies and three Phase 3 studies, and extends the initial understanding of eslicarbazepine population PK gained from previous modeling using only sparse Phase 3 data.[13] Pooling of richly sampled Phase 1 data with the sparsely sampled Phase 3 data helped to improve parameter precision and contribute information regarding absorption (allowing for estimation of the between-subject variability of k_a). The effect of body weight on CL/F and V/F was also estimated, rather than fixed allometric exponents as in earlier population PK models based on data from three Phase 3 studies[13] (data on file, Sunovion Pharmaceuticals Inc., Marlborough, MA). In addition, nearly 600 patients with eslicarbazepine PK data were added with the completion of Phase 3 Study 304, which replaced the Study 303 data that were excluded due to Good Clinical Practice deficiencies found during a sponsor audit of the trial.

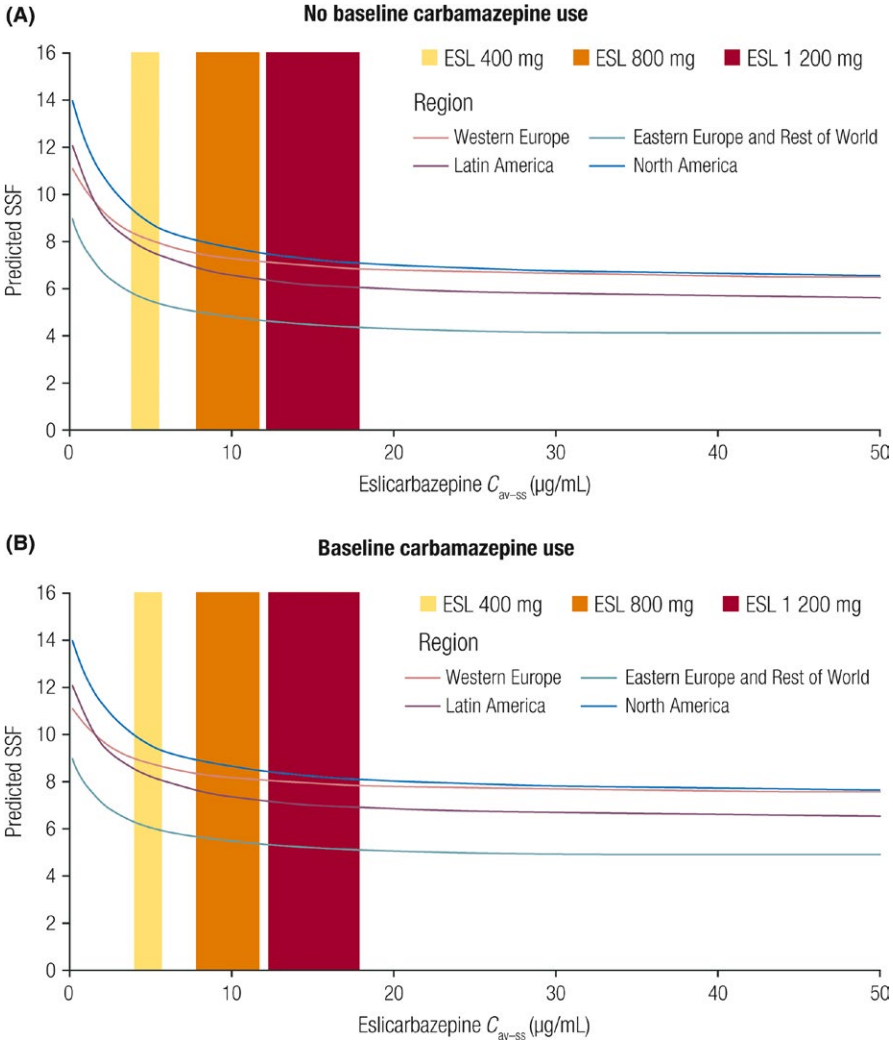

FIGURE 4 Predicted standardized seizure frequency vs eslicarbazepine C_{av-ss}, by region and baseline carbamazepine use: A, no baseline carbamazepine use; B, baseline carbamazepine use.

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

Covariate analysis was performed to identify factors predictive of variability in eslicarbazepine PK. It was not unexpected that the CL/F of eslicarbazepine was statistically significantly related to renal function, as a decrease in mean CL/F of eslicarbazepine of 38.2%, 52.9%, and 61.8% has been previously observed in patients with mild, moderate, and severe renal impairment after administration of a single 800-mg oral dose of ESL.[18] In the current analysis, subjects with a relatively low estimated CrCL had a relatively high eslicarbazepine AUC_{ss} (assuming no concomitant AEDs were administered); this effect on exposure is not expected to be clinically significant in this study population (subjects with CrCL ≥60 mL/min). For adults with CrCL <60 mL/min, a dose reduction should be considered. Eslicarbazepine CL/F and V/F were found to increase in proportion to body weight. However, for most adult patients, ESL dose is not likely to require adjustment based on weight. Weight was tested as a covariate during the model building process, by examining changes in exposure in virtual patients weighing between 34 and 140 kg. Therefore, the above conclusion holds true for most overweight/obese patients, as well as for patients of average weight.

As most patients were receiving one or more concomitant AEDs, the potential influence of AEDs (used in ≥15% of the Phase 3 analysis population, individually or as a group) on eslicarbazepine exposure was evaluated. CBZ and phenobarbital/phenobarbital-like metabolic inducers were found to lead to an increase in CL/F and a reduction in exposure (plasma AUC) of eslicarbazepine (both statistically significant), such that a dose increase of ESL may be warranted when used concomitantly. The interaction between CBZ and ESL is most likely due to CBZ-mediated induction of the uridine diphosphate glucuronosyl transferase enzymes involved in the glucuronidation of eslicarbazepine (one-third of excreted eslicarbazepine is eliminated in the glucuronidated form).[2] The reduction in eslicarbazepine AUC with concomitant phenobarbital/phenobarbital-like metabolic inducers is also consistent with the known effects of these agents as inducers of metabolic enzymes.[2] The same AEDs also increased eslicarbazepine V/F to a small degree; however, the physiologic basis for this finding is unclear and the effect is not expected to be clinically relevant.

Some adverse events occur more frequently when patients take ESL with CBZ[19] (potentially due to a PD interaction); lowering the CBZ dose may therefore be necessary to improve the tolerability of the combination.[8] Use of ESL concomitantly with CBZ also had an impact on carbamazepine PK, leading to reductions in carbamazepine AUC. Dose adjustment of CBZ may therefore be required (if

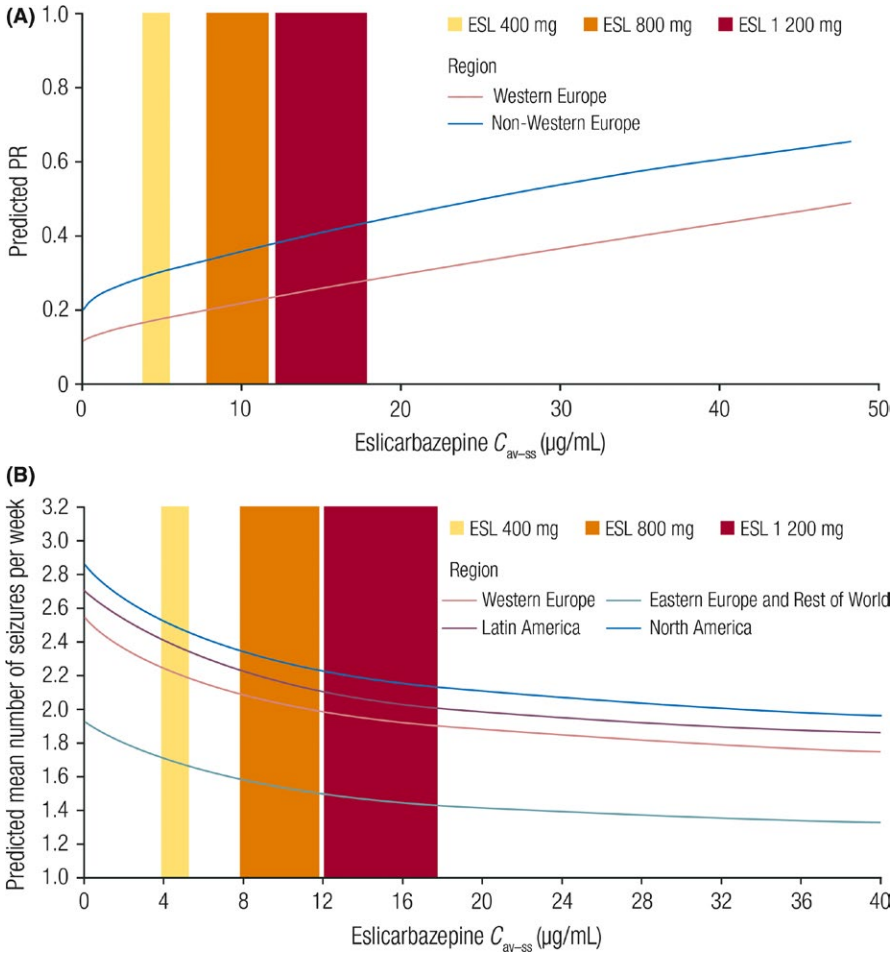

FIGURE 5 A, Model-predicted probability of response. The lines represent the model-predicted probability of response. B, Predicted mean number of seizures per week (at Week 14), vs eslicarbazepine C_{av-ss}, by region. The lines represent the model-predicted mean weekly seizure count at Week 14, assuming 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; PR, probability of response

tolerability allows) to maintain seizure control when ESL and CBZ are used together.

No evidence for an influence of lamotrigine, levetiracetam, or valproate on eslicarbazepine PK was detected, consistent with the findings of a Phase 1 drug interaction study of concomitant administration of lamotrigine and ESL in healthy subjects.[20]

Adjunctive use of ESL had no effect on exposure to valproate, levetiracetam, phenobarbital, phenytoin, or gabapentin. The lack of effect on phenytoin contrasts with the results of Phase 1 Study 2093-121[2] in which adjunct ESL was found to increase phenytoin exposure, likely due to moderate CYP2C19 inhibition by eslicarbazepine. The reasons for the difference between these findings are not clear, but may relate to differences in the study populations or combinations of concomitant AEDs taken by patients in the Phase 3 studies. The altered phenytoin exposure during adjunctive ESL use in Study 2093-121 suggests that monitoring plasma phenytoin concentrations may be warranted; in addition, dose adjustments for phenytoin may be needed, based on clinical response and plasma phenytoin levels.

Higher eslicarbazepine exposure was associated with lower probability of dizziness, headache, and somnolence. This unexpected finding may have resulted from the fact that the models only considered the first occurrence of TEAEs, which typically occur during the first 2 weeks of therapy (ie during the titration period); as patients first initiate treatment with ESL 400 mg or 800 mg, eslicarbazepine exposure during the first 2 weeks of treatment will be relatively low. In later weeks, when patients are receiving higher doses of ESL, and eslicarbazepine exposure is generally higher, new onset of dizziness, headache, and somnolence were less frequent.

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. Indeed, when evaluating investigator-reported TEAEs in the three Phase 3 trials of adjunctive ESL, Krauss et al[21] reported that initiating treatment with ESL 400 mg (vs 800 mg) QD for 1 or 2 weeks was associated with a lower incidence of TEAEs and related discontinuations. In addition, among those who began taking ESL 400 mg QD, there was no notable relationship between maintenance dose and the incidence of TEAEs. The exposure-response modelling data in this paper are a valuable confirmation of the findings obtained from Krauss et al 's post hoc exploratory analysis of clinical trial data.

Taken together, the efficacy and safety models indicate that an improved risk-benefit profile may be achieved using an initial dose of ESL QD 400 mg vs 800 mg. After accounting for the initial dose of ESL, there was no significant ascending relationship between eslicarbazepine exposure and the incidence of dizziness, headache, and somnolence, the three most frequently occurring TEAEs. Consequently, routine monitoring of eslicarbazepine plasma concentrations does not appear to be useful for predicting potential tolerability issues.

TABLE 1 Pharmacokinetic and pharmacodynamic conclusions

An improved risk-benefit profile may be achieved using a starting dose of ESL 400 mg, vs ESL 800 mg
To improve tolerability, use of a lower dose of CBZ may be considered when taken concomitantly with ESL
An increase in ESL dose (if tolerability allows) may be necessary for additional seizure control when ESL and CBZ are taken concomitantly
ESL dose may need to be increased for additional seizure control when taken concomitantly with phenobarbital or phenobarbital-like metabolic inducers (phenytoin, primidone)
For most adult patients, ESL dose adjustment based on body weight should not be required
Routine monitoring of eslicarbazepine plasma concentrations does not appear useful for informing dose adjustments of ESL for efficacy, or for predicting potential tolerability issues

CBZ, carbamazepine; ESL, eslicarbazepine acetate.

Patients taking CBZ during the baseline period are predicted to be at a greater risk of dizziness than those taking other AEDs. Both ESL and CBZ are voltage-gated sodium channel (VGSC) modulators, and dizziness is commonly reported with use of VGSC modulators.[22,23] Patients who take CBZ during the baseline period are predicted to be at less risk of somnolence than those taking other AEDs; the reason for this effect is unknown, but could be due to those patients who were taking CBZ during baseline having developed a tolerance to the adverse effects of this drug class. Patients taking lamotrigine (another VGSC modulator) during the baseline period are predicted to be at a higher risk of dizziness and headache than those taking other AEDs; again, possibly because dizziness and headache are commonly reported with use of VGSC modulators.[22,23]

Patients with higher body weight were predicted to be at less risk of dizziness, headache, and somnolence than those with lower body weight; this may be related to the increasing CL/F and V/F with increasing body weight, although the covariate analysis suggested that for most adults, ESL dose is not likely to require adjustment based on weight. The predicted risk of dizziness and somnolence differed across regions, potentially due to differences in demographic and clinical characteristics between regions.

The serum sodium model describing the overall patient population shows a shallow relationship between eslicarbazepine exposure and serum sodium level; an increase in ESL dose of 400 mg would be predicted to result in a reduction in serum sodium levels of 0.68 mEq/L, which is not expected to be clinically meaningful. To provide context, in the Phase 3 trials of ESL, decreases in serum sodium >10 times this magnitude (>10 mEq/L) were required to be considered clinically meaningful. However, a small proportion of patients (outliers) exhibited larger changes in serum sodium when exposed to eslicarbazepine. A pooled analysis of data from three Phase 3 trials of adjunctive ESL showed that both the proportion of patients with plasma sodium ≤125 mEq/L, and the proportion with hyponatremia reported as a TEAE, were dose-related[19]; these outliers appeared to be especially sensitive to eslicarbazepine. Overall, only small changes in serum sodium were observed in most patients taking ESL; however, some patients appeared to be more sensitive in this respect and exhibited clinically significant reductions in serum sodium following exposure to eslicarbazepine. In fact, the data suggest that if a patient has normal serum sodium levels after 8 weeks of treatment with ESL, the risk of subsequent reductions in levels of serum sodium is likely to be low.

The predictive model developed for SSF agreed closely with the model developed for probability of response. Both models predicted a better outcome with higher eslicarbazepine exposure ($C_{av\text{-}ss}$), in patients not from WE and those not taking CBZ at baseline. The predicted better efficacy outcomes in patients not from WE (vs WE patients) were potentially due to differences in demographic and clinical characteristics between the groups. However, as the current study was not designed to evaluate differences between populations, a future study would be required to further investigate this effect. The CBZ-related predictions from this exposure-efficacy response analysis are a valuable confirmation of the findings obtained in previous post hoc exploratory analyses of clinical trials of adjunctive ESL and ESL monotherapy, where patients not taking CBZ at baseline had better efficacy outcomes than those taking CBZ at baseline.[19,24] The predicted relationship between exposure and SSF was shallow over the range of concentrations included in this analysis. Only slight improvements in seizure control are expected at higher concentrations of eslicarbazepine (within the range expected to occur following ESL 400-1200 mg QD). Therefore, these findings do not necessarily support the use of eslicarbazepine plasma concentration monitoring to inform target dose selection or dose adjustments of ESL.

Pharmacokinetic and PK/PD modeling approaches were implemented during the development of ESL for adjunctive therapy of FOS in adults to further inform understanding of the clinical pharmacology of ESL in this patient population. For the first time, PK/PD modeling demonstrated that starting ESL dose predicted the probability of TEAEs, as well as body weight, sex, region, and baseline use of CBZ or lamotrigine. Eslicarbazepine exposure was shown to have a weak influence on serum sodium levels, SSF, and probability of response, with better efficacy outcomes predicted in patients not from WE (vs WE patients) and those not taking CBZ (vs taking CBZ) at baseline. Taken together, this quantitative approach supported decision-making during the development of ESL and contributed to dosing recommendations and labeling statements, as well as providing general guidance for the use of ESL in the clinic (Table 1).

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CONFLICT OF INTEREST

BE Gidal received funds as a Speakers Bureau member and for consultancy/as an Advisor from Sunovion Pharmaceuticals Inc., Eisai,

Upsher-Smith, Acorda, and UCB. MP Jacobson received consulting fees from Sunovion Pharmaceuticals Inc. E Ben-Menachem received research grants from Eisai, UCB, and BIAL – Portela & C[a]; and funds for consultancy/as an Advisor from BIAL – Portela & C[a], Eisai, UCB, and Abbott. M Carreño received research support from BIAL – Portela & C[a] and Eisai; and honoraria for consulting, serving on a scientific advisory board, speaking, or other activities from UCB Pharma, Eisai, BIAL – Portela & C[a], Shire, and Esteve. D Blum, T Grinnell, and S Sunkaraneni are employees of Sunovion Pharmaceuticals Inc. P Soares-da-Silva, F Rocha, and J Moreira are employees of BIAL – Portela & C[a]. A Falcão received consultancy honoraria from BIAL – Portela & C[a]. E Ludwig, J Fiedler-Kelly, and J Passarell are employees of Cognigen Corporation, which received funding from Sunovion Pharmaceuticals Inc. to perform the analyses described in this manuscript.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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