Use of pharmacokinetic-pharmacodynamic modeling and simulations to predict efficacy outcomes with eslicarbazepine acetate 800 mg once daily as monotherapy

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED), approved as adjunctive treatment for partial-onset seizures (POS) in the USA, Europe, and Canada, and as monotherapy for POS in the USA.
- Following oral dosing, ESL is rapidly and extensively metabolized to the active metabolite, eslicarbazepine,[1] which is thought to act primarily by preferentially stabilizing the inactivated state of voltage-gated sodium channels.[2]
- Conversion to ESL monotherapy (1200 mg and 1600 mg QD) has been studied in two Phase III studies (093-045 and 093-046) in patients with POS whose seizures were previously not adequately controlled while taking either one or two AEDs.[3–5] Conversion to ESL monotherapy at both the doses examined (1200 mg and 1600 mg) was found to be effective (superior to a historical control) and well tolerated.[3–5]
- The FDA-recommended dose range for ESL maintenance is 800–1600 mg QD.[6] For patients on ESL monotherapy, a maintenance dose of 800 mg QD should generally be considered for patients who are unable to tolerate a dose of 1200 mg QD.[6] Here, pharmacokinetic-pharmacodynamic (PK-PD) modeling was used to estimate the efficacy of conversion of patients to ESL monotherapy (800 mg QD; this dose was not examined as a maintenance dose in the Phase III studies). The model was also used to predict efficacy outcomes in patients converting from either one or two AEDs (approximately 70% of patients were taking one AED during the baseline period[6]).

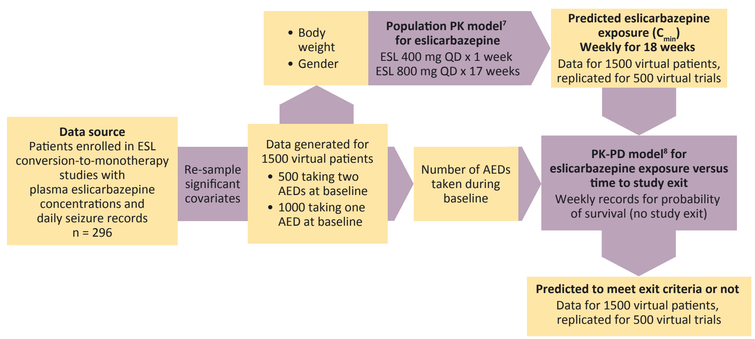
OBJECTIVE

- To predict the efficacy of conversion to ESL monotherapy at 800 mg QD, using modeling and simulation of the exposure-response relationship.

STUDY DESIGN/SIMULATION METHODS

- **Figure 1** shows the study design and simulation methods.

Figure 1. Application of the population PK model and the PK-PD model to predict probability of survival during conversion to ESL monotherapy (800 mg QD)



The development of the population PK model[7] and the PK-PD time to study exit model[8] has been described previously.
AEDs: antiepileptic drugs; ESL: eslicarbazepine acetate; PD: pharmacodynamics; PK: pharmacokinetic; QD: once daily.

Simulation of eslicarbazepine exposure data for virtual patients taking ESL 800 mg QD, using a population PK model for plasma eslicarbazepine

- A previous analysis demonstrated that during once-daily ESL monotherapy in adults, plasma eslicarbazepine concentrations are described by a one-compartment model with first-order absorption and linear elimination.[7] This population PK model was used to predict eslicarbazepine exposure (predicted minimum plasma concentration [C_{min}]) in 1500 virtual patients during 18 weeks of treatment with ESL (one week of ESL 400 mg QD and 17 weeks of ESL 800 mg QD).
- The source data were derived from 332 patients who participated in the two Phase III conversion-to-ESL-monotherapy studies.[3,4] Full PK data were unavailable for 35 patients, and one baseline seizure frequency assessment was unavailable for one patient. The remaining 296 patients comprised the PK-PD dataset; the basis of the simulation was measurements of plasma eslicarbazepine concentrations and daily seizure records for 199 patients who converted from one AED and 97 who converted from two AEDs.
- Demographic data from the 296 patients were re-sampled (drawn randomly with replacement) to create 1500 virtual patients. Re-sampling was conducted to ensure that the distribution of demographic characteristics in the virtual population was similar to that in the original (real) patient population.
  - Re-sampling was conducted for characteristics that had been shown to be significant covariates in the models:
    - Population PK model: weight, gender[7]
    - Time to study exit model (see below): number of AEDs taken during baseline[8]
  - Virtual patient re-sampling was stratified by the number of baseline AEDs; data were simulated for 500 patients taking two AEDs at baseline and 1000 patients taking one AED at baseline.
- Other assumptions (for the purpose of the simulation) were that patients received ESL 400 mg QD for 1 week, followed by 800 mg QD for 17 weeks (similar to the dosing regimen in the ESL monotherapy trials). The data were replicated for 500 clinical trials.
- For each virtual patient, an estimate of eslicarbazepine exposure (trough concentration [C_{min}]) was calculated from the individual PK parameter estimates derived from the population PK model.[7] Integration was performed using NONMEM®, Version 7.1.2 (ICON Development Solutions 2010).

Simulation of survival data for virtual patients taking ESL 800 mg QD, using the PK-PD model for time to study exit

- In the conversion-to-monotherapy trial design, patients exited the study if they met one or more predefined exit criteria indicative of worsening seizure control[3–5]: one episode of status epilepticus; one secondary generalized partial seizure (for patients without generalized seizures during 6 months prior to screening); two-fold increase from baseline in consecutive 28-day seizure rate; two-fold increase from baseline in consecutive two-day seizure rate; worsening of seizures or increase in seizure frequency (as judged by investigator).
- An exposure-response model of the relationship between eslicarbazepine exposure (C_{min}), time to study exit, and number of previous AEDs was previously developed using data from the ESL conversion-to-monotherapy trials.[8]
  - Using this PK-PD model, for each virtual patient and each virtual trial, the predicted weekly C_{min} and the number of baseline AEDs (one or two) were used to determine the probability of survival, i.e., remaining in the study each week.
- The 90% prediction interval for survival was determined at each time point, for virtual patients taking ESL 800 mg and taking one or two AEDs at baseline.

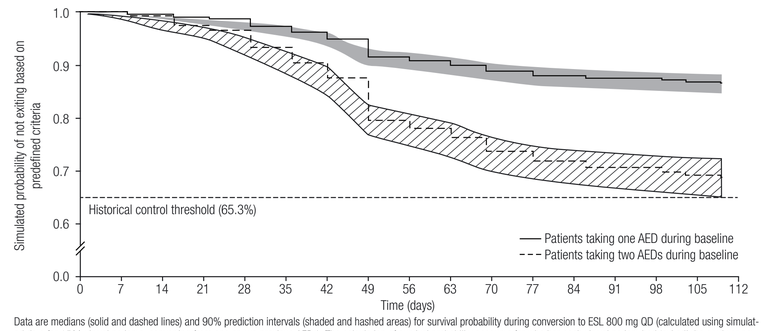
Comparison with historical control

- A 'historical control', representative of the placebo/pseudo-placebo groups in eight historical conversion to monotherapy trials, is currently the standard for comparison in conversion-to-monotherapy AED trials.[9]
- To compare the exit rate for the historical control with that for a new AED, the key statistic is the lower bound of the 95% prediction interval of the overall historical control exit rate; at a type I error rate of ≤5%, this equates to an exit rate of 65.3% at 112 days.[10] The same statistic was used to compare the simulated outcome for ESL 800 mg QD with that for the historical control; if the 95% upper confidence limit of the simulated exit rate is <65.3%, then the null hypothesis (that the exit rate for ESL 800 mg QD is equal to that for the historical control) would be rejected.

RESULTS

- Predicted exit rates at 112 days for virtual patients receiving ESL monotherapy at a dose of 800 mg QD were 13.5% (11.7–15.2%) for patients taking one AED at baseline, and 31.3% (27.5–34.7%) for those taking two AEDs at baseline.
  - The 90% upper prediction limits for the exit rates at 112 days were below the 65.3% threshold, both for patients taking one AED at baseline (15.2%) and for those taking two AEDs at baseline (34.7%; **Figure 2**). This suggests that ESL 800 mg QD reduces seizure-related exits compared with the historical control (in patients who convert from either one or two previous AEDs).

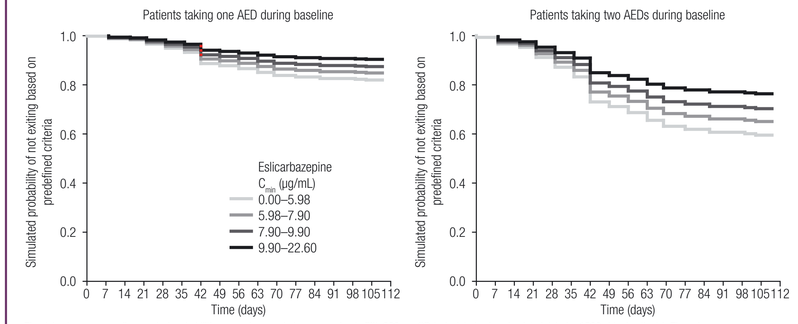
Figure 2. Simulated survival probability versus time, for ESL 800 mg QD, by number of AEDs taken during baseline



Data are medians (solid and dashed lines) and 90% prediction intervals (shaded and hashed areas) for survival probability during conversion to ESL 800 mg QD (calculated using simulated data for 1500 virtual patients, converting from one or two previous AEDs). The calculation of survival probability accounts for whether each virtual patient had 'exited' the study or not and should represent the expected outcome with ESL 800 mg QD.
AEDs: antiepileptic drugs; ESL: eslicarbazepine acetate; QD: once daily.

- **Figure 3** shows median survival probability over time for subgroups defined by quartiles of eslicarbazepine C_{min}, for patients converting from one baseline AED (left panel) or two baseline AEDs (right panel). The results indicate that during conversion to ESL 800 mg QD, the probability of survival (remaining in the trial) is greater for patients who convert from one previous AED, and for those with higher eslicarbazepine exposure (C_{min}), than for those who convert from two previous AEDs, and with lower eslicarbazepine exposure (C_{min}).

Figure 3. Simulated median survival probability versus time, for ESL 800 mg QD, by quartiles of eslicarbazepine C_{min} and number of AEDs taken during baseline



The data shown are median survival probabilities per subgroup during conversion to ESL 800 mg QD (calculated using simulated data for 1500 virtual patients). The subgroups were defined on the basis of the level of eslicarbazepine exposure (C_{min} quartiles) and the number of AEDs taken during baseline (one or two). The median survival probability per subgroup was calculated from the model-predicted survival for each virtual patient, during each week of the simulated trial. The calculation of survival probability did not take into account whether each virtual patient was judged to have 'exited' the study or not.
AEDs: antiepileptic drugs; ESL: eslicarbazepine acetate; QD: once daily.

CONCLUSIONS

- The results of the simulations provide evidence that conversion to ESL 800 mg QD monotherapy may be possible for some adults with POS who were previously taking one AED.
- Patients who had previously been taking two AEDs were predicted to be more likely to meet trial exit criteria (due to seizure worsening) under conditions of a simulated 800 mg maintenance dose, so maintenance doses of ESL 1200 mg or 1600 mg QD should be considered if conversion from two baseline AEDs to ESL monotherapy is contemplated.

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DISCLOSURES

SS, JP, TG and DB: employees of Sunovion Pharmaceuticals Inc. JAP: employee of Cognigen Corporation – a subsidiary of Simulations Plus, Buffalo, NY, USA.

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