INTRODUCTION

- Eslicarbazepine acetate (ESA) is a once-daily AED and 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, it is rapidly and extensively metabolized in the liver to the active metabolite, eslicarbazepine, which is thought to act primarily by preferentially stabilizing the inactivated state of voltage-gated sodium channels.

- Conversion to ESL monotherapy (1120 mg twice daily) has been studied in two Phase IIa studies (031-045 and 032-045). In patients with POS seizures who were previously not adequately controlled while taking one or two AEDs.

- Conversion to ESL monotherapy, at both these doses (800 mg twice daily) was found to be effective (superior to a historical control) and well tolerated.

- The FDA-recommended dose range was 800–1600 mg QD for patients on ESL, monotherapy, a maintenance dose of 1600 mg QD, which resulted in conversion rates of 85% and 92% at 17 weeks (similar to the dosing regimen in the ESL monotherapy trials). The data were replicated for 500 virtual trials.

- For each virtual patient, an estimate of eslicarbazepine exposure (trough concentration [Cmin]) was calculated from the individual PK parameters estimated for the population PK model. Integration was performed using TRAPEZOID Version 7.1.2 (Covance Development Solutions, 2013).

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 visited study 1 day before they may or may not have stabilized the seizure control (the definition of seizure control). Any secondary individual partial seizure (for the patient with previous stabilization during the prior month) was given one day of interval before it could be considered as baseline (28 days). The data were replicated for 500 virtual trials.

- An exposure-response model was used to estimate the probability of conversion to ESL monotherapy (800 mg QD). This dose was considered as a maintenance dose as it was the dose used in the Phase IIa trials. The median survival probability outcomes in patients converting from one or two AEDs (approximately 70%) of patients were taking one AED during the baseline period.

STUDY DESIGN/SIMULATION METHODS

The development of the population PK model and the PK-PD model is described by previous published data (Pretheric, 2013a; Pretheric et al., 2013).

- 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. The population PK model used was used to predict eslicarbazepine acetate concentrations (predicted plasma eslicarbazepine acetate plasma concentrations).

- The same statistic was used to compare the simulated outcome for ESL 800 mg QD with that for the historical control (at the 95% upper confidence limit of the simulated exit rate is greater for patients who convert from one previous AED, and for those with higher eslicarbazepine exposure (Cmin) compared to the historical control (in patients who convert from either one or two previous AEDs).

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 exit (delayed conversion) due to seizure worsening (under conditions of a simulated ESL 800 mg maintenance dose, seizure worsening rates of 1200 mg or 1600 mg QD should be considered if conversion from two baseline AEDs to ESL monotherapy is contemplated).

REFERENCES


CONCLUSIONS

- 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 exit (delayed conversion) due to seizure worsening (under conditions of a simulated ESL 800 mg maintenance dose, seizure worsening rates of 1200 mg or 1600 mg QD should be considered if conversion from two baseline AEDs to ESL monotherapy is contemplated).

REFERENCES


DISCLOSURES

1. JS and EC are employees of Sunovion Pharmaceuticals Inc.; JS: employee of Flagstaff Consulting, a subsidiary of Sunovion Pharmaceuticals Inc.

ACKNOWLEDGMENTS

Epileptic and medical writing support was provided by Beth Bracken (PhD) of Focus on Annuvent, company of UG HealthCare, and using fee-based Sunovion Pharmaceuticals inc.