Pharmacokinetic-pharmacodynamic modeling and simulation to predict efficacy outcomes with eslicarbazepine acetate 800 mg once-daily as monotherapy for partial-onset seizures

Soujanya Sunkaraneni,1 Julie Passarella,2 Elizabeth Ludwig,2 Janet Pitner,1 Todd Grinnell,1 David Blum1

1Sunovion Pharmaceuticals Inc., Marlborough, MA, USA; 2Cognigen Corporation – a subsidiary of Simulations Plus, Buffalo, NY, USA

Objectives: Eslicarbazepine acetate (ESL) is a once-daily (QD) oral anti-epileptic drug (AED) indicated for partial-onset seizures (POS) treatment. Conversion to ESL monotherapy (1200 mg and 1600 mg QD) was studied in patients taking one or two AEDs. Modeling and simulation using plasma eslicarbazepine (primary active metabolite of ESL) concentrations and time to monotherapy study exit data were performed to predict the efficacy of conversion to ESL monotherapy at 800 mg QD.

Methods: A population PK model for eslicarbazepine during ESL monotherapy (1-compartment, first-order absorption/linear elimination) provided minimum concentration [Cmin] prediction in 1500 virtual patients taking one (n=500) or two (n=1000) AEDs at baseline, treated with ESL 400 mg QD for one week, then 800 mg QD for 16 weeks (similar to ESL monotherapy trials). Data for 500 simulated clinical trials were generated. Model-predicted Cmin and number of baseline AEDs were used to determine the weekly probability of each patient meeting pre-defined study exit criteria indicating worsening seizure control, calculated using a PK-PD model relating eslicarbazepine exposure and time to exit in ESL monotherapy trials. The 90% prediction interval for study exit was determined for patients taking one or two AEDs at baseline.

Results: For virtual patients receiving ESL monotherapy (800 mg QD), the 90% upper prediction limits for exit rates at 112 days were below the 65.3% threshold calculated from historical control trials for patients taking either one or two AEDs at baseline (15.2% and 34.7% respectively; Figure 1).

Conclusions: The model-based assessment supports conversion to ESL 800 mg QD monotherapy for partial-onset seizures in adults previously taking one or two AEDs. For patients taking two AEDs, however, prescribers should consider maintenance doses of 1200 mg or 1600 mg QD to reduce the likelihood of seizure worsening, if conversion to ESL monotherapy is contemplated.

The results in this abstract have been previously presented in part at the American Academy of Neurology, Vancouver, BC, Canada, April 17, 2106, and published in the conference proceedings as abstract [P2.025].

Figure 1: Simulated probability of study exit versus time, for ESL 800 mg QD, by number of AEDs taken during baseline

Reference: