Pharmacokinetic-Pharmacodynamic Modeling and Simulation to Predict Efficacy Outcomes With Eslicarbazepine Acetate 800 mg Once Daily as Monotherapy for Partial-Onset Seizures

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INTRODUCTION

Eslicarbazepine acetate (ESL), a once-daily (QD) oral antiepileptic drug (AED), approved as adjunctive therapy 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, which is thought to act primarily by preferentially stabilizing the inactivated state of voltage-gated sodium channels.

Conversion to ESL monotherapy (1200 mg and 1600 mg QD) has been studied in two Phase 3 studies (393-045 and 093-046) in patients with POS whose seizures were previously not adequately controlled while taking either one or two AEDs. Conversion to ESL monotherapy at the doses examined (1200 mg and 1600 mg) was found to be effective (superior to placebo) in partial-onset seizures in adults with epilepsy.

The FDA-recommended dose range for ESL monotherapy is 800–1600 mg QD. 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. Here, pharmacokinetic-pharmacodynamic (PK-PD) modeling was used to estimate the efficacy of conversion of patients to ESL monotherapy (800 mg QD, dose was not examined as a maintenance dose). The model was also used to predict efficacy outcomes in patients converting from one to two AEDs (approximately 70% of patients were taking one AED during the baseline period).

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

1. 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)

2. The source data were derived from 332 patients who participated in the two Phase 3 conversion-to-ESL-monotherapy studies.

Figure 2. Simulation of Survival Data for Virtual Patients Taking ESL 800 mg QD, Using the PK-PD Model for Time to Study Exit

3. Figure 3 shows median survival probability over time for subgroups defined by the presence of eslicarbazepine exposure (predicted minimum plasma concentration [Cmin] at 1000 virtual patients).

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.

RESULTS

1. Predicted exit rates at 112 days for virtual patients receiving ESL monotherapy at a dose of 800 mg QD were 34.9% (32.0–37.9% for patients taking ESL 800 mg QD for 1 week and 4.70–7.40% for those baslined on two AEDs at baseline.

2. The 95% upper prediction limit for the exit rate at 112 days was below the 65.3% threshold for patients taking ESL monotherapy, which was 65.3% (62.4–68.1%) for patients who had previously been taking two AEDs at baseline, and 66.6% (62.4–70.1%) for patients who had previously been taking one AED at baseline.

REFERENCES


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