Modeling and Simulation Strategy to Support Patients with Estilcarbazepine Acetate (ESL) Development in the Treatment of Partial-Onset Seizures

S Sunkanenji, S Bihorel, E Ludwig, J Fiedler-Kelly, D Morris, S Hopkins, G Galluppi, D Blum

1Sunovion Pharmaceuticals Inc., Marlborough, MA, USA; 2Cognigen Corporation, a SimulationsPlus company, Buffalo, NY, USA

INTRODUCTION

• Estilcarbazepine acetate (ESL, Aptiom®) was FDA approved for adjunctive treatment of partial-onset seizures in adults aged 16 years and older, with or without concomitant levetiracetam use as monotherapy.

• A review of FDA analysis has provided evidence across antiepileptic drugs (AEDs) that exposure-response relationships are preserved between adult and pediatric subjects (aged 4 years and older) with ESL.

• The population pharmacokinetic (PPK) modeling of Phase 1 and Phase 3 studies supporting the ESL submission in adults was used as the basis for dose selection in pediatric patients.

• Clinical trial data were used to characterize ESL pharmacokinetics and pharmacodynamics in pediatric patients.

• Doses were selected for treating POS in pediatric subjects (aged 4 to 17 years) by targeting estilcarbazepine (primary active metabolite of ESL) exposures at levels demonstrated to be effective, as in adult studies, and in consensus with the PEGEE initiative elaborations on extrapolation.

• A modeling and simulation strategy with sequential PPK extrapolation (top-down approach) and physiologically-based pharmacokinetic (PBPK) prediction (bottom-up approach) considering maturation of relevant elimination pathways was designed to leverage prior data from the pediatric patients and adults to inform dose selection and design of a clinical trial in infants aged 1 month to 4 years old.

• An overview of key steps in the modeling and simulation strategy employed in the pediatric development of ESL is provided in Figure 1.

Figure 1. Flow Chart of Strategy for Pediatric Development and Plan for Study in Infants

• Weights were randomly assigned with a range of body weights (from 10 to 75 kg) and concomitant medication usage was randomly assigned based on the analysis population (Sunovion 2003-2032 and Sunovion 2003-305).

• Simulated pediatric exposures (maximum plasma concentrations during a dosing interval at steady state) for a typical pediatric subject across a range of body weights were provided in Figure 3, and were targeted to match exposures from adult licensed ESL formulation of 100 mg to 1200 mg subject adjusted on the basis of PBPK simulations (Rn in 2010; 11.1). Body-weight-equivalent doses were selected in pediatric patients (up to 17 years) in valid comparative exposures to the adult population (Table 2).

Table 1. Estilcarbazepine Final Model in Pediatric Subjects With Refractory Partial Epilepsy

- Pediatric PPK Model Refinement

- Pediatric PPK model was statistically modified to express the overall clearance as the sum of renal and fecal elimination pathways, ex estilcarbazepine metabolite B alone, and a renal elimination pathway.

- The simulated exposure was reduced by the inclusion of unbound renal clearance of the parent drug and the metabolite B.

- The phase 1 dose range was randomly sampled from a uniform distribution between 1 and 24 mg/kg.

- Once-daily and twice-daily ESL dosing scenarios were simulated for total daily doses of 8 to 32 mg/kg for 21 days accounting for a maximum daily dose of 1200 mg as oral suspension formulation in infant subjects aged 1 month to 4 years.

- Modeling results demonstrated that ESL concentrations in the neonatal age in adults receiving 1200 mg and the daily and the relative between biomarkers (DLc0) and maintenance doses (DLc13) were generally decreased in the studied population.

- Pharmacokinetic parameter estimation of the pediatric PPK model were derived separately for absorption and elimination.

- Concentration-dependent clearance (CLD) and volume of distribution (VdD), respectively, were used to characterize the elimination pathways.

- Concentration-dependent first-order absorption rate constant for tablet (1/h) was used to predict the oral bioavailability.

- The study results from the refined model and PBPK models indicate that predicted exposures were similar. Selected doses are shown in Table 4.

Figure 2. Visual Predictive Check of the Final PPK Model in Pediatric Subjects Aged 2 to 17 Years With Refractory Partial Epilepsy

- PBPK Model Development

- Pharmacokinetic parameter for the PBPK models were derived separately for absorption (CA for absorption and elimination (CL) for elimination).

- The PBPK model was first developed and provided a basis for describing the mean-systematic data for the pediatric development studies in Sunovion 2003-2032 and 2003-305.

- Modeling parameters were adjusted for age, sex, and body weight using population estimates for age related, sex related, and dietary differences in the PBPK models. UGT2B4 enzyme activity was derived from age-related changes in body weight and sex with concomitant carbohydrate consumption.

- The study results from the refined model and PBPK models indicate that predicted exposures were similar. Selected doses are shown in Table 4.

Table 3. Selected ESL Dose Regimens for Patients Aged 4 to <14 Years

- PK Sampling Schedule Evaluation

- Various PPK and PBPK models for the Study SEP973-383 protocol were evaluated using the refined ESL PK model on the basis of the information contained in the sampling schedules including a proband sample.

- The study results from the refined model and PBPK models indicate that predicted exposures were similar. Selected doses are shown in Table 4.

Table 4. Relative Efficiency of Various Sampling Schedules

- Study Protocol Dose Adjustment Algorithm

- The proposed dosing regimen for the low- and high-dose regimens in each age group (1 to 4 months, 5 to 12 months, and 13 to 24 months) defined for ESL 8 mg/kg/day are shown in Table 3.

- A population-based dosing recommendation will be adjusted on Day 15 (±1 d) on the basis of week 3 concentrations obtained from the first 30 subjects (10 each from the 3 youngest age groups). Analyses including development of a pediatric/PBFK model were performed to support the dose selection.

APPLICATIONS AND LEARNING

- A recent FDA analysis has provided evidence across AEDs that exposure-response relationships are preserved between adult and pediatric subjects with POS (4 years and older).

- This case study illustrates the successful application of adult-use exposure metrics for pediatric dose selection to gain approval for the indication in patients for ESL in 4 patients aged 6 months to 4 years old.

- It is a rare disorder for the treatment of POS. Without conducting a well-controlled efficacy study, it could be an integrated PPK and PBPK modeling and simulation strategy to support dosing recommendations for infants and young children in clinical trials in infants, without conducting a separate PK study.

REFERENCES


