Physiologically based and population pharmacokinetic (PBPK, PPK) modeling and simulation to support dose selection and study design for eslicarbazepine acetate (ESL) adjunctive therapy in infants with partial-onset seizures (POS)

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INTRODUCTION

- Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED), approved as adjunctive treatment in adults ≥18 years for partial-onset seizures (POS) in the USA and Canada, and as monotherapy for POS in the USA. In Europe, ESL is approved as adjunctive therapy in adults, adolescents, and children aged above 6 years, with POS with or without secondary generalization.
- The safety and efficacy of ESL as adjunctive treatment has been studied in pediatric populations and is supported for subjects ≥4 years by population pharmacokinetic (PPK) models of the plasma concentration of eslicarbazepine, the primary ESL metabolite.[1]
- A modeling and simulation strategy with sequential PPK extrapolation ('top down' approach) and physiologically based pharmacokinetic (PBPK) prediction ('bottom up' approach) was employed, using data from pediatric patients and adults, in order to inform dose selection and design of a clinical trial (Study SEP093-363) in infant and pediatric patients aged 1 month–<4 years with POS.

OBJECTIVES

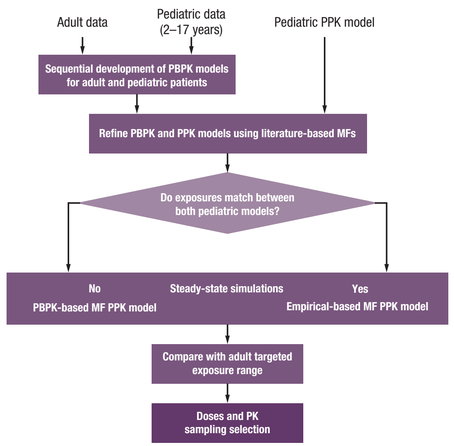
- To refine the previously developed pediatric PPK model[1] to predict eslicarbazepine PK in infant patients.
- To develop a PBPK model for eslicarbazepine in healthy adults and pediatric patients.
- To predict eslicarbazepine exposures using the pediatric PPK and PBPK models, in order to inform ESL dose selection and the design of Study 363, assessing ESL as adjunctive therapy in infants.

METHODS

Modeling and simulation strategy to inform dose and sample selection

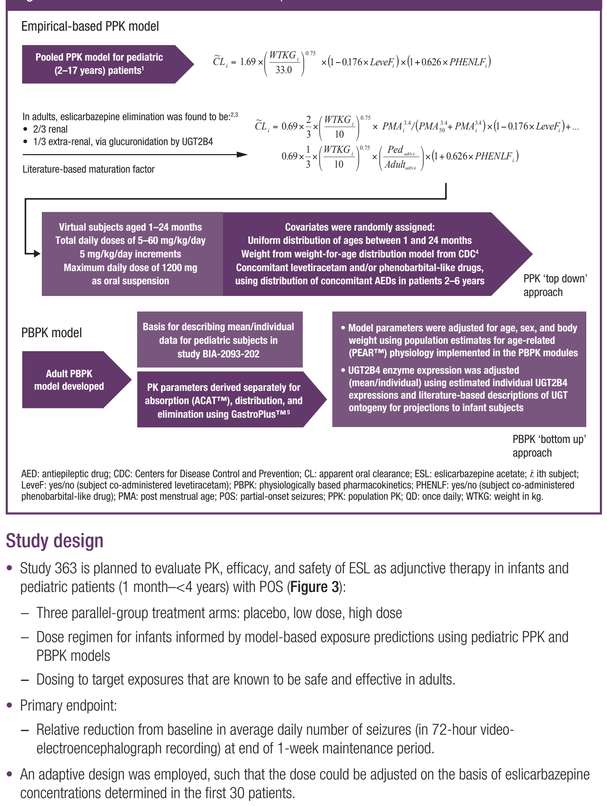
- An overview of the modeling and simulation strategy is shown in **Figure 1**, and the model development steps are outlined in **Figure 2**.

Figure 1. Overview of modeling and simulation strategy



MF: maturation factor; PBPK: physiologically based pharmacokinetics; PPK: population pharmacokinetics.

Figure 2. Pediatric PPK and PBPK model development

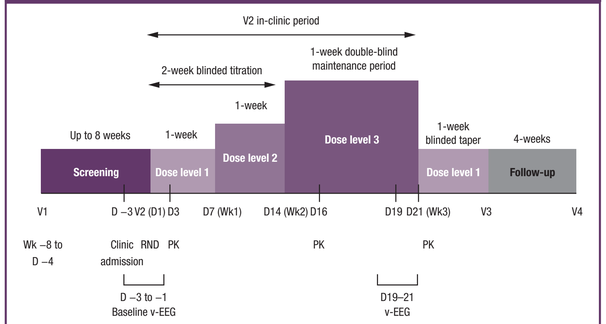


AED: antiepileptic drug; CDC: Centers for Disease Control and Prevention; CL: apparent oral clearance; ESL: eslicarbazepine acetate; *i*: ith subject; LeveF: yes/no (subject co-administered levetiracetam); PBPK: physiologically based pharmacokinetics; PHENLF: yes/no (subject co-administered phenobarbital-like drug); PMA: post menstrual age; POS: partial-onset seizures; PPK: population PK; QD: once daily; WTKG: weight in kg.

Study design

- Study 363 is planned to evaluate PK, efficacy, and safety of ESL as adjunctive therapy in infants and pediatric patients (1 month–<4 years) with POS (**Figure 3**):
  - Three parallel-group treatment arms: placebo, low dose, high dose
  - Dose regimen for infants informed by model-based exposure predictions using pediatric PPK and PBPK models
  - Dosing to target exposures that are known to be safe and effective in adults.
- Primary endpoint:
  - Relative reduction from baseline in average daily number of seizures (in 72-hour video-electroencephalograph recording) at end of 1-week maintenance period.
- An adaptive design was employed, such that the dose could be adjusted on the basis of eslicarbazepine concentrations determined in the first 30 patients.

Figure 3. Study design (Study 363)



D: day; PK: pharmacokinetic; RND: randomization; v-EEG: video-electroencephalograph; V: visit; Wk: week.

Pediatric PPK model refinement

- The pediatric PPK model was empirically modified (**Figure 3**) to express overall clearance (CL) as the sum of the renal and extra-renal elimination pathways. Eslicarbazepine acetate metabolites are eliminated by renal excretion in the unchanged (2/3) and glucuronide conjugate forms (1/3).[2,3]
  - The maturation of the renal fraction of elimination was reflected by maturation of glomerular filtration rate.[6]
  - Maturation of the extra-renal fraction of elimination was reflected by the relative expression of UGT2B4 mRNA in pediatric versus adult patients.[7]
- Concomitant AED effects on eslicarbazepine CL were re-parameterized accordingly.
  - Levetiracetam most likely exerts its effect on apparent elimination CL by altering the renal fraction of eslicarbazepine elimination.[8]
  - Phenobarbital-like AEDs most likely increase CL by induction of the hepatic fraction of eslicarbazepine elimination.

PBPK model development

- A baseline PBPK model including mechanistic absorption and elimination processes of eslicarbazepine described the mean and individual data for healthy adult patients.
- The model was extended to describe the mean and individual data for pediatric and adolescent patients by accounting for differences in age, sex, body weight and other physiologically relevant parameters (including maturation of UGT2B4 enzyme expression).
- A custom set of assumptions for the ontogeny of UGT2B4 (derived from the pediatric model), along with appropriate physiologically relevant changes (implemented in PEAR™ physiologies) were used to predict exposures in infants (1 month–<24 months).

RESULTS

Proposed dosing regimen

- The proposed dosing regimens for Study 363, based on modeling and simulations, for the low and high maintenance doses in each age group are shown in **Table 1**.

Table 1. Proposed ESL doses (mg/kg/day) for patients aged 1 month–<4 years

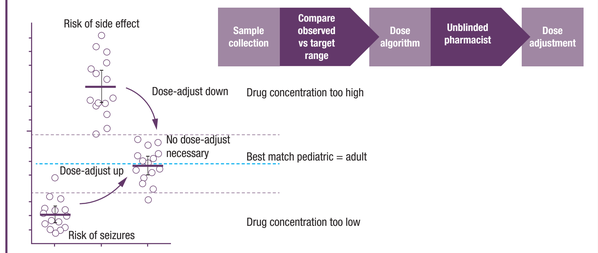
ESL group	Age category	ESL titration Week 1 (dose level 1)	ESL titration Week 2 (dose level 2)	ESL maintenance dose Week 3 (dose level 3)
1 (low dose)	1–<6 months	2.5	5	7.5
	6–<12 months	5	7.5	10
	12–<24 months	5	10	12.5
	24 months–<4 years	5	10	15
2 (high dose)	1–<6 months	5	10	15
	6–<12 months	10	15	20
	12–<24 months	10	20	25
	24 months–<4 years	10	20	30
3 (placebo)	All ages	Placebo	Placebo	Placebo

Note: Doses selected to target exposures that are known to be safe and effective in adults.
Doses in 1 month–<24 months' age categories are based on predicted exposures from the pediatric PBPK model.
Doses for the age category 24 months–<4 years are based on predicted exposures from the pediatric PPK model.

Dose adjustment

- For confirmation of the predicted exposures, a pre-dose (trough) eslicarbazepine concentration at steady state will be measured on Day 3 ($C_{Day3,obs}$) in 10 infant patients from each age group (1–<6 months, 6–<12 months and 12–<24 months).
- Instructions will be provided to the unblinded pharmacist to individually adjust dose level 3 using a dose- and age-group-based adjustment algorithm and the $C_{Day3,obs}$ measurement.
- These samples will be scaled and compared with the 1200 mg adult target concentration range (median (±30%) trough concentration at steady state) through graphical analysis as shown in **Figure 4**.
- If there is an apparent trend or difference between the observed and targeted concentrations, the targeted maintenance dose (dose level 3) will be adjusted for the remainder of the study.

Figure 4. Dose adjustment for low and high ESL maintenance dose groups using Day 3 eslicarbazepine concentration in infants (1 month–<24 months)



Target range = desired concentration range as identified with established PPK model of 1200 mg dose-exposure in adults.
ESL: eslicarbazepine acetate; PPK: population pharmacokinetic.

PK sampling schedule optimization

- Various PK sampling schedule scenarios (such as number of samples and sampling times) were evaluated using the refined pediatric PPK model using PIFM.[9]
  - Based on the relative efficiency of each scenario, a sparse sampling schedule was selected to provide sufficient information to develop a robust exposure–response model.
- The proposed sampling schedule involves collecting plasma PK trough concentrations on Days 3 and 16, and an additional sample on Day 21 between 30 minutes to 4 hours post-dose.

CONCLUSIONS

- An integrated PPK and PBPK strategy was developed to inform dose regimen and design of a study to assess the efficacy, PK, and safety of adjunctive ESL in infants, without requiring a separate intensive PK study.
- An appropriate number of patients for the initial cohort and PK sampling schedule was proposed to provide sufficient information to describe the exposure–response relationship in infants.
- A dose-adjustment algorithm was developed to inform safe and effective dose levels, based on data acquired after 3 days of treatment.

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DISCLOSURES

SS, SH, GG and DB are employees of Sunovion Pharmaceuticals Inc. SB, EL, JF-K and DM are employees of Cognigen Corporation – a Simulations Plus company.

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