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

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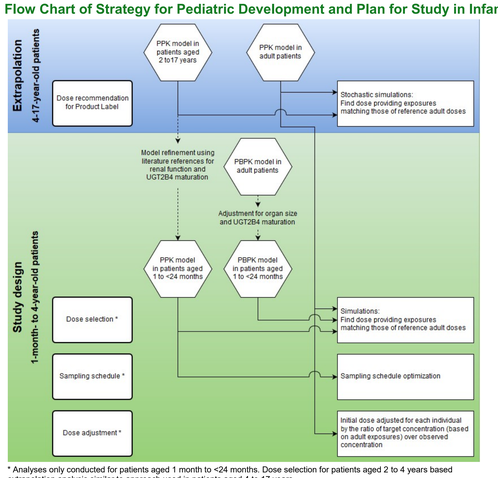
INTRODUCTION

- Eslicarbazepine acetate (ESL, Aptiom®) was FDA approved for adjunctive treatment of partial-onset seizures (POS) in adults aged 18 years and older, with subsequent approval as monotherapy.
- A recent 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 POS.[1]
- The population pharmacokinetic (PPK) modeling of Phase 1 and Phase 3 studies supporting the ESL submissions in adults was used as a basis for dose selection in pediatric patients aged 4 to 17 years.
- Doses were selected for treating POS in pediatric subjects (aged 4 to 17 years) by targeting eslicarbazepine (primary active metabolite of ESL) exposures at levels demonstrated to be effective in adults, as per FDA analysis, and consistent with the PEACE initiative deliberations on extrapolation.[2]
- 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



* Analyses only conducted for patients aged 1 month to <24 months. Dose selection for patients aged 2 to 4 years based extrapolation analysis similar to approach used in patients aged 4 to 17 years.

PEDIATRIC PPK MODEL AND SIMULATIONS FOR DOSE EXTRAPOLATION

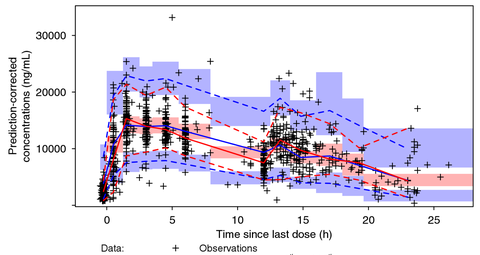
- Data: Phase 2 Study BIA-2093-202 (ESL dosages: 15 and 30 mg/kg/day) and Phase 3 Study BIA-2093-305 (10, 20, or 30 mg/kg/day). Subjects were 2- to 18-year-old children and adolescents with refractory POS receiving other concomitant AEDs.
- Once-daily ESL administration: oral suspension formulation in subjects aged 2 to 6 years; tablet formulation for older subjects.
- Frequent eslicarbazepine (primary active metabolite) pharmacokinetic (PK) sampling was performed following each of three 4-week treatment periods in the Phase 2 study. Sparse samples were collected in Study BIA-2093-305.
- Pooled PPK model development including stepwise covariate analysis performed using NONMEM® Version 7, Level 1.2[3] using standard procedures.
- Final PPK model parameter estimates/standard errors are shown in **Table 1**.
  - One-compartment model with body weight-based allometric scaling of volume and clearance (CL) and formulation-specific absorption; structurally similar to adult PPK model.
  - Carbamazepine decreases exposure.
  - Phenobarbital-like drugs increase and levetiracetam decreases CL.
- **Figure 2** shows the results of a visual predictive check model evaluation; the median concentrations predicted by the final PK model generally follow closely with the median observed concentrations.
- Stochastic model-based simulations were performed to predict steady-state exposures after repeated administrations of various once-daily doses (100 to 1200 mg, in increments of 100 mg), as tablet formulation in 500 virtual pediatric subjects per dose.
- 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 (Studies BIA-2093-202 and BIA-2093-305).
- Simulated pediatric exposures (minimum plasma concentrations during a dosing interval at steady state [$C_{min,ss}$]) for a typical pediatric subject across a range of body sizes are provided in **Figure 3**, and were targeted to match exposures from adult approved titration and maintenance doses of 400 to 1200 mg adjunct therapy. Based on model-based PK simulations (R Version 2.10.1[4]), body weight-adjusted doses were selected in pediatric patients (4 to 17 years) to yield comparable exposures to the adult population (**Table 2**).

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

Parameter	Final Parameter Estimate		IIV / RV	
	Typical Value	%SEM	Magnitude	%SEM
CL/F[a]: apparent elimination clearance (L/h)	1.69	2.92	25.0 %CV	15.5
Proportional shift in CL/F for levetiracetam use (-)	-0.176	25.6		
Proportional shift in CL/F for phenobarbital-like AEDs use (-)	0.626	18.8		
V/F: apparent volume of distribution (L)	32.8	4.78	13.2 %CV	65.1
KAT: first-order absorption rate constant for tablet (1/h)	0.895	FIXED	83.8 %CV	FIXED
KAO: first-order absorption rate constant for oral suspension (1/h)	4.18	FIXED		
F1: relative bioavailability during carbamazepine use (-)	0.679	6.76	NE	NE
RV CCV component	0.0543	11.6	328 - 23.3 %CV[b] F [100 - 50000]	NA
RV additive component	107000	53.2		

Abbreviations: AED, antiepileptic drug; CCV, constant coefficient of variation; %CV, coefficient of variation expressed as a percentage; IIV, interindividual variability; NA, not applicable; NE, not estimated; RV, residual variability; %SEM, standard error of the mean expressed as a percentage.
[a] F is bioavailability.
[b] The residual variability (%CV) was calculated using the following equation: (sqrt(F^2x0.0543+107000)/F)x100, where F is the model-predicted concentration.

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



Medians and percentiles are plotted at the median time since last dose of the data observed within each time since last dose interval.

Figure 3. Summary of Simulated Eslicarbazepine Pediatric Exposures at Selected Doses Relative to Target Adult Titration and Maintenance Dose Exposures

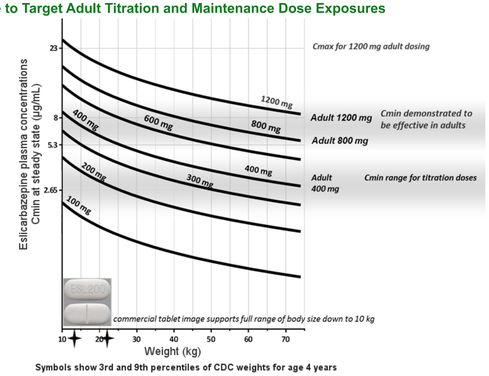


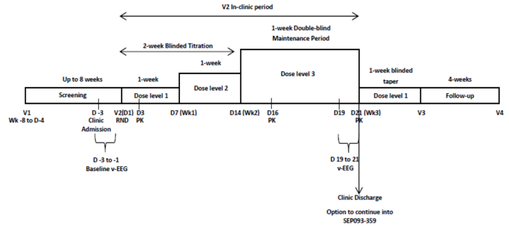
Table 2. Proposed ESL Once-Daily Dosing Regimen for the Pediatric Patients Aged 4 to 17 Years

Body Weight Range	Titration Dose (mg/day)	Maintenance Dose (mg/day), (Min to Max)
<11 kg	100	300 to 400
11 to 21 kg	200	300 to 500
22 to 31 kg	300	400 to 700
32 to 38 kg	300	600 to 800
>38 kg	400	800 to 1200

MODELING AND SIMULATION STRATEGY FOR INFANT DOSE SELECTION AND STUDY DESIGN

- To fulfill the Pediatric Written Request, Study SEP093-363 was planned, as shown in **Figure 4**. This study will include infants with POS aged 1 month to <4 years old administered ESL adjunctive therapy and evaluated PK, efficacy, and safety.
- An adaptive design was included such that dose adjustment may occur based on knowledge of eslicarbazepine concentrations obtained from the first 30 subjects (10 each from the 3 youngest age groups). Analyses including development of a pediatric/infant PBPK model were performed to support study design and dose selection.

Figure 4. Study SEP093-363 Schematic



Abbreviations: D, day; Wk, week; PK, pharmacokinetic(s); RND, randomization; V, visit; v-EEG, video electroencephalogram.
Note: Visit 2 was in-clinic, however, subjects had the option of returning home any time after the Day 3 PK blood draw and returning at (or prior to) the start of the maintenance period (Day 15[±1d]).

Pediatric PPK Model Refinement

- The pediatric PPK model (**Table 1**) was empirically modified to express the overall clearance as the sum of the renal and extrarenal elimination pathways, as eslicarbazepine metabolites are eliminated by renal excretion (2/3), in the unchanged and glucuronide conjugate forms (1/3).[5,6]
  - The maturation of the renal fraction of elimination was reflected by the maturation of the glomerular filtration rate.[7]
  - The maturation of the extrarenal fraction of elimination was reflected by the relative expression of UGT2B4 mRNA in pediatric versus adult subjects.[8]
  - Concomitant AED effects on eslicarbazepine clearance were re-parameterized accordingly. Levetiracetam most likely exerts its effect on apparent elimination CL by altering the renal fraction of eslicarbazepine elimination;[9] phenobarbital-like AEDs most likely increase CL by induction of the hepatic fraction of eslicarbazepine elimination.
- Once-daily and twice-daily ESL dosing scenarios were simulated for total daily doses of 5 to 60 mg/kg/day with 5-mg/kg/day increments and a maximum daily dose of 1200 mg as oral suspension formulation in virtual infant subjects aged 1 to <24 months.
- Covariates were randomly assigned: post-natal age was randomly sampled from a uniform distribution between 1 and 24 months, weight was randomly sampled from the weight-for-age distribution model available from the Centers for Disease Control and Prevention,[10] and use of concomitant levetiracetam and/or phenobarbital-like drugs was randomly sampled from binomial distributions, using the distribution of concomitant AEDs. Carbamazepine was assumed to not be administered in the virtual patients, because concomitant use will be prohibited in the planned trial.

PBPK Model Development

- Pharmacokinetic parameters for the PBPK model were derived separately for absorption (ACAT™), distribution, and elimination using GastroPlus™.[11]
- An adult PBPK model was first developed and provided a basis for describing the mean/individual data for the pediatric and adolescent subjects in Study BIA-2093-202. Model parameters were adjusted for age, sex, and body weight using population estimates for age related (PEAR™) physiology implemented in the PBPK modules. UGT2B4 enzyme expressions were adjusted (mean/individual) using estimated individual UGT2B4 expressions and literature-based descriptions of UGT2B4 ontogeny for projections to infant subjects.
- Simulation results from the refined PPK and PBPK models indicate that predicted exposures were similar. Selected doses are shown in **Table 3**.

Table 3. Selected ESL Dose Regimens for Patients Aged 1 Month to <4 Years

ESL Group	Age Category	ESL Titration Week 1 (DL1) (mg/kg/day)	ESL Titration Week 2 (DL2) (mg/kg/day)	ESL Maintenance Dose Week 3 (DL3) (mg/kg/day)
1 (Low dose)	1 month to <6 months	2.5	5	7.5
	6 months to <12 months	5	7.5	10
	12 months to <24 months	5	10	12.5
	24 months to <4 years	5	10	15
2 (High dose)	1 month to <6 months	5	10	15[a]
	6 months to <12 months	10	15	20[a]
	12 months to <24 months	10	20	25[a]
	24 months to <4 years	10	20	30[b]
3 (Placebo)	All ages	Placebo	Placebo	Placebo

[a] Doses are based on matching predicted exposures from an infant physiologically based pharmacokinetic model with adult exposures.
[b] Doses are based on matching predicted exposures from the pharmacokinetic model in children with adult exposures.

PK Sampling Schedule Evaluation

- Various sparse PK sampling schedules for the Study SEP093-363 protocol were evaluated using the refined infant PK model on the basis of the computation of the Fisher information matrix in PFIM.[12]
- Changes in efficiency of sampling schedule relative to a 3-trough sample schedule are reported in **Table 4**, which shows a 2-fold increase of the informational content obtained with sampling schedules including a postdose sample.
- Ultimately, samples were scheduled on Day 3 (trough), Day 16 (trough), and Day 21 (0.5 to 4 hours postdose).

Table 4. Relative Efficiency for Various Sampling Schedules

Sampling Schedule	Criterion[a]	Relative Efficiency (%)[b]
Day 3, 16, 21 (trough) - Reference	15.196	100.0
Day 3, 16 (trough)	11.610	76.4
Day 3, 21 (trough)	10.622	69.9
Day 2, 16, 21 (trough)	19.011	125.1
Day 4, 16, 21 (trough)	13.420	88.3
Day 3, 16, 19, 21 (trough)	17.731	116.7
Day 3, 16, 20, 21 (trough)	17.796	117.1
Day 3 (trough), 16 (1 hour post dose), 21 (trough)	35.256	232.0
Day 3 (trough), 16 (trough), 21 (1 hour post dose)	33.376	219.6
Day 2 (trough), 16 (1 hour post dose), 21 (trough)	35.353	232.6
Day 3 (trough), 16 (trough), 19 (1 hour post dose), 21 (trough)	41.413	272.5

[a] Metric computed from Fisher Information Matrix.
[b] Ratio of criterion from any selected sampling time to Reference.

Study Protocol Dose Adjustment Algorithm

- The proposed dosing regimens for the low- and high-dose regimens in each age group (1 to <6 months, 6 to <12 months, and 12 to <24 months) defined for Study SEP093-363 are shown in **Table 3**.
- A pre-dose eslicarbazepine concentration will be measured on Day 3 ($C_{day3,obs}$) in approximately 10 infant subjects from each age group. If the measured concentration is outside an interval defined as ± 30% of a target concentration (corresponding to the product of $C_{min,ss}$ in adults receiving 1200 mg daily and the ratio between titration [DL1] and maintenance dose), the planned maintenance dose ($DL3_{adj}$) will generally be adjusted according to the following formula:

$$DL3_{adj}(mg/day) = weight(kg) \times \alpha \times \frac{C_{min,ss\,adult1200mg}(ng/mL)}{C_{day3,obs}(ng/mL)} \times DL1(mg/kg/day)$$

with α set to 0.5 and 1 for the low- and high-dose regimens, respectively.

- For practical reasons, reference tables were developed to provide investigators with rounded formulation volumes to administer based upon age group, low- versus high-dose regimens, subject body weight, and concentration ranges in which $C_{day3,obs}$ falls.

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 of age and older).
- This case study illustrates the successful application of adult exposure-matching for pediatric dose selection to gain approval for a pediatric indication for ESL in patients 4 years and older for the treatment of POS, without conducting a well-controlled efficacy study.
- In addition, an integrated PPK and PBPK modeling and simulation strategy provided a quantitative basis to support ESL dose selection and study design for a planned clinical trial in infants, without conducting a separate PK study.

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