Modeling and simulation strategy to support eslicarbazepine acetate (ESL) pediatric dose selection in the treatment of partial-onset seizures (POS) based on matching adult exposures

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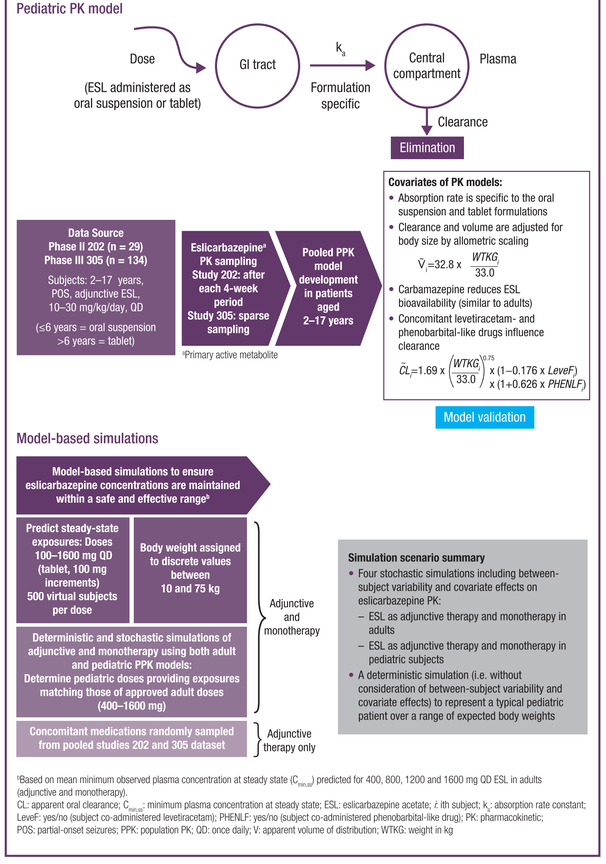
INTRODUCTION

- 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.
- A recent Food and Drug Administration (FDA) analysis has provided evidence across anticonvulsant medications that exposure–response relationships are preserved between adult and pediatric subjects (≥4 years) with POS.[1]
- The FDA specified three requirements for a submission to obtain an indication for the treatment of POS in pediatric subjects (≥4 years) that rely upon extrapolation:
  - Approved indication for treatment of POS in adults ✔
  - Pharmacokinetic (PK) analysis to determine a dosing regimen for pediatric subjects ≥4 years that results in exposures similar to those that are safe and effective in adults ✔
  - A long-term open-label (OL) safety study in pediatric subjects ≥4 years. ✔
- The FDA Division of Neurology Products has determined that it is acceptable to extrapolate the efficacy and safety of drugs for both adult and pediatric populations, approved as adjunctive therapy for the treatment of POS, to their use as monotherapy, provided that efficacy and safety have been established in the respective age range.
  - FDA analysis of such drugs showed the dosages and corresponding exposures when used as monotherapy are within the ranges of dosages and corresponding exposures when used as adjunctive therapy.
- Here we describe the application of adult exposure matching for pediatric dose selection in support of an application for a pediatric indication for ESL in US patients ≥4 years, for the treatment of POS as adjunctive therapy and monotherapy, ***without conducting a well-controlled efficacy study in pediatric subjects (≥4 years).***

DESIGN AND METHODS

- Approved indication for treatment of POS in adults: ✔
  - ESL is approved in the USA as adjunctive therapy and as monotherapy.
- PK analysis to determine a dosing regimen for pediatric subjects ≥4 years that results in exposures similar to those safe and effective in adults: ✔
  - A pediatric population PK (PPK) model was developed using concentration-time data from the adjunctive therapy pediatric studies BIA-2093-202 and BIA-2093-305 (**Figure 1**).
  - Separate exposure–response models were developed using Phase III studies BIA-2093-301, -302 and -304 (adjunctive therapy) and studies 093-045 and -046 (monotherapy); exposures were generated using a PPK model based on the appropriate Phase III studies, augmented with data from11 Phase I studies.[2,3]
  - The targeted concentration ranges (shaded regions, **Figure 2**) were based on approved adult titration (400 mg) and maintenance doses (800–1600 mg) for adjunctive and monotherapy.
  - Based on the adult and pediatric exposure–response model(s), simulations were performed for pediatric patients to match targeted concentration ranges observed in adults, to ensure that eslicarbazepine concentrations in pediatric patients would be maintained within the safe and effective range.
- Long-term OL safety study in pediatric subjects ≥4 years: ✔
  - Safety and tolerability data were collected in pediatric studies BIA-2093-208 and -305.
    - Due to the absence of safety data in pediatric patients for daily doses above 1200 mg, the maximum proposed maintenance dose in pediatric patients is 1200 mg QD (**Figure 3**).
- Additional requirement – an age-appropriate formulation: ✔
  - In studies 202 and 305, ESL was administered QD using an oral suspension in subjects aged 2–6 years and a tablet for older subjects (7–18 years). Tablet dosing was used in study 208 (subjects aged 6–16 years).
  - The FDA has recognized the bioequivalence between ESL oral suspension and the commercial tablet (crushed or intact) following clinical investigations[4–6] (**Figure 4**).

Figure 1. Strategy for pediatric development, and plan for study in pediatric patients



[b]Based on mean minimum observed plasma concentration at steady state ($C_{min,ss}$) predicted for 400, 800, 1200 and 1600 mg QD ESL in adults (adjunctive and monotherapy).
CL: apparent oral clearance; $C_{min,ss}$: minimum plasma concentration at steady state; ESL: eslicarbazepine acetate; *i*: ith subject; k_a: absorption rate constant; LeveF: yes/no (subject co-administered levetiracetam); PHENLF: yes/no (subject co-administered phenobarbital-like drug); PK: pharmacokinetic; POS: partial-onset seizures; PPK: population PK; QD: once daily; V: apparent volume of distribution; WTKG: weight in kg

RESULTS

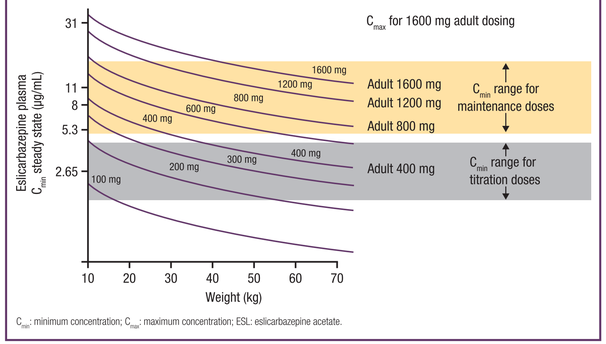
PK analysis to determine the safe and effective dosing regimen

- As displayed in **Figure 2**, model-based simulated pediatric eslicarbazepine concentrations at each dose level (solid lines), for ESL administered either as adjunctive therapy or monotherapy, were compared with targeted concentration ranges observed in adults (shaded region).
- To simplify the dose recommendation across different body sizes, body weights were grouped into five categories (<11 kg, 11–21 kg, 22–31 kg, 32–38 kg and >38 kg) with a recommended dose for each weight category.

Long-term OL safety study in pediatric patients ≥4 years

- Safety and tolerability data were available from two long-term pediatric studies, 208 and 305.
  - A total of 368 subjects across both studies were ≥4 years of age and 204 were randomized to ESL.

Figure 2. Comparison of simulated plasma concentrations of eslicarbazepine at selected dose levels (100–1600 mg/day ESL, solid lines) relative to adult targeted C_{min} ranges for titration and maintenance (shaded regions)

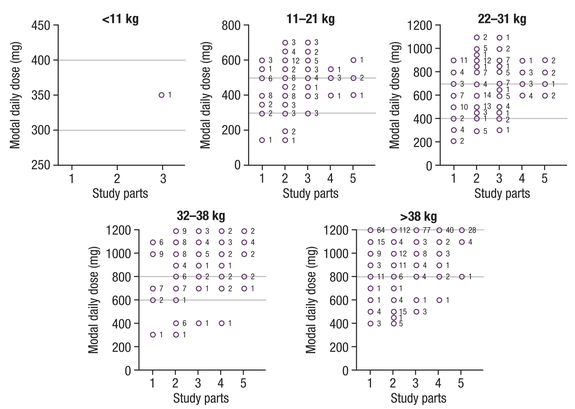


C_{min}: minimum concentration; C_{max}: maximum concentration; ESL: eslicarbazepine acetate.

- **Figure 3** summarizes the modal daily doses administered according to study part and weight group.
- There is adequate exposure information for safety assessment across weight groups up to the adult equivalent of 1200 mg, with the exception of the 11 kg group (see **Figure 3**).
- Hence, the current adult commercial dosage form was found by the FDA to be an acceptable, age-appropriate formulation for pediatric subjects 4–17 years of age.

- An overview of the key steps in the extrapolation strategy employed in the pediatric dose selection of ESL is provided in **Figure 1**.

Figure 3. Distribution of modal daily dose (the most frequently administered dose) for each part of studies 208 and 305 by weight group



Study Part 1: 12-week, randomized, double-blind, parallel-group, placebo-controlled, maintenance treatment; Study Parts 2–5: additional 1-year open-label extensions, to a maximum of 4 years.
The number next to each open circle represents the number of patients who received the corresponding modal dose during the corresponding study part.
The horizontal lines within each panel represent the lower and upper limits of the recommended maintenance dose interval (adult 800 and 1200 mg doses) for the corresponding weight range group.

Proposed ESL titration and maintenance doses for pediatric patients

- **Table 1** displays the proposed doses of ESL for titration and maintenance, that would target concentration ranges achieved by adult titration (400 mg QD) and maintenance doses (800–1200 mg QD).
  - The highest recommended doses (**Table 1**) take into account the absence of safety data above 1200 mg in pediatric patients.

Figure 4. Bioequivalence of ESL dosage forms

Crushed tablet ≡ Intact commercial tablet ≡ Intact clinical study tablet ≡ Oral suspension

ESL: eslicarbazepine acetate.

- The doses selected using the model-based simulations are for both adjunctive therapy and monotherapy as:
  - The FDA has determined it is acceptable to extrapolate the efficacy and safety from adjunctive therapy, after taking into consideration possible drug–drug interactions that may alter the metabolism of the drug.
  - Predicted exposures after adjunctive therapy and monotherapy were comparable.

Table 1. Proposed ESL titration and maintenance doses for pediatric patients (4–17 years) as adjunctive therapy or monotherapy

Body weight range[a]	Titration dose (mg/day)	Maintenance dose, (mg/day), minimum	Maintenance dose, (mg/day), maximum[b]
<11 kg	200	300	400
11–21 kg	200	300	500
22–31 kg	200	400	700
32–38 kg	300	600	800
>38 kg	400	800	1200

[a]The dose regimen presented for patients <11 kg is provided for reference only and is currently not considered as a recommended dose. Targeted age range starts from minimum body weight of 11 kg.
[b]Due to the absence of safety data in pediatric patients for daily doses above 1200 mg; the maximum proposed maintenance dose in pediatric patients is 1200 mg QD.
ESL: eslicarbazepine acetate; QD: once daily.

CONCLUSIONS

- A recent FDA analysis has provided evidence across anticonvulsant medications that exposure–response relationships are preserved between adult and pediatric patients (≥4 years) with POS.
- This case study illustrates the application of modeling and simulation to support adult exposure matching for pediatric dose selection in support of an application for a pediatric indication for ESL in US patients (≥4 years) for the treatment of POS as adjunctive therapy or monotherapy, without conducting a well-controlled efficacy study.

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DISCLOSURES

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

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