# Clinical Pharmacology Review

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|---|---|
| PRODUCT (Generic Name): | Eslicarbazepine acetate |
| PRODUCT (Brand Name): | APTIOM® |
| sNDA: | 022416/s-009 |
| DOSAGE FORM: | Tablet |
| ROUTE of ADMINISTRATION: | Oral |
| INDICATION: | Monotherapy and adjunctive therapy for the treatment of partial-onset seizures in patients 4 years of age and older |
| SUBMISSION DATE: | 3/13/2017 |
| SPONSOR: | Sunovion Pharmaceuticals Inc. |
| OCP REVIEWER: | Dawei Li, Ph.D. (Clinical pharmacology) |
| | Michael Bewernitz, Ph.D. (Pharmacometrics) |
| TEAM LEADER: | Kevin Krudys, Ph.D. (Pharmacometrics) |
| | Angela Men, M.D., Ph.D. |
| OCP DIVISION: | DPM/DCP I |

## 1 EXECUTIVE SUMMARY

ESL is currently approved in the U.S. for the treatment of partial-onset seizures (POS) (as monotherapy or adjunctive therapy) in patients with epilepsy 18 years or older. Supplement 9, an efficacy supplement, was submitted in order to pursue an indication for Aptiom (eslicarbazepine; ESL) for the treatment (monotherapy and adjunctive therapy) of partial onset seizures in patients 4 years of age and older using extrapolation. Specifically, the current submission involves efficacy extrapolation from adult patients to pediatric patients and extrapolation from adjunctive therapy to monotherapy.

1) Extrapolating ESL adjunctive therapy from adults to children 4 years of age and older for POS:
In response to DNP's policy for extrapolation of efficacy for adjunctive therapy, the Sponsor provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar ESL exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older to ESL exposure in adult subjects with POS. (b) (4) the reviewer conducted an independent analysis. To derive pediatric doses to match adult

exposure, the reviewer conducted PK simulations in a setting where there is no effect of concomitant medications. This approach is based on the well-supported assumption that PK interactions resulting from concomitant medications in pediatric patients 4 years of age and older will be similar to adults. Based on PK simulations in this setting, OCP proposes 400-600, 500-800, 600-900, and 800-1200 mg once daily as maintenance dosing for pediatric patients weighing 11 to < 22 kg, 22 to < 32 kg, 32 to ≤ 38 kg, and > 38 kg, respectively. OCP's proposed maintenance dosing was communicated to the Sponsor and the Sponsor agreed with the proposal. OCP agrees with Sponsor's proposed initial and titration increments of 200, (b) (4) 300, and 400 mg for pediatric patents weighing 11 to < 22 kg, 22 to < 32 kg, 32 to ≤ 38 kg, and > 38 kg, respectively.

2) Extrapolating ESL monotherapy from adjunctive in children for the treatment of POS:

To support use of ESL as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. Although there are some drugs that interact with ESL (i.e., carbamazepine, phenytoin and phenobarbital) in the adjunctive setting, none are clinically relevant to the extent that they require dose adjustment. Based on these considerations, and since adults have the same dosing for adjunctive therapy as for monotherapy, it is reasonable to apply the same pediatric dosing to monotherapy as is applied to adjunctive therapy in patients 4 years of age and older.

## 2 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed NDA 022,416 Supplement-009 for Aptiom (eslicarbazepine). The Sponsor's submission is acceptable from the perspective of the Office of Clinical Pharmacology and we recommend approval provided that an agreement is reached between the Sponsor and Agency regarding labeling language.

## 3 BACKGROUND

Eslicarbazepine acetate (ESL) is extensively converted to eslicarbazepine, a voltage-gated sodium-channel-blocking agent, with additional calcium-channel blocking properties. ESL was approved in the U.S. as monotherapy or adjunctive therapy for the treatment of partial-onset seizures (POS) in patients with epilepsy 18 years or older. In this supplemental NDA, the Sponsor seeks an indication for ESL as monotherapy and adjunctive therapy for the treatment of POS in patients 4 years of age and older based on extrapolation of adult data.

After discussions with the Division of Neurology Products (DNP), the sponsor agreed to the dosage regimen of ESL for pediatric patients shown in Table 1.

**Table 1: ESL Dosage Schedule for Pediatric Patients Aged 4 to 17 Years Old**

| Body Weight Range | Initial and Maximum Titration Increment Dose (mg once daily) | Maintenance Dose (mg once daily) |
|---|---|---|
| 11 to 21 kg | 200 | 400 to 600 |
| 22 to 31 kg | (b) (4) | 500 to 800 |
| 32 to 38 kg | 300 | 600 to 900 |
| 38 kg | 400 | 800 to 1200 |

## 4 GENERAL ADVICE FOR PEDIATRIC EXTRAPOLATION

On November 12, 2015 DNP sent a General Advice Letter to the Sponsor indicating that it was acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and adults as well as analyses of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS.

The following will be required to rely upon extrapolation to support an indication for the treatment of POS in subjects 4 years and older:

- An approved indication for the treatment of POS in adults.
- A pharmacokinetic (PK) analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older compared with adult subjects with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric subjects 4 years of age and older.

To support use as monotherapy for the treatment of POS based on extrapolation, the proposed dosages of a drug, when used as monotherapy, should result in exposures that are similar to those demonstrated to be safe and effective when the drug is used as adjunctive therapy for the treatment of POS. Thus, to support extrapolation, a Sponsor must provide pharmacokinetic information adequate to demonstrate such similarity, taking into consideration possible drug-drug interactions (inhibition or induction) that may alter the metabolism of the drug.

## 5 CLINICAL DEVELOPMENT IN PEDIATRIC PATIENTS

Phase 2 and Phase 3 studies of ESL in pediatric subjects include BIA-2093-202, BIA-2093-208, and BIA-2093-305. Study BIA-2093-208 was conducted in pediatric patients aged 6-16 years; however, PK assessments were not included in the study design. Study BIA-2093-305 is a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial to evaluate the efficacy and safety of ESL in subjects age 2-17 years with POS. However, the study failed to demonstrate a therapeutic effect for ESL in pediatric subjects.

[*Reviewer's comments: The results of this failed trial were submitted to the Agency and were carefully evaluated before we concluded that it was acceptable to extrapolate efficacy to pediatric patients 4 years of age from adults. Potential reasons for the failure of the pediatric trial to meet its primary endpoint were examined and include the following:*

- *A higher median baseline seizure frequency was observed for the placebo arm in BIA-2093-305 compared to the treatment arm,*
- *A high placebo response was observed in the trial, especially in younger pediatric patients (ages 2 to 6 years) and in specific geographical regions (i.e., Eastern Europe),*
- *Exposures of ESL in the 2 to 6 year age group were lower compared to older children and adults, suggesting the dose in younger patients may have been too low.*

*In the current submission the Sponsor posits that the possible enrollment of some subjects with secondary generalized epilepsies and generalized seizures, rather than POS, could also have contributed to the negative findings.*

*We also investigated differences in the pediatric trial compared to adult trials, including a different distribution of concomitant medications and a longer titration phase in pediatric patients. Other points of consideration include:*

- *Eslicarbazepine shares the same active moiety with another drug (oxcarbazepine/Trileptal) which has demonstrated effectiveness in the pediatric population. The exposure-response relationship for the active moiety has also been shown to be similar in trials of Aptiom and Trileptal.*
- *Subgroup analysis of BIA-2093-305 in patients ≥ 7 years (the subpopulation with a lower placebo response and ESL exposure similar to adults) showed a difference in favor of ESL compared to placebo when considering both titration and maintenance phases.*

*Following thorough evaluation from different perspectives, we concluded that the failure of the trial to meet the primary endpoint was likely due to study design and execution features, rather than an inherent ineffectiveness of ESL.*]

In both pediatric studies (Studies BIA-2093-202 and BIA-2093-305), ESL was administered QD using (b) (4) oral suspension (formulation FC1a) in subjects aged 2-6 years and a tablet for older subjects (7-18 years). Furthermore, the (b) (4) oral suspension FC1a and tablets were found to be bioequivalent in adults (Studies BIA-2093-109 and BIA-2093-122). Based on bioequivalence results, it can be expected that eslicarbazepine exposures are similar when administered either as a tablet or (b) (4) oral suspension.

According to the current Aptiom label, food has no effect on the pharmacokinetics of eslicarbazepine after oral administration of Aptiom. In addition, the current label indicates that eslicarbazepine is highly bioavailable, because the amount of eslicarbazepine and glucuronide metabolites recovered in urine corresponded to more than 90% of an Aptiom dose. Overall, a clinically-relevant food effect is not expected with ESL oral suspension as the suspension is bioequivalent to the ESL tablet.

A pooled population PK analysis was performed based on data collected from ESL adjunctive therapy Studies BIA-2093-202 and BIA-2093-305 of pediatric patients with refractory POS. Using the pediatric population PK model, Sponsor conducted PK simulations to arrive at pediatric dose selections expected to match exposures in adults receiving approved ESL doses.

## 6 RESULTS OF SPONSOR'S POPULATION PK ANALYSES

The Sponsor relied on population PK analysis (Report COG008041/2014/ESLIPEDS/A) to support ESL dosing regimen in pediatric patients.

Sponsor developed 3 population PK models; an adult monotherapy model, an adult adjunctive therapy model, and a pediatric adjunctive therapy model.

Adult Monotherapy Population PK Model: The adult monotherapy population PK model provided in this submission was previously reviewed by OCP and found to be acceptable from a clinical pharmacology perspective. A brief summary of key information about this adult monotherapy population PK model is summarized below (please refer to the clinical pharmacology review of NDA 022416 signed on 07/23/2015 for details).

Sponsor utilized data from Phase 1 Studies BIA-2093-105, -110, -111, -115, -116, -119, -120, -121, -127, -129, and Phase 3 Studies SEP-093-045 and SEP-093-046 to generate the adult monotherapy population PK model.

The final model utilized one-compartment, first-order oral absorption, first-order elimination, and was parameterized in terms Cl/F (apparent clearance), V/F (apparent volume of distribution, and $k_a$ (first order absorption rate constant). Between-subject variability was estimated for Cl/F, $k_a$, and V/F. Weight was a covariate on both CL/F and V/F (via allometric scaling with a power model) and sex was a covariate on both CL/F and V/F (additive shift).

$$CL/F_j = 2.56 \times \left(\frac{WTKG_j}{74.4}\right)^{0.291} - 0.24 \times SEXF_j \quad \text{(equation 1)}$$

$$V/F_j = 62.6 \times \left(\frac{WTKG_j}{74.4}\right)^{0.718} - 7.76 \times SEXF_j \quad \text{(equation 2)}$$

*Source: cog002454-2013-eslipk-rpt.pdf, page 38 of 212 (sequence 0140)*

The final model parameter estimates are found in the table below.

**Table 2: Parameter Estimates from the Adult Monotherapy Population PK Model.**

| Parameter | Final Parameter Estimate | | Interindividual Variability / Residual Variability | |
|---|---|---|---|---|
| | Typical Value | %SEM[a] | Magnitude | %SEM |
| $k_a$: Absorption rate constant (1/h) | 1.06 | 6.15 | 75.5 %CV[b,c] | 14.9 |
| CL/F: Apparent clearance (L/h) | 2.56 | 1.71 | 22.8 %CV | 10.6 |
| CL/F: Power of weight effect on CL[d] | 0.291 | 21.9 | | |
| CL/F: Additive shift for female gender on CL (L/h) | -0.240 | 26.6 | | |
| V/F: Apparent volume of distribution (L) | 62.6 | 2.30 | 18.6 %CV[c] | 18.8 |
| V/F: Power of weight effect on V[e] | 0.718 | 15.9 | | |
| V/F: Additive shift for female gender on V (L) | -7.76 | 26.8 | | |
| Ratio of additive/proportional component of RV[f] for Phase 1 | 6870 | 36.5 | NE[g] | NE |
| CCV[h] RV for Phase 1 | 0.0132 | 15.7 | 25.3 - 11.7 %CV F [3500 - 39000] | NA[i] |
| CCV RV for Phase 3 | 0.0915 | 9.40 | 30.2 %CV | NA |
| Minimum value of the objective function = 65352.751 | | | | |

The RV (%CV) was calculated using the following equation: (SQRT(0.0132×(power(F,2)+power(6870,2)))/F)×100.

[a] %SEM=standard error of the mean expressed as a percentage

[b] %CV=coefficient of variation expressed as a percentage

[c] Phase 3 data not included in the estimation of interindividual variability in $k_a$ or V/F.

[d] CL=clearance

[e] V=volume

[f] RV=residual variability

[g] NE=not estimated

[h] CCV=constant coefficient of variation

[i] NA=not available

*Source: cog002454-2013-eslipk-rpt.pdf, page 67 of 212 (sequence 0140)*

Adult Adjunctive Therapy Population PK Model: The adult adjunctive population PK model was previously reviewed by OCP and found acceptable from a clinical pharmacology perspective. A brief summary of key information about the adult adjunctive population PK model can be found below (please refer to the clinical pharmacology review of NDA 022415 signed on 09/16/2013 for details).

Sponsor utilized data from Phase 1 Studies BIA-2093-105, -110, -111, -115, -116, -119, -120, -121, -127, -129, and SEP093-150 and Phase 3 Studies SCO/BIA-2093-301, PRA/BIA-2093-302, and BIA-2093-304 to generate an adult adjunctive therapy population PK model.

The final model has the same structural design as the adult monotherapy model. Covariates on Cl/F were carbamazepine, phenobarbital-like inducers, and creatinine clearance. Covariates on V/F were sex and phenobarbital-like inducers (see equations below).

$$CL/F_j = \left[2.43 + 1.08 \times \left(\frac{dose_{carbamazepine_j}}{800}\right)^{0.411} + 1.24 \times flag_{phenobarbital\text{-}like_j} + 0.0132 \times (wt_j - 70)\right] \times \left(\frac{CrCL_j}{115.7}\right)^{0.195}$$

(equation 3)

$$V/F_j = \left(61.3 - 9.9 \times flag_{sexf_j} + 12.0 \times flag_{phenobarbital\text{-}like_j}\right) \times \left(\frac{wt_j}{70}\right)^{0.617}$$

(equation 4)

*Source: cog002419-2012-eslipk-rpt.pdf, page 34 of 423 (sequence 0053)*

The final model parameter estimates can be found in the table below.

**Table 3: Parameter Estimates from the Adult Adjunctive Therapy Population PK Model.**

| Parameter | Final Parameter Estimate | | Magnitude of Interindividual Variability (%CV[a]) | |
|---|---|---|---|---|
| | Population Mean | %SEM[b] | Final Estimate | %SEM |
| $k_a$ ($h^{-1}$) | 2.34 | 9.6 | 126.49 | 18.4 |
| CL/F for No Carbamazepine Use (L/h) | 2.43 | 1.3 | 27.04 | 10.5 |
| Additive Shift of Concomitant Phenobarbital or Phenobarbital-Like Inducers (Phenytoin, Primidone) on CL/F (L/h) | 1.24 | 6.7 | | |
| Slope Term for Effect of Body Weight on CL/F (L/h/kg) | 0.0132 | 24.0 | | |
| Power Term for Effect of Creatinine Clearance on CL/F | 0.195 | 33.9 | | |
| Additional CL/F When Carbamazepine Dose = 800 mg (L/h) | 1.08 | 5.4 | | |
| Power Term for Effect of Carbamazepine Dose on CL/F | 0.411 | 35.8 | | |
| V/F (L) | 61.3 | 2.0 | 17.69 | 15.6 |
| Additive Shift of Female Gender on V/F (L) | -9.9 | 18.2 | | |
| Additive Shift of Concomitant Phenobarbital or Phenobarbital-Like Inducers (Phenytoin, Primidone) on V/F (L) | 12.0 | 30.3 | | |
| Power Term for Effect of Body Weight on V/F | 0.617 | 15.0 | | |
| Ratio of Additive/Proportional RV Components[c] ($\sigma_2/\sigma_1$), Phase 1 | 4520 | 18.4 | NA | NA |
| Proportional RV Component ($\sigma_1$), Phase 1 | 0.0124 | 7.8 | NA | NA |
| Ratio of Additive/Proportional RV Components[d] ($\sigma_1/\sigma_2$), Phase 3 | 0.0000632 | 31.6 | NA | NA |
| Additive RV Component ($\sigma_2$), Phase 3 | 5290000 | 17.1 | NA | NA |
| Minimum value of the objective function = 99315.706 | | | | |

[a] %CV = percent coefficient of variation.
[b] %SEM = percent standard error of the mean.
[c] Residual variability was estimated to range from 23.74 %CV to 11.24 %CV at predicted eslicarbazepine concentrations ranging from 2400 ng/mL to 33000 ng/mL, respectively.
[d] Residual variability was estimated to range from 311.15 %CV to 15.68 %CV at predicted eslicarbazepine concentrations ranging from 740 ng/mL to 39200 ng/mL, respectively.

*Source: cog002419-2012-eslipk-rpt.pdf, page 83 of 423 (sequence 0053)*

Pediatric Adjunctive Therapy Population PK Model: The following is a brief summary of the pediatric adjunctive population PK model which OCP considers acceptable. For details and discussion regarding pediatric population PK model development, please refer to the appendix.

Sponsor utilized data from Phase 2 study BIA-2093-202 and Phase 3 trial BIA-2093-305 to generate an adjunctive therapy population PK model to represent pediatric patients.

(b) (4)

**Table 4: PK Parameter Estimates for Final PK Model in Pediatric Subjects with Refractory Partial Epilepsy**

(b) (4)

[*Reviewer comment: OCP disagrees with the* (b) (4) *Please refer to the appendix for discussion regarding the* (b) (4) ]

Sponsor's PK Simulations to Support Pediatric Dosing: Sponsor conducted PK simulations in virtual adult patients and virtual pediatric patients in order to derive pediatric dosing for initial dosing and maintenance dosing.

*Initiation and Titration Dose Target*: Sponsor utilized the approved adult initiation and titration dose of 400 mg once daily as a target for pediatric initiation and titration dosing.

*Maintenance Dose Target*: Sponsor utilized the approved adult maintenance doses of 800 mg once daily and 1200 mg once daily as target range for pediatric maintenance dosing.

*Simulation Methodology*: In an attempt to ensure consistent distribution of covariates between the simulated population and observed population, Sponsor randomly resampled (with replacement) a set of covariates from patients in the observed population. In addition, Sponsor also set between-subject variability for CL/F, V/F, and $k_{at}$ to zero.

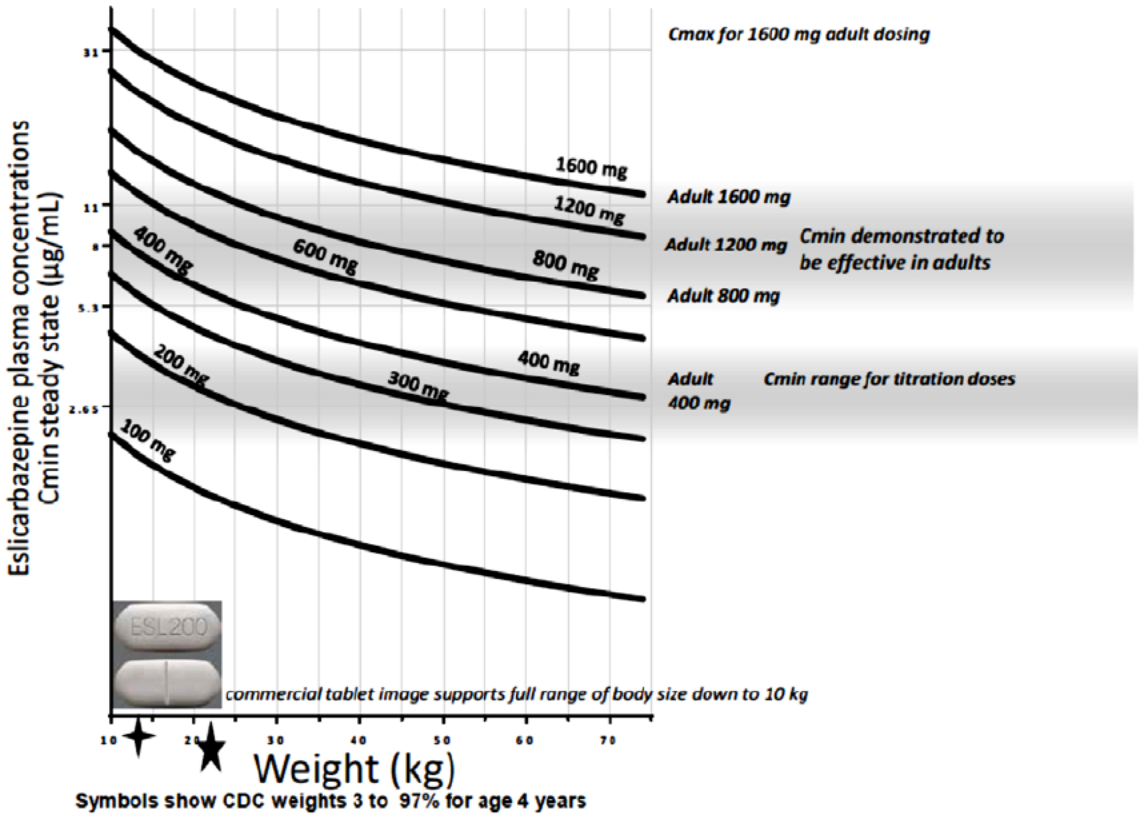
[*Reviewer comment: Sponsor utilized only the $k_{at}$, absorption rate constant for tablets, in the pediatric simulations. Sponsor did not include the oral suspension dosage form in the pediatric PK simulations. Based on the comparable bioavailability between oral suspension and tablets, and since no food effect is expected for the oral suspension, Sponsor's use of $k_{at}$ for pediatric PK simulations is acceptable.* ]

The adult simulations were conducted using the adjunctive PK model (where ESL is adjunctive to other anticonvulsant drugs) with the effect of phenobarbital-like AEDs on CL/F, effect of carbamazepine on clearance, and the effect of phenobarbital-like AEDs on V/F. The pediatric simulations were conducted with all drug interaction terms inactive.

[*Reviewer comment: Please refer to the Reviewer's Analyses in section 5 for details regarding the impact of PK interactions (carbamazepine and phenobarbital-like inducers) on the PK simulations and ultimately pediatric dose selection.*]

Using the simulated data described above, Sponsor provided the following plot demonstrating the relationship between weight and simulated ESL exposure for a range of doses in the pediatric population with comparison to the simulated ESL exposure achieved in adults receiving approved doses.

**Figure 1: Simulated Typical $C_{minss}$ Versus Body Weight in Pediatric Patients with Partial-Onset Seizures Receiving Once-Daily ESL**




*Adult $C_{maxss}$ and $C_{minss}$, represented as horizontal reference lines, are mean values predicted in adult patients with partial-onset seizures receiving daily eslicarbazepine acetate as adjunct therapy.*

*Source: cog008041-2016-eslipedsadd.pdf, page 97 of 99 (sequence 0211)*

[*Reviewer comment: Previous discussions with Sponsor indicated that though the range of 800-1600 mg ESL is approved for adults, for the purposes of deriving a pediatric dose, Sponsor can use the 800 mg – 1200 mg dose adult range. Please refer to clinical pharmacology review of NDA 022416 signed on 12/29/2011 (regarding Type C meeting occurring on 12/14/2011) for details.*

*Thus, the adult 1600 mg dose is provided for reference only. The dose selection was based on adults receiving 1200 mg and adults receiving 800 mg.*]

To provide a different view of the simulated data and facilitate comparisons between adults and pediatric patients, (b) (4)


*Source: cog008041-2016-eslipedsadd.pdf, page 98 of 99 (sequence 0211)*

Based on these PK simulations, Sponsor's initial recommendation is presented in the table below.

**Table 5: Sponsor's Proposed Initial, Titration Increment, and Maintenance Dose for Pediatric Patients age 4 to 17 Years of Age**

| Body Weight Range | Initial and Maximum Titration Increment Dose (mg/day) | Maintenance Dose (mg/day) |
|---|---|---|
| 11 to 21 kg | (b) (4) | |
| 22 to 31 kg | | |
| 32 to 38 kg | | |
| >38 kg | | |

*Source: 11412-annotated.pdf, page 4 of 57 (sequence 0211)*

(b) (4)

*the PK of ESL are expected to be similar in adults and heavier pediatric patients and the effect of drug interactions on ESL PK is expected to be comparable between adults and pediatric patients.*

(b) (4)

*For these reasons, OCP decided to conduct independent PK simulations in a monotherapy scenario in order to inform pediatric dose selection. Based on simulations conducted in the monotherapy setting, OCP proposed a new dose regimen. The new regimen was communicated to the Sponsor and the Sponsor accepted it. Please refer to section 7 for details.*]

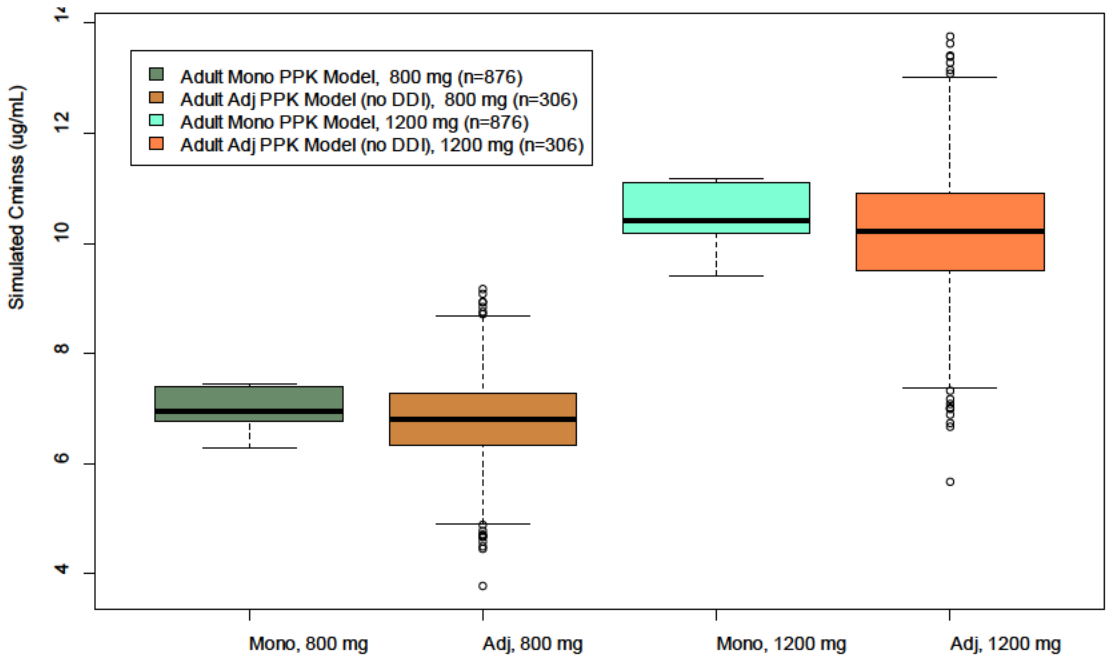
## 7 REVIEWER'S ANALYSES

(b) (4)

the reviewer conducted independent PK simulations under a monotherapy scenario.

A first step was to compare the Sponsor's adult population PK model built under the monotherapy scenario to the Sponsor's adult population PK model built under the adjunctive therapy scenario (with all drug interaction terms inactive). The figure below shows a comparison of the simulated $C_{minss}$ obtained from the adult monotherapy PK model and the adult adjunctive therapy PK model with all drug interaction terms inactive.

***Figure 3: Comparison of Simulated $C_{minss}$ From the Adult Monotherapy PK Model and Adult Adjunctive Therapy Model Without Drug Interaction Terms***




Based on the simulations presented in the figure above, the median $C_{minss}$ is comparable between the adult monotherapy model and the adult adjunctive model with drug interaction terms inactive. The increased PK variability present in the adjunctive PK model is plausible due to wide range of combinations of unique concomitant medications and as well as variations in dose of the concomitant medications. Overall, the simulations presented above support the use of the adult monotherapy PK model for comparison with simulated pediatric data.

The pediatric PK model was utilized with all drug interaction terms inactive in order to best represent the monotherapy scenario for pediatric patients. Using the adult monotherapy PK model and pediatric PK model with inactive drug interaction terms, the $C_{minss}$ was simulated for adults at the approved doses and for a range of pediatric doses.

In order to ensure consistent covariate distribution in the virtual population compared with the observed population, the reviewer followed the same approach as Sponsor

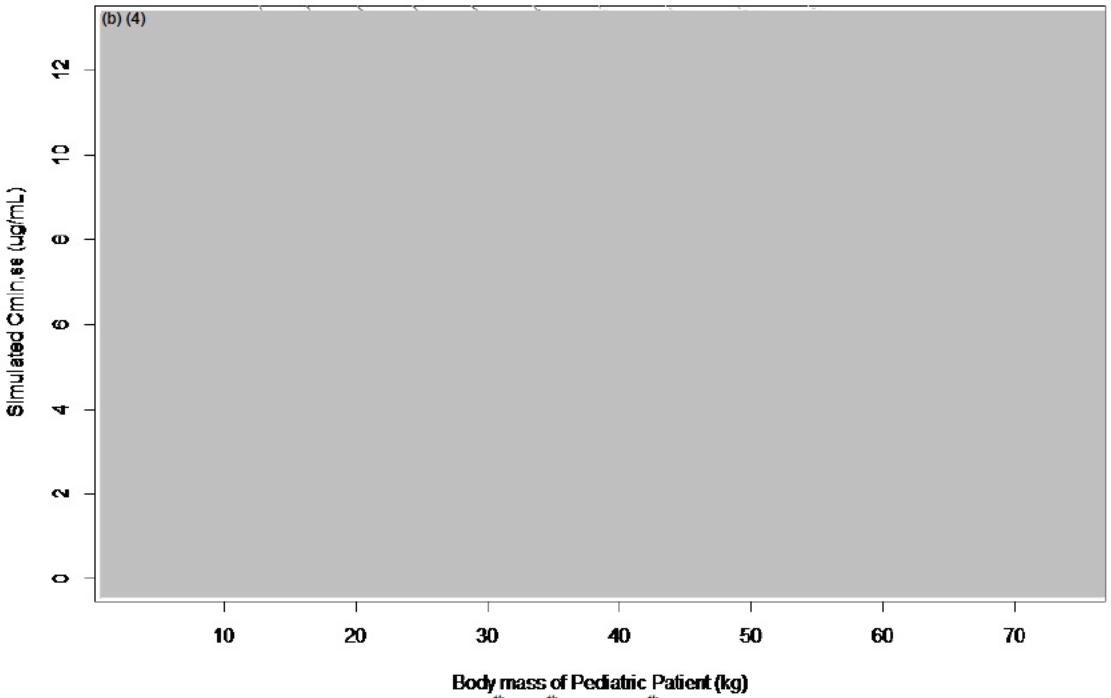
(b) (4)

Thus, samples of covariate sets from individual patients in the observed dataset were obtained to create the virtual population for both adults and pediatric patients. Between-subject variability terms were set to zero to help avoid occurrences of physiologically impossible combinations of PK parameters.

A similar approach as the Sponsor was used to generate Figure 1 was applied by the reviewer using the monotherapy adult PK model and the pediatric PK model with inactive drug interaction terms. The approved adult doses of 800 mg once daily and 1200 mg once daily were utilized to serve as target exposures for the pediatric PK simulations. Doses of 200 mg once daily to 1600 mg once daily were simulated for pediatric patients. As was the scenario with the data simulated in Figure 1, the $C_{minss}$ was simulated for pediatric patients as a function of weight and the adult exposures and plotted against the adult exposures at the approved 800 mg and 1200 mg once daily doses.

The reviewer reassessed the Sponsor's original proposed pediatric dosing using the adult monotherapy PK model for adults and the pediatric PK model using a monotherapy scenario (b) (4). The figure below shows the simulated pediatric $C_{minss}$ achieved using the Sponsor's proposed dosing regimen (b) (4) mg once daily for 11-21 kg, 22-32 kg, 32-38, > 38 kg, respectively) compared with simulated adult $C_{minss}$ for the approved 800 and 1200 mg once daily doses.

***Figure 4: Simulated $C_{minss}$ in Pediatric Patients Based on Body Weight and Dose Using Sponsor's Proposed Dosing Compared with Simulated $C_{minss}$ in Adult Patients at Approved Doses In a Monotherapy Scenario***

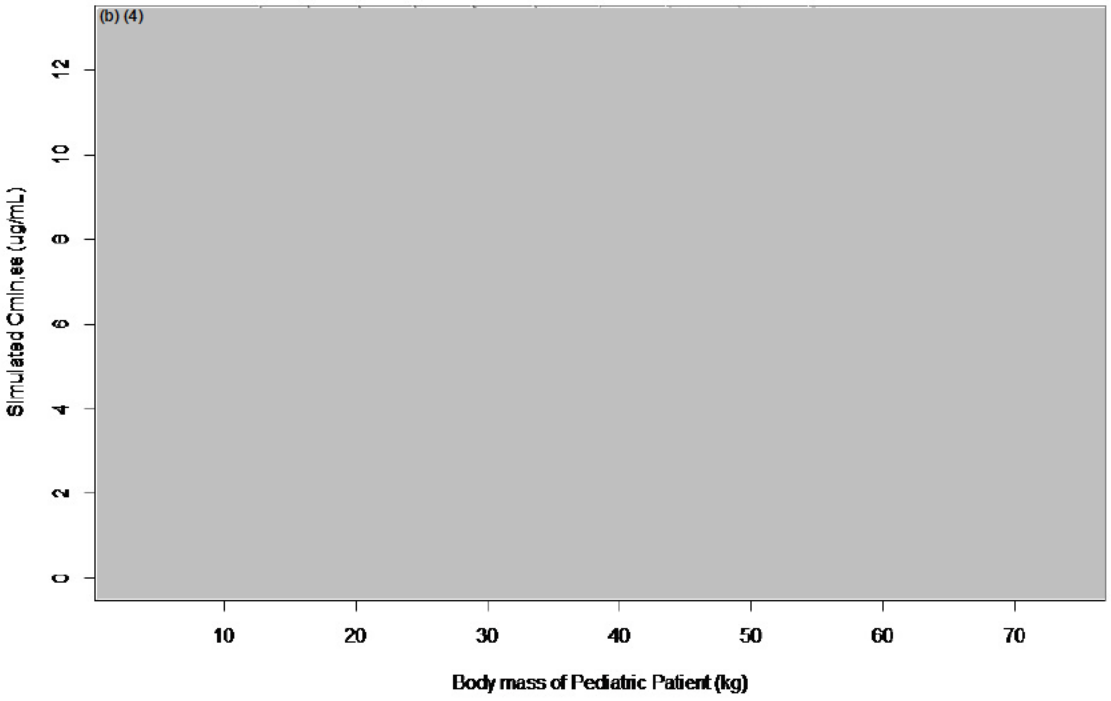



*Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{minss}$ at the approved adult doses of 800 and 1200 mg once daily. The curves represent the median simulated $C_{minss}$ for a given body weight and dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero).*

The simulations conducted using the monotherapy scenario indicate that for patients weighing < 38 kg (e.g. 11 to < 21 kg, 22 to < 32 kg, and 32 to < 38 kg), the Sponsor's proposed pediatric dosing would likely result in $C_{minss}$ lower than would be expected for adults receiving 1200 mg once daily. As such, additional simulations monotherapy scenarios were conducted to assess the potential for a dose increase in patients weighing < 38 kg to provide a better match to $C_{minss}$ for adult 1200 mg once daily. For patients weighing ≥ 38 kg, doses above 1200 mg once daily were not explored as this is the maximum adult dose agreed upon for use in the matching exercise. While 1600 mg once daily is the maximum dose approved for adult adjunctive therapy, 1200 mg once daily is the maximum dose approved for both adult monotherapy and adult adjunctive therapy. In addition, 1200 mg one daily was the maximum dose administered to pediatric patients in clinical trials. Thus, there is no available safety data to support doses above 1200 mg once daily for pediatric patients.

The simulated exposures resulting from OCP's final proposed maintenance dose are displayed in the figure below.

***Figure 5: Simulated $C_{minss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Dosing Compared with Simulated $C_{minss}$ in Adult Patients at Approved Doses in a Monotherapy Scenario***



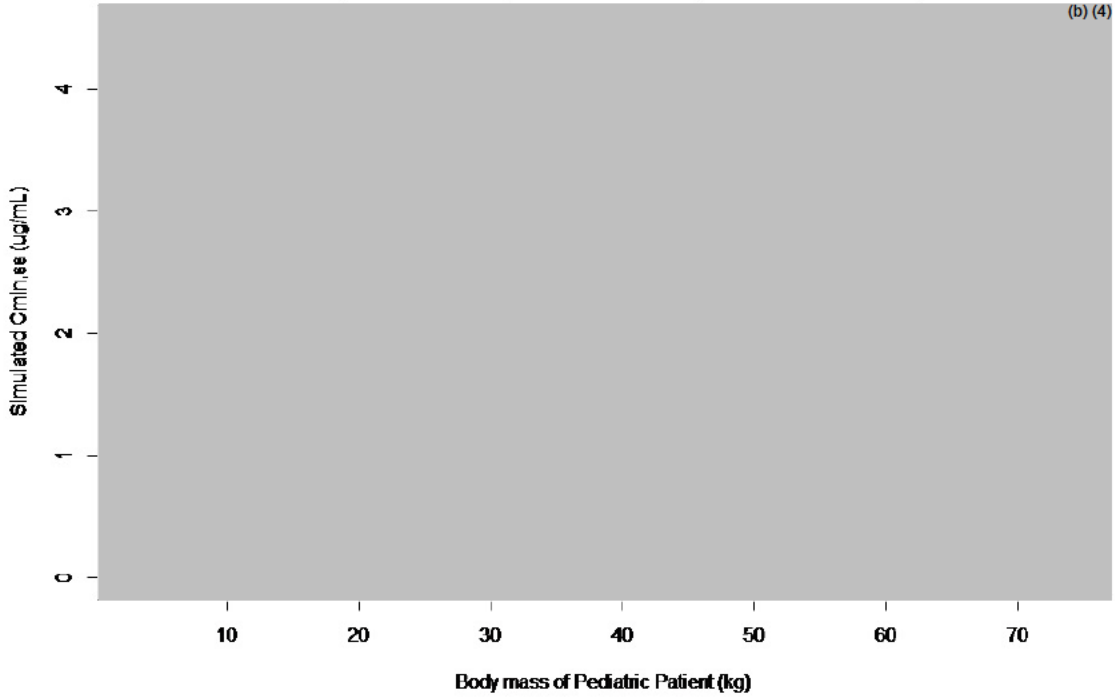

*Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{minss}$ at the approved adult doses of 800 and 1200 mg once daily. The curves represent the median simulated $C_{minss}$ for a given body weight and dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero).*

*Patients 11 to < 22 kg: Sponsor proposed* (b) (4) *mg, OCP proposes 400-600 mg*
*Patients 22 to < 32 kg: Sponsor proposed mg, OCP proposes 500-800 mg*
*Patients 32 to ≤ 38 kg: Sponsor proposed mg, OCP proposes 600-900 mg*
*Patients > 38 kg: Sponsor proposed 800-1200 mg, OCP agrees*

Based on the reviewer's simulations conducted in a the monotherapy scenario, **OCP proposes maintenance doses of 400-600, 500-800, 600-900, and 800-1200 mg for pediatric patents weighing 11 to < 22kg, 22 to < 32 kg, 32 to ⩽ 38 kg, and > 38 kg**, respectively.

A similar methodology was followed to assess the Sponsor's proposed initiation and titration doses for pediatric patients. Using monotherapy scenario simulations, the simulated $C_{minss}$ resulting from the Sponsor's proposed initiation and titration doses of (b) (4) mg for pediatric patents weighing 11 to < 22kg, 22 to < 32 kg, 32 to ≤ 38 kg, and > 38 kg, respectively were compared to the simulated $C_{minss}$ resulting from approved adult initiation and titration dose of 400 mg (see figure below).

***Figure 6: Simulated $C_{minss}$ in Pediatric Patients Based on Body Weight at Sponsor's Proposed Initiation and Titration Dose Compared with Simulated $C_{minss}$ in Adult Patients at Approved Initiation and Titration Dose in a Monotherapy Scenario***




The proposed pediatric initiation and titration dose appears to match adult exposures for all pediatric patients except patients in the 22 to < 32 kg weight group (red curve in the plot above). For the proposed initiation dose of (b) (4) (b) (4) While adults are approved to have initiation and titration increments of 400 to 600 mg, the Sponsor intentionally (b) (4) for pediatric patients. In addition, the titration time

difference between [redacted] for initiation and titration in 22 to < 32 kg age group is matter of [redacted] weeks versus [redacted] weeks titration duration towards a maintenance dose ≤ [redacted] mg once daily. In light of the modest time difference [redacted] weeks versus [redacted] weeks) when comparing the [redacted] initiation and titration doses for patients weighing 22 to < 32 kg, and in order to help reduce potential tolerability issues associated with titration, then the [redacted] mg initiation and titration dose is acceptable in patients age 22 to < 32 kg. Overall, **the Sponsor's proposed initiation and titration doses are acceptable from an OCP perspective**.

OCP's proposed changes to maintenance dosing were communicated to the Sponsor in an information request sent on 07/17/2017. The information request reads as follows:

[redacted]

*We think a more appropriate comparison of adult epilepsy patients and pediatric epilepsy patients is one in which the potential confounding effect of drug interactions is reduced (i.e., adult and pediatric patients both in a monotherapy setting). Based on this consideration, and using your simulation results (including Tables 18 to 20 in population PK report cog008041-2016-eslipedsadd) we propose the following maintenance doses:*

| *Body Weight Range* | *Maintenance Dose (mg/day), (Minimum to Maximum)* |
|---|---|
| *11 to 21 kg* | *400 to 600* |
| *22 to 31 kg* | *500 to 800* |
| *32 to 38 kg* | *600 to 900* |
| *> 38 kg* | *800 to 1200* |

*Please provide the number of pediatric patients ≥ 4 years of age who were exposed to these proposed doses (or higher doses) for at least 6 months and at least one year."*

The Sponsor responded on 07/17/2017 (sequence 0223) indicating they accept OCP's proposed dose regimen. The Sponsor also provided the number of pediatric patients exposed to doses at or in excess of OCP's proposed dose levels for a 6-month duration as well as a 1-year duration. Discussions with the Clinical review team indicate that the available safety data supports OCP's proposed dosing from a safety perspective. Please refer to the medical officer's review for additional details regarding safety.

Key label edits: The Sponsor's proposed label was edited to include the updated maintenance dosing proposed by OCP. OCP proposes to remove statements regarding a (b) (4)

Michael Bewernitz, Ph.D.

**Reviewer, Division of Pharmacometrics (DPM)**

Dawei Li, Ph.D.

**Reviewer, Division of Clinical Pharmacology 1 (DCP1)**

Kevin Krudys, Ph.D.

**Team Leader, DPM**

Concurrence:

Angela Men, M.D., Ph.D._____

**Team Leader, DCP1**

cc: HFD-120 NDA# 022416/s-009

HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Dawei Li

**Appendix A**:

**Pediatric Population PK Model Review**

Sponsor developed a population PK model to characterize the pharmacokinetics of ESL in pediatric patients with epilepsy, assess the relationship between ESL concentration with demographics and other covariates, and conduct PK simulations for informing dose selection in pediatric patients.

**Summary of PK Data**:

There were 857 measureable ESL concentrations from 146 patients available for PK analyses. In the PK dataset, the dose of eslicarbazepine acetate was converted to a dose of eslicarbazepine via molecular weight conversion since the assay measured eslicarbazepine (mg eslicarbazepine = mg eslicarbazepine acetate * 254.28 / 296.32).

Trials: Sponsor incorporated PK data from pediatric patients ages 2 to 18 years (n=38 subjects age 2-6 years, n=54 subjects age 7-11 years, and n=57 subjects age 12-18 years) that received Aptiom in Phase 2a trial BIA 2093-202 and Phase 3 trial BIA 2093-305. The following table provides key details of these two clinical trials.

**Table 6: Clinical Trials Which Provided PK Data for Pediatric Population PK Model.**

| Study Number/Phase | Study Title | Participants | Duration of Dosing | Use in Analysis |
|---|---|---|---|---|
| BIA 2093-202 / IIa | Pharmacokinetics, efficacy and tolerability of BIA 2-093[a] in children and adolescents with refractory partial epilepsy | Children and adolescents with epilepsy<br>10 subjects per group<br>Group 1: 2-6<br>Group 2: 7-11<br>Group 3: 12-17 years | Up to 14 weeks of a 20-week study duration | Eslicarbazepine (BIA 2-194[b]) concentration and seizure frequency data will be used in this analysis |
| BIA 2093-305 / III | Efficacy and safety of ESL[c] as adjunctive therapy for refractory partial seizures in children: a double-blind, randomized, placebo-controlled, parallel-group, multicentre clinical trial | Children and adolescents with epilepsy<br>Group 1: 2-6<br>Group 2: 7-11<br>Group 3: 12-16 years | Part I: Up to 22 weeks of a 34-week study phase duration<br>Part II: Up to 54 weeks of a 1-year study phase duration | Eslicarbazepine (BIA 2-194) concentration and seizure frequency data will be used in this analysis |

[a] BIA 2-093=eslicarbazepine acetate
[b] BIA 2-194=eslicarbazepine
[c] ESL=eslicarbazepine acetate

*Source: cog008041-2014-eslipeds-a.pdf, page 53 of 403 (sequence 0147)*

Dosing: In Study 202 and Trial 305 patients age 2 to 6 years received an oral suspension and older pediatric patients received tablets. In study Phase 2a study 202 patients received 4 weeks of 10 mg/kg once daily, 4 week of 15 mg/kg once daily, and 4 weeks of 30 mg/kg once daily (maximum dose 1800 mg once daily). In Phase 3 Trial 305 subjects underwent a 6-week titration followed by a maintenance phase where they received a single dose level ranging 10-30 mg/kg once daily (maximum dose 1200 mg once daily) for 12 weeks.

**Pediatric Population PK Model**:

(b) (4)

(b) (4)

Final model parameters are shown in the table below.

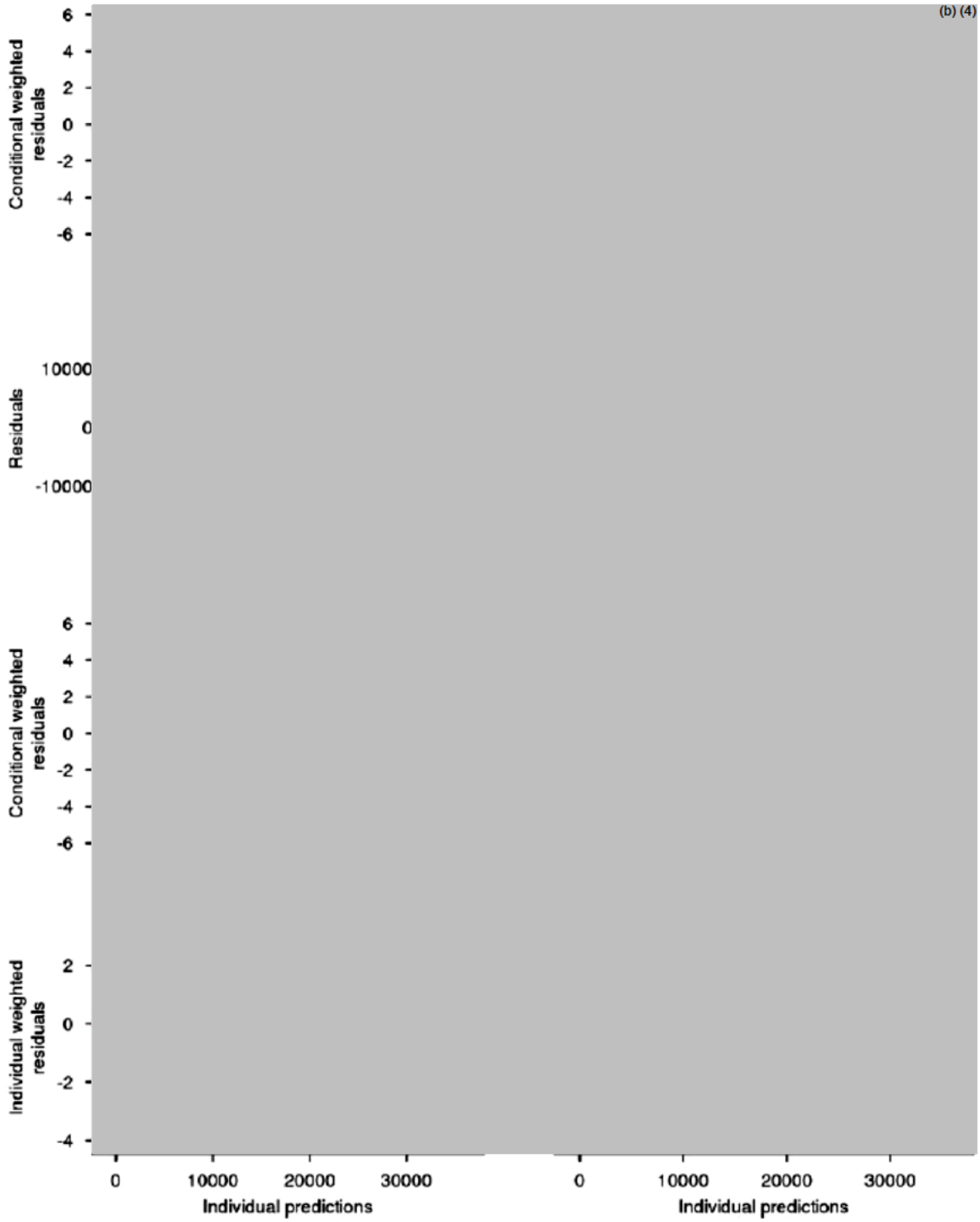
**Table 7: PK Parameter Estimates for Final PK Model in Pediatric Subjects with Refractory Partial Epilepsy**

| Parameter | Final Parameter Estimate | | Interindividual Variability / Residual Variability | |
|---|---|---|---|---|
| | Typical Value | %SEM[a] | Magnitude | %SEM |
| (b) (4) | | | | |

*Source: cog008041-2014-eslipeds-a.pdf, page 66 of 403 (sequence 0147)*

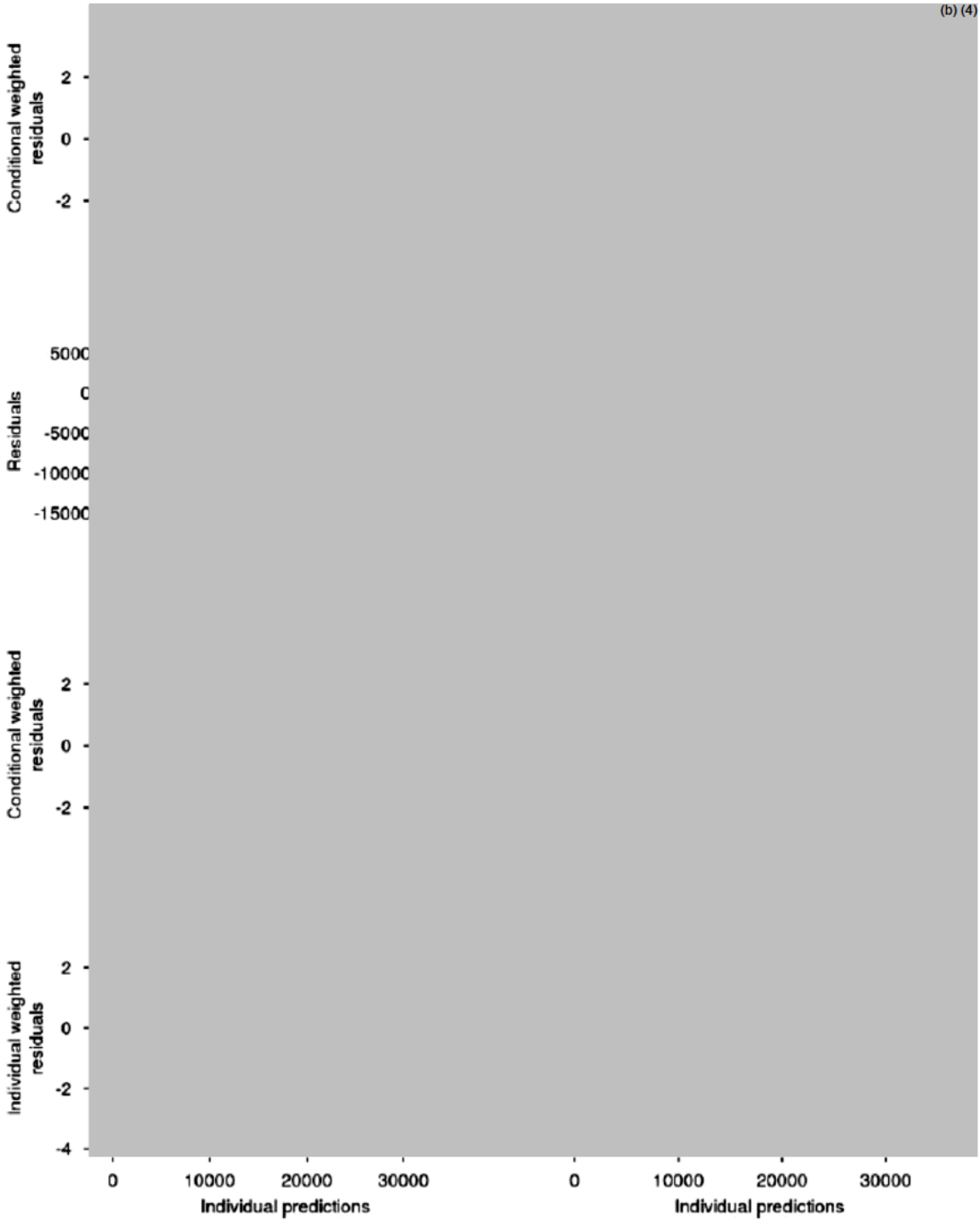
Model diagnostics are presented in the figures below.

**Figure 7: Diagnostic Plots for Final PK Model in Pediatric Patients with Refractory Partial Epilepsy: Data from Both Studies Combined**



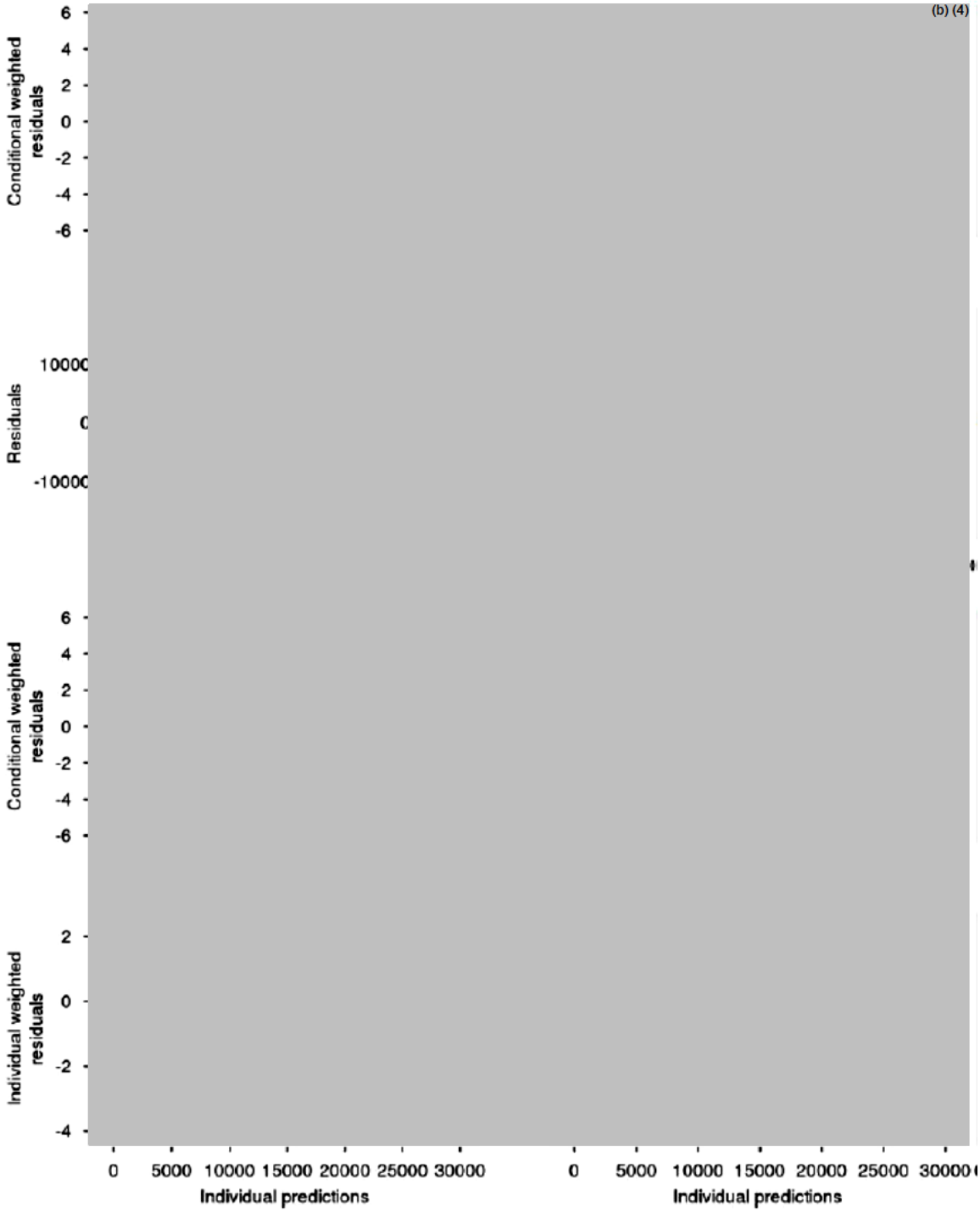

*Source: cog008041-2014-eslipeds-a.pdf, page 118 of 403 (sequence 0147)*

**Figure 8: Diagnostic Plots for Final PK Model in Pediatric Patients with Refractory Partial Epilepsy: Study 202**



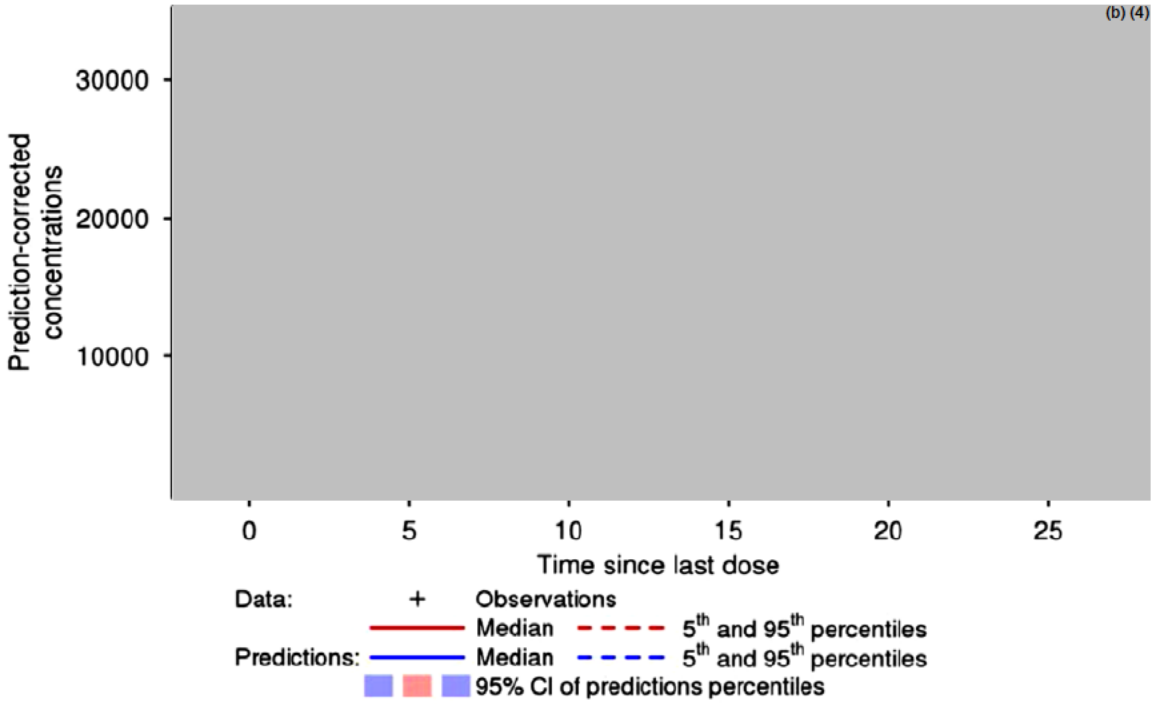

*Source: cog008041-2014-eslipeds-a.pdf, page 119 of 403 (sequence 0147)*

**Figure 9: Diagnostic Plots for Final PK Model in Pediatric Patients with Refractory Partial Epilepsy: Study 305**




*Source: cog008041-2014-eslipeds-a.pdf, page 120 of 403 (sequence 0147)*

**Figure 10: Visual Predictive Check for Final PK Model in Pediatric Patients with Refractory Partial Epilepsy**




*Source: cog008041-2014-eslipeds-a.pdf, page 125 of 403 (sequence 0147)*

[*Reviewer comment: The diagnostic plots do not demonstrate any obvious sign of systematic bias throughout the duration of the dosing interval or related to the concentration magnitude.*

*Sponsor has determined that* (b) (4)

(b) (4)

(b) (4)

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***Overall,*** (b) (4) ***(see section 7 of this review for details on regarding how this was addressed in PK simulations), the Sponsor's pediatric PK model is acceptable.***]

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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08/17/2017

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