

Clinical Pharmacology Review

PRODUCT (Generic Name):	Brivaracetam
PRODUCT (Brand Name):	BRIVIACT®
sNDA:	205836/s-005 (sequence 0077) 205837/s-004 (sequence 0071) 205838/s-003 (sequence 0073)
DOSAGE FORM:	Tablet, Solution for Injection, Oral Solution
ROUTE of ADMINISTRATION:	Oral and intravenous
INDICATION:	Monotherapy and adjunctive therapy for the treatment of partial-onset seizures in patients 4 years of age and older
SUBMISSION DATE:	July 10, 2017
APPLICANT:	UCB Pharmaceuticals Inc.
OCP REVIEWERS:	Dawei Li, Ph.D., Michael Bewernitz, Ph.D., Kevin Krudys, Ph.D., Angela Men, M.D., Ph.D.
OCP DIVISION:	DPM/DCP I

1 EXECUTIVE SUMMARY

Briviact® (brivaracetam; BRV) is currently approved in the U.S. for treatment (monotherapy and adjunctive therapy) of partial onset seizures in patients 16 years of age and older with epilepsy. Supplement 5, an efficacy supplement, was submitted under NDA 205,836 to pursue an indication for Briviact 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 BRV 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 Applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar BRV exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older to BRV exposure in adult subjects with POS. However, the Applicant's PK simulations demonstrated that pediatric patients with low body weight (e.g. < 20 kg) demonstrated lower exposures than heavier pediatric patients. For these reasons, the reviewer conducted an independent analysis.

To derive pediatric doses to match adult exposure, the reviewer conducted PK simulations comparing the median simulated exposure for each proposed pediatric dose level for comparison with each approved adult dose level. Like the Applicant, the reviewer conducted PK simulations in a monotherapy scenario. The monotherapy scenario was utilized by the Applicant after OCP expressed concern regarding conflicting drug-drug interaction assessments between adults and pediatric patients. 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 comparable to adults.

Based on PK simulations in this setting, OCP proposes maintenance dosing of 0.5 to 1.25 mg/kg twice daily (BID), 0.5 to 1.0 mg/kg BID, and 25 to 50 mg BID for pediatric patients weighing 11 kg to < 20 kg, ≥ 20 to 50 kg, and > 50 kg, respectively. For the initiation dose range in pediatric patients weighing < 20 kg, OCP proposes increasing the upper limit such that the range is 0.5 to 1.25 mg/kg BID. OCP agrees with Applicant's proposed initiation dose ranges of 0.5 to 1.0 mg/kg BID and 25 to 50 mg BID in pediatric patients weighing 20 to 50 kg, and > 50 kg, respectively. OCP's proposed initiation and maintenance dosing was communicated to the Applicant and the Applicant agreed with the proposal.

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

To support use of BRV 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 BRV in the adjunctive setting (carbamazepine and phenytoin), none are clinically relevant to the extent that they require a 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.

The Applicant agreed to the dosage regimen of BRV for pediatric patients shown in Table 1.

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

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults	50 mg twice daily (100 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 50 kg or more	25 mg to 50 mg twice daily (50 mg to 100 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 20 kg to less than 50 kg	0.5 mg/kg to 1 mg/kg twice daily (1 mg/kg to 2 mg/kg per day)	0.5 mg/kg to 2 mg/kg twice daily (1 mg/kg to 4 mg/kg per day)
Pediatric patients weighing 11 kg to less than 20 kg	0.5 mg/kg to 1.25 mg/kg twice daily (1 mg/kg to 2.5 mg/kg per day)	0.5 mg/kg to 2.5 mg/kg twice daily (1 mg/kg to 5 mg/kg per day)

As the oral solution, solution for injection, and oral tablet are bioequivalent, the dose recommendations for the tablet are applicable to the oral solution and solution for injection.

2 RECOMMENDATIONS

The Office of Clinical Pharmacology reviewers have reviewed NDA 205836,7,8 Supplement-005,-004, and -003 for Briviact® (Brivaracetam; BRV). The Applicant'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 Applicant and Agency regarding labeling language.

3 BACKGROUND

Briviact® (Briviaracetam; BRV) displays an affinity for synaptic vesicle protein 2A in the brain and has anticonvulsant properties. BRV is approved in the U.S. as monotherapy or adjunctive therapy for the treatment of partial-onset seizures (POS) in patients with epilepsy 16 years or older. In this supplemental NDA, the Applicant seeks an indication

for BRV as monotherapy and adjunctive therapy for the treatment of POS in patients 4 years of age and older based on extrapolation of adult data.

4 GENERAL ADVICE FOR PEDIATRIC EXTRAPOLATION

On November 12, 2015, DNP sent a General Advice Letter to the Applicant 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, an Applicant 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 BRV in pediatric subjects include N01263 and N01266. Applicant submitted PK and PKPD analysis reports CL0187 and CL0258.

N01263 (complete): Phase 2a, open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of BRV in n=99 pediatric epilepsy patients age ≥ 1 month to <16 years (30 subjects who were 28 days to 23 months of age, 51 subjects who were 2 to 11 years of age, and 18 subjects who were 12 to <16 years of age). Brivaracetam oral solution was administered at weekly increasing doses of approximately 0.4, 0.8, and 1.6 mg/kg twice-daily (bid) (0.8, 1.6, and 3.2 mg/kg/day) for subjects ≥ 8 years of age and 0.5, 1.0, and 2.0 mg/kg bid (1.0, 2.0, and 4.0 mg/kg/day) for subjects < 8 years of age. This study was submitted with the original NME submission (sequence 0000).

[Reviewer comment: Study N01263 has been previously reviewed by OCP. Please refer to the ISR review of NDA 205836 signed on 08/31/2015 for details.]

N01266 (ongoing): Phase 3, open-label, single-arm, multicenter, long-term, study to evaluate safety and efficacy of BRV used as adjunctive treatment in n=206 pediatric epilepsy patients age ≥ 1 month to <17 years. Rich and sparse PK samples were collected.

[Reviewer comment: PK data from N01266 has not yet been submitted to the Agency at the time of this review.]

This study is a long-term follow-up to N01263. Initially, patients age < 8 years and ≥ 8 years received 2 mg/kg BID and 1.6 mg/kg BID, respectively. However, as PK data were analyzed from N01263, Applicant determined that the initial proposed doses in N01266 were not achieving exposures associated with 100 mg twice daily in adults. As such, in Protocol Amendment 4, Applicant altered the dose to be the same mg/kg value for all subjects ≥ 1 month to ≤ 16 years (0.5, 1, and 2 mg/kg BID; 2.5 mg/kg BID if a higher dose were determined to be beneficial by the Investigator; not to exceed 100 mg twice daily).

CL0187: Report of population PK analyses

CL0187 Amended Report: Report CL0187 was previously submitted (NDA 205836, sequence 0077; 07/10/2017) and reviewed by OCP. CL0187 is the population PK study in pediatric patients with POS (N01263). The original CL0187 report used an adult exposure reference range based on an adult population PK model (described in previously-submitted report N01328) which included adult PK data from Phase 2 and Phase 3 studies (N01193, N01252, N01253, and N01254; sequence 0000). However, additional data from pivotal adult adjunctive BRV POS study N01358, which assessed 50 mg twice daily and 100 mg twice daily, came in after CL0187 was complete. Applicant updated the model described in CL0187 and provided results in CL0187 Amended Report. There were no changes to the pediatric population PK data or model. The results of CL0187 Amended Report are part of the current submission and are intended to support approval of adjunctive therapy and monotherapy in pediatric patients with POS age ≥ 4 to < 16 .

CL0258: Report CL0258 describes exposure-response modeling of BRV as an adjunctive therapy in children age ≥ 4 to < 16 years with POS.

[Reviewer comment: This current submission is based on PK matching and extrapolation. The exposure-response analyses were not reviewed.]

6 RESULTS OF APPLICANT'S POPULATION PK ANALYSES

The Applicant provided population PK analyses (Report CL0187 Amended Report) to support BRV dosing regimen in pediatric patients. The simulations in the CL0187 amended report were conducted using an adult population PK model and a pediatric model. The models are summarized below.

Adult Population PK Model: The adult population PK model provided in this submission was previously reviewed by OCP and found to be acceptable. A summary of key information about this adult population PK model is summarized below (please refer to the clinical pharmacology review of NDA 205836 signed on 07/24/2015, section 4.1.3.4 regarding report CL0028 for details).

Applicant utilized data from two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358) to generate the adult population PK model.

The final model (run20) utilized one-compartment, first-order oral absorption, first-order elimination, and was parameterized in terms clearance (CL), volume of distribution (V), first order oral absorption (k_a). Between-subject variability was estimated for CL, k_a , and V. Weight was a covariate on both CL/F and V/F (via allometric scaling with a power model). Covariates on CL/F were carbamazepine, phenytoin, and phenobarbital-like inducers. Residual error was modeled with a proportional error model.

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

Table 2: Parameter Estimates from the Final Adult Population PK Model (run20)

Parameter	Estimate (95% CI¹)	SE² (%CV)	IIV³	Shrinkage⁴
CL (L/h)	3.58 (3.50/3.66)	1.1%	24.7%	17.2%
V (L)	48.1 (45.8/50.4)	2.4%	30.5%	56.0%
Ka (1/h)	1.42 (1.26/1.57)	5.5%	101.2%	53.9%
Exponent for WT on CL	0.565 (0.499/0.631)	6.0%		
Exponent for WT on V	0.639 (0.483/0.795)	12.5%		
Effects on CL:				
CBZ ⁵	34.8% (30.5%/39.2%)	5.5%		
PHT ⁵	26.8% (20.0%/33.9%)	11.8%		
PB ⁵	23.9% (15.0%/33.4%)	17.6%		
Residual error:				
Proportional residual error (CV, %)	20.7 (19.7/21.7)	2.4%		14.0%

¹95%CI is estimate \pm 1.96*the standard error for the estimate

²Standard errors of the estimate are reported as %CV: 100*(standard error for the estimate)/estimate

³IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix

⁴Shrinkage values as reported by NONMEM

⁵effects are back-transformed log-estimates, changed from a factor to a percentage change

Source: cl0028-pk-report.pdf, page 46 of 270 (sequence 0000)

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

Applicant utilized data from n=96 pediatric patients in the Phase 2a study N01263 to generate a population PK model to represent pediatric patients.

The final model (run411) utilized one-compartment, first-order oral absorption, first-order elimination, and was parameterized in terms apparent clearance (Cl/F), apparent (V/F), and k_a (oral rate constant). Covariates for Cl/F included weight, concomitant use of phenobarbital-like inducers, concomitant use of carbamazepine, and concomitant use of valproic acid. The only covariate for V/F was lean body weight. Lean body weight was related to Cl/F and V/F using allometric scaling normalized to 50 kg.

[Reviewer comment: Brivaracetam is BCS class 1 and bioavailability is nearly 100%. As such, it can be assumed that $Cl/F = Cl$ and $V/F = V$ in pediatric patients.]

In addition, the clinical pharmacology review of NDA 205836 signed on 08/31/2015 (the Individual Study Review document, page 254 of 269) indicates that the oral solution and the oral tablets are bioequivalent. Thus, it is acceptable that the Applicant estimated a single absorption rate constant applicable to both oral solution as well as oral tablet forms in pediatric patients.]

Final model parameters are shown in the table below.

Table 3: PK Parameter Estimates for Final PK Model in Pediatric Subjects with Refractory Partial Epilepsy (run411)

Parameter	Estimate	SE ¹ (%CV)	95% CI ²	IIV ³	Shrinkage (%)
CL/F (L/hr.) (θ3)	3.63	3.0%	3.42/ 3.85	22.8%	6.1%
V/F (L) (θ4)	47.8	5.0%	43.1/ 52.5	16.7%	45.6%
Ka (1/hr.) (θ5)	1.84	25.9%	0.906/ 2.78	31.9%	73.4%
Allometric scaling factor CL/F (θ6)	0.750 Fixed				
Allometric scaling factor V/F (θ7)	1.00 Fixed				
Change in CL with PB co-administration (%) (θ8)	40.8%	23.9%	19.9%/ 65.2%		
Change in CL with CBZ co-administration (%) (θ9)	47.9%	19.1%	27.8%/ 71.2%		
Change in CL with VPA co-administration (%) (θ10)	-10.1%	47.1%	-18.5%/ -0.81%		
Proportional residual error (CV, %) (θ1)	23.4	8.2%	19.6/ 27.1		9.2%

¹Standard errors of the estimate are reported as %CV: 100* standard error for the estimate /estimate

²95%CI is estimate±1.96*the standard error for the estimate

³IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix

Source: cl0187-pk—report-amended.pdf, page 35 of 244 (sequence 0077)

[Reviewer comment: The pediatric population PK model differs from the adult model in terms of drug interaction estimates. In particular,

- PB increases CL by 40.8% in pediatric patients and but 23.9% in adults,
- CBZ increases BRV CL by 47.9% in pediatric patients but 34.8% in adults
- the adult model has a PHT interaction which is not present in the pediatric model, and
- the pediatric model has a VPA term which is not present in adults.

However, the effect of PK interaction is expected to be comparable between adult patients and pediatric patients, which suggests that other factors (i.e., modest sample size of pediatric patients receiving phenobarbital or carbamazepine, study design, variability) may be affecting the PK interaction estimates in pediatric patients. Please refer to Appendix A for details regarding the impact of PK interactions (inducers such as

phenobarbital and carbamazepine as well as inhibitors such as valproic acid) on the PK simulations and ultimately the selection of the dose in pediatric patients.]

Applicant's PK Simulations to Support Pediatric Dosing: Applicant obtained data on pediatric weight and age distribution from the Nhanes DXA database for 1999-2004 provided by CDC. The virtual pediatric patient population was designated as age < 16 years and mass \leq 100 kg.

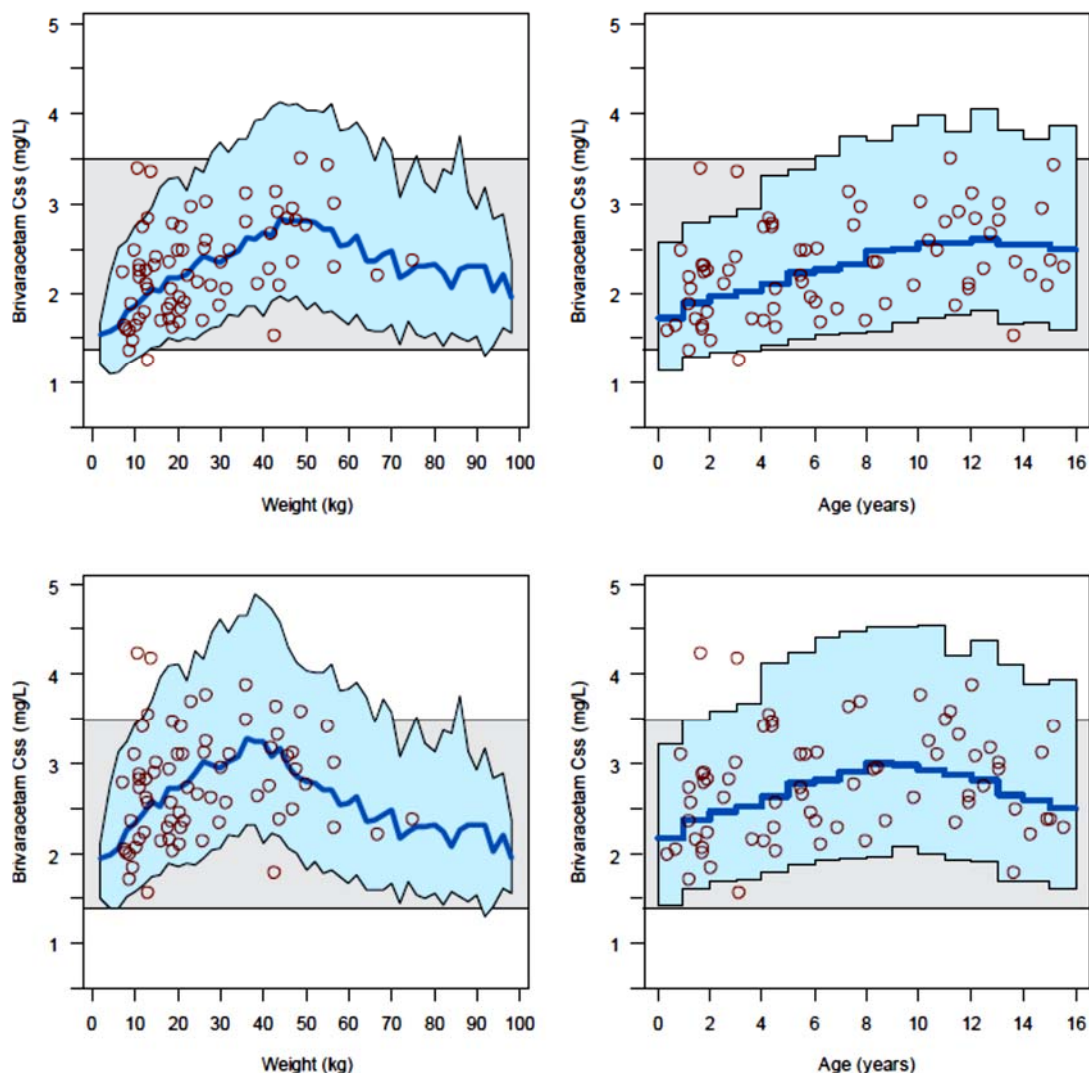
Maintenance dose target: Applicant selected the approved maintenance dose of 100 mg twice daily as the target for determining maintenance dosing in pediatric patients.

Simulation Methodology: Applicant originally proposed to conduct PK simulations in an adjunctive therapy setting. However, during a pre-sNDA meeting, OCP expressed concerns regarding PK simulations conducted in the adjunctive setting due to differing drug interaction estimates between adult patients and pediatric patients. As a result of these concerns, the Applicant conducted PK simulations in a monotherapy setting (for details please refer to the meeting minutes for Type B pre-sNDA meeting, IND 070205, signed on 04/03/2017).

The average steady-state concentration ($C_{av,ss}$, also referred to as C_{ss} in the Applicant's plots and reports) was the exposure metric selected for the PK simulations. The $C_{av,ss}$ in adults was computed to represent steady-state exposure resulting from the maximum recommended dose of 100 mg twice daily. First, AUC_{ss} was computed with the equation $AUC_{ss} = \text{Dose} / CL$ where Dose is the dose of drug administered per dosing interval (i.e. maximum of 100 mg per dosing interval in adults). Using a dosing interval of 12 hours, the $C_{av,ss}$ is computed as $C_{av,ss} = AUC_{ss} / 12$. The Applicant derived the 5th percentile and 95th percentile of the $C_{av,ss}$ in adults to use as a reference range for assessing the exposures achieved in the proposed pediatric regimen.

The Applicant's PK simulations generated to support the proposed dose regimen are shown below.

Figure 1: Simulated $C_{av,ss}$ by Body Weight (Left) and Age (Right) in Pediatric Patients with Partial-Onset Seizures Receiving Twice Daily BRV As Simulated by the Applicant



Red circles are the individual predictions for patients without inducer AED co-administration. The light blue shaded area is the predicted ranges for children from the Nhanes database <16 years and ≤ 100 kg receiving 2 mg/kg BID with 100 mg BID maximum maintenance dose for all patients (top) or 2.5 mg/kg BID with 100 mg BID maximum maintenance dose for all patients (bottom). The blue shaded area encompasses 90% of the simulated pediatric patients and the blue line is the median simulated pediatric $C_{av,ss}$. The horizontal gray bar is the predicted 90% CI $C_{av,ss}$ of the adults receiving 100 mg BID administered without concomitant inducer AEDs.

Source: sequence 0077, cl0187-pk-report-amended-addendum.pdf, page 6 of 8

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

Table 4: Applicant's Proposed Initial Dose, Minimum Maintenance Dose, and Maximum Maintenance Dose for Pediatric Patients age ≥ 4 to < 17 Years

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults	50 mg twice daily (100 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 50 kg or more	25 mg twice daily (50 mg per day)	25 mg to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing less than 50 kg	0.5 mg/kg twice daily (1 mg/kg per day)	0.5 - 2 mg/kg twice daily (1 mg/kg to 4 mg/kg per day)

Source: annotated-201706 Section 2.1, page 3 of 20 (sequence 0077)

[Reviewer comment: The adult reference used for assessing the pediatric dose is expressed as a 5th-95th percentile prediction interval. However, it is not clear how the simulated exposure in pediatric patients compares with a measure of central tendency in simulated adult exposure. In addition, only the highest approved adult dose, 100 mg BID, is represented in the plot. Furthermore, Applicant was previously notified that the proposed dose may lead to underexposure in lower end of the pediatric body weight range and that an increase up to 2.5 mg/kg BID may be warranted (e.g. see response to question 4 in the written responses to Type C meeting questions under IND 110606 signed on 05/01/2017 for details).

For these reasons, OCP decided to conduct independent PK simulations using the full range of approved adult maintenance dose levels to inform pediatric dose selection. Based on simulations conducted in the monotherapy setting, OCP proposed a new dose regimen. The new initiation dosing and maintenance dosing was communicated to the Applicant and was accepted by the Applicant. Please refer to section 7 for details.]

7 REVIEWER'S ANALYSES

Maintenance Dose Selection

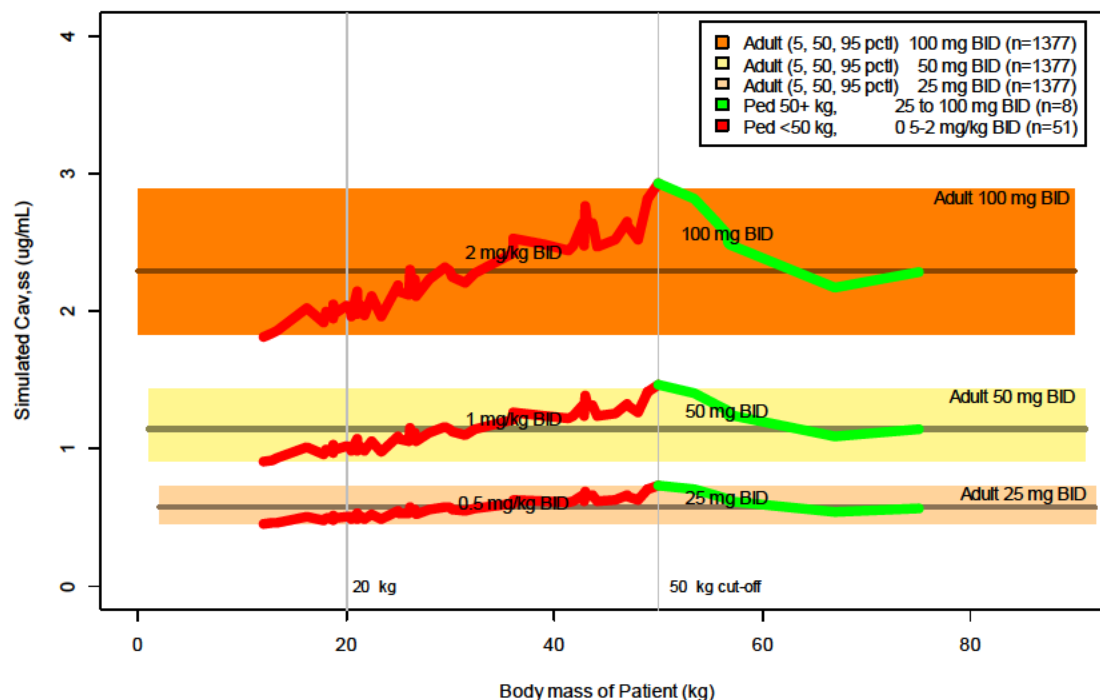
The Applicant computed the 5th percentile and 95th percentile of expected adult exposures for the highest approved dose level. However, there is a range of approved adult maintenance dose levels (25, 50, and 100 mg BID). In addition, the Applicant included median simulated pediatric exposures but not median simulated exposures for adults. While the pediatric exposures were mostly contained within the adult range, it is not clear how close the pediatric median exposures were to the adult median exposures at the range of approved dose levels. For these reasons, the reviewer conducted independent PK simulations for the range of adult dose levels (25, 50, and 100 mg BID).

The adult PK model was utilized with all drug interaction terms inactive to best represent the monotherapy scenario for adult patients and pediatric patients. For the adult simulations, the observed weight values from the adult patient PK dataset were utilized to determine the effect of weight on volume and weight on clearance. For the pediatric patients, the lean body weight values from trial N01263 PK dataset were utilized to account for the effect of lean body weight on volume and lean body weight on clearance. As the indication being sought is for pediatric patients age ≥ 4 years, only lean body weights from patients age ≥ 4 years were included in the PK simulations. Between-subject variability terms were set to zero to help avoid occurrences of physiologically impossible combinations of PK parameters. Under these conditions, the adult PK model and pediatric PK model were applied to simulate $C_{av,ss}$.

The approved adult doses of 25, 50, and 100 mg BID dose levels were utilized to serve as target exposures for the pediatric PK simulations. Similar to Figure 1, the $C_{av,ss}$ was simulated for pediatric patients as a function of weight plotted against the adult exposures at the approved 25, 50, and 100 mg BID dose levels. The typical adult exposure as a function of body weight was summarized as a median, 5th percentile, and 95th percentile adult $C_{av,ss}$ for 3 dose levels in the approved adult dose range.

The reviewer reassessed the Applicant's original proposed pediatric dosing using the expected adult exposures at each of the 3 dose levels selected to represent the approved adult dose range. The figure below shows the simulated pediatric $C_{av,ss}$ achieved using the Applicant's proposed dosing regimen (0.5 to 2 mg/kg BID for patients weighing < 50 kg and 25 to 100 mg BID for pediatric patients weighing ≥ 50 kg.) compared with simulated adult $C_{av,ss}$ for the approved 25, 50, and 100 mg BID.

Figure 2: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using Applicant's Proposed Maintenance Dosing Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 20 kg is included as a visual aid for comparison with OCP's proposed dosing.

[Reviewer comment: The pediatric population PK model utilizes lean body weight. However, the adult model utilizes unmodified body weight. To allow comparison between the pediatric and adult exposures using a common body size metric, the unmodified pediatric patient body weight was utilized for comparison with adult exposures. The variability in the relationship between pediatric body weight and pediatric lean body weight results in variability in the simulated pediatric $C_{av,ss}$ across the range of pediatric body weight.]

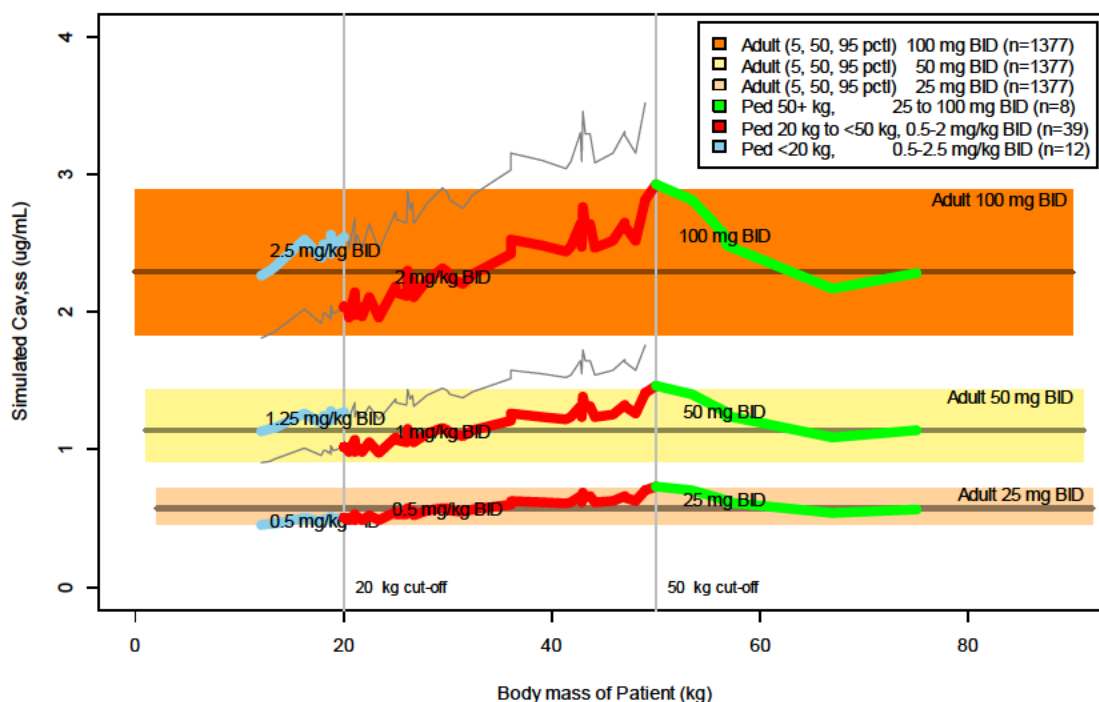
The simulated pediatric $C_{av,ss}$ values, when plotted against the range of adult doses, suggests that the pediatric patients with lower body weights are likely to experience lower $C_{av,ss}$ compared to the approved adult dose levels. This is particularly apparent when comparing the pediatric exposure to the median adult exposure. Ideally, a pediatric dose range should be selected such that pediatric patients can be expected to achieve exposures consistent with the approved adult dose range. As such, additional simulations were conducted to assess the potential for a dose increase in pediatric patients with low body weight.

Doses ranging from 0.5 mg/kg BID to 2.5 mg/kg BID were simulated for pediatric patients. The 2.5 mg/kg BID dose level was previously recommended by the Division for the Applicant to consider (see written responses for Type Interaction signed on 05/01/2017 under IND 110606 for details).

The “weight cut off” for increasing the dose level was explored. Values of 15, 20, and 25 kg were assessed as potential cut off values. The 20-kg body weight appears to provide a reasonable breakpoint in terms of matching adult exposure. For simulations using the 15 kg and 25 kg cut off values, please refer to Appendix B. The minimum weight value in the pediatric patients age ≥ 4 years for which PK data are available is 12.1 kg (patient from trial N01263) and thus is the lowest weight on the plot.

The simulated exposures resulting from OCP’s final proposed maintenance dose at the 20-kg cut-off for dose increase are displayed in the figure below.

Figure 3: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Maintenance Dosing and OCP’s Proposed 20 kg Weight-Cut off Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 20 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Patients 11 to < 20 kg: Applicant proposes 0.5 – 2 mg/kg BID, OCP proposes 0.5 – 2.5 mg/kg BID

Patients 20 to < 50 kg: Applicant proposes 0.5-2 mg/kg BID, OCP agrees

Patients ≥ 50 kg: Applicant proposes 25 to 100 mg BID, OCP agrees

The reviewer’s PK simulations suggest that administration of 2.5 mg/kg BID to pediatric patients weighing < 20 kg will achieve exposures that are comparable to exposures achieved when administering 2.0 mg/kg BID to pediatric patients weighing ≥ 20 to 50 kg (see figure 3 for details). OCP’s recommendation of a higher dose in patients < 20 kg to

match exposures to those in heavier patients is supported by the safety experience at the 2.0 mg/kg BID in pediatric patients weighing ≥ 20 to 50 kg

In addition, the Applicant increased the upper dose limit in ongoing study N01266 from 2.0 to 2.5 mg/kg BID in protocol amendment 4. The interim report indicates that $n = 96$ patients were treated with a modal dose ≥ 2.0 mg/kg BID. While it is plausible that the 2.5 mg/kg BID dose level was administered to patients prior to completion of the interim report, there is no specific mention of the 2.5 mg/kg BID dose level in the interim report. Thus, the current interim report for N01266 does not provide information to assess the safety of the 2.5 mg/kg BID dose level.

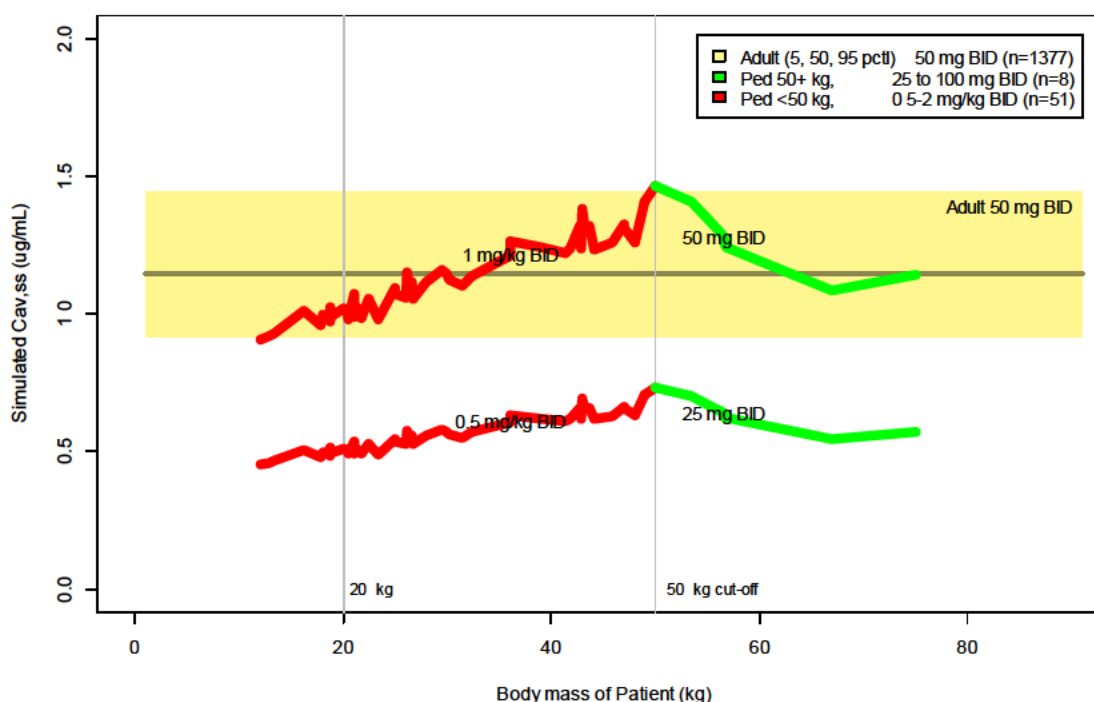
The lowest body weight recorded in a pediatric patient that provided PK data (in trial N01263) was 12.1 kg. However, the lowest body weight recorded when considering patients from all available trials is 11.0 kg (from a patient enrolled in trial N01266). OCP and DNP agree that the label can include patients weighing at least 11.0 kg for the proposed indication in patients age ≥ 4 years.

As the exposures predicted for 2.5 mg/kg BID in pediatric patients weighing < 20 kg are expected to be comparable to exposures predicted for 2.0 mg/kg BID in pediatric patients 20 to 50 kg, and as there are no safety signals associated with the 2.0 mg/kg BID dose, **OCP proposes maintenance doses of 0.5 – 2.5 mg/kg BID, 0.5 – 2 mg/kg BID, and 25 to 100 mg BID for pediatric patients weighing 11 to < 20 kg, 20 to < 50 kg, and ≥ 50 kg, respectively.**

Initiation Dose Selection

The Applicant's proposed initial dose is 25 mg BID for patients weighing ≥ 50 kg and 0.5 mg/kg BID for patients weighing < 50 kg. As the PK are time-independent, the PK simulations for $C_{av,ss}$ can be used to inform the single-dose C_{av} . Thus, the PK simulation methodology used to select the maintenance dose can be used for evaluating the initiation regimen. The following plot provides a comparison of the exposures achieved using the Applicant's initial dosing recommendation for pediatric patients with the approved adult initial dose.

Figure 4: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using Applicant's Proposed Initial Dosing Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Initial Dosing

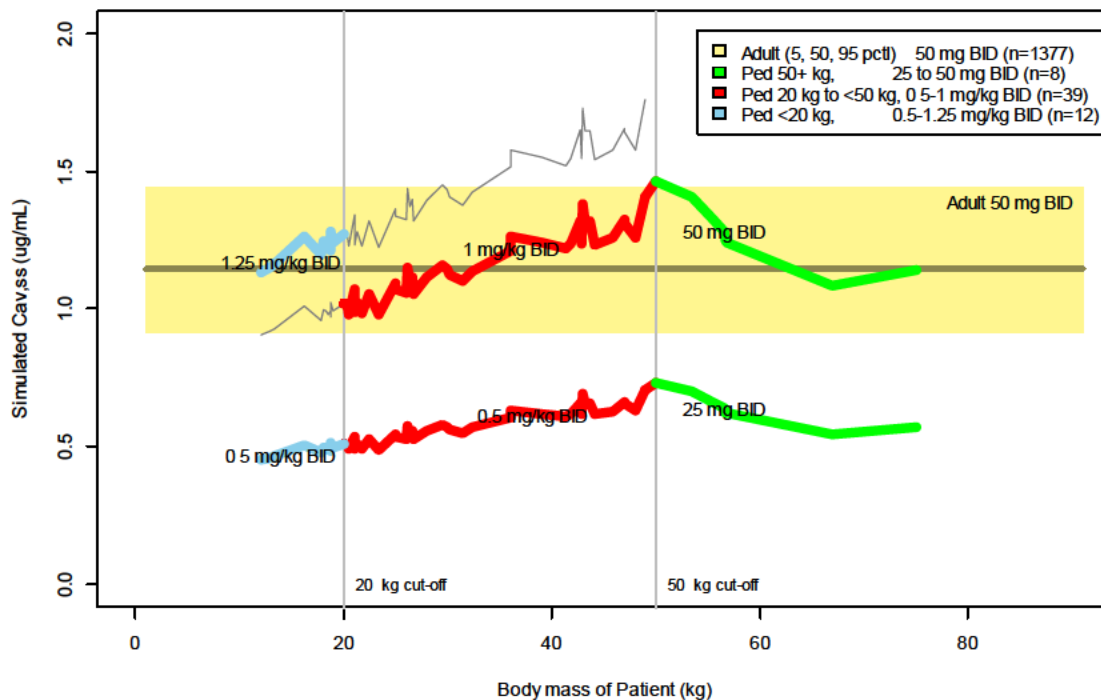


Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved initial adult dose of 50 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and initiation dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 20 kg is included as a visual aid for comparison with OCP's proposed dosing.

As is shown above, the 0.5 mg/kg BID dose level in patients < 50 kg and 25 mg BID level in patients ≥ 50 kg provides an exposure expected to be lower than the minimum approved adult initiation dose level of 50 mg BID. However, the applicant has clinical trial experience with these initiation dose levels as 0.5 mg/kg BID and 25 mg BID were utilized as the initiation dose levels in pediatric clinical trial N01266. In addition, while the 0.5 mg/kg BID and 25 mg BID initiation dose levels may result in exposures lower than the adult initiation dose, patients are expected to remain at such exposures for only a matter of days before the dose is increased during titration. Following internal discussions, it was decided that the label should provide flexibility for the healthcare professional to have the option to initiate pediatric patients less aggressively with a minimum initiation dose of 0.5 mg/kg BID in patients < 50 kg and 25 mg BID in patients ≥ 50 kg.

The Applicant's upper dose limit for initiation, 1.0 mg/kg BID, appears to result in patients who weigh less than ~20 kg to experience exposures that are lower than median adult exposures at the approved adult initiation dose of 50 mg BID. OCP conducted PK simulations to assess the potential of an initiation dose increase in patients < 20 kg to better match adult exposures for the approved 50 mg BID adult initiation dose (see figure below).

Figure 5: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCP's Proposed Initial Dosing Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Initial Dosing



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved initial adult dose of 50 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and initiation dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 20 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Overall, the PK simulations indicate that increasing the upper limit for initiation dosing in patients weighing < 20 kg is likely to provide a better match to the exposures in adults at the approved initiation dose. **Thus, OCP recommends the initiation dose range in pediatric patients to be 0.5 to 1.25 mg/kg BID in patients weighing 11 kg to < 20 kg. OCP agrees with the Applicant's proposed initiation dose ranges in pediatric patients 0.5 to 1.0 mg/kg BID in patients weighing ≥ 20 to < 50 kg and 25 to 50 mg BID in patients weighing ≥ 50 kg.**

The minimum weight in the ongoing safety study N01266 is 11.0 kg. Based on internal discussions with DNP medical review team, the minimum weight recommended for pediatric dosing is 11 kg for patients age ≥ 4 years.

Key label edits: The Applicant's proposed label was edited to include the updated maintenance dosing proposed by OCP and updated initial dosing proposed by OCP. In section 12.3, Specific Populations, Age, Pediatric Patients, several edits were proposed by OCP. The age range in this section was modified to mention that the PK data include

patients in the age range for the proposed indication (≥ 4 years to $<^{(b) (4)}$ years). The statement ^{(b) (4)}

was removed as ^{(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

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

Summary of PK Data:

There were 600 measurable BRV concentrations from n=96 patients available for PK analyses.

Studies: Applicant utilized PK data from pediatric patients ages 0.2 to 15.6 years (n=29 subjects age 1 month to < 2 years; n=26 subjects age 2-6 years, n=24 subjects age 6-11 years, and n=17 subjects age 12-15 years) that received Briviact in Phase 2a study N01263.

Study N01263 was a Phase 2a, open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of brivaracetam oral solution in subjects from ≥ 1 month to <16 years old with epilepsy. Patients received 3 dose levels, one week at each dose level, for a total of 3 weeks followed by a 2-week down-titration. Patients age ≥ 8 years of age received 0.4, 0.8, and 1.6 mg/kg twice daily during Weeks 1, 2, and 3, respectively. Patients < 8 years of age received 0.5, 1.0, and 2.0 mg/kg twice daily during Weeks 1, 2, and 3, respectively. Please refer to the clinical pharmacology review of NDA 205836, individual study review (ISR), section 4.4.30 for additional details regarding study N01263.

Pediatric Population PK Model:

The structural model was a one-compartment model with first order absorption. PK parameters included Cl/F, V/F, and k_a (absorption rate constant).

Allometric Scaling: Cl/F and V/F had allometric scaling applied using lean body weight normalized to 50 kg.

Inter-individual variability: exponential

Residual variability: proportional error model

Final model parameters are shown in the table below.

**Table 5: PK Parameter Estimates for Final PK Model in
Pediatric Subjects with Refractory Partial Epilepsy (run411)**

Parameter	Estimate	SE¹ (%CV)	95% CI ²	IIV³	Shrinkage (%)
CL/F (L/hr.) (θ3)	3.63	3.0%	3.42/ 3.85	22.8%	6.1%
V/F (L) (θ4)	47.8	5.0%	43.1/ 52.5	16.7%	45.6%
Ka (1/hr.) (θ5)	1.84	25.9%	0.906/ 2.78	31.9%	73.4%
Allometric scaling factor CL/F (θ6)	0.750 Fixed				
Allometric scaling factor V/F (θ7)	1.00 Fixed				
Change in CL with PB co- administration (%) (θ8)	40.8%	23.9%	19.9%/ 65.2%		
Change in CL with CBZ co- administration (%) (θ9)	47.9%	19.1%	27.8%/ 71.2%		
Change in CL with VPA co- administration (%) (θ10)	-10.1%	47.1%	-18.5%/ -0.81%		
Proportional residual error (CV, %) (θ1)	23.4	8.2%	19.6/ 27.1		9.2%

¹Standard errors of the estimate are reported as %CV: 100* standard error for the estimate /estimate

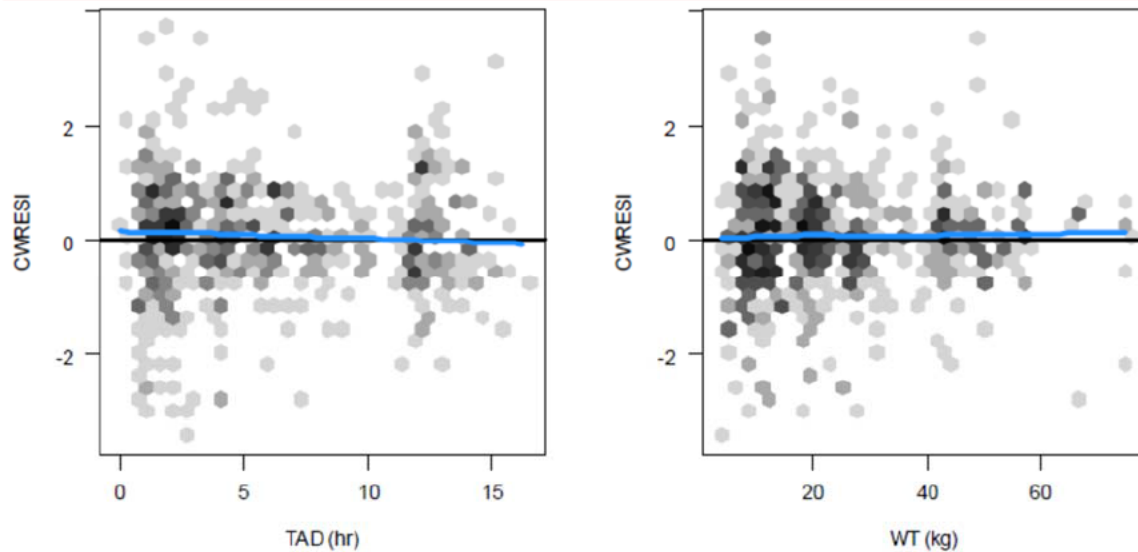
²95%CI is estimate±1.96*the standard error for the estimate

³IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix

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Model diagnostics are presented in the figures below.

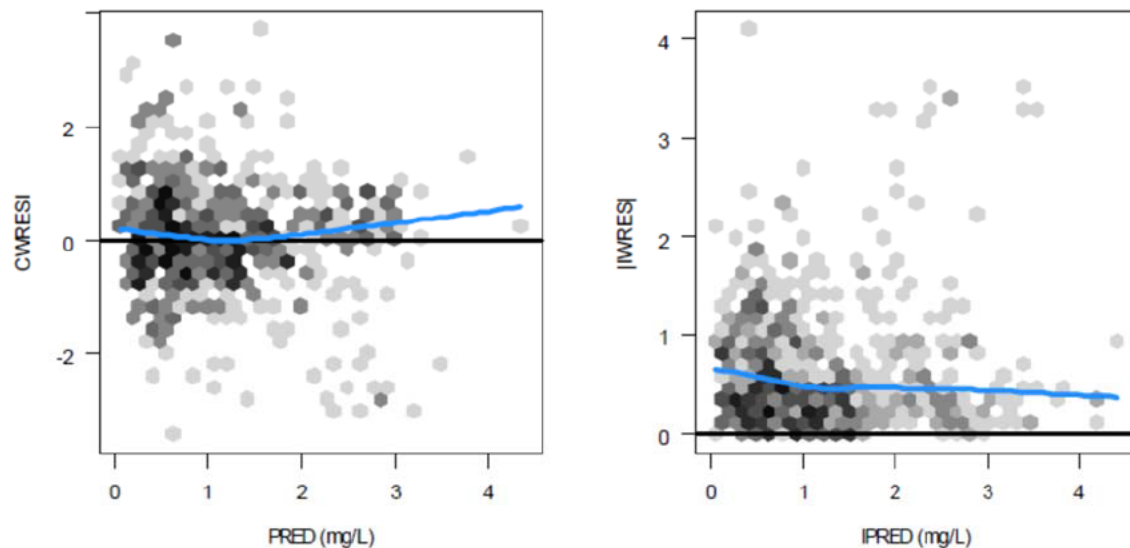
Figure 6: Diagnostic Plots for Final PK Model (run411) in Pediatric Patients with Refractory Partial Epilepsy



The black lines are zero lines, the blue lines are “smoothed” approximations of the data. CWRESI vs. TAD, WT, LBW and age. The darkness of the hexagons corresponds to the data density at that location.

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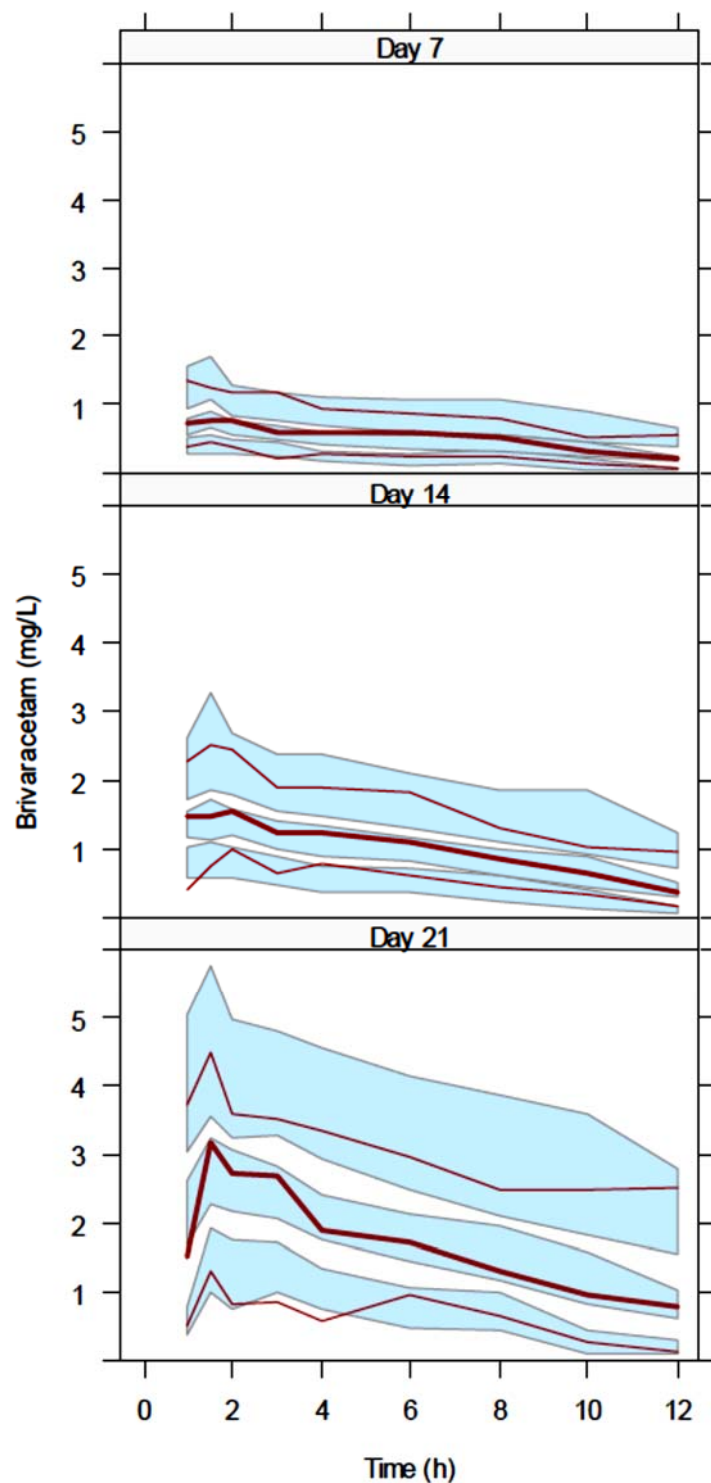
Figure 7: Diagnostic Plots for Final PK Model (run411) in Pediatric Patients with Refractory Partial Epilepsy



The black lines (top) are zero lines, the blue lines are “smoothed” approximations of the data. The darkness of the hexagons corresponds to the data density at that location. The black lines (bottom) are the normal curves generated using the calculated mean and standard deviation of the residuals.

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Figure 8: Visual Predictive Check for Final PK Model in Pediatric Patients with Refractory Partial Epilepsy



Red lines are the 5th, 50th (median) and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles.

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[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.

Applicant has determined that weight is a covariate on BRV PK. Applicant implemented allometric scaling to account for changes in BRV clearance and volume due to maturation of organ systems involved in BRV disposition, which is acceptable.

Applicant has determined that phenobarbital use, carbamazepine use, and valproic acid use are covariates on BRV CL. However, the pediatric PK model has numerous differences from the adult PK model in terms of PK drug interactions. For example, the adult PK model has phenytoin causing a 26.8% increase in BRV CL yet phenytoin is not present in the pediatric PK model. The pediatric PK model has valproic acid changing BRV CL by -10.1% but valproic acid is not present in the adult PK model. Differences in drug-interactions are not expected to affect adults different than pediatric patients. Some other potential sources contributing to the difference in drug interaction terms (PHT is present only in adult model, VPA is present only in pediatric model) and magnitude of phenobarbital (40.8% versus 23.9% CL increase in pediatric versus adult patients) and carbamazepine (47.9% versus 34.8% CL increase in pediatric versus adult patients) may include the modest sample size of pediatric patients receiving phenobarbital (e.g. only 15 out of 99 patients received concomitant phenobarbital; 15.2%) and carbamazepine (e.g. 24 out of 99 patients received concomitant carbamazepine; 24.2%), and confounding effects other concomitant medications. Overall, these points further support the Applicant's decision to conduct independent simulations in a monotherapy scenario (e.g. where drug interaction terms are not active in the PK simulations).

The VPC suggests that the model appears to predict concentrations near the median and higher concentrations well. The model appears to under-predict the lower end of the concentrations at 4 hours post-administration on Days 7 and Day 21. This finding supports the reviewer's decision to conduct PK simulations focus on the typical exposure with exclusion of random effects. Overall, the pediatric PK model performance is expected to perform adequately to for the purpose of simulating PK data in order to inform pediatric dose selection.

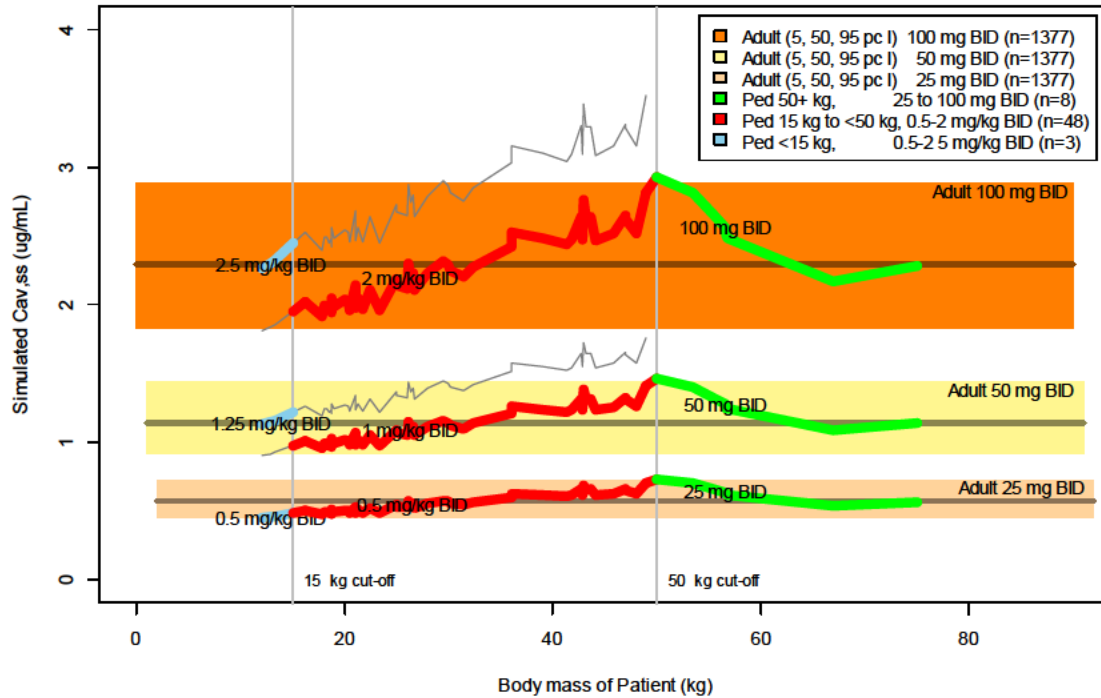
Overall, aside from drug interaction terms which may not be reliable, the Applicant's pediatric PK model is acceptable.]

Appendix B:

Selection of Cut-off Weight for Maintenance Dose in Low Body Weight Pediatric Patients

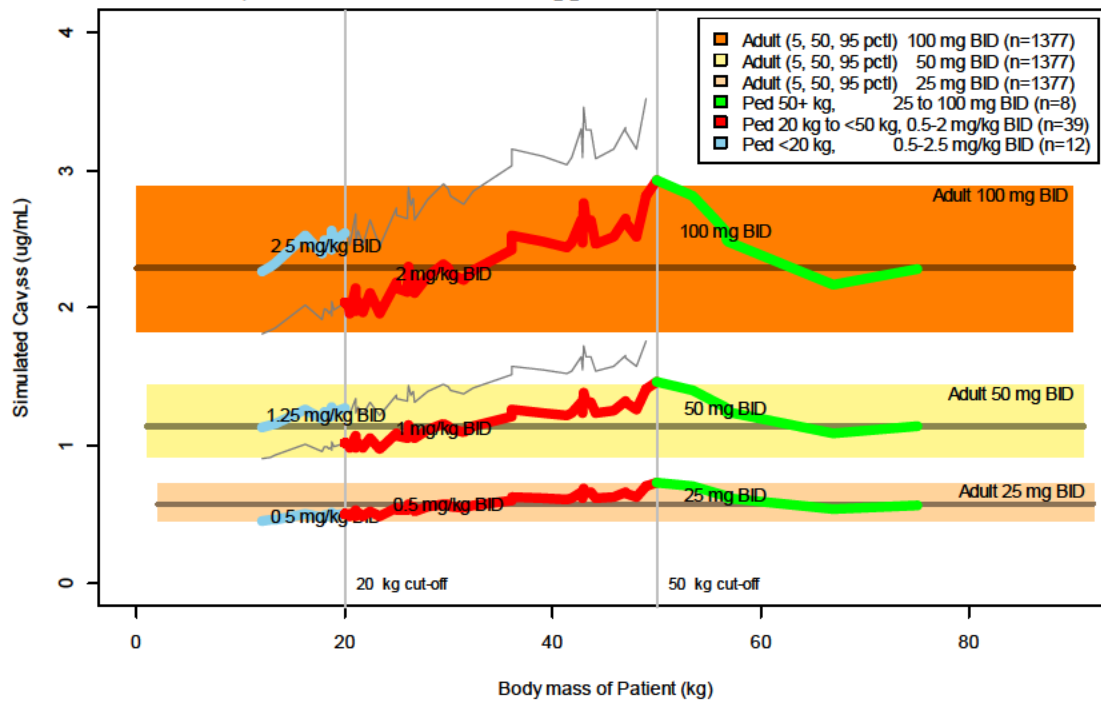
The values of 15, 20, and 25 kg were explored as potential candidates for the cut-off weight value. The effect of these various cut-off weight values is presented in the figures below.

Figure 9: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Maintenance Dosing with a 15 kg Weight-Cut off Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses



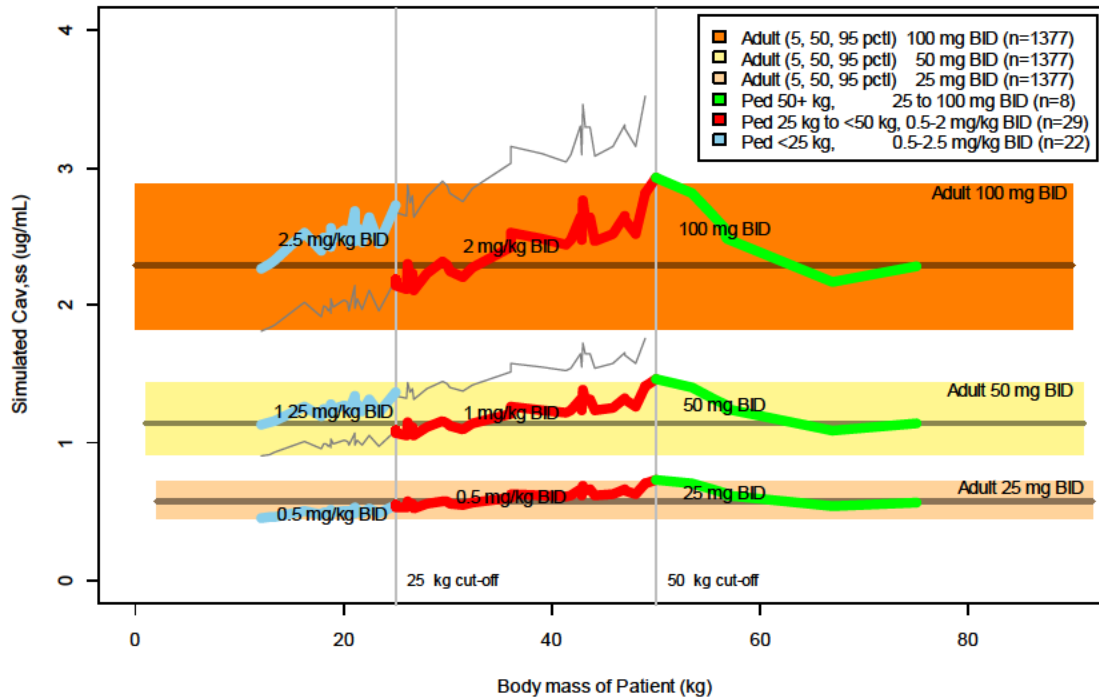
Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 15 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Figure 10: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Maintenance Dosing with a 20 kg Weight-Cut off Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 20 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Figure 11: Simulated $C_{av,ss}$ in Pediatric Patients Based on Body Weight and Dose Using OCPs Proposed Maintenance Dosing with a 25 kg Weight-Cut off Compared with Simulated $C_{av,ss}$ in Adult Patients at Approved Maintenance Doses



Solid horizontal bars and lines represent the 5th, 50th, and 95th percentiles of simulated $C_{av,ss}$ at the approved adult maintenance doses of 25, 50, and 100 mg BID. The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. These simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The vertical line at 25 kg is included to visualize the cut-off weight for increasing the mg/kg dose for low body weight pediatric patients.

Looking at Figure 10 (the plot generated using the 20 kg weight cut off), the following observations are apparent:

- As weight increases from < 20 kg towards 20 kg, the pediatric exposure overshoot above adult median exposure appears modest.
- As weight decreases from > 20 kg towards 20 kg, the pediatric exposures undershoot below adult median exposure appears modest.

Overall, the 20 kg value is a reasonable choice for a cut-off weight value for increasing the dose in low body weight pediatric patients.

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/s/

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