Integrated Clinical Pharmacology Review

Product (Generic Name)	Brivaracetam
Product (Brand Name)	BRIVIACT®
Link to EDR	\\cdsesub1\evsprod\NDA205836\0106 \\cdsesub1\evsprod\NDA205837\0097 \\cdsesub1\evsprod\NDA205838\0100
sNDA	205836/s-009 (sequence 0106) 205837/s-007 (sequence 0097) 205838/s-006 (sequence 0100)
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 1 month of age and older
Submission Date	10/28/2020
Applicant	UCB Pharmaceuticals, Inc.
OCP review team	Muzeeb Syed, Ph.D., Michael Bewernitz, Ph.D. Atul Bhattaram, Ph.D. Gopichand Gottipati, Ph.D. Sreedharan Sabarinath, Ph.D.
OCP divisions	Division of Neuropsychiatric Pharmacology, Division of Pharmacometrics

1. Executive Summary

Brivaracetam (BRIVIACT®, BRV) is an antiepileptic agent, originally approved in the US in 2016 for use as adjunctive therapy, and in 2017 as a monotherapy in the treatment of partial onset seizures (POS) in patients 16 years age and older with epilepsy. Three dosage forms were approved – tablet (NDA 205836), solution for intravenous (I.V.) injection (NDA 205837) and oral solution (NDA 205838). In 2018, efficacy supplements (205836/s-005, 205837/s-004 and 205838/s-003) were approved for treatment (monotherapy and adjunctive therapy) of POS in patients 4 years of age and older based on extrapolation of efficacy from adults. This expansion of indication for treatment of POS to include patients ≥ 4 years to < 16 years was only for BRV tablets and oral solution dosage forms since safety of BRV I.V. injection in pediatric patients was not established at the time of approval.

In October 2020, UCB Inc., submitted the current sNDA applications [205836/s-009, 205837/s-007, 205838/s-006] to support the following indication and dosing (Table 1):

- treatment (monotherapy and adjunctive therapy) of POS in patients ≥ 1 month to < 4 years of age with BRV oral tablets and oral solution
- treatment (monotherapy and adjunctive therapy) of POS in patients in patients ≥ 1 month to < 16 years of age with BRV I.V. injection

Table 1 BRV Dosage Schedule for Pediatric Patients Aged 1 Month to 17 Years

Age and Body Weight	Initial Dosage	Minimum and Maximum Maintenance Dosage
Adults	50 mg twice daily (100 mg per day)	25 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 to 100 mg per day)	25 to 100 mg twice daily (50 to 200 mg per day)
Pediatric patients weighing 20 kg to less than 50 kg	0.5 to 1 mg/kg twice daily (1 to 2 mg/kg per day)	0.5 to 2 mg/kg twice daily (1 to 4 mg/kg per day)
Pediatric patients weighing 11 kg to less than 20 kg	0.5 to 1.25 mg/kg twice daily (1 to 2.5 mg/kg per day)	0.5 to 2.5 mg/kg twice daily (1 to 5 mg/kg per day)
Pediatric patients weighing ~~3 kg to*~~ less than 11 kg	**0.75 to 1.5 mg/kg twice daily (1.5 to 3 mg/kg per day)**	**0.75 to 3 mg/kg twice daily (1.5 to 6 mg/kg per day)**

The proposed update to Briviact dosing, inclusion of dosing for subjects age 1 month to < 4 years (3 kg to < 11 kg), is denoted by the grey shaded boxes in the table above; *OCP review team recommends deletion of lower weight cut-off (please refer sections 3.6 and 3.7 for additional details).

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

The applicant followed Agency's advice on 'exposure-matching' approach (outlined in section 3.1 below) and provided population PK analyses report (Amended Report CL0482) to support BRV dosing regimen (noted in Table -1 above) in pediatric patients. PopPK based simulations included in CL0482 were based on adult and pediatric popPK models. The adult popPK model utilized data from two Phase 2 studies (N01114 and N01193) and three Phase 3 studies (N01252, N01253, and N01358) [Please refer Integrated Clinical Pharmacology review for original submission, DARRTS dated 07/24/2015 for additional details). The pediatric popPK model utilized data from the 3 pediatric studies – EP0065, N01263, N01266 (please refer section 3.2 for additional details on study design and dosing considerations).

(b) (4)

The primary objectives of this review are:

(1) evaluate the appropriateness of the dosing recommendations in 1 month to < 4 years (3 kg to < 11 kg), and

(b) (4)

2. Office of Clinical Pharmacology Recommendations

Based on the information provided in this supplemental NDA applications (205836/s-009, 205837/s-007, 205838/s-006), the Office of Clinical Pharmacology review team recommends approval of BRV formulations for the treatment of POS in patients 1 month of age and older.

(b) (4)

The review team disagrees with the applicant's proposal to include the labeling statement that (b) (4) and recommends the deletion of such a statement from the label (in section 12.3).

3. Dosing Recommendations in Pediatric Subjects of 1 Month of Age and Older

3.1. Background - General Advice for Pediatric Extrapolation in POS

On November 12, 2015, Division of Neurology Products 2 (DNP2) 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 POS in adults. Based on subsequent ongoing discussions within the Clinical team before and during the review of this submission (general advice letter sent to applicant in DARRTS dated 02/26/2021), DNP2 has agreed to extend this concept down to 1 month of age.

The following will be required to rely upon extrapolation to support an indication for the treatment of POS:

- 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 1 month of age and older compared with older subjects with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (1 month of age and older) populations.
- Long-term open-label safety study(ies) in pediatric subjects 1 month 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.

3.2. Clinical Development in Pediatric Patients

The Phase 2 and Phase 3 studies of BRV in pediatric subjects include EP0065, N01263, and N01266, and various study considerations are summarized below. The sample size included in this section reflects all the subjects enrolled in the studies, while only measurable (i.e., non-BLQ PK samples) and non-missing PK data were used in popPK modeling and simulation. Applicant submitted PKPD analysis report CL0428 (not considered necessary for PK based efficacy extrapolation and not reviewed) and PK analysis report CL0482.

EP0065: Phase 2, open-label, pharmacokinetic, safety, and tolerability study of I.V. BRV administered as a 15-minute IV infusion and an I.V. bolus (up to 2-minute infusion) in n=50 pediatric epilepsy patients age ≥ 1 month to <16 years of age originally conducted to fulfill PMR study 3042-2 (please refer the original NDA approval letter, DARRTS dated 02/18/2016 for additional details). Patients enrolled in the study included: 13 subjects who were 1 month to < 2 years of age of age, 13 subjects who were 2 to < 6 years of age, 12 subjects who were 6 to <12 years of age, and 12 subjects 12 to < 16 years of age.

- For subjects initiating BRV therapy (not currently on BRV at enrollment), the initial dose was 1 mg/kg (up to 50 mg) and subsequently increased to a level no greater than 4 mg/kg/day (2 mg/kg twice daily).
- For subjects already receiving BRV at enrollment (receiving BRV in an open-label extension study or receiving prescription BRV from a commercial supply), subjects received the same BRV dose level via IV as the last oral BRV dose administered (up to a maximum of 5 mg/kg/day).

No subject received a BRV dose greater than 200 mg/day (maximum labelled dose level). I.V administrations were administered every 12 ± 2 hours. While 2 consecutive IV administrations were planned for each subject, in some subjects, based on medical need, up to 10 consecutive doses of IV BRV were administered. PK samples were collected prior to, and 15 minutes and 3 hours post-initiation of IV administration during the first IV administration and one other IV administration.

N01263: 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 and the clinical pharmacology review of NDA 205836 signed on 04/27/2018 in DARRTS for details.*]

N01266: This is an ongoing study. Interim report of a 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.

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 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).

CL0428: Report CL0428 describes exposure-response modeling of BRV as an adjunctive therapy in children age ≥ 1 month to <16 years with POS.

[*Reviewer comment: This current submission is based on PK matching and extrapolation. As such, the exposure-response analyses were not reviewed.*]

CL0482: Report of population PK analyses in pediatric subjects down to 1 month of age.

CL0482 Amended Report: The original CL0482 report was submitted to sequence 0106. An updated version of CL0482 (rep-ucb-cl0482-brv-pediatrics-update-210118.pdf; which includes the final complete EP0065 dataset) was submitted in sequence 0113. As such, the earlier version of CL0482 will not be further discussed. The amended CL0482 report describes PPK analyses of BRV in pediatric epilepsy patients age ≥ 1 month to < 16 years from EP0065, N01263, and N01266.

Together, these PK modeling and simulation analyses are intended to support approval of adjunctive therapy and monotherapy in pediatric patients with POS age 1 month to < 4 years.

3.3 Applicant's Population PK Analyses

The Applicant provided population PK analyses (CL0482 Amended Report) to support BRV dosing regimen in pediatric patients. The simulations in the CL0482 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 as well as the review for the same NDA signed on 04/27/2018 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% CI[1])***	***SE[2] (%CV)***	***IIV[3]***	***Shrinkage[4]***
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%

*[1]95%CI is estimate±1.96*the standard error for the estimate*
[2]Standard errors of the estimate are reported as %CV: 100(standard error for the estimate)/estimate*
[3]IIV is the CV of the inter-individual variability calculated as the square root of the diagonal element in the omega matrix
[4]Shrinkage values as reported by NONMEM
[5]effects 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 1.

Applicant utilized measurable (non-BLQ) PK data from study EP0065 (n=43), N01263 (n=96), and N01266 (n=225) and study to generate a population PK model to represent pediatric patients. There are n=55 subjects age < 4 years with PK data. The youngest subjects that provided PK data were all 0.17 years or 2 months at enrollment (three subjects in total).

The final model (run552) utilized two-compartment, first-order oral absorption, first-order elimination, and was parameterized in terms clearance (Cl), volume of distribution of the central compartment (V_c), volume of distribution of the peripheral compartment (V_p), and oral absorption rate constant (k_a). Covariates for Cl include weight, concomitant use of phenobarbital or primidone, and concomitant use of phenytoin. The only covariate for V_c or V_p is body weight. Due to the age range of 1 month, a model relating post-conceptional age (PCA) to maturation of enzymes relevant to BRV metabolism was incorporated into the final model. Bioavailability was fixed at 100%.

[*Reviewer comment: Brivaracetam belongs to BCS class 1 (Clinical Pharmacology review DARRTS dated 07/24/2015) and bioavailability is nearly 100%. In addition, the Applicant conducted a visual predictive check (VPC) which demonstrated that the previously-developed PPK model (from report CL0187) built using only oral PK data was able to describe the IV PK data from study EP0065 (sequence 0113, rep-ucb-cl0482-brv-pediatrics-update-210118.pdf, figure 10, page 34; figure not shown in review). Overall, fixing oral bioavailability to 100% is acceptable.]*

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 (run552)

Parameter	*Estimate (95% CI)*	*IIV*	*Shrinkage**
CL (L/h)	3.86 (3.47/4.24)	29.1%	15.9%
Vc (L)	41.0 (24.1/57.8)	25.7%	65.4%
ka (1/h)	0.840 (0.150/1.53)	53.4%	55.4%
Vp (L)	52.0 (15.0/89.1)	121.0%	43.5%
Q (L/h)	15.5 (10.3/20.6)	50.1%	69.4%
F (fraction)	1.00 Fixed		
Allometric scaling CL and Q	0.533 (0.405/0.661)		
Allometric scaling Vc and Vp	1.00 Fixed		
Hill factor PCA related CL maturation	1.09 (0.457/1.73)		
PCA at 50% maturation	0.750 (-0.000461/1.50)		
PB coadministration	1.39 (1.16/1.67)		
PHT coadministration	1.15 (1.03/1.28)		
Proportional RUV (fraction)	0.343 (0.319/0.367)		6.6%

Source: rep-ucb-cl0482-brv-pediatrics-update-210118.pdf, page 43 of 182 (sequence 0113)

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

- *Use of "phenobarbital or primidone" increases CL by 39% in pediatric patients, whereas phenobarbital increases CL 23.9% in adults, and primidone increases CL 26.8% in adults.*
- *the adult model has a CBZ interaction term which is not present in the pediatric model*

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 primidone, study design, variability) may be affecting the PK interaction estimates in pediatric patients. Please refer to the appendix for details regarding the impact of PK interactions (phenobarbital / primidone and phenytoin). For these reasons, the PK simulations conducted independently by OCP were performed in a monotherapy setting (please refer to section 6 of this review for details).]

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, as well as the Nhanes Early Childhood dataset (2015-2016) provided by CDC. The virtual pediatric patient population was designated as age 1 month to < 17 years. The Applicant also utilized weight values associated with birth from this database.

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

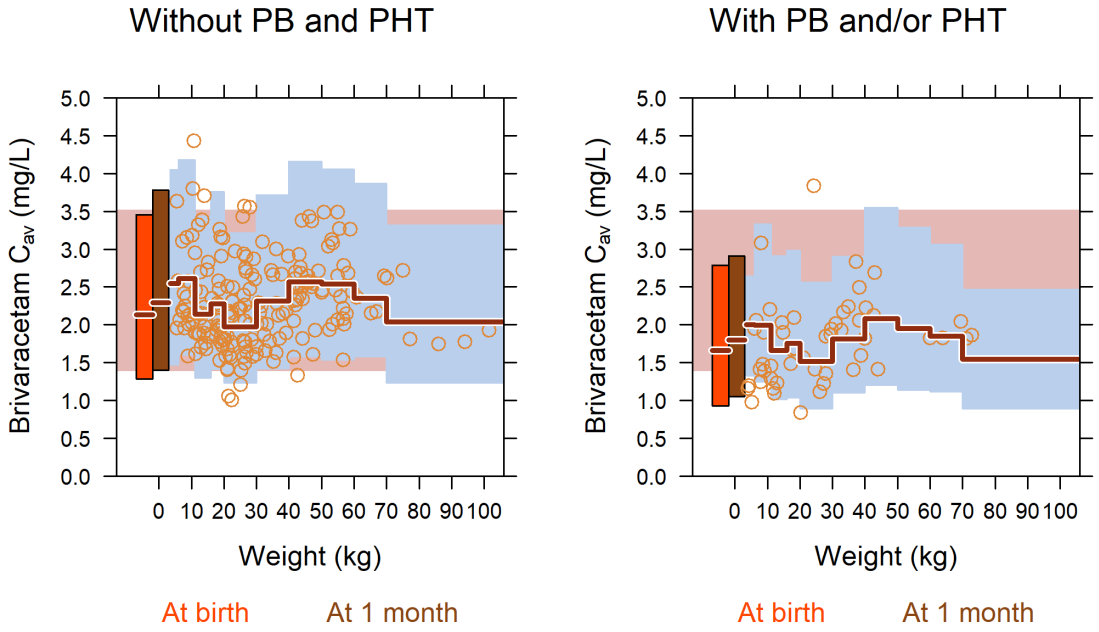
Simulation Methodology: Applicant conducted PK simulations in an adjunctive therapy setting as well as a monotherapy setting.

[*Reviewer comment: During a pre-sNDA meeting for the earlier Supplement 5, 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 as well as the adjunctive setting (for details please refer to the meeting minutes for Type B pre-sNDA meeting, IND 070205, signed on 04/03/2017). For this reason, OCP's evaluation of the pediatric dosing in Supplement 5 focused on the monotherapy setting (see the clinical pharmacology review of NDA 205836 archived on 04/27/2018, sections 6 and 7). As such, the reviewer conducted PK simulations in a monotherapy setting to assess the dosing regimen for the current submission, Supplement 9 (please see section 6 of this review for details).*]

The average steady-state concentration ($C_{av,ss}$, also referred to as C_{av} 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} = 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 5^{th} percentile and 95^{th} 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 in Table -1.

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



Orange circles are the predicted $C_{av,ss}$ for individual patients. All shaded areas represent the 5th to 95th percentile of predictions across a population. The light blue shaded area represents the predicted $C_{av,ss}$ for children from the Nhanes database <17 years receiving the 3 mg/kg bid dose proposed for weight <11 kg, as well as the approved labelled dosing for other subjects (a 2.5 mg/kg bid dose for a weight of ≥ 11 kg to <20 kg, a 2 mg/kg bid dose for ≥ 20 kg to <50 kg, and a 100 mg bid dose for weight ≥ 50 kg for children). The dark red line segments are the median simulated pediatric $C_{av,ss}$. The horizontally-oriented pink rectangle (behind the blue shaded area) represents the predicted $C_{av,ss}$ for adults receiving 100 mg BID administered without concomitant inducer AEDs (without PB, without PHT). The narrow, vertically-oriented rectangles with a black outline represent the predictions for subjects at birth (bright-red rectangle) and at 1 month (brown rectangle), respectively.

Source: sequence 01113, rep-ucb-cl0482-brv-pediatrics-update-210118.pdf, page 14

[*Reviewer comment: The Applicant compared simulated adult PK without concomitant medications to simulated pediatric PK with concomitant medications, as well as to simulated pediatric PK without concomitant medications.*]

Based on these PK simulations, the Applicant's recommended dose for subjects age 1 month to 4 years is presented in the Table-1.

[*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.*

For these reasons, OCP review team conducted independent PK simulations using the full range of approved adult maintenance dose levels to inform pediatric dose selection. The independent simulations conducted by OCP review team to verify the Applicant's proposed dosing regimen for pediatric subjects age 1 month to < 4 years are described below.

3.4. Reviewer's Independent Analyses

Maintenance Dose Selection

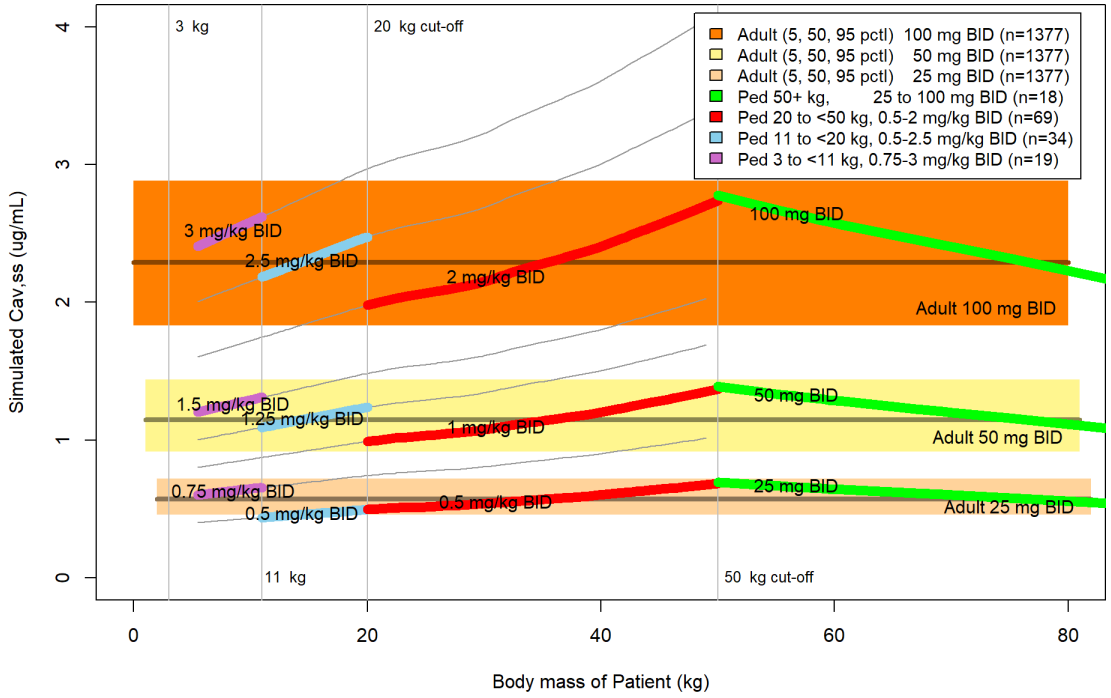
The Applicant simulated the 5th percentile and 95th percentile of adult $C_{av,ss}$ for the highest approved dose level, 100 mg twice daily. However, there is a range of approved adult maintenance dose levels (25, 50, and 100 mg twice daily). In addition, the Applicant included median simulated *pediatric* $C_{av,ss}$ but not the median simulated *adult* $C_{av,ss}$. While the pediatric $C_{av,ss}$ were mostly contained within the adult range, it is not clear how close the pediatric median $C_{av,ss}$ were to the adult median $C_{av,ss}$ 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 twice daily).

The adult PK model and pediatric PK model were utilized with all drug interaction terms inactive to best represent the monotherapy scenario. 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. Between-subject variability terms were set to zero to help avoid occurrences of physiologically impossible combinations of PK parameters. For the pediatric patients, the individual patient predictions were utilized. 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 twice daily dose levels were utilized to serve as target $C_{av,ss}$ for the pediatric PK simulations. As in Figure 1, the $C_{av,ss}$ was simulated for pediatric patients and the simulated data were plotted by weight against the adult $C_{av,ss}$ at the approved 25, 50, and 100 mg twice daily dose levels. The typical adult $C_{av,ss}$ as was summarized across the adult PPK population 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 $C_{av,ss}$ at each of the 3 dose levels selected to represent the approved adult dose range. The figure below shows the simulated pediatric $C_{av,ss}$ values for the Applicant's proposed dosing regimen (0.75 to 1.5 mg/kg twice daily for patients weighing 3 to < 11 kg) compared with simulated C_{avss} for older virtual pediatric patients receiving the approved pediatric dosing and virtual adults receiving the approved adult dosing.

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



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 adult simulations do not include between subject variability (e.g. all elements of the omega matrix are set to zero). The curves represent the median simulated $C_{av,ss}$ for a given body weight and maintenance dose. The thin grey curves depict simulated $C_{av,ss}$ in pediatric patients at a dose level and weight range that are neither approved nor proposed for the label (and serve only as a reference). The wider colored curves represent the approved pediatric dosing (blue, red, and green curves at weights ≥ 11 kg) and proposed pediatric dosing (purple curve for weights from 3 to < 11 kg). The vertical lines at 3, 11, 20, and 50 kg denote the breakpoints for weight-based dosing scheme.

Based on the figure above, the reviewer's PK simulations suggest that administration of the proposed dosing to pediatric patients weighing 3 to < 11 kg will achieve $C_{av,ss}$ that are comparable to $C_{av,ss}$ achieved when administering the approved doses to adults and approved doses to pediatric patients weighing ≥ 11 kg.

As the $C_{av,ss}$ predicted for the proposed dosing in pediatric patients weighing < 11 kg are expected to be comparable to the $C_{av,ss}$ predicted for approved doses in adults and for approved doses in pediatric patients ≥ 20 kg, and as decreased appetite (occurring at higher frequency than in adult studies; see medical officer's review for details) is the only safety difference between < 4 year old cohort versus adults or older children, then the proposed dosing in pediatric maintenance doses of 0.75 – 3 mg/kg twice daily is acceptable from an OCP perspective.

Initiation Dose Selection

The Applicant's proposed initial dose for subjects weighing 3 to < 11 kg is 0.75 to 1.5 mg/kg twice daily. As the PK are time-independent and proportional over the dose ranges explored in this submission, the $C_{av,ss}$ simulations used to inform maintenance dose selection can be to inform single-dose C_{av} comparisons among age groups (and thus inform initial dosage selection). Based on PK simulations presented in Figure 2, it is apparent that:

- $C_{av,ss}$ for 0.75 mg/kg twice daily in subjects 3 to < 11 kg are comparable to $C_{av,ss}$ for 0.5 mg/kg twice daily in subjects 20 to < 50 kg.

- $C_{av,ss}$ for 1.5 mg/kg twice daily in subjects 3 to < 11 kg are comparable to $C_{av,ss}$ for 1 mg/kg twice daily in subjects 20 to < 50 kg.

Thus, as the approved initial dosage for subjects weighing 20 to < 50 kg is 0.5 to 1 mg/kg twice daily, and since the 0.75 to 1.5 mg/kg twice daily can be expected to produce comparable single-dose C_{av} in subjects 3 to < 11 kg, and as decreased appetite (see medical officer's review for details) is the only safety difference between < 4 year old cohort versus older children or adults, then the Applicant's proposed initiation dosing of 0.75 to 1.5 mg/kg twice daily in patients weighing 3 to < 11 kg is acceptable from an OCP perspective.

The lowest body weight recorded in a pediatric patient that provided PK data was subject (b) (6) in Study N01263 who weighed 3.9 kg (age 6 months). The youngest age for pediatric subjects that provided PK were Subject (b) (6) (weight 5.1 kg) from Study N01263 and Subjects (b) (6) (weight 5.8 kg) and 11431 (weight 6.4 kg) from Study EP0065, all three of which were age 0.17 years (2 months). OCP review team concurs with applicant's proposed dosing recommendations in patients 1 month and older, because the predicted exposures for pediatric subjects 1 – 2 months are expected to be similar to those in subjects ≥ 2 months.

Further, based on the clinical growth charts in infants (birth to 36 months) for boys[2] and girls[3] by Centers for Disease Control and Prevention, the 3rd percentile weight for a 1 month old boy and girl is reported to be ~3.2 and ~2.9 kg respectively. Therefore, OCP review team discussed with DN2 and reached consensus to delete the lower weight bound in the dosing table, as it is extremely rare (< 3 percentile) for pediatric subjects ≥ 1 month to be < 3 kg.

[2] https://www.cdc.gov/growthcharts/data/set2clinical/cj41c067.pdf
[3] https://www.cdc.gov/growthcharts/data/set2clinical/cj41c068.pdf

3.5. Office of Study Integrity and Surveillance (OSIS) – Inspection Summary

Study N01263 is considered as one of the pivotal studies which evaluated the pharmacokinetic, safety, and efficacy study of adjunctive administration of BRV in pediatric epilepsy patients age ≥ 1 month to <16 years. Therefore, OCP requested OSIS for the clinical site and bioanalytical inspection for this particular study.

OSIS concluded that the data from study N01263 are acceptable for regulatory decision making (please refer OSIS inspection reports, DARRTS dated 07/08/2021 (reference ID 4822838) and 07/15/2021 (reference ID 4826671)

3.6. Summary of Key Conclusions

Consistent with Agency's current policy for extrapolation of efficacy from adults, the Applicant provided a pharmacokinetic analysis to determine a dosing regimen that would provide similar BRV exposure in pediatric subjects 1 months to < 4 years of age to BRV exposure levels demonstrated to be effective in adult subjects with POS. The applicant's proposed dosing recommendations for treatment initiation and maintenance regimen for BRV in patients 1 months to < 4 years of age (weighing 3 to < 11 kg) is acceptable, and the agency recommends deletion of the lower weight bound of 3 kg.

3.7. Key Labeling Edits

In sections 2 and 12.3, Specific Populations, Age, Pediatric Patients, several edits were proposed by OCP.

a) Deletion of lower weight bound of 3 kg in dosing table in general population (Table 1 in label) and patients with hepatic impairment (Table 2 in label).

b) The age range of subjects enrolled in study N01263 was modified such that the minimum age is 2.4 months (the youngest patient enrolled in the study) (b) (4)

c) Regarding EP0065, the description of (b) (4) was removed since this information is not informative to healthcare practitioners.

d) The estimates of pediatric CL by weight were computed using an outdated pediatric PPK model. OCP recommends the Applicant utilize the current pediatric PPK model to compute the pediatric CL estimates for this section.

The final label language will reflect additional discussions within the review team and with the Applicant that may occur after this review is archived.

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Appendix 1 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 2268 measurable (non-BLQ) BRV concentrations from n=255 subjects available for PK analyses. These PK data were available from n=43 subjects in EP0065, n=96 subjects from N01263, and n=225 subjects from study N01266.

[*Reviewer comment: The total number of subjects in the PK dataset, 255, is less than the sum of the number of subjects from the 3 studies. This is because some subjects enrolled in N01263 were subsequently enrolled in study N01266.*]

The pediatric PK dataset included data from subjects age 2 months to 22.1 years (n=55 subjects age < 4 years; n=200 subjects age 4 and older). Within the dataset, PK data are available from n=18 subjects age < 1 year. Additional details about studies EP0065, N01263, and N01266 can be found in section 5 of this review.

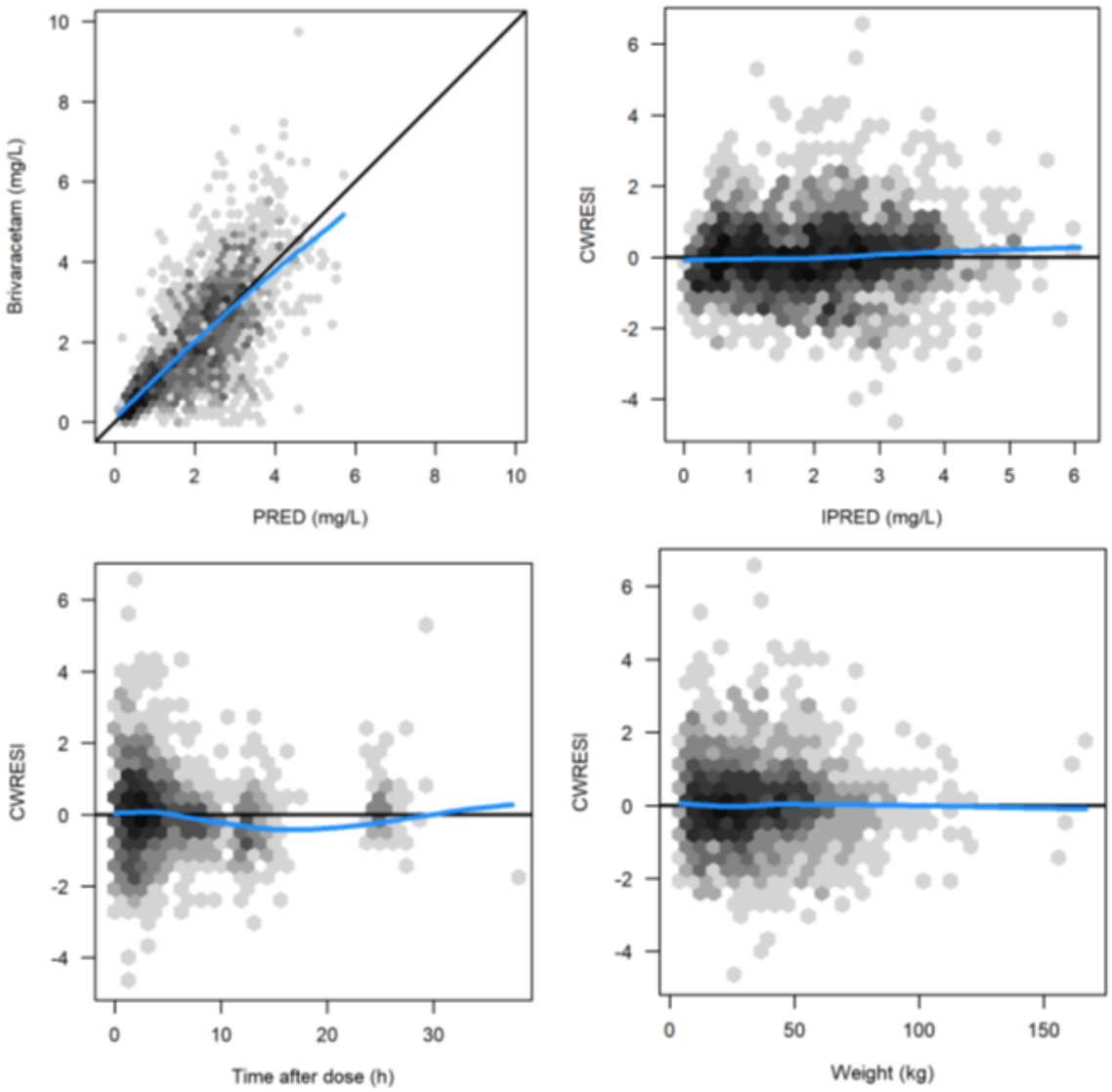
Pediatric Population PK Model:

The structural model utilized two-compartments and first order absorption. PK parameters included Cl, Vc, Vp, k_a (absorption rate constant), and F (absolute bioavailability, fixed to 1).

Allometric Scaling: An exponent was estimated for Cl and Q using body weight normalized to 70 kg. A fixed exponent of 1 was utilized for Vp and Vc using body weight normalized to 70 kg.
Clearance Maturation: Post-conceptional age (PCA) was utilized with a sigmoid-E_{max} function to characterize the maturation of BRV Cl. The maturation function is parameterized in terms of M_{50} (PCA associated with 50% of maximum Cl) and the "Hill-coefficient" which affects the shape ("sigmoidicity") of the E_{max} curve. The E_{max} value is 1 (representing full maturation).
Inter-individual variability: exponential
Residual variability: proportional error model
Covariates: Phenytoin as well as "phenobarbital or primidone" use are categorical covariates on Cl.

Parameter estimates for the final model (run552) are shown in the Table 3 in Section 3 of this review. Model diagnostics are presented in the figures below.

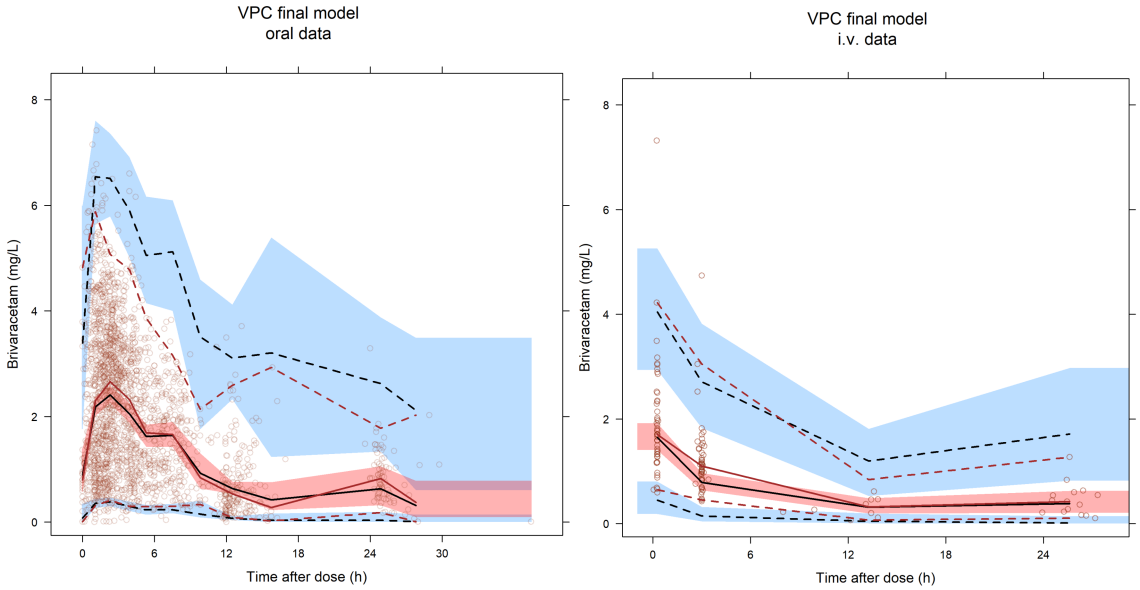
Figure 4 Diagnostic Plots for Final PK Model (run552) in Pediatric Patients with Refractory Partial Epilepsy



The black lines are zero lines for all panels except the top-left pane where the line of identity is black. the blue lines are "smoothed" approximations of the data. The darkness of the hexagons corresponds to the data density at that location.

Source: sequence 0113, module 5335, rep-ucb-cl0482-brv-pediatrics-update-210118.pdf,
pages 47-48

Figure 5: Visual Predictive Check for Final PK Model (run552) in Pediatric Patients with Refractory Partial Epilepsy



Red lines: 2.5th, 50th, 97.5th quantiles of observed data,
black lines: median value of 2.5th, 50th, 97.5th quantiles of simulated data,
blue and red shaded areas: 95% prediction interval of 2.5th, 50th, 97.5th quantiles of simulated data,
circles: BRV observations.

Source: sequence 0113, module 5335, rep-ucb-cl0482-brv-pediatrics-update-210118.pdf,
pages 52-53

[*Reviewer comment: The goodness-of-fit plots do not suggest signs of systematic bias or related to the concentration magnitude or across time.*

Applicant implemented allometric scaling to account for changes in BRV clearance and volume, as well as implemented maturation of Cl as a function of PCA. This is appropriate, considering the age range of patients assessed.

Applicant has determined that use of phenytoin and use of either phenobarbital or primidone are covariates on BRV CL. However, the drug interaction terms for the adult PK model differ from the pediatric PK model. For example, the adult PK model has phenytoin causing a 26.8% increase in BRV CL 15% increase in BRV Cl. It is not clear whether the phenobarbital effects of 23.9% increase in BRV Cl in the adult PPK model can be compared to the "phenobarbital or primidone" increase of 39% the pediatric PPK model. In addition, the adult PPK model has carbamazepine as a covariate on Cl but the pediatric PK model does not include carbamazepine as a covariate. Drug-interactions are

not expected to affect adults differently than pediatric patients. Some potential sources of the difference in drug interaction terms include the small proportion of pediatric subjects receiving phenytoin (e.g. 26 subjects received it; 10% of population) and phenobarbital/primidone (e.g. 28 subjects received either one; 11% of the population), and confounding effects other concomitant medications. Overall, these points further support approach to assess the dosing regimen in a monotherapy scenario review (e.g. where drug interaction terms are not active in the PK simulations).

The VPC suggests that the model appears to predict central tendency and lower concentrations well. The model may overpredict the highest exposures among the population for up to ~12 hours. Overall, the pediatric PK model performance is expected to perform adequately to for predicting $C_{av,ss}$ inform dose selection in pediatric patients.

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

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/s/

MUZEEB SYED
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