

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215910Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA	NDA 215910/S-0001
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Associated IND	132342
Submission Date	02/17/2022
PDUFA Goal Date	11/17/2022
Submission Type	505(b)(2)
Unapproved product	Phenobarbital (West-Ward Pharmaceuticals)
Proposed Product	Phenobarbital (Tradename: SEZABY™)
Proposed Dosage Forms	100 mg/vial lyophilized powder (to be reconstituted in (b) (4))
Proposed Dosage Regimen	All doses to be administered as 15 min IV infusion 1 st loading dose: 20 mg/kg 2 nd loading dose* (if seizures persist): 20 mg/kg *2 nd loading dose in preterm infants: 10 mg/kg or 20 mg/kg Maintenance dose: 1.5 mg/kg q8h or 2.25 mg/kg q12h (total daily dose: 4.5 mg/kg) up to 5 days
Proposed Indication	Treatment of neonatal seizures in term and preterm infants
Applicant	Sun Pharma Advanced Research Company, Ltd.
OCP Division	Division of Neuropsychiatric Pharmacology (DNP)
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1. EXECUTIVE SUMMARY

The Applicant, Sun Pharma Advanced Research Company (SPARC) Inc, is seeking approval for phenobarbital (SEZABY™) via the 505(b)(2) pathway for the treatment of neonatal seizures. Currently, there are no FDA approved therapies for the treatment of neonatal seizures. However, phenobarbital (PHB) has been used in clinical practice as first-line of therapy for the treatment of neonatal seizures for several decades.

The Applicant is relying on NEOLEV2, a multicenter, randomized, double-blind clinical study in which term neonates experiencing seizures were randomized to PHB or levetiracetam, both administered intravenously (IV), for safety and efficacy of PHB for the treatment of neonatal seizures. The study was originally designed to evaluate the efficacy of levetiracetam in treating neonatal seizures relative to PHB, but the clinical division deemed it as an appropriate study to evaluate the efficacy of PHB. The study showed that the seizures terminated for at least 24 hours, the primary efficacy endpoint, in a statistically significantly greater number of PHB-treated subjects than those treated with levetiracetam.

During the early development, the agency noted that it was unclear if PK of PHB was adequately characterized in NEOLEV2 study, which used a currently marketed (but unapproved) PHB formulation manufactured by West-Ward Pharmaceuticals. The agency noted that an adequate scientific PK bridge between West-Ward's drug product and the Applicant's product is needed to support reliance on the efficacy/safety findings from NEOLEV2 study if there is no scientific justification that the potential differences between the two products could impact PK/efficacy/safety. Therefore, the Applicant conducted a bridging study (PHEN-20-01) in healthy adults to establish a PK bridge between their product and West-Ward's product. The Applicant also conducted in vitro studies to evaluate the drug-interaction liability of PHB with drug metabolizing enzymes and transporters and provided information on the impact of extrinsic and intrinsic factors on PHB PK from scientific literature.

The primary focus of this review was to evaluate (1) the appropriateness of PHB dosing regimen for the treatment of neonatal seizures in term and preterm infants; (2) the appropriateness of the scientific bridge between the Applicant's product and West-Ward's product and (3) in vitro drug-interaction data and scientific literature on the impact of extrinsic and intrinsic factors to support labeling recommendations.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) team reviewed the information submitted in this NDA and recommends approval of PHB for the treatment of neonatal seizures in term and preterm infants.

Key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal evidence of effectiveness	The efficacy of PHB for the treatment of neonatal seizures is based on NEOLEV2, a multicenter, randomized, double-blind, active-controlled study in neonates experiencing seizures. PHB was administered as an IV loading dose of 20 mg/kg (with an option of a second loading dose of 20 mg/kg if seizures persisted 15 minutes after the first loading dose) followed by a maintenance dose of 1.5 mg/kg given every 8h for up to 5 days. A significantly higher percentage of PHB-treated subjects achieved seizure freedom at 24h compared to levetiracetam. PK modeling & simulation showed that the recommended dosing, i.e., with one or two loading doses of 20 mg/kg (depending on persistence or recurrence of seizures) followed by maintenance dosing every 8 hours in preterm infants is expected to result in PHB plasma concentrations comparable to those in term infants. Additionally, a second loading dose of 10 mg/kg in preterm infants is also an acceptable option to control seizures while mitigating the potential risk of adverse events. PK modeling & simulation showed that the total daily maintenance dosage of 4.5 mg/kg PHB given in 2 or 3 divided doses (i.e., 1.5 mg/kg every 8h or 2.25 mg/kg every 12h respectively) resulted in comparable PHB plasma concentrations over 5 days.
General dosing instructions	PHB dosing regimen consists of a loading dose followed by a maintenance dosage. All doses are to be administered via 15 min IV infusion. <u>Loading dose:</u> Recommended loading dose of 20 mg/kg. If seizures persist 15 minutes after 1st loading dose, administer a 2nd loading dose: • Term infants: 20 mg/kg • Preterm infants: 10 mg/kg* or 20 mg/kg Maximum loading dose: Up to 40 mg/kg * A 2nd loading dose of 10 mg/kg is an additional option to allow physicians to control seizures.

Review Issue	Recommendations and Comments
General dosing instructions	<u>Maintenance dose:</u> 1.5 mg/kg q8h or 2.25 mg/kg q12h (total daily dose: 4.5 mg/kg) for up to 5 days. Initiate maintenance dosage at 8 to 12 hours after the first loading dose and administer every 8 hours (if given 1.5 mg/kg) or every 12 hours (if given 2.25 mg/kg).
Dosing in patient subgroups (extrinsic and intrinsic factors)	Published literature reports that PHB is metabolized by CYP2C9, 2C19, 2E1 and UGT(s), and is an inducer of CYP3A, 2B6, 2Cs and UGTs. Based on evidence from in-vitro studies, scientific literature in neonatal and non-neonatal populations, known PHB metabolic pathways, and the potential impact on safety and efficacy of PHB or other drugs administered concomitantly, the following instructions are proposed: • CYP2C9, 2C19, 2CE1, UGT Inhibitors: Concomitant administration of PHB with inhibitors of CYP2C9, 2C19, 2E1 or UGTs may increase plasma concentrations of PHB. Closely monitor for adverse reactions including prolonged QTc interval and decrease PHB dosage, if needed. • CYP2C9, 2C19, 2E1, UGT Inducers: Concomitant administration of PHB with inducers of CYP2C9, 2C19, 2E1 or UGTs may decrease plasma concentrations of PHB. Closely monitor and increase PHB dosage, if needed. • CYP3A4, 2B6, 2C(s), UGT Substrates: Concomitant administration of PHB with substrates of CYP3A4, 2B6, 2C(s) or UGT(s) may affect plasma concentrations of substrates of these isoforms. Dosage of these substrates may need to be adjusted, if needed. • Drugs that Prolong QT Interval: Concomitant administration of PHB with drugs that prolong QTc interval may increase the risk of QT prolongation. Avoid concomitant use of PHB with drugs that prolong QTc interval. Monitor for QTc interval prolongation if concomitant use is unavoidable. The impact of sex, race, hepatic impairment or renal impairment on PHB in neonates is not known.

Review Issue	Recommendations and Comments
Bridge between the to-be-marketed and clinical trial formulations	NEOLEV2 study used West Ward's product, which is a marketed, but unapproved product different from the Applicant's to-be-marketed product. The Applicant established an adequate scientific PK bridge (for C_{max} , AUC_{0-t} and AUC_{inf}) by demonstrating bioequivalence between their proposed product and West Ward's product in adult healthy volunteers.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

The mechanism by which PHB inhibits seizures is not fully characterized; however, it likely involves potentiation of synaptic inhibition through an action on the GABA_A receptors.

The ADME characteristics of PHB, based on data from healthy adults in the current development program or evidence from scientific literature is summarized below:

Following administration of a single 2 mg/kg dose to healthy adults, peak mean total (bound + unbound) plasma concentrations of 4.72 µg/mL are achieved.

Distribution:

In adults, the mean volume of distribution ranged from 0.6-0.68 L/kg. Published literature reports that PHB is moderately bound to plasma proteins (35-60%). In a PK study in adult healthy volunteers, the ratio of unbound to total PHB measured in plasma was ~50%.

Metabolism:

PHB is primarily metabolized by hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19, CYP2E1, and UGTs. Published literature reports that the primary metabolic pathways include hydroxylation to p-hydroxy PHB with sequential glucuronidation to hydroxy-PHB-O-glucuronide and formation of PHB N-glucoside. The metabolites of PHB are inactive. Published literature reports that at birth, the expression of CYP2C9 is negligible, which results in the longer half-life in neonates compared to older populations (see Appendix 4.5 for additional details).

Excretion:

Published literature reports that following intraduodenal administration of a radiolabeled PHB dose in healthy adults, approximately ~25% of the dose is excreted unchanged in urine.

In adults, after a single dose of 2 mg/kg, the total body clearance for unbound PHB is 628 mL/h (10.5 mL/min) and terminal elimination half-life ($t_{1/2}$) is 106 h. Published literature reports that the elimination $t_{1/2}$ of phenobarbital in neonates is ~1 week.

Published literature reports a prolonged phenobarbital $t_{1/2}$ in adult subjects with either cirrhosis or viral hepatitis relative to healthy subjects.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

PHB has been used in clinical practice as the first-line therapy for the treatment of neonatal seizures for several decades. West-Ward Pharmaceuticals' currently marketed (but unapproved) PHB sodium injection formulation contains benzyl alcohol (preservative) and propylene glycol (solvent). The Applicant's PHB drug product which is a lyophilized powder formulation to be reconstituted in saline (0.9% sodium chloride) prior to IV infusion is free of benzyl alcohol and propylene glycol.

At the pre-IND discussion in 2016, the Agency advised the Applicant that [REDACTED] (b) (4) was unacceptable, and that they had to conduct a prospective, double-blind randomized, study in neonates. In a type C WRO dated November 2019, the agency (1) indicated that the adequacy of data obtained from the NEOLEV2 study to support a 505(b)(2) application would be a matter of review, (2) an adequate scientific PK bridge between West-Ward's drug product and the Applicant's product is needed to support reliance on the efficacy/safety findings from NEOLEV2 study if there is no scientific justification that the potential differences between the two products could impact PK/efficacy/safety; and (3) disagreed with the Applicant's proposal on use of physiologically-based PK (PBPK) modeling for information related to metabolism of PHB, effect of ontogeny on drug metabolizing enzymes and effect of concomitant antiepileptic drugs on PK of PHB in neonates. In a type C WRO dated July 2020, the Agency indicated that raw datasets along with final study report for NEOLEV2 study, and bioequivalence data from a PK bridging study between the marketed drug product (used in NEOLEV2 study and the Applicant's product) were needed for NDA review. In a written response dated January 2021, the agency noted its intention to review the assay validation data from the Applicant's PK bridging study in healthy adults, results from the application of published population PK models to neonatal data obtained from NEOLEV2 study, and cross-validation of the bioanalytical methods used in bridging study and NEOLEV2 study, in-lieu of a PK study in neonates. In meeting minutes dated July 2021, the agency reiterated its requirement to access, verify and query the raw datasets and a formal study report for NEOLEV2 study, and noted that the adequacy of NEOLEV2 study and acceptability of literature data to support safety will be a matter of review.

Overall, the clinical development program consists of a PK bridging study (PHEN-20-01) in adult healthy volunteers, in vitro drug-interaction studies, and a literature study (NEOLEV2) to support safety and efficacy of PHB in neonates. The PHEN-20-01 study was conducted to evaluate the relative bioavailability of the Applicant's product and West-Ward's product (marketed but unapproved in the US). NEOLEV2 was originally designed to evaluate the efficacy of levetiracetam in treating neonatal seizures relative to PHB, but the clinical division deemed it as an appropriate study to evaluate efficacy of PHB.

The Applicant obtained a right of reference to the NEOLEV2 study. The Applicant included evidence from scientific literature to support labeling recommendations.

3.2 Clinical Pharmacology Review Questions

3.2.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of PHB for treatment of neonatal seizures is based on NEOLEV2, a multicenter, randomized, double-blinded, controlled, efficacy and safety study¹. In this study, eligible term infants (gestational age 36-44 weeks), less than 2 weeks of post-natal age, and suspected of having seizures or at risk of developing seizures were enrolled with continuous video electroencephalography (cvEEG) monitoring. Those with confirmed seizures were randomized to levetiracetam or PHB in 60:40 allocation ratio, stratified by site.

Initial interventions of either 20 mg/kg PHB or 40 mg/kg levetiracetam were administered as IV infusions over 15 minutes. If electrographic seizures persisted or recurred 15 minutes after the first infusion was completed, subjects received an additional loading dose of the same drug, i.e., second dose of 20 mg/kg of PHB or 20 mg/kg of levetiracetam respectively. If seizures persisted for an additional 15 minutes, the subjects were switched to the other treatment for up to 2 doses, i.e., patients who received PHB previously were to receive 40 mg/kg of levetiracetam, and another dose of 20 mg/kg of levetiracetam if seizures persist; and patients who received levetiracetam previously were to receive 20 mg/kg PHB, and another dose of 20 mg/kg PHB if seizures persist. After the loading dose(s) of treatment was given, subjects were continued on maintenance doses of the same treatment, regardless of whether seizures persisted. The maintenance dose of PHB was 1.5 mg/kg administered every 8 hours (i.e., total daily dosage of 4.5 mg/kg), while for levetiracetam, it was 10 mg/kg every 8 hours (i.e., total daily dosage of 30 mg/kg) for up to 5 days. If electrographic seizures were still apparent following treatment with loading doses of both levetiracetam and PHB, or if they recurred during the 5 days during which the study protocol was active, the subject was considered to have failed the experimental treatment regime, and institutional specific standard seizure management dictated the ongoing direction.

A statistically significantly greater percentage of PHB-treated subjects showed seizure freedom at 24 hours post-dose, the trial's primary efficacy endpoint compared to levetiracetam. The primary efficacy endpoint results are summarized in Table below.

¹ Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial Pediatrics. 2020 Jun; 145(6); PMID: 32385134

Table 1: Primary efficacy endpoint: Seizure freedom for 24 h results from NEOLEV2

	Phenobarbital (N=33) n (%)	Levetiracetam (N=61) n (%)	P-value
Seizure termination for 24 hours			
Yes	24 (72.7)	15 (24.6)	<0.001
No	9 (27.3)	46 (75.4)	

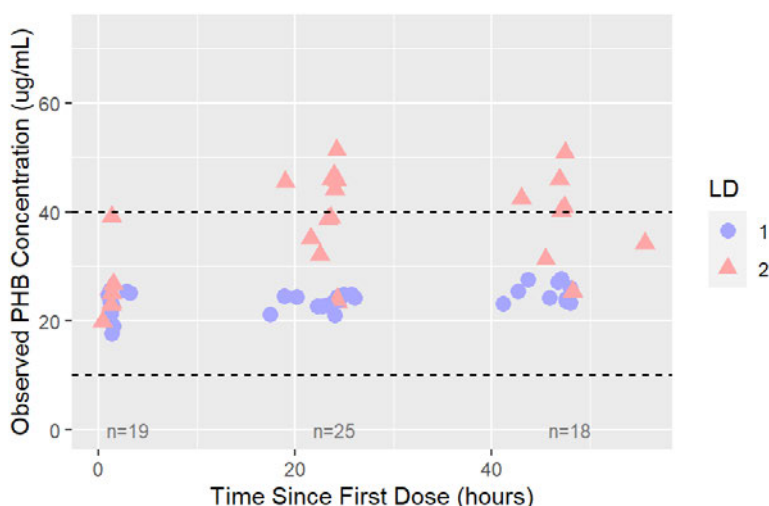
Source: Statistical review by Dr. Yunfan Deng

The most common adverse reactions (occurring in greater than 5% of patients receiving PHB only) were respiration abnormal, sedation, feeding disorder and hypotension.

Please refer to Clinical review by Drs. Amy Kao and Phillip Sheridan and Statistical review by Drs. Yunfan Deng and John Lawrence for further details on safety/efficacy/statistical analyses.

Serum concentrations of PHB were measured at 1, 24 and 48h post-loading dose(s) by a commercial ELISA kit. Refer to Appendix **Section 4.1** for additional details on method validation and cross validation results of ELISA with LC-MS/MS assay. Individual patient level PHB concentrations measured for up to 48 hours based on 1 or 2 loading doses are shown in **Figure 1**. In this figure, PHB serum concentrations ($\mu\text{g/mL}$) in term neonates receiving one (red symbols) or two (blue symbols) 20 mg/kg IV loading doses followed by 1.5 mg/kg every 8h are shown.

Figure 1: Individual serum concentrations of PHB in n=28 neonates after 1 or 2 loading doses from Study NEOLEV2



Each point represents an observed PHB concentration in NEOLEV2. The blue circles represent subjects that received a single loading dose. The red triangles represent subjects that received two loading doses across the course of the study. The horizontal dashed lines are for reference. Source: Reviewer's independent analysis

3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

3.2.2.1 Dosing in Preterm Neonates and Term Neonates

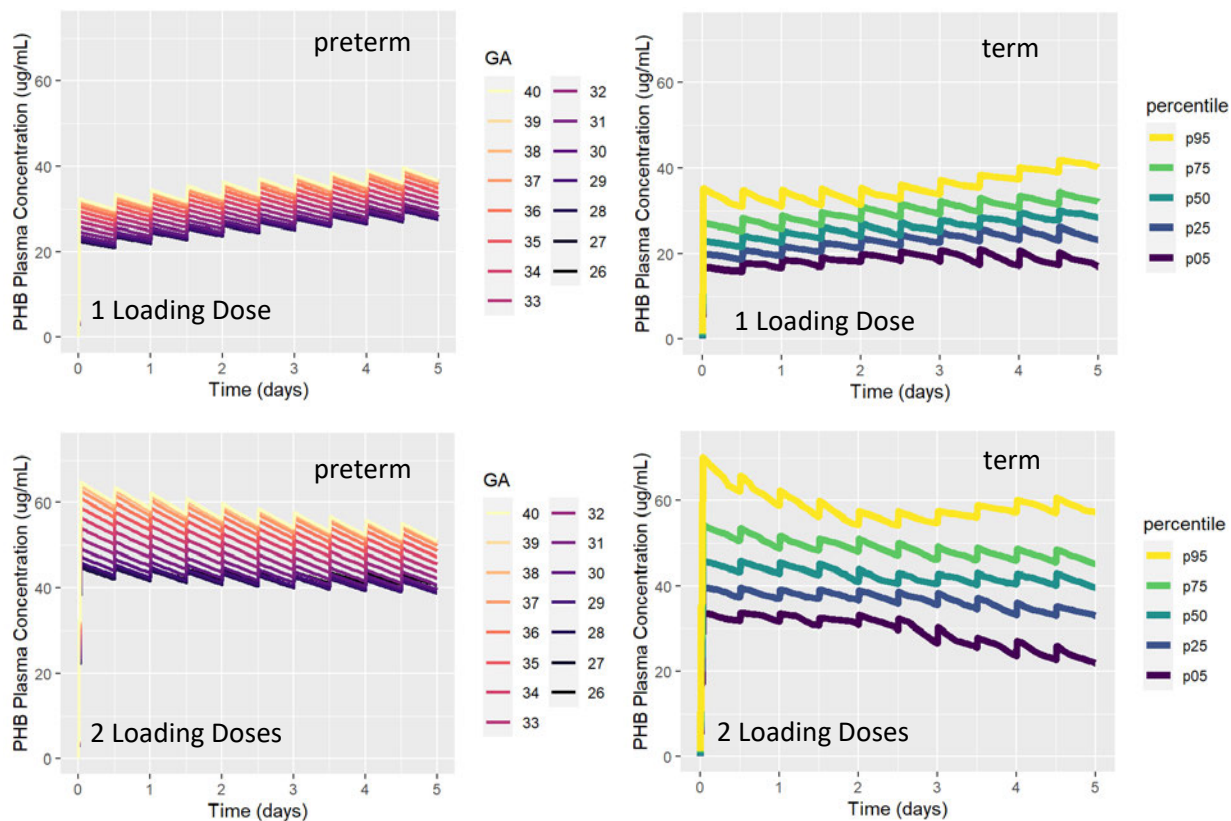
Yes, the proposed dosing regimen is appropriate for the patient population. The Applicant assessed multiple PHB population PK models for term neonates from the literature. Following a validation process, three models were selected by the Applicant for use in evaluating the proposed dosing regimen in term infants. Upon review of the Applicant's analyses, the reviewer selected one of these three models to represent PHB PK in term infants. The Applicant did not address preterm infants in this submission. The reviewer utilized a PHB PK model from the literature, built using PHB PK data from preterm infants down to 26 weeks gestational age, to assess dose selection for preterm infants. Please refer to **Section 4.4** for details on the PK analyses conducted by the Sponsor and the reviewer.

The proposed dosing regimen with the 1st loading dose of 20 mg/kg followed by a 2nd loading dose of 20 mg/kg (if clinically necessary for seizure control) is appropriate for term and preterm infants (gestational age ≥ 26 weeks). Though the NEOLEV2 study included infants who were term infants, the OCP review team utilized modeling and simulation with literature population PK models to derive the PK exposures and confirmed that a second loading dose of 20 mg/kg to preterm infants (across a range of gestational age) yields comparable exposures as term infants receiving both loading doses at 20 mg/kg loading doses, as shown in Figure below. The proposed loading dose of 20 mg/kg in preterm infants has been reported to be used in clinically in preterm infants^{2,3}.

² Marsot, A., Brevaut-Malaty, V., Vialet, R., Boulamery, A., Bruguerolle, B. and Simon, N. (2014), Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. *Fundam Clin Pharmacol*, 28: 465-471.

³ De Carolis MP, Muzii U, Romagnoli C, Zuppa AA, Zecca E, Tortorolo G. Phenobarbital for treatment of seizures in preterm infant: a new administration scheme. *Dev Pharmacol Ther*. 1989;14(2):84-9. PMID: 2630236.

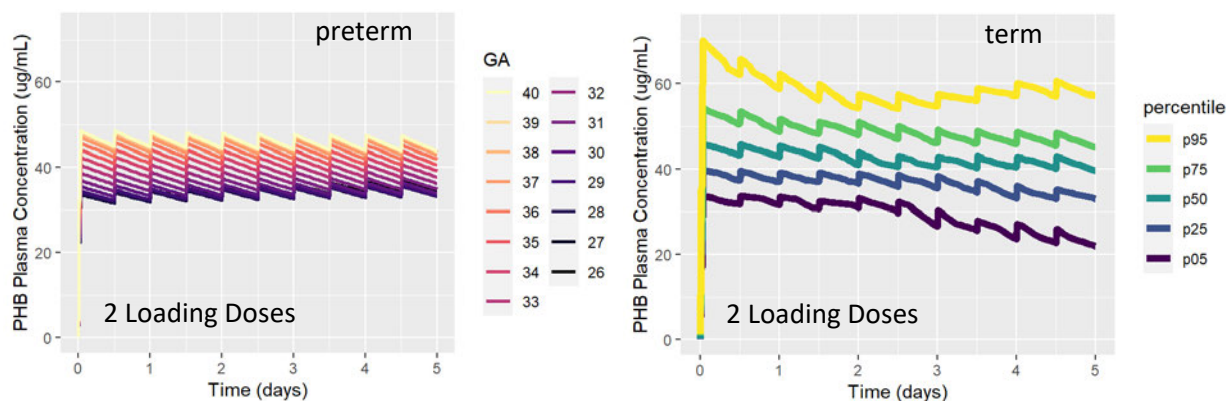
Figure 2: Simulated Population PK Profile for Preterm Neonates Versus Term Neonates: Proposed Dosing



The top row represents 1 loading dose (20 mg/kg administered at time=0 hours) and the bottom row represents two loading doses (20 and 20 mg/kg, administered at time=0 and time=0.5 hours, respectively). In all scenarios, maintenance dosing is 2.25 mg/kg q12h. The left two panels represent preterm neonates. The right two panels represent term neonates. GA = gestational age in units of weeks. Source: Reviewer's independent analysis.

The OCP review team evaluated 10 mg/kg as an alternative option for the second loading dose in preterm infants (across a range of gestational age), to allow physicians flexibility to control seizures, while mitigating the potential risk of adverse events. Based on the simulations shown in Figure 3, administration of second loading dose of 10 mg/kg in preterm infants resulted in plasma PHB concentrations that are within the range predicted for term infants.

Figure 3: Simulated Population PK Profile for Preterm Neonates Versus Term Neonates: Reduced 2nd Loading Dose in Preterm Neonates



The left panel represents pre-term infants receiving two loading doses with the second loading dose at a reduced level (20 mg/kg and 10 mg/kg, administered at time=0 and time=0.5 hours, respectively). The right panel represents term infants receiving two loading doses with both loading doses at the proposed level (20 and 20 mg/kg, administered at time=0 and time=0.5 hours, respectively). In both panels, maintenance dosing is 2.25 mg/kg q12h. GA = gestational age in units of weeks.

Source: Reviewer’s independent analysis.

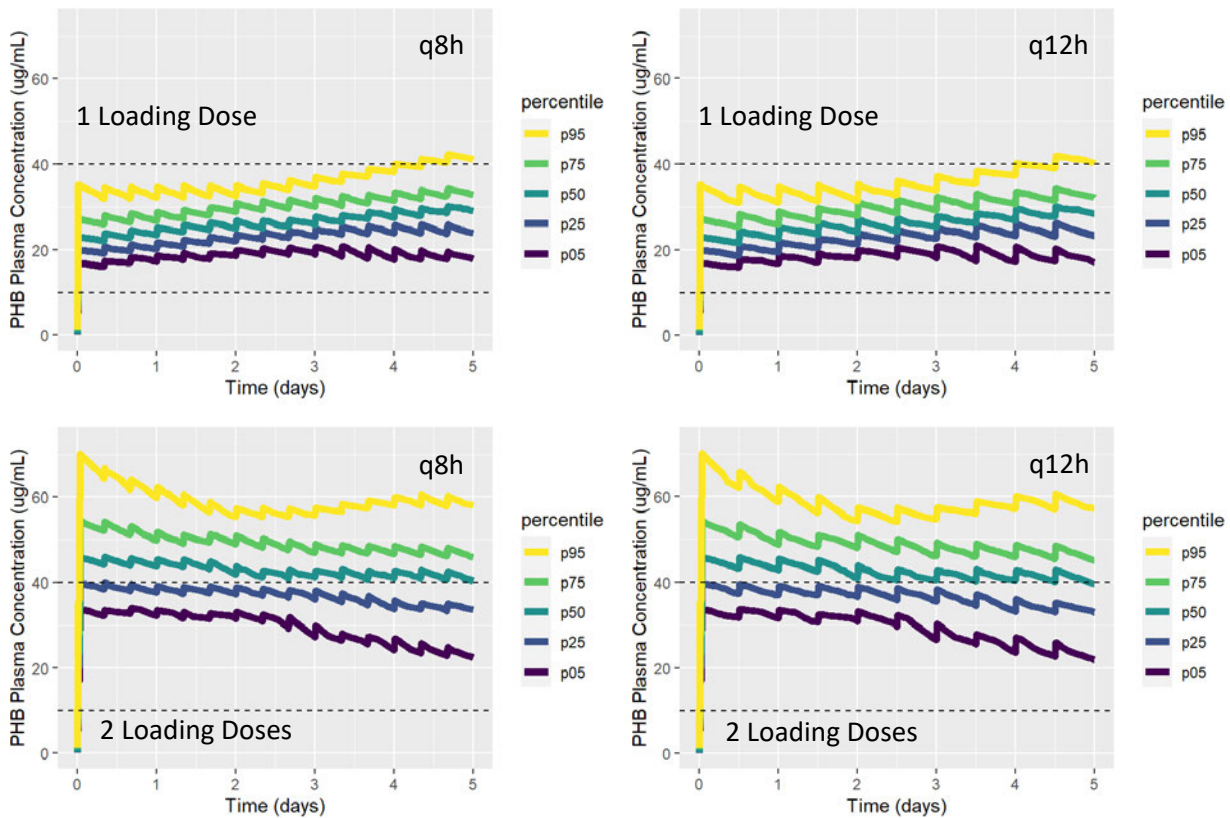
In conclusion, the OCP review team recommends two options for second loading dose in preterm infants: 10 or 20 mg/kg PHB for flexibility in managing seizures. See Appendix **Section 4.4.8** for additional details.

3.2.2.2 Alternate Dosing Frequency: 8-hour Dosing Interval vs. 12-hour Dosing Interval

In NEOLEV2 study, a maintenance dose of PHB was administered at 8 hour intervals, to maintain the blinding with the 8 hour interval dosing for levetiracetam. During the discussions in the review cycle, the Clinical and Pediatrics disciplines noted that the maintenance dose of PHB is routinely administered at every 12 hours in clinical practice. Therefore, the OCP review team conducted modeling and simulations to assess an alternate dosing frequency, i.e., every 12 hours dosing in addition to every 8 hours dosing. The following section presents the key analyses and summary of findings.

The review team utilized modeling and simulation with literature popPK models to assess the effect of administering the total daily maintenance dose in three equal divided doses administered q8h or two equal divided doses administered q12h. The analyses confirmed that for either one or two loading doses, administering the same total daily maintenance dose as either q8h or as q12 results in comparable PHB exposures.

Figure 4: Simulated Population PK Profile for q8h Versus q12h Maintenance Dosing



The top row represents 1 loading dose (20 mg/kg administered at time=0 hours) and the bottom row represents two loading doses (20 and 20 mg/kg, administered at time=0 and time=0.5 hours, respectively). The left two panels represent maintenance dosing starting at 8 hours and being administered 1.5 mg/kg q8h. The right two panels represent maintenance dosing starting at 12 hours and being administered 2.25 mg/kg q12h. The dashed horizontal lines are for reference.

Source: Reviewer's independent analysis.

A comparison of PK metrics between the q8h maintenance regimen and the q12h maintenance regimen was assessed during the first 24 hours (time 0 to 1 day) and the last 24 hours (time 4 to 5 days) for the one loading dose scenario and two loading dose scenarios. The minimum concentration across the time interval (C_{min}), maximum concentration across the time interval (C_{max}), and area under the concentration curve (AUC) over the time interval were computed for each virtual subject in each time interval for the q8h maintenance regimen and the q12h maintenance regimen. The geometric mean for each exposure metric and the geometric mean ratio (GMR) were computed. The geometric mean ratios are presented in **Table 2**.

Table 2: GMR of Simulated PK metrics for q8h to q12h

Number of Loading Doses	First 24 hours (Time 0 to 1 day)			Last 24 hours (Time 4 to 5 days)		
	C _{min} GMR	C _{max} GMR	AUC GMR	C _{min} GMR	C _{max} GMR	AUC GMR
1	1.024	1.012	1.018	1.026	0.998	1.008
2	1	1.002	1.009	1.018	0.996	1.006

Source: Reviewer's independent analysis.

Overall, the GMR values range from 0.996 to 1.026, indicating that administering the same total daily dose as q8h or q12h is expected to result in a difference of < 3% in C_{max}, C_{min}, or AUC. Overall, the PK profile for q8h maintenance dosing is comparable to the PK profile for q12h maintenance dosing for the same total daily dose.

See Appendix **section 4.4.7** for additional details.

Considering the comparable PK profiles of q8h and q12h maintenance regimens, OCP recommends that the total daily dose can be administered as 2.25 mg/kg q12h or 1.5 mg/kg q8h. To allow appropriate flexibility for healthcare providers, OCP recommends allowing maintenance dosing to start in the range of 8 to 12 hours after initiation of the first loading dose.

3.2.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

PHB is currently being proposed for treatment of neonatal seizures in term and preterm infants.

Renal/Hepatic impairment:

The impact of hepatic impairment or renal impairment on PHB in term or preterm infants is not known.

Genetic polymorphism, Gestational Age, Sex, Race, and Body Weight:

Published studies indicate that neonatal CYP2C9 or CYP2C19 expression is variable and at most approaches 40% and 15% of adult levels during the neonatal period, respectively. Given the ontogeny, the effect (if any) of CYP2C9 or CYP2C19 polymorphisms could influence the metabolism of PHB in neonates. See Appendix **Section 4.5** for more details. Sex and race were not found to influence PHB PK. As body weight was found to be a significant covariate, PHB is dosed on a mg/kg basis. Based on PK modeling and simulation PHB PK varies with gestational age from 26 weeks to 40 weeks. However, due to the increase in weight that accompanies an increase in gestational age, the weight-based dosing regimen for term neonates is acceptable for preterm neonates down to 26 weeks gestational age. The PK modeling and simulation also

indicate that a 50% reduction in the second loading dose for preterm neonates down to 26 weeks of age is an acceptable alternative.

3.2.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

PHB is primarily metabolized by CYP2C9 and to a lesser extent by CYP2C19, CYP2E1, and UGTs. Published literature reports that at birth expression of CYP2C9 is negligible, which results in the longer half-life in neonates compared to older populations. No dedicated clinical studies evaluating the drug interaction potential of PHB in term or preterm infants have been conducted. The Applicant conducted in vitro studies to evaluate the drug-interaction liability with major transporters and enzymes, and the results of these studies are summarized below.

CYPs: PHB is an inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. Phenobarbital is an inducer of CYP3A4, CYP2B6, and CYP2Cs.

UGTs: PHB is an inhibitor of UGT1A1 and UGT2B7. Published literature reports that PHB is an inducer for UGTs.

Transporters: PHB is not a substrate of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K transporters. PHB is an inhibitor of BCRP, OAT1, OAT3, OCT2, OATP1B1, MATE1, and MATE2K.

PHB is not expected to be an inhibitor for enzymes or transporters at clinically relevant exposures following the proposed dosing in neonatal population. However, the potential for PHB to induce enzymes noted above is consistent with published literature.

The OCP review team sent an information request (IR sent on 07/05/2022) to the Applicant to summarize the published literature regarding the list of concomitant medications administered in NEOLEV2 study and published literature in neonates. The Applicant's response (received on 07/19/2022) is located in Appendix **Section 4.2**. The OCP team reviewed the list of medications (including anti-seizure medications) that are likely to be concomitantly administered in the neonatal population and concluded that majority of these medications are unlikely to affect PK of PHB. However, there are some limitations with some of the studies owing to administration of a cocktail of drugs, and therefore the lack of observed changes in PHB PK could be a net effect, rather than true absence of an effect. PHB was reported to increase midazolam clearance by 2.3-fold in neonates treated with therapeutic hypothermia⁴. Published literature regarding these interactions in adults may have some limitations in extrapolation to neonatal population due to differences in expression of CYP2C9 and possibly other phenobarbital metabolic enzymes in term and preterm infants, and therefore, the clinical significance of these findings is not known.

⁴ Kearns L. G et al., Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children N Engl J Med 2003; 349:1157-1167

However, based on the known PHB metabolic pathways, published literature in neonates, in-vitro studies and the potential impact on safety and efficacy of PHB or other drugs used concomitantly, the OCP review team proposed the following recommendations.

CYP2C9, 2C19, 2E1 and UGT Inhibitors:

As noted above, PHB is a substrate of these CYP isoforms and UGT(s). Therefore, concomitant use with inhibitors of these enzymes may increase PHB exposures, and consequently may increase the risk of adverse reactions. It is recommended to closely monitor for adverse reactions including QTc interval prolongation, and decrease PHB dose if needed, when used concomitantly with inhibitors of these CYP isoforms and UGT(s).

CYP2C9, 2C19, 2E1 and UGT Inducers:

As noted above, PHB is a substrate of these CYP isoforms and UGT(s). Therefore, concomitant use with inducers of these enzymes may decrease PHB exposures, and consequently may reduce the efficacy of PHB. It is recommended to closely monitor, and increase PHB dose if needed, when used concomitantly with inducers of these CYP isoforms and UGT(s).

CYP3A4, 2B6, 2C(s), and UGT Substrates:

Published literature reports that PHB is an inducer of these CYP isoforms and UGT(s). Therefore, concomitant use with PHB may decrease the exposures of substrates of these enzymes. The dosage of substrates of these CYP isoforms and UGT(s) may need to be increased, if needed, when administered concomitantly PHB.

3.2.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the approval of the to-be-marketed formulation?

Yes. The Applicant conducted a PK bridging study to evaluate the relative bioavailability of their proposed product (test) and West Ward's product (reference).

Study PHEN-20-01 is a randomized, open-label, two-period, two-sequence, two-way crossover, single dose study in adult healthy volunteers. The study results demonstrated bioequivalence between the test and reference arms as 90% CI for GMR of C_{max} , AUC_{0-t} and AUC_{inf} was within 80.00 – 125.00%, supporting the PK bridge between the Applicant's product and West Ward's product. See Appendix 4.3 for additional details on study design and discussion of the results.

A consult request for biopharmaceutical inspections of the analytical site for study PHEN-20-01 was sent to the Office of Study Integrity and Surveillance (OSIS). The OSIS concluded that based on their remote record review of the analytical site in (b) (4), which falls within the surveillance interval, an additional inspection for this NDA was not warranted (DARRTS 06/01/2022).

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical analyses from study PHEN-20-01 (PK bridging study in healthy volunteers) were performed using two validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays for quantification of total PHB (Method AP 066_00) and free (unbound) PHB (Method AP 067_00).

Table 3: Summary of Bioanalytical Method Validation for Total PHB

Information Requested	Data
Analyte	Phenobarbital
Internal standard (IS)	Phenobarbital-D ₅
Method description	Protein precipitation extraction
Limit of quantitation	0.1000 µg/mL
Average recovery of drug (%)	81.5%
Average recovery of IS (%)	88.7%
Standard curve concentrations (µg/mL)	0.1000, 0.2000, 0.5000, 2.000, 10.00, 30.00, 64.00 and 80.00
QC concentrations (µg/mL)	0.1000, 0.3000, 3.000, 32.00, 60.00, and 160.0
QC Intraday precision range (%)	0.7 to 4.5%
QC Intraday accuracy range (%)	-6.5 to 7.9%
QC Interday precision range (%)	1.1 to 7.8%
QC Interday accuracy range (%)	-1.8 to -0.2%
Bench-top stability/Short term stability (hrs)	26 hours @ 5°C ± 3°C
Stock stability (hrs)	12 days @ 5°C ± 3°C and room temperature (Analyte) 12 days @ -20°C ± 10°C and room temperature (IS)
Working solution stability (hrs/days)	288 hours @ 5°C ± 3°C and room temperature (Analyte) 12 days @ 5°C ± 3°C and room temperature (IS)
Processed stability (hrs)	101 hours @ 10°C ± 3°C
Freeze-thaw stability (cycles)	6 cycles @ -70°C ± 20°C
Long-term storage stability (days)	188 days @ -20°C ± 10°C 349 days @ -70°C ± 20°C
Dilution integrity	160.0 µg/mL diluted 10-fold
Selectivity	No interfering peaks noted in 10 blank plasma samples
Matrix Effect	No suppression or enhancement noted in six out of six matrix lots
Over the Counter Medications (OTC)	No significant baseline interference was detected at the retention times of Phenobarbital Total or IS
Hormone Interference	No significant baseline interference was detected at the retention times of Phenobarbital Total or IS
Carry-over	Carry-over assessments met overall acceptance criteria
Re-injection reproducibility stability (hrs)	75 hours @ 10°C ± 3°C
Blood stability (hrs)	2 hours @ room temperature and on wet ice
Robustness	288 samples

Source: Study report v2020004-00.pdf, Bioanalytical Method AP 066_00, page 188 of 249

Table 4: Summary of Bioanalytical Method Validation for Free (Unbound) PHB

Information Requested	Data
Analyte	Phenobarbital
Internal standard (IS)	Phenobarbital-D ₅
Method description	Protein precipitation extraction
Limit of quantitation	0.05000 µg/mL
Average recovery of drug (%)	96.6%
Average recovery of IS (%)	97.6%
Standard curve concentrations (µg/mL)	0.05000, 0.1000, 0.2500, 1.000, 5.000, 16.00, 32.00, and 40.00
QC concentrations (µg/mL)	0.05000, 0.1500, 2.000, 20.00, 30.00, and 80.00
QC Intraday precision range (%)	0.9 to 4.9
QC Intraday accuracy range (%)	-6.4 to 7.0
QC Interday precision range (%)	2.1 to 6.0
QC Interday accuracy range (%)	-5.4 to 3.8
Bench-top stability/Short term stability (hrs)	24 hours @ 5°C ± 3°C (Filtered) 25 hours @ 5°C ± 3°C (Unfiltered)
Stock stability (hrs)	12 days @ 5°C ± 3°C and room temperature (Analyte) 12 days @ -20°C ± 10°C and room temperature (IS)
Working solution stability (hrs/days)	288 hours @ 5°C ± 3°C and room temperature (Analyte) 12 days @ 5°C ± 3°C and room temperature (IS)
Processed stability (hrs)	99 hours @ 10°C ± 3°C
Freeze-thaw stability (cycles)	6 cycles (Filtered) 3 cycles (Unfiltered)
Long-term storage stability (days)	64 days @ -20°C ± 10°C (Filtered) 161 days @ -70°C ± 20°C (Filtered) 139 days @ -70°C ± 20°C (Unfiltered)
Dilution integrity	80.00 µg/mL diluted 10-fold
Selectivity	No interfering peaks noted in 10 blank plasma samples
Matrix Effect	No suppression or enhancement noted in six out of six matrix lots
Over the Counter Medications (OTC)	No significant baseline interference was detected at the retention times of Phenobarbital Free or IS
Hormone Interference	No significant baseline interference was detected at the retention times of Phenobarbital Free or IS
Carry-over	Carry-over assessments met overall acceptance criteria
Re-injection reproducibility stability (hrs)	91 hours @ 10°C ± 3°C
Blood stability (hrs)	2 hours @ room temperature and on wet ice
Robustness	288 samples

Source: Study report v2020005-00.pdf, Bioanalytical Method AP 067_00, page 161 of 227

Reviewer's Comments:

- 1. As shown in **Table 3** and **Table 4**, LC-MS/MS method validation parameters were found acceptable as per FDA guidance.*
- 2. The validated long term stability (LTS) duration for total PHB is 349 days and for free (unbound) PHB is 161 days -70°C in human serum. This is adequate for analyzing PK samples from study PHEN-20-01. However, as PK samples from NEOLEV2 study were stored up to 54 months, the Applicant was sent an IR (on 10/12/2022) to inquire on the status of additional LTS data beyond the 349 days. The Applicant responded on 10/14/2022 that they will be providing additional LTS data for up to 54 months (with interim LTS data at 2y and 3y time points) as it becomes available post-approval. This is acceptable.*

The Applicant used commercially available ELISA kit (EMIT 2000 immunoassay kit) to analyze PK samples from the NEOELV2 study. The two methods used were PHB by immunoassay on AU680 validation (CHA TX.V147) and PHB by Beckman Coulter AU680#2 (CHA TX.V223). Although these commercial ELISA kits were partially validated (for linearity, precision, recover, carryover), they were found inadequately validated from FDA's perspective (b) (4) (). The Applicant was asked to revalidate the commercial ELISA kits as per FDA's 2018 Bioanalytical Method Validation Guidance.

As PK samples from the NEOLEV2 study were not available anymore, the Applicant's newly validated ELISA assay (report # V21-060) was used to quantify PHB levels in QC samples from PK bridging study PHEN-20-01 (blank serum spiked with known PHB concentration) as part of a cross-validation (report C2816). The method validation parameters for commercial ELISA assay conducted by the Applicant are shown in **Table 5**.

Table 5: Validation of ELISA EMIT 2000 by the Applicant

Lower Limit of quantitation (LLQ):	2.00 µg/mL
Validated Range:	2.00 µg/mL to 70.0 µg/mL
QC levels:	2.00, 2.24, 11.2, 31.1, 54.5 and 70.0 µg/mL
QC Intraday precision range (%):	0.0 to 2.1
QC Intraday accuracy range (%):	-10 to 7.0
QC Interday precision range (%):	1.1 to 4.5
QC Interday accuracy range (%):	-8.2 to 8.3
Bench-top stability:	4 hours at ambient temperature ((15°C to 25°C)
Freeze-thaw stability (cycles):	3 additional freeze/thaw cycles
Selectivity:	No interference noted in 10 blank plasma and serum samples
Carry-over:	Carry-over assessments met overall acceptance criteria

Source: 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, page 15 of 20

The purpose of validating this study was to assess the performance of this assay (comparator method) in comparison to a validated LC-MS/MS method (reference method) by analyzing incurred K2 EDTA human plasma PK samples and QC samples. Six replicates of each QC level and 132 incurred adult plasma samples were analyzed over different analytical runs.

Reviewer's Comments:

- The percent CV for the six aliquots at MQC-1 (3.0 µg/mL), MQC-2 (32.0 µg/mL), HQC-1 (60.0 µg/mL), and for 132 incurred samples from PK bridging study (PHEN-20-01) were within the acceptance criteria (±30% difference). From these 132 incurred samples, the Applicant mentioned that 96 were outside the validated stability range and 36 were within the established stability range (349 days at -70°C ± 20°C). Thus, the impact of storage conditions did not impact data from this cross-validation study.*

4.2 In Vitro Studies and Published Literature in Neonates

4.2.1 In-vitro Study Report

CYP Phenotyping (ADME-SUP-200715-CYP Phenotyping), **CYP Inhibition** (ADME-SUP-200715-CYP Inhibition), and **CYP Induction** (ADME-SUP-200715-CYP Induction).

No significant turnover (based on intrinsic clearance (CL_{int}) and the half-life ($t_{1/2}$)) of PHB was observed in human recombinant CYP isoforms; CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5.

In human liver microsomes, PHB inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4-hydroxylation) with IC_{50} values ranging from 2548 to 3881 μ M while did not inhibit (or weak inhibitor) CYP1A2, CYP2D6, and CYP3A4 (as measured by midazolam 1'-hydroxylation) with IC_{50} greater than 10,000 μ M.

In human hepatocytes, PHB has caused a concentration-dependent induction of CYP2B6 (EC_{50} ranged from 138-380 μ M) and CYP3A4 (~187 μ M) but did not cause significant induction of CYP1A2.

UGT Inhibition (ADME-SUP-200715-UGT Inhibition)

PHB inhibited UGT1A1 and UGT2B7 with an IC_{50} of 6269 and 1964 μ M, respectively.

Transporter inhibition (ADME-SUP-200715-P-gp Inhibition, ADME-SUP-200715-BCRP Inhibition, and ADME-SUP-200715-SLC Inhibition)

PHB inhibited efflux transporter BCRP with an IC_{50} of 3298 μ M but not P-gp with IC_{50} greater than 10,000 μ M. It has inhibited the uptake of transporters OAT1, OAT3, OCT2, OATP1B1, MATE1, and MATE2K with IC_{50} values ranging from 1327 to 7118 μ M while did not inhibit (or weak inhibitor) of OATP1B3 with IC_{50} greater than 10,000 μ M.

As per the Applicant, the predicted maximum PHB concentration based on simulations using the population PK model (Report number 262385) is 45 μ g/mL with two loading doses (20 mg/kg). Considering a free fraction of 50% observed in study PHEN-20-01, unbound C_{max} would be 22.5 μ g/mL, which would be 97 μ M (mol. wt. 232.2 g/mol). *Thus, the unbound C_{max} would be about 27-40 fold lower than IC_{50} for CYPs, 20-65 fold lower for UGTs and 14-73 fold lower for transporters.*

Transporter substrate specificity ADME-SUP-200715-P-gp Substrate, ADME-SUP-200715-BCRP Substrate, ADME-SUP 200715-SLC Substrate

PHB is not a substrate of efflux transporters P-gp and BCRP and uptake transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2K.

Reviewer's comments:

- 1. The observed mean conc. in NEOLEV2 study were ~40 μ g/mL at 48h after 2 loading doses. At these clinical concentrations, PHB is not a clinically relevant inhibitor of CYPs, UGTs or transporters.*

4.2.2 Published Literature in Neonates

This section summarizes the responses to the FDA’s Information Request (received on July 19, 2022) regarding published literature in neonates

(1) Summarize a list of drugs that are likely to be used concomitantly in the neonatal population

Based on studies of cohorts of neonates in neonatal intensive care units (NICUs) or with seizures (including the NEOLEV2 trial), medications typically used in this setting include antiepileptic medications (phenobarbital, fosphenytoin / phenytoin, levetiracetam, midazolam), opiates (primarily in the setting of therapeutic hypothermia for hypoxic ischemic encephalopathy, HIE), antibiotics (ampicillin, amoxicillin, gentamicin, cefotaxime) and vasopressors (e.g., dopamine, epinephrine) (Ahmad et al., 2017; Glass et al., 2016; Hsieh et al., 2014) (Table 1).

Table 1: Commonly Used Medications in Neonates in NICUs or with Seizures

Study	Population	Top Medications (% of patients exposed*)
Studies Reporting All Concomitant Medications		
NEOLEV 2	106 neonates with EEG diagnosis of seizures who were randomized to receive levetiracetam and / or phenobarbital	ampicillin (61%), cefotaxime (50%), gentamicin (45%), acyclovir (39%), morphine (36%), amoxicillin (25%), nystatin (18%), poractant-alfa (8%), fentanyl (6%), acetaminophen (5%), atropine (4%), vecuronium (4%), dexmedetomidine (4%), insulin (4%), adrenaline (3%), furosemide (3%), cisatracurium-besilate (3%), dexamethasone (3%), dobutamine (3%), milrinone (3%), nitric oxide (3%), phenytoin (2%), phenylephrine (2%), pancuronium (2%) ^b
Study	Population	Top Medications (% of patients exposed*)
Studies Reporting All Concomitant Medications		
(Hsieh et al., 2014)	450,386 neonates admitted to 305 NICUs in the USA between 2005- 2010 for any cause (not just for seizures) ^a	ampicillin (68%), gentamicin (68%), caffeine citrate (16%), vancomycin (9%), beractant (8%), furosemide (8%), fentanyl (7%), dopamine (6%), midazolam (6%), calfactant (6%), metoclopramide (5%), ranitidine (5%), poractant alpha (5%), morphine (5%), cefotaxime (4%), acetaminophen (4%), indomethacin (4%), phenobarbital (4%) ^b
(Al-Turkait, Szatkowski, Choonara, & Ojha,	Sample size, reported in 77 studies, ranged from 34 to 450,386 infants (not just for seizures and inclusive of	ampicillin (8 studies), gentamicin (8 studies), furosemide (6 studies), surfactant (6 studies), penicillin (5 studies), vancomycin (6 studies), caffeine citrate (6 studies), cefotaxime (4 studies), dopamine (5 studies), calcium gluconate (4 studies) Only related to North America.

2020) *	global studies)	
Studies Reporting only Seizure Medications		
(Glass et al., 2016)	426 neonates with clinically suspected seizures	phenobarbital (92%), levetiracetam (31%), fosphenytoin (28%), benzodiazepine – intermittent doses (20%), benzodiazepine infusion (7%), topiramate (4%), carbamazepine / oxcarbazepine (2%), vitamins (8%)
(Ahmad et al., 2017)	1613 neonates with diagnosis of seizures treated in USA-based NICUs between 2013-2014	phenobarbital (96%), phenytoin (11%), levetiracetam (14%), carbamazepine (0.2%), lidocaine (0.4%)

* - The data on usage of medications is provided as % patients exposed except in in Al-Turkait et al article which was provided as number of studies.

(2) Discuss the potential impact of the maturation of drug metabolizing enzymes and concomitant drugs (e.g., but not limited to CYP modulators) on phenobarbital pharmacokinetics in the neonatal population.

Phenobarbital is cleared by multiple elimination pathways; unchanged drug in urine and metabolism by multiple CYP enzymes (2C9, 2C19 and 2E1) and direct conjugation to form phenobarbital N-glucoside (Tang, Kalow, & Grey, 1979) (Pacifi, 2016) (Battino, Estienne, & Avanzini, 1995). Neonates possess the P450 enzyme system to perform hydroxylation early in life, while the glucoside and glucuronide pathway develops later, possibly after 2 weeks of age (Bhargava & Garrettson, 1988) (Battino et al., 1995).

It was reported that the total renal elimination of phenobarbital is almost as rapid in the sick newborns as it is in healthy adults (Boréus, Jalling, & Kållberg, 1978). During the first days of treatment, a high proportion of phenobarbital is recovered in urine as unchanged drug (70 to 80% vs 20 to 30% as metabolites) (Battino et al., 1995) suggesting that low metabolism capacity in neonates may be compensated by renal clearance. The metabolism/parent ratio gradually changes so that over 8 days of treatment approximately 50% is excreted as unchanged and 50% as p-hydroxy phenobarbital possibly due to maturation of CYP/UGT enzymes.

Thus, the evolving maturation of metabolizing enzymes with age may have a limited potential for co-mediations to affect the PK of phenobarbital due to presence of compensatory elimination pathways as explained below with findings from the clinical studies. In a prospective open-label clinical study (Šíma, Pokorná, Hronová, & Slanař, 2015) in thirty-seven full term newborns (gestational age $\geq$ 37 weeks) with hypoxic-ischemic encephalopathy (HIE) treated with phenobarbital, there was no effect of the majority of co-administered medications (provided below) on phenobarbital PK (including clearance, volume of distribution and half-life) (Table 2).

In this study, phenobarbital loading doses ranged from 5.04 to 34.29 mg/kg body weight and the maintenance dose ranged between 1.07 and 20.31 mg/kg/day. In the NEOLEV2 study, the loading

and maintenance doses were 10 to 20 mg/kg and 1.5 mg/kg, respectively.

Table 2: Median (95% CI) phenobarbital clearance (L/h/kg) in subjects co-administered various medications

Concomitant Medication	Number of Subjects Who Received Concomitant Medication (%)	Clearance for Those Administered the Concomitant Medication(s)	Clearance for Those Not Administered the Concomitant Medication
All 37 Subjects (with or without concomitant medications)	N/A	0.0034 (0.0028-0.0040)	
Any vasoactive (inotropic) drug	32 (87)	0.0034	0.0043
Dopamine	31 (84)	0.0033 *	0.0044
Dobutamine	30 (81)	0.0034	0.0043
Norepinephrine	4 (11)	0.0052	0.0034
Phenytoin (loading dose of 15-20 mg/kg iv, followed by maintenance dose of 2.5-4 mg/kg iv twice a day)	11 (30)	0.0034	0.0035
Sufentanil	27 (73)	0.0034	0.0039
Midazolam (0.05-0.3 mg/kg iv as continuous infusion)	26 (70)	0.0034	0.0037
Tramadol	14 (38)	0.0034	0.0037
Furosemide	26 (70)	0.0034	0.0035

Source: Reproduced from ([Šíma et al., 2015](#))

* $p < 0.05$ vs. group without co-administered drug, all others not statistically significant. Authors note the statistically significant result is likely an artifact.

Despite the theoretical possibility of phenytoin affecting phenobarbital PK by induction of CYP2C9, there was no effect. In another study ([Pokorna et al., 2019](#)) as well it was shown that in newborns, clearance (L/kg) of phenobarbital was non-significantly reduced (0.0033 vs 0.0042 L/kg) in cases exposed to phenytoin at clinically relevant doses. (15–20 mg/kg iv in a single or divided loading dose, and 5–8 mg/kg/day iv in two divided dosages as a maintenance dose).

It was reported that co-administration of sodium valproate resulted in increased serum levels of

phenobarbital in epileptic children and adults possibly due to inhibition of the direct N-glucosidation of phenobarbitone (Kapetanović et al., 1981). (Fernandez de Gatta et al., 1986). Since valproate is rarely used in neonates (Baudou, Benevent, Montastruc, Touati, & Hachon LeCamus, 2019) and was also not part of commonly used medications in neonates (Table 1), no such interaction data is available in neonates.

As mentioned earlier, the glucoside pathway develops little later after birth, possibly after 2 weeks of age (Bhargava & Garrettson, 1988) (Battino et al., 1995), the extent of interaction could be low but the extent cannot be predicted accurately.

However, since there is evidence for severe CNS depression with or without significant elevations of barbiturate or valproate serum concentrations, all patients receiving concomitant valproate therapy should be closely monitored for neurological toxicity. Serum phenobarbital concentrations should be obtained, if possible, and the phenobarbital dosage decreased, if appropriate ("Highlights of Prescribing information: DEPAKENE (valproic acid), capsules, USP, for oral use.," Revised 11/2016). In neonates, plasma concentrations of phenobarbital between 20 and 40 µg/mL are therapeutically safe and effective and concentrations over 60 µg/mL may be associated with significant intoxication.

Phenobarbital is not a substrate of efflux transporters P-gp and BCRP and uptake transporters OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2K (Module 2.7.2). Hence any co-medications that inhibit or induce these transporters are unlikely to affect the pharmacokinetics of phenobarbital.

Among the frequently used drugs listed in Table 1, the effect of potential interactions of the most commonly co-administered medications in neonates are summarized in Table 3. The majority of potentially co-administered medications in neonates are unlikely to impact the pharmacokinetics of phenobarbital, as they are neither inducers nor inhibitors of metabolic pathways of phenobarbital metabolism. There is a potential for CYP2C inducers carbamazepine / oxcarbazepine to decrease phenobarbital levels. However, phenobarbital, itself being an inducer of CYP3A that is involved in the clearance of carbamazepine, makes the extent of any interaction low, though it is complex to predict the net effect of this interaction. Although a few drugs like phenytoin have a theoretical potential to affect the PK of phenobarbital, the observed lack of interaction (Pokorna et al., 2019 and Šíma et al., 2015) may be due to the short overlap of treatment in actual clinical settings and/or due to the fact that there are multiple elimination pathways involved in phenobarbital metabolism and elimination.

Table 3: Likely Effect of Commonly Used Medications on Phenobarbital PK

List of the most likely used co-meds in Neonates	Sparc's Assessment of potential to affect the PK of PB	Rationale (based on FDA database and literature; also see section 2 below)	Clinical Relevance
Antibiotics (ampicillin, amoxicillin, gentamicin, cefotaxime)	Unlikely	None of these antibiotics are reported as inhibitors or inducers of major enzymes involved in the metabolism of phenobarbital (CYP2C9 and UGT) (Niwa et al., 2016)	No predicted interaction
Phenytoin/fosphenytoin	Possibly	Can induce phenobarbital metabolism via CYP2C9 and UGT	In neonates, there was no effect of phenytoin on clearance of phenobarbital (Pokorna et al., 2019 ; Šíma et al., 2015)
Morphine	Unlikely	No reported data on morphine as an inhibitor or inducer of CYP2C9/UGT	No predicted interaction
Fentanyl	Unlikely	No reported data on fentanyl as an inhibitor or inducer of CYP2C9/UGT	No predicted interaction
Midazolam	Unlikely	No reported data on midazolam as an inhibitor or inducer of CYP2C9/UGT	In neonates, there was no effect of midazolam on clearance of phenobarbital (Šíma et al., 2015)
Vasoactive drugs (dopamine, dobutamine, and norepinephrine)	Possibly	Could alter phenobarbital clearance by possible changes in renal perfusion	In neonates, there was no effect of vasoactive drugs on the clearance of phenobarbital (Šíma et al., 2015)

Tramadol	Unlikely	No reported data on tramadol as an inhibitor or inducer of CYP2C9/UGT	In neonates, there was no effect of tramadol on the clearance of phenobarbital (Šima et al., 2015)
Furosemide	Possibly	Could alter the volume of distribution of phenobarbital through altered body water content in various compartments	In neonates, there was no effect of furosemide on the clearance of phenobarbital (Šima et al., 2015)
Sufentanil	Unlikely	No reported data on sufentanil as an inhibitor or inducer of CYP2C9/UGT	In neonates, there was no effect of sufentanil on the clearance of phenobarbital (Šima et al., 2015)
Levetiracetam	Unlikely	Levetiracetam and its major metabolite, at concentrations well above C _{max} levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzyme ("Highlights of prescribing information: KEPPRA (levetiracetam) tablets, for oral use.," Revised 4/2017)	No predicted interaction

Carbamazepine / oxcarbazepine	Possibly	Carbamazepine is a weak inducer of CYP2C9 and a strong inducer of UGT1A1.	Unlikely a safety risk as carbamazepine / oxcarbazepine may decrease phenobarbital levels. Further, phenobarbital is an inducer of CYP3A and carbamazepine is cleared through CYP3A4; the extent of any interaction is anticipated to be low though complex to predict.
Acetaminophen	Unlikely	Acetaminophen is not reported as an inhibitor or inducer of major enzymes involved in the metabolism of phenobarbital (CYP2C9 and UGT)	No predicted interaction
Nystatin	Unlikely	In adults dosed with warfarin (a sensitive probe substrate of CYP2C9) and oral nystatin there was no significant effect on the International Normalized Ratio (INR). (Hellfritzsche et al., 2017)	No predicted interaction
Acyclovir	Unlikely	No reported data on acyclovir as an inhibitor or inducer of CYP2C9/UGT	No predicted interaction
Valproic acid	Likely	Can decrease phenobarbital metabolism by inhibiting UGT enzymes involved in N-glucosidation.	Co-administration of sodium valproate resulted in increased serum levels of phenobarbital in epileptic children and adults (Fernandez de Gatta et al., 1986 ; Kapetanović et al., 1981).

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4.3 Clinical PK Assessments

Study Title: A Two Sequence, Two-Period Crossover, Single Dose Comparative Bioavailability Study of PHB Sodium Intravenous Formulations in Healthy Adult Subjects.

Reference Product (R): PHB Sodium Injection, USP (West-Ward Pharmaceuticals) – 130 mg/1 mL vial.

Test Product (T): PHB Sodium for Injection (SPARC) – 100 mg lyophilized powder.

Study Design: Randomized, open-label, two-period, two-sequence, two-way crossover, single dose study. On two occasions separated by at least 5 weeks, eligible subjects received a single intravenous infusion of 2 mg/kg PHB.

PK sampling: In each period, blood samples were collected at pre-dose (0.00 hour) (within 60 minutes prior to dose administration) and post-dose at 0.083, 0.25 (end of infusion), 0.5, 1, 2, 4, 6, 8, 12, and 24 hours, and on the morning of Days 3, 4, 7, 10, 14, 17 and 21.

No. of subjects: 25 enrolled, 24 completed (14 males and 10 females), 23 considered for PK and BE analysis.

Inclusion criteria: Healthy, adult, male and female subjects, ages between 21 to 45 years, with body mass index (BMI) between 20.76 - 29.99 kg/m² (both inclusive), and mean weight of 73.9 kg at screening.

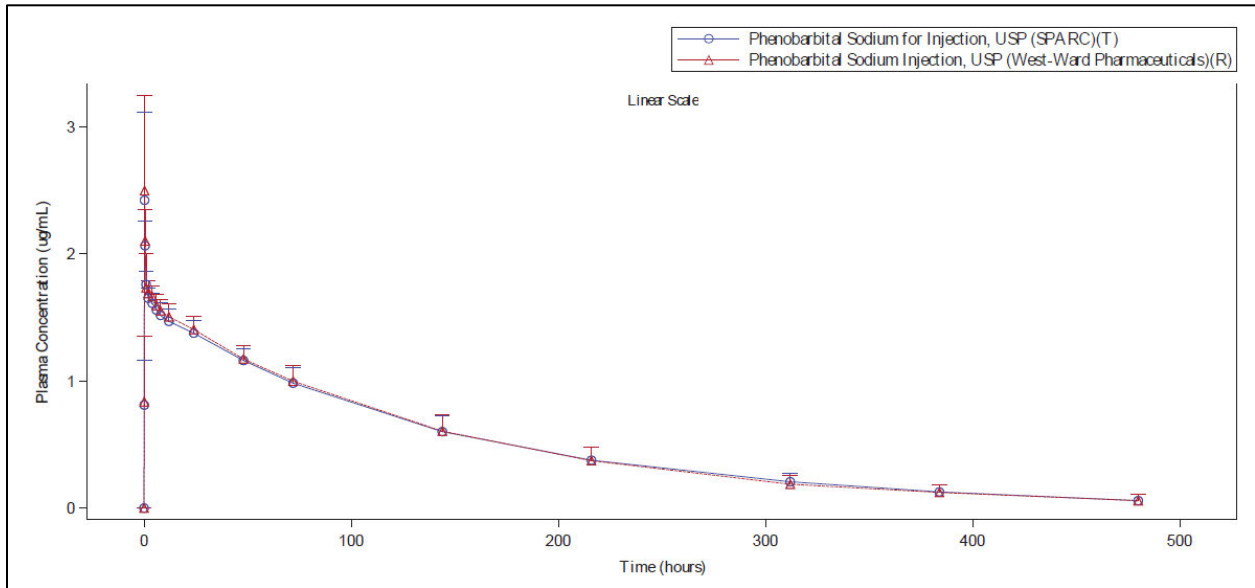
Washout Period: A washout period of at least 5 weeks (35 days) was maintained between each dose.

Pharmacokinetic Analysis: Primary pharmacokinetic parameters of C_{max}, AUC_{0-t}, and AUC_{inf} and secondary pharmacokinetic parameters of T_{max}, t_{1/2}, K_{el}, CL, and V_z for total and unbound PHB were calculated for the test and reference treatments for each subject in each study period.

Bioequivalence criteria: Geometric mean ratios were calculated from the least squared method values of both treatments. The bioavailability comparisons were based on the 90% confidence intervals constructed to determine the interval estimates of the geometric mean ratio for AUC_{0-t}, AUC_{inf}, and C_{max}.

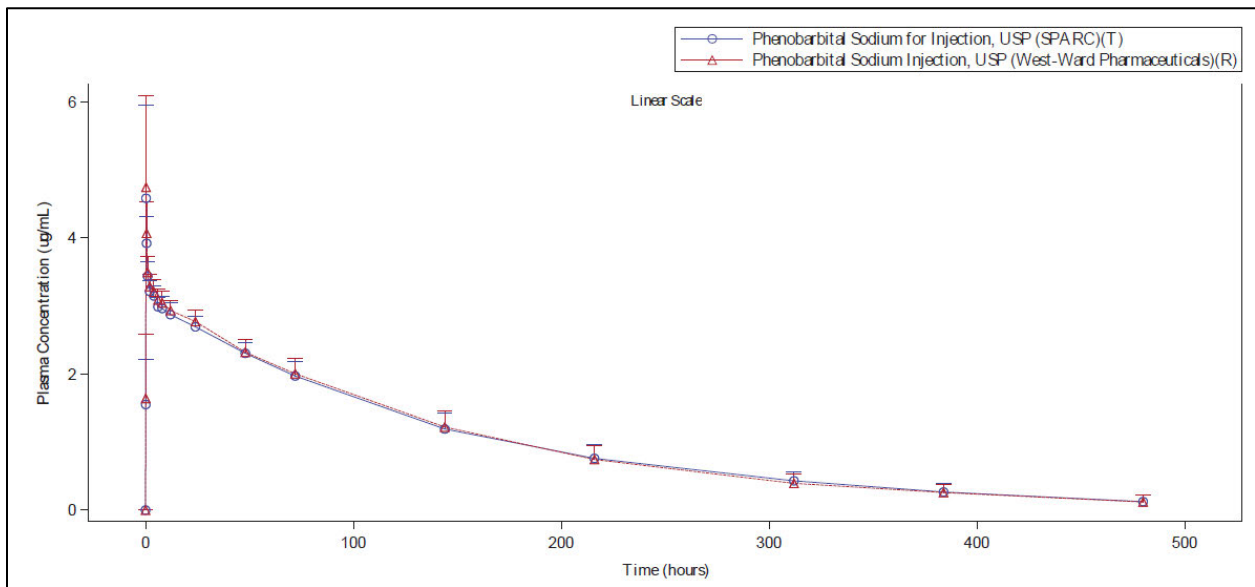
Results: The Applicant demonstrated bioequivalence (**Figure 5**, and **Figure 6**) between Test (SPARC) and Reference (West-Ward Pharmaceuticals) formulations in adult healthy subjects. The 90% CI of the geometric least square mean ratios for AUC_{0-t}, AUC_{inf} and C_{max} for unbound and total (bound + unbound) PHB were within the 80.00% to 125.00% boundary (See **Table 6** and **Table 7**).

Figure 5 Mean (+SD) Plasma Concentrations of Unbound PHB versus Time



Source: PHEN-20-01 study report, page 150 of 518

Figure 6 Mean (+SD) Plasma Concentrations of Total PHB versus Time



Source: PHEN-20-01 study report, page 152 of 518

Table 6: Average bioequivalence between Test (SPARC) and Reference (West-Ward) for total (bound + unbound) PHB

PK Parameter (unit)	Geo. Mean Test (SPARC)	Geo. Mean Ref. (West-Ward)	Geo. Mean ratio (Test/Reference)	90% CI of ratio
Ln(C _{max})	4.59	4.64	98.74	89.47 – 108.98
Ln(AUC _{0-t})	452.86	457.95	98.89	96.53 – 101.30
Ln(AUC _{inf})	481.87	485.38	99.28	96.82 – 101.79

Source: Reviewer analysis using Phoenix WinNonlin

Table 7: Average bioequivalence between Test (SPARC) and Reference (West-Ward) for free (unbound) PHB

PK Parameter (unit)	Geo. Mean Test (SPARC)	Geo. Mean Ref. (West-Ward)	Geo. Mean ratio (Test/Reference)	90% CI of ratio
Ln(C _{max})	2.41	2.44	98.73	89.52 – 108.87
Ln(AUC _{0-t})	226.02	228.34	98.99	96.81 – 101.21
Ln(AUC _{inf})	240.08	241.23	99.52	97.32 – 101.77

Source: Reviewer analysis using Phoenix WinNonlin

The two formulations are deemed bioequivalent if the 90% CI around the geometric mean ratios for AUC_{0-t}, AUC_{inf}, and C_{max} are within the limits of 80.00% to 125.00% for both total (bound + unbound) and unbound PHB.

Reviewer's comments:

1. The review team confirmed that the Applicant demonstrated bioequivalence between the Test (SPARC) and Reference (West-Ward) PHB formulations.

4.4. Population PK Analyses

The Applicant submitted report *262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf*, titled “*PHB Use in Full Term Neonatal Patients with Epilepsy: Dosing Simulations and PK Parameter Derivation*” to module 5335 in sequence 0001. The report describes population pharmacokinetic (PPK) analyses to model and simulate PHB pharmacokinetic (PK) data. The Applicant screened numerous PHB PK models published in the literature for these analyses. The Applicant obtained 11 original articles, two review articles describing the published PPK models, and two papers that performed external validation of the previously published models. The Ryu et al.⁵ article describes an external validation of seven models that were identified in the Applicant’s literature search. As such, these seven models were further considered for use in the Applicant’s analyses. Out of the seven models, the Applicant selected models by Shellhaas et al.⁶, Marsot et al.⁷, and Voller et. al.⁸ for use in their analyses based on the predictive accuracy, predictive precision, and deviation from the theoretical distribution as reported in the Ryu et al. paper.

[Reviewer comment: Neither the Shellhaas, Marsot, nor Voller models include genetic polymorphisms as covariates on PHB PK. However, the respective publications for these models do not mention genetic polymorphisms. Overall, the Applicant’s PPK analyses do not inform whether there is an effect of genetic polymorphisms on PHB PK.]

The Applicant’s analyses address 3 objectives:

1) Objective 1: Assess Validity of Literature Models

The Applicant assessed how well the three models describe the observed PK dataset obtained from the NEOLEV2 study. These analyses include conducting 1000 simulations for each of the three published PK models and overlaying the observed PK data with the simulation results.

⁵ Sunae Ryu, Woo Jin Jung, Zheng Jiao, Jung-Woo Chae, and Hwi-Yeol Yun. External evaluation of the predictive performance of seven population pharmacokinetic models for phenobarbital in neonates. *British journal of clinical pharmacology*, February 2021.

⁶ Renée A. Shellhaas, Chee M. Ng, Christina H. Dillon, John D. E. Barks, and Varsha Bhatt-Mehta. Population pharmacokinetics of phenobarbital in infants with neonatal encephalopathy treated with therapeutic hypothermia. *Pediatric critical care medicine*, 14:194–202, February 2013.

⁷ Amélie Marsot, Véronique Brevaut-Malaty, Renaud Vialet, Audrey Boulamery, Bernard Bruguerolle, and Nicolas Simon. Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. *Fundamental & clinical pharmacology*, 28:465–471, August 2014.

⁸ Swantje Völler, Robert B. Flint, Leo M. Stolk, Pieter L. J. Degraeuwe, Sinno H. P. Simons, Paula Pokorna, David M. Burger, Ronald de Groot, Dick Tibboel, Catherijne A. J. Knibbe, and D. I. N. O. study group. Model-based clinical dose optimization for phenobarbital in neonates: An illustration of the importance of data sharing and external validation. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 109S:S90–S97, November 2017.

2) Objective 2: Derivation of PHB PK Parameters:

The Applicant conducted an estimation run with MAXEVAL=0 with initial estimates for each fixed and random effect set to the final values reported in all three papers in order to assign individual PK parameters according to each reported model. Using the individual PK parameter values, the Applicant simulated the values of individual exposure metrics.

3) Objective 3: Simulation of PHB:

The Applicant utilized weight and age values obtained from the World Health Organization to simulate the distribution of PHB exposures following one or two loading doses (20 mg/kg IV, with the second loading dose administered at the min, median, and maximum loading dose time in the NEOLEV2 study) followed by maintenance doses of 1.5 mg/kg IV q8h for up to 4 days.

Based on this assessment, the Applicant selected the Shellhaas model and Voller model for conducting simulations to further assess the dosing regimen from the NEOLEV2 study in the proposed patient population.

All modeling and simulation exercises were conducted using the NONMEM software package version 7.4.4.

4.4.1 Study from Which PK Data Were Collected

PK data for these analyses were collected from subjects enrolled in the study titled “*Efficacy of Intravenous Levetiracetam in the Treatment of Neonatal Seizures: A Phase 2 Study of Levetiracetam in the Treatment of Neonatal Seizures*” (protocol 111361-NEOLEV2; referred to as NEOLEV2 from here on). NEOLEV2 is a randomized, double-blinded, study to assess the safety and efficacy of escalating doses of levetiracetam compared to PHB in n=30 neonatal patients with electrographically confirmed seizure activity. Subjects that received PHB were administered a loading dose of 20 mg/kg, with an optional second loading dose of 20 mg/kg if seizure activity persists or reoccurs more than 15 minutes after first infusion, followed by maintenance dosing of 1.5 mg/kg q8h for up to 5 days. Each PHB administration was delivered as a 15-minute IV infusion. PK samples were collected prior to the first infusion, and at 1, 24, and 48 hours after onset of the first infusion. The PK dataset included 62 PK samples from n=28 neonatal subjects in NEOLEV2.

[Reviewer comment: the q8h dosing interval for PHB maintaining dosing was implemented to help maintain the blind as LEV is administered q8h. In clinical practice, PHB maintenance dosing is generally administered at q12h intervals.]

For additional details on NEOLEV2, please refer to section 3.2.1.

4.4.2 Validation of Literature Models

4.4.2.1 Shellhaas et al. PPK Model

The PPK model described by Shellhaas et al. (referred to hereafter as “the Shellhaas model”) utilizes one-compartment. Covariates on clearance include weight normalized to 70 kg (power model with a fixed exponent of 0.75) and post-natal age (PNA) in an $E_{\max}$ function. Weight normalized to 70 kg is a covariate on volume of distribution as a power model with a fixed exponent of 1. Between subject variability is estimated for clearance and volume of distribution. Residual variability is modelled with a combined proportional error and additive error terms. The PK parameters for the Shellhaas model are summarized in **Table 8**.

Table 8: PHB PPK Parameters in Neonates: Shellhaas Model

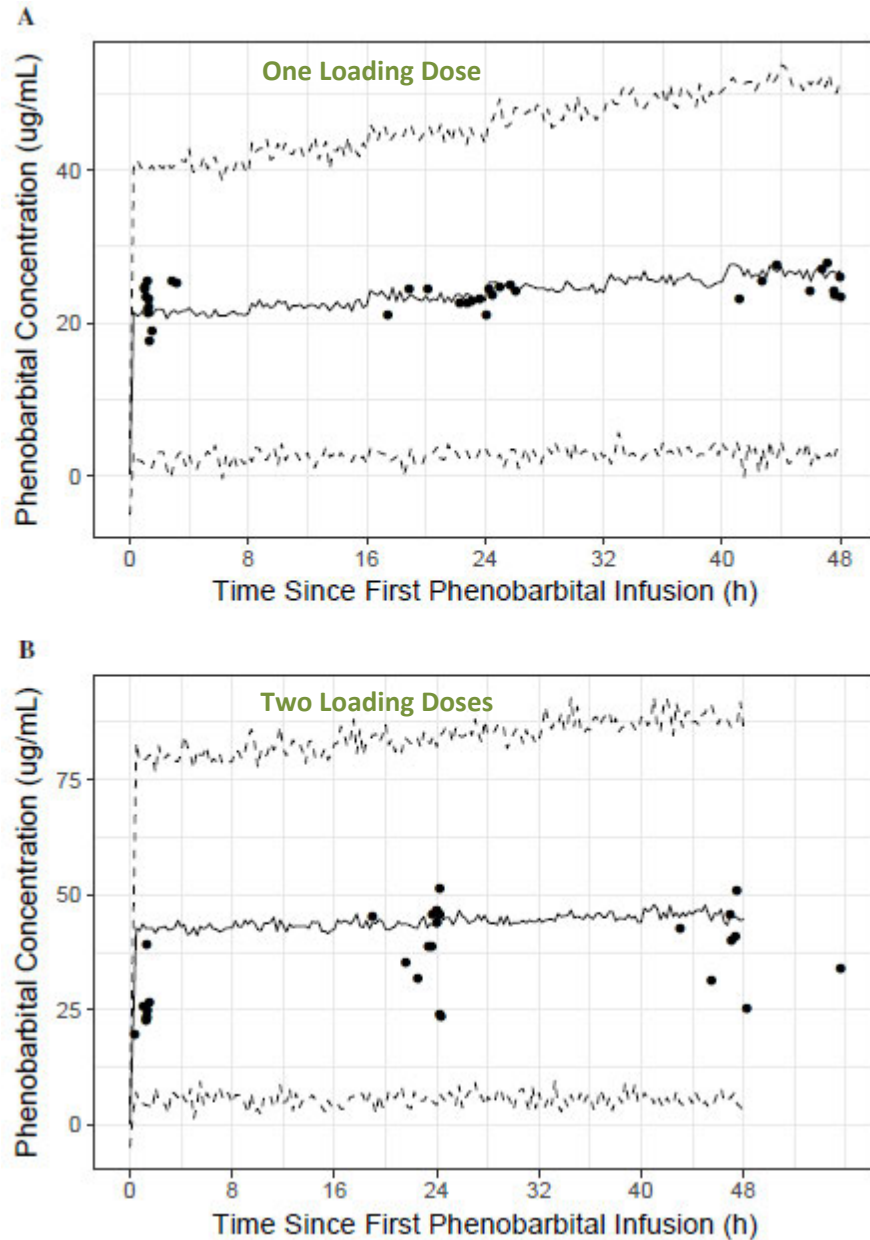
Parameters	Estimate	SE
Clearance (CL, L/h)	0.672	0.177
WT effect on CL	0.75 (Fixed)	–
PNA ₅₀ effect on CL (days)	22.1	8.50
Central volume of distribution (V _c , L)	64.9	2.05
WT effect on V _c	1.0 (Fixed)	–
ω^2 CL	0.175	0.0616
ω^2 V _c	–	–
Proportional error σ_{prop}	0.197	0.0194
Additive error	6.12	0.830

Where CL=clearance, WT=weight, V_c is volume of distribution, PNA = post-natal age, PNA50 is the age at which the 50% of age-related effect on CL maturation occurs.

Source: sequence 0001, module 5335,
262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 24 of 111

Figure 7 shows the observed PK data overlaid with 1000 simulations generated using the Shellhaas model.

Figure 7: Model Validation: Shellhaas Model



The dots are the observed PHB concentrations from NEOLEV2 study. The solid line is the median and the dashed lines are the 2.5th and 97.5th percentiles (i.e. 95% PI) of the simulated PHB concentrations. A) Administration of one loading dose of PHB (20 mg/kg IV) followed by 1.5 mg/kg q8h. B) Administration of two loading doses of PHB (20 mg/kg IV, 30 minutes apart) followed by 1.5 mg/kg q8h IV.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 6 of 111

4.4.2.2 Marsot et al. PPK Model

The PPK model developed by Marsot et al. (referred to hereafter as “the Marsot model”) utilizes one-compartment. Weight is a covariate on clearance as a power model with a fixed exponent of 0.75 and on volume of distribution as a power model with a fixed exponent of 1. Between subject variability is estimated for clearance and volume of distribution. Residual variability is modelled with an additive error model. PK parameters for the Marsot model are summarized in **Table 9**.

Table 9: PHB PPK Parameters in Neonates: Marsot Model

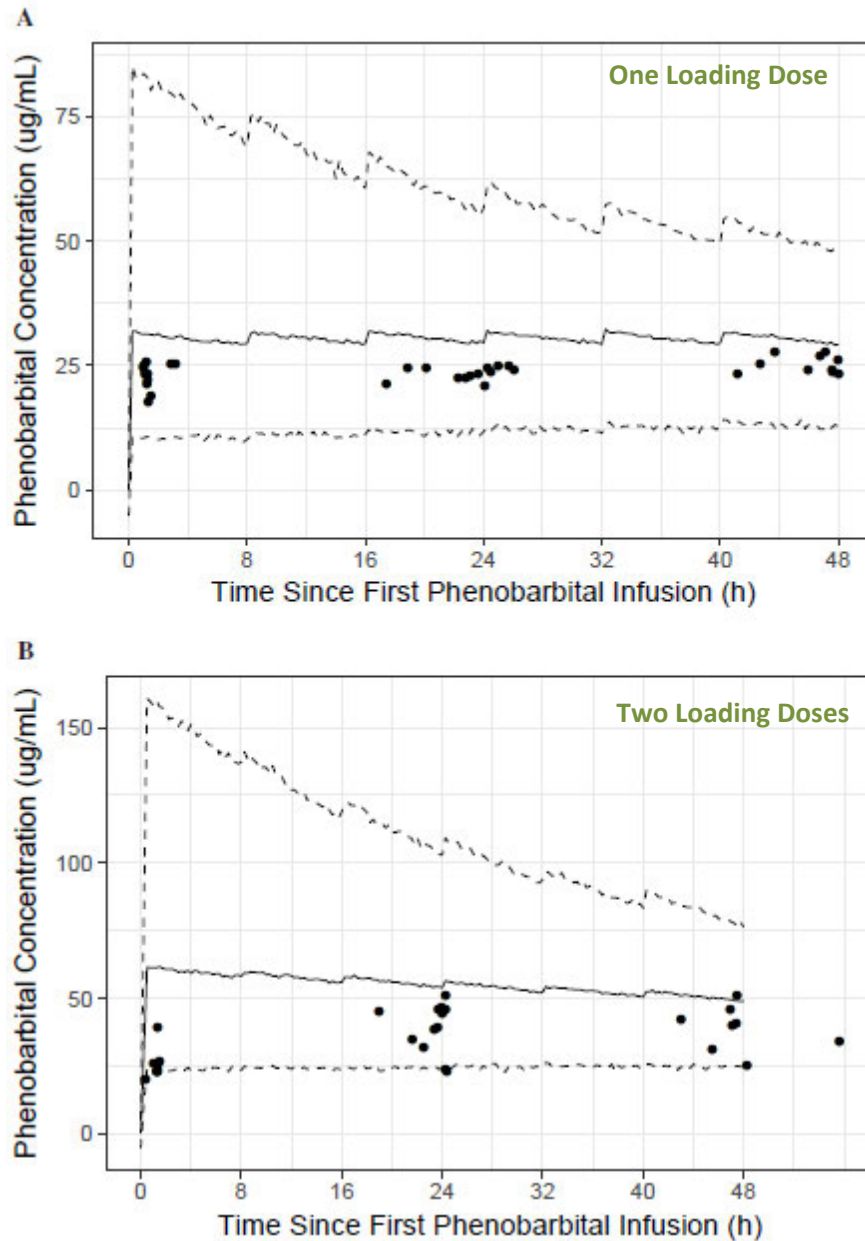
Parameters	Estimate	RSE%
Clearance (CL, L/h)	0.191	7.4
WT effect on CL	0.75 (Fixed)	–
Central volume of distribution (V_c , L)	44.6	15.1
WT effect on V_c	1.0 (Fixed)	–
Between-subject variability for CL (%)	16.6	31.3
Between-subject variability for V_c (%)	49.5	27.2
Additive error (mg/L)	7.22	28.9

Where CL=clearance, WT=weight, V_c is volume of distribution.

Source: sequence 0001, module 5335,
262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 25 of 111

Figure 8 shows the observed PK data overlaid with 1000 simulations generated using the Marsot model.

Figure 8: Model Validation: Marsot Model



The dots are the observed PHB concentrations from NEOLEV2 study. The solid line is the median and the dashed lines are the 2.5th and 97.5th percentiles (i.e. 95% PI) of the simulated PHB concentrations. A) Administration of one loading dose of PHB (20 mg/kg IV) followed by 1.5 mg/kg q8h. B) Administration of two loading doses of PHB (20 mg/kg IV, 30 minutes apart) followed by 1.5 mg/kg q8h IV.

Source: *sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 7 of 111*

4.4.2.3 Voller et al. PPK Model

The Voller et al. publication describes a PHB PPK model (referred to hereafter as “the Voller model”) that utilizes one-compartment. Weight is a covariate on clearance as a proportional change based on the difference from median weight [$1 + \Theta_{WT,CL} * (WT_i - WT_{med})$]. The same approach is used to model the effect of post-natal age (PNA) on clearance [$1 + \Theta_{PNA,CL} * (PNA_i - PNA_{med})$] and the effect of weight on volume of distribution [$1 + \Theta_{WT,V} * (WT_i - WT_{med})$]. Between subject variability is estimated for clearance and volume of distribution. Residual variability is modelled with a proportional error term. The PK parameters for the Voller model are summarized in **Table 10**.

Table 10: PHB PPK Parameters in Neonates: Voller Model

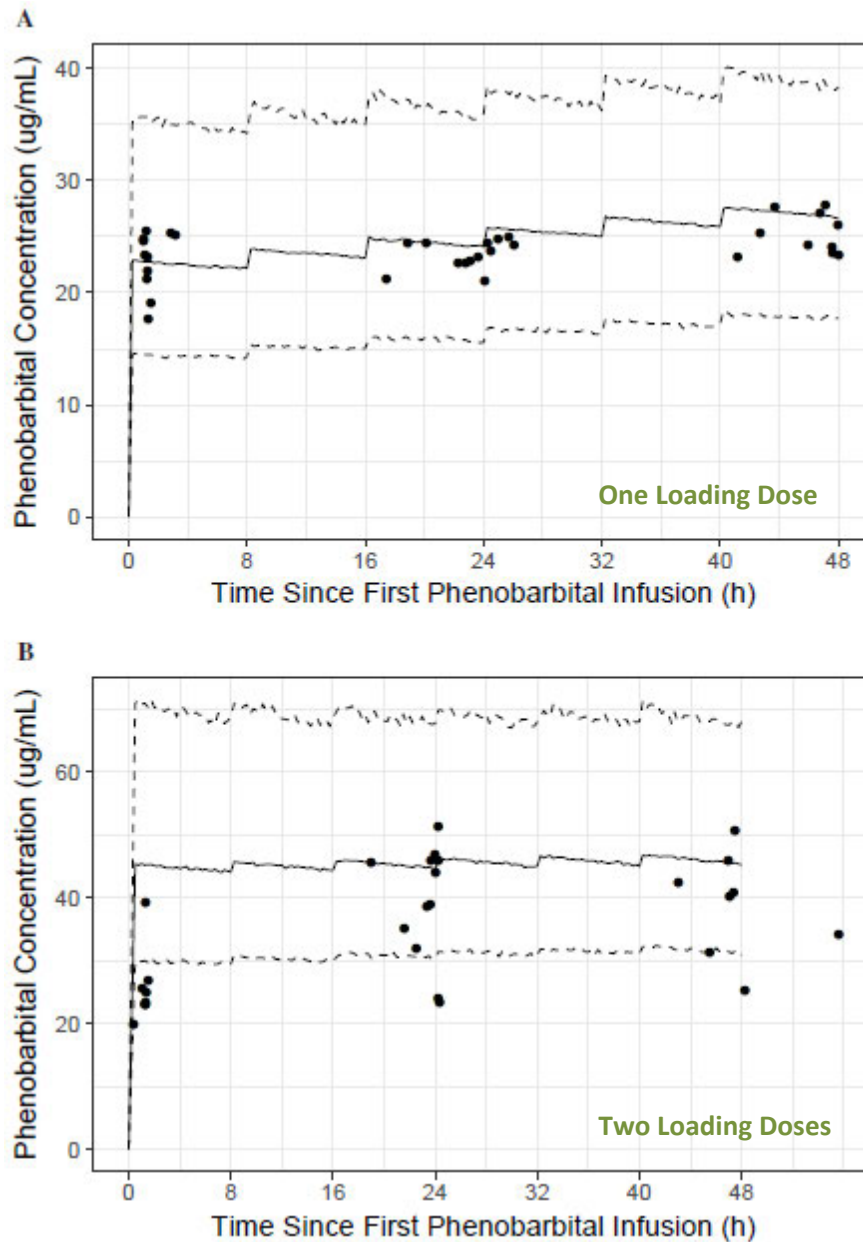
Parameters	Estimate	RSE%
Clearance (CL, L/h)	0.0091	9
WT effect on CL	0.369	8
PNA effect on CL	0.0533	27
Central volume of distribution (V_c , L)	2.38	5
WT effect on V_c	0.309	8
Between-subject variability for CL (%)	30.0	29
Between-subject variability for V_c (%)	22.4	40
Proportional error (%)	2.58	22

Where CL=clearance, WT=weight, V_c is volume of distribution.

Source: sequence 0001, module 5335,
262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 26 of 111

Figure 9 shows the observed PK data overlaid with 1000 simulations generated using the Voller model.

Figure 9: Model Validation: Voller Model



The dots are the observed PHB concentrations from NEOLEV2 study. The solid line is the median and the dashed lines are the 2.5th and 97.5th percentiles (i.e. 95% PI) of the simulated PHB concentrations. A) Administration of one loading dose of PHB (20 mg/kg IV) followed by 1.5 mg/kg q8h. B) Administration of two loading doses of PHB (20 mg/kg IV, 30 minutes apart) followed by 1.5 mg/kg q8h IV.

Source: sequence 0001, module 5335,
262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 8 of 111

4.4.2.4 Applicant's Validation Conclusions

The Applicant concludes the following:

- All three models were able to capture the observed data from the NEOLEV2 study such that most of the observed data are within the 95% prediction interval of the simulated data.
- the Shellhaas and Voller models present minimal bias in the median simulated concentrations
- the Marsot model demonstrates mild to moderate over prediction in the median simulated concentration

[Reviewer comment: The reviewer agrees that the Marsot model demonstrates over prediction whereas the Shellhaas and Voller models present minimal bias according to **Figure 7, Figure 8, and Figure 9**. For this reason, the Shellhaas model and Voller model were considered by the reviewer for assessments of maintenance dosing interval and dosing in preterm infants (see **Section 4.4.7 and Section 4.4.8** of this review).]

4.4.5 Derivation of PHB PK Parameters

The Applicant derived individual PK parameters for subjects in the NEOLEV2 study based on the three PHB PK models; Shellhaas, Marsot, and Voller. The individual PK parameters along with derived exposure metrics were summarized for each model. The results of the derived values are shown below.

Table 11: PHB PK Parameters Following One Loading Dose: Shellhaas Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Shellhaas	N	17	17	17	17
	Mean	21.6	12300	0.00264	0.927
	SD	0.00622	7330	0.00214	0.00000000853
	CV%	0.0288	59.8	81.1	0.000000092
	95% CI	21.6–21.6	8500–16000	0.00154–0.00374	0.927–0.927
	Min	21.5	2530	0.000883	0.927
	Median	21.6	11800	0.0017	0.927
	Max	21.6	22600	0.00792	0.927
	GeoMean	21.6	9890	0.00202	0.927
	GeoMean CV%	0.0288	84	84	0

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 9 of 111

Table 12: PHB PK Parameters Following One Loading Dose: Marsot Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Marsot	N	17	17	17	17
	Mean	24.1	3470	0.00578	0.836
	SD	2.35	157	0.000261	0.0736
	CV%	9.76	4.53	4.51	8.8
	95% CI	22.9–25.3	3390–3550	0.00565–0.00592	0.798–0.874
	Min	20.9	3220	0.00527	0.637
	Median	24	3460	0.00578	0.833
	Max	31.4	3790	0.0062	0.954
	GeoMean	24	3460	0.00578	0.833
	GeoMean CV%	9.24	4.52	4.52	9.25

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 10 of 111

Table 13: PHB PK Parameters Following One Loading Dose: Voller Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Voller	N	17	17	17	17
	Mean	22.5	5870	0.00409	0.894
	SD	2.12	2790	0.0018	0.0857
	CV%	9.42	47.5	44	9.58
	95% CI	21.4–23.6	4430–7300	0.00316–0.00501	0.85–0.938
	Min	19.1	2580	0.0014	0.782
	Median	23	5630	0.00355	0.869
	Max	25.6	14200	0.00776	1.05
	GeoMean	22.4	5350	0.00374	0.891
	GeoMean CV%	9.52	46.1	46.1	9.54

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 10 of 111

Table 14: PHB PK Parameters Following Two Loading Doses: Shellhaas Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Shellhaas	N	12	12	12	12
	Mean	43.4	12900	0.00235	0.927
	SD	1.74	7360	0.00184	0.00000000845
	CV%	4	57	78.2	0.0000000911
	95% CI	42.3–44.5	8240–17600	0.00118–0.00352	0.927–0.927
	Min	38.4	3070	0.000853	0.927
	Median	43.7	11300	0.00178	0.927
	Max	45.2	23500	0.00652	0.927
	GeoMean	43.3	10700	0.00187	0.927
	GeoMean CV%	4.18	77.2	77.2	0

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 10 of 111

Table 15: PHB PK Parameters Following Two Loading Doses: Marsot Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Marsot	N	12	12	12	12
	Mean	46.1	3440	0.00583	0.859
	SD	6.04	220	0.000384	0.145
	CV%	13.1	6.38	6.59	16.9
	95% CI	42.3–50	3300–3580	0.00558–0.00607	0.767–0.951
	Min	36	3070	0.00523	0.587
	Median	46.4	3500	0.00571	0.838
	Max	54.1	3830	0.00652	1.11
	GeoMean	45.8	3440	0.00582	0.848
	GeoMean CV%	13.4	6.49	6.49	17.5

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 11 of 111

Table 16: PHB PK Parameters Following Two Loading Doses: Voller Model

Model	Summary Statistic	Cmax ug/mL	AUC h.ug/mL	CL L/h/kg	Vz L/kg
Voller	N	12	12	12	12
	Mean	45.1	5050	0.0049	0.877
	SD	5.78	2140	0.00278	0.148
	CV%	12.8	42.3	56.8	16.9
	95% CI	41.4–48.7	3690–6410	0.00314–0.00667	0.782–0.971
	Min	34.6	1620	0.00234	0.597
	Median	44.8	4800	0.00423	0.868
	Max	54	8560	0.0123	1.18
	GeoMean	44.7	4590	0.00436	0.865
	GeoMean CV%	13.2	51.5	51.5	17.3

N = number. SD = standard deviation. CV = coefficient of variation. CI = confidence interval. Min = minimum. Max = maximum. GeoMean = geometric mean. Cmax is following the loading dose.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 11 of 111

The Applicant concludes that the three models produced consistent mean values of volume of distribution (i.e. range 0.836 L/kg to 0.927 L/kg) and that these values are consistent with the range of values reported in the literature (i.e. 0.48 L/kg to 1.56 L/kg Pacifici⁹, Lutz et al.¹⁰).

The three models produced clearance values spanning a two-fold range across the three models (0.0026 L/h/kg, 0.0058 L/h/kg, and 0.0041 L/h/kg for the Shellhaas, Marsot, and Voller models, respectively). Despite the variation among models, these clearance values are consistent with values reported in the literature (0.0021 L/h/kg to 0.0076 L/h/kg; Pacifici, Lutz et al.). The Applicant reports that the Shellhaas model produced lower clearance values than the other two models. This is likely due to the model PNA50 (time to 50% of CL maturation) estimate of 22.1 days and the median PNA of NEOLEV2 subjects being 2 days.

⁹ Gian M. Pacifici. Clinical pharmacology of phenobarbital in neonates: Effects, metabolism and pharmacokinetics. Current pediatric reviews, 12:48–54, 2016.

¹⁰ Isabelle Claire Lutz, Karel Allegaert, Jan N. de Hoon, and Heleen Marynissen. Pharmacokinetics during therapeutic hypothermia for neonatal hypoxic ischaemic encephalopathy: a literature review. BMJ paediatrics open, 4:e000685, 2020.

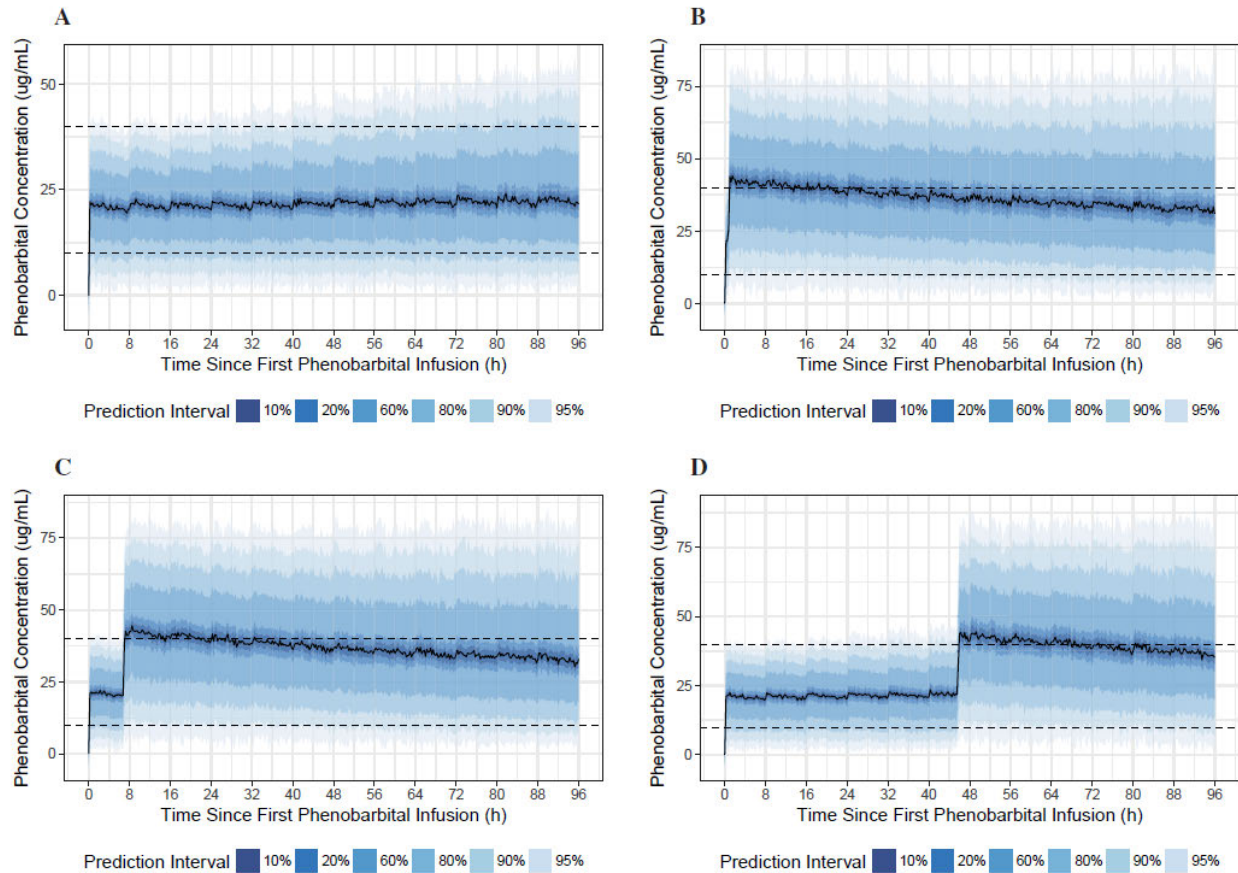
4.4.6 Applicant's PK Simulations of Proposed Dose Regimen

The Applicant conducted simulations to predict the PK profile for the proposed dosing regimen using the Shellhaas model, Marsot model, and Voller model. Four scenarios were simulated. In each scenario, a 20 mg/kg loading dose was administered immediately (time = 0). Scenario A utilized only a single loading dose. Scenarios B, C, and D utilized a second loading dose of 20 mg/kg administered at 0.7 hours, 6.82 hours, and 45.6 hours, respectively. These time values were selected to represent the range of times that second loading doses were administered in NEOLEV2. Maintenance dosing of 1.5 mg/kg q8h (4.5 mg/kg/day) began 8 hours after the onset of the initial loading dose. All doses were administered as IV infusions 15-minutes in duration. The virtual population for these simulations was obtained by selecting the median weight associated with ages of range 0 to 4 weeks from the World Health Organization weight-for-age table^{11,12}. The simulations are summarized as prediction intervals across the population. The results of the simulations are summarized in **Figure 10**, **Figure 11**, and **Figure 12**.

¹¹ World Health Organization. The WHO child growth standards. <http://www.who.int/childgrowth/en/>.

¹² Cole TJ and Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. *Statistics in Medicine*, 11:1305–1319, 1992.

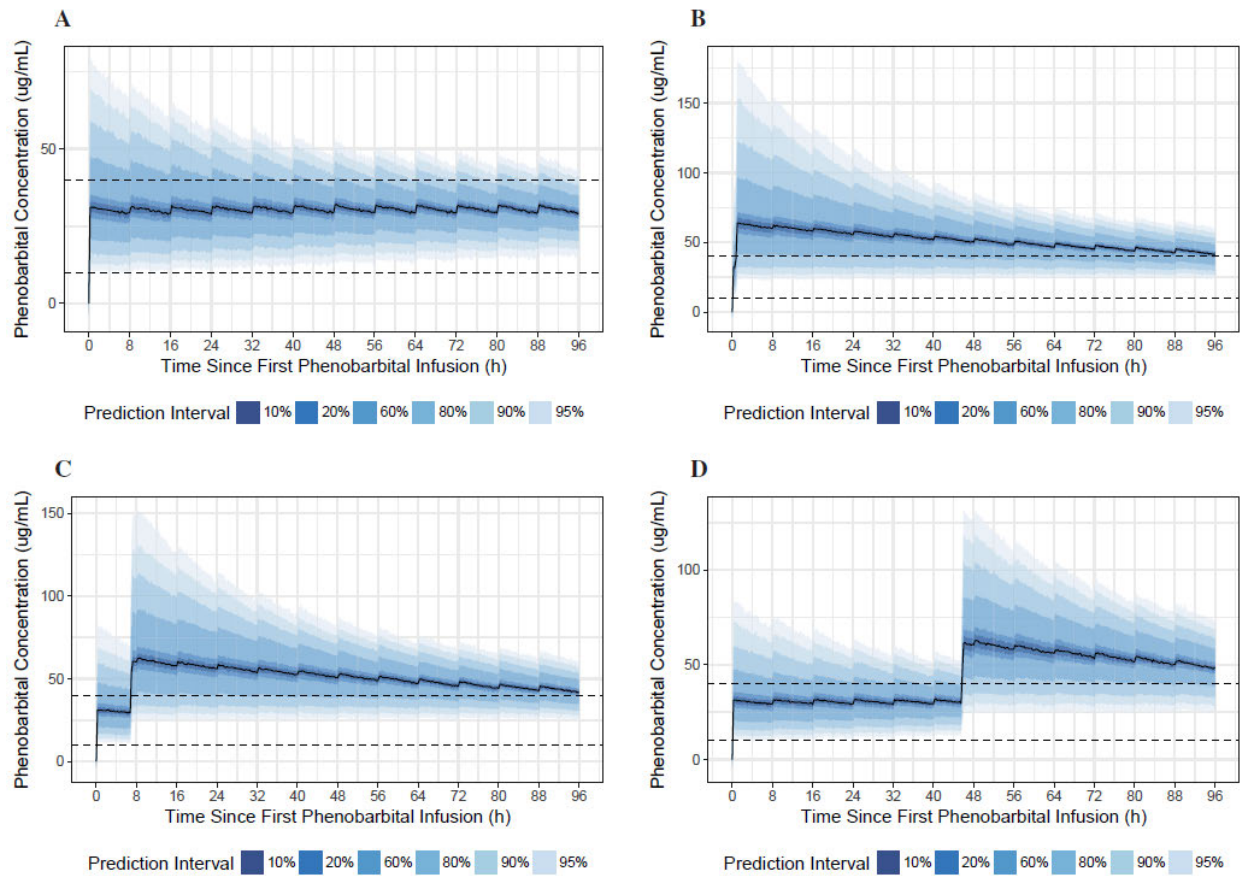
Figure 10: Simulation of PHB Exposures: Shellhaas Model



The solid black line is the median of the simulated concentration time-profiles. The shaded areas are the different prediction intervals based on 1000 simulations. A) Administration of one loading dose of PHB (20 mg/kg IV) at time=0 hours. Scenarios B), C), and D) along with the loading dose described in A), administration of a second 20 mg/kg IV loading dose administered at 0.7 h, 6.82 h, and 45.6 h after the initiation of the first loading dose, respectively. In all 4 scenarios, maintenance dosing of 1.5 mg/kg q8h IV began 8 hours after onset of the first loading dose. All administrations occur as a 15-minute IV infusion. The dashed lines show 10 $\mu\text{g}/\text{mL}$ and 40 $\mu\text{g}/\text{mL}$.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 12 of 111

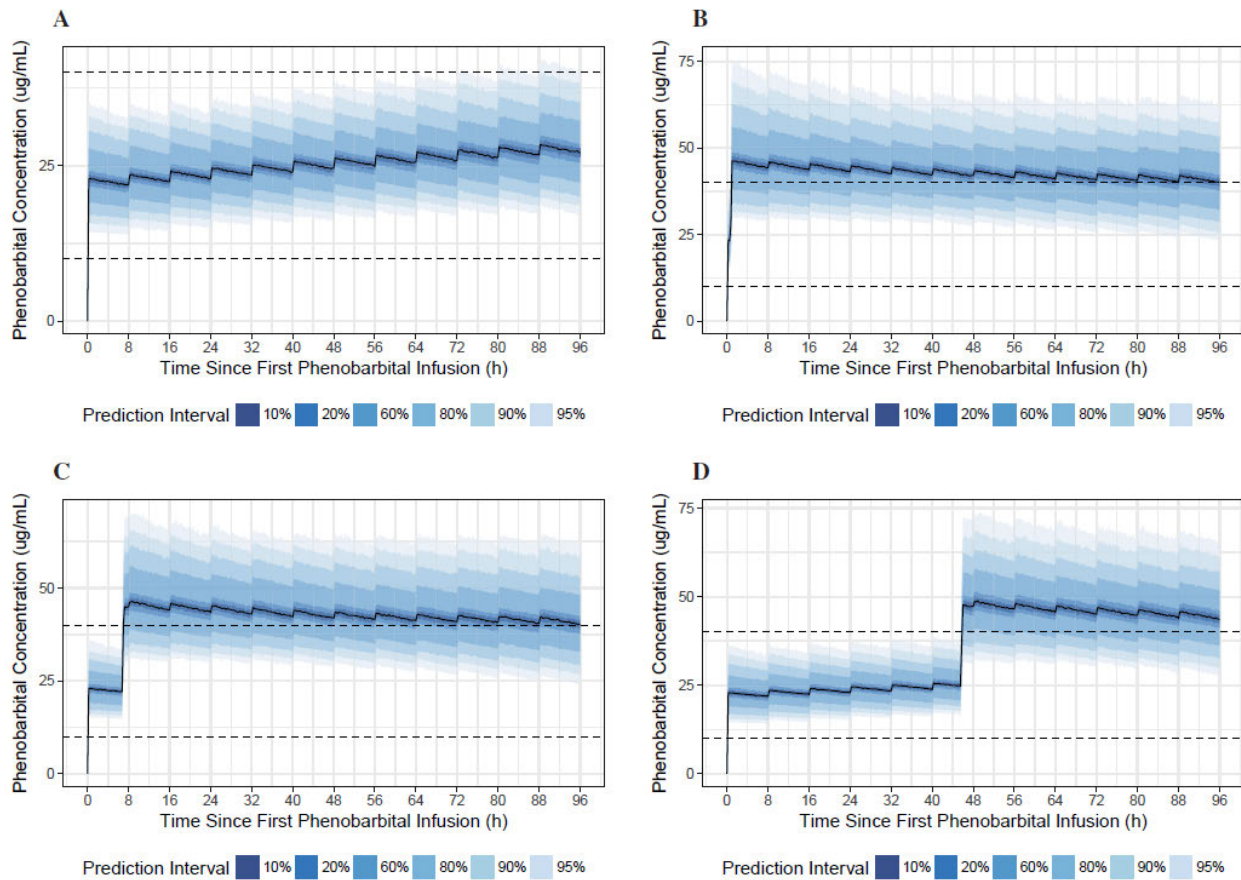
Figure 11: Simulation of PHB Exposures: Marsot Model



The solid black line is the median of the simulated concentration time-profiles. The shaded areas are the different prediction intervals based on 1000 simulations. A) Administration of one loading dose of PHB (20 mg/kg IV) at time=0 hours. Scenarios B), C), and D) along with the loading dose described in A), administration of a second 20 mg/kg IV loading dose administered at 0.7 h, 6.82 h, and 45.6 h after the initiation of the first loading dose, respectively. In all 4 scenarios, maintenance dosing of 1.5 mg/kg q8h IV began 8 hours after onset of the first loading dose. All administrations occur as a 15-minute IV infusion. The dashed lines show 10 μ g/mL and 40 μ g/mL.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 13 of 111

Figure 12: Simulation of PHB Exposures: Voller Model



The solid black line is the median of the simulated concentration time-profiles. The shaded areas are the different prediction intervals based on 1000 simulations. A) Administration of one loading dose of PHB (20 mg/kg IV) at time=0 hours. Scenarios B), C), and D) along with the loading dose described in A), administration of a second 20 mg/kg IV loading dose administered at 0.7 h, 6.82 h, and 45.6 h after the initiation of the first loading dose, respectively. In all 4 scenarios, maintenance dosing of 1.5 mg/kg q8h IV began 8 hours after onset of the first loading dose. All administrations occur as a 15-minute IV infusion. The dashed lines show 10 μ g/mL and 40 μ g/mL.

Source: sequence 0001, module 5335, 262385-phenobarbital-dosing-sim-report-20210810-final-v1.pdf, page 14 of 111

The Applicant provides the following conclusions based on these simulations:

- For one loading dose, the Shellhaas and Voller models predicted that most neonates would have PHB concentration ≤ 40 $\mu\text{g/mL}$ over 4 days of therapy.
- For two loading doses, the Shellhaas and Marsot models predicted the median PHB concentration to be > 40 $\mu\text{g/mL}$.
- The highest exposure was produced with the second loading dose was given closer in time to the first loading dose.

[Reviewer comment: The Applicant's conclusions are acceptable. The Applicant cites (b) (4) as support for the claim that (b) (4). However, the review team does not consider this claim to be adequately supported.]

4.4.7 Reviewer's Analyses of Maintenance dosing at q8h and q12h intervals

In the NEOLEV2 study, all subjects received maintenance dosing of study medication (levetiracetam or PHB) at 8-hour dosing intervals. The Applicant proposed a q8h maintenance dosing interval for the PHB label. The Clinical team expressed interest in possibility of a q12h interval. To address this, OCP conducted PK simulations to assess the effect of administering the same total daily maintenance dose at a q8h interval versus a q12h interval.

The reviewer utilized the Voller model for conducting the PK simulations. This is due to the bias pointed out by the Applicant in prediction of the median PK values (see **Section 4.4.2.4** for details) for the Marsot model. The Shellhaas model was considered for these simulations. However, the Shellhaas model does not include a between subject variability term on volume of distribution. As such, the only source of variability in PK during the initial infusion is due to residual variability, and thus all subjects have nearly identical individual subject's PK profiles (when removing residual variability from the simulations) at the end of the first infusion (at time=0.25 hours). For these reasons, the Voller model was selected.

The proposed labelled dosing of 20 mg/kg IV loading doses and 4.5 mg/kg/day maintenance dosing were applied in the simulations. One and two loading dose scenarios were assessed with the second loading dose occurring at 30 minutes (the earliest time possible). Maintenance dosing for q8h and q12h started at 8 hour and 12 hours after the onset of the first loading dose, respectively. The simulations with between-subject

(b) (4)

variability were conducted on virtual term neonates spanning birth to 4 weeks. The CDC growth charts¹⁴ were used to determine median weight values associated with term neonates in this age range. Female subjects were arbitrarily selected as the effect of dosing interval on PK is not expected to depend on the neonate sex. The median weight for each age was selected. The weight range is 3.40 kg to 4.17 kg for birth to 4 weeks. A total of 500 virtual subjects were generated with a uniform distribution across this age range for each simulation scenario.

The simulation results are summarized in **Figure 4** for one loading dose or two loading doses at 1.5 mg/kg q8h or 2.25 mg/kg q12h maintenance dosing intervals for 5 days. Based on geometric mean ratios comparing the q8h to q12h maintenance dosing intervals (**Table 2**, based on simulations depicted in **Figure 4**) for the same total daily maintenance dose level (4.5 mg/kg/day), administering maintenance dosing as q8h or q12h results in no more than 3% difference in PK metrics for one or two loading doses. As such, administering q8h or q12h maintenance dosing for the same total daily dose results in a comparable PK profile for one or two loading doses. Overall, the differences in PK shape are not expected to cause a clinically relevant effect on safety, tolerability, or efficacy. As such, OCP concludes that it is acceptable to administer the maintenance dosing at q8h or q12h intervals for the 4.5 mg/kg/day total daily dose. The final label language regarding the maintenance dosing interval will reflect discussions within the review team and with the Applicant that will continue after this review is archived.

¹⁴ https://www.cdc.gov/growthcharts/clinical_charts.htm

4.4.8 Reviewer's Analyses of Preterm PHB Dosing

The Clinical team expressed interest in determining the appropriate dose regimen for preterm infants. To address this, OCP conducted PK simulations in preterm infants to compare exposures against the term infants.

The reviewer used the PHB PK model developed from preterm neonates described by Touw et al¹⁵ to assess dosing in preterm neonates. The Touw PPK model was developed using n=19 preterm neonates gestational age 26 6/7 to 41 4/7 weeks, weighing 0.590 to 4.070 kg, that received PHB loading doses 4 to 43 mg/kg, and PHB maintenance doses 2.8 to 7.4 mg/kg/day. Touw et. al. calculated individual PK parameters from a one-compartment model using a Bayesian approach. The individual PK parameters were linearly correlated with patient gestational age. The result is an expression of clearance as a function of gestational age and expression of volume of distribution as a function of gestational age.

The reviewer obtained data relating preterm infant weight to gestational age from the PediTools^{16,17} website which uses the 2013 Fenton Growth Charts. Using the PediTools data, a virtual preterm neonatal population was constructed for subjects starting at gestational age 26 weeks, and for each week of gestational age until 40 weeks (a total of 15 virtual preterm neonates per scenario). Each virtual subject was assigned the median weight for the given gestational age. Female subjects were arbitrarily selected for use in this comparison of dosing between preterm neonates and term neonates as the results are not expected to depend on the neonate sex. The PK simulation results described in **Section 4.4.7** were used to represent the PK exposures for term infants at the proposed dosing. The q12h dosing interval was selected for maintenance dosing. The q8h dosing interval was not assessed in this exercise as the q8h and q12h dosing intervals are expected to produce comparable PK profiles (see **Section 4.4.7**).

Figure 2 shows the results of preterm neonates versus term neonates receiving one or two loading doses at the proposed dose levels and the proposed maintenance dose. The plots in **Figure 2** demonstrate that the proposed dosing produces exposures in preterm neonates that within the range of values in the term neonate population for one or two loading doses. For two loading doses, the predicted preterm neonate exposure is generally above the median exposure in term neonates.

The reviewer explored the effect of administering the second loading dose at a reduced dose level. The plots in **Figure 3** show a comparison of the proposed dosing in term neonates with preterm neonates with a reduced second loading dose (first loading dose

¹⁵ Touw DJ, Graafland O, Cranendonk A, Vermeulen RJ, van Weissenbruch MM. Clinical pharmacokinetics of phenobarbital in neonates. *Eur J Pharm Sci.* 2000 Dec;12(2):111-6.

¹⁶ <https://peditools.org/fenton2013/>

¹⁷ Chou JH, Roumiantsev S, Singh R. PediTools Electronic Growth Chart Calculators: Applications in Clinical Care, Research, and Quality Improvement. *J Med Internet Res.* 2020 Jan 30;22(1):e16204.

20 mg/kg, second loading dose 10 mg/kg) and an identical maintenance dosing regimen. The plots in **Figure 3** indicate that when modifying the proposed dosing regimen so that, if a second loading dose is administered to preterm neonates, a 50% reduction in the second loading dose (from the proposed 20 mg/kg level to 10 mg/kg), the preterm neonate exposure is still within the range values for the term neonate exposure at the proposed dosing. As such, in instances where a second loading dose is warranted, the PK simulations support an optional reduction of 50% (from 20 mg/kg to 10 mg/kg) for the second loading dose when administering to preterm neonates. The final label language regarding the dosing in preterm neonates reflect discussions within the review team and with the Applicant that will continue after this review is archived.

4.5. OCP Genomics Team Review

NDA/BLA Number	215910
Submission Date	02/17/2022
Applicant Name	Sun Pharma Advanced Research Company, Ltd.
Generic Name	Phenobarbital
Proposed Indication	Treatment of neonatal seizures
Primary Reviewer	Hobart Rogers Pharm.D., Ph.D.
Secondary Reviewer	Sarah Dorff Ph.D.

EXECUTIVE SUMMARY

The Applicant submitted an NDA for phenobarbital in the treatment of neonatal seizures using a new formulation that does not contain benzyl alcohol, which can be toxic to neonates. The Applicant proposed labeling (b) (4)

(b) (4)

(b) (4). The findings of this review conclude that the Applicant's proposed labeling (b) (4) is not adequately supported by the literature and is not warranted. In addition, the findings of this review also conclude that (b) (4) (b) (4) the proposed labeling is not warranted (b) (4)

1 Background

The Applicant (Sun Pharma Advanced Research Company, Ltd) submitted an NDA for phenobarbital in the treatment of neonatal seizures. The Applicant has a reformulated phenobarbital solution that does not utilize benzyl alcohol, which can be toxic to neonates. Phenobarbital is primarily metabolized via CYP2C9 with some contribution from CYP2C19, CYP2E1, and UGT. The Applicant's proposed labeling includes a (b) (4)

(b) (4). No pharmacogenomic information is currently present in drug labeling for phenobarbital for any approved indications.

2 Submission Contents Related to Genomics

The Applicant has submitted the following labeling recommendations:

The Applicant did not submit any new clinical studies investigating pharmacogenetic interactions with phenobarbital. The Applicant has reviewed published literature (b) (4) (specific references provided in section 3.1.1). A literature search was performed to identify additional references describing pharmacokinetics of phenobarbital in neonates as well as the effect of CYP2C9 and CYP2C19 genotypes.

3 Key Question and Summary of Findings

3.1 Are genetic variants in either CYP2C9 or CYP2C19 likely to significantly influence the pharmacokinetics of phenobarbital in the neonatal population?

3.1.1 Applicant's Analysis

The Applicant has not conducted any new pharmacogenetic investigations (b) (4)

The Applicant provides the following summary of the literature related to CYP2C pharmacogenetics and ontogeny:

2.7.2.5.5 Summary of Clin Pharm: Studies have examined genetic polymorphism in CYP2C9 and/or CYP2C19 on the disposition of phenobarbital in adults and neonates (PMIDs: 11294510, 24674673, 22331680, 10805060, 29283396). In Japanese subjects, overall disposition kinetics of phenobarbital were not different

between extensive metabolizers and poor metabolizers of S-mephenytoin, and therefore polymorphic CYP2C19 seems to have no major clinical implications (PMIDs: 11294510, 10805060). Similarly, the effect of CYP2C19 polymorphism on the PK of phenobarbital in neonates did not show any meaningful differences in clearance, the volume of distribution, or serum concentrations in neonates with wild type, extensive metabolizers or poor metabolizers (PMID: 28506869). Overall, due to the multiple pathways of the drug elimination involved, the possible effect of these polymorphisms is expected to be minor if any.

2.7.2.2.2 Metabolism and Excretion: At birth, expression of CYP2C is negligible, increases rapidly up to 40% expression within 2 weeks, and may take 1-2 years to reach the expression in adults (PMIDs: 11294510, 11169155, 24674673). The extent of p-hydroxylation is the same between newborn patients and adults, whereas glucosidation is minimal at birth and takes a few weeks to mature (PMIDs: 626078, 3383723). However, poor conjugating capacity in the newborn may not have any serious consequences as phenobarbital has major alternative routes of excretion exists (unchanged drug and unconjugated metabolite).

3.1.2 Reviewer's Analysis

The reviewer conducted an independent literature review of phenobarbital in neonates and has summarized the findings of select publications of note below.

Review of Selected Literature:

Ontogeny:

Phenobarbital is primarily metabolized by CYP2C9 and to a lesser extent CYP2C19, CYP2E1, and UGT. Phenobarbital is also a known inducer of CYP2C19.

The Applicant defines the neonatal period as the day of birth plus 27 days for full-term infants and as the day of birth through the expected date of delivery plus 27 days for preterm infants.

The ontogeny of both CYP2C9 and CYP2C19 activity changes during the neonatal period. Namely, expression of both CYP2C9 and CYP2C19 is negligible at birth but increases rapidly during the first few weeks of life.

In a review of the literature, Hines demonstrated that expression of CYP2C9 and CYP2C19 increase over time in neonates (defined as from birth to 30 days in Figure 1 below) with CYP2C9 maximally at 40% of adult expression levels and CYP2C19 less than 15% of adult expression levels (PMID: 17936930). Moreover, this same paper identified that "in liver samples obtained from donors who succumbed between one and ten years of age, CYP2C9 and 2C19 expression remained at levels that were 40–50% of those reported in adults." Thus, indicating that CYP2C9 and 2C19 is still not fully expressed by age two.

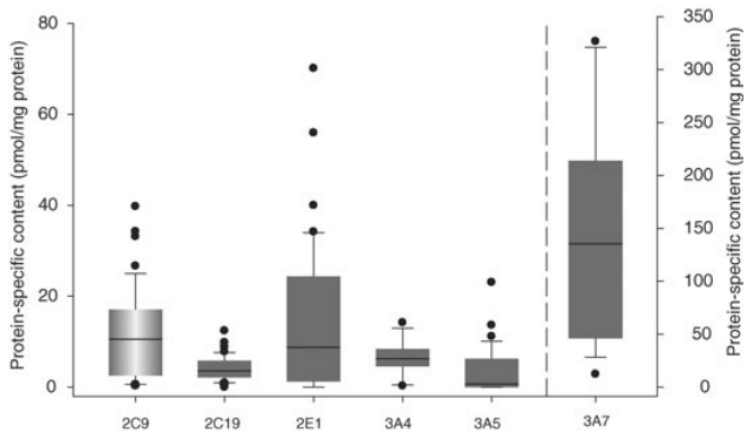


Figure 1. Expression of key hepatic cytochrome P450 (CYP) enzymes in the neonatal liver. A box and whisker plot of CYP2C9, CYP2C19, CYP2E1, CYP3A4, CYP3A5, and CYP3A7 specific content is depicted. The boxes represent the 25th to 75th percentiles and the horizontal bar the median of the data. The vertical bars represent 10th to 90th percentiles. Outliers (circles) were defined as having specific contents outside 1.5 times the 25th or 75th percentiles.

Source: Figure 1 from Hines, RN PMID: 17936930

Pharmacogenetics:

One study evaluated CYP2C19 genotype effects on phenobarbital pharmacokinetics. Lee et al., (PMID: 22331680) in a study of 52 neonates and infants with seizures, found no significant differences between CYP2C19 extensive metabolizers (EMs; now referred to as normal metabolizers [NMs]) and poor metabolizers (PMs) in the clearance or volume of distribution of phenobarbital (Table 1). Moreover, the addition of CYP2C19 genotyping to PK models did not improve the dosing strategies in the neonates in this study. The study did not collect CYP2C9 genotype in these patients. While this study demonstrated no impact of CYP2C19 genotype on phenobarbital pharmacokinetics, it has the following limitations ^{(b) (4)}:

1. The study excluded eight neonates in the early neonatal period (defined by first week of birth) thus it is not possible to rule out differences in that period.
2. The remaining 42 patients had an age range of 8 days to 6 months and were divided into two groups by age (8 days to 3 months, and 4-6 months). Both groups contain infants that are outside the neonatal period. Infants outside the range of neonates made up the majority of the study populations, thus heavily influencing the results.

Table 1. Pharmacokinetic analysis by CYP2C19 genotype in infants in group 1.

	Wild type (*1/*1)	EMs (*1/*2, *1/*3)	PMs (*2/*2, *2/*3)	p Value
Number	17	10	4	
PB concentration, µg/ml†	29.6 (17.0–38.2)	27.8 (19.9–61.8)	24.8 (20.3–33.7)	0.614
Vd, litres/kg†	0.85 (0.58–1.1)	0.92 (0.47–1.34)	0.60 (0.60–0.99)	0.235
CL, ml/kg/ht	6.5 (4.2–13.1)	6.6 (5.1–9.9)	7.0 (4.4–7.9)	0.761

†Median (range).

CL, clearance; EM, extensive metaboliser; PB, phenobarbital; PM, poor metaboliser; Vd, volume of distribution.

Three studies have evaluated CYP2C19 genotype effects on phenobarbital pharmacokinetics in adults, all of which were conducted in Japan). Goto et al., (PMID: 17304159) in a population of 79 adult Japanese patients with epilepsy, used modeling to show that CYP2C19 metabolizer status did not affect the clearance of phenobarbital but did find a difference between CYP2C9 *1/*3 (intermediate metabolizers, IMs) compared to *1/*1 (NMs). Specifically, the authors identified a 48% lower clearance comparing CYP2C9 IMs to NMs. However, it is not appropriate to extrapolate either of these results to a neonatal population given the variable expression of CYP2C in neonates. This study was not cited by the Applicant.

The following two studies were cited by the Applicant (b) (4):

Mamiya et al. (PMID: 10805060) also evaluated CYP2C19 genotype in 74 Japanese patients with epilepsy. They identified an approximate 18% lower clearance of phenobarbital in the PMs (*2/*2, *2/*3) compared to the NMs (*1/*1) and IMs (*1/*2, *1/*3). Patients with CYP2C9 variants other than NMs were excluded from this study. While the authors did find a gradient in clearance of phenobarbital with reduced metabolizer status, these results are also not appropriate to extrapolate to a neonatal population given the variable expression of CYP2C19 in neonates.

Hadama et al. (PMID: 11294510) demonstrated in ten healthy Japanese adult volunteers that CYP2C19 had no major impact on the kinetics of phenobarbital between EMs (NMs) and PMs. However, it is not appropriate to extrapolate these results to a neonatal population given the variable expression of CYP2C19 in neonates.

The Applicant also cited PMIDs: (24674673, 29283396) however, it is unclear how both of these review articles were utilized (b) (4). Fanni et al., (PMID: 24674673) summarized the role of CYP450 genetic metabolism in neonates, however this paper only made a cursory note to the CYP2C family having limited expression in the neonatal period and rather focused on the ontogeny of CYP3A enzymes. Daly et al., (PMID: 29283396) conducted an extensive review of the pharmacogenomics of CYP2C9, however it primarily only references CYP2C9 and phenobarbital in relation to enzyme induction. It does not examine any neonatal CYP2C9 expression.

4 Summary and Conclusions

Our findings (b) (4) from the literature indicate that expression of CYP2C9 and CYP2C19 in children up to age ten only reaches 40-50% of adult levels. Moreover, studies indicate that neonatal CYP2C9 or CYP2C19 expression is variable and at most approaches 40% and 15% of adult levels during the neonatal period respectively.

Given the ontogeny, it is possible that CYP2C9 or CYP2C19 polymorphisms, if an effect existed, could influence the metabolism of phenobarbital in neonates. Most pharmacogenetic studies related to CYP450 metabolism of phenobarbital were conducted in adults. The Applicant references one pediatric study that did not find a significant impact of CYP2C19 polymorphisms on several pharmacokinetic parameters of phenobarbital. However, the neonate group included patients over 1 month of age and neonates ≤ 8 days of age were excluded (PMID: 22331680).

The effect of CYP2C9 polymorphisms were not evaluated in the pediatric study and the effect is unknown.

5 Recommendations

The Applicant has submitted information related to CYP2C19 and CYP2C9 pharmacogenetic interactions with phenobarbital. The assertions are of limited clinical relevance. We recommend revising the labeling as summarized below.

5.1 Post-marketing studies

None.

5.2 Labeling recommendations

12.3 Pharmacokinetics

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADARSH S GANDHI
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MICHAEL A BEWERNITZ
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HOBART ROGERS
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SARAH E DORFF
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SREEDHARAN N SABARINATH on behalf of GOPICHAND GOTTIPATI
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