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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
 Amy Kao, MD
 NDA 215910
 Sezaby (phenobarbital sodium)

CLINICAL REVIEW

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Established/Proper Name	Phenobarbital sodium
(Proposed) Trade Name	Sezaby
Applicant	Sun Pharma Advanced Research Company, Ltd.
Dosage Form(s)	100 mg/10 ml single-use vial for intravenous injection
Applicant Proposed Dosing Regimen(s)	• Loading Dose: 20 mg/kg infused intravenously over 15 minutes. If seizures persist or recur after completion of the initial loading dose, a second infusion of 20 mg/kg is administered over the subsequent 15 minutes for a total loading dose of 40 mg/kg. • Maintenance Dose: 1.5 mg/kg intravenously every 8 hours (total daily dose 4.5 mg/kg/day) for 5 days.
Applicant Proposed Indication(s)/Population(s)	Treatment of neonatal seizures
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of neonatal seizures in term and preterm infants

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No figures.

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Glossary

AC	advisory committee
AE	adverse event
ALAS1	δ -aminolevulinic acid synthase 1
AR	adverse reaction
ARIA	active risk identification and analysis
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	contraindication
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
cvEEG	continuous video EEG
DAIDS	Division of AIDS
DEPI-I	Division of Epidemiology 1
DPMH	Division of Pediatric and Maternal Health
DPV	Division of Pharmacovigilance
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
EMA	European Medicines Agency
FD	Financial disclosure form
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
GABA	gamma aminobutyric acid
GCP	good clinical practice
hERG	human ether-a-go-go related gene
HIE	hypoxic ischemic encephalopathy
ICH	International Council for Harmonization
ILAE	International League Against Epilepsy
IND	Investigational New Drug Application
IR	Information Request
IRT	Interdisciplinary Review Team
ITT	intention to treat
IV	intravenous

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LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat
NCE	new chemical entity
NDA	new drug application
NICU	neonatal intensive care unit
NME	new molecular entity
NZ	New Zealand
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OPT	Office of Pediatric Therapeutics
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PHB	phenobarbital
PHT	phenytoin
PI	principal investigator
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetic
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
q8	every 8
q12	every 12
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
REDcap	Research Electronic Data Capture
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens-Johnson syndrome
SPARC	Sun Pharma Advanced Research Company Ltd
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
UCSD	University of California—San Diego Medical Center
UCSF	University of California San Francisco
US	United States
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Phenobarbital (PHB) is a barbiturate which was first synthesized in 1911 and marketed in 1912 by F. Bayer and Co, under the trade name Luminal for its hypnotic (sleep-inducing) properties. Its antiseizure properties were recognized shortly thereafter and PHB has been used for the treatment of seizures since the early 1920's. It is an agonist of the gamma aminobutyric acid (GABA) receptor and therefore increases GABA-mediated inhibition. Phenobarbital has been used historically for sedation (e.g., preoperative sedation) and for the treatment of insomnia and seizures. Because PHB was marketed before the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 required new drugs to be approved for safety before marketing, PHB as a single drug has not been previously submitted in a New Drug Application (NDA) to the Food and Drug Administration (FDA) and therefore has not been approved. There were NDAs for multi-ingredient, phenobarbital-containing products between 1938 and 1962, the year that the Kefauver-Harris Amendments to the FD&C Act were passed and began requiring new drugs to be approved for safety and efficacy before marketing, but no phenobarbital-containing products have been approved after 1962.

The currently marketed formulation in the United States (US) is manufactured and marketed by Hikma Pharmaceuticals (parent company of its US subsidiary, West-Ward Pharmaceuticals Corp). The Applicant for this NDA 215910, Sun Pharma Advanced Research Company Ltd (SPARC), submits this NDA for its formulation, phenobarbital sodium for injection (SEZABY), which has the same active ingredient as the West-Ward product. The proposed indication is the treatment of neonatal seizures, for which the proposed dosing regimen is a loading dose of 20 mg/kg infused intravenously over 15 minutes, followed by a second infusion of 20 mg/kg if seizures persist or recur 15 minutes after completion of the initial loading dose, and by maintenance dosing of 1.5 mg/kg every 8 hours (total daily dose 4.5 mg/kg/day) for 5 days.

In NDA 215910, the proposed product is a sterile single-dose 10-ml vial which contains 100 mg of phenobarbital sodium as a lyophilized powder and does not contain benzyl alcohol, a preservative, or propylene glycol, a solvent. The lyophilized phenobarbital powder is to be reconstituted with 10 ml of 0.9% sodium chloride to give a final concentration of 10 mg/ml.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for PHB for the treatment of neonatal seizures is based on positive results from a single adequate and well controlled trial (NEOLEV2) and on demonstration of bioequivalence between the proposed product and marketed product through a single-dose crossover comparative bioavailability study in healthy adults (PHEN-20-01). NEOLEV2 was an investigator-initiated, randomized, double-blind, active-controlled study in which the available marketed (West-Ward) product was administered. NEOLEV2 demonstrated that PHB met a

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clinically meaningful endpoint in a population with a life-threatening and debilitating disease with unmet need, at a robust, statistically-significant level, which was consistent across pertinent subgroups and across study centers.

The long history of experience with and the substantial use of PHB in the treatment of neonatal seizures¹ provide a supportive context for the safety and efficacy demonstrated by NEOLEV2. The level of evidence provided is adequate to support the conclusion that PHB is effective for the treatment of neonatal seizures.

1.3. Benefit-Risk Assessment

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¹ Yasiry Z and Shorvon SD (2012). How phenobarbital revolutionized epilepsy therapy: The story of phenobarbital therapy in epilepsy in the last 100 years. *Epilepsia* 53(Suppl 8):26-39.

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Benefit-Risk Integrated Assessment

Neonatal seizures represents a serious condition which has been estimated to occur in 1 to 5 of every 1000 live births, although higher rates have been described in preterm infants, in low-income countries, and when electroencephalography (EEG) is used in addition to clinical observation for diagnosis. Neonatal seizures are associated with significant morbidity and mortality. Mortality has been reported in up to 20% of patients; epilepsy has been reported to develop in 13-33% of patients; and neurodevelopmental disabilities such as intellectual disability, cerebral palsy, and global developmental delay have been reported to occur in 40-55% of patients. Although the underlying cause of the neonatal seizures is thought to be the main determining factor for these consequences, there are other influencing factors, such as the response to treatment, the need for more than one medication to treat the neonatal seizures, the presence of recurrent or prolonged seizures, the degree of seizure burden, and the use of therapeutic hypothermia for hypoxic ischemic encephalopathy (HIE).

There are currently no FDA-approved drugs for the treatment of neonatal seizures. Phenobarbital (PHB), a gamma aminobutyric acid receptor agonist, has been used (off-label) to treat seizures since the 1920's and has been used as first-line treatment for neonatal seizures for at least 4 decades, but has not been approved for efficacy. Most published studies on PHB have been open-label, uncontrolled, observational studies, which may not have been performed with EEG confirmation of seizures and/or were performed before the current standard use of therapeutic hypothermia for HIE. The single adequate and well-controlled efficacy trial submitted in this application, the NEOLEV2 study, was a randomized, double-blind, active-controlled clinical trial (the comparator was treatment with levetiracetam [LEV]). One hundred and six neonates with seizures who were younger than 14 days of age with a gestational age at birth between 36 and 44 weeks were randomized (42 to the PHB arm and 64 to the LEV arm; although 12 total subjects did not have electrographically-confirmed seizures at baseline and were excluded from any efficacy analyses). Subjects could receive up to 2 loading doses of the treatment they were randomized to (separated by 15 minutes), followed by maintenance dosing every 8 hours for 5 days. Subjects who did not respond to the treatment they were randomized to would then receive both treatments for the duration of the trial.

NEOLEV2 demonstrated a clinically meaningful and statistically significant difference in the percentage of subjects who met the primary endpoint of seizure freedom for at least 24 hours without the need for a second drug for treatment of their seizures (72.7% of the PHB group compared to 24.6% of the LEV group). Despite the relatively small size of the population studied, this was a robust effect size which persisted across subgroup analyses of subjects with and without HIE, subjects who were treated or not treated with hypothermia, and subjects who were treated at US sites and non-US sites. A statistically- and clinically-significantly greater percentage of PHB-treated subjects also demonstrated 48 hours of seizure freedom (an analysis also controlled for Type I error).

In addition to the 1.5 mg/kg/dose every 8-hour maintenance regimen for up to 5 days that was studied in the NEOLEV2 study, modeling and simulation analyses support maintenance dosing with doses of 2.25 mg/kg every 12 hours (which is the dosing frequency typically used in clinical practice). Modeling and simulation analyses also support the safety of dosing in preterm infants (not enrolled in the NEOLEV2 study).

NEOLEV2 identified adverse events (AEs) of PHB of abnormal respiration, hypotension, sedation, and feeding disorder (consistent with the AEs commonly associated with PHB treatment in the published literature). These risks are monitorable, particularly in the intensive care setting where patients with neonatal seizures typically receive treatment and will be described in labeling. Published literature and AE reports with currently marketed formulations of PHB suggest that exacerbation of acute porphyria, serious hypersensitivity reactions (including drug reaction with eosinophilia and systemic symptoms [DRESS], Steven-Johnson's syndrome [SJS], anaphylaxis), and infusion- or injection-site reactions, are also possible, and these risks will be described in labeling. Product labeling will also include language related to concomitant use with opioids, dependence and withdrawal reactions, and abuse, misuse, and addition with unapproved use in adolescents and adults. Finally, the risk of suicidal ideation and behavior common to labeling for all drugs approved for the treatment of seizures (in this case, with unapproved use in adolescents and adults), will also be included in labeling.

In the context of the frequent neurodevelopmental morbidity of neonatal seizures and weighed against the neurodevelopmental and systemic risks of ongoing neonatal seizures, the need for an assessment of the potential negative effects of PHB on neurodevelopmental outcome should not prevent the approval of Sezaby for the treatment of neonatal seizures but will be addressed as a postmarketing requirement (PMR). In addition, further characterization of Sezaby's effect on QTc should not prevent its approval for the treatment of neonatal seizures but will be addressed as a PMR.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The neonatal brain is particularly vulnerable to seizures in response to insults; neonatal seizures affect 1 to 5 of every 1000 live births. Hypoxic ischemic encephalopathy (HIE) is the most common cause of neonatal seizures. • Risk factors for the development of post-neonatal epilepsy and of long-term neurologic impairment, which are independent from the underlying	Neonatal seizures are a serious condition that often leads to poor short- and long-term outcomes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cause of the neonatal seizures, include the response to seizure treatment, the recurrence and duration of seizures, and the amount of seizure burden.	
Current Treatment Options	• There are no approved treatment options for neonatal seizures. • Phenobarbital (PHB) has been used as first-line treatment (off-label) for neonatal seizures for a significant time, despite a paucity of controlled clinical trial data supporting its efficacy.	There are no approved treatments for neonatal seizures. Marketed unapproved formulations of PHB are the standard-of-care for neonatal seizures; however, this use has not been supported by rigorous clinical trial data.
Benefit	• The NEOLEV2 study was a randomized, double-blind, active-controlled trial that evaluated the efficacy of intravenous PHB in comparison to levetiracetam (LEV) in subjects with electrographic-confirmed neonatal seizures. • Randomized subjects received an initial infusion over 15 minutes of either 20 mg/kg PHB or 40 mg/kg LEV. If electroencephalographic seizures persisted or recurred any time after 15 minutes after the initial infusion was completed, an additional infusion of the same treatment was given (the dose of a second infusion for both drugs was 20 mg/kg infused over 15 minutes). If seizures persisted or recurred any time after 15 minutes after the second infusion was completed, the subject was also given the alternate treatment. After a loading dose(s) of a treatment was given (i.e., PHB or LEV), maintenance dosing of that treatment was continued, regardless of whether seizures subsided. Maintenance regimens of 1.5 mg/kg/dose PHB and/or 10 mg/kg/dose LEV were given via infusion every 8 hours	The findings from the NEOLEV2 study establish the efficacy of PHB for the treatment of neonatal seizures. In addition to the 1.5 mg/kg/dose every 8-hour maintenance regimen for up to 5 days that was studied in the NEOLEV2 study, modeling and simulation analyses also support maintenance dosing with doses of 2.25 mg/kg every 12 hours (which is the dosing frequency typically used in clinical practice). Modeling and simulation analyses also support dosing in preterm infants (not enrolled in the NEOLEV2 study).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and continued for up to 5 days. • The primary efficacy endpoint was electrographic seizure freedom for at least 24 hours without the need for a second drug for the treatment of the seizures. Seventy-three (72.7) percent of the PHB group met the primary endpoint, compared to 24.6% of the LEV group ($p < 0.001$). The findings of the primary endpoint were statistically significant across subgroups, including subjects with HIE or without HIE who were or were not treated with therapeutic hypothermia, and subjects treated at US sites and non-US sites. • The percentage of subjects who demonstrated electrographic seizure freedom for at least 48 hours without the need for a second drug for the treatment of their seizures was also higher in the PHB group (54.6%), compared to the LEV group (13.1%) [$p < 0.001$]. • The comparative bioavailability study PHEN-20-01 demonstrates the bioequivalence of the Applicant's formulation to the currently marketed West-Ward formulation, which was administered at the US sites in NEOLEV2. • Using the NEOLEV2 data, modeling and simulation of the total daily maintenance dose of PHB 4.5 mg/kg/day divided every 12 hours demonstrates comparable PHB concentration levels to the same total dose divided every 8 hours, which was the regimen administered in NEOLEV2 with the purpose of maintaining the blind with the active comparator LEV. • NEOLEV2 enrolled neonates who were 36 to 44 weeks gestation; 36 weeks is considered late preterm and 37 weeks or greater is considered term. Modeling and simulation of 2 loading doses of 20 mg/kg followed by 1.5 mg/kg every 8 hours in preterm infants	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrates similar PHB levels to those in term infants. In addition, modeling and simulation in preterm neonates of a 20 mg/kg load, followed by a 10 mg/kg second load demonstrates similar PHB levels to 2 loading doses of 20 mg/kg.	
Risk and Risk Management	• In the NEOLEV2 study, the most common adverse reactions (occurring in greater than 5% of subjects who received PHB only) were respiration abnormal, hypotension, sedation, and feeding disorder. • Respiration abnormal occurred in 25% of subjects who received PHB only, compared to 5% of subjects who received LEV only. No subjects discontinued from the study due to respiration abnormal; however, 1 subject who received PHB had a serious adverse event (SAE) of respiration abnormal. Respiration abnormal included but was not limited to apnea, meconium aspiration syndrome, and oxygen saturation abnormal. Neonates may have various presentations of abnormal respiration. • Hypotension occurred in 16% of subjects who received PHB only, compared to 0% of subjects who received LEV only. Four subjects (12.5%) who received PHB only had an SAE of hypotension. Hypotension was the reason for study withdrawal in 1 subject who received PHB only. • Sedation occurred in 16% of subjects who received PHB only, compared to 5% of subjects who received LEV only. Several subjects stopped maintenance dosing due to sedation. • Feeding disorder, which included the designation of subjects as receiving “nothing by mouth,” or active difficulty feeding, occurred in 16% of subjects who received PHB only, compared to 5% of subjects who received LEV only.	The risks associated with PHB are acceptable to support approval. The Sezaby PI will include a boxed warning and relevant WARNINGS AND PRECAUTIONS sections related to risks from concomitant use with opioids, dependence and withdrawal reactions, and abuse, misuse, and addition with unapproved use in adolescents and adults. Labeling will include WARNINGS AND PRECAUTIONS sections for porphyria, serious hypersensitivity reaction (including drug reaction with eosinophilia and systemic symptoms [DRESS], Steven-Johnson’s syndrome [SJS], anaphylaxis), and infusion- or injection-site reactions. Labeling will include a WARNINGS AND PRECAUTIONS sections for the risk of suicidal ideation and behavior common to labeling for all drugs approved for the treatment of

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	• The concern for potential negative effects of PHB on neurodevelopment and on QTc prolongation could not be assessed based on the submitted data. • There are risks which have been identified during the long history of PHB use which are rare but have been reported in the neonatal population. These include but are not limited to exacerbation of acute porphyrias, serious hypersensitivity reactions (including DRESS, SJS, anaphylaxis), and infusion- or injection-site reactions.	seizures (in this case, with unapproved use in adolescents and adults). The risk of long-term neurodevelopmental effects of PHB should be weighed against the significant systemic and neurologic risks of continuing seizures. A prospective assessment of the impact of PHB exposure during the neonatal period on long-term neurodevelopmental outcomes will be evaluated as a PMR. An evaluation of any effect of PHB on QTc prolongation will also be assessed with a PMR.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application. This is appropriate because the objective of the NEOLEV2 study was to assess efficacy and safety of treatment administered for the acute management of neonatal seizures in the NICU and therefore used outcome measures based on electroencephalograms (EEGs) and adverse events (AEs) documented by healthcare providers.

2. Therapeutic Context

Neonatal seizures are seizures which occur during the first 28 days of life. The most recent (2017) International League Against Epilepsy (ILAE) seizure classification considers neonatal seizures to be distinct from seizures in older children and adults. There are differences in the incidences, causes, manifestations, and diagnostic and treatment approaches between neonatal seizures and seizures in older individuals. Neonatal seizures tend to be subtle or focal, rather than generalized, relating to lack of myelination. Limbic system, midbrain, and brain stem development are also more advanced than cerebral cortical development at this age.

Neonatal seizures are often electrographic-only (seen on EEG but without clinical signs and often described as “subclinical”), and movements and behaviors that are suspicious for seizures are often not seizures. This phenomenon is described as clinical-electrophysiologic disconnect or uncoupling. Certain therapeutic interventions in neonates have been demonstrated to increase the uncoupling of clinical and electrographic signs of neonatal seizures, and cause electroclinical seizures to become electrographic-only seizures. These include therapeutic hypothermia, which became standard-of-care treatment for hypoxic ischemic encephalopathy (HIE) after the results of multicenter randomized controlled trials (RCTs) were published in the first decade of the 2000’s, and drugs that treat neonatal seizures. Therapeutic hypothermia also decreases seizure burden.

The incidence of seizures in general is highest during the neonatal period. Neonatal seizures have been estimated to occur in 1 to 5 of every 1000 live births, with higher rates in preterm infants and in low-income countries. The incidence of neonatal seizures increases with decreasing gestational age and birth weight and with increasing severity of illness. The most common causes of neonatal seizures include HIE (caused by inadequate blood flow and oxygen delivery to the brain), ischemic stroke, intracranial hemorrhage, central nervous system infection, cortical malformation, acute or inborn errors of metabolism, and genetic etiologies. The reported incidence and prevalence of neonatal seizures has also been higher in studies in which the diagnosis of neonatal seizures is based not on clinical observation alone but include EEG.

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Motor manifestations of neonatal seizures include focal clonic, focal tonic, myoclonic, and epileptic spasms. Sequential seizures may be seen, in which a sequence of clinical features occur in a given seizure, sometimes with changing lateralization. Subtle clinical seizures may be characterized by tonic eye movements/deviation; motor automatisms such as lip smacking, swimming, and bicycling; behavioral arrest; and autonomic changes such as heart rate and blood pressure changes and apnea. The movements within the seizures may be categorized as focal, multifocal, bilateral asymmetric, and bilateral symmetric. Continuous EEG monitoring is necessary to reliably detect neonatal seizures and monitor treatment effect; expense and real-time monitoring and interpretation of continuous EEGs are challenges.^{2,3} Because there are electrographic features which are unique to neonatal seizures as compared to seizures in older infants and children, personnel who are responsible for interpreting neonatal EEGs must have appropriate training and experience.

Regarding the short-term clinical course of the seizures, neonatal seizures which are due to an acute brain insult typically stop after the acute period, and in those patients who develop post-neonatal epilepsy, there may be a latent period of variable length. Therefore, after acute seizures cease, some practitioners withdraw the medication used to treat the seizures after a few days to a few months. Guidelines regarding duration of acute treatment do not exist; it is unclear whether long-term use of drugs for neonatal seizures prevents development of epilepsy, and there has been concern of negative effects on the developing brain, particularly with PHB.

Regarding the overall clinical course, mortality occurs in up to 20% of patients with neonatal seizures and occurs at a higher incidence in preterm infants. Later development of epilepsy has been reported to occur in 13-33% of patients with neonatal seizures. Neurodevelopmental disabilities occur frequently in patients with neonatal seizures, including global developmental delay, cerebral palsy, and intellectual disability, which have been reported to occur up to a frequency of 55%, 43%, and 40%, respectively. Characterization of prognostic factors for the outcome of neonatal seizures has been pursued, but the magnitude of contribution of and the independence of the effect of various factors has not been completely defined. It appears that the type and severity of the underlying etiology is one of the main prognostic factors for long-term sequelae. However, the response to therapy, the presence of recurrent or prolonged seizures, and the degree of seizure burden (defined as electrographic seizure seconds in a given period) appear to have independent effects on the development of post-neonatal epilepsy and on neurodevelopmental outcome beyond those due to the underlying etiology. Other

² Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E et al (2017). Operational classification of seizure types by the International League Against Epilepsy: Position paper of the ILAE commission for classification and terminology. *Epilepsia* 58(4): 522-530.

³ Pressler RM, Cilio MR, Mizrahi EM, Moshe SL, Nunes ML et al (2021). The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE task force on neonatal seizures. *Epilepsia* 62: 615-628.

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influencing factors include therapeutic hypothermia, need for more than one medication to treat the neonatal seizures, abnormal neuroimaging, multifocal (versus focal) seizures, spread of seizure to the contralateral hemisphere, and persistently abnormal EEG background. In turn, the efficacy of a drug for the treatment of neonatal seizures in an individual patient may also be affected by these factors which influence longer-term outcome.^{4,5, 6, 7}

2.1. Analysis of Current Treatment Options

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⁴ Kang SK and Kadam SK (2015). Neonatal seizures: impact on neurodevelopmental outcomes. *Front Pediatr* 3:101.

⁵ Pisani F, Spagnoli C, Falsaperla R, Nagarajan L, and Ramantani G (2021). Seizures in the neonate: A review of etiologies and outcomes. *Eur J Epilepsy* 85: 48-56.

⁶ Shellhaas R (2020). Etiology and prognosis of neonatal seizures. In JF Dashe (Ed), UpToDate. Retrieved May 18, 2022, from <https://www.uptodate.com/contents/etiology-and-prognosis-of-neonatal-seizures>.

⁷ Glass HC, Soul JS, Chang T et al (2021). Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. *JAMA Neurol* 78(7):817-825.

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For the purposes of this review, neonatal seizures which necessitate specific treatments, such as neonatal seizures due to correctable electrolyte disturbances (e.g., hypocalcemia, hypoglycemia) are excluded. Treatment may also be tailored to a diagnosis of a particular inborn error of metabolism, or to a genetic mutation associated with infantile epilepsy, if appropriate testing is available and performed.

For the treatment of neonatal seizures, there are currently no FDA-approved products; therefore, all drugs which are used in the treatment of neonatal seizures are used off-label. PHB has been used in the management of neonatal seizures since the 1970s (based on earliest citations found by this reviewer) and is considered the drug of first choice for the treatment of neonatal seizures, based predominantly on clinical experience, observational studies, and a limited number of randomized trials. The World Health Organization (WHO) recommends that PHB be used as first-line therapy for the treatment of neonatal seizures; this recommendation was classified as a strong recommendation, which was based on very low quality of evidence.⁸ The next most commonly-used first-line therapy for neonatal seizures is phenytoin (PHT) or fosphenytoin. Challenges with PHT include poor enteral absorption in neonates, a non-linear PK profile, and hepatic metabolism. An overlying goal of treating neonatal seizures is to prevent further neuronal damage and associated poor neurodevelopmental outcomes. However, animal model studies of many drugs used to treat seizures, including PHB and PHT, in developing animal brains have demonstrated increased apoptotic neurodegeneration at plasma concentrations relevant for seizure control in humans.⁹ There is also concern for potential negative cognitive effects in clinical studies of many drugs used to treat seizures, including PHB.^{10,11}

RCTs which assess treatments for neonatal seizures in the setting of current standard of care for HIE (therapeutic hypothermia) are sparse. Painter et al (1999) was a randomized controlled trial which randomized neonates to receive either PHB or PHT, followed by the other drug if seizures persisted. Efficacy rates, based on EEG monitoring, were similar between the 2 drugs: 43% of neonates who were randomized to PHB had seizures controlled whereas 45% of neonates who were randomized to PHT had seizures controlled. A total of 57% of neonates had seizure control after receiving PHB followed by PHT and a total of 62% of neonates had seizure

⁸ World Health Organization (2011). Guidelines on Neonatal Seizures.

⁹ Bittigau P, Siffringer M, Genz K et al (2002). Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. *Proc Natl Acad Sci USA* 99(23):15089-15094.

¹⁰ Reinisch JM, Sanders SA, Mortensen E, and Rubin DB (1995). In utero exposure to phenobarbital and intelligence deficits in adult men. *JAMA* 274:1518-1525.

¹¹ Farwell JR, Lee YJ, Hirtz DG et al (1990). Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. *N Engl J Med* 322:364-369.

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control after receiving PHT followed by PHB. The trial, however, was performed prior to the use of hypothermia.¹²

Other medication options include benzodiazepines such as lorazepam and midazolam; these are typically used in the initiation of acute treatment prior to the availability and administration of a longer-acting medication, or third-line as infusions. Medications that are typically administered as second-line therapies after failure of PHB include fosphenytoin, LEV, continuous infusion of midazolam, and lidocaine. LEV has been used frequently, due to its availability as an intravenous (IV) formulation, lack of side effects seen in older children and adults, and findings of reduction of neuronal apoptosis and possible neuroprotection in rodent models.¹³ Subsequent third-line therapies have included drugs such as topiramate, bumetanide, lorazepam, midazolam, lidocaine, and oxcarbazepine.

In general, treatments currently used for neonatal seizures are based on clinical consensus, with sparse evidence of robust efficacy and sparse data regarding adverse effects on the developing brain.

3. Regulatory Background

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¹² Painter MJ, Scher MS, Stein AD et al (1999). Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med*; 341:485-489.

¹³ Shellhaas R (2022). Treatment of neonatal seizures. In JF Dashe (Ed), UpToDate. Retrieved May 5, 2022, from <https://www.uptodate.com/contents/treatment-of-neonatal-seizures>.

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3.1. U.S. Regulatory Actions and Marketing History

NDA 215910 is a Type 3 NDA, per the OPQ NDA Classification Codes, i.e., an application for a new dosage form of an active ingredient that has been approved or marketed in the United States by the same or another applicant but in a different dosage form. Although the Regulatory Program Manager filing review dated April 5, 2022, and the product quality filing review dated April 29, 2022, both identify the NDA as a Type 7 NDA, upon further consideration, the NDA was reclassified as a Type 3 during the review cycle. This change was made because FDA concluded that the NDA does not meet the definition of a Type 7 NDA because it does not “contain an active moiety that has not been previously approved in an application but has been marketed in the United States” (see CDER’s Manual of Policies and Procedures 5018.2, NDA Classification Codes). As noted in the OPQ NME/NCE Questionnaire dated September 19, 2022, there were NDAs for PHB-containing products that became effective before 1962 (for example, NDA 000597 for Phenobarbital and Atropine).

Based on review of the DailyMed database (on July 11, 2022), phenobarbital sodium injection has been marketed by Hikma Pharmaceuticals USA, Inc (previously known as West-Ward Pharmaceuticals Corp. which was acquired by Hikma Pharmaceuticals PLC in January 1991) since January 1971; by Cameron Pharmaceuticals beginning in February 2020; Nivagen Pharmaceuticals, Inc, beginning in September 2021; and BPI Labs LLC beginning in January 2022.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 132342 was submitted to FDA on June 1, 2020, with a Phase 1 comparative bioavailability study and was determined to be safe to proceed on July 1, 2020.

Significant interactions between FDA and the Applicant include the following:

- Type B Pre-IND written responses issued February 1, 2017: Limitations of the Applicant’s proposal to rely on published literature to support the safety and efficacy of its product were discussed. These limitations included the following: the majority of published studies were unblinded or single-arm studies that lacked control groups; the reliance on clinical identification of seizures without EEG confirmation could lead to overdiagnosis of seizures and lack of recognition of electrographic seizures which persist after resolution of clinical seizures; many published studies did not use therapeutic hypothermia which limits the ability to generalize their findings to current clinical standards; and published studies would not provide the degree of detail or original datasets required for independent analysis.
- October 2, 2019: Orphan Drug designation was granted for the treatment of neonatal seizures.
- Type C written responses issued November 1, 2019: In response to the Applicant’s

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proposal to provide data from the NEOLEV2 trial in addition to published literature to support an NDA 505(b)(2) application, the Agency noted that bioavailability/bioequivalence data to establish a PK bridge between the drug product used in the NEOLEV2 study would be needed. Reliance on studies described in the literature would also require establishment of a bridge to those studies. Long-term neurodevelopmental outcomes for neonates who received PHB would need to be characterized, either through the literature or future long-term studies.

- Type C written responses issued July 29, 2020: The Agency noted that if the Applicant were able to adequately describe the PK data collected in the NEOLEV2 study using population PK analyses, a further PK study in neonates might not be required. It was also noted that Painter et al (1999) could not be used as a study to demonstrate efficacy, due to the inability to access the data for independent analysis, due to its design limitations (single-blind, superiority design with failure to demonstrate superiority of PHB nor PHT), and due to the lack of use of therapeutic hypothermia.
- Type C teleconference meeting July 1, 2021: The Applicant had submitted a pre-NDA meeting request April 30, 2021. The meeting was converted to a Type C guidance because the content of the Applicant's background package was determined to be premature for a pre-NDA meeting. The Agency discussed that demonstrating an adequate PK bridge between the Applicant's and West-Ward formulations using study PHEN-20-01 might be sufficient to bridge to clinical safety data in the literature, and that the NEOLEV2 study safety data must also be reviewed. The clinical efficacy of the Applicant's product could not be supported by bridging to the West-Ward product in the literature because efficacy had not been established with that product. In addition, because "labeling" information from West-Ward's product was not previously reviewed nor approved by the Agency, it could not be relied upon for the proposed product label. The Applicant noted that it had provided resources to reproduce the NEOLEV2 data because the Applicant was not granted access to patient-level data, and that the NEOLEV2 principal investigator (PI) would submit the datasets, tables, listings, figures, and statistical analysis plan (SAP) to the PI's IND 109622. The Agency emphasized the need to access the NEOLEV2 study data in order to perform independent analyses, verify the raw datasets, and trace them back to the individual patient (i.e., Case Report Form [CRF]). The Agency noted that this process could require communication with the dataset holder, so recommended that the Applicant develop an algorithm for Agency inquiries during review about the datasets.
- August 4, 2021: Fast Track designation was granted.
- August 26, 2021: Rare Pediatric Disease designation for the treatment of neonatal seizures was granted.
- February 17, 2022: NDA 215910 was submitted. Priority Review was granted. This application was determined to not be eligible for a Rare Pediatric Disease Priority Review Voucher because the active ingredient has previously been approved in another application.
- During the review cycle, FDA inspection by the Office of Study Integrity and

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Surveillance (OSIS) of the drug product manufacturing site found significant deficiencies. On June 3, 2022, the Applicant submitted an amendment which provided for inclusion of Sun Pharmaceutical Medicare Limited (SPML)-Baska as an additional drug product manufacturing site. The Applicant subsequently withdrew Sun Pharmaceutical Industries Limited (SPIL) – Halol as a manufacturing site, and a Major amendment with 3-month clock extension was granted.

3.3. Foreign Regulatory Actions and Marketing History

Phenobarbital is authorized by the European Medicines Agency (EMA). On August 13, 2021, modification of an agreed pediatric investigation plan (originally issued December 6, 2019) to develop and study an ethanol-free PHB oral suspension was accepted; the indication was for treatment of all forms of epilepsy except absence seizures, in birth to less than 18 years of age.

A preservative-free formulation of PHB for injection was approved for marketing in December 2008 in Japan.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit of 4 of the 6 study sites was requested. These included University of California—San Diego Medical Center (UCSD), Rady Children’s Hospital—San Diego, Sharp Mary Birch Hospital for Women and Newborns in San Diego, and University of California San Francisco—Oakland (UCSF-Oakland) and were based primarily on the relatively large numbers of enrolled subjects. Inspections were not requested for Auckland Hospital, which is in New Zealand, and for Loma Linda University, which enrolled only 6 subjects, only 2 of whom were included in the Intention to Treat (ITT) population. No AEs were reported at UCSD and Loma Linda, which the ORA investigators were asked to verify. OSI’s overall assessment was that some protocol deviations were observed at each site, including documentation laxity, however the study appeared to have been conducted adequately, and the clinical data appeared to be reliable. Please see Dr. Sellers’ review for a complete discussion of OSI’s findings.

The Division of New Drug Study Integrity within OSIS determined that an audit of the clinical and analytical site for the comparative bioavailability study was not warranted because a Remote Record Review of the analytical site and inspection of the clinical site had been recently completed.

4.2. Product Quality

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Please see the OPQ review for any issues related to product quality.

4.3. Clinical Microbiology

Please see the OPQ review.

4.4. Nonclinical Pharmacology/Toxicology

The Nonclinical review concluded that the published literature information provided in this application is adequate for describing risks to the neonatal population, based on nonclinical studies. Please see the Nonclinical review for details.

4.5. Clinical Pharmacology

The pharmacokinetics (PK) of PHB in neonates is affected by the ontogeny of metabolizing enzymes, renal clearance, and other pharmacological functions. In general, PHB is largely cleared through hepatic metabolism (predominantly by the CYP2C9 enzyme), and partly cleared by renal excretion. PHB is moderately protein-bound and has a long half-life of approximately 5 days in adults and 1 to 2 weeks in neonates.

The Applicant demonstrated bioequivalence between the Applicant's PHB formulation and West-Ward's formulation by conducting a comparative bioavailability study in healthy volunteers. In addition, the NEOLEV2 study performed sparse PK sampling at 3 study sites (in San Diego) at baseline, 1 hour after starting treatment, at 24 hours, and at 48 hours. The Applicant used 3 population pharmacokinetic (popPK) models from the literature to simulate the PHB profile in neonates using the NEOLEV2 regimen and asserted that these models captured the observed NEOLEV2 data with the majority being within 95% of the prediction interval of the simulated data. This was confirmed by Office of Clinical Pharmacology (OCP) reviewers, Dr. Adarsh Gandhi and Dr. Michael Bewernitz (Division of Pharmacometrics).

Please see the Integrated OCP review for issues related to PK.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

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5.1. Table of Clinical Studies

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Table 1. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
111361- NEOLEV2 NCT- 01720667	Randomized, blinded, active- comparator- controlled efficacy, dose- escalation, and safety study	PHB arm: - At onset of seizure activity confirmed on EEG, PHB 20 mg/kg IV was given over 15 minutes; - If seizures persisted or recurred at any time > 15 minutes after the 1st loading dose completed, another PHB 20 mg/kg IV was given over 15 minutes; - If seizures persisted or recurred at any time > 15 minutes after the 2nd load was done, LEV 40 mg/kg IV was given over 15 minutes; - If seizures persisted or recurred at any time >15 minutes after 1st LEV load done, LEV 20 mg/kg IV was given over 15 minutes LEV arm was given a similar regimen to above, starting however with LEV 40 mg/kg IV, then LEV 20 mg/kg IV, then PHB 20 mg/kg IV, and PHB 20 mg/kg IV if seizures persisted/recurred. If a subject received a PHB load, maintenance dosing would start 8 hours after the first load at a dosing of 1.5 mg/kg/dose IV every 8 (q8) hours. If a subject received a LEV load,	Primary: percentage of neonates whose seizures were terminated for 24 hours following initiation of treatment and who did not go on to require a second anticonvulsant Key secondary: percentage of neonates whose seizures were terminated for 48 hours after initiation of treatment and who did not require a second anticonvulsant	Treatment was continued for 5 days after onset of EEG-confirmed seizure activity.	280 subjects underwent EEG monitoring 106 subjects were treated with study drugs after seizures were diagnosed on EEG	- Term infants with “corrected gestational age” 36 to 44 weeks - Postnatal age <14 days - Weight ≥ 2.2 kg - Serum creatinine ≤ 1.6 mg/dL - At risk for or having clinical or electrographic seizures	6 centers in 2 countries: - Auckland, NZ - San Francisco, CA, USA - Loma Linda, CA, USA 3 centers in San Diego, CA, USA PK samples were obtained at the 3 sites in San Diego

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		maintenance dosing would start 8 hours after the first load at a dosing of 10 mg/kg IV q8 hours.					
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							
PHEN-20-01	Randomized, open-label, 2-period, 2-sequence, crossover study	Single IV dose of 2 mg/kg PHB prepared from 2 parenteral formulations (SPARC as test treatment and West-Ward as reference treatment), given over 15 minutes, separated by at least 5 weeks	PK parameters including C_{max} , AUC_{0-t} , $AUC_{0-\infty}$, T_{max} , K_{el} , $T_{1/2}$, CL , V_z Adverse events	Single dose. Assessments were done 24 hours postdose, then participants were discharged. Assessments were done in-clinic through day 21 in each study period.	25 enrolled 24 completed, 1 of whom did not receive the second dose	• healthy male or female • 21 to 45 years • BMI 20.76 to 29.99 kg/m²	Clinical operations (b) (4) (b) (4) Minnesota, USA

CA = California; EEG = electroencephalogram; IV = intravenous; LEV = levetiracetam; NZ = New Zealand; PHB = phenobarbital; PK = pharmacokinetics; SPARC = Sun Pharma Advanced Research Company Limited; USA = United States of America

5.2. Review Strategy

Efficacy and safety determinations were made by evaluating the results from the NEOLEV2 study and the comparative bioavailability study. I assessed the primary efficacy endpoint of the NEOLEV2 study by examining the source data submitted to IND 109622. Statistical analysis of the data was performed and reported by Dr. Yunfan Deng and was used as the basis of the clinical efficacy analyses in this clinical review.

I performed safety analyses on the NEOLEV2 study data. Because the safety data from the healthy adult participants of the comparative bioavailability study PHEN-20-01 are not entirely relevant to the proposed indication and population of newborns with neonatal seizures, it was not appropriate to pool these studies. I will briefly discuss the safety data from study PHEN-20-01 to support my primary safety analysis of the NEOLEV2 data. Dr. Adarsh Gandhi of OCP performed and reported the analysis of the PK data from study PHEN-20-01.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Efficacy of Intravenous Levetiracetam in the Treatment of Neonatal Seizures: A Phase 2 Study of Levetiracetam in the Treatment of Neonatal Seizures (NEOLEV2)

6.1.1. Study Design

Overview and Objective

NEOLEV2 was an investigator-initiated Phase 2 preliminary efficacy, dose-escalation, and safety study of LEV, using an active comparator control of PHB, as first-line treatment of neonatal seizures. The study was supported by an FDA Orphan Products Development Grant and was conducted between June 2013 and October 2017. Aims included to study the preliminary efficacy of IV LEV as first-line treatment for neonatal seizures and to study the pharmacokinetics of IV LEV at high dosage. Because of privacy issues relating to personal information, the Applicant did not have direct access to the raw data; rather, the Sponsor-investigator for NEOLEV2, Dr. Richard Haas, submitted datasets to IND 109622, under which the study was originally conducted. In the NDA, the Applicant included a letter of authorization from Dr. Haas which authorizes the Agency to cross-reference the NEOLEV2 study information contained in IND 109622 to support any regulatory evaluations required during review of the Applicant's NDA. The NEOLEV2 study was originally designed with PHB planned as an active comparator control for LEV; however, the focus of this clinical review will be on PHB.

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- Basic study design
NEOLEV2 was a randomized, double-blind, active-controlled trial which was conducted in the NICUs of its study sites. Study duration was 5 days, regardless of whether the study participants continued to receive care in the NICU.
- Trial location
NEOLEV2 was conducted at 5 sites in California, USA, and 1 site in Auckland, NZ.

Reviewer comment: The location of one study site outside of the US, in NZ, does not raise concerns regarding applicability to the US population; neonatal care is expected to be standard across NICUs in developed countries. Of note, the formulation used at the NZ site was manufactured by Martindale, whereas the formulation used at the US sites was manufactured by West-Ward. This difference was considered during my efficacy and safety analyses.

- Choice of control group
NEOLEV2 was developed with the goal of studying LEV as first-line treatment for neonatal seizures and planned for PHB to be the active control because of PHB's history as the drug-of-choice for initial treatment of neonatal seizures. The Sponsor-investigator's justification for studying LEV as first-line treatment included previous publications that documented benefit of IV LEV in neonatal seizures and preliminary efficacy results from an open-label pilot PK, safety, and efficacy study of LEV which had recently been completed at 3 of the NEOLEV2 study sites.

Reviewer comment: The use of an active comparator control was appropriate, considering the ethical and medical concerns of using a placebo control and not treating or delaying treatment of neonatal seizures.

- Key inclusion/exclusion criteria
Newborns in the NICUs who were less than 14 days-old and had a corrected gestational age between 36 and 44 weeks inclusive (term being 37 weeks or older) and weight of at least 2.2 kg (10th percentile for 37 weeks gestation), who were having seizures or at risk for having seizures, were enrolled and started on continuous video EEG (cvEEG) monitoring. Treatment with the study drugs would be started if electrographic seizures were seen on the cvEEG. Site study investigators and technicians from a commercial EEG monitoring company with remote access monitored the cvEEG.

Patients were excluded if anticonvulsants had already been administered, if serum creatinine was higher than 1.6 mg/dL, if seizures were due to correctable metabolic abnormalities, or if the treating neonatologist felt death was imminent.

Reviewer comment: The inclusion and exclusion criteria were appropriate. The inclusion

criteria were consistent with the definition of the diagnosis of neonatal seizures. The protocol made note that recruitment would be ethically conducted without delay of care, and appropriate study candidates would include patients in whom clinical seizures were brief and stopped spontaneously, or patients in whom seizure activity was suspected but EEG confirmation was necessary before treatment. The inclusion of infants with gestational age between 36 and 37 weeks was appropriate; these infants who are at the older margin of the “late pre-term” stage are likely physiologically similar to term infants, whereas infants with younger gestational age have increasing immaturity of PK processes. The decision to randomize to treatment based on electrographic seizure activity (as opposed to solely clinical seizure activity) increased the validity of the diagnosis, considering the high occurrence of subclinical seizures and non-epileptic movements in neonates, as discussed above in Section 2 [Therapeutic Context](#).

- Dose selection

LEV dosing was based on the pilot PK, safety, and efficacy study mentioned above, in which the high dose of LEV administered as a second-line agent after failure of PHB was a loading dose of 40 mg/kg followed by 10 mg/kg/day as a single daily dose. This dose was chosen with the aim of producing steady-state trough concentrations typically seen with therapeutic doses in adults. 33% of subjects responded to LEV, most at this high dose, with mild sedation noted to be an AE. PHB dosing was based on typical doses used in clinical care.

- Assignment to treatment

When determined to have an electrographic seizure, the subject was randomly assigned to LEV or PHB in a 60:40 allocation ratio (using a block randomization design), stratified by site.

- Study treatments

At the onset of electrographically-confirmed seizure activity, subjects in the LEV group were given a loading dose of LEV 40 mg/kg IV over 15 minutes. If electrographic seizures persisted or recurred more than 15 minutes after the first loading dose was complete, a 20 mg/kg IV load of LEV was given over 15 minutes. If electrographic seizures persisted or recurred more than 15 minutes after the second LEV load was complete, PHB 20 mg/kg IV was administered over 15 minutes. If electrographic seizures persisted or recurred more than 15 minutes after the first PHB load was complete, a second 20 mg/kg IV load of PHB was given over 15 minutes.

The planned sequence of treatment was opposite in subjects in the PHB group. Subjects in the PHB group were given a loading dose of PHB 20 mg/kg IV over 15 minutes at the onset of electrographically-confirmed seizure activity. If electrographic seizures persisted or recurred more than 15 minutes after the first loading dose was complete, a second 20 mg/kg IV load of PHB was given over 15 minutes. If electrographic seizures

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persisted or recurred more than 15 minutes after the second PHB load was complete, LEV 40 mg/kg IV was administered over 15 minutes. If electrographic seizures persisted or recurred more than 15 minutes after the first LEV load was complete, a load of LEV 20 mg/kg IV was given over 15 minutes.

Subjects given any LEV loading doses were continued on maintenance LEV at 10 mg/kg/dose IV every 8 (q8) hours for at least 5 days. Subjects given any PHB loading doses were continued on maintenance PHB at 1.5 mg/kg/dose IV q8 hours through the end of the study.

- **Blinding**

The randomization lists were communicated directly from the statistician to the site research pharmacy, who then provided blinded study drugs to the NICUs such that all study investigators, medical staff, neurophysiologists, and patient families were blinded to the treatment arm. Blinding was maintained by appropriate dilution of the study drugs such that the same volume (ml/kg) was given to both treatment groups. The dosing interval for maintenance doses for both treatment groups was q8 hours because of the shorter half-life of LEV requiring q8 hour dosing, although PHB is typically administered every 12 (q12) hours in clinical practice.

Reviewer comment: Blinding appeared appropriate.

- **Administrative structure**

Site investigators and remote EEG monitoring staff monitored the cvEEG during conduct of the study. Site investigators or site study coordinators obtained de-identified clinical data from the study participants' medical records and recorded the data onto CRFs. Site study coordinators entered the data into a REDcap (Research Electronic Data Capture) database. A data and safety monitoring board (DSMB) was appointed to monitor AEs and to report conclusions and recommendations to the Sponsor-investigator. After completion of the study on a participant, 3 designated study neurophysiologists reviewed the EEG to confirm electrographic seizures for study inclusion and outcome.

- **Procedures**

Per the protocol, as part of standard clinical care in the NICU, vital signs were monitored continuously and were recorded at baseline and at 15 minutes after each drug infusion started. Daily physical examinations were performed and the occurrence of hypotonia, sedation, poor feeding irritability, or infection was documented. Laboratory monitoring including CBC with differential, chemistry panel with renal and liver function tests at baseline, 24 hours, and 48 hours postdose. At the 3 sites at which PK tests (PHB and LEV levels) were drawn, investigators remained blinded to the drug levels. EEG was collected for 24 to 48 hours after study drug administration, with duration of collection impacted by clinical need, i.e., shorter if the subject was seizure-free for 24 hours and eligible for

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discharge from the hospital, and longer if undergoing therapeutic hypothermia which requires cvEEG monitoring for 24 hours after the start of rewarming. After completion of the study on each subject, the full cvEEG record was archived on the UCSD server for analysis by 2 independent neurophysiologists who were blinded to the subjects' group assignment and demographic information. A third neurophysiologist adjudicated discrepancies between the first 2 reviewers.

The protocol had also planned for an add-on neurodevelopmental outcome study in which the study population of the infants who had seizures and were treated would be compared to a control group of the infants who were at risk for seizures but did not have seizures; however, it appears that this was not performed.

Study Endpoints

After EEG data were curated for data extraction, before breaking the blind and data analysis, the Sponsor-investigator proposed to change the primary efficacy endpoint from seizure cessation at 48 hours to seizure cessation at 24 hours, due to the recognition that many subjects were disconnected from cvEEG before 48 hours to enable transport to neuroimaging or discharge. The Agency accepted this change but recommended that seizure cessation at 48 hours be analyzed as a secondary or exploratory endpoint. Therefore, the primary endpoint was the percentage of neonates whose seizures were terminated with treatment and did not go on to require a second anticonvulsant agent for 24 hours. The key secondary endpoint was seizure termination at 48 hours after treatment, without requiring a second agent. Other secondary endpoints were seizure termination at 1 hour after treatment and length of seizure freedom.

The outcome measure for the efficacy endpoints was electrographic seizure freedom. The site investigator reviewed the cvEEGs and made decisions based on his/her EEG interpretation, including randomization and administration of study drug(s). However, it was the study neurophysiologists who subsequently reviewed the full EEG record after completion, to confirm or not confirm the occurrence of seizures, toward inclusion of subjects in efficacy analysis and toward assessment of the primary efficacy endpoint.

LEV and PHB levels were drawn at 3 study sites (in San Diego) at baseline, 1 hour, 24 hours, and 48 hours postdose.

Reviewer Comment: Basing seizure response on EEG interpretation is appropriate and desired, for the reasons discussed in Section 2 [Therapeutic Context](#).

Based on the language in the protocol, it appeared that neonates that required a second load would receive that second load at 30 minutes after onset of treatment, and that

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neonates who required a second agent would receive that second agent at 1 hour after onset of treatment. In that context, seizure cessation for a period of 24 hours without additional treatment is definitely a clinically-meaningful endpoint; at 24 hours of seizure freedom, discharge from the hospital could be considered in a patient who does not have other diagnostic or therapeutic needs. Forty-eight hours of seizure freedom would provide additional reassurance, particularly in a newborn who may be undergoing evaluation for the etiology underlying the seizures or is otherwise more medically complicated. The immediate goal of treating neonatal seizures is to achieve rapid, acute seizure cessation; seizure freedom at 1 hour would support the immediate efficacy of the study drug, however longer-lasting seizure freedom would enable neuronal recovery and potentially prevent secondary damage from excitotoxicity. See the Results section for further discussion of endpoint analysis.

PK sampling had potential to contribute to determining a dose-response relationship. See the Results section for further discussion.

Statistical Analysis Plan

A discussion of the SAP for the NEOLEV2 study may be found in Dr. Deng's Biostatistics review.

On September 4, 2018, the Agency accepted the Sponsor-investigator's proposal to change the primary efficacy endpoint from seizure cessation at 48 hours to seizure cessation at 24 hours prior to breaking the blind. The Agency recommended that seizure cessation at 48 hours be analyzed as a secondary or exploratory endpoint. The SAP was updated to reflect those changes and was finalized on September 14, 2019 (Version 2.0) prior to database lock of the clinical database for NEOLEV2. Version 3.0 (dated 05 Jan 2022) was submitted in this NDA, to note that Wilcoxon-rank sum test and Fisher's Exact test would not be performed for demographic and clinical characteristics, that Fisher's Exact test would not be performed for AE data, and to add tables, listings, and figures to meet regulatory requirements.

The NEOLEV2 study was planned with the objective of obtaining preliminary evidence of efficacy of LEV as first line treatment for neonatal seizures, in order to determine if a Phase 3 trial was warranted and to obtain sample size estimates for such a Phase 3 study. Therefore 300 subjects were planned to be enrolled, in order to achieve 100 treated subjects; assuming a seizure cessation rate of 50% in the PHB arm, this sample size had 80% power to detect a difference in seizure outcome rates of 28% or higher in the LEV arm.

Populations for analysis were defined by the Applicant as follows:

- Intent-to-Treat (ITT) population: all randomized subjects
- Safety Analysis population: all subjects who received at least 1 dose of assigned study drug
- Per Protocol (PP) population: all subjects who were randomized and followed the

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protocol (based on neurophysiologist review)

- modified Intent-to-Treat (mITT) population: all randomly assigned subjects with neurophysiologist-confirmed seizures and a seizure-termination assessment at 24 hours.

Planned subgroup analyses included subjects with and without HIE, and subjects who were treated or not treated with hypothermia. Tests of group differences for the primary and secondary endpoints were to be conducted at 0.05 level of significance, with no adjustment for multiple comparisons. Based on the SAP, no missing data handling was performed for the efficacy analysis.

Protocol Amendments

The original NEOLEV2 study protocol was dated February 20, 2013. An amendment dated February 25, 2014, changed the age inclusion criterion from “term infants with corrected gestational age between 37 and 44 weeks” to “term infants with corrected gestational age between 36 and 44 weeks.” The February 2014 protocol also noted that cvEEG would be “collected for 24 to 48 hours after study drug administration” rather than “for 48 hours after study drug administration.” An amendment dated June 19, 2015, added specifications of the DSMB data monitoring plan. On July 20, 2018, the Applicant submitted a note to file protocol change for changing the primary efficacy endpoint from seizure cessation at 48 hours to seizure cessation at 24 hours. Changes made in other amendments did not alter the analysis.

6.1.2. Study Results

Compliance with Good Clinical Practices

It was noted that the investigators for NEOLEV2 agreed to conduct the study in compliance with the study protocol, with the International Standard of Good Clinical Practice (GCP) procedures, and with the Declaration of Helsinki (1964) principles and relevant amendments. An attestation was provided in the clinical study report that NEOLEV2 was conducted in conformance with GCP standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Financial Disclosure

Financial disclosure forms (FDs) submitted in the original NDA were incomplete. In response to the Agency’s request for the outstanding forms for missing individuals, the Applicant appeared to have acted with due diligence in its attempt to reach investigators who had not provided FDs. The Applicant was unable to provide FDs on 6 of 84 NEOLEV2 study investigators, 5 of whom were from a study site which randomized only 2 subjects. The following disclosures were provided on institutional conflict of interest forms:

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- (b) (6) reported grant funding for a study (b) (6) and a study (b) (6), and participation in a scientific advisory committee for (b) (6).
- (b) (6) reported grant funding for a study (b) (6) and grant funding for (b) (6).
- (b) (6) disclosed grant funding for a study (b) (6).

Reviewer comment: The above conflict of interest disclosures made to the site investigators' institution are not pertinent to the study focus, conduct, or outcome of NEOLEV2. Because NEOLEV2 was planned as a research study without sponsorship from a commercial entity, because the missing FDs are from investigators at a study site which provided minimal contribution to study data, and because the randomized, blinded study design minimizes potential bias, it is unlikely that the missing disclosures would impact data integrity.

Subject Disposition

A total of 280 subjects were enrolled and placed on cvEEG monitoring. 106 subjects were determined by the site investigator to have had electrographic seizure activity and therefore were randomized in a 3:2 ratio to LEV (n=64) and PHB (n=42). All 106 were included in the ITT and safety analysis populations. As [Table 2: Subjects Excluded from Efficacy Analysis Based on Neurophysiologist Review](#) displays, 23 subjects (12 in the PHB group, 11 in the LEV group) were excluded from efficacy analysis because either the study neurophysiologist did not agree that there had been electrographic seizures (12 subjects total) or the primary outcome measure at 24 hours could not be obtained (11 subjects). Reasons for absence of the 24-hour primary outcome measure were EEG missing or lost at critical times (e.g., when seizures were reported to have occurred or when study drugs were given) or EEG data being uninterpretable (e.g., the treating neurologist had not seen a seizure which later was seen by the study neurophysiologists so study drugs were not given; subject received both study medications but the study neurophysiologist did not see seizures in between the study medications; or pretreatment with PHB).

This left 83 subjects in the mITT population (30 in the PHB group, 53 in the LEV group) on which the Applicant performed its primary efficacy analysis. One subject in each treatment group was excluded from the PP population (leaving 29 in the PHB group and 52 in the LEV group in the PP population). [Table 3: Disposition Events by Arm for Randomized Subjects \(ITT population\)](#) lists the disposition of all randomized subjects. Table 3 differs from the Applicant's disposition table in its clinical study report (CSR); the Applicant included a category of "serious adverse event"

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(SAE) in its disposition table, a category which included some subject deaths. Table 3 also lists subjects who were terminated early from the study due to AEs (not differentiating SAEs and AEs) and a separate category of subjects whose study participation stopped early due to death. Of note, if a subject did not continue to receive the study drug(s) as specified by the protocol (by IV administration) or were no longer being treated in the study center (discharged or transferred to another hospital), the subject was considered to have discontinued the study.

Table 2: Subjects Excluded from Efficacy Analysis Based on Neurophysiologist Review

	PHB (N=42) n(%)	LEV (N=64) n(%)	Total (N=106) n(%)
Lack of seizures on EEG based on neurophysiologist review	9 (21.4)	3 (4.7)	12 (11.3)
Primary outcome at 24 hours could not be obtained			
EEG data completely lost or missing at critical times	1 (2.4)	4 (6.3)	5 (4.7)
Efficacy data (EEG) uninterpretable	2 (4.8)	4 (6.3)	6 (5.7)
Total excluded from efficacy analysis	12 (28.6)	11 (17.2)	23 (21.7)

Source: reviewer analysis using ADL2 (subject-level dataset which includes reason for exclusion); JMP

Table 3: Disposition Events by Arm for Randomized Subjects (ITT population)

Disposition Event	PHB (N=42) n(%)	LEV (N=64) n(%)	Total (N=106) n(%)
Completed (full 5 days of study)	29 (69.0)	37 (57.8)	66 (62.3)
Full 5 days of maintenance dosing not completed			
Because ready for discharge	1 (2.4)	4 (6.3)	5 (4.7)
Because transported to outside hospital and study drugs stopped (seizures to be monitored clinically)	1 (2.4)	0	1 (0.9)
Because of communication error	0	1 (1.6)	1 (0.9)
Because of medication error	1 (2.4)	0	1 (0.9)
Because study drugs expired and transition to unblinded meds necessary anyways	1 (2.4)	0	1 (0.9)
Because change in medication required for burst suppression pattern	0	1 (1.6)	1 (0.9)
Because transferred to other hospital for possible ECMO due to respiratory issues	0	1 (1.6)	1 (0.9)

Disposition Event	PHB (N=42) n(%)	LEV (N=64) n(%)	Total (N=106) n(%)
"Other": All study drugs failed and maintenance meds not continued for 5 days because of sedation	0	1 (1.6)	1 (0.9)
Study withdrawal due to AE	2 (4.8)	6 (9.4)	8 (7.5)
Study withdrawal due to lack of efficacy ("all study drugs failed")	5 (11.9)	9 (14.1)	14 (13.2)
Study withdrawal due to death	1 (2.4)	2 (3.1)	3 (2.8)
Study withdrawal due to diagnosis of GLUT1 deficiency disorder and need for alternative treatment	0	1 (1.6)	1 (0.9)
Study withdrawal due to having not met inclusion criteria (pretreated)	0	1 (1.6)	1 (0.9)
Study withdrawal due to parent request	1 (2.4)	0	1 (0.9)

Source: reviewer analysis using ADL2 and narratives (JMP); ECMO = extracorporeal membrane oxygenation

Protocol Violations/Deviations

Thirty-two protocol deviations were recorded across 29 subjects in the randomized/ITT population; 11 (26.2%) subjects in the PHB group and 18 (28.1%) subjects in the LEV group. Many of these PDs were minor and unlikely to impact the efficacy outcomes, e.g., PK sample was not run, creatinine was 1.6 or 1.8 (higher than the original inclusion criterion of creatinine less than 1.6), or parent refusal of further maintenance doses. Some of the subjects in which the protocol deviations occurred (6 of the PHB group and 3 of the LEV group) were excluded from the mITT population and the Applicant's primary efficacy analysis; however, the majority of the subjects were excluded for reasons unrelated to the PD, i.e., they were excluded for having not had a seizure on EEG based on neurophysiologist review and having EEG lost or missing at critical times. Two subjects who were excluded due to "EEG efficacy data uninterpretable" had protocol deviations of inadvertent EEG discontinuation during administration of the first assigned treatment load (Subject (b) (6); LEV group), and of pre-treatment with PHB (Subject (b) (6); LEV group), respectively, which impacted the interpretability of the EEG in regard to the efficacy endpoints.

Of the remaining protocol deviations, only one theoretically could have had an impact on the efficacy outcome because earlier treatment of seizures may be more likely to be successful: Subject (b) (6) in the LEV group had delay in administration of the first load due to difficulty with stable IV access and this subject's seizures persisted through all 4 loads of the 2 study drugs. The potential impact of the other PDs in some cases would likely be in the favorable direction for LEV or in the unfavorable direction for PHB, but ultimately did not alter the favorable outcome for PHB. For instance, Subject (b) (6) in the LEV group (retained in the mITT and PP populations) had been pre-treated with another drug. In addition, 3 subjects in the PHB group ((b) (6)) had a delay in initial study medication; however, each of these subjects

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responded to a single PHB load.

Demographic and other Baseline Characteristics

The baseline characteristics of the subjects randomized in the NEOLEV2 study (ITT population) were similar between groups as noted in [Table 4](#) below, including gestational age, birth weight, and country. There was a slightly higher proportion of males in the PHB group; gender is not known to impact the outcome of neonatal seizures. Of note, there were missing race and ethnicity data in both treatment groups (11.9% and 9.4% of the PHB and LEV groups respectively for race, and 16.7% and 11% of the PHB and LEV groups respectively for ethnicity). An impact of this on outcome of neonatal seizures would not be expected. Regarding disease characteristics, the percentage of subjects in the ITT population who were diagnosed with HIE as the etiology of their seizures is consistent with the reports of 40-60% of neonatal seizures being caused by HIE. However, there was a relatively higher percentage of subjects with HIE who were treated with hypothermia in the PHB group as compared to the LEV group. Dr. Deng performed a subgroup analysis to determine if this impacted efficacy outcome, as described in Efficacy Endpoints below.

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Table 4: Demographic characteristics (ITT population), NEOLEV2

Demographic characteristic	Treatment Group		
	PHB arm (N= 42) n (%)	LEV arm (N= 64) n (%)	Total (N= 106) n (%)
Sex			
Male	24 (57.1)	31 (48.4)	55 (51.9)
Female	18 (42.9)	33 (51.6)	51 (48.1)
Gestational Age (weeks)			
Mean (SD)	39.13 (1.3)	39.34 (0.9)	39.25 (1.3)
Median	39.22	39.5	39.43
Min, max	36, 42	36.43, 41.57	36, 42
Birth Weight (grams)			
Mean (SD)	3317 (501)	3342 (577)	3332 (546)
Median	3297.5	3302.5	3297.5
Min, Max	2200, 4300	2070, 4880	4880
Race			
White	25 (59.5)	34 (53.1)	59 (55.66)
Black or African American	1 (2.4)	4 (6.3)	5 (4.7)
Asian	3 (7.1)	2 (3.1)	5 (4.7)
American Indian or Alaska Native	0	1 (1.6)	1 (0.9)
Native Hawaiian or Other Pacific Islander	2 (4.8)	7 (10.9)	9 (8.5)
Mixed	1 (2.4)	3 (4.7)	4 (3.8)
Other	5 (11.9)	7 (10.9)	12 (11.3)
Missing	0	1 (1.6)	1 (0.9)
Unknown	5 (11.9)	5 (7.8)	10 (9.4)
Ethnicity			
Hispanic or Latino	10 (23.8)	18 (28.1)	28 (26.4)
Not Hispanic or Latino	25 (59.5)	39 (60.9)	64 (60.4)
Not reported	6 (14.3)	6 (9.4)	12 (11.3)
Missing	0	1 (1.6)	1 (0.9)
Unknown	1 (2.4)	0	1 (0.9)
Region			
United States	30 (71.4)	45 (70.3)	75 (70.8)
New Zealand	12 (28.6)	19 (29.7)	31 (29.3)

Source: analysis using ADL2 with reviewer-converted gestational age from weeks and days to decimals (JMP)

Because underlying etiology is an important prognostic factor for both response to treatment and long-term neurodevelopmental outcome, the ITT population was analyzed for etiology, as conveyed in [Table 5](#): Etiology of seizures by arm (ITT population). The listings in Table 5 differ somewhat from the Applicant's analysis of etiologies, due to my recoding of some etiologies as follows:

- identification of the primary etiology, e.g., if HIE was listed along with other causes (e.g., "hemorrhage_subarachnoid," "hemorrhage_subdural"), etiology was recoded as "HIE" (as the primary etiology). Etiologies of "stroke," "hemorrhage_parenchymal," "hemorrhage_subarachnoid," "hemorrhage_subdural" for one subject were recoded as the overlying etiology of "birth trauma" after review of details provided in the subject-level dataset.
- consolidation of similar etiologies into a broader etiology, e.g., "stroke_arterial embolic in utero" and "cortical laminar necrosis" were recoded as "stroke_arterial" (based on review of details provided in the subject-level dataset); and "brain malformation_pachygyria," "brain malformation_lissencephaly," and "brain malformation_tuberous sclerosis" were recoded as "brain malformation."

Table 5: Etiology of seizures by arm (ITT population)

Etiology	Treatment Group		
	PHB arm (N= 42) n (%)	LEV arm (N= 64) n (%)	Total (N= 106) n (%)
HIE	22 (52.4)	35 (54.7)	57 (53.8)
Treated with hypothermia	18 (42.9)	24 (37.5)	42 (39.6)
Arterial stroke	3 (7.1)	10 (15.6)	13 (12.3)
Unknown	6 (14.3)	7 (10.9)	13 (12.3)
Brain malformation	1 (2.4)	2 (3.1)	3 (2.8)
Benign familial neonatal seizures	1 (2.4)	1 (1.6)	2 (1.9)
Drug withdrawal	1 (2.4)	1 (1.6)	2 (1.9)
Subdural hemorrhage	1 (2.4)	1 (1.6)	2 (1.9)
Intraventricular hemorrhage	0	1 (1.6)	1 (0.9)
Parenchymal hemorrhage	0	1 (1.6)	1 (0.9)
Hemorrhagic stroke	0	1 (1.6)	1 (0.9)
Venous stroke	0	1 (1.6)	1 (0.9)
Birth trauma	1 (2.4)	0	1 (0.9)
KCNQ2 mutation	0	2 (3.1)	2 (1.9)
Pyridoxine responsive epilepsy	2 (4.8)	0	2 (1.9)
GLUT1 transporter defect	0	1 (1.6)	1 (0.9)
Neonatal onset epilepsy (no	1 (2.4)	0	1 (0.9)

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further details available)			
Ohtahara syndrome	1 (2.4)	0	1 (0.9)
Meningitis/possible meningitis	2 (4.8)	0	2 (1.9)

Source: reviewer analysis using ADZS and ADSL2 (JMP)

Reviewer comment: The inequality in the percentages of particular etiologies across treatment groups would be unlikely to create a significant imbalance that would impact the overall efficacy outcome. Etiologies of seizures which tend to respond to drugs more readily (e.g., arterial stroke) and etiologies which are often characterized by intractable seizures (Ohtahara syndrome, meningitis) were distributed across the treatment groups.

Because seizure burden is an important prognostic factor, I assessed pretreatment seizure burden across treatment groups, as displayed in [Table 6](#): Pretreatment seizure burden by arm (ITT population).

Table 6: Pretreatment seizure burden by arm (ITT population)

	Treatment Group	
	PHB arm (n=32) hours:minutes:seconds	LEV arm (n=57) hours:minutes:seconds
mean	0:10:37	0:13:42
median	0:06:20	0:08:18
min	0:00:14	0:00:32
max	0:45:06	0:50:26

Source: reviewer analysis using ADZE (JMP, Excel)

n = subjects with nonmissing data

Reviewer comment: Although the pretreatment seizure burden in the PHB group is somewhat shorter than the pretreatment seizure burden in the LEV group, a difference in the mean of 3 minutes would not appear to be clinically significant.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance is not a concern in this study which was performed in the inpatient setting in which medications are administered via IV by nursing staff. Concomitant medications were administered as part of standard neonatal care and therefore were similar across subjects. If a subject required a “rescue medication,” in the form of the alternate treatment to which the subject had not been randomized or in the form of a non-study drug, the subject was considered a non-responder.

Efficacy Results – Primary Endpoint

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The Applicant performed its efficacy analysis ([Table 7](#): Efficacy outcome by arm (Applicant-defined mITT population) on the mITT population which it defined as all randomly assigned subjects with neurophysiologist-confirmed seizures and a seizure-termination assessment at 24 hours; this excluded subjects who ultimately did not have seizures confirmed by the designated study neurophysiologist and subjects who had missing or uninterpretable efficacy assessment (EEG). The mITT population is typically defined in epilepsy trials as the population which received at least 1 dose of study drug and underwent at least 1 post-baseline efficacy assessment. Excluding subjects based on a post-randomization event introduces potential bias. Therefore, we performed an independent analysis using the population of subjects who had neurophysiologist-confirmed seizures, i.e., the ITT population (all randomized subjects), but excluding the 12 subjects who did not have neurophysiologist-confirmed seizures (and, in hindsight, should not have been randomized). Our analysis retained the 11 subjects who had either missing EEG or uninterpretable efficacy outcome (3 in the PHB group and 8 in the LEV group) and imputed them as nonresponders. The p-value from the primary analysis was still highly significant (see [Table 8](#)).

The Applicant also performed sensitivity analyses for the primary efficacy endpoint with imputation of EEG data in the 23 subjects who were excluded from the mITT population based on study neurophysiologist review. Sensitivity analysis giving all of these subjects an outcome of seizure termination not achieved still resulted in a statistically-significant higher percentage of subjects in the PHB group who had seizure termination at 24 hours compared to the percentage of subjects in the LEV group who had seizure termination at 24 hours. This was confirmed by Dr. Deng's analysis.

Table 7: Efficacy outcome by arm (Applicant-defined mITT population)

	PHB (N=30) n (%)	LEV (N=53) n (%)	P-value ¹	PB vs LEV Difference (95% CI) ²
Seizure termination for 24 hours				
Number of subjects	30	53		
Yes	24 (80.0)	15 (28.3)	<0.001	51.7% (32.9%, 70.5%)
Seizure termination for 48 hours				
Number of subjects (% of total arm)	28 (93.3)	47 (88.7)		
Yes	18 (64.3)	8 (17.0)	<0.001	44.9% (24.9%, 64.9%)
Seizure termination for 1 hour				
Number of subjects	30	53		
Yes	28 (93.3)	26 (49.1)	<0.001	44.3% (28.1%, 60.4%)

¹ p-value is based on Fisher's exact test

² The 95% CI was based on normal approximation.

Table 8: Efficacy outcome by arm (all randomized subjects with neurophysiologist-confirmed seizures)*

	PHB (N=33) n (%)	LEV (N=61) n (%)	P-value ¹	PB vs LEV Difference (95% CI) ²
Seizure termination for 24 hours				
Yes	24 (72.7)	15 (24.6)	<0.001	48.1% (29.5%, 66.8%)
Seizure termination for 48 hours				
Yes	18 (54.6)	8 (13.1)	<0.001	41.1% (22.5%, 60.4%)
Seizure termination for 1 hour				
Yes	28 (84.9)	26 (42.6)	<0.001	42.2% (24.8%, 59.7%)

* Missing outcomes (missing or lost EEGs or uninterpretable efficacy outcome data in 11 subjects) were imputed as treatment failure.

¹ p-value is based on Fisher's exact test

² The 95% CI was estimated using normal approximation.

Source: Dr. Deng's Biostatistics review

The Applicant performed subgroup analyses to assess the effect on the primary efficacy endpoint of an underlying etiology of HIE and of the use of therapeutic hypothermia. We repeated these analyses, particularly because a slightly higher proportion of subjects with HIE in the PHB group received therapeutic hypothermia compared to the LEV group (see [Table 5: Etiology of seizures by arm \(ITT population\)](#)). These analyses, as displayed in [Table 9](#) suggest that the benefit of PHB occurs in patients with HIE who are treated with hypothermia and in patients with HIE who are not treated with hypothermia. Although the small numbers in each subgroup make a conclusive inference difficult, the effect size is large, which suggests a high likelihood that the benefit of PHB over LEV is not solely due to chance or to the natural course of neonatal seizures. Further assessment of whether therapeutic hypothermia is an independent contributor to control of neonatal seizures cannot be conclusively addressed.

Table 9: Seizure Termination for 24 hours by Hypothermia Treatment Status in the HIE Positive Subgroup (all randomized subjects with neurophysiologist-confirmed seizures)

HIE Positive	PHB (N=17) n(%)	LEV (N=33) n(%)
Seizure termination for 24 hours		
Yes	12 (70.6)	6 (18.2)
Pts with Hypothermia Treatment	N=13	N=23

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Seizure termination for 24 hours	9 (69.2)	6 (26.1)
Pts w/o Hypothermia Treatment	N=4	N=10
Seizure termination for 24 hours	3 (75.0)	0 (0.0)

Source: Reviewer analysis using ADZE and ADSL2 datasets (JMP)

[Table 10](#): Number of Subjects by Study Site shows the distribution of subjects in the ITT and mITT populations and of subjects who had neurophysiologist-confirmed seizures by study site. Approximately 2/3 of study subjects were treated in the US. That proportion, in addition to the similar clinical practice in neonatal care, provides reassurance that the data from NEOLEV2 is applicable to our US population. Regarding the primary efficacy endpoint, a higher percentage of neonates had cessation of seizures on PHB than on LEV in the NZ study site as well as US sites, as shown in [Table 11](#): Seizure Termination for 24 Hours by Study Site Country (all randomized subjects with neurophysiologist-confirmed seizures).

Table 10: Number of Subjects by Study Site

Site	ITT n(%)	Population with neurophysiologist- confirmed seizures n(%)	mITT n(%)
Auckland Hospital, New Zealand (NZ)	31 (29.2)	31 (33.0)	28 (33.7)
US	75 (70.7)	63 (67.0)	55 (66.3)
University of California—San Diego (UCSD)	9 (8.5)	8 (8.5)	8 (9.6)
Rady Children's Hospital, San Diego	30 (28.3)	28 (29.8)	25 (30.1)
Sharp Mary Birch Hospital, San Diego	19 (17.9)	13 (13.8)	9 (10.8)
Loma Linda University School of Public Health	2 (1.9)	1 (1.1)	1 (1.2)
University of California at San Francisco (UCSF) Benioff Children's Hospital, Oakland	15 (14.2)	13 (13.8)	12 (14.5)
Total	106	94	83

Source: ADSL2 (JMP)

Table 11: Seizure Termination for 24 Hours by Study Site Country (all randomized subjects with neurophysiologist-confirmed seizures)

	PHB (N=33) n(%)	LEV (N=61) n(%)
Seizure termination for 24 hours (Overall)		
Yes	24 (72.7)	15 (24.6)
Seizure termination for 24 hours (New Zealand)	N=12	N=19
Yes	10 (83.3)	6 (31.6)

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Seizure termination for 24 hours (US)	N=21	N=42
Yes	14 (66.7)	9 (21.4)

Source: Reviewer analysis using ADZE and ADSL2 datasets (JMP), confirmed by Dr. Deng's Biostatistics analysis

Reviewer comment: NEOLEV2 demonstrated that PHB had greater efficacy than LEV based on the primary efficacy endpoint of seizure termination for 24 hours without requirement of additional treatment, and the support of the key secondary endpoint of seizure termination for 48 hours without requirement of additional treatment. This demonstrated statistical significance despite the relatively small sample size. The efficacy was demonstrated in several analyses, including analysis of the ITT population excluding the subjects who did not have neurophysiologist-confirmed seizures, sensitivity analyses with imputation of missing data, and analyses of subgroups including subjects with HIE treated with hypothermia or not treated with hypothermia. There also did not appear to be a difference in efficacy between the study site in NZ and study sites in the US, which supports the efficacy of the active moiety.

Data Quality and Integrity

It is notable that this application relies on the data generated from an investigator-initiated research protocol in which the Applicant was not involved, but for which the Applicant provided resources to generate the necessary documents and datasets for regulatory submission, following regulatory standards, after the study and original database lock had already been completed. This required curation of the data from the NEOLEV2 REDCap database (which was generated from the original CRFs) and then submission of the datasets to the protocol's IND. The Applicant did not have direct access to these datasets, which raised the concern that the Applicant's knowledge of the protocol and data may not be complete and accurate. Prior to NDA submission, the Agency therefore asked the Applicant to develop an algorithm for Agency inquiries during review about the datasets. The inquiry process relied on the Applicant to ensure that it forwarded inquiries to the NEOLEV2 PI to confirm or provide details such that the responses were accurate. This process appeared to be efficient, and it appeared that the NEOLEV2 PI was providing support to the Applicant. However, because of the concern of accuracy, I particularly relied on my own analyses to formulate conclusions.

An SDTM to ADaM traceability assessment was requested from and performed by the Office of Computational Science (OCS) for key datasets (demographics, adverse events, laboratory monitoring, and vital signs). I reviewed all potential traceability findings that were identified and determined them to be of low impact. The NEOLEV2 PI also submitted a detailed list of values from the original NEOLEV2 REDCap database which required manual hard-coding for the purpose of correcting the data for the submission for this NDA. The OSI inspections determined that the study conduct and data collection was acceptable and reliable. Therefore, the data quality and integrity appear to be acceptable.

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Regarding data reliability, EEG as an outcome measure by 2 experienced neurophysiologists, and a 3rd to adjudicate if needed, was a relatively reliable outcome measure which should not have been susceptible to bias under the blinded reading conditions. The CRF included a number of fields which required or enabled comments; these comments, as transcribed into the datasets, could not be mechanically analyzed themselves, but provided narratives through which other fields could be confirmed or better understood.

Efficacy Results – Secondary and other relevant endpoints

In the SAP, seizure termination for 48 hours was defined as the only key secondary endpoint, tested sequentially right after the primary efficacy endpoint. Seizure termination for 1 hour was defined as the first among five other secondary endpoints; the SAP did not explicitly specify the testing of these other secondary endpoints. The key secondary endpoint, seizure termination for 48 hours without need for the second study drug, was statistically greater in the PHB arm as compared to the LEV arm. This was not proposed by the Applicant for inclusion in the labeling. However, it is important because it demonstrates the durability of response. The secondary endpoint of seizure freedom at 1 hour after treatment onset supports an effect on the acute management of neonatal seizures, which is clinically meaningful due to the urgent nature of neonatal seizure treatment.

Dose/Dose Response

Sparse PK sampling was performed at 3 of the 6 study sites, in 30 total participants (19 in the PHB group, 11 in the LEV group). These small sample sizes preclude definitive determination of a dose-response or exposure-response relationship for PHB.

Durability of Response

The primary efficacy endpoint and key secondary efficacy endpoint captured the durability of efficacy through 48 hours after treatment onset.

Persistence of Effect

Data regarding follow-up after the 5-day duration of the trial was not provided.

Additional Analyses Conducted on the Individual Trial

OCP performed additional analyses of the NEOLEV2 data using modeling and simulation. In the NEOLEV2 study, PHB maintenance dosing was administered as 1.5 mg/kg IV q8 hours in order to maintain blinding, because of the shorter half-life and need for q8-hour dosing of LEV. Related to the long half-life of PHB, the historical practice has been to administer PHB as 2 to 2.5 mg/kg q12 hours (total daily dose 4 to 5 mg/kg). OCP compared PK simulations using q8-hour and q12-hour administration of the same total daily dose (4.5 mg/kg/day) and using 1 and 2 loading doses (of 20 mg/kg). The simulated profiles were consistent across a range of weight

values, clearance values, and 2 literature-based models, and informed the labeling.

The NEOLEV2 study did not enroll pre-term infants. Thus far, PHB has been administered as first-line treatment for neonatal seizures at a regimen based on historical experience and clinical consensus, with the same regimen used for pre-term infants as for term infants, although typically with increased monitoring of serum PHB levels in the preterm neonates. Our OCP team used modeling and simulations to determine if the proposed dosing was also appropriate for preterm neonates. These simulations demonstrated that PHB concentrations in preterm neonates after two 20 mg/kg loading doses followed by maintenance dosing of 1.5 mg/kg q8 hours are expected to be within the range of the concentrations in term neonates. In addition, PHB concentrations in preterm neonates after a 20 mg/kg loading dose and a subsequent 10 mg/kg loading dose followed by the maintenance dosing above are expected to be similar to the levels after two 20 mg/kg loading doses. See the OCP review for full details. This provides support for the clinical judgment that providers sometimes currently use to determine the dosage of a second loading dose in a preterm infant. For instance, providers weigh the neonate's ability to tolerate a higher dose of 20 mg/kg against the urgency of the need for seizure cessation, based on factors such as gestational age, presence of AEs such as level of sedation, and severity of seizures.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only a single efficacy study included in this review and therefore this section is not applicable.

7.1.1. Primary Endpoints

There is only a single efficacy study included in this review.

7.1.2. Secondary and Other Endpoints

There is only a single efficacy study included in this review.

7.1.3. Subpopulations

There is only a single efficacy study included in this review.

7.1.4. Dose and Dose-Response

There is only a single efficacy study included in this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Because the NEOLEV2 study assessed only neonates with seizures, efficacy with off-label use in other populations of older children or adults is not known.

7.2.2. Other Relevant Benefits

The proposed formulation, which is manufactured in single-use vials, lacks benzyl alcohol and propylene glycol, which the Applicant asserts is a positive safety feature; however, the Applicant did not submit data that demonstrates the additional safety of the proposed product over currently marketed formulations of PHB.

The concern relating to benzyl alcohol originated from reports in 1982 of premature (26 to 34 weeks gestation) or low-weight (less than 1250 grams) neonates who died after metabolic acidosis, seizures, bradycardia, hypotension, gasping respirations, and multisystem organ failure. These infants were reported to have high levels of benzyl alcohol and its metabolites in their urine and/or blood, which was speculated to have resulted from high exposures through IV administration of bacteriostatic sodium chloride for catheter flushing and medication reconstitution and from immature hepatic oxidative and conjugation function.^{14,15} As a result, the FDA, Center for Disease Control, and American Academic of Pediatrics issued a recommendation against using fluids and diluents preserved with benzyl alcohol in neonates.^{16,17} Specific systemic thresholds at which benzyl alcohol and its derivatives would be considered safe in the pediatric population are unknown. Therefore, the clinical significance of the lack of benzyl alcohol and propylene glycol in the proposed formulation is unclear; however, because of the reports of adverse outcomes in neonates associated with benzyl alcohol, this information is informative to healthcare providers and will be included in the label.

7.3. Integrated Assessment of Effectiveness

¹⁴ Brown WJ, Buist NRM, Gipson HTC, et al (1982). Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1:1250.

¹⁵ Gershanik J, Boecler B, Ensley H, et al (1982). The gasping syndrome and benzyl alcohol poisoning. *N Eng J Med* 1384-1388.

¹⁶ Centers for Disease Control (1982). Neonatal deaths associated with use of benzyl alcohol—United States. *MMWR* 31(22):290-291.

¹⁷ Committee on Fetus and Newborn and Committee on Drugs (1983). Benzyl alcohol: toxic agent in neonatal units. *Pediatrics* 72(3):356-358.

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The data submitted in this application provides substantial evidence of effectiveness of PHB for the treatment of neonatal seizures. The primary basis of this evidence is the NEOLEV2 study which is reviewed in detail in [Efficacy of Intravenous Levetiracetam in the Treatment of Neonatal Seizures: A Phase 2 Study of Levetiracetam in the Treatment of Neonatal Seizures \(NEOLEV2\)](#), along with the PHEN-20-01 comparative bioavailability study which establishes a bridge between the Applicant's formulation and the formulation administered in the NEOLEV2 study and is reviewed in detail in the Clinical Pharmacology review. This relies on a single statistically strong efficacy study, which demonstrated benefit across subgroups including subjects with HIE who were treated with or not treated with therapeutic hypothermia. The extensive past history of PHB use in neonatal seizures provides a confirmatory context for the findings.

There are no other treatments for neonatal seizures which are currently FDA-approved. Although PHB has been used for decades to treat neonatal seizures and has been recommended by clinical guidelines as the first-line treatment of neonatal seizures, its use and dosing regimen have primarily been based on clinical experience/consensus and observational studies and had not been rigorously studied in the context of current standard of neonatal care. The data in this application provide evidence which confirms the effectiveness of this regimen.

The dosing administered in the pivotal study was a loading dose of 20 mg/kg IV, followed by an additional 20 mg/kg IV if seizures persist or recur after 15 minutes after the completion of the first load, followed by maintenance dosing of 1.5 mg/kg IV q8 hours. A statistically significant higher responder rate was demonstrated in subjects who were randomized to receive PHB as the first treatment drug, in comparison to subjects who were randomized to receive LEV as the first treatment drug was demonstrated. A duration of seizure freedom for 24 hours following loading dose administration, without the need for administration of a second drug, is clinically meaningful. However, the sample size is not adequate to demonstrate a clear exposure-response relationship; therefore, a precise therapeutic range of PHB levels cannot be defined.

8. Review of Safety

8.1. Safety Review Approach

This safety review addresses the safety of PHB as treatment of neonatal seizures. Although some neonates may continue to receive PHB past their initial hospitalization for acute treatment of neonatal seizures, the data upon which this review is primarily based (from the NEOLEV2 study) was collected only through 5 days of treatment with an IV formulation, and therefore does not address long-term safety. The Applicant also submitted a review of publications which discussed AEs and deaths after PHB administration. These publications, in addition to the long history of clinical experience with the use of PHB for treatment of neonatal

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seizures, support the AEs which were observed in NEOLEV2, but cannot be relied upon for regulatory approval.

Based on PHB's drug class of barbiturates, particular attention by the Applicant and in this review was placed on effects on respiration, blood pressure, and sedation. I assessed the NEOLEV2 safety in subjects who only received their assigned treatment (i.e., did not require the second agent), and in subjects who received both study drugs (i.e., whose AEs would not be clearly attributable to an individual study drug and who may have been more likely to have AEs due to more severe disease).

The safety data generated by the Applicant's comparative bioavailability study (PHEN-20-01), comparing single doses of 2 mg/kg of its PHB sodium formulation and the formulation marketed by West-Ward, are not entirely relevant to the proposed indication nor population. However, it provides some controlled data comparing AEs after administration of the proposed investigational product and the available marketed product in healthy adults.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Because the PHEN-20-01 population (healthy adults) is not relevant to the proposed population of use (neonates), and the PHEN-20-01 dosing regimen (single 2 mg/kg IV dose) is not relevant to the proposed indication of use (neonatal seizures), the focus of this safety review was on the NEOLEV2 data. However, [Table 12](#): Safety Populations of NEOLEV2 and PHEN-20-01 (studies were not pooled for further analysis) shows the total safety database of the Applicant's NDA.

Table 12: Safety Populations of NEOLEV2 and PHEN-20-01 (studies were not pooled for further analysis)

Clinical Trial Groups	PHB (SPARC) (N=66)	PHB (West-ward) (n=25)	LEV (n=64)
Healthy volunteers (PHEN-20-01)	24	25	
Controlled trial conducted for neonatal seizures (NEOLEV2)	42		64

8.2.2. Relevant characteristics of the safety population:

See [Table 3](#): Disposition Events by Arm for Randomized Subjects (ITT population) and [Table 4](#): Demographic characteristics (ITT population), NEOLEV2 for demographic and etiological characteristics of the NEOLEV2 safety population (which is the same as the ITT population). The most common cause of neonatal seizures, HIE, is appropriately represented in both treatment groups.

PHEN-20-01 enrolled 11 females and 14 males between 21 and 45 years old (mean 31.8, SD 6.3; median 32 years). Nineteen participants (76%) were white; 4 were Asian (16%); 2 were black (8%).

8.2.3. Adequacy of the safety database:

In the context of the significant body of clinical experience with PHB in the neonatal population and the limited duration of the indication of neonatal seizures, the size of the safety database is adequate. The NEOLEV2 study population was exposed to appropriate dosing and duration of treatment and reflected appropriate demographic and underlying disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The process of capturing AEs in the CRF and the roles of the AE pages in the CRF was unclear and required Information Requests (IRs) to the Applicant and particular attention to ensure the accuracy of analysis. "Side Effect and Adverse Event Monitoring" page captured a daily checklist of events and recognized AEs, and included fields for hypotension, heart rate abnormality, respiratory abnormality, sedation, irritability, poor feeding, infection, and "other new medical problem." The "Side Effect and Adverse Event Monitoring" page also captured interventions, including ventilation, oxygen, pressors, and rewarming. The entries on this page were captured in the "ADFA" dataset.

A separate page of the CRF was titled, "Final AE/SAE designation" and reportedly served to reclassify the AEs with the Division of AIDS (DAIDS) table for grading of severity of adult and pediatric adverse events. The "Final AE/SAE designation" page reportedly listed every AE recognized and reported during the treatment with the study drugs regardless of whether the Investigators felt they were due to drug treatment or not. The entries on this page were captured in the "ADAE" dataset. I reviewed both the ADFA and ADAE datasets and clinical details provided in comment fields in those datasets and the ADSL (subject level), ADZE (efficacy), and ADZS (etiology) datasets in order to better understand the role of both CRF pages and to verify that the data included in ADAE were adequate for the safety analysis. Section 8.4 [Safety Results](#) of this review gives additional detail of my safety analysis. Ultimately, the data in ADAE appeared to be adequate for the safety analysis and were the data that the Applicant and I used for safety analysis.

[Table 13](#): Adverse Events by Study Site (Safety Population) shows AEs by study site. Of note, ORA investigators were asked to verify that no AEs were reported at UCSD and Loma Linda. The lack of AEs may have been related to these 2 sites having the lowest proportions of subjects in the safety population. Other AEs, including SAEs and deaths, appear to be proportional and not excessive for a population of neonates with serious illness.

Refer to Section 6.1.1 [Study Design](#) for description of the Procedures. Because this was an investigator-initiated study, the safety monitoring specified in the protocol was typically already performed in the context of standard clinical care and was appropriate. In the CRF, no raw values (i.e., vital signs other than weight, length, and head circumference; lab results) were collected; rather, the CRF captured investigator interpretation of the values were normal or abnormal. It is likely that providers and site study coordinators at a NICU would capture these variables accurately. In addition, stratification of randomization per site should account for differences in particular investigator/site practices, such as different thresholds for management decisions. The day that an AE occurred could be based on the CRF (daily checklist) but the precise timing of AEs in relation to drug administration was not necessarily captured.

Table 13: Adverse Events by Study Site (Safety Population)

Site	Total Subjects n(%)	Subjects with AEs n(%)	Total AEs	SAEs	Deaths
Total (N)	106	27	89	10	6~
Auckland, NZ	31 (29.2)	11 (40.7)	29 (32.6)	2 (20)	2* (33.3)
UCSD	9 (8.5)	0	0	0	0
Rady, San Diego	30 (28.3)	9 (33.3)	38 (42.7)	3 (30)	1† (16.7)
Sharp, San Diego	19 (17.9)	6 (22.2)	21 (23.6)	4 (40)	2‡ (33.3)
Loma Linda	2 (1.9)	0	0	0	0
UCSF	15 (14.2)	1 (3.7)	1 (1.1)	1 (10)	1# (16.7)

Source: reviewer analysis using ADL2 and ADAE datasets (JMP)

~ Total deaths, 3 occurring during the study timeframe and 3 occurring after.

* One death occurred during the study timeframe and was classified as an SAE.

† This death occurred outside of the study timeframe.

‡ One death occurred during the study timeframe and was classified as an SAE.

This death was classified as an SAE.

8.3.2. Categorization of Adverse Events

Site investigators or site study coordinators obtained de-identified clinical data from the study participants' medical records and recorded the data onto CRFs. The specific data and terms documented on the CRF were reviewed in Section 8.3.1 [Issues Regarding Data Integrity and Submission Quality](#). AEs were recorded and reported through 5 days after the onset of study treatment. Some of the recorded verbatim terms for AEs were general, because they were specified as such in the form of a checklist for the CRF. Because I was concerned about the accuracy of the use of these terms when I was unable to analyze the raw values, I sent an IR about the parameters that the investigators used to determine if the AEs occurred. The response was essentially that the investigators used the standard parameters used in clinical care. Specifically, blood pressure was expected to be above 35 mmHg, heart rate was expected to be 120-180/minute, and respiratory rate was expected to be up to 60/minute. Excursions outside these parameters were noted by NICU staff in the clinical record as hypotension,

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bradycardia, tachycardia, apnea (pause in breathing of at least 20 seconds), or tachypnea.

“Respiratory abnormality” on the CRF therefore included apnea, tachypnea, the requirement for ventilatory support or oxygen, or increased work of breathing. “Arrhythmia” included any rhythm other than sinus rhythm 120-180/minutes as detected by continuous electrocardiogram (ECG) monitoring. “Sedation” was graded per DAIDS criteria for altered mental status, grade 1 being sedation causing no or minimal interference with usual social or functional activities; grade 2 mild lethargy or somnolence causing greater than minimal interference; grade 3 significant enough to be described as lethargy or somnolence causing inability to perform usual social and functional activities; and grade 4 obtundation or coma.

The Applicant used the DAIDS grading scale to assign the severity of all AEs as follows: Grade 1—mild event; Grade 2—moderate event; Grade 3—severe event; Grade 4—potentially life-threatening event; Grade 5—death. Therefore, all AEs with Severity Grade 4 and 5 were appropriately classified as SAEs. All AEs were categorized as treatment-emergent AEs (TEAEs). In my analysis, the Applicant’s attribution of relationship to study drug was ignored. The Applicant performed analyses by preferred term and primary system organ class level, using MedDRA Version 24.0. AEs, SAEs, and study withdrawal due to AEs were assessed by frequency rates across assigned treatment groups and by treatment administered, because subjects could receive both study drugs if seizures persisted beyond administration of the assigned study drug. Because the participants enrolled in the NEOLEV2 study were at high risk for severe medical complications and death related to the underlying etiology of the neonatal seizures, the protocol noted the following to be considered expected AEs: clinical or electrographic seizures, EEG abnormalities, multiorgan failure, abnormal lab values associated with organ failure, death, and other AEs associated with systemic asphyxia and HIE in neonates.

Reviewer comment: The process for recording, coding, and categorizing AEs, as well as the Applicant’s approach to safety analyses was ultimately determined to be appropriate. Because NEOLEV2 was an investigator-initiated research study which was performed in NICUs with continuous monitoring with cardiorespiratory monitoring machines as well as by NICU staff, AEs were not likely to be missed, and would be expected to be accurately identified based on the expertise of the NICU staff. The AEs observed and captured were consistent with those known to be AEs based on the long clinical experience with PHB in neonatal seizures. Any inaccuracy or bias based on individual staff’s or particular site practice would be expected to be balanced by randomization and stratification of randomization by site. It was appropriate to approach all AEs as TEAEs, considering the course of the subjects’ serious underlying conditions, the efficiency of initiation of treatment, and the continued maintenance dosing might make it difficult to definitively determine whether AEs began after the start of study drug or worsened after or during study drug administration.

8.3.3 Routine Clinical Tests

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The neonates were monitored continuously, as per standard NICU care, during the study period for heart rate, respiratory rate, and blood pressure. The protocol noted that vital signs were to be recorded at baseline and at 15 minutes after each drug infusion commenced, and that complete blood count and serum chemistries were performed at baseline, at 24 hours, and at 48 hours. CBC and chemistry results were recorded on the CRF at baseline and after 48 hours of treatment. Daily physical examinations were performed and occurrence of hypotonia, sedation, poor feeding, irritability, or infection was documented. The protocol also noted that, "Following the last dose of study drug, a phone review of the same symptoms will be conducted every 3 days and a visit and physical examination will be conducted 1 week after the last dose of study drug." The data resulting from those follow-up encounters after the study was completed did not appear to be provided in a systematic fashion, although some data was captured in the NICU discharge summary and other comment fields.

Reviewer comment: The safety assessment methods and time points described in the protocol are reasonable and consistent with typical clinical care of neonates treated in the NICU.

8.4. Safety Results

8.4.1. Deaths

Six deaths occurred in NEOLEV2; three occurred during the study timeframe and 3 occurred after the study ended for the individual subject but within the neonatal period. One occurred in the PHB group and 5 occurred in the LEV group. The primary cause of death in 4 subjects was noted to be severe HIE; although the cause of death in the other 2 were noted, respectively, to be "fetal sepsis with widespread brain necrosis and infarction" and "brain herniation from extensive brain infarction," those subjects also had diagnoses of HIE with findings consistent with severe injury on brain magnetic resonance imaging (MRI). All deaths were after withdrawal of life support; the context of poor prognosis for the decision to withdraw support was often mentioned in the narratives. All 6 subjects received 2 loads of both study drugs; administration of additional drugs for persistent seizures was noted in the majority of the narratives.

Reviewer comment: Patients with severe HIE are very ill, typically with multiorgan failure due to diffuse ischemia. Withdrawal of active support in these patients after consideration of very poor prognosis is not uncommon in this population. Although more of these deaths occurred in subjects randomized to LEV as the first treatment, all of these subjects required both study drugs. The failure of both study drugs in terminating their seizures suggests that the severity of disease is greater in these subjects. It would not be logical to attribute these deaths to study drug.

8.4.2. Serious Adverse Events

In NEOLEV2, 9 (8.5% of the total safety population) subjects experienced 10 SAEs. These 9

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subjects consisted of 6 (14.3%) subjects in the PHB treatment group (42 total subjects), and 3 (4.7%) subjects in the LEV treatment group (64 total subjects). I reviewed the provided narratives for these 9 subjects and agree with the designation of SAE. The SAEs are similar to the AEs seen in general in NEOLEV2 ([Table 16](#): Subjects with AEs by Treatment Group (Safety Population), [Table 17](#): Subjects with AEs by Drug Received (Safety Population), [Treatment Emergent Adverse Events and Adverse Reactions](#)), and are displayed in [Table 14](#): SAEs by Treatment Received (Safety Population), based on the actual treatment(s) received (only PHB, only LEV, or both).

Based on details in the narratives, these SAEs occurred in infants with severe systemic illness, with diagnoses such as sepsis, severe persistent pulmonary hypertension, and diffuse right lung atelectasis. However, some details were suggestive of causality or at least contribution of PHB to the SAE. In Subject (b) (6), worsening of hypotension and desaturation occurred 2 hours after one load of PHB and required fresh frozen plasma and initiation of pressors. Subject (b) (6) had increased adrenaline need for grade 4 decreased mean arterial pressures 1 ½ hours after PHB. Subject (b) (6) had low blood pressure after receiving 2 loads of PHB, requiring dopamine increase during the load, additional FFP, and slowing of the PHB infusion rate. Subject (b) (6) had hypotension during PHB infusion requiring dopamine and intubation. Subject (b) (6) had been discontinued from dopamine prior to initiation of study drug but required restarting of pressors after PHB.

Table 14: SAEs by Treatment Received (Safety Population)

Dictionary-Derived Term	PHB (N=32) n(%)	PHB + LEV (N=55) n(%)	LEV (N=19) n(%)	Total (N=106)
Death	0 (0)	3 (5.5)	0	3 (2.8)
Hypotension	4 (12.5)	2 (3.6)	0	6 (5.7)
Respiration abnormal	1 (3.1)	0	0	1 (1)

Reviewer comment: In isolation, the cause of reported SAEs as drug or as the underlying cause of the neonatal seizures and associated systemic complications can be difficult to differentiate. The subjects who received both PHB and LEV likely had increased severity of underlying illness and therefore would have been more likely to have systemic complications. However, the difference between the frequency of the SAEs of hypotension and respiration abnormal in subjects who received PHB only and in subjects who received LEV only, and details of narratives of subjects who received PHB, suggest causality or at least a contribution of PHB to exacerbation of potential underlying susceptibility.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Based on my analysis (which approached subjects with death in a separate category), 8 total

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subjects in NEOLEV2 discontinued the study due to AEs (2 randomized to PHB, 6 randomized to LEV). Four received both PHB and LEV; 2 received only PHB; and 2 received only LEV. The AE which most frequently led to study discontinuation was sedation, which occurred in 4 subjects, 1 of whom received only LEV, 1 of whom received only PHB, and 2 of whom received both LEV and PHB. Hypotension was the reason for study withdrawal in 2 subjects, 1 of whom received only PHB and 1 of whom received both LEV and PHB. One subject who received LEV only was withdrawn due to arrhythmia, specifically premature ventricular contractions. One subject who received both LEV and PHB was withdrawn due to concern that the drugs were contributing to burst suppression.

Safety withdrawal criteria were not specified in the protocol; rather, the discretion of the investigator/treating physician was relied upon. This was appropriate because this study was conducted in NICUs which were experienced with the study treatments as part of standard clinical care.

Reviewer comment: It is possible that hypotension as a reason for study withdrawal occurred more frequently in subjects who received PHB; however, the small sample size precludes a definitive conclusion.

8.4.4. Significant Adverse Events

Table 15: Grading of Specific AEs as per the DAIDS Scale

AE	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)
abdominal distension	causing no or minimal interference with usual social and functional activities	greater than minimal interference with usual social and functional activities	inability to perform usual social and functional activities	not applicable
arrhythmia	no symptoms and no intervention indicated	no symptoms and non-urgent intervention indicated	non-life-threatening symptoms and non-urgent intervention indicated	life-threatening arrhythmia or urgent intervention indicated
hepatic enzyme elevated	1.25 to <2.5 x upper limit of normal (ULN)	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥ 10.0 x ULN
hyperbilirubinemia: 24 to < 48 hours of age 48 to <72 hours 72 hours to <7 days	5 to <8 mg/dL 8.5 to <13 mg/dL 11 to <16 mg/dL	8 to <12 mg/dL 13 to <15 mg/dL 16 to <18 mg/dL	12 to <19 mg/dL 15 to <22 mg/dL 18 to <24 mg/dL	≥19 mg/dL ≥22 mg/dL ≥24 mg/dL
hyponatremia	130 to <135 mEq/L or mmol/L	125 to <130 mEq/L or mmol/L	121 to <125 mEq/L or mmol/L	≤120 mEq/L or mmol/L
hypotension	no symptoms	symptoms corrected with oral fluid replacement	symptoms and IV fluids indicated	shock requiring use of vasopressors or

				mechanical assistance to maintain blood pressure
oliguria (creatinine)	1.1 to 1.3X ULN	>1.3 to 1.8X ULN or increase to 1.3 to <1.5X baseline	>1.8 to <3.5 x ULN or increase to 1.5 to <2X baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0X baseline
respiratory distress	no or minimal interference with usual social/functional activities or wheezing or minimal increase in respiratory rate	greater than minimal interference with social and functional activities or nasal flaring or intercostal retractions or pulse oximetry 90-<95%	inability to perform usual social and functional activities or pulse oximetry <90%	respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
sedation (altered mental status)	no or minimal interference with usual social and functional activities	mild lethargy or somnolence causing greater than minimal interference with social and functional activities	confusion, memory impairment, lethargy, somnolence causing inability to perform usual activities	delirium or obtundation or coma
vomiting	transient/intermittent and no or minimal interference with oral intake	frequent episodes with no or mild dehydration	persistent vomiting resulting in orthostatic hypotension or IV fluids indicated	hypotensive shock

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; ULN = upper limit of normal
Source: adapted from Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017

Nineteen of the 89 total AEs (21.3%) were graded as severe (grade 3 on the DAIDS scale; [Table 15: Grading of Specific AEs as per the DAIDS Scale](#)). These occurred across 8 subjects, 6 of whom received both PHB and LEV, 1 of whom received PHB only, and 1 of whom received LEV only. The AEs which were graded as severe included: respiration abnormal (4), feeding disorder (3), hypotension (2), sedation (2), and one each of abdominal distension, apnea, hepatic enzyme elevated, hyperbilirubinemia, hyponatremia, oliguria, sepsis, and vomiting.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In NEOLEV2, 89 AEs occurred across 27 subjects (25.5% of the safety population). Fifty-three AEs occurred across 13 subjects in the PHB treatment group (31% of the subjects randomized to PHB); 36 AEs occurred across 14 subjects in the LEV treatment group (21.9% of the subjects randomized to LEV). [Table 16: Subjects with AEs by Treatment Group \(Safety Population\)](#) displays the number of subjects with particular AEs in each treatment group.

Based on available details in comment fields (e.g., NICU discharge summary details), I reviewed the ADAE dataset and recoded the findings to be as specific as possible. The preferred terms (PTs) which were recoded are the following: “heart rate abnormal” (Applicant’s PT) recoded to “bradycardia” or “arrhythmia” (reviewer PT) as appropriate; “apnoea,” “meconium aspiration syndrome,” “oxygen saturation abnormal” (Applicant’s PTs) recoded to “respiration abnormal” (reviewer PT). With recoding, the safety analysis results were not significantly altered; the AEs

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which were the most common AEs observed in NEOLEV2 remained unchanged (respiration abnormal in 28.6% of subjects randomized to PHB versus 12.5% of subjects randomized to LEV; sedation in 19% of subjects randomized to PHB versus 10.9% of subjects randomized to LEV; hypotension in 16.7% of subjects randomized to PHB versus 4.7% of subjects randomized to LEV; and feeding disorder in 16.7% of subjects randomized to PHB versus 9.4% of subjects randomized to LEV).

Some subjects ultimately required treatment with both study drugs (10/42 [23.8%] of the PHB group and 45/64 [70.3%] of the LEV group). In those subjects, it may be difficult to associate AEs with a particular study drug. [Table 17](#): Subjects with AEs by Drug Received (Safety Population) displays the number of subjects with AEs by the drug received using the same recoded PTs. Comparing the occurrence of AEs in subjects who received only PHB to the occurrence of AEs in subjects who received only LEV decreases potential confounding from the subjects' severity of illness. Increased severity of the underlying condition which caused the neonatal seizures could lead to more difficulty achieving seizure control (thus need for more than one drug to treat seizures) and to the higher occurrence of AEs (whether associated with the underlying illness or increased susceptibility to adverse reactions [AR]). Respiration abnormal occurred in 8/32 (25%) of subjects who received PHB only versus 1/19 (5.3%) of subjects who received LEV only. Hypotension occurred in 5/32 (15.6%) of subjects who received PHB only versus none of subjects who received LEV only. Sedation occurred in 5/32 (15.6%) of subjects who received PHB only versus 1/19 (5.3%) of subjects who received LEV only. Feeding disorder occurred in 4/32 (12.5%) of subjects who received PHB only versus 1/19 (5.3%) of subjects who received LEV only. The 6 deaths that occurred in NEOLEV2 occurred in subjects who received both PHB and LEV (10.9%).

Table 16: Subjects with AEs by Treatment Group (Safety Population)

System Organ Class Dictionary-Derived Term	PHB (N=42) n(%)	LEV (N=64) n(%)	Total (N=106)
Respiratory, thoracic, and mediastinal disorders	12 (28.6)	8 (12.5)	20 (18.9)
Respiration abnormal	12 (28.6)	8 (12.5)	20 (18.9)
Metabolism and nutrition disorders	9 (21.4)	6 (9.4)	15 (14.2)
Feeding disorder	7 (16.7)	6 (9.4)	13 (12.3)
Hyponatraemia	2 (4.8)	0 (0)	2 (1.9)
Nervous system disorders	8 (19)	7 (10.9)	15 (14.2)
Sedation	8 (19)	7 (10.9)	15 (14.2)
Vascular disorders	7 (16.7)	3 (4.7)	10 (9.4)
Hypotension	7 (16.7)	3 (4.7)	10 (9.4)
Hypoperfusion	1 (2.4)	0 (0)	1 (0.9)

System Organ Class Dictionary-Derived Term	PHB (N=42) n(%)	LEV (N=64) n(%)	Total (N=106)
General disorders and administration site conditions	1 (2.4)	6 (9.4)	7 (6.6)
Death	1 (2.4)	5 (7.8)	6 (5.7)
Infusion site extravasation	0 (0)	1 (1.6)	1 (0.9)
Cardiac disorders			
Bradycardia	1 (2.4)	2 (3.1)	3 (2.8)
Arrhythmia	0 (0)	1 (1.6)	1 (0.9)
Investigations	1 (2.4)	2 (3.1)	3 (2.8)
Blood lactic acid increased	0 (0)	1 (1.6)	1 (0.9)
C-reactive protein increased	0 (0)	1 (1.6)	1 (0.9)
Hepatic enzyme increased	1 (2.4)	0 (0)	1 (0.9)
Infections and infestations	2 (4.8)	1 (1.6)	3 (2.8)
Sepsis	1 (2.4)	1 (1.6)	2 (1.9)
Meningitis	1 (2.4)	0 (0)	1 (0.9)
Pneumonia	1 (2.4)	0 (0)	1 (0.9)
Gastrointestinal disorders	2 (4.8)	0 (0)	2 (1.9)
Abdominal distension	1 (2.4)	0 (0)	1 (0.9)
Haematochezia	1 (2.4)	0 (0)	1 (0.9)
Vomiting	1 (2.4)	0 (0)	1 (0.9)
Hepatobiliary disorders	1 (2.4)	0 (0)	1 (0.9)
Hyperbilirubinaemia	1 (2.4)	0 (0)	1 (0.9)
Renal and urinary disorders	1 (2.4)	0 (0)	1 (0.9)
Oliguria	1 (2.4)	0 (0)	1 (0.9)

Source: reviewer analysis of ADAE dataset (JMP)

Table 17: Subjects with AEs by Drug Received (Safety Population)

System Organ Class Dictionary-Derived Term	PHB (N=32) n(%)	PHB + LEV (N=55) n(%)	LEV (N=19) n(%)	Total (N=106)
Respiratory, thoracic, and mediastinal disorders	8 (25)	11 (20)	1 (5.3)	20 (18.9)
Respiration abnormal	8 (25)	11 (20)	1 (5.3)	20 (18.9)
Metabolism and nutrition disorders	6 (18.8)	8 (14.5)	1 (5.3)	15 (14.2)

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System Organ Class Dictionary-Derived Term	PHB (N=32) n(%)	PHB + LEV (N=55) n(%)	LEV (N=19) n(%)	Total (N=106)
Feeding disorder	5 (15.6)	7 (12.7)	1 (5.3)	13 (12.3)
Hyponatraemia	1 (3.1)	1 (1.8)	0 (0)	2 (1.9)
Nervous system disorders	5 (15.6)	9 (16.4)	1 (5.3)	15 (14.2)
Sedation	5 (15.6)	9 (16.4)	1 (5.3)	15 (14.2)
Vascular disorders	5 (15.6)	5 (9.1)	0 (0)	10 (9.4)
Hypotension	5 (15.6)	5 (9.1)	0 (0)	10 (9.4)
Hypoperfusion	1 (3.1)	0 (0)	0 (0)	1 (0.9)
General disorders and administration site conditions	0 (0)	6 (10.9)	1 (1.6)	7 (6.6)
Death	0 (0)	6 (10.9)	0 (0)	6 (5.7)
Infusion site extravasation	0 (0)	0 (0)	1 (1.6)	1 (0.9)
Cardiac disorders	1 (3.1)	2 (3.6)	1 (1.6)	4 (3.8)
Bradycardia	1 (3.1)	2 (3.6)	0 (0)	3 (2.8)
Arrhythmia	0 (0)	0 (0)	1 (1.6)	1 (0.9)
Investigations	0 (0)	2 (3.6)	1 (1.6)	3 (2.8)
Blood lactic acid increased	0 (0)	1 (1.8)	0 (0)	1 (0.9)
C-reactive protein increased	0 (0)	0 (0)	1 (1.6)	1 (0.9)
Hepatic enzyme increased	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Infections and infestations	2 (6.3)	1 (1.8)	0 (0)	3 (2.8)
Sepsis	1 (3.1)	1 (1.8)	0 (0)	2 (1.9)
Meningitis	1 (3.1)	0 (0)	0 (0)	1 (0.9)
Pneumonia	1 (3.1)	0 (0)	0 (0)	1 (0.9)
Gastrointestinal disorders	1 (3.1)	1 (1.8)	0 (0)	2 (1.9)
Abdominal distension	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Haematochezia	1 (3.1)	0 (0)	0 (0)	1 (0.9)
Vomiting	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Hepatobiliary disorders	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Hyperbilirubinaemia	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Renal and urinary disorders	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Oliguria	0 (0)	1 (1.8)	0 (0)	1 (0.9)

Source: reviewer analysis of ADAE dataset (JMP)

Reviewer comment: The most common AEs in NEOLEV2 were respiration abnormal,

hypotension, sedation, and feeding disorder. These are expected potential effects based on the mechanism of action of PHB as a GABA receptor agonist, in the drug class of barbiturates. A higher proportion of the total AEs occurred in the PHB group across a relatively higher proportion of subjects assigned to PHB as compared to the number of AEs and number of subjects who experienced AEs in the LEV group. The continued observation of this difference between the subjects who received only PHB and the subjects who received only LEV supports a contribution of PHB to causality of these AEs, independent from association with underlying illness. A dose response (i.e., increase in AEs in subjects who received 2 loads of PHB as compared to subjects who received only 1 load) was not demonstrated; this may have been related to the small sample size (10 subjects who received 2 loads; 22 subjects who received 1 load). The expected relative lack of AEs with LEV is supported by the NEOLEV2 findings and lends strength to the attribution to PHB. Considering the high incidence of mortality in infants with neonatal seizures (reported up to 20%), the occurrence of all study deaths in subjects who received both PHB and LEV would likely be indicative of severity of underlying illness rather than an AE caused by the study drugs or drug interaction.

8.4.6. Laboratory Findings

In NEOLEV2, safety monitoring laboratory test results were captured in the majority of the 106 subjects in the safety population at baseline and at 48 hours after onset of treatment with study drug. Some subjects had single missing laboratory tests results at 48 hours, most frequently calcium. Subject (b) (6) did not have lab results at 48 hours due to the lack of clinical necessity for the 48-hour laboratory tests and inability to charge to the research study funds; a protocol deviation was noted. A few subjects were missing results at 48 hours, including: hematology (subjects (b) (6)), chemistry (subjects (b) (6)), ALT (subjects (b) (6)). Abnormalities were noted to be “low” or “high” and graded as per the DAIDS scale ([Table 18](#): Grading of Lab Abnormalities as per the DAIDS Scale*).

Table 18: Grading of Lab Abnormalities as per the DAIDS Scale*

AE	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (potentially life-threatening)
ALT high	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Calcium (mg/dL)				
High				
≥ 7 days of age	10.6 to < 11.5	11.5 to < 12.5	12.5 to < 13.5	≥ 13.5
< 7 days of age	11.5 to < 12.4	12.4 to < 12.9	12.9 to < 13.5	≥ 13.5
Low				
≥ 7 days of age	7.8 to < 8.4	7.0 to < 7.8	6.1 to < 7.0	< 6.1
< 7 days of age	6.5 to < 7.5	6.0 to < 6.5	5.50 to < 6.0	< 5.50
Calcium (Ionized)				
High	> ULN to < 6.0	6.0 to < 6.4	6.4 to < 7.2	≥ 7.2

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Low	< LLN to 4.0	3.6 to < 4.0	3.2 to < 3.6	< 3.2
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Glucose (mg/dL) Fasting, High Nonfasting, High < 1 month, Low	110 to 125 116 to 160 50 to 54	> 125 to 250 > 160 to 250 40 to < 50	> 250 to 500 > 250 to 500 30 to < 40	≥ 500 ≥ 500 < 30
Hemoglobin (g/dL), Low ≤ 7 days of age 8 to ≤ 21 days 22 to 35 days	13.0 to 14.0 11.0 to 13.0 9.5 to 11.0	10.0 to < 13.0 9.0 to < 11.0 8.0 to < 9.5	9.0 to < 10.0 8.0 to < 9.0 6.7 to < 8.0	< 9.0 < 8.0 < 6.7
Platelets, (cells/mm ³), Decreased	100,000 to < 125,000	50,000 to < 100,000	25,000 to < 50,000	< 25,000
Potassium (mEq/L) High Low	5.6 to < 6.0 3.0 to < 3.4	6.0 to < 6.5 2.5 to < 3.0	6.5 to < 7.0 2.0 to < 2.5	≥ 7.0 < 2.0
Sodium (mEq/L) High Low	146 to < 150 130 to < 135	150 to < 154 125 to < 130	154 to < 160 121 to < 125	≥ 160 ≤ 120
White Blood Cells, (cells/mm ³) Decreased > 7 days of age ≤ 7 days of age	2,000 to 2,499 5,500 to 6,999	1,500 to 1,999 4,000 to 5,499	1,000 to 1,499 2,500 to 3,999	< 1,000 < 2,500

* Some lab parameters were not noted in the DAIDS Table, including high carbon dioxide, chloride
Source: adapted from Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events,
Corrected Version 2.1, July 2017

All laboratory findings, including those which were categorized as “normal,” were included in the analysis dataset ADLB. My analysis focused on laboratory test values which were documented as being normal at baseline but abnormal at 48 hours, or which had a higher grade of severity at 48 hours as compared to baseline. There were 91 such abnormalities across 51 subjects. Seven lab abnormalities were noted across 4 subjects who received LEV only; 23 abnormalities across 14 subjects who received PHB; and 61 abnormalities across 33 subjects who received LEV and PHB.

Abnormalities which occurred in none of the subjects who received LEV only but occurred in some subjects who received PHB only included the following:

- Platelets low occurred in 7 subjects who received PHB only (and 11 subjects who received LEV and PHB). Thrombocytopenia is not typically associated with PHB except in cases of hypersensitivity. A search of the FDA Adverse Events Reporting System Public

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Dashboard (FAERS) for reports with PHB and PHB sodium yielded 54/8130 (0.66%) cases of thrombocytopenia.

- ALT high occurred in 2 subjects who received PHB only (and 8 subjects who received LEV and PHB). Abnormal liver function is associated typically with chronic PHB use. A FAERS search yielded 78/8130 cases (0.96%) of ALT increased and 70/8130 cases of AST increased (0.86%).
- Hemoglobin low occurred in 2 subjects who received PHB only (and 10 subjects who received LEV and PHB). PHB is typically not associated with anemia, except in cases of hypersensitivity. A FAERS search yielded 44/8130 (0.54%) cases of anemia and 2 cases of neonatal anemia.
- Abnormal sodium occurred in 3 subjects who received PHB only; in 2 of those subjects, high sodium was noted. Neither hyponatremia nor hypernatremia is associated with PHB. A FAERS search yielded 10 cases of blood sodium decreased and 5 cases of blood sodium increased.

Reviewer comment: No significant occurrence of laboratory abnormalities was noted by the Applicant. Independent analysis showed that there was an increased incidence of laboratory abnormalities in the group of subjects who received both LEV and PHB; this likely relates to the severity of underlying illness in this group. Although the small sample size prevents definitive conclusion of causality, those laboratory abnormalities which occurred in none of the subjects who received LEV only and occurred in some of the subjects who received PHB only were reviewed in more detail. The low number of FAERS reports of those abnormalities (thrombocytopenia, anemia, abnormal sodium) in the context of a long history of PHB use suggests that routine pharmacovigilance is appropriate.

8.4.7. Vital Signs

In NEOLEV2, vital sign (heart rate, respiratory rate, blood pressure, oxygen level) values were not captured; however, the subjects were on continuous cardiorespiratory monitoring as per neonatal standard of care. The “vital sign” dataset submitted in this NDA included weight, height, and head circumference measurements. Abnormalities, including arrhythmia, respiratory abnormality, and hypotension, were captured as AEs.

8.4.8. Electrocardiograms (ECGs)

In NEOLEV2, raw ECG data was not captured; however, the subjects were on continuous cardiorespiratory monitoring as per neonatal standard of care. “Abnormal heart rate” was captured on the CRF.

8.4.9. QT

The Applicant has not performed thorough QT clinical studies but included language regarding the risk of prolongation of the QT interval by PHB in its proposed labeling. This was based on in

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vitro (hERG; human ether-a-go-go related gene) study data which demonstrated that PHB blocked potassium channel currents with an IC50 (half maximal inhibitory concentration) of 3mM (approximately 700 µg/ml), and an open-label prospective study of adults with late post-stroke seizures who were randomized to PHB or to LEV, which showed QT prolongation in 3 of 25 patients randomized to PHB as compared to 1 of 24 randomized to LEV and 1 of 50 who received no treatment. An Interdisciplinary Review Team (IRT) consult was performed and concluded that the available nonclinical and limited clinical data suggests a possibility for QTc prolongation, but that the literature report was inadequate to support characterization of PHB's QTc effects, and that the Applicant should characterize QTc interval effects. Because there has been a relative lack of recognized QT issues in the extensive history of PHB use for neonatal seizures, post-approval investigation was determined to be acceptable (see Section 12 Postmarketing Requirements and Commitments).

The Applicant proposed language in the label's Sections 5.6 QT Prolongation, 12.2 Pharmacodynamics—Cardiac Electrophysiology

(b) (4)

(b) (4)

The proposed language was edited in the 3 sections as per IRT recommendations.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

In its proposed labeling, the Applicant included conditions in the Contraindications (CIs) and Warning and Precautions sections which were not observed in the NEOLEV2 study or Study PHEN-20-01 but which the Applicant noted have been associated with PHB use in adults in standard medical textbooks. The following safety issues were reviewed through a literature search: porphyria, hypersensitivity, and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

8.5.1. Porphyria

Porphyrias are disorders which result from enzymatic abnormalities in the heme biosynthesis pathway, and subsequent accumulation of heme precursors 5-aminolevulinic acid, porphobilinogen, and porphyrins. Acute porphyrias are characterized by episodes which may be life-threatening and include symptoms and signs such as anxiety, confusion, limb or abdominal pain, hyponatremia, seizures, and muscle weakness. These episodes typically present in

adulthood and rarely before puberty but have been reported in a 3-year-old after administration of PHB.¹⁸ Acute episodes are triggered by conditions that either induce hepatic δ -aminolevulinic acid synthase 1 (ALAS1) or increase the demand for heme synthesis in the liver, such as hormonal changes, fasting, smoking, infections, and drugs which induce cytochrome P450 enzymes and increase hepatic heme turnover,¹⁹ such as PHB.

8.5.2. Hypersensitivity

Drugs used to treat seizures are associated with hypersensitivity reactions, the severity of which occurs in a spectrum, from mild rashes to severe reactions with systemic organ involvement manifesting as fever, lymphadenopathy, hepatitis, pneumonitis, myocarditis, nephritis, and colitis. Drugs with an aromatic amine structure, including PHB, PHT, carbamazepine, oxcarbazepine, and lamotrigine, have higher rates of hypersensitivity reactions, with cross-reactivity appearing to be greater between these aromatic drugs.²⁰ Although rare in neonates and infants, antiseizure drug-induced hypersensitivity syndrome has been reported in those populations, including with administration of PHB²¹ and PHT.²²

Some of the most severe cases of drug-induced hypersensitivity syndrome, in which the hypersensitivity reaction manifests with multiorgan involvement and hematologic changes including eosinophilia and atypical lymphocytes, have been termed Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).²³ I have not been able to find publications of neonates with the named syndrome of DRESS; however at least 1 neonatal case of drug-induced hypersensitivity syndrome appeared to have features consistent with DRESS.²⁰

8.5.3. Serious Dermatologic Reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

Although SJS and TEN are rare in neonates, and they are more frequently associated with infections in neonates and infants than in older patients, SJS and TEN have been reported in

¹⁸ Sykes RM (2001). Acute intermittent porphyria, seizures, and antiepileptic drugs: a report on a 3-year-old Nigerian boy. *Seizure* 10:64-66.

¹⁹ Puy H, Gouya L, and Deybach JC (2010). Porphyrrias. *Lancet* 375:924-937.

²⁰ Mani R, Monteleone C, Schalock PC et al (2019). Rashes and other hypersensitivity reactions associated with antiepileptic drugs: A review of current literature. *Seizure: Eur J Epilepsy* 71:270-278.

²¹ Chen CJ, Huang YC, Wang CY, Lin TY (2003). Fatal anticonvulsant hypersensitivity syndrome in an infant. *Eur J Pediatr* 162:893-894.

²² Yigit S, Korkmaz A, Sekerel B (2005). Drug-induced hypersensitivity syndrome in a premature infant. *Pediatr Dermatol* 22:71-74.

²³ Corneli HM (2017). DRESS syndrome: drug reaction with eosinophilia and systemic symptoms. *Pediatr Emer Care* 33:499-504.

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neonates due to drugs, including PHB or PHT.²⁴ These serious skin reactions are characterized by painful rash, mucositis, and systemic signs such as fever, and may be fatal. Death is often due to sepsis.

8.6. Safety Analyses by Demographic Subgroups

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²⁴ Iriarte C, Karim SA, Nassim JS, Grenier PO, Massey KJ (2022). Infantile Stevens Johnson syndrome and toxic epidermal necrolysis: A systematic review of clinical features and outcomes in children ages 12 months and under. *Pediatr Dermatol* 2022:1-7.

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This application includes a single study performed in the single age group of neonates so the sample size is small. With that in mind, no obvious differences in AEs based on sex were seen in NEOLEV2 ([Table 19](#): AEs by Sex (Total Safety Population) and [Table 20](#): Number of Subjects with AEs per Sex by Drug Received (Safety Population)). Because of the small sample size in most racial categories and the high number of missing race designations, conclusions about differences based on race cannot be made.

Table 19: AEs by Sex (Total Safety Population)

System Organ Class Dictionary-Derived Term	F (N=51)	M (N=55)	Total (N=106)
Any Adverse Event	51 (100)	55 (100)	106 (100)
Respiratory, thoracic, and mediastinal disorders	9 (17.6)	11 (20)	20 (18.9)
Respiration abnormal	9 (17.6)	11 (20)	20 (18.9)
Apnea	0 (0)	1 (1.8)	1 (0.9)
Meconium aspiration syndrome	1 (2)	0 (0)	1 (0.9)
Metabolism and nutrition disorders	6 (11.8)	9 (16.4)	15 (14.2)
Feeding disorder	6 (11.8)	7 (12.7)	13 (12.3)
Hyponatremia	0 (0)	2 (3.6)	2 (1.9)
Nervous system disorders	8 (15.7)	7 (12.7)	15 (14.2)
Sedation	8 (15.7)	7 (12.7)	15 (14.2)
Vascular disorders	5 (9.8)	5 (9.1)	10 (9.4)
Hypotension	5 (9.8)	5 (9.1)	10 (9.4)
Hypoperfusion	0 (0)	1 (1.8)	1 (0.9)
General disorders and administration site conditions	4 (7.8)	3 (5.5)	7 (6.6)
Death	4 (7.8)	2 (3.6)	6 (5.7)
Infusion site extravasation	0 (0)	1 (1.8)	1 (0.9)
Investigations	3 (5.9)	4 (7.3)	7 (6.6)
Heart rate abnormal	2 (3.9)	2 (3.6)	4 (3.8)

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System Organ Class Dictionary-Derived Term	F (N=51)	M (N=55)	Total (N=106)
Blood lactic acid increased	0 (0)	1 (1.8)	1 (0.9)
C-reactive protein increased	0 (0)	1 (1.8)	1 (0.9)
Hepatic enzyme increased	0 (0)	1 (1.8)	1 (0.9)
Oxygen saturation abnormal	1 (2)	0 (0)	1 (0.9)
Infections and infestations	2 (3.9)	1 (1.8)	3 (2.8)
Sepsis	1 (2)	1 (1.8)	2 (1.9)
Meningitis	1 (2)	0 (0)	1 (0.9)
Pneumonia	1 (2)	0 (0)	1 (0.9)
Gastrointestinal disorders	1 (2)	1 (1.8)	2 (1.9)
Abdominal distension	0 (0)	1 (1.8)	1 (0.9)
Haematochezia	1 (2)	0 (0)	1 (0.9)
Vomiting	0 (0)	1 (1.8)	1 (0.9)
Hepatobiliary disorders	0 (0)	1 (1.8)	1 (0.9)
Hyperbilirubinemia	0 (0)	1 (1.8)	1 (0.9)
Renal and urinary disorders	0 (0)	1 (1.8)	1 (0.9)
Oliguria	0 (0)	1 (1.8)	1 (0.9)

Source: Applicant's dataset ADAE (unchanged), JMP Clinical

Table 20: Number of Subjects with AEs per Sex by Drug Received (Safety Population)

Sex	PHB (N=32) n(%)	PHB + LEV (N=55) n(%)	LEV (N=19) n(%)	Total (N=106) n(%)
Female	4 (12.5)	9 (16.4)	1 (5.3)	14 (13.2)
Male	5 (15.6)	6 (10.9)	2 (10.5)	13 (12.3)

Source: ADAE (unchanged); JMP

[Table 21](#): Number of Subjects with AEs by Drug Received and HIE Diagnosis (Safety Population) displays the number of subjects who had AEs based on the drug received and whether they had

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HIE, treated or untreated with hypothermia. 57 subjects (53.8%) of the safety population had HIE; 20 (35%) of those subjects had AEs. Of the 49 subjects (46.2%) in the safety population who did not have HIE, 7 (14.2%) had AEs. Fifteen (36%) of the 42 total subjects with HIE who were treated with hypothermia had AEs, whereas 5 (33.3%) of the 15 subjects with HIE who did not receive therapeutic hypothermia had AEs. It is difficult to make a definitive conclusion, however the suggestion is that subjects with HIE are more likely to have AEs, which could be related to the severity of underlying illness.

Table 21: Number of Subjects with AEs by Drug Received and HIE Diagnosis (Safety Population)

	PHB (N=32) n(%)	PHB+LEV (N=55) n(%)	LEV (N=19) n(%)	Total (N=106) n(%)
HIE	7 (21.9)	11 (20)	2 (10.5)	20 (18.9)
Hypothermia	6 (18.8)	8 (14.5)	1 (5.3)	15 (14.2)
No hypothermia	1 (3.1)	3 (5.5)	1 (5.3)	5 (4.7)
No HIE	2 (6.3)	4 (7.3)	1 (5.3)	7 (6.6)

8.7. Study PHEN-20-01 A Two Sequence, Two-Period Crossover, Single Dose Comparative Bioavailability Study of Phenobarbital Sodium Intravenous Formulations in Healthy Adult Subjects.

The Applicant conducted a randomized, open-label study to compare the PK of PHB following a single IV infusion of 2 mg/kg, administered over 15 minutes, of the Applicant's formulation and of the West-Ward formulation. Twenty-five healthy adults, ages 21 to 45 years, 11 female and 14 male, were included in the safety population. The most common AEs (those which occurred in more than 1 subject between either formulation) occurred at similar frequencies between both formulations (see [Table 22](#)). These were somnolence, dizziness, headache, euphoric mood, lethargy, and vessel puncture site pain.

I qualitatively examined the observed vital sign measurements and used relatively arbitrary cutoff blood pressure (BP) values of less than 90/60, a 15 point or greater decrease in systolic blood pressure (no subjects had as high as a 20-point decrease), or a 10-point or greater decrease in diastolic blood pressure (DBP) as indicators of possible hypotension. Two subjects who had a 10-point or greater decrease in DBP were subjects who had the AE of dizziness, however in relation to the BP measurements, there was no intervention, no repeating of the BP measurement, and no notation of clinical significance. Similarly, the significance of changes in heart rate and respiratory rate from baseline was unclear.

Table 22: Subjects with AEs by Formulation Administered (PHEN-20-01 Safety Population)

Dictionary-derived term	PHB (Applicant formulation) (N = 24) n(%)	PHB (West-Ward formulation) (N=25) n(%)
Somnolence	6 (25)	7 (28)
Dizziness	2 (8.3)	2 (8)
Headache	2 (8.3)	1 (4)
Euphoric mood	1 (4.2)	1 (4)
Lethargy	1 (4.2)	1 (4)
Vessel puncture site pain	1 (4.2)	1 (4)
Abdominal discomfort	0	1 (4)
Back pain	0	1 (4)
Dysarthria	0	1 (4)
Dysmenorrhea	1 (4.2)	0
Dyspepsia	0	1 (4)
Feeling cold	0	1 (4)
Herpes zoster	0	1 (4)
Palpitations	1 (4.2)	0
Post-traumatic stress disorder	0	1 (4)
Visual impairment	0	1 (4)
Total AEs	15	21

Source: reviewer analysis of PHEN-20-01 ADSL and ADAE datasets (JMP)

Reviewer comment: The most common AEs seen in this healthy adult population after a single IV dose of 2 mg/kg are consistent with PHB's known mechanism of action, but do not inform the safety of PHB in the proposed indicated population of neonates with seizures. Vital sign changes did not appear to be clinically significant. Laboratory testing after a single dose in a healthy adult also would not inform the risk of laboratory abnormalities in neonates with seizures. In addition, ECGs were performed only at baseline and at end of study (day 21 of the second treatment period, and therefore 20 days after a dose).

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Tumor development was not assessed during the NEOLEV2 study and was not necessary based on the indicated population, short duration of the study, and lack of observed tumor development in the long history of PHB use.

8.8.2. Human Reproduction and Pregnancy

The NEOLEV2 study was performed in neonates. No pregnancies occurred in the participants of the comparative bioavailability study. Therefore, no exposures in pregnancies nor lactating

woman occurred. A consult was obtained from the Division of Pediatric and Maternal Health (DPMH) Maternal Health Team to assist with discussion of pregnancy and lactation in the labeling. The Maternal Health Team identified reports of neonatal withdrawal and sedation and of increased risk of bleeding in infants exposed to PHB in utero. They also identified reports of potentially clinically significant PHB levels in breastfed infants exposed to mothers taking PHB; these studies were limited by lack of confirmation of assay validation and inability to determine excretion in breast milk. Labeling recommendations for pertinent safety issues as recommended by the Maternal Health Team were incorporated into labeling.

8.8.3. Pediatrics and Assessment of Effects on Growth

Compliance with the Pediatric Research Equity Act (PREA) is not applicable due to the product's orphan drug designation. However, because of the population of the proposed indication, particularly because no treatments have at this point been approved for the treatment of neonatal seizures, DPMH's Pediatric Team and the Office of Pediatric Therapeutics (OPT) Neonatology and Pharmacovigilance Team were consulted and closely involved throughout the review cycle.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Controlled Substance Staff (CSS) performed a consult. CSS concluded that the available abuse-related data submitted in this NDA and generated in an Office of Surveillance and Epidemiology (OSE) review of PHB utilization, abuse, misuse, diversion, and overdose which CSS requested are consistent with the Applicant's proposal that PHB remained controlled under schedule IV of the Controlled Substances Act. This data includes nonclinical data which demonstrates the reinforcing effects and ability of PHB to produce dependence, withdrawal, and tolerance; abuse-related AEs (somnolence, euphoric mood, dizziness) demonstrated in PHEN-20-01; and epidemiological data showing that PHB is abused for sedation, relaxation, or mitigation of side effects from other substances, and therefore is typically abused with polysubstance use.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Because of the extensive past history of PHB use and marketing, the Division of Pharmacovigilance (DPV) was consulted to assess FAERS reports and the literature for an association between PHB and AEs which were in unapproved PHB product labels and/or were in the labeling proposed in this NDA. These included serious hypersensitivity reactions (including DRESS, SJS/TEN, anaphylaxis), infusion-site or injection-site reactions (including tissue necrosis/gangrene, thrombosis, thrombophlebitis), laryngospasm, hypotension, and hypertension. Several cases were identified which had reasonable evidence of causal association to PHB of DRESS and SJS/TEN. Two of 4 cases of administration site necrosis/gangrene were assessed as having a probable causal association with PHB; the other 2

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cases were assessed with a possible causal association because of the administration of other concomitant medications at the site. All 4 cases of necrosis had serious outcomes of amputation or skin grafting; 2 occurred in neonates. One of 2 cases of administration site thrombophlebitis had probable causal association with PHB; the 2 cases were non-serious and did not require intervention. One of 3 cases of anaphylaxis had probable causal association with PHB; 1 case in association with polydrug dependence and detoxification was associated with laryngospasm. Two of 4 cases of infusion-related hypotension had probable causal association with PHB. One case was identified which reported hypertension after IV PHB, however the provided details supported only a possible causal association with PHB.

Reviewer comment: Postmarketing reports and publications support the inclusion within labeling of warnings and precautions regarding hypersensitivity reactions, serious dermatologic reactions, and infusion site reactions. Hypotension is included in the label as one of the most common ARs observed in the pivotal trial. It is unclear if PHB was the cause of laryngospasm and hypertension in single reported cases.

8.9.2. Expectations on Safety in the Postmarket Setting

Similar to the off-label use of PHB for neonatal seizures, PHB has been used despite lack of approval for epilepsy treatment in older children and adults. Anticipated risks would be similar in those populations.

8.9.3. Additional Safety Issues from Other Disciplines

None.

8.10. Integrated Assessment of Safety

As discussed in Section [8.4.5](#), the safety data from the NEOLEV2 study in 106 neonates who received at least 1 dose of PHB 20 mg/kg IV demonstrate that the risks of PHB include abnormal respiration, hypotension, sedation, and feeding disorder. Hypotension and abnormal respiration occurred more often as SAEs in subjects who received PHB compared to those who received LEV (Section [8.4.2](#)). However, abnormal respiration did not appear to be a reason for withdrawal from the study. Hypotension may have been more likely to lead to study discontinuation, with the caveat that small sample sizes prevent a definitive conclusion (Section [8.4.3](#)). AEs related to PHB did not appear to contribute to deaths in the study. No deaths occurred in the subjects who received PHB only; all deaths occurred in subjects who required 2 loads of both PHB and LEV and were often noted to have occurred after a decision to withdraw life support in the context of poor prognosis. This suggests that the hypotension and abnormal respiration, even when serious, is monitorable and treatable. The abnormal respiration may have been more amenable to supportive treatment, or it may have been that many subjects already required ventilatory support prior to the administration of PHB, making withdrawal from the study unnecessary. Refractory hypotension which does not adequately respond to

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pressor support, whether solely related to the drug or also contributed to by underlying cardiovascular instability, would be a reason to withdraw.

This safety profile demonstrated in NEOLEV2 is consistent with PHB's known mechanism of action and is supported by the long-term experience with the active moiety for the treatment of seizures since the 1920's and in neonatal seizures for over 40 years. The risk of these ARs which potentially require intervention such as pressors and ventilation needs to be weighed against the risks of continued seizures, which include further physiologic stress and potential additional brain injury related to processes such as excitotoxicity. If PHB is administered in a controlled setting in which monitoring of vital signs and cardiorespiratory function is performed, these risks are "monitorable," i.e., the severity may be controlled and managed until exposure levels are lower and the ARs lessen.

Limitations of the safety data in this NDA include the following:

- The lack of collection of ECG data in NEOLEV2 and the lack of ECG data while on treatment in PHEN-20-01 precludes characterization of the potential effect of PHB on QTc prolongation, which was a concern raised by in vitro findings and by a single open-label study in adults which provided limited information (see Section [8.4.9](#)).
- The lack of data regarding potential effects of PHB on neurodevelopment, which is a concern raised by nonclinical findings and a small number of clinical studies (see Section [2.1](#) and Section [12](#)).

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not deemed necessary for this submission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information (most recent version dated 11/8/2022) have been proposed, but the labeling has not been finalized at the time of this review.

Notable recommended edits to the Applicant's proposed prescribing information include:

- Addition of dosing recommendations based on modeling and simulation, including an alternative maintenance dosing interval of 12 hours (in addition to a dosing interval of 8 hours) and loading and maintenance dosing for preterm infants.
- Addition of warnings and precautions pertinent to potential off-label use.

Of note, the general term, “respiration abnormal” as an AE was retained, based on the occurrence of various abnormal respiratory patterns in neonates.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the volume of experience with phenobarbital and its safety profile, there are no additional risk management strategies required beyond the recommended labeling.

12. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMRs) were identified:

- 1) A prospective study with appropriate comparator(s) to assess long-term neurodevelopmental effects of Sezaby in patients with neonatal seizures. Ensure capture of an adjustment for potential confounders. Assess neurodevelopmental effects using validated age-appropriate developmental assessments of motor skills, cognition, language, and behavior. Follow patients for a minimum of 5 years.
- 2) An evaluation of the effects of SEZABY on the QTc interval designed according to ICH E14 guidance for industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (October 2015) and E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (February 2022).

PHB has been used off-label for the treatment of neonatal seizures with the assumed risk of possible long-term neurodevelopmental effects, balanced against the acute and long-term risks of untreated seizures. The concern for long-term neurodevelopmental effects is based on the nonclinical data on apoptotic neurodegeneration in rodents,⁸ and on mainly an RCT comparing the use of PHB and placebo for treatment of febrile seizures which showed lower intelligence quotient (IQ) scores in children who had received PHB¹⁰ and an observational study which showed low scores on verbal and intelligence scales in men who had been exposed to PHB in utero.⁹ The Division of Epidemiology 1 (DEPI-1) of OSE was consulted to determine if Active Risk Identification and Analysis (ARIA) assessment of the Sentinel safety surveillance system would be sufficient to investigate this concern; it was deemed insufficient.

13.1. References

See footnotes throughout document.

13.2. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators.

Covered Clinical Study (Name and/or Number): NEOLEV2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>84</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>6</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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Covered Clinical Study (Name and/or Number): PHEN-20-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>n/a</u> Significant payments of other sorts: <u>n/a</u> Proprietary interest in the product tested held by investigator: <u>n/a</u> Significant equity interest held by investigator in Sponsor of covered study: <u>n/a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>n/a</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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APPEARS THIS WAY ON ORIGINAL

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/

AMY KAO
11/16/2022 06:39:30 PM

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11/16/2022 08:05:40 PM