CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215910Orig1s000

SUMMARY REVIEW

Summary Review

Date	November 17, 2022
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Review
NDA#	NDA 215910
Applicant	Sun Pharma Advanced Research Company, Ltd.
Date of Submission	February 17, 2022
PDUFA Goal Date	November 17, 2022
Proprietary Name	Sezaby
Established or Proper Name	Phenobarbital
Dosage Form(s)	100 mg/vial lyophilized powder (to be reconstituted in 10 ml of 0.9% sodium chloride to a final concentration of 10 mg/ml (b) (4))
Applicant Proposed Indication(s)/Population(s)	Treatment of neonatal seizures
Applicant Proposed Dosing Regimen(s)	All doses to be administered as 15 min intravenous (IV) infusion 1st loading dose: 20 mg/kg 2nd loading dose (if seizures persist): 20 mg/kg Maintenance dose: 1.5 mg/kg every 8 hours for up to 5 days
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of neonatal seizures in term and preterm infants
Recommended Dosing Regimen(s) (if applicable)	All doses to be administered as 15 min IV infusion 1st loading dose: 20 mg/kg 2nd loading dose* (if seizures persist): 20 mg/kg *2nd loading dose in preterm infants: 10 mg/kg or 20 mg/kg Maintenance dose: 1.5 mg/kg every 8 hours or 2.25 mg/kg every 12 hours (total daily dose: 4.5 mg/kg) up to 5 days

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

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 long-term 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 1920s 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 the treatment of their seizures (72.7% of the PHB group compared to 24.6% of the levetiracetam 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 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 the safety of dosing in preterm infants (not enrolled in the NEOLEV2 study).

NEOLEV2 identified adverse events (AEs) associated with PHB including 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 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 outcomes 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 it will also 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 thought to be independent from the underlying cause of the neonatal seizures, include the response to seizure treatment, the recurrence and duration of seizures, and the amount of seizure burden.	Neonatal seizures are a serious condition that often lead to poor short- and long-term outcomes.
Current Treatment Options	• There are no approved treatments for neonatal seizures. • PHB has been used as first-line treatment (off-label) for neonatal seizures for a significant time, despite a lack 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	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).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 and continued for up to 5 days. • The primary efficacy endpoint was electrographic seizure freedom for at least 24 hours without the need for treatment 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 consistent 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 (54.5%), 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 daily 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 demonstrates similar PHB levels to those in term	Modeling and simulation analyses also support dosing in preterm infants (not enrolled in the NEOLEV2 study).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 trial 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 concern for potential negative effects of PHB on neurodevelopment and on QTc prolongation could not be assessed based on the submitted data.	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 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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• 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 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.	seizures. A prospective assessment of the impact of PHB exposure during the neonatal period on long-term neurodevelopmental outcomes will be evaluated as a postmarketing requirement (PMR). An evaluation of any effect of PHB on QTc prolongation will also be assessed with a PMR.

2. Background

This new drug application (NDA), submitted on February 17, 2022, contains data intended to support the safety and effectiveness of Sezaby (phenobarbital injection) for the treatment of neonatal seizures. This application is submitted using the 505(b)(2) pathway because of its reliance on information contained in published literature.

There are currently no FDA-approved treatments for neonatal seizures.

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 1920s. It is an agonist of the gamma aminobutyric acid (GABA) receptor and therefore increases GABA-mediated inhibition. PHB has been historically used for sedation (e.g., preoperative sedation), and for the treatment of insomnia, anxiety, 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 an NDA to the Food and Drug Administration (FDA) and therefore has not been approved.

PHB has been used in clinical practice as the first-line treatment for neonatal seizures for decades. 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).

Sezaby received orphan drug designation on October 2, 2019, was granted Fast Track designation on August 24, 2021, and received a Rare Pediatric Disease designation on August 26, 2021, for the treatment of neonatal seizures.

The current application contains the results of an adequate and well-controlled clinical trial that compared PHB to levetiracetam (LEV) for the treatment of neonatal seizures (NEOLEV2). This trial used the marketed West-Ward Pharmaceuticals' PHB formulation, to which the Applicant has attempted to establish a pharmacokinetic (PK) bridge.

The detailed regulatory history of the Sezaby development program is provided in Dr. Amy Kao's clinical review. This application was designated as a priority review; however, as discussed in Section 3 of this Summary Review, the review clock was extended from its original goal date of August 17, 2022, to November 17, 2022, due to the submission of a major amendment that made a change to the planned manufacturing site.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application.

Refer to the OPQ review for details of the product quality assessment.

The OPQ review notes that Sezaby consists of sterile, lyophilized phenobarbital sodium with no preservatives or other excipients and is to be reconstituted with 0.9% Sodium Chloride Injection USP to achieve a 10 mg/mL solution. Unlike the currently marketed unapproved phenobarbital for injection, the OPQ review notes that Sezaby does not contain alcohol or propylene glycol which is preferable for drugs intended for use in the neonatal population because these preservative/excipients could be toxic to neonates receiving multiple drugs containing them.

The OPQ review states that no drug substance deficiencies were identified during the review of the NDA and supporting drug master file (DMF).

The OPQ review notes that deficiencies related to the manufacturing process and microbiology/sterility were identified in a site inspection at the drug product manufacturing facility proposed in the original NDA (Halol site). To address the site issue, the Applicant proposed an alternate manufacturing site (Baska site) in a major amendment and withdrew Halol site. The OPQ review notes that the Applicant has provided adequate CMC/microbiology information to support the Baska site, including 6 months long-term and accelerated stability data for commercial scale batches.

The OPQ review recommends approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Ed Fisher, with Dr. Lois Freed performing the secondary review. The main findings and conclusions from the nonclinical reviews are discussed below.

The nonclinical review notes that the Applicant has not conducted standard nonclinical studies but has relied on previous human experience with PHB in neonates (as reported in the published literature) to provide the nonclinical safety data required for labeling.

The nonclinical review team has incorporated its conclusions regarding the relevant nonclinical safety issues addressed by the published literature into the negotiated Sezaby labeling as follows. Section 8.4 Pediatric Use of labeling addresses the induction of apoptosis observed in rodent studies during the period of synaptogenesis that corresponds to the first

several years of human life. Section 12.1 Mechanism of Action discusses potentiation of synaptic GABAergic transmission as the most likely mechanism of action for PHB. Section 13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility discussed the evidence from experimental animals for the carcinogenicity of phenobarbital after long-term exposure. (b) (4) (b) (4). The nonclinical review notes that there are no reports of standard fertility studies of PHB in published literature but that a published rat study found no adverse effects on fertility.

The nonclinical review concluded that the published literature information provided in the NDA is adequate for describing risks to the neonatal population based on nonclinical studies and that this information should be included in the relevant sections of labeling as discussed above.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Adarsh Gandhi (clinical pharmacology reviewer), Dr. Gopichand Gottipati (clinical pharmacology team lead), Dr. Michael Bewernitz (pharmacometrics reviewer), Dr. Atul Bhattaram (pharmacometrics team lead), Dr. Hobart Rogers (pharmacogenomics reviewer), and Dr. Sarah Dorff and Dr. Michael Pacanowski (pharmacogenomics team leads).

The OCP review explains that the Sezaby clinical development program consisted of the NEOLEV2 study, a PK bridging study (Study PHEN-20-01) in adult healthy volunteers (intended to bridge the to-be-marketed formulation to the formulation used in the NEOLEV2 study), and published literature intended to characterize the drug-drug interaction potential of Sezaby.

The OCP review states that Study PHEN-20-01 was conducted to evaluate the relative bioavailability of Sezaby and the PHB product used in the NEOLEV2 study manufactured by West-Ward's Pharmaceuticals (See Section 7 of this review for a discussion of the design of the NEOLEV2 study).

Table 1 summarizes the conclusions of the OCP review with respect to the pharmacologic and clinical PK properties of PHB. The OCP review notes that these conclusions are based on data from adult healthy volunteers in the current development program or evidence from the published literature provided in the application.

Table 1: Summary of OCP Review Findings

Mechanism of Action	The mechanism of action likely involves potentiation of synaptic inhibition through an action on the GABA-A receptors, blocking high-voltage activated calcium channels to facilitate intrinsic chloride channel function, inhibiting as well by blocking AMPA and kainate receptors.
Formulation	100 mg/vial lyophilized powder (to be reconstituted in 10 ml of 0.9% sodium chloride to a final concentration of 10 mg/ml (b) (4)).
Metabolism	PHB is primarily metabolized by hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19, CYP2E1, and UGTs. Published literature reports that the primary metabolic pathways include hydroxylation to p-hydroxy-PHB with sequential glucuronidation to hydroxy-PHB-O-glucuronide and formation of PHB-N-glucoside. The metabolites of PHB are inactive. The published literature indicates that, at birth, the expression of CYP2C9 is negligible, which results in the longer half-life in neonates compared to older populations. The published literature also reports that the elimination $t_{1/2}$ of PHB in neonates is about 1 week.
Absorption	Following administration of a single 2 mg/kg dose to healthy adults, peak mean total (bound and unbound) plasma concentrations of 4.72 µg/mL are achieved.
Distribution	In adults, the mean volume of distribution (Vc) ranged from 0.6-0.68 L/kg. Published literature reports that PHB is moderately bound to plasma proteins (35-60%). In a PK study in adult healthy volunteers, the ratio of unbound to total PHB measured in plasma was about 50%.
Excretion	The published literature reports that, following intraduodenal administration of a radiolabeled PHB dose in healthy adults, approximately ~25% of the dose is excreted unchanged in urine. In adults, total body clearance for unbound PHB is 628 mL/h (10.5 mL/min) and terminal elimination half-life (t1/2) is 106 hours after a single dose.

The OCP review notes that there are no clinically significant differences in the PK properties of PHB in neonates administered therapeutic hypothermia, and that sex and race were not found to influence the PK properties of PHB. The OCP review further states that the impact of hepatic or renal impairment on the PK properties of PHB in neonates is unknown.

Refer to the Dosing Recommendations discussion below with respect to the recommended dosing in pre-term infants.

Dosing Recommendations

The OCP review explains that the recommended dosing for term infants is based on the dosing used in NEOLEV2, discussed in Section 7 of this Summary Review. PK modeling and simulation showed that total daily maintenance dosing of 4.5 mg/kg of PHB given in 2 or 3 divided doses (i.e., 1.5 mg/kg every 8 hours or 2.25 mg/kg every 12 hours) resulted in

comparable PHB plasma concentrations. Notably, dosing every 12 hours with the currently marked formulation of PHB is commonly employed in clinical practice (compared to the every 8 hour regimen used in NEOLEV2 to maintain blinding with the maintenance dosing regimen for LEV).

An important consideration during the review was the recommended dosing for pre-term neonates, who were not enrolled in the NEOLEV2 study. The OCP review comments that published literature suggest that gestational age effects the PK properties of PHB in pre-term neonates, related largely to a lack of maturation of the CYP2C9 enzyme. Based on modeling and simulation analyses, the OCP review team recommends that a 50% reduction (from 20 mg/kg to 10 mg/kg) should also be offered in labeling for the second loading dose of PHB in pre-term neonates (i.e., prescribers could select either dose for a second loading dose based on clinical judgment).

Table 1 summarizes the recommended dosing regimen for Sezaby (all doses are to be administered via a 15-minute IV infusion).

Table 1: Recommended Dosage of SEZABY for Neonatal Seizures

Loading Dose (maximum total loading dose is 40 mg/kg)		
First loading dose	20 mg/kg	
Second loading dose (If clinically indicated)[1]	Preterm Infants	10 mg/kg or 20 mg/kg *[see Clinical Pharmacology (12.3)]*
	Term Infants	20 mg/kg
Maintenance Dosage (total daily dose is 4.5 mg/kg/day and the total duration is up to 5 days) Initiate 8 to 12 hours after the last loading dose		
Option 1	1.5 mg/kg every 8 hours	
Option 2	2.25 mg/kg every 12 hours	

Drug-Drug Interactions

The OCP review notes that the Applicant did not conduct dedicated clinical studies to evaluate the drug-drug interaction potential of PHB in term or preterm infants; however, based on evidence from the published literature, the OCP review proposes the following instructions given the known PHB metabolic pathways and potential impact on the safety and efficacy of PHB or other drugs administered concomitantly.

- **CYP2C9, 2C19, 2CE1, UGT Inhibitors**: Concomitant administration of PHB with inhibitors of CYP2C9, 2C19, 2E1 or UGTs may increase plasma concentrations of PHB. Closely monitor for adverse reactions including prolonged QTc interval and decrease PHB dosage, if needed.
- **CYP2C9, 2C19, 2E1, UGT Inducers**: Concomitant administration of PHB with inducers of CYP2C9, 2C19, 2E1 or UGTs may decrease plasma concentrations of PHB. Closely monitor and increase PHB dosage, if needed.

- **CYP3A4, 2B6, 2C(s), UGT Substrates**: Concomitant administration of PHB with substrates of CYP3A4, 2B6, 2C(s) or UGTs may affect plasma concentrations of PHB. Dosage of these substrates may need to be adjusted, if needed.
- **Drugs that Prolong QT Interval**: Concomitant administration of PHB with drugs that prolong QTc interval may increase the risk of QT prolongation. Avoid concomitant use of PHB with drugs that prolong QTc interval. Monitor for QTc interval prolongation if concomitant use is unavoidable.

Scientific Bridge between West-Ward Pharmaceutical's PHB Product and Sezaby

The OCP review explains that, because the NEOLEV2 study used West-Ward Pharmaceuticals' marketed but not approved PHB product, the Applicant established an adequate scientific PK bridge (based on an analysis of C_{max}, AUC_{0-t} and AUC_{inf}) by demonstrating bioequivalence between Sezaby and the West-Ward Pharmaceutical's product in adult healthy volunteers (Study PHEN-20-01). See appendix 4.3 of the OCP review for additional details of these data.

The OCP review recommends approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Amy Kao conducted the clinical efficacy review of this application. Dr. Yunfan Deng was the biometrics reviewer and Dr. John Lawrence was the biometrics team lead.

The Applicant submitted data from the NEOLEV2 study that were intended to support the effectiveness of PHB for the treatment of neonatal seizures. NEOLEV2 was a randomized, multi-center, double-blind, active-controlled clinical trial in neonates experiencing seizures.

The trial was conducted at six clinical study sites; five in the United States and one in New Zealand.

Eligible subjects were neonates younger than 14 days of age with gestational ages at birth between 36 and 44 weeks and a weight of at least 2.2 kg.

Subjects were randomized to receive either LEV or PHB in a 3:2 allocation ratio, stratified by site. Notably, the allocation ratio reflected the expectation that LEV would be superior to PHB. As discussed in Dr. Deng's review, with a sample size of 60 subjects receiving LEV and 40 subjects receiving PHB, and assuming a seizure-cessation rate of 50% in the PHB arm,

the trial had 80% power to detect an absolute difference in seizure outcome rates of at least 28% in the LEV arm.

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 and continued for up to 5 days.

The primary efficacy endpoint was the percentage of subjects whose seizures were terminated (as demonstrated on EEG) for at least 24 hours without the need for a second drug for the treatment of their seizures. The percentage of subjects who were seizure-free for 48 hours was defined as a key secondary efficacy endpoint (i.e., the analysis was controlled for Type I error). In addition to several other exploratory endpoints, seizure termination at 1-hour post-treatment was also evaluated. The analyses of the 1-, 24-, and 48-hour seizure cessation endpoints were conducted using a Fisher's exact test.

The Applicant defined the modified intention-to-treat (mITT) population, which included all randomly assigned subjects with electrographically-confirmed seizures at baseline and a seizure termination assessment (by EEG) at 24 hours following the initiation of treatment, as the primary efficacy analysis population. Dr. Deng prefers that the primary efficacy analysis population instead comprise all randomized subjects with electrographically-confirmed seizures at baseline (i.e., without also requiring that the 24-hour assessment have been completed), in order to avoid any bias introduced by the post-randomization removal of subjects from the analyses.

Results (Primary and Secondary Efficacy Analyses)

One hundred and six subjects were randomized: 42 to the PHB arm, and 64 to the LEV arm. Twelve randomized subjects failed to have electrographically-confirmed seizures at baseline and were therefore excluded from any efficacy analysis. The Applicant's mITT population comprised 83 subjects (30 subjects randomized to the PHB arm, and 53 subjects randomized to the LEV arm). Dr. Deng's preferred efficacy analysis population (i.e., the ITT population without the 12 subjects lacking electrographically-confirmed seizures at baseline) comprised 94 subjects (33 subjects randomized to the PHB arm, and 61 subjects randomized to the LEV arm). In her analyses, Dr. Deng imputed the 11 subjects lacking a 24-hour seizure termination assessment as non-responders.

Fifty-two percent of subjects were male. Fifty-six percent of subjects were White, 9% were Native Hawaiian or other Pacific Islander, 5% were Black, 5% were Asian, 4% were mixed,

1% were American Indian or Alaska Native, and 22% were identified as other, or were missing or unknown.

Table 2 presents the results of the trial's primary and secondary efficacy analyses based on Dr. Deng's preferred analysis approach, as discussed above.

Table 2: Seizure Efficacy Endpoints in Neonates (NEOLEV2 Study)

	Phenobarbital (N=33) n (%)	**Levetiracetam** (N=61) n (%)	**P-value***
Primary Endpoint			
Seizure termination for 24 hours			<0.001
Yes	24 (72.7)	15 (24.6)	
No	9 (27.3)	46 (75.4)	
Secondary Endpoints			
Seizure termination for 48 hours			<0.001
Yes	18 (54.6)	8 (13.1)	
No	15 (45.5)	53 (86.9)	
Seizure termination for 1 hour			<0.001**
Yes	28 (84.9)	26 (42.6)	
No	5 (15.2)	35 (57.4)	
N = Total number of subjects in each treatment group.			
n = Number of subjects with non-missing data.			
*P value is based on two-sided Fisher's Exact Test for categorical variables comparing the treatment arms. **Not controlled for Type I error			

As Table 2 indicates, subjects randomized the PHB arm had statistically-significantly greater reductions in seizures compared to subjects randomized the LEV arm. These effects were highly consistent across all endpoints and were clearly clinically meaningful. Although not presented here, Dr. Deng's review confirms that these results were aligned with those of the Applicant's pre-specified analyses in the mITT population. Dr. Deng's review also discusses the results of sensitivity analyses which were also highly consistent with the efficacy results presented in Table 2.

Subgroup Analyses

Dr. Deng observes that despite the relatively small size of the population studied, the observed effect size was robust and persisted across subgroup analyses of subjects of either sex, 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.

Efficacy Conclusions

The 2019 FDA Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products describes scenarios where evidence from a single clinical study can fulfil the criteria for providing substantial evidence for effectiveness under 21 CFR 314.126.

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 the treatment of their seizures (72.7% of the PHB group compared to 24.6% of the levetiracetam group; $p<0.001$). Analyses of trial's secondary endpoints were highly consistent with this finding. The clinical importance of this degree of seizure reduction is clear, particularly for the neonatal subject population for which there are currently no approved drugs for the treatment of seizures. The results of these analyses remained robust in the setting of several conservative sensitivity analyses conducted by Dr. Deng, including the use of the mITT population proposed by the Applicant. Additionally, these results were consistent across all subgroups based on age, sex, and geographical region.

Ultimately, consistent with the elements outlined in the 2019 FDA Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products, the results of the NEOLEV2 study were robust, highly statistically- and clinically-meaningful, and consistent across endpoints and a variety of sensitivity analyses. Therefore, the efficacy data from the NEOLEV2 study establish the effectiveness of PHB for the treatment of neonatal seizures.

8. Clinical - Safety

Dr. Amy Kao conducted the clinical safety review of this application.

Dr. Kao's review focused primarily on the safety data obtained from the NEOLEV2 study. The application also included published literature intended to support the safety of PHB for the treatment of neonatal seizures. Dr. Kao reviewed this information with respect to informing specific aspects of safety labeling, described below.

The principal conclusions of Dr. Kao's safety review of the application are summarized below.

Exposure in Subjects with Neonatal Seizures

There were 106 neonates who were exposed to at least a single dose of PHB. The entire treatment period was five days. The mean duration of PHB exposure in NEOLEV2 was 4.3 days (and 4 days for LEV).

Deaths

Dr. Kao notes that six deaths occurred in NEOLEV2; three occurred during the trial timeframe and 3 occurred after the trial ended for the individual subject but while the subject was still within the neonatal period. One death occurred in the PHB group and 5 occurred in the LEV group. The primary cause of death in 4 subjects was reported to be severe HIE; although the cause of death in the other 2 subjects were reported, respectively, to be "fetal sepsis with widespread brain necrosis and infarction" and "brain herniation from extensive brain infarction". Those 2 subjects also had diagnoses of HIE with findings consistent with severe injury on brain magnetic resonance imaging (MRI). All deaths occurred 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 loading doses of both study drugs; administration of additional drugs for the treatment of persistent seizures was noted in the majority of the narratives.

Dr. Kao comments that neonates with severe HIE are very ill, typically with multiorgan failure due to systemic ischemia. Withdrawal of active support in these subjects after consideration of the 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 (plus additional drugs for the treatment of seizures) in terminating their seizures suggests that the severity of disease is greater in these subjects. Therefore, Dr. Kao does not attribute these deaths to either study drug.

Serious Adverse Events (SAEs)

Dr. Kao states that 9 subjects (8.5% of the total NEOLEV2 safety population) experienced 10 SAEs; 6 subjects in the PHB group (14.3 % of 42 subjects in the PHB group), and 3 (4.7%) subjects in the LEV treatment group (4.7% of the 64 subjects in the LEV group). Dr. Kao noted that the nature of these SAEs was similar to the treatment emergent adverse events (TEAEs) observed in general in NEOLEV2 (discussed below).

Based on details in the narratives, Dr. Kao observed that these 9 subjects experiencing SAEs had severe systemic illness, with diagnoses such as sepsis, severe persistent pulmonary hypertension, and diffuse right lung atelectasis. However, the timing of the appearance or worsening of hypotension in 5 of the subjects receiving PHB suggested that PHB may have caused or contributed to this SAE. In Subject (b) (6), worsening of hypotension and desaturation occurred 2 hours after a single loading dose of PHB and required fresh frozen plasma (FFP) and initiation of pressors. Subject (b) (6) required increased adrenaline for grade 4 decreased mean arterial pressures 1.5 hours after PHB. Subject (b) (6) experienced hypotension after receiving 2 loading doses of PHB, requiring a dopamine increase during the loading dose, 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 treatment, but required restarting of pressors after PHB.

Dr. Kao concluded that it is not possible to determine with certainty what the contribution of

either one of the study drugs and/or the underlying causes of the neonatal seizures and systemic complications was to these events. She notes that subjects who received both PHB and LEV likely had a greater severity of their 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 compared to subjects who received LEV only, and details of narratives of subjects who received PHB, suggest the potential contribution of PHB to an exacerbation of an underlying susceptibility to the these SAEs.

Discontinuations Due to Adverse Events:

Dr. Kao notes that specific safety withdrawal criteria were not specified in the protocol; rather, the clinical judgment of the investigator/treating physician was relied upon. Dr Kao considers this appropriate because the trial was conducted in neonatal intensive care units (NICUs) where the staff were experienced with the study treatments as part of standard clinical care.

Dr. Kao found that 8 total subjects in NEOLEV2 discontinued the trial due to adverse events (AEs) (2 randomized to PHB, 6 randomized to LEV). Of these 8 subjects, 4 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 on EEG.

Treatment-Emergent Adverse Events (TEAEs)

Dr. Kao summarizes the TEAEs that occurred in 2% or more of neonates in NEOLEV2 as shown in Table 3. Incidences are displayed for neonates who received PHB only and for neonates who received LEV only. Because subjects in NEOLEV2 were neonates, TEAEs that would otherwise be verbally reported by subjects could not be assessed in this trial.

Table 3: Adverse Reactions Occurring in At Least 2% of Neonates Overall in NEOLEV2 by Treatment Received

	Phenobarbital (N = 32) * %	**Levetiracetam (N = 19) %**
Respiration abnormal	25	5
Sedation	16	5
Feeding disorder	16	5
Hypotension	16	0
Bradycardia	3	0
Hyponatremia	3	0
Sepsis	3	0

* Fifty-five subjects received both PHB and LEV. These subjects had a similar profile of TEAEs to the PHB-only group.

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

Dr. Kao concludes that this pattern of TEAEs is largely consistent with that observed with other drugs approved for the treatment of other seizure syndromes. As Table 3 indicates, abnormal respiration, sedation, feeding disorder (apparently secondary to sedation, and hypotension are the most commonly observed TEAEs with PHB treatment. Dr. Kao notes that the product labeling will contain a WARNINGS AND PRECAUTIONS statement for the risk of respiratory depression or insufficiency. She further notes that respiratory depression or insufficiency, sedation, and hypotension will be routinely monitored for and addressed in the NICU where the treatment will be administered.

Clinical Laboratory Findings

Dr Kao's review demonstrates that there was an increased incidence of laboratory abnormalities in the group of subjects who received both LEV and PHB which she believes is likely related to the severity of underlying illness in this group requiring both drugs. Although Dr. Kao notes that some laboratory abnormalities (thrombocytopenia, anemia, abnormal sodium) did not occur in any of the subjects who received LEV only but did occur in some of the subjects who received PHB only; however, the small number of subjects effected, and the setting of significant comorbid medical illness, prohibits any clear attribution of these findings to treatment with PHB.

Vital Signs

Dr. Kao explains that, in NEOLEV2, vital signs (heart rate, respiratory rate, blood pressure, oxygen level) values were not recorded; however, the subjects were on continuous cardiorespiratory monitoring according to standard of care in NICUs. Therefore, abnormalities, including arrhythmia, respiratory abnormality, and hypotension, were captured as AEs. Except for hypotension and respiration abnormal, as discussion above, Dr. Kao did not find any significant difference in the pattern of any other vital sign abnormalities between the subjects randomized to PHB compared to subjects randomized to LEV.

Electrocardiograms (ECGs)

Dr. Kao notes that the Applicant has not performed a thorough QT (tQT) study, but included language regarding the risk of prolongation of the QT interval by PHB in its proposed labeling. This was based on in 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 published study of adults with late post-stroke seizures who were randomized to PHB or to LEV, which showed QT prolongation in 3 of 25 subjects randomized to PHB as compared to 1 of 24 randomized to LEV and 1 of 50 who received no treatment.

Dr. Kao notes that the QT Interdisciplinary Review Team (QT-IRT) consultation review

concluded that the available nonclinical and limited clinical data suggest 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, this study can be required as a postmarketing requirement (PMR) as discussed in Section 13 of this Summary Review.

Postmarketing Experience
Dr. Kao indicates that, because of the extent of the historical use of PHB, the Division of Pharmacovigilance (DPV) was consulted to help evaluate both the published literature and any relevant reports to the FDA Adverse Event Reporting System (FAERS) for any additional safety information that could be obtained from these sources.

Dr. Kao's review and the DPV consultation review provide the details of this evaluation. Based on these reviews, porphyria, serious hypersensitivity reaction (including drug reaction with eosinophilia and systemic symptoms [DRESS], Steven-Johnson's syndrome [SJS], anaphylaxis), infusion- or injection-site reactions, and hypotension (also identified in the NEOLEV2 data), were identified as relevant findings, and were used to inform the final product labeling (primarily in the WARNINGS AND PRECAUTIONS section of the prescribing information [PI]).

Published literature also suggests the possible association of PHB exposure during the neonatal period and an adverse impact on long-term neurodevelopmental outcomes. There are limitations to this information, however, and the current development program did not assess patients for any abnormal such outcomes. Therefore, a prospective study of the effect of PHB on long-term neurodevelopmental outcomes in exposed neonates will be required as a PMR.

Conclusion

The overall safety profile of PHB is consistent with that of many drugs approved for the treatment of other seizure syndromes and supports the approval of Sezaby for the treatment of neonatal seizures. Additionally, Sezaby will be administered in highly-monitored treatment settings capable of rapidly detecting and managing any adverse drug effects that might arise as a result of treatment. Labeling will reflect the known and potential risks of treatment and PMRs will be issued to evaluate long-term neurodevelopmental outcomes in exposed neonates, as well as the effect of PHB on the QTc interval.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of Sezaby is acceptable for the intended population, the clinical trial design is acceptable, and the efficacy findings were clear.

10. Pediatrics

The clinical efficacy trial was conducted in a neonatal patient population. Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

A Neonatal-Perinatal Medicine consultation was provided by Dr. An Massaro (reviewer) and Dr. Gerri Baer (supervisory reviewer) from the Office of Pediatric Therapeutics (OPT). Dr. Massaro and Dr. Baer participated in the labeling discussions.

A Division of Pediatrics and Maternal Health (DPMH) consultation review was provided by Dr. Catherine Roca, Dr. Miriam Donatale, and Dr. Lynne Yao. This review proposed revisions to subsections 5.11, 5.12, and 17 of labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

11. Other Relevant Regulatory Issues

Clinical

No Good Clinical Practice (GCP) issues were identified in Dr. Kao's clinical review.

Dr. Kao concludes that the Applicant has adequately disclosed financial interests/arrangements with clinical investigators.

Office of Scientific Investigations (OSI)

Dr. Jenn Sellers was the OSI reviewer for this application and Dr. Phillip Kronstein the OSI team lead. An OSI audit of 4 of the 6 study sites for the NEOLEV2 study was conducted. These were 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 Intent 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 trial 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 the Office of Study Integrity and Surveillance (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.

Controlled Substance Staff (CSS)

Dr. Emily Deng was the CSS reviewer for this application. The CSS review concludes that the nonclinical and clinical abuse-related data submitted in this application demonstrate that PHB has abuse potential and should remain controlled under schedule IV of the Controlled Substances Act (CSA). Please refer to the CSS review for a detailed discussion of the basis for their conclusion. The CSS review recommends approval.

Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA review indicates that the final agreed-upon PI, instructions for use (IFU), medication guide (MG), and carton and container labeling are acceptable.

12. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes.

In addition to the WARNINGS AND PRECAUTIONS sections discussed in Section 8 of this review, the Sezaby PI will also 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.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategy (REMS)

The Division of Risk Management (DRM) has determined that a REMS is not necessary for Sezaby.

Postmarketing Requirements (PMRs)

The following studies are recommended as PMRs:

1. Conduct a prospective study with appropriate comparator(s) to assess long-term neurodevelopmental effects of Sezaby in patients with neonatal seizures. Ensure capture of and 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.

Draft Protocol Submission:	06/2023
Final Protocol Submission:	02/2024
Study Completion:	02/2034
Final Report Submission:	02/2035

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).

Draft Protocol Submission:	06/2023
Final Protocol Submission:	12/2023
Study/Trial Completion:	12/2025
Final Report Submission:	12/2026

14. Recommended Comments to the Applicant

See action letter.

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/

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11/17/2022 08:55:14 AM

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