CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215910Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 215910
Supplement #:	0001
Drug Name:	Sezaby® (phenobarbital)
Indication(s):	Treatment of neonatal seizures
Applicant:	Sun Pharma Advanced Research Company, Ltd.
Date(s):	Submitted: 02/17/2022 Review Completion Goal Date: 10/24/2022 PDUFA Goal date: 11/17/2022
Review Priority:	Priority with a 3-month Extension
Biometrics Division:	DBI
Statistical Reviewer:	Yunfan Deng, Ph.D.
Concurring Reviewer(s):	John Lawrence, Ph.D., Hsien Ming J. Hung, Ph.D.
Medical Division:	Division of Neurology II
Clinical Team:	Amy Kao, M.D., Clinical Reviewer Philip Sheridan, M.D., Team Leader
Project Manager:	Josephine Little

Keywords: neonatal seizure, superiority, active control

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This NDA seeks approval of Sezaby® (phenobarbital) for the short-term treatment of neonatal seizure.

One randomized, double-blinded, multi-center, and active-controlled study (Study NEOLEV2) was conducted to support the efficacy and safety of phenobarbital (PHB/PB) (20-40 mg/kg) compared with levetiracetam (LEV) (40-60mg/kg) in the first-line treatment of neonatal seizures. One hundred and six subjects were randomized at 2:3 ratio to receive PB (42 subjects) or LEV (64 subjects).

In Study NEOLEV2, PB demonstrated statistically superiority to LEV for the primary efficacy endpoint – the percentage of neonates whose seizures were terminated for 24 hours and did not go on to require a second anticonvulsant agent. Of the 94 subjects who had neurophysiologist-confirmed seizures at baseline, 24 among 33 (72.7%) subjects in the PB group had seizure termination for 24 hours, compared with 15 among 61 (24.6%) subjects in the LEV group; the treatment difference is 48.1% with the 95% confidence interval of (29.5%, 66.8%) and the p-value for the Fisher's exact test is < 0.001. PB also demonstrated superiority to LEV in the secondary endpoints of the rate of seizure termination for 48 hours and 1-hour following treatment (Table 1).

Based on these efficacy results, I recommend the approval of Sezaby® (phenobarbital) for the short-term treatment of neonatal seizure.

Table 1: Summary of Seizure Termination for 24, 48 and 1 Hours (All randomized with neurophysiologist-confirmed seizures)

	PB (N=33)	LEV (N=61)	P-value[1]	Difference (95% CI)[2]
Primary Efficacy Endpoint				
Seizure termination for 24 hours				
Yes	24 (72.7)	15 (24.6)	<0.001	48.1% (29.5%, 66.8%)
Secondary Efficacy Endpoints				
Seizure termination for 48 hours				
Yes	18 (54.6)	8 (13.1)	<0.001	41.4% (22.5%, 60.4%)
Seizure termination for 1 hour				
Yes	28 (84.9)	26 (42.6)	<0.001	42.2% (24.8%, 59.7%)

[1] p-value is based on Fisher's exact test; [2] The 95% CI was estimated using normal approximation. In these analyses, missing outcomes were imputed as treatment failure.
Source: Tables 11-4 of Study NEOLEV2 CSR and Statistical Reviewer's Analyses.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

According to literature, neonatal seizures, defined as seizures occurring in patients from birth to 28 days of age, occur with an estimated incidence of 1/1000 to 5/1000 live births in population-based studies and are associated with poor outcomes. Based on literature search, the applicant (Sun Pharma Advanced Research Company, Ltd. [SPARC]) reported that twenty percent to 30% of infants with neonatal seizures die, 20-30% develop epilepsy outside the neonatal period, and 20-40% develop cerebral palsy and/or mental retardation. Currently, there are no FDA-approved treatments for neonatal seizures.

Phenobarbital, (also known as [aka] phenobarbitone), which was synthesized in 1904 and first marketed by the trade name Luminal in 1912, is a medication of the barbiturate type. It is recommended by the World Health Organization (WHO) for the treatment of certain types of epilepsy in developing countries. In the developed world, it is commonly used to treat seizures in young children, while other medications are generally used in older children and adults. According to the applicant, in the United States, phenobarbital is used as the first-line therapy in about 90% of cases of neonatal seizures. However, it is not approved by the FDA.

The applicant has developed a benzyl alcohol-free phenobarbital injection for intravenous formulation for the treatment of neonatal seizures, defined as seizures occurring in subjects from birth to 1 month of age.

2.1.2 History of Drug Development

The initial pre-IND132342 was submitted in December 2016, where the applicant proposed to rely on published literatures to demonstrate the safety and efficacy of PB for the intended indication for a potential NDA submission and didn't plan to conduct any clinical studies. The Agency didn't agree with the proposal in the written response to the applicant on 02/02/2017.

In September 2019, the applicant submitted another written response only meeting background package under IND132342. In this submission, the applicant referred to results from Study NEOLEV2 that's already completed under IND109622 to fulfill the Agency's previous request for additional evidence to support the eventual registration of preservative free phenobarbital for treatment of neonatal seizures in addition to supportive scientific literature. The Agency responded that the NEOLEV2 study might be capable of being considered an adequate and well-controlled trial in support of the safety and efficacy of intravenous phenobarbital for the treatment of neonatal seizures.

IND109622 was led by Dr. Richard Haas at the University of California San Diego as an Investigator-Initiated IND. The initial IND109622 was submitted in August 2010 along with a Phase I study protocol (NEOLEV1) to evaluate the use of IV Levetiracetam (LEV) in the neonatal population with seizures. The NEOLEV2 study was an investigator-initiated, FDA Orphan Products Division funded study (1 RO1FD004147). NEOLEV2 was a phase IIb efficacy and safety study of levetiracetam compared with phenobarbital in the first-line treatment of neonatal seizures.

On July 20, 2018, Dr. Haas requested that the primary outcome measure changed from 48-hour seizure cessation to 24-hour seizure cessation before breaking blind of Study NEOLEV2. On September 4, 2018, the clinical reviewer responded: "Your proposal to change the primary efficacy endpoint from seizure cessation at 48 hours to seizure cessation at 24 hours in your study (NEOLEV 2) prior to breaking the blind is acceptable. However, we recommend that you analyze seizure cessation at 48 hours as a secondary or exploratory efficacy endpoint." This led to 24-hour seizure cessation as the primary efficacy endpoint and 48-hour seizure cessation as the key secondary endpoint.

2.1.3 Studies Reviewed

This review focuses on Study NEOLEV2. Table 2 below contains a summary of this study.

Table 2: Summary of Efficacy Study to be assessed in the Statistical Review

Study No	Design	Objective	Treatment / Sample Size	Study Population	Primary Endpoint
NEOLEV2	Multi-center, randomized, double-blinded, parallel group, active-controlled	To evaluate the efficacy and safety of LEV (40-60mg/kg) compared with PHB (20-40 mg/kg) in the first-line treatment of neonatal seizures	LEV / 64 PHB / 42	Term infants with corrected gestational age between 36 and 44 weeks, less than 2 weeks of age, at risk of developing seizures or suspected of having seizures	the rate of achieving and maintaining electrographic seizure freedom for 24 hours, validated by neurophysiologist review of the EEG

Source: Statistical Reviewer's Summary.

2.2 Data Sources

The data sources for this review include clinical study reports, protocols, statistical analysis plan (SAP), and datasets. All data sources were electronic submitted and located at \\cdsesub4\NONECTD\IND109622\7689015\ind109622\0021

The seizure termination for 24 hours assessments were included in the "adze.xpt" dataset with the identifying flag of "SZFREE24" of the variable "ZETESTCD" and the variable name

"ZEORRES" for the seizure termination outcomes. The treatment variable, given both as numeric (TRT01PN) and character (TRT01P), was also included in the "adze.xpt" dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be verified by the statistical reviewer with minor data manipulation. The statistical reviewer's analyses were primarily based on the analysis datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

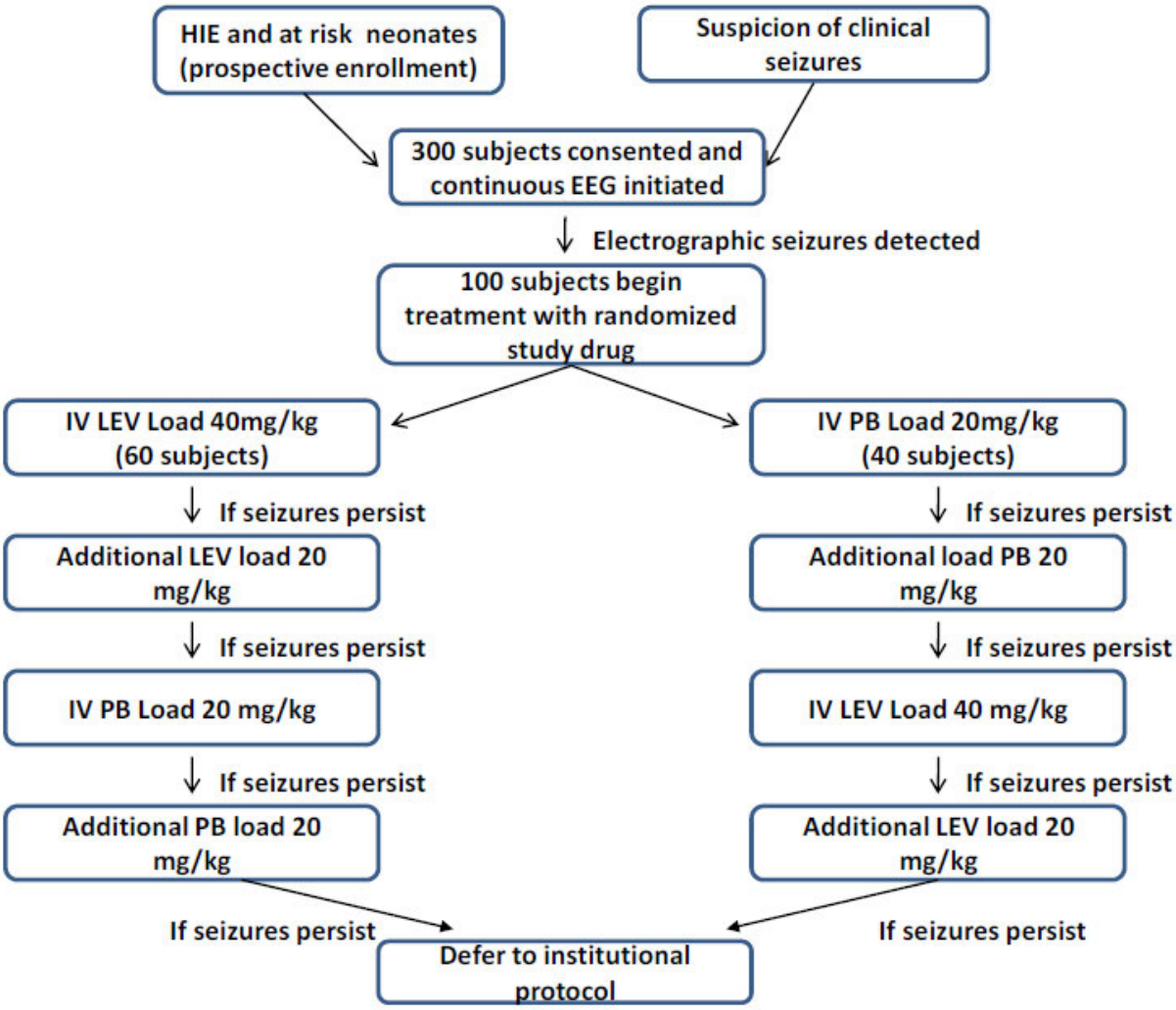
Study NEOLEV2 was a randomized, double-blinded, multi-center, and active-controlled study to evaluate the efficacy and safety of LEV (40-60mg/kg) compared with PHB (20-40 mg/kg) in the first-line treatment of neonatal seizures.

Once eligibility and consent were confirmed, subjects were randomly assigned to the LEV or PHB treatment group in a 3:2 allocation ratio, stratified by the site.

Subjects randomized to receive LEV at the onset of electrographically confirmed seizure activity received an intravenous loading dose of LEV of 40mg/kg given over 15 minutes. If electrographic seizures were confirmed to persist or recur more than 15 minutes after the first infusion was completed, a further 20mg/kg load of LEV was administered IV over 15 minutes. Maintenance LEV at 10 mg/kg/dose was given IV every 8 hours (q8h) and continued for at least 5 days. If seizures persisted or recurred more than 15 minutes after the second LEV infusion was completed, a PHB loading dose of 20 mg/kg was administered IV over 15 minutes. If seizures persisted or recurred more than 15 minutes after the first loading dose of PHB was completed, a second 20mg/kg load was administered IV over 15 minutes (Figure 9-1). This resulted in PB being started within 1 hour of the onset of seizures if and when loading with LEV was ineffective. Subjects given PB loading doses were started on maintenance PHB with 1.5 mg/kg/dose given IV q8h and continued at least until the end of the study. If electrographic seizures were still apparent following treatment with both LEV and PHB, or if they recurred during the 5 days during which the study protocol was active, the patient was considered to have failed the experimental treatment regime, and institutional specific standard seizure management dictated the ongoing management.

The study flow chart displays in the following figure.

Figure 1: Study NEOLEV2 Flow Chart



Source: Figure 9-1 of the NEOLEV2 Clinical Study Report (CSR).

The key inclusion criteria were:

1) Term infants (gestational age between 36 and 44 weeks) and at least 2.2 kg weight.
2) Post-natal age < 14 days.
3) Serum creatinine ≤ 1.6 mg/dL at the time of enrollment
4) Were still experiencing clinical or electroencephalographic seizures or at risk for neonatal seizures.
5) For whom parental consent to participate in the study was obtained.

The primary endpoint was the percentage of neonates whose seizures were terminated for 24 hours and did not go on to require a second anticonvulsant agent. The original primary endpoint was 48-hour seizure freedom. After recruitment was complete, because EEG data were curated for data extraction, it was evident that EEG monitoring had been discontinued before 48 hours in many patients for clinical reasons, for example, to allow magnet ic resonance imaging (MRI) or transfer

of patients. Therefore, after FDA approval, the primary outcome measure was changed to 24-hour seizure cessation. Since this change of endpoint was done before the unblinding of the study, FDA reviewer considered it acceptable.

The key secondary endpoint was the percentage of seizure termination for 48 hours.

In addition, there were five other secondary endpoints:

- Seizure termination at 1 hour after treatment.
- Seizure termination at 24 hours following 60mg/kg LEV, having not responded to 40mg/kg.
- Length of seizure freedom.
- Phenobarbital dose
- Drug that worked by treatment group

3.2.2 Statistical Methodologies

The primary analysis set is the sponsor-defined modified Intent-to-Treat (mITT) Population, which included all randomly assigned subjects with neurophysiologist-confirmed seizures and a seizure-termination assessment at 24 hours. The applicant-defined mITT excluded patients who do not have any efficacy assessments at 24 hours, which could potentially lead to bias. I recommend that the primary analysis set be all randomized subjects with neurophysiologist-confirmed seizures at baseline, therefore, analyses of the primary and secondary endpoints based on this analysis set were conducted. In addition, I conducted sensitivity analyses in the all-randomized population (ITT) to investigate the robustness of the efficacy results. In these analyses, any missing outcomes were imputed as treatment failure (seizure didn't terminate).

The primary outcome of 24-hour seizure termination rates was compared between the two treatment arms using Fisher's exact test. Secondary outcomes of 1- and 48-hour seizure-termination rates were analyzed similarly. A multivariate logistic regression analysis, adjusting for hypothermia treatment and HIE etiology, was also performed as a supportive analysis.

The proportion of subjects with seizure termination for 48 hours was defined by the sponsor as the only key secondary endpoint, tested sequentially right after the primary efficacy endpoint. Seizure termination for 1 hour was defined as the first one among the five other secondary endpoints; the sponsor didn't explicitly say how they were going to test the other secondary endpoints in the statistical analysis plan (SAP) though.

Power calculation was based on a 2-sided chi-square test for detecting a difference between two proportions, assuming a Type I error of 0.05. 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 study had 80% power to detect an absolute difference in seizure outcome rates of ≥28% in the LEV group.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

One hundred six (106) subjects were randomized and treated with study drugs for seizures, and all were included in the ITT and safety analysis populations. Forty (37.7%) subjects discontinued the treatment; 5 subjects discontinued treatment before achieving the study endpoint, and 35 subjects discontinued treatment after the study endpoint but before completing 5 days of maintenance treatment. Twelve (12) subjects were excluded from the modified intent-to-treat (mITT) population because neurophysiologists reviewing the EEG did not confirm the presence of seizures. In addition, in 11 subjects, the primary outcome measure could not be obtained; in 5 of the 11, EEG data were either completely lost or missing at critical times, and in 6 of the 11, efficacy data became uninterpretable. Altogether, 23 subjects were excluded for the efficacy analysis, and 83 subjects were included in the efficacy mITT population.

Table 3: Subject Disposition (Enrolled Subjects)

	Phenobarbital (N=42) n (%)	**Levetiracetam (N=64) n (%)**	**Overall (N=106) n (%)**
All Randomized	42	64	106
ITT Population	42 (100)	64 (100)	106 (100)
Safety Population	42 (100)	64 (100)	106 (100)
mITT Population	30 (71.4)	53 (82.8)	83 (78.3)
Excluded from the mITT Population	12 (28.6)	11 (17.2)	23 (21.7)
EEG did not confirm the presence of seizures	9 (21.4)	3 (4.7)	12 (11.3)
Primary outcome measure could not be obtained	3 (7.1)	8 (12.5)	11 (10.4)
# of subjects who discontinued early from the treatment	13 (31.0)	27 (42.2)	40 (37.7)
Reasons for treatment Discontinuation			
Serious Adverse Event	1 (2.4)	3 (4.7)	4 (3.8)
Parent Request	1 (2.4)	0	1 (0.9)
Death	1 (2.4)	1 (1.6)	2 (1.9)
Other	10 (23.8)	23 (35.9)	33 (31.1)
All study drugs failed	5 (11.9)	9 (14.0)	14 (13.2)
All study drugs failed and maintenance meds not continued for 5 days because of sedation	0	1 (1.6)	1 (0.9)
Does not meet inclusion criteria	0	1 (1.6)	1 (0.9)
Maintenance medications discontinued prior to 5th day			
patient ready for discharge	1 (2.4)	4	5
change in meds required clinically for burst suppression pattern	0	1 (1.6)	1 (0.9)
medication error with study drugs	1 (2.4)	0	1 (0.9)
study drugs expired and transition to unblinded meds necessary anyway	1 (2.4)	0	1 (0.9)
communication error	0	1 (1.6)	1 (0.9)
sedation	1 (2.4)	4	5
Transfer to other hospital	1 (2.4)	1 (1.6)	2 (5.0)
Unblinded for clinical care concerns re metabolic disease	0	1 (1.6)	1 (2.5)
Patient's Disposition at the End of the Study	42	64	106
Unstable, requiring complex critical care	4 (9.5)	2 (3.1)	6 (5.7)

Requiring intensive care	10 (23.8)	14 (21.9)	24 (22.6)
Requiring intermediate care	10 (23.8)	13 (20.3)	23 (21.7)
Continuing care	6 (14.3)	8 (12.5)	14 (13.2)
Discharged home	11 (26.2)	20 (31.3)	31 (29.2)
Other	0	1 (1.6)	1 (0.9)
Death	1 (2.4)	5 (7.8)	6 (5.7)
Missing	0	1 (1.6)	1 (0.9)

Source: Table 10-2 and Figure 10-1 of Study NEOLEV2 CSR.

Demographic and baseline characteristics were generally balanced between treatment groups in this study (Table 4).

Table 4: Demographic and Baseline Characteristics (ITT)

	Phenobarbital (N=42) n (%)	**Levetiracetam (N=64) n (%)**	**Overall (N=106) n (%)**
Gender			
Girl	18 (42.9)	33 (51.6)	51 (48.1)
Boy	24 (57.1)	31 (48.4)	55 (51.9)
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)
Unknown	1 (2.4)	0	1 (0.9)
Not Reported	6 (14.3)	6 (9.4)	12 (11.3)
Missing	0	1 (1.6)	1 (0.9)
Race			
American Indian or Alaska Native	0	1 (1.6)	1 (0.9)
Asian	3 (7.1)	2 (3.1)	5 (4.7)
Native Hawaiian or Other Pacific Islander	2 (4.8)	7 (10.9)	9 (8.5)
Black or African American	1 (2.4)	4 (6.3)	5 (4.7)
White	25 (59.5)	34 (53.1)	59 (55.7)
Mixed Race	1 (2.4)	3 (4.7)	4 (3.8)
Unknown	5 (11.9)	5 (7.8)	10 (9.4)
Other	5 (11.9)	7 (10.9)	12 (11.3)
Missing	0	1 (1.6)	1 (0.9)
Pregnancy			
Normal	20 (47.6)	35 (54.7)	55 (51.9)
Abnormal	22 (52.4)	29 (45.3)	51 (48.1)
Delivery Situation			
Inpatient Delivery Suite	42 (100)	62 (96.9)	104 (98.1)
Precipitous Delivery in Community	0	0	0
Planned Home Birth	0	2 (3.1)	2 (1.9)
Mode of Delivery			
Spontaneous Vaginal	13 (31.0)	18 (28.1)	31 (29.2)
Vacuum	5 (11.9)	11 (17.2)	16 (15.1)
Forceps	0	2 (3.1)	2 (1.9)

Scheduled C-Section	9 (21.4)	13 (20.3)	22 (20.8)
Emergency C-Section	15 (35.7)	18 (28.1)	33 (31.1)
Missing	0	2	2 (1.9)
Anesthesia			
No	13 (31.0)	21 (32.8)	34 (32.1)
Yes	24 (57.1)	38 (59.4)	62 (58.5)
Missing	5 (11.9)	5 (7.8)	10 (9.4)
Family History Seizure/Neurologic Abnormality			
No	23 (54.8)	45 (70.3)	68 (64.2)
Yes	8 (19.0)	5 (7.8)	13 (12.3)
Missing	11 (26.2)	14 (21.9)	25 (23.6)
Hypothermia Treatment			
No	24 (57.1)	40 (62.5)	64 (60.4)
Yes	18 (42.9)	24 (37.5)	42 (39.6)
Birth Weight(grams)			
Mean (SD)	3317.3 (501.14)	3341.7 (576.52)	3332.0 (545.56)
Median	3297.5	3302.5	3297.5
Min, Max	2200, 4300	2070, 4880	2070, 4880
Head Circumference at Birth (cm)			
n	34	59	93
Mean (SD)	34.59 (1.482)	34.00 (1.849)	34.22 (1.739)
Median	34.50	34.00	34.00
Min, Max	31.5, 37.7	29.5, 39.0	29.5, 39.0
Gestational Age at Birth (days)			
Mean (SD)	273.9 (9.24)	275.4 (9.43)	274.8 (9.34)
Median	274.5	276.5	276.0
Min, Max	252, 294	255, 291	252, 294

SD: Standard Deviation
Source: Table 11-1 of Study NEOLEV2 CSR.

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint

Table 5 presents the efficacy results for the primary endpoint in the sponsor-defined modified Intent-to-Treat (mITT) Population. Phenobarbital (PB) demonstrated superiority to levetiracetam (LEV) in eradicating all seizures for 24 hours. Of the subjects randomly assigned to PB, 24 of 30 (80.0%) subjects remained seizure- free for 24 hours, compared with 15 of 53 (28.3%) of subjects randomly assigned to LEV (p <0.001).

Table 5: Results for the Primary Endpoint (Applicant-defined mITT)

Seizure termination for 24 hours	**PB (N=30)**	**LEV (N=53)**	**P-value[1]**	**PB vs LEV Difference (95% CI)[2]**

Yes	24 (80.0)	15 (28.3)	<0.001	51.7% (32.9%, 70.5%)
No	6 (20.0)	38 (71.7)		

[1] p-value is based on Fisher's exact test
[2] The 95% CI was based on normal approximation.
Source: Tables 11-4 of Study NEOLEV2 CSR.

I recommend that the primary analysis set be all randomized subjects with neurophysiologist-confirmed seizures at baseline, therefore, primary analysis based on this analysis set were conducted. In addition, I conducted sensitivity analyses in the all-randomized population (ITT) to investigate the robustness of the efficacy results. In these analyses, any missing outcomes were imputed as treatment failure (seizure didn't terminate). These analyses results are consistent with the results of the sponsor-defined primary analysis (Table 6).

Table 6: Results for the Primary Endpoint in Different Analysis Sets

Statistical Reviewer Proposed Primary Analysis: All randomized with neurophysiologist-confirmed seizures	**PB (N=33)**	**LEV (N=61)**	**P-value**	**PB vs LEV Difference (95% CI)[1]**
Yes	24 (72.7)	15 (24.6)	<0.001	48.1% (29.5%, 66.8%)
No	9 (27.3)	46 (75.4)		
ITT	**PB (N=42)**	**LEV (N=64)**	**P-value[1]**	**PB vs LEV Difference (95% CI)[2]**
Yes	24 (57.1)	15 (23.4)	<0.001	33.7% (15.5%, 51.9%)
No	18 (42.9)	49 (76.6)		

In these analyses, missing outcomes were imputed as treatment failure
[1] p-value is based on Fisher's exact test; [2] The 95% CI was based on normal approximation
Source: Statistical Reviewer's Analyses.

3.2.4.2 Secondary Endpoints

APPEARS THIS WAY ON ORIGINAL

Error! Reference source not found. Table 7 presents the efficacy results for the key secondary endpoint of 48-hour seizure free rate and the first other secondary endpoint of 1-hour seizure free rate. PB demonstrated superiority to LEV in eradicating all seizures for 48 hours and for 1 hour. There were 18 subjects among 28 subjects (64.3%) in the PB remained seizure-free for 48 hours compared to 8 among 47 subjects
(17.0%) in the LEV group. Similarly, 93.3% (28/30) of subjects in PB group were seizure- free for at least 1 hour, compared with 49.1% (26/53) of LEV subjects.

Table 7: Results for the Key Secondary Endpoints (Applicant-defined mITT)

	PB (N=28)	**LEV (N=47)**	**P-value[1]**	**Difference (95% CI)[2]**

Seizure termination for 48 hours				
Yes	18 (64.3)	8 (17.0)	<0.001	44.9% (24.9%, 64.9%)
	PB (N=30)	**LEV (N=53)**	**P-value[1]**	**Difference (95% CI)[2]**
Seizure termination for 1 hour				
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.
Source: Tables 11-6 of Study NEOLEV2 CSR and statistical reviewer's analysis.

As the same for the primary efficacy endpoint, I recommend that the primary analysis set be all randomized subjects with neurophysiologist-confirmed seizures at baseline for these secondary endpoints. In addition, sensitivity analyses in the all-randomized population (ITT) were conducted to investigate the robustness of the efficacy results. In these analyses, any missing outcomes were imputed as treatment failure (seizure didn't terminate). These analyses results are consistent with the results presented above (Table 8).

Table 8 Results for the Key Secondary Endpoints in Different Analysis Sets

	PB n/N (%)	**LEV n/N (%)**	**p-value[1]**	**Difference (95% CI)[2]**
Seizure termination for 48 hours				
Statistical Reviewer Proposed Analysis Set: All randomized with neurophysiologist-confirmed seizures	18/33 (54.6)	8/61 (13.1)	<0.001	41.1% (22.5%, 60.4%)
ITT	18/42 (42.9)	8/64 (12.5)	<0.001	30.4% (13.3%, 47.4%)
	PB n/N (%)	**LEV n/N (%)**	**p-value[1]**	**Difference (95% CI)[2]**
Seizure termination for 1 hour				
Statistical Reviewer Proposed Analysis Set: All randomized with neurophysiologist-confirmed seizures	28/33 (84.9)	26/61 (42.6)	<0.001	42.2% (24.8%, 59.7%)
ITT	28/42 (66.7)	26/64 (40.6)	0.01	26.0% (7.4%, 44.7%)

In these analyses, missing outcomes were imputed as treatment failure
[1] p-value is based on Fisher's exact test; [2] The 95% CI was based on normal approximation
Source: Statistical Reviewer's Analyses.

3.2.4.3 Supporting Endpoints

The applicant summarized the length of seizure freedom in their-defined mITT population as presented in the following table. These results showed that a larger proportion of subjects remained seizure-free for ≥ 24 hours with PB.

Table 9: Length of Seizure Freedom (Applicant-defined mITT)

	PB	**LEV**

	(N=30) n (%)	(N=53) n (%)
<30 mins	0	20 (37.7)
≥30 mins & <6 hours	4 (13.3)	17 (32.1)
≥6 hours & <24 hours	2 (6.7)	1 (1.9)
≥24 hours	24 (80.0)	15 (28.3)

N = Total number of subjects in each treatment group under the stated population.
n = Number of subjects with non-missing data. Percentages are based on N.
Source: Tables 11-10 of Study NEOLEV2 CSR.

Based on the protocol, subjects would switch treatment if the treatment they were randomized to at the onset of seizure activity failed to stop seizure after the first two loading doses. The applicant summarized the drugs that worked in terminating seizures for 24 hours by treatment group. The results demonstrate that 70% (21/30) responses were seen with one dose of 20mg/kg of PB compared to 20.8% (11/53) of subjects who responded to one dose of Levetiracetam 40mg/kg. Five subjects among the 30 (16.7%) subjects in the PB arm failed to achieve any response compared to 15 subjects among the 53 subjects (28.3%) in the LEV arm.

Table 10: Drugs that Worked by Treatment Group (Applicant-defined mITT)

	PB (N=30)	LEV (N=53)
A1	21 (70.0)	11 (20.8)
A1+A2	3 (10.0)	4 (7.5)
A1+A2+B1	0	14 (26.4)
A1+A2+B1+B2	1 (3.3)	6 (11.3)
A1 and A2 failed, B1 not given	0	1 (1.9)
A1 and A2 failed, B1 failed B2 not given	0	2 (3.8)
All failed	5 (16.7)	15 (28.3)

Phenobarbital: A1 represents the number of subjects taken the Phenobarbital 20 mg/kg, A2 represents the number of subjects taken the additional Phenobarbital 20 mg/kg, B1 represents the number of subjects taken the Levetiracetam 40 mg/kg and B2 represents the number of subjects taken the additional Levetiracetam 20 mg/kg.
Levetiracetam: A1 represents the number of subjects taken the Levetiracetam 40 mg/kg, A2 represents the number of subjects taken the additional Levetiracetam 20 mg/kg, B1 represents the number of subjects taken the Phenobarbital 20 mg/kg and B2 represents the number of subjects taken the additional Phenobarbital 20 mg/kg.
Source: Table 11-11 of Study NEOLEV2 CSR.

I conducted additional sensitivity analysis summarizing the percentage of subjects who were seizure-free after a single load of treatment **during the 5 days when the study protocol was active**. The results demonstrate that 53.3% (16/30) responses were seen with one dose of 20mg/kg of PB compared to 17.0% (9/53) of subjects who responded to one dose of Levetiracetam 40mg/kg.

Table 11: Percentage of Patients Who Were Seizure-Free during the 5 Days When the Study Protocol was Active After a Single Load of Treatment (Applicant-defined mITT)

	Phenobarbital (N=30)	Levetiracetam (N=53)	Difference (95% CI)[1]
Yes	16 (53.3%)	9 (17.0%)	36.4% (15.8%, 56.9%)
No	14 (46.7%)	44 (83.0%)	

[1] The 95% CI was based on normal approximation.

3.2.4.4 Conclusion

In this study, phenobarbital demonstrated superiority to levetiracetam in eradicating seizures for 24 hours (primary outcome measure), for 48 hours (key secondary efficacy measure), and for 1 hour (the first other secondary endpoint) following treatment.

Therefore, I conclude that the study provided statistically significant evidence that PB is superior to LEV for eradicating seizure for up to 48 hours in neonatal subjects.

3.3 Evaluation of Safety

A total of 27 (25.5%) subjects experienced at least one treatment emergent adverse events (TEAE) overall during the study; 9 (28.1%) subjects in the group that received PB alone, 15 (27.3%) subjects in the group that received PB + LEV, and 3 (15.8%) subjects in the group that received LEV alone.

For a comprehensive review of safety, please refer to Dr. Amy Kao's clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Site, and Baseline Hypothermia Treatment

Subgroup analyses based on gender, race, site, and baseline hypothermia treatment status were performed by the statistical reviewer. The subgroup analyses results were similar to those seen for the overall population for each demographic subgroup.

Table 12: Subgroup Analyses of Seizure termination for 24 hours by Gender, Age, Site, and Baseline Hypothermia Treatment (All randomized with neurophysiologist-confirmed seizures)

		PB n/N (%)	LEV n/N (%)	PB vs LEV Difference (95% CI)[1] (%)
Gender	**Boy**	17/21 (81.0)	8/30 (26.7)	54.3 (31.2, 77.4)
	Girl	7/12 (58.3)	7/31 (22.6)	35.8 (4.2, 67.3)
Race	**White**	13/18 (72.2)	7/33 (21.2)	51.0 (26.1, 76.0)
	Non-White	11/15 (73.3)	8/28 (28.6)	44.8 (16.8, 72.7)
Site	**US**	14/21 (66.7)	9/42 (21.4)	45.2 (21.6, 68.9)
	Non-US	10/12 (83.3)	6/19 (31.6)	51.8 (22.1, 81.4)
Hypothermia Treatment	**Yes**	9/13 (69.2)	6/23 (26.1)	43.1 (12.3, 74.0)
	No	15/20 (75.0)	9/38 (23.7)	51.3 (28.0, 74.6)

[1] The 95% CI was based on normal approximation.
Source: Statistical reviewer's analyses.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for this NDA submission.

5.2 Collective Evidence

For the primary efficacy endpoint of seizure termination at 24 hours, PB demonstrated statistically superiority to LEV. Among the 94 subjects with neurophysiologist-confirmed seizures at baseline, 72.7% (24/33) subjects in the PB group had seizure termination for 24 hours, compared with 24.6% (15/61) subjects in the LEV group; the p-value for the Fisher's exact test is < 0.001 and the estimated treatment difference is 48.1% with the 95% confidence interval of (29.5%, 66.8%). PB also demonstrated superiority to LEV in the secondary endpoints of the rate of seizure termination for 48 hours and 1-hour following treatment.

Subgroup analyses showed a consistent treatment effect of PB across subgroups of sex, race, site, and baseline hypothermia treatment status.

5.3 Conclusions and Recommendations

In conclusion, the study provided sufficient evidence to support the treatment effect of PB comparing to LEV in eradicating seizure for up to 48 hours in neonatal subjects. Therefore, I recommend the approval of Phenobarbital for the short-term treatment of neonatal seizure.

5.4 Labeling Recommendations

In Section 14 clinical studies of the label, the applicant's proposed (b) (4) . I recommend the results with all randomized subjects who had neurophysiologist-confirmed seizures at baseline be presented in the label.

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/

YUNFAN DENG
11/10/2022 03:05:33 PM

JOHN P LAWRENCE
11/10/2022 03:08:01 PM

HSIEN MING J HUNG
11/10/2022 08:17:37 PM