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 Numbers:	022253 Supplement 46 022254 Supplement 36 022255 Supplement 27
Drug Name:	Vimpat (lacosamide)
Indication:	Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients (b) (4) 4 years and older
Applicant:	UCB, Inc.
Dates:	Receipt date: January 16, 2020 PDUFA Goal Date: November 16, 2020
Review Priority:	Standard
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Keywords: clinical study, NDA review

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1 EXECUTIVE SUMMARY

On January 16, 2020, UCB, Inc (the Applicant) submitted a new drug application (NDA) efficacy supplement for Vimpat (lacosamide [LCM]). The application relies on clinical study SP0982 to demonstrate the drug efficacy for the proposed indication "adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients (b) (4) 4 years and older." The study was a randomized, double-blind, placebo-controlled, parallel-group, clinical study that had two treatment groups (LCM and placebo) and used the time to the second PGTCS during the 24-week Treatment Period (Day 166) as the primary endpoint. The hazard ratio of the LCM group relative to the placebo group was 0.548 (95% confidence interval = (0.381, 0.788)) and statistically significant (p-value = 0.001).

2 INTRODUCTION

2.1 Overview

This NDA efficacy supplement relies on one randomized, double-blind, placebo-controlled clinical study to demonstrate the drug efficacy. This study is summarized below and reviewed in Section 3.

Table 1. Clinical study in this review

Study ID	Design	Study Arm (Number of randomized subjects per arm)	Study Population
SP0982	Randomized, double-blind, placebo-controlled, parallel-group, multi-center	Lacosamide (121) Placebo (121)	Patients with idiopathic generalized epilepsy aged 4 years and older currently taking 1 to 3 concomitant antiepileptic drugs.

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of this NDA resubmission is located at

\\cdsesub1\evsprod\NDA022253\0229\

The study reports are located at

\\cdsesub1\evsprod\NDA022253\0229\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ep\5351-stud-rep-contr\sp0982\

The datasets are located at

\\cdsesub1\evsprod\NDA022253\0229\m5\datasets\sp0982\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

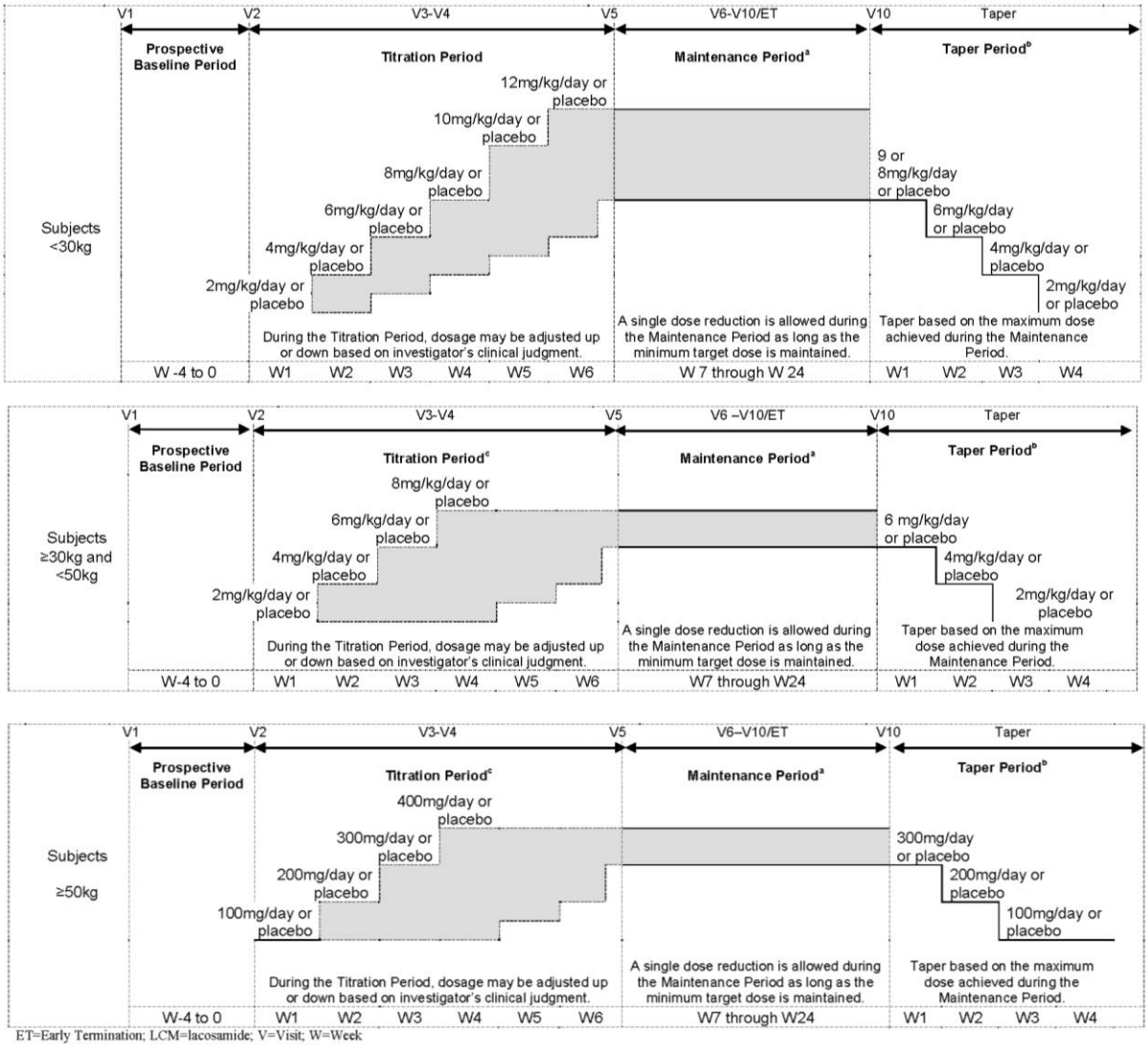
The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Design and Endpoints

Study SP0982 was a randomized, double-blind, placebo-controlled, 2-arm, multi-center clinical study to evaluate the efficacy of oral LCM as adjunctive therapy for uncontrolled PGTCS in subjects aged four years or older with IGE currently taking 1 to 3 concomitant anti-epileptic drugs (AEDs). The planned sample size in terms of the occurrence of each subject's second PGTCS was 125 events. Approximately 250 subjects from 150-180 centers in the United States, Europe, Asia, and Australia were planned to be randomized in a 1:1 ratio to receive LCM or placebo.

Figure 1. Study SP0982 design



ET=Early Termination; LCM=lacosamide; V=Visit; W=Week

Note: Lacosamide dosing is designated as "mg/kg/day" (oral solution) and "mg/day" (tablets) and matching placebo is shown as "placebo."

[a] Subjects will be required to achieve and maintain a minimum LCM (or matching placebo) dose for at least the final 3 days of Week 6 to be eligible for entry into the Maintenance Period.

[b] If the subject discontinues from the study at any time and is not eligible or chooses not to enter EP0012, the subject must complete the ET Visit or Visit 10 (Week 24) and an up to 4-week blinded taper followed by an End of Taper Visit. There will be a 30-day Safety Follow-up Period for subjects who complete the End of Taper Visit. After the 125th event occurs, the 30-day Safety Follow up Period will be done as part of EP0012, except if the subject refuses to sign the EP0012 informed consent form. If the subject signs the informed consent form for a short Safety Follow-up as part of EP0012, the 30-day Safety Follow-up will be performed as part of EP0012; otherwise, the Safety Follow-up will be performed in SP0982.

[c] If the subject is in the Titration Period when the 125th event occurs, the subject will proceed to the Transition/Taper period directly after their ET/V10 Visit.

Source: Figure 5-2 in the protocol amendment 5

Figure 1 depicts the design of Study SP0982. The study consisted of a 4-week Baseline Period, a 24-week Treatment Period (6-week Titration Period and 18-week Maintenance Period), and a Transition Period (for eligible subject who chose to enter the open-label, extension study EP0012) or a Taper Period (for other subjects).

The primary efficacy endpoint was the time to the second PGTCS (defined as an event) during the 24-week Treatment Period (Day 166). The study continued until the 125th event occurred.

The key secondary efficacy variable is seizure freedom for PGTC seizures for the 24-week Treatment Period.

3.2.2 Statistical Methodologies

The efficacy analysis population was the full analysis set (FAS), defined as all randomized subjects who had at least one seizure diary assessment during the Treatment Period.

The primary efficacy endpoint was analyzed using a Cox proportional hazards model with treatment as an effect, stratifying for subjects' Baseline PGTCS frequency (≤ 2 per 28 days, >2 per 28 days) and age at informed consent (≥ 4 to < 12 years of age, ≥ 12 to < 18 years of age, ≥ 18 years of age). The censoring for the primary efficacy analysis is summarized below (source: the list in Section 3.2.4 of the protocol amendment 4)

- Subjects who complete the Treatment Period without having an event during the Treatment Period will be censored as of Day 167.
- If the subject's Treatment Period participation is less than or equal to 166 days (premature discontinuation), their PGTCS information will be censored on the date after the last dose of study drug.
- If the subject's Treatment Period participation is greater than 166 days, their PGTCS information will be censored as of Day 167.
- For the subjects who are ongoing in the study when the 125th event occurs, their PGTCS information for the primary efficacy endpoint analysis will be censored as of the day after the 125th event, even if the subjects experience an event after the date of the 125th event but before 166 days of treatment is completed.
- Only 125 events will be included in the primary efficacy endpoint analyses. In case of ties on the same date in reporting the 125th event, the first event reported to IRT will be deemed the 125th event. Data after the 125th event will be censored.

The key secondary efficacy endpoint was planned to be estimated using an extended Mantel-Haenszel technique which combines Kaplan-Meier estimates within each stratum. The Kaplan-Meier estimates of the proportions of subjects who have not experienced a second PGTCS at the end of week 24 were planned to be calculated and tested.

The primary and key secondary endpoints were planned to be tested sequentially.

In order to determine the strata for efficacy analyses, the following pooling rule was pre-specified in the statistical analysis plan (SAP) amendment 4:

- For subjects with Baseline PGTCS frequency ≤ 2 per 28 days:
  - If 2 of the age at informed consent categories combined have < 3 total events, then all age categories are combined for the analysis.
  - If ≥ 4 to < 12 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥ 12 and < 18 years of age category.

- If ≥ 18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the ≥ 12 and < 18 years of age category.
- If ≥ 12 and < 18 years of age is the category with the smallest number of events that are 2 events or less, it should be combined with the strata with the second smallest number of events.

- For subjects with Baseline PGTCS frequency > 2 per 28 days, repeat the same exercise.

An interim analysis for futility was planned when 50% of subjects have experienced an event (i.e. 62 events). Whether the study should stop for futility depends on the conditional power and the upper bound of the one-sided 85% confidence interval (CI_{UPPER}). The specific criteria are as follows (source: interim statistical analysis plan):

- If CI_{UPPER} is ≤ 0.3, the trial should be stopped for futility
- If $0.3 < CI_{UPPER} \leq 0.4$, futility is not clear (gray area). The IDMC should review all available data along with the CP and CI_{UPPER} to determine a recommendation regarding stopping the study. [The safety reports will also be available to the IDMC for the futility assessment.]
- If $CI_{UPPER} > 0.4$, the trial should not be stopped due to futility

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

A total of 350 subjects were screened in 115 sites and 242 were randomized. Among the randomized subjects, 121 subjects (50%) were randomized to the LCM group and 121 (50%) to the placebo group. A total of 240 subjects out of the 242 randomized subjects were included in the FAS.

Table 2. Subject demographics, full analysis set

Subgroup	Category	Placebo N=121 n (%)	LCM N=119 n (%)	All study participants N=240 n (%)
Age at enrollment	≥4 to <12 years	9 (7.4)	8 (6.7)	17 (7.1)
	≥12 to 18 years	16 (13.2)	16 (13.4)	32 (13.3)
	≥18 to <65 years	95 (78.5)	94 (79.0)	189 (78.8)
	≥65 years	1 (0.8)	1 (0.8)	2 (0.8)
Racial group	White	89 (73.6)	95 (79.8)	184 (76.7)
	Non-white	32 (26.4)	24 (20.2)	56 (23.3)
Gender	Male	45 (37.2)	54 (45.4)	99 (41.3)
	Female	76 (62.8)	65 (54.6)	141 (58.8)

Source: selected from Table 7-10 in the clinical study report

Table 2 summarizes the demographics of all randomized and treated subjects. The subjects in the LCM group and placebo group appeared similar in terms of age, sex, and race. Overall, the average

age of subjects in the FAS was approximately 27.7 years (standard deviation (SD) = 12.8). Most of the subjects were female. Most of the subjects were white.

3.2.4 Results and Conclusions

The interim analysis was performed when there were 64 events. The conditional power was 76.4% and the CI_{UPPER} was 78.7%. The independent data monitoring committee recommended that the study should continue.

Table 3. Post-hoc analysis of time (days) to second PGTCS during the 24-week Treatment Period, full analysis set

	Placebo N=121		LCM N=118	
	Cumulative number of events	**KM survival estimate (%)**	**Cumulative number of events**	**KM survival estimate (%)**
Treatment Period	76	33.37	49	55.27
KM analysis				
Time to event (days)				
Median	77.0		-	
95% CI	49.0, 128.0		144.0, -	
Study participants censored [a], n (%)	45 (37.2)		69 (58.5)	
Treatment comparison				
LCM – Placebo				
HR [b]	0.540			
95% CI of HR	0.377, 0.774			
p-value	<0.001			

CI=confidence interval; FAS=Full Analysis Set; HR=hazard ratio; KM=Kaplan-Meier; LCM=lacosamide; No=number; PGTCS=primary generalized tonic-clonic seizure

Note: Comparison of LCM versus Placebo was based on a Cox proportional hazards regression model with an effect for treatment, stratifying for the study participants' Baseline PGTCS frequency (≤2 per 28 days versus >2 per 28 days in the Combined Baseline Period) and age at informed consent (≥4 to <12 years of age,≥12 to <18 years of age versus ≥18 years of age). The reference group was Placebo.

Note: Study Participant [redacted] (b) (6) (LCM) was randomized after the 125th event and does not appear in this analysis.

Note: Significance was at the p<0.05 level.

[a] Study participants who completed the Treatment Period without having a second PGTCS during the Treatment Period were censored. If the study participant's Treatment Period participation was less than 166 days, they were censored on the date of the last dose of study medication. If the study participant's Treatment Period participation was greater than 24 weeks minus the visit window for Visit 10, they were censored as of Day 167 or the date after the 125th event.

[b] An HR <1 indicates time to second PGTCS was improved for LCM compared with Placebo.

Source: Table 8-1 in the clinical study report

Table 3 presents the analysis results initially reported in the clinical study report for the primary endpoint. The results show that the hazard ratio of LCM vs placebo was 0.540 (p-value < 0.001, 95% confidence interval = (0.3777, 0.774)), indicating that LCM group had a lower risk of developing a second PGTCS.

The strata used in the Applicant's analysis were (source: Table 3 in the August 12, 2020 response to information request):

SAP post-specification strata	
Stratum A	Baseline PGTCS frequency ≤2 per 28 days and pediatric (≥4 to <18 years of age)
Stratum B	Baseline PGTCS frequency ≤2 per 28 days and adult (≥18 years of age)
Stratum C	Baseline PGTCS frequency >2 per 28 days and All (pediatric and adult)

FAS=Full Analysis Set; PGTCS=primary generalized tonic-clonic seizures; SAP=statistical analysis plan

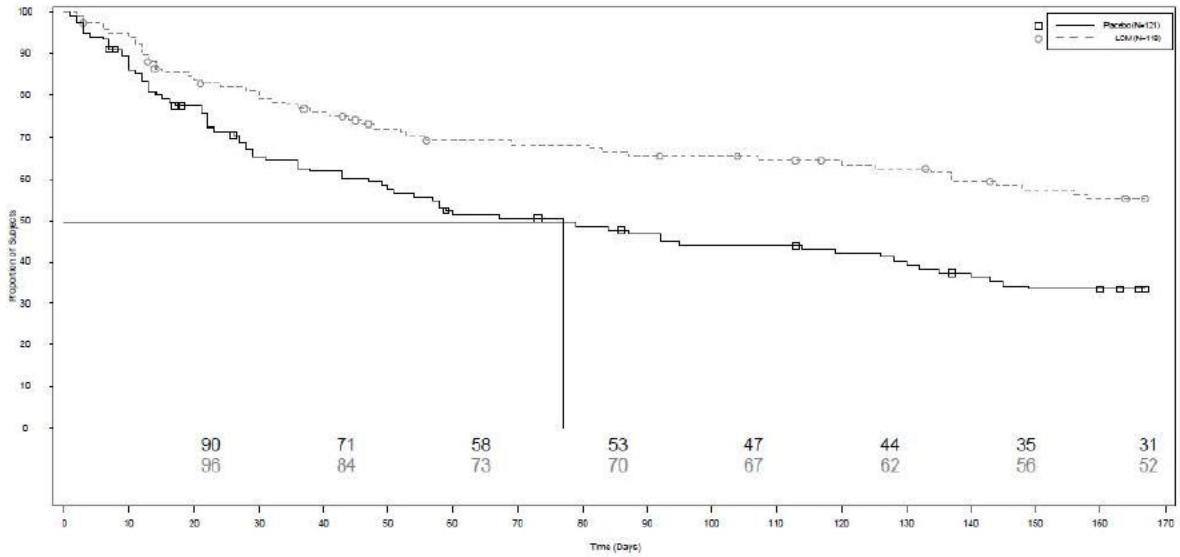
The Applicant disclosed that the strata deviated from the statistical analysis plan (SAP) pre-specification. In the August 12, 2020 response to information request, the Applicant explained that "since the diagnosis of PGTCS is rare in patients under 6 years of age and the diagnosis of PGTCS is uncommon in patients from 6 to 11 years of age, the enrollment of pediatric study participants in the 4 to 11 years of age category was low and using age category became a non-informative analysis stratification factor" and that the "pre-specification strata mostly were modified due to the key secondary efficacy endpoint, seizure freedom and its corollary, time to first PGTCS".

If the SAP pre-specification were followed, there would be six strata (source: Table 1 in the August 12, 2020 response to information request):

SAP pre-specification strata	
Stratum 1	Baseline PGTCS frequency ≤2 per 28 days and ≥4 to <12 years of age (pediatric)
Stratum 2	Baseline PGTCS frequency ≤2 per 28 days and ≥12 to <18 years of age (pediatric)
Stratum 3	Baseline PGTCS frequency ≤2 per 28 days and ≥18 years of age (adult)
Stratum 4	Baseline PGTCS frequency >2 per 28 days and ≥4 to <12 years of age (pediatric)
Stratum 5	Baseline PGTCS frequency >2 per 28 days and ≥12 to <18 years of age (pediatric)
Stratum 6	Baseline PGTCS frequency >2 per 28 days and ≥18 years of age (adult)

The results based on the SAP pre-specified strata had a hazard ratio of 0.548 (p-value = 0.001, 95% confidence interval = (0.381, 0.788)), also indicating that LCM group had a lower risk of developing a second PGTCS.

Figure 2. Kaplan-Meier curves for time (days) to second PGTCS during the 24-week Treatment Period, full analysis set



FAS=Full Analysis Set; LCM=lacosamide; PGTCS=primary generalized tonic-clonic seizure.
Note: The numbers represent the number of study participants at risk at the start of each 3-week period.
Note: The symbols represent censored study participants.
Note: Study Participant (b) (6) (LCM) was randomized after the 125th event and does not appear in this graph.

Source: Figure 8-1 in the clinical study report

Figure 2 demonstrates the Kaplan-Meier curves for time to second PGTCS during the 24-week Treatment Period. The median survival time was 77 days for the placebo group; the median survival time was not estimated for the LCM group because more than 50% of the subjects in the LCM group did not experience a second PGTC by end of week 24. Treatment difference between the LCM group and placebo group is observed from the Kaplan Meier curves. The log-rank test had a consistent conclusion with the primary analysis, favoring the treatment effect of the LCM group (nominal p-value = 0.001).

Table 4. Analysis of the key secondary endpoint, full analysis set

Parameter	Placebo N=121	LCM N=118
Overall		
Number of study participants	121	118
Number of study participants with a seizure, n (%)	97 (80.2)	79 (66.9)
Number of study participants censored, n (%) [a]	24 (19.8)	39 (33.1)
KM seizure free (%) (95% CI)	17.3 (10.3, 24.3)	31.0 (22.4, 39.6)
Stratum 1: Baseline PGTCS frequency ≤2 per 28 days and pediatric		
Number of study participants	21	21
Number of study participants with a seizure, n (%)	18 (85.7)	16 (76.2)
Number of study participants censored, n (%) [a]	3 (14.3)	5 (23.8)
KM seizure free (%) (95% CI)	14.3 (0.0, 29.3)	22.9 (4.4, 41.3)
Stratum 2: Baseline PGTCS frequency ≤2 per 28 days and adult		
Number of study participants	74	72
Number of study participants with a seizure, n (%)	56 (75.7)	46 (63.9)
Number of study participants censored, n (%) [a]	18 (24.3)	26 (36.1)
KM seizure free (%) (95% CI)	22.3 (12.5, 32.1)	34.2 (23.0, 45.5)
Stratum 3: Baseline PGTCS frequency >2 per 28 days		
Number of study participants	26	25
Number of study participants with a seizure, n (%)	23 (88.5)	17 (68.0)
Number of study participants censored, n (%) [a]	3 (11.5)	8 (32.0)
KM seizure free (%) (95% CI)	4.9 (0.0, 14.3)	30.0 (11.3, 48.7)
Stratified [b]		
KM seizure free (%) (95% CI)	17.2 (10.4, 24.0)	31.3 (22.8, 39.9)
LCM - Placebo		
KM seizure free (%) (95% CI)	14.1 (3.2, 25.1)	
Superiority of LCM versus Placebo p-value [c]	0.011	

CI=confidence interval; FAS=Full Analysis Set; KM=Kaplan-Meier; IRT=interactive response technology; LCM=lacosamide; PGTCS=primary generalized tonic-clonic seizures

Note: Study Participant (b) (6) (LCM) was randomized after the 125th event and does not appear in this analysis.

Note: Baseline PGTCS Frequency from Combined Baseline and development (age from IRT) are calculated from IRT.

[a] Study participants censored prior to Day 166.

[b] Estimated by extended Mantel Haenszel methods.

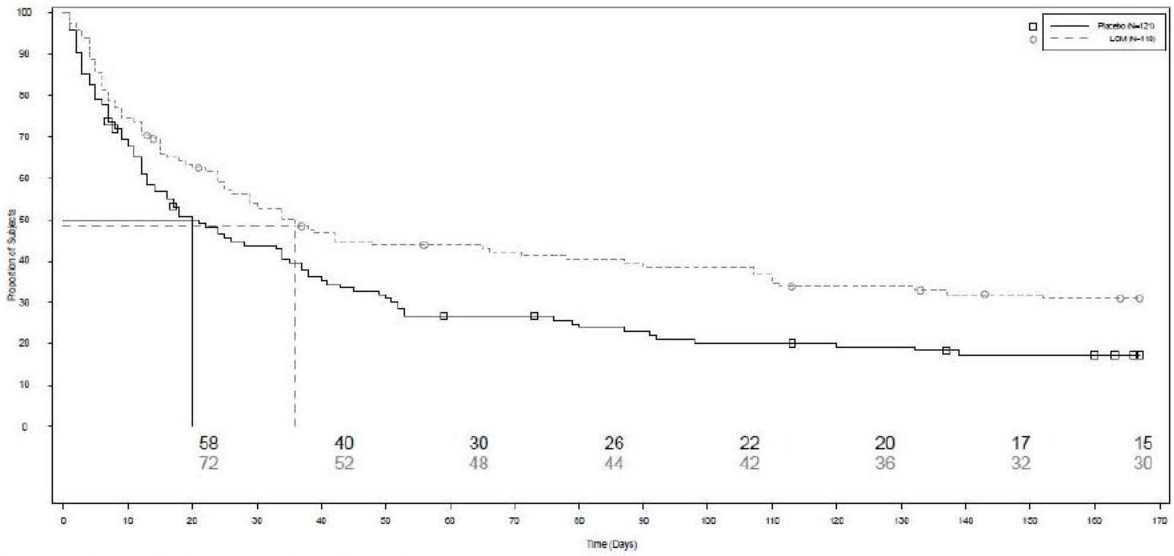
[c] Based on a chi-square test on 1 degree of freedom.

Data source: Table 8.2.1

Source: Table 8-4 in the clinical study report

Table 4 presents the analysis results of the key secondary endpoint. The estimated strata-weighted proportions of subjects that did experience a PGTCS by end of week 24 were 31.3% and 17.2% for the LCM group and placebo group, respectively; the LCM-placebo difference was 14.1% (95% CI = (3.2%, 25.1 %)) and statistically significant (p-value = 0.011). The three strata used in the analysis for this key secondary endpoint were derived based on SAP pre-specified rule and different from those in the SPA pre-specified analysis for the primary endpoint.

Figure 3. Kaplan-Meier curves for time (days) to first PGTCS during the 24-week Treatment Period, full analysis set



FAS=Full Analysis Set; LCM=lacosamide; PGTCS=primary generalized tonic-clonic seizure
Note: The numbers represent the number of study participants at risk at the start of each 3-week period.
Note: The symbols represent censored study participants.
Note: Study Participant [redacted] (b) (6) (LCM) was randomized after the 125th event and does not appear in this graph.
Data source: Figure 2.1

Source: Figure 8-2 in the clinical study report

Figure 3 demonstrates the Kaplan-Meier curves for time to first PGTCS during the 24-week Treatment Period. The median survival time was 36 days for the LCM group and 20 days for the placebo group. Treatment difference between the LCM group and placebo group is observed from the Kaplan Meier curves.

3.3 Evaluation of Safety

Please refer to Dr. Emily Freilich's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 5. Subgroup analyses of time (days) to second PGTCS during the 24-week Treatment Period, full analysis set

	Placebo (n=121)			LCM (n=119)			LCM - Placebo	
Subgroup	N	Cumulative number of events	KM survival estimate (%)	N	Cumulative number of events	KM survival estimate (%)	HR [a]	95% CI of HR
Age from IRT								
≥4 to 12 years	9	5	44.44	8	2	75.00	0.492	0.089, 2.731
≥12 to 18 years	16	9	41.25	16	7	54.14	0.740	0.265, 2.062
≥18 years	96	62	31.25	94	40	53.60	0.527	0.354, 0.786
Development								
Pediatric	25	14	41.54	24	9	61.03	0.650	0.271, 1.561
Adult	96	62	31.25	94	40	53.60	0.527	0.354, 0.786
Race								
White	89	49	40.45	94	40	53.52	0.713	0.469, 1.083
Non-white	32	27	15.00	24	9	61.76	0.261	0.120, 0.565
Gender								
Male	45	26	39.71	54	15	70.68	0.397	0.209, 0.752
Female	76	50	29.35	64	34	42.24	0.685	0.442, 1.061
Region								
North America	13	10	16.92	16	7	53.00	0.446	0.158, 1.260
Latin America	11	8	24.24	5	3	30.00	0.946	0.238, 3.756
Western/Central Europe	36	16	48.30	41	21	46.22	1.298	0.671, 2.511
Eastern Europe	22	7	66.53	29	6	77.75	0.522	0.172, 1.585
Asia/Pacific/Other	39	35	10.26	27	12	52.32	0.263	0.134, 0.515

Source: selected from Table 8-2 in the clinical study report

Table 5 presents the exploratory analyses of the primary endpoint by age group, race, gender, and region. Except for the western/central Europe region that had a hazard ratio greater than 1 from the exploratory cox regression analysis, other subgroups all had a hazard ratio smaller than 1 and there is no compelling evidence from the subgroup analyses that a specific subgroup benefits differently from LCM.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues that affect the efficacy conclusion.

5.2 Collective Evidence

This section is not applicable because the NDA supplement only included one efficacy study.

5.3 Conclusions and Recommendations

Lacosamide is approvable from a statistical standpoint. Study SP0982 provided statistical evidence that lacosamide is effective as an adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients (b) (4) 4 years and older.

We recommend that the prescribing label presents results from the SAP pre-specified analysis for the primary endpoint, rather than results from an analysis with post-hoc modified strata.

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/s/

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I concur with the review.

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