CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212839Orig1s000

SUMMARY REVIEW

Summary Review

Date	November 21, 2019
From	Philip H. Sheridan, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Summary Review
NDA/BLA # and Supplement#	212839
Applicant	SK Life Science , Inc.
Date of Submission	November 21, 2018
PDUFA Goal Date	November 21, 2019
Proprietary Name	Xcopri
Established or Proper Name	Cenobamate
Dosage Form(s)	Tablet 12.5mg, 25mg, 50mg, 100mg, 150mg, 200mg
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures in adult patients
Applicant Proposed Dosing Regimen(s)	Initial dose of Xcopri is 12.5 mg once daily for two weeks; followed by 25 mg once daily for two weeks; followed by 50 mg once daily for two weeks. Increase the dose in bi-weekly increments by no more than 50 mg once daily to a recommended maintenance dose of (b) (4) mg once daily. Maximum daily dose is 400 mg.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Xcopri is indicated for the treatment of partial-onset seizures in adult patients.
Recommended Dosing Regimen(s)	The recommended initial dosage of Xcopri is 12.5 mg once daily for two weeks; followed by 25 mg once daily for two weeks; followed by 50 mg once daily for two weeks. Increase the dose in bi-weekly increments by no more than 50 mg once daily to a recommended maintenance dose of 200 mg once daily. The maximum daily dosage is 400 mg.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Cenobamate is proposed for the treatment of partial-onset seizures (POS) in adult patients. POS are the most common type of epileptic seizures. These seizures impose a severe limitation to a patient's quality of life and pose a significant risk to a patient's health, particularly when loss of consciousness is part of the POS. In some circumstances, POS may be fatal. A high frequency of POS is associated with an increased risk of sudden unexpected death in epilepsy (SUDEP). Frequent partial seizures may promote a propensity for progression of the seizure disorder through kindling. Even when an outcome is not a threat to life, all events are disruptive to quality of life. Although there are nearly 20 approved drugs for the treatment of POS, about 30% of patients with POS remain refractory to treatment.

Cenobamate is a novel tetrazole-derived compound shown to reduce repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of 6 subtypes of the γ-aminobutyric acid ion channel. The exact mechanism of its effectiveness against POS is not known.

The efficacy of cenobamate was established by the results from two adequate and well-controlled clinical trials. Both were double-blind, randomized, placebo-controlled, parallel-group, multicenter, multinational studies (Studies 013 and 017). Both studies utilized a prospective 8-week baseline period to establish patients' baseline 28-day seizure frequency. Study 013 had a 12-week treatment period (6-week titration followed by 6-week maintenance) and Study 017 had an 18-week treatment period (6-week titration followed by a 12-week maintenance period). The primary efficacy endpoint for both trials was a comparison of the change in 28-day median percent seizure frequency in the treatment period relative to the baseline period, compared to placebo.

Study 013 was a two-arm study that randomized 109 adult patients to placebo and 113 patients to a 200 mg/day cenobamate treatment arm. There was a statistically significant difference between the placebo and treatment arms in the 28-day median percent seizure reductions from baseline, with a reduction in the treatment arm of 56%, representing a 34% greater reduction than the placebo arm.

Study 017 was a 4-arm study that randomized 108, 109, 111, and 106 adult patients to the 100 mg/day, 200 mg/day, and 400 mg/day cenobamate treatment arms and placebo, respectively. The median percent reductions from baseline in seizure frequency per 28 days were 55.3%, 55.2%, 36.3%, and 24.3% for the 400 mg/day, 200 mg/day, 100 mg/day cenobamate treatments arms, and placebo, respectively. All three cenobamate dose arms were statistically significantly superior to placebo. Although the median reductions from baseline were similar between the 200 mg/day and 400 mg/day arms, more patients treated with the 400 mg/day arm had the largest greater relative reductions from their baseline seizure frequencies (e.g., greater than 75% to 100% reductions), which supports the conclusion that the 400 mg/day dose may lead to greater

efficacy in some patients.

Three cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were observed in the cenobamate development program, including one fatality in a healthy volunteer participating in a Phase 1 safety trial. DRESS is a potentially fatal hypersensitivity reaction involving multiple organ systems and is characterized by rash, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver dysfunction. Onset of DRESS can occur 2-8 weeks after the initiation of a drug; DRESS is an established risk with several other anticonvulsant drugs (e.g., carbamazepine, phenytoin, lamotrigine). The applicant suspected that the risk of DRESS could be reduced through the implementation of a lower initial dose and slower titration schedule than was used in the controlled clinical efficacy trials. To evaluate this possibility, the applicant enrolled 1339 patients into a single-arm 12-month safety study (Study 021). No cases of DRESS were observed in Study 021 with the more cautious approach to dosing, which statistically suggests that the maximum risk of DRESS is no greater than 0.3%. However, it is difficult to determine the extent to which the controlled and vigilant trial conditions also contributed to this decreased risk. The DRESS risk of cenobamate is consistent with several other approved anticonvulsant agents and should not prohibit approval in the setting of established efficacy; however, product labeling, including a patient medication guide, will clearly convey the risk of DRESS, the associated signs and symptoms, and the need to seek immediate medical help if DRESS is suspected. The applicant will also be required to conduct enhanced pharmacovigilance for DRESS in the postmarketing setting, along with assessments of whether any genomic factors can be identified that contribute to an increased risk in certain individuals.

Additional serious potential risks that were identified in the development program were QTc shortening and central nervous system (CNS) adverse events (e.g., somnolence and fatigue, dizziness and gait disturbance, cognitive impairment, and visual changes). Labeling for cenobamate will also include the anticonvulsant class labeling language with respect to the risk of suicidal behavior and ideation as well as the need to gradually withdraw treatment unless otherwise medically indicated. Possible associations with liver enzyme elevations, elevated potassium, and appendicitis were also identified and will be described in labeling. There was an abuse potential risk identified in the development program, and a scheduling recommendation will be made to the Drug Enforcement Agency (DEA) upon approval.

The potential benefit of a novel anticonvulsant drug provides practitioners in the epilepsy community an additional option for treatment of this serious medical illness. The identified risks of treatment are not disproportionate to the potential benefit in the patient population with POS. Thus, these data support the approval of cenobamate for the treatment of POS in adults.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Partial-onset seizures (POS) are the most common type of epileptic seizures. These seizures impose a severe limitation to a patient's quality of life and pose a significant risk to a patient's health, particularly when loss of consciousness is part of the POS. • In some circumstances, POS may be fatal. A high frequency of POS is associated with an increased risk of sudden unexpected death in epilepsy (SUDEP). • Frequent partial seizures may promote a propensity for progression of the seizure disorder through kindling. • Even when an outcome is not a threat to life, all events are disruptive to quality of life.	POS are a common and serious manifestation of epilepsy.
Current Treatment Options	• There are nearly 20 available therapies for the treatment of POS; however, 30% of patients with partial onset seizures remain refractory.	Although there nearly 20 available drugs for the treatment of POS, in clinical practice patients who fail one such drug will be given a trial of an alternate drug to assess benefit. This is an ongoing process, and it is unpredictable on an individual basis who will benefit from a particular agent. There is a continuing need for available alternatives.
Benefit	• The effectiveness of cenobamate for the treatment of POS was established in two adequate and well-controlled trials. Each trial was a randomized, double-blind, placebo-controlled design. • 100 mg/day, 200 mg/day, and 400 mg/day doses of cenobamate resulted in statistically significantly greater percent reductions in 28-day median seizure frequency during treatment (12- and 18-weeks, respectively) relative to an 8-week baseline period, compared to placebo. • The effects of treatment were dose-proportional with median 28-day percent reductions in seizure frequency of between 36 to 56% on treatment, compared to 22 to 24% on placebo.	The effectiveness of cenobamate for the treatment of POS in adult patients has been demonstrated at a variety of doses. Given the variable response in individual patients, substantial benefit in particular individuals is likely to occur with clinical use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Cenobamate has a favorable effect size at the upper end of effect size seen in products for the treatment of POS.	
Risk and Risk Management	• The most significant risk of cenobamate treatment is the risk of DRESS. Three cases of DRESS were observed in the development program, including a fatality in a healthy volunteer subject enrolled in a Phase 1 safety study. The applicant suspected that the risk of DRESS could be reduced through the implementation of a lower initial starting dose and slower titration schedule than was used in the controlled clinical trials. To evaluate this possibility, the applicant conducted a large single-arm 12-month safety study that enrolled 1339 patients. No cases of DRESS were observed, which statistically suggests a maximum potential risk of no greater than 0.3%; however, it is unclear the extent to which the controlled and vigilant conditions of the trial contributed to this finding. • Additional serious potential risks that were identified in the development program were QTc shortening and CNS adverse events (e.g., somnolence and fatigue, dizziness and gait disturbance, cognitive impairment, and visual changes). • Dose-dependent increases in the percentages of patients in the controlled clinical trials who experienced at least one alanine aminotransferase (ALT) level of at least three times the upper limit of normal were observed in up to 2.6% of patients in the 400 mg/day cenobamate arm compared to 0% in placebo. The maximum ALT elevation was 7.6 times the upper limit of normal in patients treated with 400 mg/day of cenobamate. • Relatively small but dose-dependent increases in potassium greater than the upper limit of normal (ULN) were observed in the controlled clinical trials, with a maximum potassium value of 5.9 meq/L noted in two patients. • There was an incidence of appendicitis in the overall clinical trial safety population of 2.9 cases/1000 patient years of exposure that is in excess of the expected background rate in the general population.	The DRESS risk of cenobamate is consistent with several other approved anticonvulsant agents and should not prohibit approval in the setting of established efficacy; however, product labeling, including a patient medication guide, will clearly convey the risk of DRESS, the associated signs and symptoms, and the need to seek immediate medical help if DRESS is suspected. The applicant will also be required to conduct enhanced pharmacovigilance for DRESS in the postmarketing setting, along with assessments of whether any genomic factors can be identified that contribute to an increased risk in certain individuals. Labeling will describe the risk of CNS adverse events. These events can be monitored for and resolve with the removal of treatment, if necessary. QTc shortening presents an uncertain risk in the general population. Labeling will contraindicate patients with a known QTc shortening syndrome and also caution against use with other medications that shorten the QT interval. Additional nonclinical experiments to determine the anti-arrhythmic class of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There was an abuse potential risk identified in the development program.	cenobamate will also be required postmarketing. Labeling for cenobamate will also include the anticonvulsant class labeling language with respect to the risk of suicidal behavior and ideation as well as the need to gradually withdraw treatment unless otherwise medically indicated. Labeling will describe the potential association with cenobamate treatment and increases in ALT and potassium, as well as appendicitis. A controlled substance scheduling recommendation will be made to the DEA upon approval.

2. Background

This application provides data intended to support the safety and effectiveness of cenobamate (YK3089) for the treatment of partial-onset seizures (POS) in adult patients.

The cenobamate drug substance (a novel tetrazole-derived compound with one chiral center) is a new molecular entity (NME) that is not currently approved in any country. The applicant asserts that cenobamate has been shown to reduce repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also reported to be a positive allosteric modulator of 6 subtypes of the γ-aminobutyric acid ion channel; however, the exact mechanism of action by which it exerts an anticonvulsant effect is not known.

Epilepsy is a well-known and common condition, typically resulting in seizures of various types, with POS occurring in most. Though numerous medications have been approved for POS, a substantial number of patients with epilepsy continue to have incomplete seizure control, and there can be considerable variability in individual responses to these different medications.

Refer to the clinical review of this application for a detailed regulatory history of this development program.

The applicant is seeking the approval of an oral tablet formulation of cenobamate for the treatment of POS in adult patients. Efficacy and safety data are primarily provided by two randomized, double-blind, placebo-control trials. Results from a single-arm safety study to investigate the potential of a lower initial dose and slower titration schedule than was used in the controlled trials to reduce the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) were also included in the application (discussed in Sections 7 and 8 of this summary review).

3. Product Quality

The technical lead from the Office of Product Quality (OPQ) is Dr. Wendy Wilson-Lee. Refer to the OPQ review for details of the product quality assessment and for a full listing of the members of the OPQ Review Team that were involved with the review of this application.

The OPQ review team recommends approval of this application and has concluded that, from a quality perspective, the application provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

Stability and release testing were found to be acceptable to support the applicant's requested (b) (4)-month retest period for the drug substance stored at (b) (4) There were no outstanding issues

identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. Ed Fisher, with Dr. Lois Freed performing a secondary review. Drs. Fisher and Freed conclude that the application is approvable from a nonclinical standpoint. The following are among the key conclusions of the nonclinical review:

- In the safety pharmacology studies of orally administered cenobamate, the most notable findings were CNS toxicity (e.g., ataxia, reduced muscle tone and locomotor acitivity) in the rat. No cardiovascular effects were identified in the in vitro hERG assay or in vivo in telemetered male cynomolgus monkey.

- In the pivotal oral toxicity studies, conducted in rat, mouse, and monkey, the primary toxicities were death (primarily premature sacrifice following severe clinical signs) and CNS signs. Clinical signs (including ataxia, decreased activity, uncoordinated gait, recumbency, tremors, labored respiration) were dose-related in incidence and severity. Additional clinical signs observed in monkey included clonic convulsions (later determined in special investigative studies in monkey to be myoclonic jerks, which were also observed in mouse), nystagmus, severe hyperextension of the neck, and abnormal cranial nerve function and spinal segmental reflexes.

- Cenombamate was negative in in vitro and in vivo genetic toxicology assessments. Cenobamate was also negative for drug-induced tumors in carcinogencity studies in mouse and rat.

Cenobamate was assessed in a standard battery of reproductive and development toxicology studies: fertility and early embryonic development (to implantation), embryofetal development, and pre- and postnatal development in rat and an embryofetal development study in rabbit. Effects on emryofetal development were observed, and are discussed in detail in the nonclinical review. These findings will also be described in labeling. Dr. Freed also notes that the embryofetal studies that were completed were inadequate to fully assess the teratogenic potential of cenobamate and recommends a repeat embryofetal study in rat be conducted as a post-marketing requirement (PMR).

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Drs. Jagan Parapelly and Michael Bewernitz. Drs. Angela Men and Atul Bhattaram were the pharmacometrics team leads.

Summary of Clinical Pharmacology and Pharmacokinetics

Mechanism of Action (MOA): Cenobamate reduces repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of six subtypes of the γ-aminobutyric acid ($GABA_A$) ion channel. However, the exact mechanisms by which cenobamate exerts its anticonvulsant effect in humans is unknown.

Dose Proportionality: The pharmacokinetic (PK) parameters of cenobamate generally increased in a greater than dose-proportional manner following increasing single oral doses ranging from 5 mg to 750 mg; however, the C_{max} of cenobamate increased in a dose-proportional manner. The PK of cenobamate was essentially dose-proportional following multiple doses ranging from 50 mg/day to 500 mg/day.

Variability: Inter-subject variability of cenobamate in humans was up to 25% for C_{max} and up to 35% for AUC_{0-t}. The intrasubject variability of cenobamate was estimated to be 14% for C_{max} and up to 5% for AUC_{0-t}.

Absorption: Cenobamate was well-absorbed, based on a mass-balance study demonstrating that at least 88% was recovered in urine following oral administration. Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.

T_{max}: The median cenobamate T_{max} was between 1 to 4 hours after single- or multiple-dose administration under fasted conditions over the dose range of 10 to 400 mg.

Distribution: Plasma protein binding of cenobamate is moderate (60%) and independent of concentration. Cenobamate mainly binds with human albumin protein and not with α1-acid glycoprotein. Cenobamate is mainly confined to plasma. The whole blood to plasma ratio of cenobamate was 0.6. The estimated volume of distribution was 40 L to 50 L.

Metabolism: Cenobamate is extensively metabolized in liver, primarily by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5. The applicant conducted a series of drug-drug interaction studies to investigate the PK interactions of cenobamate with other drugs metabolized by the CYP enzymes,

including commonly used anticonvulsant drugs. The OCP reviewers have made dosing recommendations for labeling based on the results of these studies. One such recommendation of note is that the effectiveness of hormonal oral contraceptives is reduced by CYP3A4 inducers, such as cenobamate; therefore, women of reproductive potential concomitantly using hormonal oral contraceptives with cenobamate should use additional or alternative non-hormonal birth control.

There were no major circulating metabolites (i.e., greater than 10% of total drug related material) identified in human plasma. In a mass-balance study, administration of radiolabeled cenobamate, unchanged cenobamate accounted for greater than 98% of the total AUC of radioactivity in plasma. M1 (N-glucuronide of cenobamate) was the only metabolite found in human plasma, and the exposure (AUC) of M1 was found to be 1.2% of the parent drug. In urine and feces, the N-glucuronide metabolite (39.4% of the dose), oxidative O-phenyl glucuronide (20.4% of the dose), dihydrodiol and its glucuronide (17.1% of the dose), and side chain O-glucuronide (3.9% of the dose) appeared to be the major metabolites of cenobamate in vivo. Unchanged cenobamate accounted for 6.8% of the dose which was mainly excreted in the urine (6.4%).

Renal and Hepatic Impairment: The results of a renal impairment trial in patients with mild, moderate, or severe renal impairment demonstrated a 1.4-1.5-fold increase in the geometric mean for total plasma exposure ($AUC_{0\text{-}inf}$) in subjects with mild and moderate renal impairment. The results in subjects with severe renal impairment were comparable to normal subjects; a result that could not be explained by inter-subject variability, inter-occasion variability, or demographic factors. Based on the results this trial, the OCP review recommends that cenobamate be used with caution in patients with mild, moderate, or severe renal impairment.

The results of a study in subjects with hepatic impairment primarily demonstrated that the geometric mean for total plasma exposure ($AUC_{0\text{-}inf}$) increased by 1.93- and 2.3-fold in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. Therefore, the OCP reviewers recommend that in patients with mild and moderate hepatic impairment, the dose of cenobamate should be reduced by 50% during the titration phase, and the maximum daily dose should not exceed 200 mg. Cenobamate is not recommended for use in patients with severe hepatic impairment. The OCP review recommends a specific population study to further evaluate the effect of severe hepatic impairment on the PK properties of cenobamate as postmarketing requirement (PMR).

Excretion: Following administration of radiolabeled cenobamate, a mean of 93.0% of the total radioactive dose was recovered in urine (87.8%) and feces (5.2%). The mean terminal half-life for cenobamate ranged from 50 to 60 hours following single oral doses of 100 to 400 mg.

Dose Response

The OCP review evaluated the extent to which a dose-response relationship with cenobamate was evident in the controlled efficacy trials. The details of the designs of these trials are

discussed in Section 7 of this review; however, note that that Study 013 (originally designed as a Phase 2 proof-of-concept study) evaluated a maximum target dose of 200 mg/day while Study 017 evaluated up to a maximum target dose of 400 mg/day. To assess dose-response over time, the OCP reviewer created plots of change from baseline seizure frequency by study epochs in the titration and maintenance dose periods and dose arms to examine the effect of treatment over time in each of the controlled clinical efficacy trials, as well as the conversion to the open-label extension (OLE) periods. As indicated in the following figures, reproduced from the OCP review, these analyses reveal a trend of increased effectiveness (based on reductions in monthly seizure frequency) as the treatment interval progresses through titration into maintenance periods.

Figure 1 Percent Change from Baseline Monthly Seizure Frequency by Arm and By Time Period in Phase 2 Study C013

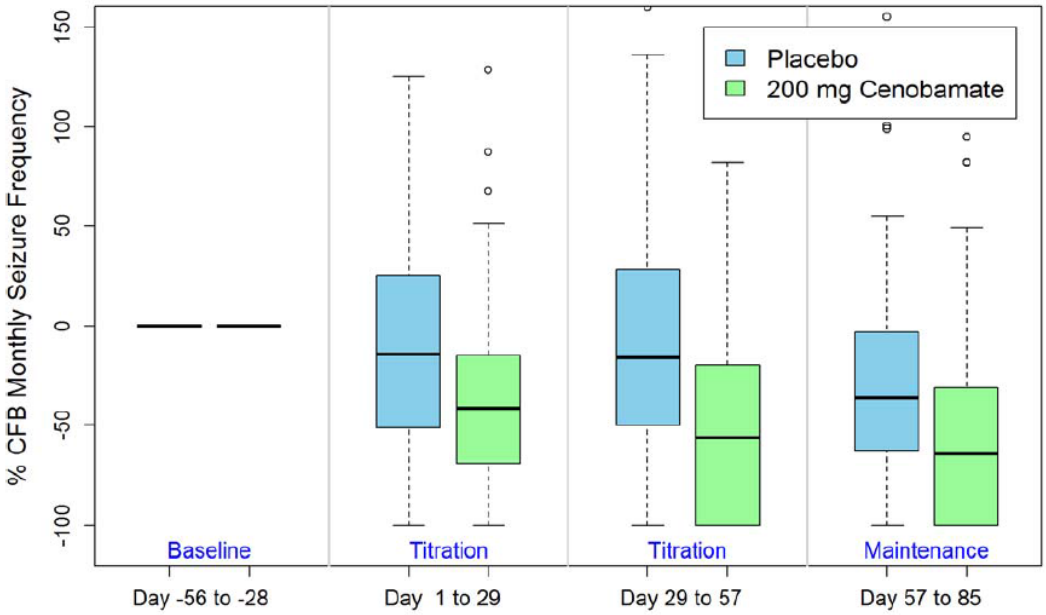
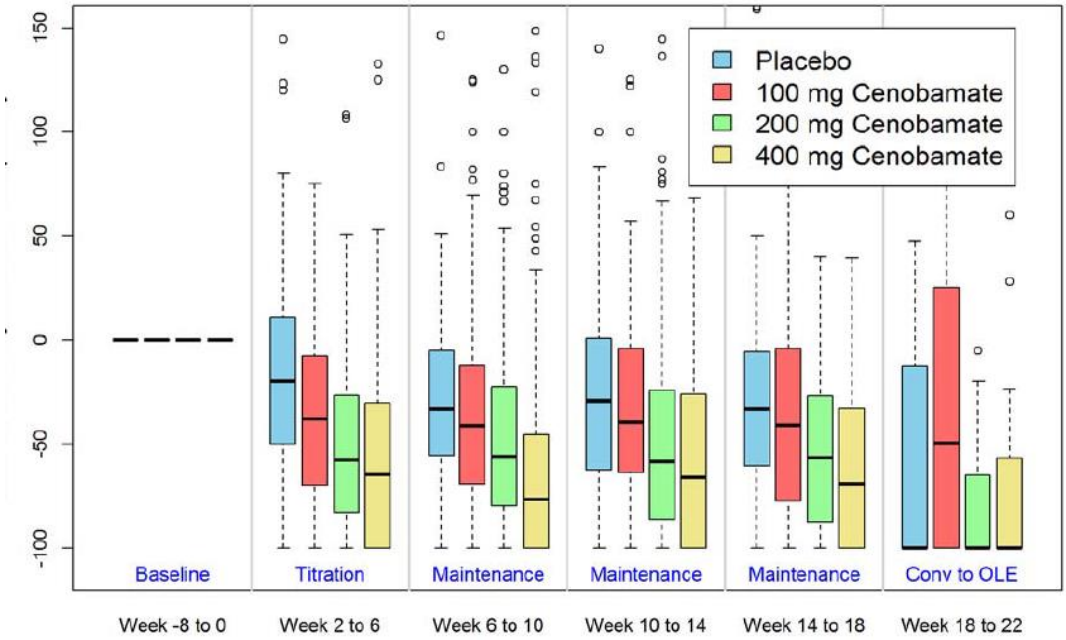


Figure 2 Percent Change from Baseline Monthly Seizure Frequency by Arm and By Time Period in Phase 3 Study C017



Titration Rate versus Clinical Efficacy

As discussed in Section 8 of this review, serious cases of DRESS were observed in the development program, including one fatality in a healthy volunteer subject in a Phase 1 safety study. The applicant suspected that this risk could be reduced by the implementation of a lower starting dose and slower titration schedule than was used in the controlled efficacy trials, and, following extensive discussion with the Division, evaluated both a lower starting dose and a slower titration schedule in Study 021 (a large single-arm safety study discussed in Section 8 of this review). Based on the lack of DRESS in Study 021, the applicant is proposing this revised dosing schedule for final labeling; therefore, the OCP review sought to evaluate any impact that this more cautious dosing schedule would have on clinical efficacy.

The OCP reviewer conducted an analysis comparing the efficacy study titration scheme to the modified schedule of reduced escalation rate in proposed labeling (referred to as the "label titration" in the figures below). The analysis examined the concentration-time profile (Figure 3) and the seizure frequency (Figure 4) comparing the different titration regimens.

The OCP reviewers conclude that the slower titration scheme proposed for the label can be expected to produce approximately half the maximum effect by 5 weeks and maximum effect at 14 to 18 weeks. In addition, on visual inspection of the graphic analysis displayed in Figure 4, a therapeutic effect in the range of the 100 mg treatment arm of Study 017 is expected to be present at approximately 7 weeks of titration.

Figure 3 Predicted Mean Plasma Concentration-Time Profile For Both Titration Regimens

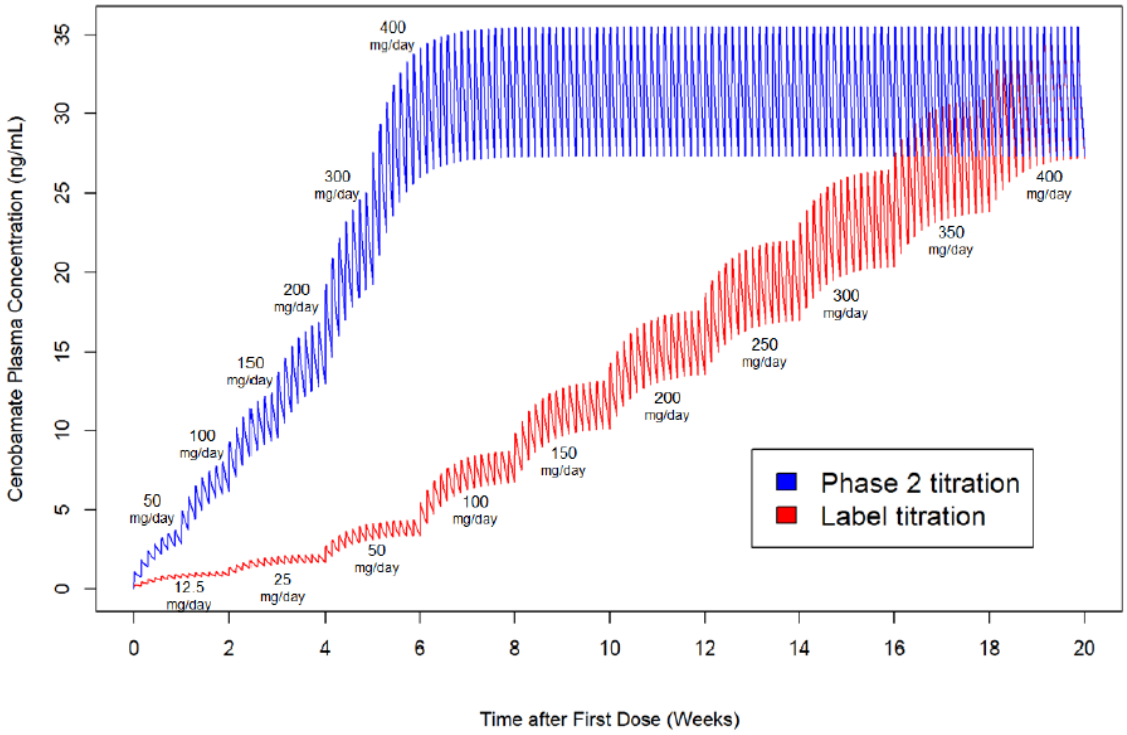
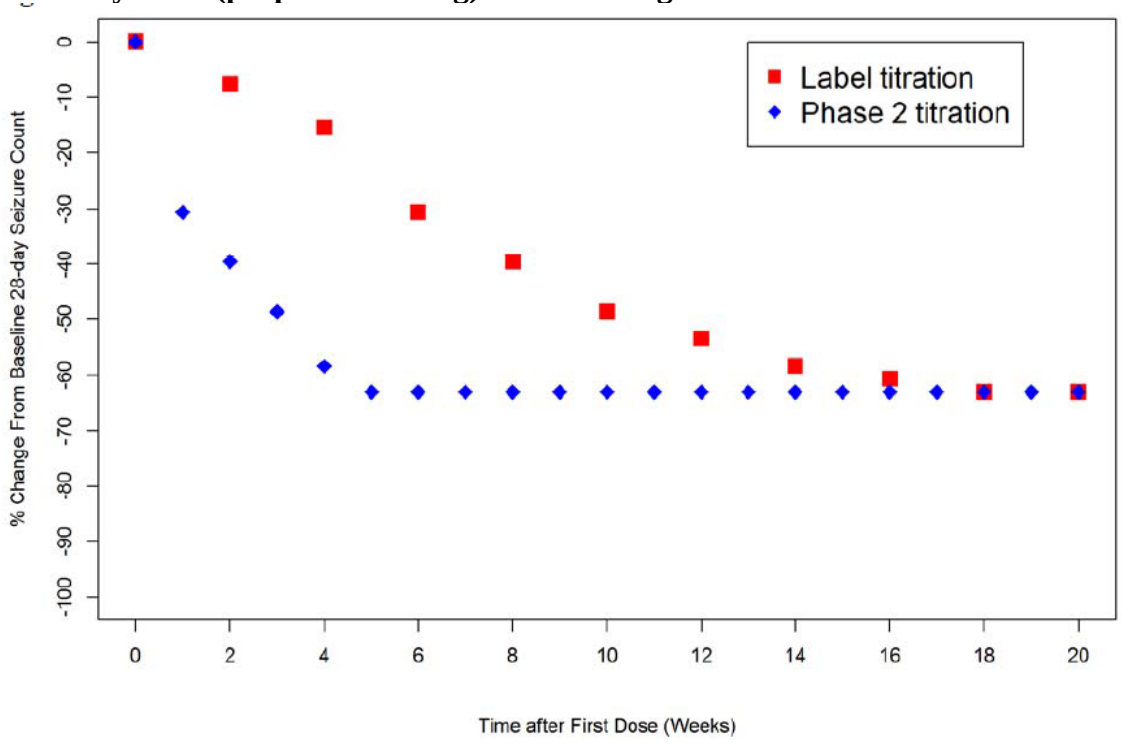


Figure 4 Predicted Change from Baseline 28-day Seizure Rate for Both Pivotal Study and Study C021 (proposed labeling) Titration Regimens



Monotherapy Assessment

The controlled efficacy trials with cenobamate were conducted as adjunctive therapy trials in combination with background anticonvulsant use. However, the OCP reviewers have determined that the applicant has provided appropriate analyses to support the conclusion that cenobamate monotherapy can be expected to result in exposures that have been demonstrated to be safe and effective when studied as adjunctive therapy for the treatment of POS. Therefore, the labeled indication will only state that cenobamate is indicated for the treatment of POS in adult patients (i.e., there is no need to stipulate either adjunctive or monotherapy use).

Overall Clinical Pharmacology Recommendation

The OCP review team recommends approval from a clinical pharmacology perspective and proposes a required postmarketing study to further evaluate the effect of severe hepatic impairment on the PK properties of cenobamate.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Steven Dinsmore was the clinical reviewer for this application. Dr. Xiangmin Zhang was the biometrics reviewer and Dr. Kun Jin was the biometrics team lead.

The efficacy of cenobamate for the treatment of POS was evaluated in two multicenter, randomized, double-blind, placebo-controlled studies in adult patients (Study 013 and Study 017). As discussed below, Study 013 was originally designed as a Phase 2 proof-of-concept trial.

Adult patients 18-65 years of age were eligible for enrollment in the studies if they had a history of POS with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant anticonvulsant drugs. Both trials included an 8-week baseline period to establish a baseline seizure frequency, where patients were required to have at least 3 or 4 POS per 28 days on average with no seizure-free period exceeding 3 to 4 weeks.

Study 013 compared a cenobamate 200 mg/day dose with placebo. Study 017 compared doses of cenobamate 100 mg/day, 200 mg/day, and 400 mg/day with placebo. Following the 8-week baseline period, patients in each study were randomized to one of the respective treatment arms (each study had an equal randomization between the treatment arms). Patients then entered a treatment period consisting of an initial titration phase (6 weeks), and a subsequent maintenance phase (6 weeks for Study 013 and 12 weeks for Study 017). In Study 013, patients were started on a daily cenobamate dose of 50 mg and subsequently increased by 50 mg/day every two weeks, until the final daily target dose of 200 mg/day was achieved. In Study 017, patients were started on a daily cenobamate dose of 50 mg and subsequently increased by 50 mg/day every week until 100 mg/day or 200 mg/day was reached. Patients randomized to the 400 mg/day arm were then increased by an additional 100 mg/day weekly for two more weeks. Importantly, as discussed in Section 8 of this review, a lower starting dose and slower titration schedule than were used in the controlled efficacy trials will be recommended for labeling because of the risk of DRESS.

In these studies, patients had a mean duration of epilepsy of approximately 24 years and median baseline seizure frequency of 8.5 seizures per 28 days. More than 80% of patients were taking 2 or more concomitant anticonvulsants.

In Study 013, the cenobamate and placebo groups appeared similar in terms of sex, race, and age. The average age of the patients was approximately 36.9 years [standard deviation (SD) = 11.3]. The percentage of females or males was around 50%. Over 50% of the randomized population were White. The second largest race was Asian, representing over 40% of randomized population.

In Study 017, the cenobamate and placebo groups were similar in terms of sex, race, and age. The average age of the patients was approximately 39.8 years (SD = 11.8). The percentage of females or males was around 50%. The majority of the randomized population were White.

The primary efficacy outcome measure in Studies 013 and 017 was the percent change from baseline in seizure frequency per 28 days in the treatment period (including both titration and maintenance). Seizure types that were included in the primary efficacy analysis comprised simple partial seizures with a motor component, complex partial seizures, and secondarily

generalized tonic-clonic seizures. The primary analysis population was the modified intention-to-treat (mITT) population, defined as all randomized patients who took at least one dose of study drug and had a post-dose evaluation. The primary analysis was conducted using an analysis of covariance (ANCOVA) model fit to the ranked values of the primary endpoint and included ranked baseline seizure frequency and treatment group. Table 1 summarizes the results of the primary endpoint analyses for each study.

Table 1. Percent Change from Baseline in Seizure Frequency per 28 Days in the Treatment Period (Study 013 and Study 017)

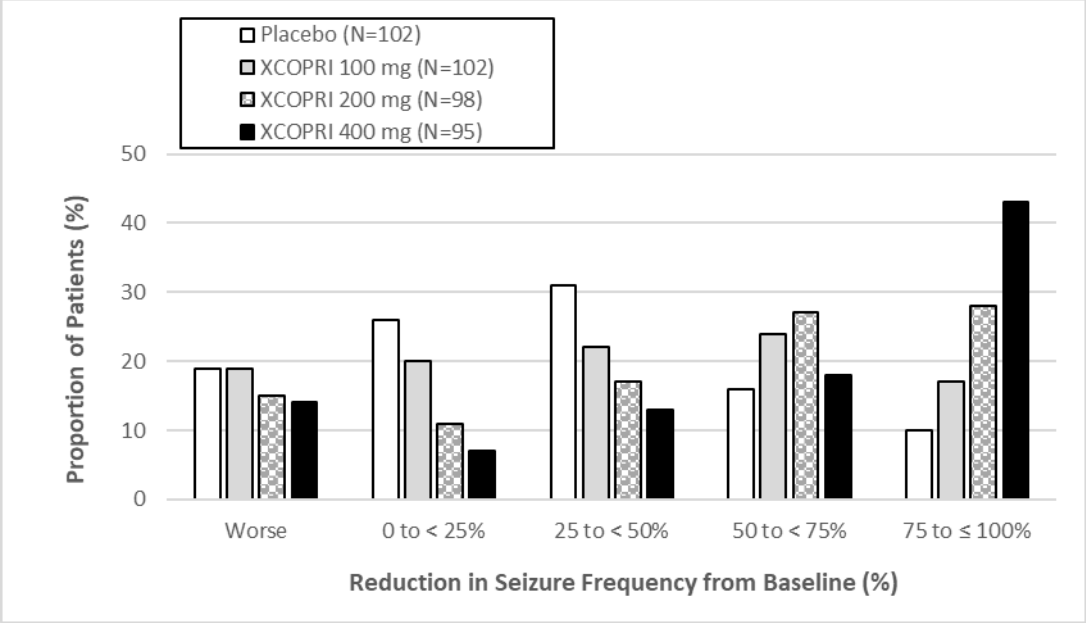
	N	Median Percent Change from Baseline in Seizure Frequency per 28 Days (%)*	p-value (Compared to Placebo)
Study 013			
Placebo	108	-21.5	--
Cenobamate 200 mg/day	113	-55.6	< 0.0001**
Study 017			
Placebo	106	-24.3	--
Cenobamate 100 mg/day	108	-36.3	0.006**
Cenobamate 200 mg/day	109	-55.2	< 0.001**
Cenobamate 400 mg/day	111	-55.3	< 0.001**

* A negative percent change from baseline in seizure frequency indicates reduction in seizure frequency from baseline.

** Statistically significant compared to placebo (based on a two-sided significance level of 0.05)

Treatment with cenobamate resulted in a greater reduction in median seizure frequency relative to placebo in both trials. A dose-response relationship was also present; however, the results in the 200 mg and 400 mg cenobamate arms in Study 017 were largely similar. To further understand any potential additional benefit of the 400 mg dose, patients in Study 017 were grouped by the relative reductions from baseline seizure frequency, as depicted in the following figure.

Figure 5: Proportion of Patients Exhibiting Different Percent Reductions During the Maintenance Phase over Baseline in Study 017



As Figure 5 indicates, in the grouping that includes the greatest reductions from baseline (75 to ≤ 100%), there was an additional benefit from the 400 mg dose compared to the 200 mg dose. Therefore, the 400 mg dose should be described in labeling; however, because of the risk of DRESS, all patients should first be titrated to the 200 mg dose (the recommended maintenance dose) with additional increases to the 400 mg dose (the maximum recommended dose) when clinically indicated.

Additionally, in Study 107, 4 of 102 (4%) patients in the XCOPRI 100 mg/day group, 11 of 98 (11%) patients in the XCOPRI 200 mg/day group, and 20 of 95 (21%) patients in the XCOPRI 400 mg/day group and 1 of 102 (1%) of patients in the placebo group reported no partial seizures during the maintenance phase.

Dr. Zhang's review discusses the fact that Study 013 was originally designed as a proof-of-concept study. As a result, several details with respect to the conduct of an unblinded interim analysis were not prespecified. Dr. Zhang further comments that although she did not find any changes in the study conduct following the interim analysis, the impact of this lack of prespecification is difficult to determine. However, despite these concerns, Dr. Zhang finds reassurance in the fact that Study 013 resulted in similar treatment effects as Study 017.

Analyses by gender, race, and geographic region for Studies 013 and 017 revealed no substantial differences in treatment response. Informative subgroup analysis by age was not possible because all the patients were adults and only five patients were 65 years of age or greater.

As concluded by the clinical and statistical reviews, Studies 013 and 017 can be considered adequate and well-controlled clinical trials that establish that cenobamate is effective for the treatment of POS in adult patients.

8. Safety

Dr. Steven Dinsmore conducted the clinical safety review of this application, with Dr. Gerard Boehm conducting a review specific to DRESS.

The primary focus of Dr. Dinsmore's safety review was the data from the two randomized, double-blind, placebo-controlled efficacy studies (Studies 013 and 017). A total of 659 patients were randomized into Studies 013 and 017 (but one placebo patient was never treated, leaving 658 patients) with 108, 223, 111, and 216 patients treated in the 100 mg, 200 mg, 400 mg, and placebo treatment arms, respectively.

Adding the two pivotal studies' patients to the open-label extension patients and Study 021 (a reduced titration rate study to characterize DRESS risk) patients, there were a total of 865 patients with exposure to cenobamate for at least 6 months and 710 patient for at least one year. The modal dose in the safety dataset had a peak at 200 mg for 710 patients. There were 288 patients and 127 patients with a modal dose of 300 mg and 400 mg respectively. These exposure data are adequate to characterize the safety of cenobamate for the proposed indication.

The following are the principal conclusions of Dr. Dinsmore's safety review of the application.

Deaths

There were 15 deaths during the development program, including the 120-day safety update, representing 0.8% of patients exposed to cenobamate.

Eleven of the deaths occurred within 349 days of cenobamate treatment initiation while the remaining 4 deaths occurred after 1.9 years of treatment. No deaths occurred in the treatment or placebo arms of the double-blind study intervals (12 weeks in Study 013 and 18 weeks in Study 017).

There were 2 suicides, one that occurred after 132 days of cenobamate treatment, 46 days after entering the open-label phase, the second occurred after 3.7 years of cenobamate treatment. There were two traumatic deaths, both instances of pedestrian patients struck by an automobile. There were 3 events of sudden unexplained death in epilepsy (SUDEP); this SUDEP frequency does not exceed the SUDEP frequency reported overall in patients with refractory epilepsy (the category of POS patients participating in the cenobamate studies). There were 3 cardiogenic events, none before 1.9 years of treatment, one in a 39-year-old male after 2.3 years of treatment with little explanation but no compelling temporal relationship to cenobamate treatment. There were 3 deaths related to infection, two subsequent to pneumonia. The third infection-related death followed a urinary tract infection in a medically fragile

patient. There was one death due to a seizure with associated head injury, and one death due to DRESS in a normal volunteer at day 84 of the thorough QT study (discussed further, below).

Dr. Dinsmore notes that there is temporal dispersion of death events with considerable variation in the category of underlying medical characteristics of the events. There is absence of clear causal relationship to cenobamate in all but in the death of the subject who developed DRESS.

Serious Adverse Events

Analysis of serious adverse events (SAEs) in the double-blind periods of the two controlled efficacy studies reveals a higher frequency overall in the cenobamate treatment arms but without a clear dose-response relationship. The most frequent SAEs are events related to epilepsy with seizure terms almost equally divided between placebo and treatment arms and a minimum in the 400 mg arm. "Nervous System Disorder" events that predominate in the cenobamate treatment arm are related to central nervous system (CNS) dysfunction, suicidality, and drug hypersensitivity. In addition to the risk of DRESS discussed subsequently in this review, the serious safety events to include in labeling are CNS adverse events, drug hypersensitivity, and suicidality. A single patient experienced an event of alanine aminotransferase (ALT) elevation that reached a maximum of 7.6x the upper limit of normal (ULN) while on 400 mg cenobamate. The ALT value improved to 2 x ULN 12 days after study drug discontinuation. A single event of "pulmonary embolism" occurred in the 100 mg cenobamate treatment arm associated with a cerebral infarction.

Examination of SAEs in the pooled Phase 2/3 safety datasets reveal that the most frequently experienced serious safety issue is central nervous system dysfunction that may be severe but generally occurs early after initiation of cenobamate. The reduced titration rate may mitigate this effect to some extent, although there were reports of these SAE events after long periods of exposure. Also of note are psychiatric disorders where the observed suicidality frequency is in alignment with the current AED class labeling. There were four reports of psychotic disorder that indicate a signal for an adverse psychoactive effect of cenobamate. There were reports of appendicitis with a frequency higher than expected background rate. Hypersensitivity reactions were evident and could emerge very early after the start of cenobamate exposure. There was a case of DRESS in Study 017 but no new DRESS cases were identified in Study 021 at the reduced cenobamate titration rate (see section on DRESS Risk below).

Dropouts and/or Discontinuations Due to Adverse Effects

In Studies 013 and 017, the discontinuation rates because of adverse events were 11%, 9%, and 21% for patients randomized to receive cenobamate at doses of 100 mg/day, 200 mg/day, and 400 mg/day, respectively, compared to 4% in patients randomized to receive placebo. The adverse reactions most commonly (at least 1% in any cenobamate treatment group, and greater

than placebo) leading to discontinuation, in descending order of frequency, were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo.

DRESS Risk

During the development program, DRESS was identified as a serious safety risk associated with cenobamate treatment. A DRESS case occurred in the thorough QT healthy volunteer study that had a fatal outcome. Two additional cases of DRESS occurred, one in a healthy volunteer participating in a multiple ascending dose PK study and one in a patient participating in the open-label extension of Study 017. These latter two patients recovered but required hospitalization and corticosteroid treatment. The details of these cases are discussed in Dr. Boehm's focused review of this issue. At the time of the identification of these cases, 833 patients had taken at least 1 dose of cenobamate, yielding a DRESS risk of 0.36% (3/833).

Following the identification of these cases, the Division and the applicant had agreed to the conduct of a single-arm study (Study 021) to evaluate whether a lower starting dose and slower titration schedule than were used in the controlled efficacy trials could reduce the risk for DRESS. The study had a planned enrollment of 1000 patients based on the assumption that no cases of DRESS would occur; a result that would allow for the conclusion that the risk of DRESS could be capped at 0.3% (the upper bound of the 95% confidence interval). The acceptability of this threshold was based on the fact that a similar approach was used in the evaluation of Stevens-Johnson syndrome risk with lamotrigine. The limitations of a historical comparison to the risk from the controlled trials were noted (e.g., operational bias); however, exposing patients to the regimen associated with DRESS, which resulted in imposition of a clinical hold, was not acceptable.

Study 021 initiated treatment at 12.5 mg daily for two weeks, followed by 25 mg daily for two weeks, followed by increases of 50 mg daily every two weeks to a target dose of 200 mg daily. The maximum dose of 400 mg daily was reached following additional titration steps of 50 mg daily every two weeks. Patients with perceived benefit after 12 months were offered the ability to continue on treatment at the discretion of the investigator.

No cases of DRESS were identified among 1339 patients treated with cenobamate in Study 021, including 1110 patients treated with cenobamate for at least 6 months. However, Dr. Boehm observes that the safeguards that were utilized in Study 021, including the use of laminated patient cards, intensive follow-up of suspected cases of rash, and differences in exclusion criteria, were not all present in the controlled trials and need to be taken into consideration when evaluating the relative risk of DRESS. Dr. Boehm also comments that 44 patients in Study 021 discontinued for AEs related to skin or subcutaneous tissue; of these, he identified 2 particular cases of interest that he discusses in detail in his review that may have represented at-risk cases for DRESS.

Dr. Boehm concludes that although the use of a lower starting dose and slower titration regimen than were used in the controlled clinical trials appears to reduce the risk of DRESS, no definitive conclusions can be made based on the operational limitations of Study 021. Dr. Boehm does not believe that a Risk Evaluation and Mitigation Strategy (REMS) for this risk is

necessary, but cautions that the risk of DRESS must be clearly conveyed in labeling, including the limitations of the data derived from Study 021. Dr. Boehm also states that the applicant should conduct enhanced pharmacovigilance for DRESS in the postmarketing setting, as well as perform genomic studies to attempt to identify any predictive factors. A patient medication guide will also be issued, consistent with those approved for other anticonvulsant drugs that have a DRESS risk.

QTc Shortening

Dr. Lars Johannesen was the QT-Interdisciplinary Review Team (QT-IRT) reviewer for this application.

In a placebo-controlled study investigating the impact of cenobamate on the QT interval, a higher percentage of subjects who took cenobamate (31% at 200 mg and 66% at 500 mg) had a QT shortening of greater than 20 ms compared to placebo (6-17%). Formal cardiac ECG studies demonstrated shortening of the QT interval (mean = 16 msec, for doses greater than 400 mg daily) with cenobamate. Reductions of the QTc interval below 300 ms were not observed. The degree of QT shortening induced by cenobamate is without any known clinical risk. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Nonclinical data also indicate that QT shortening is associated with ventricular fibrillation.

Dr. Johannesen comments that the available nonclinical information suggests that the observed QT shortening is mediated via blockade of the cardiac sodium channel. He notes that some drugs that inhibit the cardiac sodium channel have been observed to increase mortality in patients with structural heart disease (e.g., encainide, flecainide, moricizine, and mexiletine) but states that whether or not cenobamate carries the same risk is unknown. He also observes that some sodium channel blocking drugs have an apparent association with the potential to unmask Brugada syndrome, but, again, notes that it is unclear if cenobamate has such a risk.

Patients with Familial Short QT syndrome should not be treated with cenobamate, and this will be listed as a contraindication in labeling. Caution should be used when administering cenobamate and other drugs that shorten the QT interval as there may be a synergistic effect on the QT interval that would increase the QT shortening risk. The QT-IRT review also recommends that additional nonclinical experiments to determine the anti-arrhythmic class of cenobamate are required postmarketing.

Other Significant Adverse Events

Neurologic adverse events (e.g., somnolence and fatigue, dizziness and gait disturbance, cognitive impairment, and visual changes) had a high frequency with cenobamate treatment. These dose-dependent adverse events are frequently observed with anticonvulsant therapy. These may be monitored, will resolve with discontinuation, and generally diminish with accommodation to the drug treatment.

Dr. Dinsmore observes that 9 cases of appendicitis were observed in the development program (2.9 cases/1000 patient-years of exposure), occurring at a rate higher than the reported

background rate of 1.1/1000. Any potential causal relationship to treatment is unclear; however, this event will be added to the prescribing information to inform prescribers of the observation.

Treatment Emergent Adverse Events and Adverse Reactions

Table 2, reproduced from Dr. Dinsmore's review, summarizes the most common treatment-emergent adverse events (TEAEs) that occurred in the controlled clinical efficacy trials.

Table 2 Adverse Reactions in Pooled Placebo-Controlled Adjunctive Therapy Studies in Patients with Partial-Onset Seizures with Cenobamate Frequency In Any Treatment Arm Greater Than 1% Over Placebo

Adverse Reaction	Cenobamate			Placebo
	100mg	200mg	400mg	
	n=108 %	n=223 %	n=111 %	n=216 %
Cardiac Disorders				
Palpitations	0	0	2	0
Ear and Labyrinth Disorders				
Vertigo	1	1	6	1
Eye Disorders				
Diplopia	6	7	15	2
Vision Blurred	2	2	4	0
Gastrointestinal Disorders				
Nausea	6	6	9	3
Constipation	2	4	8	0
Diarrhea	1	3	5	0
Vomiting	2	4	5	0
Dry Mouth	1	1	3	0
Abdominal Pain	2	2	1	0
Dyspepsia	2	2	0	0
Toothache	3	1	0	1
General Disorders and Administration Site Conditions				
Fatigue	12	14	24	7
Gait Disturbance	1	3	8	1
Asthenia	0	1	3	1
Infections and Infestations				
Nasopharyngitis	2	4	5	3
Pharyngitis	1	2	0	0
Urinary Tract Infection	2	5	0	2
Injury, Poisoning and Procedural Complications				
Head Injury	1	0	2	0

Investigations				
Alanine Aminotransferase Increased*	1	1	4	0
Aspartate Aminotransferase Increased	1	1	3	0
Weight Decreased	2	0	1	0
Metabolism and Nutrition Disorders				
Decreased Appetite	3	1	5	1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	4	2	5	3
Musculoskeletal Chest Pain	2	1	0	0
Nervous System Disorders				
Somnolence	19	22	37	11
Dizziness	18	22	33	15
Headache	10	12	10	9
Balance Disorder	3	5	9	1
Dysarthria	2	1	7	0
Nystagmus	3	7	6	0
Ataxia	2	3	6	2
Aphasia	2	1	4	0
Dysgeusia	2	0	2	0
Memory Impairment	2	1	2	0
Migraine	0	0	2	0
Sedation	1	1	2	0
Tremor	0	3	1	1
Psychiatric Disorders				
Confusional State	2	2	3	0
Euphoric Mood	0	0	2	0
Irritability	1	0	2	0
Suicidal Ideation	2	1	0	0
Renal and Urinary Disorders				
Pollakiuria	0	1	0	0
Reproductive System and Breast Disorders				
Dysmenorrhea	1	2	1	0
Respiratory, Thoracic and Mediastinal Disorders				
Hiccups	0	1	1	0
Dyspnea	0	3	0	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	2	1	0	0
Rash Papular	2	0	0	0

* Reported as an adverse reaction; see Laboratory Abnormalities for ALT changes from collected laboratory values

Laboratory Findings

Dr. Dinsmore identified a trend of hyperkalemia that he proposes be described in labeling to alert prescribers; however, he further comments that no critical values were identified that were associated with adverse cardiac adverse events. The events of potassium elevated out of reference range to high value tended to be sporadic which leads to uncertainty about any possible causal association with treatment. Dr. Dinsmore concludes that enhanced clinical chemistry monitoring need not be recommended in labeling.
In Study 017, there was a post-baseline elevation of ALT to greater than 3 X ULN in 1 (0.9%) patient treated with 100 mg cenobamate, 2 (1.8%) patients treated with 200 mg, and 3 (2.7%) patients treated with 400 mg compared to no patients who took placebo. The maximum ALT elevation was 7.6 X ULN in one patient treated with 400 mg.

Vital Signs

There were no clinically meaningful changes from baseline in vital signs.

Electrocardiograms (ECGs)

See discussion of QTc shortening above. There were no other clinically meaningful changes from baseline in ECG results.

Integrated Assessment of Safety

The overall safety profile of cenobamate, including the risk of DRESS, appears generally consistent with many other anticonvulsant drugs previously approved for POS and supports the approval of cenobamate for the treatment of POS in adults. Although the risk of DRESS appears to be reduced with a lower starting dose and slower titration than was used in the controlled efficacy trials, no definitive conclusions can be made about the ability of this approach to fully mitigate this risk. Product labeling, including a patient medication guide, will be clear about this risk as well as the limitations of the data with respect to the recommended dosing approach, and instruct patients to seek immediate medical advice if signs and symptoms consistent with DRESS are present. The applicant will also be required to perform enhanced reporting and genomic evaluations of any DRESS cases observed in the postmarketing setting.

9. Advisory Committee Meeting

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

10. Pediatrics

Section 13 of this review outlines the pediatric postmarketing studies that will be required under the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

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

Dr. Dinsmore concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Office of Scientific Investigation (OSI) completed inspections of three clinical sites from Studies 013 and 017, as well as the sponsor, SK Life Science, and the clinical research organization (CRO), (b) (4) Please see the Clinical Inspection Report by Cara Alfaro for details. The overall assessment was that the studies were conducted adequately and that the data generated by these sites appear acceptable in support of the proposed indication.

The Controlled Substance Staff (CSS) review concluded that the application should be approved. However, the CSS reviewers will recommend that cenobamate should be a federally controlled substance (CX, pending DEA decision) because it can be abused or lead to dependence. After evaluating the nonclinical and clinical data in this application, CSS concludes that cenobamate has a relative abuse potential lower than substances in Schedule IV but greater than placebo and should be placed into Schedule V of the Controlled Substance Act. CSS will convey this recommendation to the Drug Enforcement Agency (DEA) who will make a final determination regarding scheduling.

12. Labeling

Please refer to the final negotiated product labeling. Labeling negotiations with the applicant have been completed, and the applicant has accepted all recommended changes. A patient medication guide will accompany the prescribing information.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management (DRISK) reviewer for this application was Dr. Linsey Crist. Dr. Crist concluded that a risk evaluation and mitigation strategy (REMS) is not necessary to ensure that the benefits of cenobamate outweigh its risks. The risks associated with cenobamate, including the risk of DRESS, are adequately communicated through the labeling and the medication guide.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following studies are recommended as PMRs and PMCs:

3712-1 An embryofetal development study of cenobamate in rat.

Final Protocol Submission:	09/2020
Study Completion:	05/2021
Final Report Submission:	11/2021

3712-2 Develop an age appropriate formulation of cenobamate that can be used in children 1 month to less than 2 years old.

Final Report Submission:	01/2021

3712-3 Evaluate bioavailability of the age appropriate formulation for children 1 month to less than 2 years old relative to the approved tablet formulation.

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Study Completion:	07/2021
Final Report Submission:	11/2021

3712-4 A study to evaluate the pharmacokinetics, safety, and tolerability of an age-appropriate formulation of cenobamate in children ages 1 month to less than 2 years with partial-onset seizures. This study should identify doses to be used in the efficacy and long-term extension studies for children 1 month to less than 2 years of age.

Draft Protocol Submission:	07/2021
Final Protocol Submission:	11/2021
Study Completion:	04/2025
Interim Report Submission:	04/2026
Final Report Submission:	12/2030

The interim report should provide for the final study analysis to allow for consideration of dosing requirements in the efficacy and safety studies for children 1 month to less than 2 years of age.

3712-5 A prospective, randomized, controlled, double-blinded, efficacy and safety study of cenobamate for the treatment of partial-onset seizures in children from

1 month to less than 2 years of age. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon video/electroencephalographic data. The placebo and drug treatment groups will be compared by inferential statistical methods to identify a treatment effect.

Draft Protocol Submission:	06/2025
Final Protocol Submission:	12/2025
Study Completion:	12/2028
Final Report Submission:	12/2030

3712-6 Long-term safety study of cenobamate in the treatment of partial-onset seizures in children from 1 month to 2 years of age. Routine safety measures should be monitored. Behavioral and cognitive endpoints should be included.

Draft Protocol Submission:	07/2021
Final Protocol Submission:	11/2021
Study Completion:	12/2029
Final Report Submission:	12/2030

3712-7 A study to evaluate the pharmacokinetics, safety, and tolerability of an age appropriate formulation of cenobamate to determine a dosing regimen as therapy for partial-onset seizures in children ages 2 years to 17 years of age that provides drug exposure that is similar to the exposure that is effective in adult patients with partial-onset seizures. This analysis will require pharmacokinetic data from studies of both the adult and pediatric patients.

Draft Protocol Submission:	07/2020
Final Protocol Submission:	11/2020
Study Completion:	05/2022
Interim Report Submission:	03/2023
Final Report Submission:	11/2025

The interim report should provide for the final study analysis to allow for consideration of dosing requirements in the efficacy and safety studies for children 2 years to 17 years of age.

3712-8 The efficacy of cenobamate in children ages 2 years to 17 years of age for the treatment of partial-onset seizures will be addressed by a report demonstrating matched exposure to that in adults supporting pediatric extrapolation.

Study Completion:	05/2024
Final Report Submission:	11/2025

3712-9 An open-label long term safety and tolerability study of cenobamate in children ages 2 years to 17 years of age.

Draft Protocol Submission:	07/2020
Final Protocol Submission:	11/2020
Study Completion:	11/2024
Final Report Submission:	11/2025

3712-10 Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Xcopri (cenobamate) during pregnancy compared to an unexposed control population.

Draft Protocol Submission:	08/2020
Final Protocol Submission:	07/2021
Annual Interim Report Submissions:	07/2022
	07/2023
	07/2024
	07/2025
	07/2026
	07/2027
	07/2028
	07/2029
	07/2030
Study Completion:	07/2031
Final Report Submission:	07/2032

3712-11 Perform additional nonclinical experiments to characterize the effects of cenobamate on the cardiac sodium channel, which should allow for determining the anti-arrhythmic sub-class of cenobamate (i.e., Ia, Ib, or Ic).

Draft Protocol Submission:	04/2020
Final Protocol Submission:	06/2020
Study Completion:	03/2021
Final Report Submission:	06/2021

3712-12 Conduct a clinical pharmacokinetic trial to determine an appropriate dose of Xcopri (cenobamate) to minimize toxicity in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA

Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Trial Completion:	09/2021
Final Report Submission:	03/2022

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/

NICHOLAS A KOZAUER on behalf of PHILIP H SHERIDAN
11/21/2019 03:22:14 PM

NICHOLAS A KOZAUER
11/21/2019 03:22:39 PM

WILLIAM H Dunn
11/21/2019 03:25:04 PM