FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study

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Abstract

Objective: During the development of cenobamate, an antiseizure medication (ASM) for focal seizures, three cases of drug reaction with eosinophilia and systemic symptoms (DRESS) occurred. To mitigate the rate of DRESS, a start-low, go-slow approach was studied in an ongoing, open-label, multicenter study. Also examined were long-term safety of cenobamate and a method for managing the pharmacokinetic interaction between cenobamate, a 2C19 inhibitor, and concomitant phenytoin or phenobarbital.

Methods: Patients 18-70 years old with uncontrolled focal seizures taking stable doses of one to three ASMs were enrolled. Cenobamate 12.5 mg/d was initiated and increased at 2-week intervals to 25, 50, 100, 150, and 200 mg/d. Additional biweekly 50 mg/d increases to 400 mg/d were allowed. During titration, patients taking phenytoin or phenobarbital could not have their cenobamate titration rate or other concomitant ASMs adjusted; phenytoin/phenobarbital doses could be decreased by 25%-33%.

Results: At data cutoff (median treatment duration = 9 months), 1347 patients were enrolled, of whom 269 (20.0%) discontinued, most commonly due to adverse events (n = 137) and consent withdrawn for reason other than adverse event (n = 74); 1339 patients received ≥1 treatment dose (median modal dose = 200 mg). The most common treatment-emergent adverse events (TEAEs) were somnolence (28.1%), dizziness (23.6%), and fatigue (16.6%). Serious TEAEs occurred in 108 patients (8.1%), most commonly seizure (n = 14), epilepsy (n = 5), and pneumonia, fall, and dizziness (n = 4 each). No cases of DRESS were identified. In the phenytoin/phenobarbital groups, 43.4% (36/114) and 29.7% (11/51) of patients, respectively, had their doses decreased. At the end of titration, mean plasma phenytoin/phenobarbital levels were generally comparable to baseline.

Significance: No cases of DRESS were identified in 1339 patients exposed to cenobamate using a start-low (12.5 mg/d), go-slow titration approach. Cenobamate was generally well tolerated in the long term, with no new safety issues found. Phenytoin/phenobarbital dose reductions (25%-33%), when needed during cenobamate titration, maintained stable plasma levels.

KEYWORDS

antiepileptic drugs, cenobamate, DRESS, refractory epilepsy, safety/tolerability

1 | INTRODUCTION

A substantial portion of patients with epilepsy (up to 30%) discontinue antiseizure medication (ASM) treatment because of intolerable side effects,[1–3] diminishing their ability to achieve seizure control.[4] Cenobamate (XCOPRI, SK Life Science, Inc.) is a carbamate compound[5] approved by the US Food and Drug Administration for the treatment of adults with focal (partial onset) seizures.[6] Cenobamate has a long terminal half-life (50-60 hours) within the 100- to 400-mg/d dose range, with steady-state concentrations attained in approximately 2 weeks following once-daily dosing.

Two previous randomized and controlled studies demonstrated that adjunctive treatment with cenobamate significantly decreased seizure frequency and was associated with high rates of seizure freedom in patients with uncontrolled focal seizures receiving one to three ASMs. In the first study,[7] patients titrated to a target dose of 200 mg/d cenobamate during a 12-week study had a 55.6% median percentage reduction in focal seizure frequency per 28 days, compared with 21.5% for placebo ($P < .0001$); 28.3% of cenobamate-treated patients achieved seizure freedom during the 6-week maintenance phase, compared with 8.8% of placebo patients ($P = .0001$). In the second study,[8] the median percentage reduction in focal seizure frequency per 28 days was 35.5% ($P = .0071$), 55.0% ($P < .0001$), and 55.0% ($P < .0001$) for cenobamate 100, 200, and 400 mg/d, respectively, compared with 24.0% for placebo during the 18-week double-blind period. During the 12-week maintenance phase, 4%, 11%, and 21% of patients treated with 100, 200, and 400 mg/d cenobamate, respectively, were seizure-free compared with 1% for placebo.

During early clinical development, three cases of drug reaction with eosinophilia and systemic symptoms (DRESS) were identified among the first 953 participants exposed to cenobamate, including one fatality.[9] Skin reactions are a common idiosyncratic side effect associated with ASMs.[10] Most skin reactions are mild in severity, but serious and potentially life-threatening reactions, such as DRESS, Stevens-Johnson syndrome (SJS), and toxic epidermal necrosis (TEN) can occur.[10–13] The rate of DRESS has been estimated to occur at a frequency of 1/1000 to 1/10 000 exposures[14]; higher rates

Key Points

- An interim report from the largest phase 3 study of adjunctive cenobamate to date in patients (n = 1339) with uncontrolled focal seizures
- Cenobamate was initiated at 12.5 mg and titrated over 10-12 weeks to a target of 200 mg, with further allowed increases up to 400 mg
- High retention (82.9% [1110/1339] of patients took cenobamate ≥6 months) suggested good tolerability; most adverse events were central nervous system–related
- No cases of DRESS occurred, suggesting that initiating cenobamate at a low dose and slowing the titration rate may lower the risk of DRESS
- Periodic dose reductions of concomitant phenytoin or phenobarbital maintained steady plasma levels during cenobamate titration

have been reported with phenytoin (up to 4.5 cases per 10 000 exposures) and carbamazepine (up to 4.1 cases per 10 000 exposures).[12,15] A lower starting dose and slower titration rate have been shown to mitigate the occurrence of immune-mediated hypersensitivity reactions, possibly by development of immune tolerance,[10] and may improve tolerability. For example, cases of serious rash have been reported in up to 0.3% of adults treated with lamotrigine; however, rates as low as 0% were reported following updated dosing recommendations using a lower starting dose and slower titration rate.[16,17]

This large phase 3, open-label study (YKP3089C021, clinicaltrials.gov NCT 02535091) was designed primarily both to assess the long-term safety of adjunctive cenobamate and to test the hypothesis that the rate of DRESS would be lower when initiating cenobamate at a low dose (12.5 mg/d) and titrating every 2 weeks.

Earlier pharmacokinetic studies indicated that cenobamate administration significantly increases phenytoin and phenobarbital exposure via inhibition of CYP2C19.[18] Use of concomitant phenytoin and phenobarbital were excluded

from the earlier efficacy studies of cenobamate. Thus, a secondary objective of this study was to evaluate the pharmacokinetic effects of cenobamate on concomitant phenytoin and phenobarbital, to provide dosing guidance when adding cenobamate to existing phenytoin- or phenobarbital-containing regimens. Interim results from the ongoing phase 3 safety study are presented.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This is an ongoing, multicenter, open-label safety study being conducted at 139 centers in 17 countries (Argentina, Australia, Bulgaria, Chile, Czech Republic, Germany, Hungary, Mexico, Poland, Republic of Korea, Serbia, Spain, Sweden, Russia, Thailand, Ukraine, and USA). Enrollment began on November 3, 2015 and ended on February 8, 2018. This analysis used a data cutoff of April 23, 2018. The study design includes a screening period of up to 21 days and a 12-month open-label treatment period, consisting of a 12-week titration phase followed by a maintenance phase (Figure 1). After 12 months, patients benefiting from treatment may continue on cenobamate per the discretion of the investigator.

Eligible patients were adults 18-70 years old with a diagnosis of focal (partial onset) epilepsy according to the International League Against Epilepsy's Classification of Epileptic Seizures.[19,20] Patients' focal seizures had to be uncontrolled despite treatment with at least one ASM within the past 2 years. Patients were required to have an electroencephalographic reading consistent with the diagnosis of focal epilepsy and a computed tomography or magnetic resonance imaging scan performed within the previous 10 years to rule out a progressive cause of epilepsy. Patients must have been currently taking stable doses of one to three concomitant ASMs for at least 3 weeks prior to the start of cenobamate. Vagus nerve stimulation was permitted and did not count as an ASM, but the device must have been implanted at least 5 months prior to screening and the parameters must have been stable for at least 4 weeks prior to baseline. Patients with a history of any drug-induced rash or hypersensitivity reaction or who had first-degree relatives with a serious cutaneous, drug-induced adverse reaction were excluded. Patients taking vigabatrin or ezogabine within the past year or felbamate for less than 18 consecutive months were also excluded. Additional exclusion criteria included a history of status epilepticus within 3 months of screening, history of alcohol or drug abuse within the past 2 years, clinically significant psychiatric illness or history of suicidal ideation within the past 6 months, suicidal behavior in the past 2 years, or more than one lifetime suicide attempt.

During the titration phase, patients initiated cenobamate treatment at 12.5 mg/d for 2 weeks, followed by 25 mg/d for 2 weeks and 50 mg/d for 2 weeks. The dose was then increased by 50-mg/d increments at 2-week intervals to the target dose 200 mg/d (Figure 1). Except for patients taking concomitant phenytoin or phenobarbital, patients' concomitant ASMs could be removed, added, or adjusted, and cenobamate doses could be adjusted during the titration phase, as clinically needed. Monotherapy with cenobamate was not allowed at any point in the study. A minimum cenobamate dose of 50 mg once daily
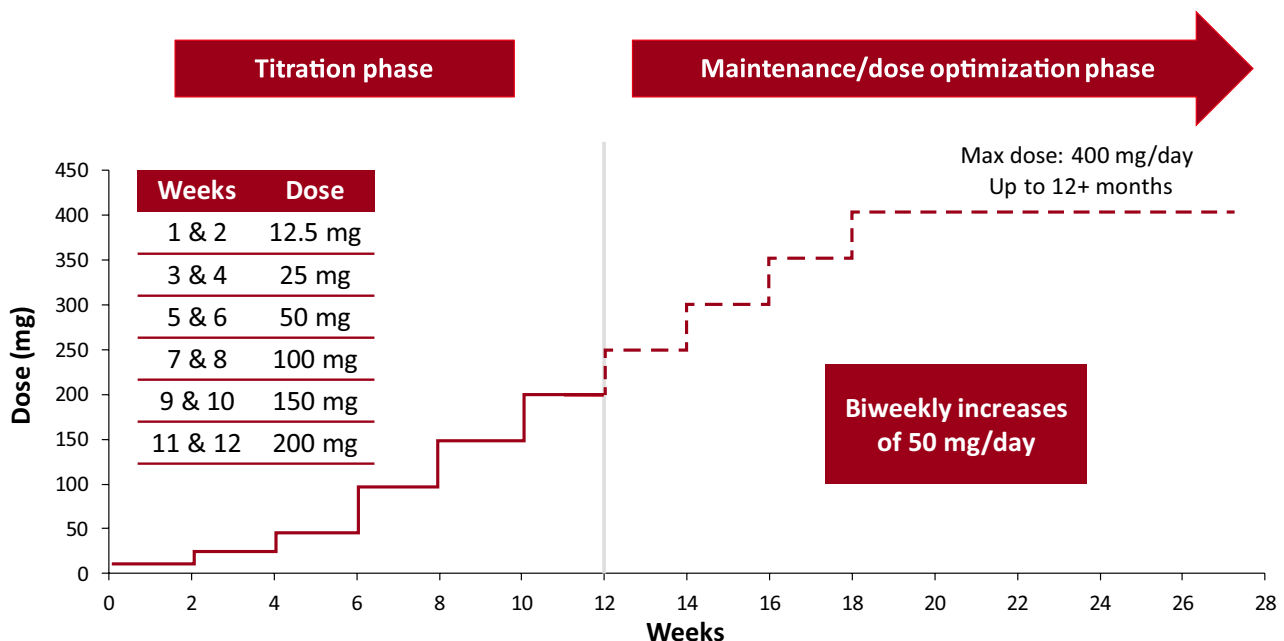

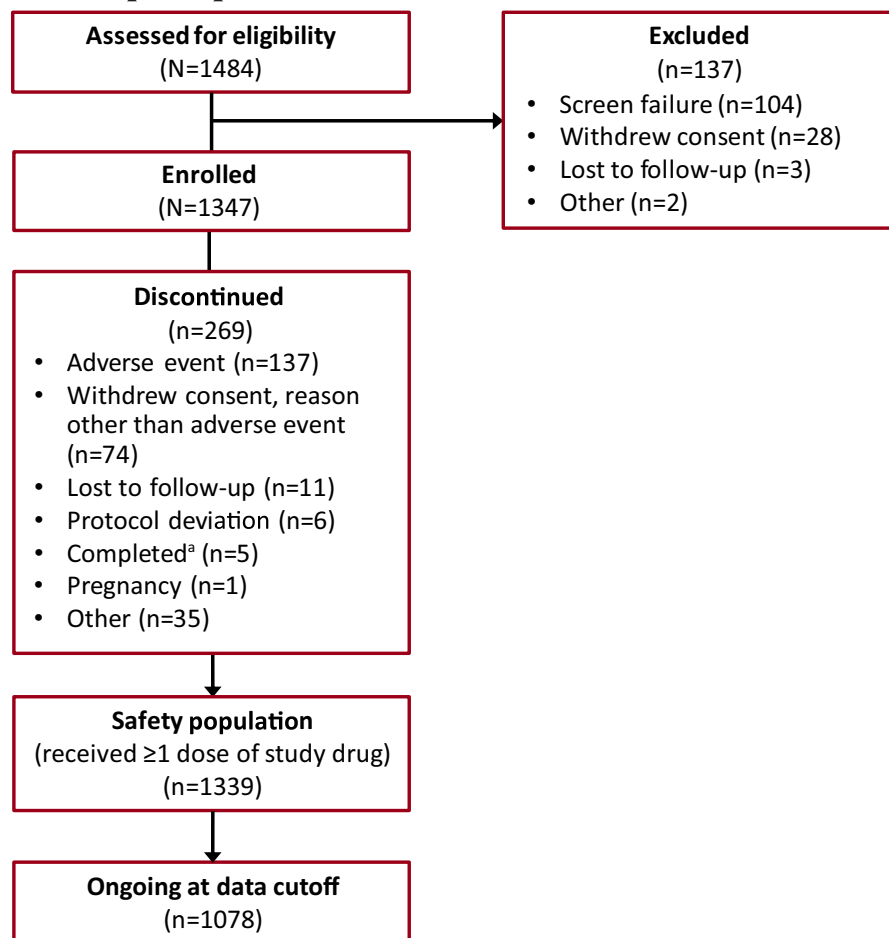
FIGURE 1 Dose titration schedule

FIGURE 2 Patient disposition. [a]As reported on the end of the study case report form

was necessary to continue in the study. For patients receiving concomitant phenytoin or phenobarbital, no dose reduction or interruption of cenobamate titration was allowed and other concomitant ASMs could not be added, removed, or adjusted during titration. If patients were experiencing dose-related toxicity, a plasma level could be obtained and their dosage of phenytoin or phenobarbital could be reduced by 25%-33% per clinical discretion. Further reductions in phenytoin or phenobarbital dose up to approximately two-thirds the total baseline dose were allowed. During the maintenance phase, further cenobamate dose increases to 400 mg/d using biweekly increments of 50 mg/d were allowed for all patients. Downward dose adjustments for tolerability could also occur during the maintenance phase for all patients once the target dose of 200 mg was reached. Concomitant medications, including phenytoin and phenobarbital, could be adjusted during the maintenance phase; concomitant ASMs could also be added (except phenytoin or phenobarbital) or removed.

The study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation guidelines[21] and all applicable country-specific regulations. The study protocol was approved by an independent ethics committee or institutional review board at each site according to local

regulations. Written informed consent was obtained from each patient prior to participation in the study.

2.2 | Safety/tolerability outcomes

Safety assessments included reported adverse events (AEs), coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0, in addition to clinical laboratory tests, 12-lead electrocardiographic (ECG) measurements, vital signs, physical and neurologic examinations, and Columbia Suicide Severity Rating Scale scores. Monthly reviews of all AEs in the clinical database via Standardized MedDRA Queries for hypersensitivity and DRESS were performed. In addition, physical examinations to identify signs of hypersensitivity were performed every 2 weeks during the first 4 months of treatment, at year 1, and yearly thereafter.

2.3 | Pharmacokinetic outcomes

To assess the effect of cenobamate on the pharmacokinetics of phenytoin and phenobarbital, plasma concentrations of phenytoin and phenobarbital were obtained before the start of

cenobamate and compared with those obtained during the 12-week titration phase. Blood samples were collected at baseline (day 1), before the first dose of cenobamate, to assess trough levels of phenytoin and phenobarbital. During the titration phase, scheduled phenytoin and phenobarbital plasma levels were obtained at the end of weeks 4, 6, 8, 10, and 12; two blood samples were collected, one in the morning and one 30 minutes to 2 hours after taking a dose of phenytoin or phenobarbital.

2.4 | Data analysis

All patients who enrolled in the study and received at least one dose of cenobamate were included in the safety analysis. To assess the rate of DRESS, at least 1000 patients were planned to be enrolled and treated for at least 6 months. An incidence rate of 0 for DRESS during the treatment period would establish 0.003 (3/1000) as the upper limit of the 95% confidence interval for the rate of DRESS. All patients included in the safety analysis who had at least one blood sample were included in the pharmacokinetic analysis. Safety and pharmacokinetic data were summarized with descriptive statistics.

3 | RESULTS

3.1 | Patients

At the data cutoff, 1347 patients were enrolled, and 1339 had received at least one dose of cenobamate and were included in the safety analysis population (Figure 2). The most common reason for discontinuation was AEs (10.2% [137/1347]), followed by withdrawal of consent for reasons other than AEs (5.5% [74/1347]). Because this study was not designed to evaluate efficacy and did not collect seizure counts, "lack of efficacy" was not provided as a choice for discontinuation. Investigators could include information regarding lack of efficacy under comments associated with "withdrew consent" or "other" reasons for discontinuation. Based on investigator comments, 48 of the 1339 patients (3.6%) who took at least one dose of cenobamate discontinued because of lack of efficacy (24 of 74 withdrew consent; 24 of 35 other).

Baseline demographics and patient characteristics are shown in Table 1. Mean epilepsy duration was 22.9 years. Most patients (82% [1098/1339]) were receiving two or three ASMs at baseline (defined as ASMs started prior to and ongoing at the time of first dose of study medication). The most frequently used concomitant ASMs were levetiracetam (39.1%), lamotrigine (33.3%), all forms of valproic acid (30.8%), carbamazepine (27.6%), and lacosamide (24.2%). In addition, 114 patients were receiving concomitant phenytoin and 51 patients were receiving phenobarbital, of whom 83 and 37, respectively, had blood samples and were included in the pharmacokinetic analyses.

TABLE 1 Patient demographic characteristics and disease characteristics (safety population)

	Cenobamate patients, n = 1339
Mean age, y (SD)	39.7 (12.84)
Female, n (%)	666 (49.7)
Race, n (%)	
White	1063 (79.4)
Black or African American	47 (3.5)
Asian	73 (5.5)
American Indian or Alaska Native	59 (4.4)
Other	97 (7.2)
Mean BMI, kg/m^2 (SD)	26.93 (5.984)
Mean time since epilepsy diagnosis, y (SD)[a]	22.9 (14.35)
Current seizure type, n (%)[b]	
Focal aware nonmotor	271 (20.2)
Focal aware motor/observable component	324 (24.2)
Focal impaired awareness	1036 (77.4)
Focal to bilateral tonic-clonic	786 (58.7)
Number of baseline ASMs, n (%)[c]	
0	3 (0.2)
1	238 (17.8)
2	510 (38.1)
3[d]	588 (43.9)
Concomitant ASMs in ≥10% of patients, n (%)[e]	
Levetiracetam	523 (39.1)
Lamotrigine	446 (33.3)
Valproic acid, all forms	412 (30.8)
Carbamazepine	369 (27.6)
Lacosamide	324 (24.2)
Clobazam	179 (13.4)
Topiramate	175 (13.1)
Oxcarbazepine	174 (13.0)

Abbreviations: ASM, antiseizure medication; BMI, body mass index.

[a]n = 1336.

[b]Patients could have >1 seizure type.

[c]Baseline ASMs were defined as ASMs that started prior to and were ongoing at the time of first dose of cenobamate.

[d]One patient taking four concomitant ASMs was enrolled into the study.

[e]Concomitant ASMs were defined as ASMs that started prior to and were ongoing at the time of first dose of cenobamate or started after the first dose of cenobamate.

3.2 | Exposure and retention rate

Median (minimum, maximum) exposure to cenobamate was 9 (0.03, 20.5) months. The majority of patients (82.9% [1110/1339]) were exposed to cenobamate for ≥6 months; 22.9% (306/1339) were exposed for ≥12 months. The median modal daily dose was 200 mg. The last available dose

received at or before the cutoff for most patients was 200 mg (35.1%, 470/1339). In 58.2% of patients (779/1339), the last available dose received was between 200 and 300 mg; in 11.2% (150/1339), the last available dose received was >300 mg. The 1-year retention rate was 79% based on Kaplan-Meier estimates (Figure 3).

3.3 | Safety

At least one treatment-emergent AE (TEAE) was reported in 1128/1339 patients (84.2%; Table 2). The most frequent TEAEs were somnolence (376 [28.1%]), dizziness (316 [23.6%]), and fatigue (222 [16.6%]). The majority of TEAEs reported during the study were mild or moderate in severity (77.8% [1042/1339]). Skin and subcutaneous tissue disorders were reported in 189 patients (14.1%). Grouped and individual preferred terms reported by at least 1% of patients included rash (grouped terms: rash, erythematous rash, papular rash, etc) in 44 patients (3.3%), pruritis (grouped terms: pruritus and pruritus generalized) in 34 patients (2.5%), dermatitis (grouped terms: dermatitis, dermatitis contact, dermatitis allergic, etc) in 27 patients (2.0%), and alopecia in 15 patients (1.1%).

No cases of DRESS were identified. The rate of DRESS was therefore zero, with an upper bound of the 95% confidence interval of 0.003 among patients exposed to cenobamate for >6 months, and 0.002 among all patients exposed.

At least one serious TEAE was reported in 108 (8.1%) patients (Table S1). Seizure (n = 14, 1.0%) and epilepsy (n = 5, 0.4%) were the most frequently reported serious TEAEs. Additional serious TEAEs reported in more than two patients included fall, pneumonia, and dizziness (n = 4 each, 0.3%) and vomiting, appendicitis, mental status change, suicide attempt, and papular rash (n = 3 each, 0.2%). In addition to papular rash, other serious TEAEs related to skin

and subcutaneous tissue disorders occurred in six patients, including allergic dermatitis, erythema, rash, maculopapular rash, facial swelling, and urticaria (n = 1 each). There was no history of rash noted for these patients. One patient had a history of eczema. In each case, the patient recovered following discontinuation of cenobamate.

Psychiatric AEs occurring in ≥1% of patients included anxiety (2.3%, n = 31), irritability (2.2%, n = 29), insomnia (2%, n = 27), depression (1.9%, n = 26), and confusional state (1.2%, n = 16). Three patients had a serious TEAE of suicide attempt (none completed). The first patient was a 52-year-old man with a history of ongoing depression. He was not receiving any concomitant medications for depression; concomitant ASMs included phenytoin, lamotrigine, and perampanel. The second patient was a 32-year-old woman with a history of ongoing depression and mood disorder (concomitant desvenlafaxine, quetiapine as needed, and diazepam as needed) and prior episodes of self-harm. Concomitant ASMs included clobazam, oxcarbazepine, and levetiracetam. Both events were considered by the investigator to be unrelated to the study drug. The third patient was a 38-year-old man with no history of depression. The patient had a history of vagus nerve stimulator implantation and gastric bypass. Concomitant ASMs included topiramate and clobazam. The investigator considered the event's relationship to the study drug to be remote. One additional patient, a 46-year-old woman with a history of ongoing depression, had a serious AE of suicidal ideation. She was receiving concomitant ASM treatment with lacosamide. She did not receive any concomitant medications for depression. The event was considered unrelated to the study drug.

At data cutoff, four deaths had been reported (sudden death with no autopsy, traumatic intracerebral hemorrhage after a fall, fatal injuries after being struck by a car, and respiratory failure in a patient with Angelman syndrome). Three were considered unrelated to the study drug. The
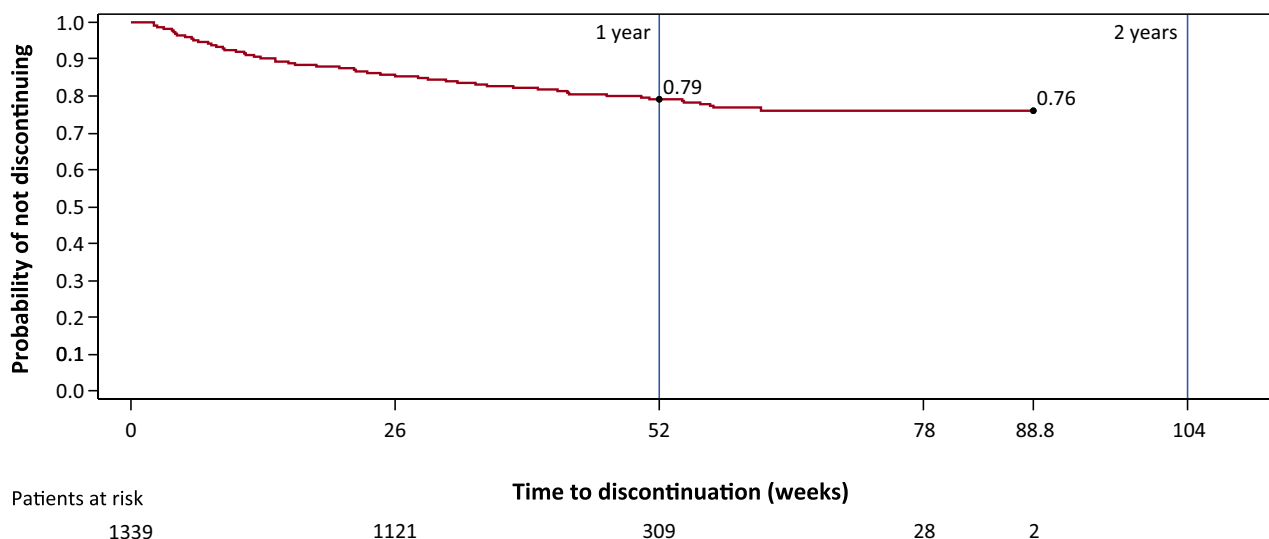

FIGURE 3 Kaplan-Meier plot of estimated time to discontinuation

TABLE 2 Summary of treatment-emergent adverse events (safety population)

	Cenobamate patients, n = 1339
Any TEAE	1128 (84.2)
TEAEs leading to discontinuation	147 (11.0)
Treatment-related TEAEs	935 (69.8)
Serious TEAEs	108 (8.1)
TEAEs ≥5%	
Somnolence	376 (28.1)
Dizziness	316 (23.6)
Fatigue	222 (16.6)
Headache	152 (11.4)
Viral upper respiratory tract infection	98 (7.3)
Upper respiratory tract infection	82 (6.1)
Nausea	80 (6.0)
Diplopia	78 (5.8)
Balance disorder	74 (5.5)

Abbreviation: TEAE, treatment-emergent adverse event.

relationship between sudden death and the study drug was considered remote by the investigator. TEAEs resulting in discontinuation of cenobamate were reported in 11% (n = 147) of patients (Table S2). The most common TEAEs that led to study discontinuation were nervous system disorders (45 patients [3.4%]), with dizziness (n = 14), seizure (n = 9), and somnolence (n = 9) the most frequently reported, followed by skin and subcutaneous tissue disorders (44 patients [3.3%]), with rash (n = 9), rash erythematous, papular rash, pruritus, and urticaria (all n = 3) the most frequently reported. Most TEAEs leading to discontinuation, including rashes, occurred during the titration period. All were rated as mild or moderate in severity. One patient discontinued due to a TEAE of hypersensitivity. The patient, a 53-year-old woman, experienced mild facial erythema with swelling and pruritus following the second dose of cenobamate 12.5 mg. She was afebrile, and symptoms resolved upon discontinuation of the study drug. Concomitant medications included fexofenadine once daily for allergies and concomitant ASM treatment with eslicarbazepine 1800 mg daily.

There were no remarkable changes during the study in hematology, clinical chemistry, laboratory values, ECG readings, vital sign measurements, or physical or neurological examinations.

3.4 | Pharmacokinetics

The mean trough plasma level of phenytoin was 11.80 μg/mL at baseline. Morning levels rose slightly at week 4 (12.70 μg/mL) and week 6 (14.92 μg/mL) and remained stable thereafter through week 12 (Figure 4A). The mean trough plasma phenobarbital level was 24.11 μg/mL at baseline and remained stable during titration (Figure 4B). Thirty-six patients (43.4%) in the phenytoin group and 11 patients (29.7%) in the phenobarbital group had their doses decreased during titration. The mean total daily doses of phenytoin decreased from 330 mg at baseline to 253 mg at the end of the titration phase and beginning of the maintenance phase (week 14); the mean total daily dose of phenobarbital decreased from 138 to 118 mg (Figure S1).

4 | DISCUSSION

This interim report from the ongoing phase 3 study provides results of a strategy to lower the occurrence of DRESS and characterizes the long-term safety of cenobamate in patients with uncontrolled focal seizures, 58.7% of whom had focal to bilateral tonic-clonic seizures. An important feature of this study was the initial dose and titration rate used for cenobamate. Whereas the target and maximum doses (200 and 400 mg, respectively) were similar to those used in previous clinical studies, the starting dose (12.5 mg) was lower and the titration rate (every 2 weeks for 12 weeks) was slower. In the first adequate and well-controlled study, the starting dose was 50 mg and was uptitrated by a rate of 50 mg/d every other week.[7] In the second adequate and well-controlled study, the starting dose was 100 mg and was uptitrated by a rate of 100 mg weekly. Later, a protocol amendment lowered the starting dose to 50 mg and reduced the titration rate to 50 mg weekly until 200 mg and then uptitrated by a rate of 100 mg weekly to 400 mg.[7,8]

In this study, long-term treatment with cenobamate as adjunctive therapy to approved ASMs was generally safe and well tolerated, as indicated by the high retention rates, with >80% of patients continuing cenobamate for ≥6 months. The AE profile and frequency associated with cenobamate in this long-term study was generally consistent with those of the earlier clinical studies.[7,8] The most common TEAEs were central nervous system–related, primarily somnolence and dizziness. Neurologic side effects are among the most frequently reported AEs associated with other available ASMs.[22,23] The most common serious TEAEs associated with cenobamate were seizure and epilepsy, which are not unexpected in a patient population with uncontrolled seizures. There were three suicide attempts (none completed) reported during the study, two of which were considered unrelated to treatment and the last only remotely related.

The occurrence of rash is a well-known idiosyncratic AE observed with other ASMs, with rates ranging from 5% to 17%.[10,17,24] Serious skin adverse reactions including DRESS, SJS, and TEN are most frequently reported with phenytoin,

A

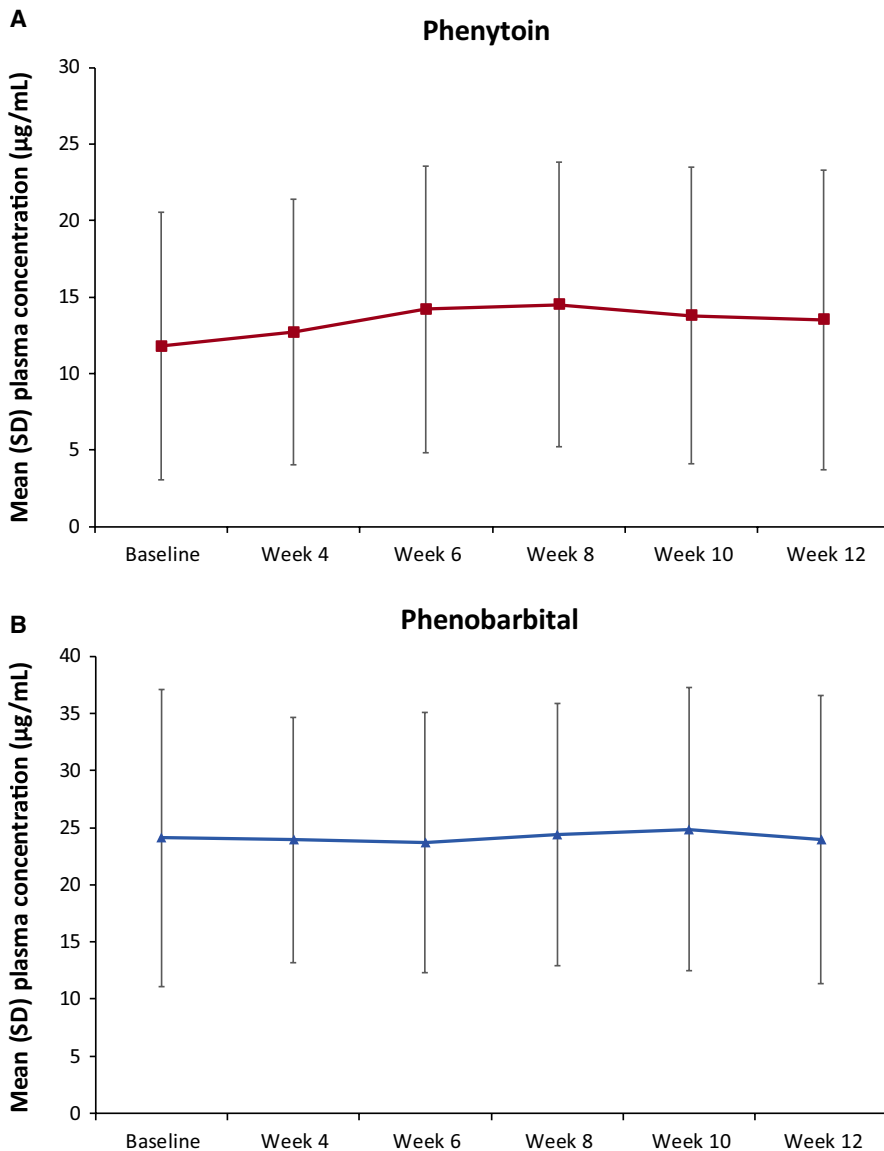## Phenytoin

B

Phenobarbital

FIGURE 4 Mean plasma trough concentrations of concomitant antiseizure medications during the titration phase. A, Phenytoin. B, Phenobarbital

carbamazepine, phenobarbital, and lamotrigine[10–13]; however, cases with other ASMs have also been reported in the literature.[13,25–27] A recent analysis of 198 cases of SJS/TEN identified eight additional ASMs, including zonisamide and rufinamide, that also carry a significantly elevated risk of these reactions.[13] The true incidence of DRESS remains unknown.[14] In this study, no cases of DRESS, SJS, or TEN occurred among the 1339 treated patients. Although the study is still ongoing, the majority of patients in this analysis were treated for >6 months, allowing for an in-depth assessment for signs and symptoms of DRESS, which typically occur within 1-12 weeks after initiating therapy.[10,14]

Although these data do not establish that the risk of DRESS is prevented by a slower titration,[9] the findings suggest that lowering the initial dose of cenobamate to 12.5 mg and slowing the titration rate to 2-week intervals lowers the occurrence of DRESS. A similar strategy was shown to reduce the risk of severe rashes with lamotrigine.[16,17]

Because cenobamate inhibits CYP2C19,[18] dosing guidance is needed when adding cenobamate to ASM regimens containing phenytoin or phenobarbital. In this phase 3 study, concomitant phenytoin and phenobarbital doses could be adjusted downward periodically by 25%-33% during cenobamate titration based on the patient's clinical condition and plasma levels. A substantial portion of patients taking phenytoin and phenobarbital had their doses decreased during titration (43.4% and 29.7%, respectively). Mean phenytoin plasma levels increased slightly by week 4, indicating that the interaction may occur relatively early during cenobamate initiation (during cenobamate dose titration from 25 to 50 mg/d). At the end of the titration phase, the mean plasma levels of phenytoin and phenobarbital were generally comparable to baseline (precenobamate) plasma levels, suggesting that the periodic dose reductions were effective at maintaining stable plasma levels.

Similar to other studies in patients with uncontrolled epilepsy, the use of concomitant ASMs may have confounded the reporting of AEs with cenobamate. In contrast with randomized, placebo-controlled clinical studies of cenobamate, this study had less stringent eligibility criteria with regard to seizure frequency and also allowed clinicians to make changes to concomitant ASMs and cenobamate dose, which may be more reflective of real-world clinical practice settings. Although preplanned assessments of efficacy were not collected in this study, retention rates with adjunctive cenobamate were high, which may be an indicator of its therapeutic benefit.[28,29]

In conclusion, the interim results of this large safety study support the concept that initiating cenobamate at a lower dose and slowing the initial titration rate may lower the rate of DRESS. No cases of DRESS were identified in 1339 patients initiating cenobamate using a start-low, go-slow approach of 12.5 mg/d and titrating every 2 weeks to a maximum of 400 mg/d. Cenobamate was generally well tolerated, with somnolence, dizziness, and fatigue the most common side effects. Phenytoin or phenobarbital dose reductions of 25%-33% in response to AEs during cenobamate titration maintained stable plasma levels. The ongoing phase 3 study as well as the open-label portions of the phase 2 studies will provide additional data on the long-term safety profile of adjunctive cenobamate when used in patients with uncontrolled focal epilepsy.

CONFLICT OF INTEREST
M.R.S. is a consultant/advisor for Medtronic (fee to institution); is a consultant for NeurologyLive; has received research support (to institution) from Eisai, Engage, Medtronic, Neurelis, Pfizer, SK Life Science, Inc., Takeda, UCB, and Xenon; and has been a speaker for Eisai. P.K. is a consultant for AbbVie, Alliance, Eisai, Engage, and UCB Pharma; has participated on advisory boards for Aquestive and SK Life Science, Inc.; and has been a speaker for Eisai, Sunovion, and UCB Pharma. He has received research support from Eisai and Lundbeck. S.A. has participated on advisory boards for Eisai and SK Life Science, Inc., and has been a speaker for Sunovion and Eisai. M.G. has received research support from Aquestive, Biogen, Eisai, Engage, SK Life Science, Inc., and Upsher-Smith. J.J.H. is a consultant/advisor for Brain Sentinel, Takeda, and NCGH; investigator for clinical trials funded by Biogen, Brain Sentinel, the Epilepsy Study Consortium, Greenwich Biosciences, SK Life Science, Inc., and Takeda; and member of the board of directors (stock owner) for CortiCare. G.L.K. is a consultant/advisor for Adamas, Eisai, Otsuka, and Shire; and has received research support from Biogen, SK Life Science, Inc., UCB Pharma, and Upsher-Smith. W.E.R. is currently a consultant/advisor for SK Life Science, Inc. and previously for Eisai; has received honoraria for speaking from Eisai, Greenwich Biosciences (GW Pharmaceuticals), Sunovion, and UCB Pharma; and has received grant/research support from Greenwich Biosciences, Marinus, Medtronic, Neurelis, Ovid, SK Life Science, Inc., Takeda, UCB Pharma, and Upsher-Smith. D.G.V. has received research support (to institution) from Biogen, Eisai, SK Life Science, Inc., and UCB Pharma; has participated on advisory boards for Otsuka and SK Life Science, Inc.; and has been a speaker for Eisai, Greenwich Biosciences, Lundbeck, Sunovion, and UCB Pharma. R.W. has been an advisor/consultant for Brain Sentinel, Eisai, Engage, Greenwich Biosciences, Lundbeck, SK Life Science, Inc., Sunovion, and UCB Pharma; has been a clinical investigator for Aquestive, Biogen, Eisai, Engage, Greenwich Biosciences; Lundbeck, Pfizer, SK Life Science, Inc., Sunovion, UCB Pharma, Xenon, and Zogenix; and has been a speaker for Aquestive, Eisai, Greenwich Biosciences, LivaNova, Sunovion, and UCB Pharma. L.B. and M.K. are employees of SK Life Science, Inc. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY
The data for the analyses described in this article are available upon request from the author, investigators, or SK Life Science, the company sponsoring the clinical development of cenobamate for the treatment of focal epilepsy.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.