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RESEARCH ARTICLE

A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of adjunctive cenobamate in Asian patients with focal seizures

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Abstract

Objectives: This randomized, double-blind, placebo-controlled study (NCT04557085), conducted in China, Japan, and the Republic of Korea, evaluated the efficacy and safety of adjunctive cenobamate in patients with uncontrolled focal seizures.

Methods: Adults 18–70 years of age with ≥8 seizures (focal aware motor, focal impaired awareness, or focal to bilateral tonic–clonic) during an 8-week baseline, despite treatment with 1–3 antiseizure medications (ASMs), were randomized 1:1:1:1 to placebo or cenobamate 100, 200, or 400 mg/day. The study included an 18-week titration phase and a 6-week maintenance phase. The primary efficacy analysis was a hierarchical step-down comparison of the percent change from baseline in 28-day seizure frequency vs placebo during the maintenance phase for cenobamate 200, then 400, and then 100 mg/day.

Results: Among 519 patients randomized, 446 received ≥1 dose of study drug and had ≥1 efficacy measure during the maintenance phase (placebo, $n = 117$; 100 mg/day, $n = 113$; 200 mg/day, $n = 113$; and 400 mg/day, $n = 103$). Median percent change in seizure frequency during the maintenance phase was −25.9% for

Lee and Yu are co-first authors.

Study Registry: Study NCT04557085 was registered at Clinicaltrials.gov on September 14, 2020. Available at: https://clinicaltrials.gov/search?term=%20NCT04557085.

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placebo vs −42.6%, −78.3%, and −100% for cenobamate 100, 200, and 400 mg/day, respectively (all p's < .001). During the 12-week period encompassing the last 6 weeks of titration and the 6-week maintenance phase (secondary outcome), the median percent change in seizure frequency was −20.1% for placebo vs −42.6%, −77.1%, and −89.2% for cenobamate 100, 200, and 400 mg/day, respectively. Seizure-free rates during the maintenance phase were 2.6% of patients for placebo vs 12.4%, 30.1%, and 52.4% for cenobamate 100, 200, and 400 mg/day, respectively, and during the 12-week period were 0.8% for placebo vs 8.5%, 19.7%, and 30.6% for the cenobamate groups. The most common treatment-emergent adverse events in cenobamate patients (≥20%) were dose-related dizziness and somnolence.

Significance: Cenobamate 100, 200, and 400 mg/day reduced focal seizures in Asian patients in a dose-related fashion and was generally well tolerated.

KEYWORDS
antiseizure medication, focal epilepsy, phase 3, refractory

1 | INTRODUCTION

Epilepsy is one of the most common neurologic diseases, affecting over 50 million people worldwide.[1] Cenobamate is an antiseizure medication (ASM) that has been commercially available in the United States for the treatment of focal seizures since 2020, and with approvals in Europe, Canada, Israel, and Hong Kong, has now been used to treat over 220 000 patients.[2,3] Cenobamate has a unique mechanism of action, involving preferential inhibition of the persistent sodium current and positive allosteric modulation of the γ-aminobutyric acid type A ($GABA_A$) receptor-mediating tonic current.[4–6] The efficacy and safety of cenobamate for the treatment of focal seizures was initially demonstrated in two randomized, double-blind, placebo-controlled studies.[7,8] During the 6- and 12-week maintenance phases of these studies, seizure-free rates ranged from 11% to 28% in the cenobamate 200- and 400-mg/day groups, compared to 1.0% and 8.8% for the placebo groups, respectively.[7,8]

During the early development of cenobamate, when more rapid titration rates were being used, three cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome were observed.[9] In a large (n = 1339) open-label safety study initiating cenobamate at 12.5 mg/day for 2 weeks followed by 25 mg/day for 2 weeks, and then increasing by 50 mg/day every 2 weeks, no cases of DRESS syndrome were identified.[10] This is now the titration schedule found in the approved prescribing information for cenobamate globally.[9,11–13]

Key points

- We evaluated the efficacy and safety of adjunctive cenobamate (100, 200, and 400 mg/day) in Asian patients with uncontrolled focal seizures.
- This 24-week study was the first randomized, placebo-controlled efficacy trial of cenobamate to use the globally approved titration schedule.
- Adjunctive cenobamate 100, 200, and 400 mg/day significantly reduced 28-day seizure frequency over 6 and 12 weeks vs placebo (all p's < .001).
- 100% responder rates (last 6 weeks of treatment) were 2.6% for placebo vs 12.4%, 30.1%, and 52.4% for cenobamate 100, 200, and 400 mg/day.
- Cenobamate was generally well tolerated; dizziness and somnolence were the most commonly reported treatment-emergent adverse events.

To evaluate the efficacy and safety of adjunctive cenobamate 100, 200, and 400 mg/day in Asian patients with uncontrolled focal seizures, a randomized, double-blind, placebo-controlled study (YKP3089C035, clinicaltrials.gov NCT04557085) with open-label extension was conducted in patients from China, Japan, and the Republic of Korea. Notably, this is the first randomized, controlled efficacy study in focal epilepsy to use the approved titration

schedule.[9] Here we report the results from the completed double-blind portion of the study.

2 | METHODS

2.1 | Study design and patients

This randomized, double-blind, placebo-controlled, multicenter study was conducted at 70 sites in China, Japan, and the Republic of Korea. The study included an 8-week baseline period and a 24-week double-blind treatment period, consisting of an 18-week titration phase and a 6-week maintenance phase (Figure 1). Adults 18–70 years of age with a diagnosis of focal (partial-onset) seizures, according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures[14] and confirmed by the Epilepsy Study Consortium, were included. Patients must have been treated with at least one ASM during the past 2 years. Patients were required to have ≥8 focal seizures (focal aware motor, focal impaired awareness, or focal to bilateral tonic–clonic) during the 8-week baseline period (at least 3 seizures in each consecutive 4-week baseline period), with no consecutive 25-day seizure-free period despite receiving stable doses of 1–3 concomitant ASMs for at least 4 weeks prior to screening/baseline.

Patients with only focal non-motor seizures or primary generalized epilepsies, a history of Lennox–Gastaut syndrome, or using phenytoin or phenobarbital, were excluded from the study. Vagus nerve stimulation (VNS) or deep brain stimulation (DBS) were permitted and did not count as an ASM. VNS/DBS stimulators had to be implanted at least 5 months before screening/baseline and the stimulation parameters must have been stable for at least 4 weeks prior; adjustment of parameters was not allowed during the study. A ketogenic diet was permitted provided the diet was stable for ≥3 months prior to Visit 1 and remained stable throughout the study.

Eligible patients were randomized 1:1:1:1 via an interactive response technology system to receive either placebo or adjunctive cenobamate 100, 200, or 400 mg administered orally in tablet form once daily. Randomization was stratified by country. Patients, investigators, and study personnel were all masked to randomized treatment assignments. Study medications and packaging were visually identical to ensure adequate masking.

During the titration phase, patients received an initial dose of either 12.5 mg cenobamate or matching placebo. The dose of cenobamate was increased to 25 mg and then 50 mg (or matching placebo) at 2-week intervals. The dose was then titrated by 50 mg every 2 weeks to the target dose. After the first 6 weeks of titration, one 50-mg dose reduction for tolerability was permitted and the dose was increased to the previous dose at the next visit. After 18 weeks, patients entered the maintenance phase (required minimum dose, 100 mg/day), where they maintained their dose of cenobamate for 6 weeks. Cenobamate dose adjustments were not allowed during the maintenance phase; patients who continued to have tolerability issues were discontinued from the study. No changes to concomitant ASM total daily doses or dosing frequency were allowed during the double-blind treatment period.

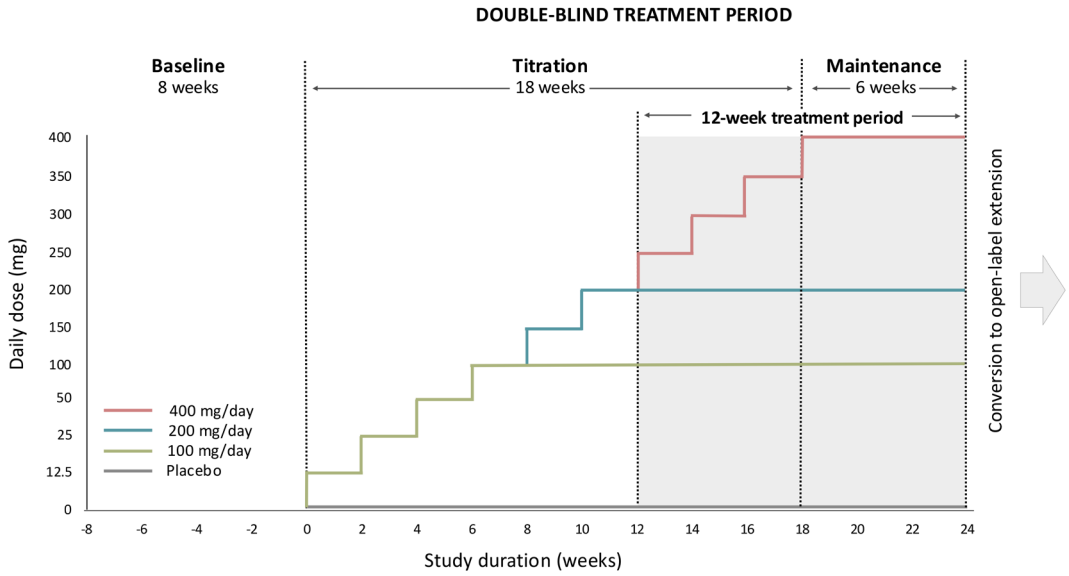

FIGURE 1 Study design. The 12-week treatment period combined the last 6 weeks of the titration phase and the 6-week maintenance phase.

The study was conducted in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice,[15] in addition to any applicable country-specific regulations. An independent ethics committee or institutional review board approved the study protocol according to local regulations at each site. Written informed consent was obtained from each individual before study participation.

2.2 | Study outcomes

The primary efficacy outcome was the median percent change from baseline in 28-day seizure frequency for all focal seizure types (focal aware motor, focal impaired awareness, and focal to bilateral tonic–clonic) during the 6-week maintenance phase. The decision to include a 6-week maintenance phase considered the 18-week cenobamate titration schedule and the strict dosing requirements for cenobamate and concomitant ASMs. The study design also took into account the efficacy of cenobamate shown during the 6- and 12-week maintenance phases of the previous randomized, clinical studies.[7,8] Based on the dosing requirements and the length of the titration period, it was determined that a 6-week maintenance phase (24-week double-blind period) would be sufficient to initially demonstrate efficacy. A prespecified analysis of the final 12 weeks of the double-blind period (encompassing the last 6 weeks of titration plus the 6-week maintenance phase; see Figure 1) was performed to compensate for the shorter 6-week maintenance phase. The 6- and 12-week results were also compared to the entire 24-week treatment period.

Median percent change from baseline in focal seizure frequency during the 12-week treatment period and during the entire 24-week double-blind treatment period was assessed as secondary outcomes. Because the first 6 weeks of the 12-week treatment period corresponded to the last 6 weeks of titration, patients in the 12-week treatment period who were randomized to the cenobamate 400-mg/day group received the 400-mg dose for only 6 weeks, whereas patients randomized to cenobamate 100 or 200 mg/day received the assigned dose for the full 12 weeks. The percentage of patients with ≥50%, ≥75%, ≥90%, and 100% reduction from baseline in focal seizure frequency during the 6-week maintenance phase and the 12-week treatment period were also assessed as secondary outcomes. Safety outcomes included the incidence of treatment-emergent adverse events (TEAEs); serious adverse events (SAEs); treatment discontinuations due to AEs; hypersensitivity assessments; and changes from baseline in clinical laboratory evaluations, vital signs, physical and neurologic examinations, 12-lead electrocardiography (ECG), and Columbia-Suicide Severity Rating scale responses.

2.3 | Statistical analyses

The modified intent-to-treat (MITT) population included all patients who received at least 1 dose of study drug and had at least one efficacy measure during the double-blind period. The MITT maintenance (MITT-M) population included all randomized patients who received at least one dose of study drug and had at least one efficacy measurement during the maintenance phase. The MITT 12-week population included all randomized patients who received at least one dose of study drug and had at least one efficacy evaluation during the 12-week treatment period. The safety population included patients who received at least one dose of study drug during the double-blind treatment period.

Assuming a standard deviation (SD) of 50%, a sample size of 107 participants per treatment group in the MITT-M population was required to detect a 20% treatment difference in the median percent seizure frequency from baseline at a two-sided significance level of .05 with 80% power.

Seizure frequency rates during the baseline and double-blind treatment periods were calculated by summing the number of seizures in each period and dividing by the total duration (days) and multiplying by 28 to normalize to a monthly rate. Seizure frequency and type were recorded in patient diaries. Days with no available seizure diary data were excluded from the analysis.

The primary outcome, median percent change in 28-day seizure frequency from baseline during the 6-week maintenance phase, was analyzed using an analysis of covariance (ANCOVA) model fitted to the ranked values of the primary efficacy outcome, with treatment group and country as fixed effects and ranked baseline seizure rate as covariate. The primary outcome was analyzed using a hierarchical step-down approach. The first comparison was cenobamate 200 mg/day vs placebo. If that test was significant, then cenobamate 400 mg/day vs placebo was tested. If that test was significant, cenobamate 100 mg/day vs placebo was tested. Secondary outcomes assessing median percent changes in seizure frequency were analyzed using the same ANCOVA method as described. Responder rates were analyzed using the Cochran–Mantel–Haenszel test, unless otherwise specified. Statistical analyses were performed using SAS version 9.4. Safety data were analyzed descriptively. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.1 or higher).

3 | RESULTS

3.1 | Patient disposition and demographics

The double-blind study was conducted from April 27, 2021, to February 16, 2024. In total, 519 patients were randomized; 516 were included in the safety population, 514 in the MITT population, 478 in the MITT 12-week population, and 446 in the MITT-M (maintenance phase) population (Figure 2). Ninety-one patients (17.6%) discontinued the study; most discontinuations ($n = 69$, 13.4%) occurred during the titration phase. The most common reasons for discontinuation were AEs ($n = 47$, 9.1%) and withdrawal by patient ($n = 33$, 6.4%). There were 16 discontinuations among patients on placebo and 17, 19, and 39 discontinuations, respectively, among patients on cenobamate 100, 200, and 400 mg/day.

Baseline demographics and epilepsy characteristics of the safety population were generally similar across treatment groups (Table 1). Mean (SD) body mass index (BMI) was 23.5 (4.1) kg/m^2 for all patients. Most patients (63.2% [326/516]) were taking three concomitant ASMs during the study. The most frequently used concomitant ASMs (>20%) included levetiracetam (47.5% [245/516]), valproate/valproic acid/valpromide (36.4% [188/516]), lacosamide (32.0% [165/516]), lamotrigine (27.9% [144/516]), perampanel (25.4% [131/516]), carbamazepine (24.4% [126/516]), and oxcarbazepine (23.3% [120/516]).

3.2 | Efficacy

During the 6-week maintenance phase, there was a statistically significant median percent reduction in 28-day focal seizure frequency in the cenobamate 100-, 200-, and 400-mg/day groups compared to the placebo group (42.6%, 78.3%, and 100% vs 25.9%, respectively; $p < .001$ for each comparison) (Figure 3A). Median percent reductions in

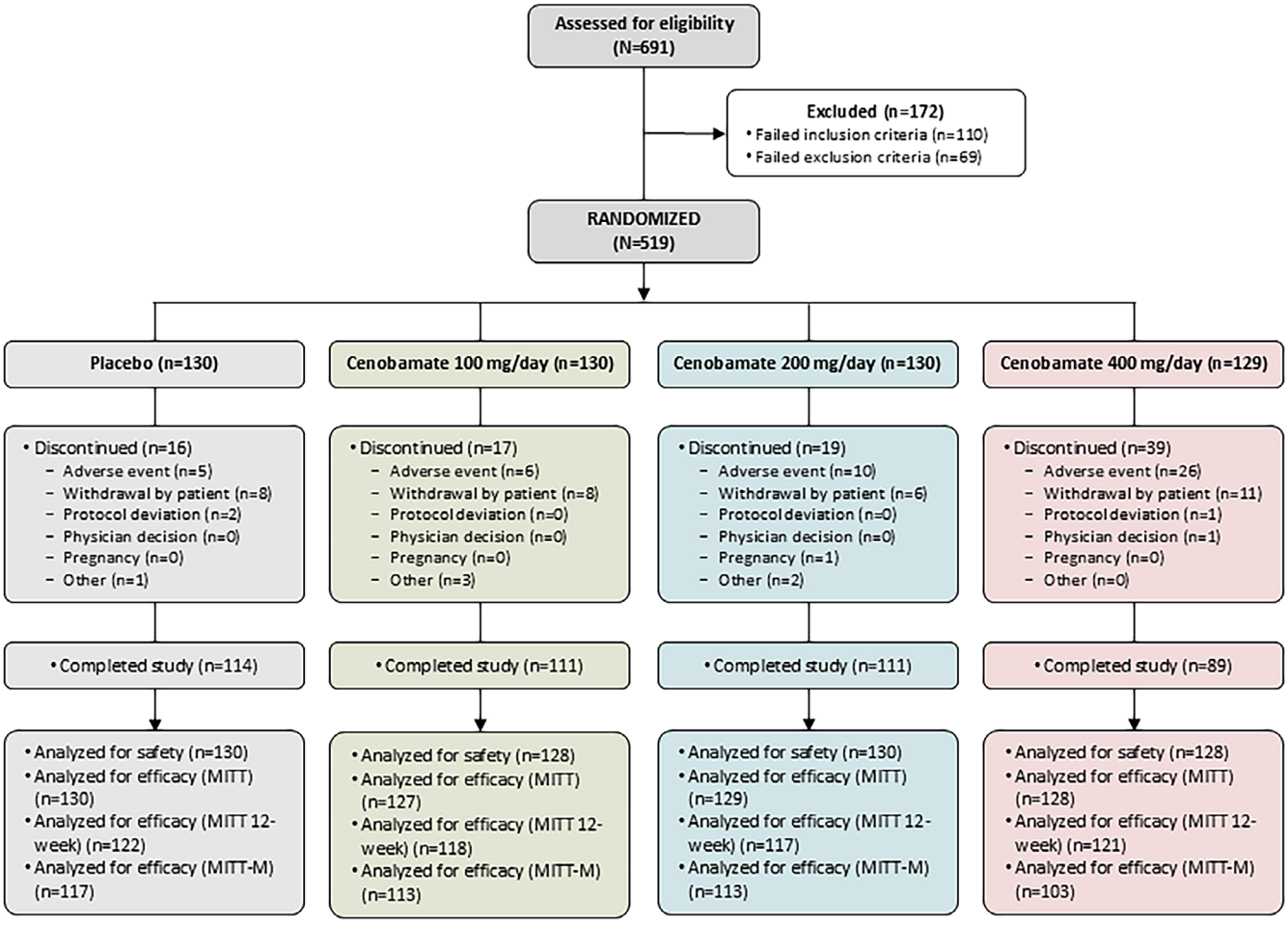

FIGURE 2 Patient disposition for double-blind study. MITT, modified intent-to-treat population; MITT-M, modified intent-to-treat maintenance population; MITT 12-week, modified intent-to-treat 12-week population. Three patients (two in the 100 mg/day group and one in the 400 mg/day group) were randomized to treatment but did not receive any dose of study drug ($n = 516$ for safety population). Two patients received study drug but had no efficacy evaluations ($n = 514$ for MITT population).

TABLE 1 Baseline demographics and clinical characteristics of the safety population ($n = 516$).

Characteristic	Placebo ($n = 130$)	Cenobamate 100 mg/day ($n = 128$)	Cenobamate 200 mg/day ($n = 130$)	Cenobamate 400 mg/day ($n = 128$)
Age (years) at screening, mean (SD)	34.2 (11.29)	37.3 (12.61)	36.2 (11.20)	35.4 (11.16)
Female, *n* (%)	63 (48.5)	51 (39.8)	59 (45.4)	65 (50.8)
BMI (kg/m^2), mean (SD)	23.4 (4.26)	23.7 (3.68)	23.8 (3.99)	23.1 (4.54)
Country, *n* (%)				
China	57 (43.8)	55 (43.0)	56 (43.1)	57 (44.5)
Japan	34 (26.2)	33 (25.8)	34 (26.2)	33 (25.8)
Republic of Korea	39 (30.0)	40 (31.3)	40 (30.8)	38 (29.7)
Baseline 28-day seizure frequency, median (min, max)	10.2 (1.5, 1029.0)	9.0 (4.0, 617.5)	9.3 (3.1, 333.5)	11.5 (4.0, 616.5)
No. of prior ASMs, *n* (%)[a]				
1	29 (22.3)	22 (17.2)	20 (15.4)	17 (13.3)
2	15 (11.5)	23 (18.0)	18 (13.8)	24 (18.8)
3	18 (13.8)	23 (18.0)	26 (20.0)	21 (16.4)
	28 (21.5)	22 (17.2)	31 (23.8)	27 (21.1)
No. of concomitant ASMs, *n* (%)[b]				
1	8 (6.2)	9 (7.0)	8 (6.2)	9 (7.0)
2	43 (33.1)	27 (21.1)	38 (29.2)	33 (25.8)
3	75 (57.7)	90 (70.3)	81 (62.3)	80 (62.5)
>3[c]	4 (3.1)	2 (1.6)	3 (2.3)	6 (4.7)
Concomitant ASMs (≥10% of patients in any treatment group), *n* (%)				
Levetiracetam	53 (40.8)	70 (54.7)	60 (46.2)	62 (48.4)
Valproate/valproic acid/ valpromide	52 (40.0)	39 (30.5)	46 (35.4)	51 (39.8)
Lacosamide	40 (30.8)	39 (30.5)	45 (34.6)	41 (32.0)
Lamotrigine	37 (28.5)	35 (27.3)	37 (28.5)	35 (27.3)
Oxcarbazepine	27 (20.8)	35 (27.3)	26 (20.0)	32 (25.0)
Carbamazepine	32 (24.6)	33 (25.8)	32 (24.6)	29 (22.7)
Perampanel	32 (24.6)	27 (21.1)	35 (26.9)	37 (28.9)
Topiramate	21 (16.2)	26 (20.3)	24 (18.5)	22 (17.2)
Clobazam	14 (10.8)	14 (10.9)	7 (5.4)	7 (5.5)

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

[a]Prior ASMs are ASMs that ended before the date of first dose of study drug.

[b]Concomitant ASMs are ASMs that were used at the time of initiation of the study drug and continued after the first dose of study drug.

[c]Patients who received temporary treatment with a fourth ASM.

28-day focal seizure frequency during the 12-week treatment period and the entire 24-week double-blind treatment period were also significant (all *p*'s < .001 vs placebo) for the cenobamate treatment groups compared to placebo (Figure 3B,C). In the 6-week maintenance (MITT-M) population, significantly more patients in the cenobamate 100-, 200-, and 400-mg/day groups were ≥50%, ≥75%, ≥90%, and 100% responders compared to patients in the placebo group (Figure 4A). The ≥50% responder rates during the maintenance phase for the cenobamate 100-, 200-, and 400-mg/day groups were 40.7% (46/113; $p = .046$), 68.1% (77/113; $p < .001$), and 81.6% (84/103; $p < .001$), compared to 28.2% (33/117) for placebo. The 100% responder rates during the maintenance phase for the cenobamate 100-, 200-, and 400-mg/day groups were 12.4% (14/113; $p = .004$), 30.1% (34/113; $p < .001$), and 52.4% (54/103; $p < .001$),

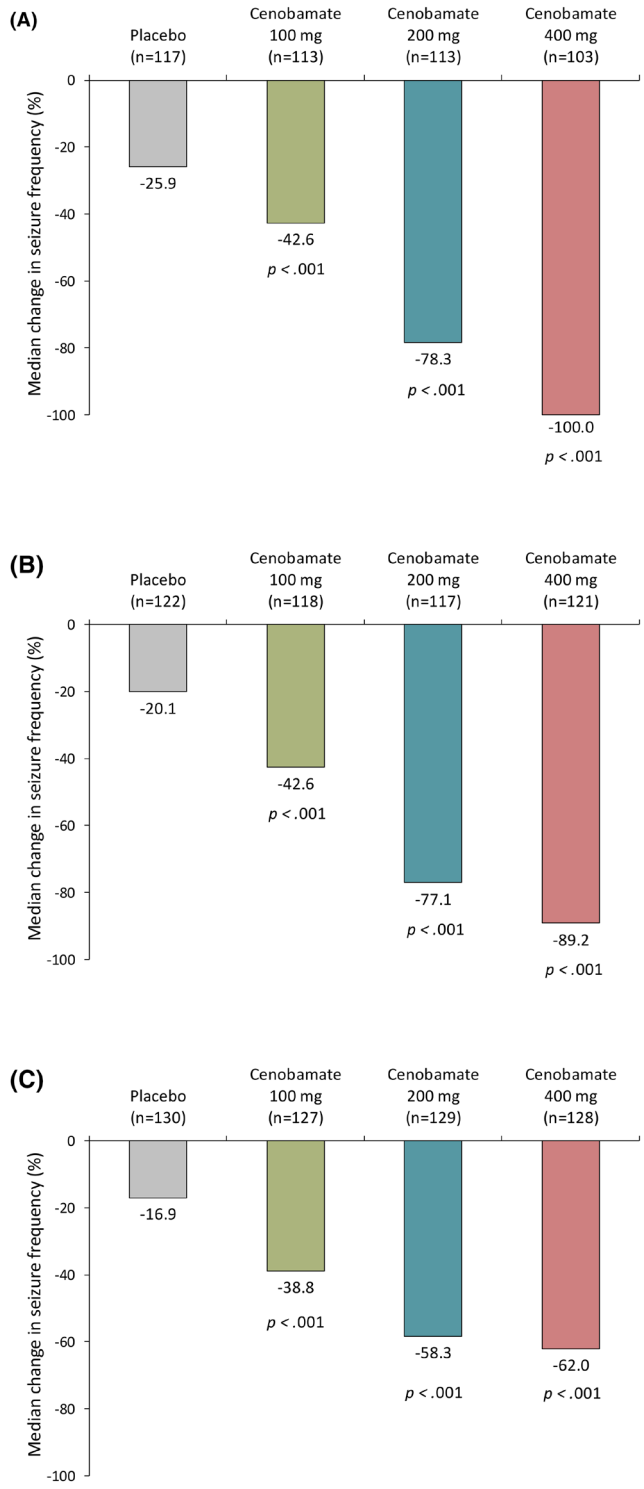

FIGURE 3 Median percentage change in 28-day focal seizure frequency during the (A) 6-week maintenance phase (MITT-M population, $n = 446$; primary outcome), (B) 12-week treatment period (MITT 12-week population, $n = 478$), and (C) and 24-week double-blind treatment period (MITT population, $n = 514$). MITT, modified intent-to-treat; MITT-M, modified intent-to-treat maintenance. The 12-week treatment period combined the last 6 weeks of the titration phase with the 6-week maintenance phase. *p*-values are vs placebo.

compared to 2.6% (3/117) for placebo. Responder rate analyses during the 12-week treatment period were similar to those observed during the maintenance phase, showing an increasing percentage of responders with increasing cenobamate dose, and responder rates were statistically significant for each of the cenobamate dose groups compared to placebo (Figure 4B).

The median modal oral daily cenobamate dose during the 24-week double-blind period was 100 mg (interquartile range [IQR] 100–100 mg) for the 100-mg dose group, 200 mg (IQR 200–200 mg) for the 200-mg dose group, and 350 mg (IQR 300–400 mg) for the 400-mg dose group (see Table S1 for additional dosing statistics). During the 6-week maintenance phase, the median modal daily dose was 100 mg (IQR 100–100 mg) for the 100-mg dose group, 200 mg (IQR 200–200 mg) for the 200-mg dose group, and 400 mg (IQR 300–400 mg) for the 400-mg dose group.

3.3 | Safety

During the 24-week double-blind treatment period, TEAEs were reported in 86 of 130 patients (66.2%) in the placebo group, 101 of 128 (78.9%) in the cenobamate 100-mg/day group, 111 of 130 (85.4%) in the cenobamate 200-mg/day group, and 123 of 128 (96.1%) in the cenobamate 400-mg/day group (Table 2). The most commonly reported TEAEs in all cenobamate dose groups were dizziness (21.9–70.3% of patients) and somnolence (22.7–46.9%). Other frequently reported TEAEs (≥10% of patients) with cenobamate included increased γ-glutamyl transferase (GGT) in the cenobamate 200- and 400-mg/day groups and diplopia, vomiting, headache, coronavirus disease 2019 (COVID-19) infection, ataxia, and nausea in the cenobamate 400-mg/day group. Dizziness, somnolence, and COVID-19 infection were the most frequently reported TEAEs in the placebo group. Most TEAEs (96.9%) were mild or moderate in severity. Mild to moderate TEAEs were reported in 84 of 130 patients (64.6%) in the placebo group, 99 of 128 (77.3%) in the cenobamate 100-mg/day group, 109 of 130 (83.8%) in the cenobamate 200-mg/day group, and 84 of 128 (88.3%) in the cenobamate 400-mg/day group.

Cutaneous adverse events are a TEAE of interest, particularly in Asian populations, who may have a higher incidence of idiosyncratic cutaneous reactions.[16] During the double-blind treatment period, there were no serious or severe cutaneous TEAEs. Rash was reported as a TEAE by 1.6% (8/516) of patients: 2 patients in the cenobamate 100-mg/day group, 2 in the cenobamate 200-mg/day group, 2 in the cenobamate 400-mg/day group, and 2 in the placebo group. All cases of rash in the cenobamate

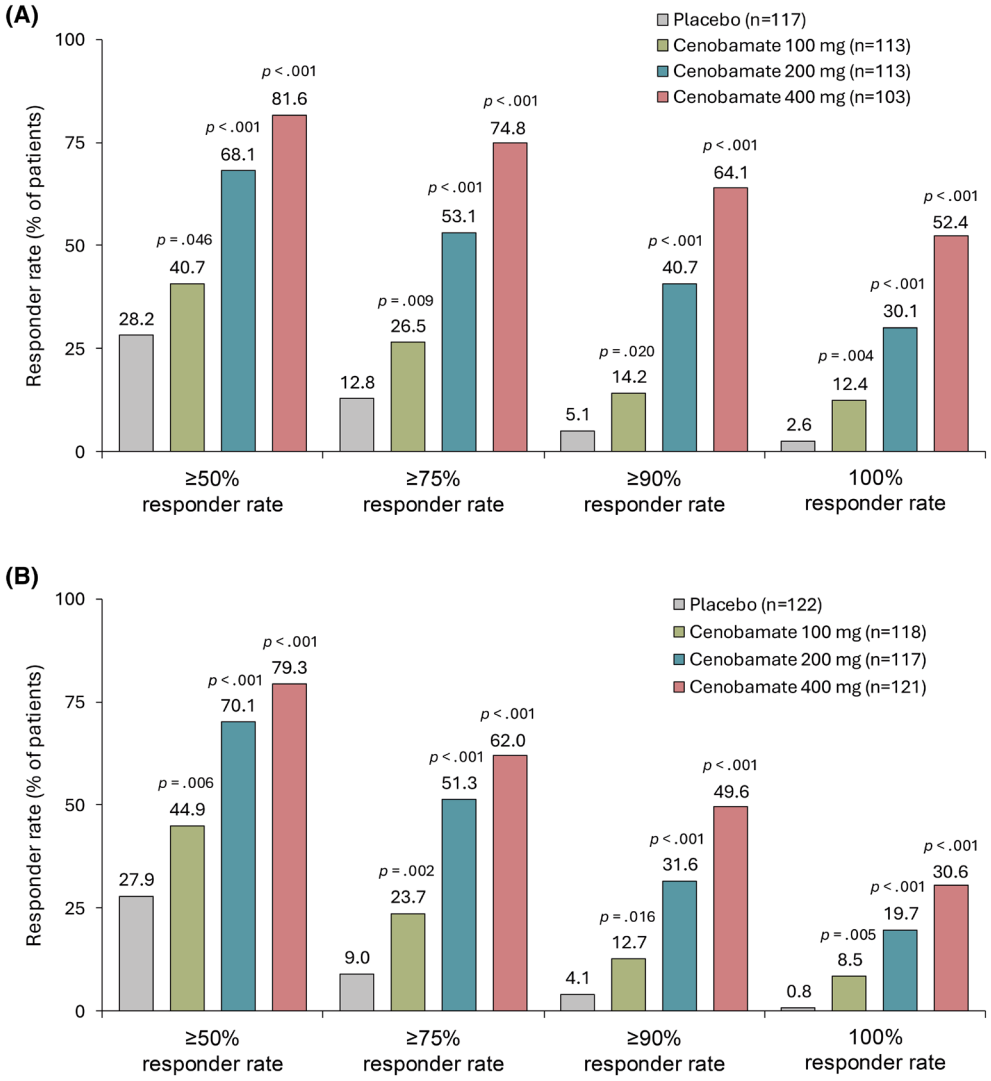

FIGURE 4 Responder rates during the (A) 6-week maintenance phase (MITT-M population, $n = 446$), and (B) 12-week treatment period (MITT 12-week population, $n = 478$). MITT, modified intent-to-treat; MITT-M, modified intent-to-treat maintenance. The 12-week treatment period combined the last 6 weeks of the titration phase with the 6-week maintenance phase. *p*-values are vs. placebo.

dose groups were mild in severity, and one case of rash in the placebo group was of moderate severity. Study discontinuations due to rash were reported for one patient in the cenobamate 100-mg/day dose group and two patients in the placebo group. Drug eruption, which was mild and did not result in study discontinuation, was reported by two patients (1.5%) in the placebo group. Pruritus was reported by one patient in the placebo group, and two, three, and one patient in the cenobamate 100-, 200-, and 400-mg/day groups, respectively. All cases were mild. No study discontinuations occurred due to pruritus. There were no deaths and no cases of DRESS syndrome reported during the double-blind study.

A higher proportion of patients in the cenobamate 400-mg/day group reported severe and serious TEAEs in comparison with the cenobamate 200-mg/day, cenobamate 100-mg/day, and placebo groups (Table 2). There were 26 serious TEAEs (400 mg/day, 17; 200 mg/day, 5; 100 mg/day, 4) reported in 20 patients in the cenobamate groups, including 8.6% (11/128) of patients in the cenobamate 400-mg/day group, 3.8% (5/130) of patients in the cenobamate 200-mg/day group, 3.1% (4/128) of patients in the cenobamate 100-mg/day group, and 2.3% (3/130) of patients in the placebo group (Table S2). Pneumonia ($n = 2$; cenobamate 400 mg/day) was the only serious TEAE occurring in more than one patient in any treatment group. In the safety population ($n = 516$), TEAEs leading to study drug withdrawal/study discontinuation were reported more frequently among patients in the cenobamate 400-mg/day group (21.9% [28/128]) than in the cenobamate 200-mg/day (9.2% [12/130]), cenobamate 100-mg/day (4.7% [6/128]), and placebo (4.6% [6/130]) groups. The most common adverse events resulting in study discontinuation were dizziness and somnolence. Dizziness that

TABLE 2 Summary of adverse events in the safety population ($n = 516$).

Event	Placebo ($n = 130$)	Cenobamate 100 mg/day ($n = 128$)	Cenobamate 200 mg/day ($n = 130$)	Cenobamate 400 mg/day ($n = 128$)
Any TEAE	86 (66.2)	101 (78.9)	111 (85.4)	123 (96.1)
Treatment-related adverse events	51 (39.2)	69 (53.9)	94 (72.3)	116 (90.6)
Severe TEAEs	2 (1.5)	2 (1.6)	2 (1.5)	10 (7.8)
Serious TEAEs	3 (2.3)	4 (3.1)	5 (3.8)	11 (8.6)
TEAEs ≥5%				
Dizziness	17 (13.1)	28 (21.9)	50 (38.5)	90 (70.3)
Somnolence	19 (14.6)	29 (22.7)	36 (27.7)	60 (46.9)
GGT increased	8 (6.2)	12 (9.4)	19 (14.6)	22 (17.2)
Diplopia	2 (1.5)	3 (2.3)	4 (3.1)	17 (13.3)
Vomiting	4 (3.1)	4 (3.1)	3 (2.3)	16 (12.5)
Headache	9 (6.9)	7 (5.5)	9 (6.9)	15 (11.7)
COVID-19 infection	14 (10.8)	8 (6.3)	8 (6.2)	14 (10.9)
Ataxia	0	3 (2.3)	4 (3.1)	14 (10.9)
Nausea	4 (3.1)	4 (3.1)	5 (3.8)	13 (10.2)
Nasopharyngitis	6 (4.6)	6 (4.7)	7 (5.4)	12 (9.4)
Fall	8 (6.2)	1 (.8)	10 (7.7)	10 (7.8)
Decreased appetite	3 (2.3)	4 (3.1)	5 (3.8)	10 (7.8)
Upper respiratory tract infection	7 (5.4)	4 (3.1)	5 (3.8)	7 (5.5)
Constipation	1 (.8)	5 (3.9)	4 (3.1)	7 (5.5)
Vision blurred	1 (.8)	3 (2.3)	3 (2.3)	7 (5.5)
Muscular weakness	1 (.8)	0	0	7 (5.5)
Pyrexia	9 (6.9)	2 (1.6)	6 (4.6)	4 (3.1)
White blood cell count decreased	3 (2.3)	2 (1.6)	12 (9.2)	3 (2.3)

Note: Data are given as *n* (%). Safety population included all randomized patients who received ≥1 dose of study drug.

Abbreviations: COVID-19, coronavirus disease 2019; GGT, γ-glutamyl transferase; TEAE, treatment-emergent adverse event.

led to study discontinuation occurred in 1.5% of patients (2/130) in the placebo group, 1.6% of patients (2/128) in the cenobamate 100-mg/day group, 4.6% of patients (6/130) in the cenobamate 200-mg/day group, and 14.1% of patients (18/128) in the cenobamate 400-mg/day group. Somnolence that led to study discontinuation occurred in .8% of patients (1/130) in the placebo group, 0 patients in the cenobamate 100-mg/day group, 1.5% of patients (2/130) in the cenobamate 200-mg/day group, and 4.7% of patients (6/128) in the cenobamate 400-mg/day group.

Few patients were reported to have TEAEs of suicidal behaviors (suicide attempt, $n = 1$ placebo) or suicidal ideation ($n = 1$ placebo; $n = 2$ cenobamate 100 mg; $n = 1$ cenobamate 200 mg). Consistent with the known safety profile of cenobamate,[17] ECG findings showed small and clinically insignificant QTcF interval shortenings and slower heart rate. Small, clinically insignificant mean decreases from baseline in leukocytes, erythrocytes, and platelets were observed for cenobamate-treated patients relative to placebo. Dose-related elevations in GGT occurred during the double-blind treatment period, although the majority of these elevations were isolated findings and were only occasionally accompanied by modest elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Most of the GGT elevations that were reported as TEAEs were mild in severity; none were severe or serious. Clinically significant liver enzyme elevations (AST or ALT >3× upper limit of normal [ULN]) were uncommon ($n = 1$ placebo, $n = 2$ cenobamate 100 mg/day, and $n = 1$ cenobamate 200 mg/day) and occurred in a similar percentage of patients in the placebo (.8% [1/130] of patients) and cenobamate (.8% [3/386] of patients) arms. The maximum

observed elevation occurred in one patient (cenobamate 100 mg/day group), who experienced an isolated occurrence of ALT elevation that was >5 times and <10 times the ULN.

No clinically meaningful changes from baseline were observed for vital signs or physical or neurologic examinations.

4 | DISCUSSION

This was the first randomized, placebo-controlled efficacy study of cenobamate for focal seizures using its approved titration schedule starting at 12.5 mg/day. In this study, adjunctive cenobamate 100, 200, and 400 mg/day provided significant dose-related reductions in focal seizure frequency per 28 days compared to placebo during the 6-week maintenance phase (primary endpoint). Significantly higher proportions of patients in the cenobamate 100-, 200-, and 400-mg/day groups also achieved ≥50%, ≥75%, ≥90%, and 100% seizure reduction relative to placebo during the 6-week maintenance phase, with seizure-free rates up to 52.4%, vs 2.6% for placebo. Similarly significant efficacy outcomes compared to placebo were observed in the cenobamate 100-, 200-, and 400-mg/day groups during the 12-week treatment period, which included the last 6 weeks of titration, with median percent reductions up to 89.2% and seizure-free rates up to 30.6%. Of note, patients in the 12-week treatment period who were randomized to the cenobamate 400-mg/day group received the 400-mg dose for only 6 weeks because the titration was ongoing (2-week increments of 250, 300, and 350 mg/day), whereas patients randomized to cenobamate 100 or 200 mg/day received the assigned dose for the full 12 weeks. Despite the differences in study designs and patient populations, these efficacy rates, particularly the 12-week rates, were for the most part in line with, if not stronger than, the rates demonstrated in the previous controlled clinical studies of cenobamate.[7,8]

Cenobamate was generally well tolerated, with no cases of DRESS syndrome reported, as was the case with the long-term open-label Phase 3 safety study that first used the approved biweekly titration schedule.[10] Dose-related dizziness and somnolence were the most commonly reported TEAEs, similar to previous studies of adjunctive cenobamate.[7,8,10,18,19] The frequency of dizziness and somnolence in the 200- and 400-mg/day cenobamate groups was higher than the rates reported in previous randomized clinical studies.[7,8] This may have been due to differences in the study design, which included a longer study duration (24 weeks vs 12 and 18 weeks), multiple dose transitions, and in particular, restricted dose adjustments of cenobamate and concomitant ASMs. In addition, a higher proportion of patients in this study were taking three or more concomitant ASMs compared to the previous clinical studies.[7,8] The lower BMI observed in this Asian study population compared to previous cenobamate clinical study populations may also have contributed to the higher frequency of AEs. The mean BMI in this study ranged from 23.1 to 23.8 kg/m^2 in cenobamate-treated groups, whereas in the previous randomized, double-blind studies, BMIs for cenobamate-treated patients[8,10] ranged from 25.6 to 26.1 kg/m^2. Slowing the cenobamate titration rate and/or reducing concomitant ASM doses, particularly ASMs that have pharmacokinetic or pharmacodynamic interactions with cenobamate, including clobazam and sodium channel blockers, is recommended to mitigate dizziness or sedation.[10,20–22]

There were frequent elevations in GGT during adjunctive cenobamate treatment, although these were generally clinically insignificant. The changes were dose related, not associated with any clinical symptoms, and were only occasionally associated with other hepatic enzyme changes. GGT is a nonspecific marker for hepatic pathology, although it also may occur secondary to hepatic enzyme induction.[23] Previous clinical studies of cenobamate did not examine GGT levels. The incidence of ALT elevations >3× ULN across the cenobamate groups (~.8%) was low and comparable to placebo. The presence of GGT elevation, which generally occurred without accompanying AST/ALT level increases in this study, suggests that it resulted from hepatic enzyme induction, similar to the GGT increases observed with other enzyme-inducing medications, including ASMs such as carbamazepine, valproate, phenytoin, and phenobarbital.[23–27] In addition, COVID-19 infection ($n = 30$ in the three cenobamate dose groups), a frequently reported TEAE during the study, has been associated with transient elevations in liver enzymes.[28–30] Because GGT is a sensitive but nonspecific liver function test, it is difficult to distinguish between viral and drug-induced effects on these parameters.[31] Based on these findings, it is likely that cenobamate causes elevation in GGT similar to that observed with other enzyme-inducing ASMs.

As with other controlled studies of ASMs, study limitations included fixed titration (only one cenobamate dose adjustment for tolerability allowed after the first 6 weeks), strict patient inclusion criteria, and restrictions to concomitant ASM dose adjustments. Co-administration of cenobamate increases phenobarbital and phenytoin plasma exposures by ~37% and 84%, respectively.[9] Because dosing requirements during this study precluded adjustments to concomitant ASMs, patients taking concomitant phenytoin or phenobarbital were excluded. In clinical practice, it is recommended to proactively lower doses of phenytoin and phenobarbital during cenobamate titration.[20]

Although the 24-week treatment duration was adequate for a randomized, placebo-controlled study, the relatively short maintenance duration can be considered a limitation to this study. Data from short-term trials may be biased by the "honeymoon effect," a term that refers to patients who exhibit a temporary response but become resistant to the same ASM with prolonged use. However, the strong efficacy and retention rates observed during the Phase 2 trials (Study C013, Chung et al.[7]; Study C017, Krauss et al.[8]) and the C017 open-label extension (Klein et al.[18]) suggests that the honeymoon effect is not a significant issue for patients with uncontrolled focal seizures who are taking cenobamate. To compensate for the relatively short maintenance phase in the current study, efficacy during the 12-week period encompassing the last 6 weeks of titration plus the 6-week maintenance phase was analyzed. The inclusion of the 12-week treatment period provides an analysis that is more comparable to Krauss et al., although a limitation of the 12-week period is that the 400-mg/day dose group received their full dose for 6 of the 12 weeks. For further comparison, an analysis of the entire 24-week double-blind period was performed. When comparing the 6-week maintenance phase results to the 12-week analysis there was a slight decrease in efficacy outcomes for the 12-week period. The 12-week and 24-week analyses align more closely with maintenance responses from the Krauss study. The open-label extension phase of this study will provide further insight into the long-term efficacy and safety of adjunctive cenobamate in Asian patients with focal seizures.

5 | CONCLUSIONS

Adjunctive cenobamate at dosages of 100, 200, and 400 mg/day administered according to the currently approved titration schedule was associated with significant dose-related reductions in focal seizure frequency and notable response rates (including seizure-free rates up to 52.4% during the maintenance phase) relative to placebo and was generally well tolerated. The results of this study were consistent with the existing benefit–risk profile of cenobamate.

AUTHOR CONTRIBUTIONS

E.C., L.F., Y.H.J., J.J., M.K., M.W.K., J.P., and S.N.M. contributed to the study design. As study investigators, S.K.L., P.Y., K.H., S.B.H., Z.H., K.I., K.K., J.H.K., X.L., T.Y., D.Z., and S.Z. provided patient data. All authors interpreted the results, contributed to the writing, and reviewed the manuscript. All authors reviewed and approved the final draft for submission.

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CONFLICT OF INTEREST STATEMENT

S.K.L., P.Y., K.H., S.B.H., Z.H., J.H.K., X.L., D.Z., and S.Z.: Nothing to disclose. E.C., Y.H.J., J.J., M.W.K., and J.P.: Employees, SK Biopharmaceuticals Co., Ltd. L.F., M.K., and S.N.M.: Employees, SK Life Science, Inc. K.I.: Consultant/advisor: Eisai; Speaker: Daiichi-Sankyo, Eisai and UCB Japan; Research funding: Ricoh, UCB Japan, and Zimmer Biomet. K.K.: Consultant/advisor: EP Medical, UCB Japan, and Zimmer Biomet; Speaker: Daiichi-Sankyo and Eisai. W.E.R.: Consultant/advisor: SK Life Science, Inc.; Speaker: SK Life Science, Inc.; Research support: SK Life Science, Inc. and UCB Pharma. T.Y.: Consultant/advisor: Eisai, and UCB Japan; Speaker: Daiichi-Sankyo, Eisai, LivaNova Japan, UCB Japan, and Zimmer Biomet.

DATA AVAILABILITY STATEMENT

The data for the analyses described in this paper are available by request from the corresponding author or from SK Biopharmaceuticals Co., Ltd. or SK Life Science, Inc., the companies sponsoring the clinical development of cenobamate for the treatment of focal epilepsy.

ETHICS STATEMENT

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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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