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RESEARCH ARTICLE

Early response rates with adjunctive cenobamate in uncontrolled focal seizures: Prospective analysis of a randomized, double-blind, placebo-controlled study in a multinational Asian population

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Abstract

Objective: To examine early responses to cenobamate therapy using prospective data from a dose–response study in Asian patients with focal seizures (YKP3089C035, C035) that employed a titration regimen starting at 12.5 mg/day.

Methods: In Study C035, adults 18–70 years of age with uncontrolled focal seizures despite treatment with 1–3 antiseizure medications were randomized 1:1:1:1 to receive placebo or adjunctive cenobamate 100, 200, or 400 mg/day. The 24-week double-blind study included an 18-week titration and 6-week maintenance phase. During the first 8 weeks of titration ("early titration phase"), all cenobamate patients received the same dosing regimen: 12.5 mg/day for 2 weeks, 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, and 100 mg/day for 2 weeks. Change in seizure frequency from baseline and responder rates were assessed at these 2-week intervals for combined cenobamate dose groups vs placebo. Analyses were performed on the modified intent-to-treat maintenance (MITT-M) population (≥1 study drug dose and seizure data in the maintenance phase); all patients completed early titration.

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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Results: Of 519 patients randomized, 446 were included in the MITT-M population (placebo $n = 117$, cenobamate $n = 329$). During Weeks 1–2, 3–4, 5–6, and 7–8 of titration, cenobamate patients experienced a median reduction in 28-day seizure frequency of 16.0% (vs 20.0% placebo, $p = .81$), 27.3% (vs 22.2% placebo, $p = .42$), 42.9% (vs 15.4% placebo, $p = .002$), and 55.6% (vs 20.0% placebo, $p < .001$), respectively. During Weeks 5–6 and 7–8, the 100% responder rates for cenobamate 50 and 100 mg/day were 17.0% (vs 12.8% placebo, $p = .29$) and 26.7% (vs 8.5% placebo, $p < .001$), respectively.

Significance: Statistically significant responses to cenobamate treatment occurred within the first 8 weeks of titration, including a 42.9% median reduction in 28-day seizure frequency (Weeks 5–6) and a seizure-free rate of 26.7% (Weeks 7–8). These data show that substantial seizure reductions occurred in many patients early during cenobamate titration.

KEYWORDS
antiseizure medication, efficacy, epilepsy, refractory, titration

1 | INTRODUCTION

Cenobamate is an antiseizure medication (ASM) indicated for the adjunctive treatment of focal seizures in adults.[1–4] The efficacy of cenobamate was shown previously in the Phase 2 fixed-dose trial (Study C013, Chung et al.[5]) at a dose of 200 mg/day and in the Phase 2 multidose trial (Study C017, Krauss et al.[6]) at doses of 100, 200, and 400 mg/day, where cenobamate was initiated at 50 mg/day with a 6-week titration phase, a higher initial dose and faster titration rate than the currently approved titration schedule. In both trials, cenobamate at 200 and 400 mg/day significantly decreased seizure frequency, including maintenance phase seizure-free rates of 11%–28% (vs 1.0% and 8.8% for respective placebo groups).[5,6] The most commonly reported adverse events during the double-blind studies included dizziness, somnolence, headache, fatigue, and diplopia.

The occurrence of three cases of the serious adverse event of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome during cenobamate's early clinical development[1] prompted the conduct of a Phase 3 open-label safety study (Study C021, Sperling et al.[7]) that was designed to evaluate the effect of a lower starting dose and slower titration rate on the occurrence of DRESS syndrome.[7] Cenobamate was initiated at 12.5 mg/day for 2 weeks followed by 25 mg/day for 2 weeks and 50 mg/day for 2 weeks, with subsequent increases in 50 mg/day increments every 2 weeks.[7] No cases of DRESS syndrome occurred among 1339 patients exposed to cenobamate.[7] This lower starting dose, slower titration regimen is now standard in all countries where cenobamate is approved,[1–4] and it has been used to treat more than 220 000 adult patients worldwide, with no additional confirmed cases of DRESS syndrome.[8,9] Although C021 was designed as a safety study, a post hoc analysis conducted in a subset of patients ($n = 240$) with quality seizure data showed clinical efficacy during the first 8 weeks of cenobamate titration at doses of 12.5–100 mg/day.[10]

Key points

- This is the first placebo-controlled cenobamate efficacy study to use the globally approved cenobamate titration schedule.
- Median seizure frequency reductions reached statistical significance vs placebo at Weeks 5–8 of the early titration phase.
- Weeks 5–8 median reduction in 28-day seizure frequency with adjunctive cenobamate was at least 42.9% (vs up to 20% with placebo).
- Statistically significant seizure freedom rates occurred at Weeks 7–8 of early titration (26.7% cenobamate 100 mg/day vs 8.5% placebo).

Study C035 (YKP3089C035, clinicaltrials.gov NCT04557085) was a randomized, double-blind, placebo-controlled dose–response study that evaluated the efficacy and safety of cenobamate 100, 200, and 400 mg/day as adjunctive therapy in adult Asian patients with uncontrolled focal seizures.[11] It was the first randomized, placebo-controlled efficacy study in focal epilepsy to use the currently approved cenobamate titration schedule. The 24-week study included an 18-week titration phase and a 6-week maintenance phase. The primary analysis

demonstrated statistically significant median percent seizure reductions during the maintenance phase in each cenobamate dose group (modified intent-to-treat maintenance [MITT-M] population, ≥1 dose and any seizure data during the maintenance phase): 25.9% for placebo vs 42.6%, 78.3%, and 100% for cenobamate 100, 200, and 400 mg, respectively ($p < .001$ vs placebo for all dose groups).[11]

The objective of the prospective analysis described here was to investigate trends in responses to cenobamate therapy (median seizure reduction, responder rates) during the first 8 weeks of the label-approved titration regimen, at doses between 12.5 and 100 mg/day, in the C035 study. We also summarize trends in focal seizure reductions during the rest of the 18-week titration phase and the 24-week double-blind treatment period.

2 | METHODS

2.1 | Study design and patients

Details of the 24-week double-blind treatment period of the multicenter, randomized, placebo-controlled study (Study C035), conducted at 70 sites in China, the Republic of Korea, and Japan, have been described.[11] The double-blind study was conducted from April 27, 2021, to February 16, 2024. The study included adults 18–70 years old (inclusive) with a diagnosis of focal-onset (partial-onset) seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981),[12] with diagnosis confirmed by an independent consulting physician group (The Epilepsy Study Consortium). Patients were required to have ≥8 focal seizures with observable seizure semiology (e.g., focal aware motor, focal impaired awareness, and/or focal to bilateral tonic–clonic) during the 8-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.

Eligible patients were randomized 1:1:1:1 via an interactive response technology system to receive either placebo or adjunctive cenobamate titrated to a target dose of 100, 200, or 400 mg once-daily using the currently approved titration schedule (Figure 1). Randomization was stratified by country. Patients, investigators, and study personnel were masked to the randomized treatment assignment. Study medications and packaging were visually identical to ensure adequate masking. Although randomized to different cenobamate dose groups, all cenobamate patients received the same treatment plan during the first 8 weeks of titration: 12.5 mg/day during Weeks 1–2, 25 mg/day during Weeks 3–4, 50 mg/day during Weeks 5–6, and 100 mg/day during Weeks 7–8. After the first 6 weeks of titration, one 50-mg dose reduction was permitted and the dose was increased to the previous dose at the next visit. No changes to concomitant ASM total daily doses or dosing frequency were allowed during the double-blind treatment period.

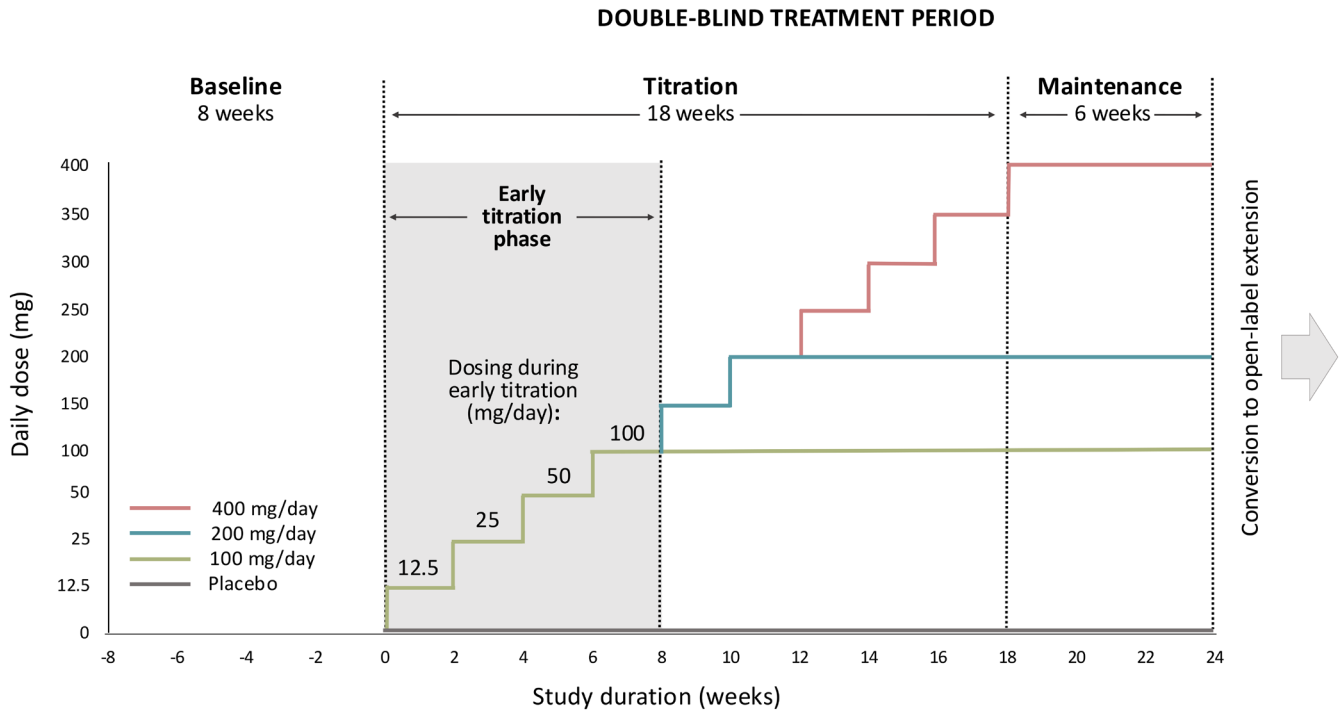

FIGURE 1 Study design.

The study was conducted in accordance with the International Council for Harmonisation's Guideline for Good Clinical Practice,[13] 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

For this analysis of early responses during the first 8 weeks of the titration phase of the main C035 study described above, changes in median seizure frequency and responder rates (≥50%, ≥75%, ≥90%, and 100% seizure frequency reductions) at 2-week intervals during the first 8 weeks of titration for all cenobamate dose groups combined were compared to placebo. Seizure reductions over the entire 18-week titration phase and the entire 24-week double-blind treatment period for each treatment group were also evaluated. Treatment-emergent adverse events (TEAEs) were assessed in the safety population during the double-blind treatment period, and a post hoc analysis of TEAEs during the 8-week early titration period was performed.

2.3 | Statistical analyses

Assuming a standard deviation of 50%, a sample size of 107 participants per treatment group in the MITT-M population of the main study 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. The modified intent-to-treat (MITT) population included all patients who received at least one dose of study drug and had at least one efficacy measure during the double-blind treatment period. The 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. Examining early response during titration by analyzing the MITT-M population ensured that the combined cenobamate group was made up of patients who had completed the initial 8 weeks of titration. Seizure counts (including focal seizure subtypes) were recorded in patient diaries during the 8-week baseline period and the 24-week double-blind treatment period. Days with no available seizure diary data were excluded from the analysis. Seizure frequency during the baseline and treatment intervals was calculated by summing the number of seizures in each interval and dividing by the total duration (days) and multiplying by 28 to obtain a 28-day rate. For the early response analysis, a pooled comparison of all cenobamate patients and all placebo patients during the first 8 weeks of the study was performed. The median percent change from baseline in seizure frequency (seizure rate per 28-day interval) of all focal aware motor, focal impaired awareness, and/or focal to bilateral tonic–clonic seizures during every 2-week interval in the first 8 weeks of the titration phase were analyzed by active treatment vs placebo, 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. Responder rates were analyzed using the Cochran–Mantel–Haenszel test, unless otherwise specified. In addition, the same analyses were used to assess efficacy at 4-week intervals during the first 8 weeks of titration as well as for the entire titration phase and the entire double-blind treatment period by treatment group. Seizure frequency reductions during the entire titration phase and the double-blind treatment period were assessed in the MITT and MITT-M populations. Safety data were analyzed descriptively. The safety population included patients who received at least one dose of study drug during the double-blind treatment period.

3 | RESULTS

3.1 | Patient disposition and demographics

Among 519 patients randomized in the main study, 516 were included in the safety population, 514 in the MITT population (placebo, $n = 130$; cenobamate, $n = 384$), and 446 in the MITT-M population (placebo, $n = 117$; cenobamate, $n = 329$) (Figure 2, Table 1). In the MITT-M population, the mean age was 35.2 years and 45.7% of patients were female. The overall median baseline 28-day seizure frequency was 10.0 (range: 3.1–1029.0), and 99.3% (443/446) experienced ≥4 seizures per 28 days. Most patients (63.2% [326/516] in the safety population) were taking three concomitant ASMs during the double-blind 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]), oxcarbazepine (23.3% [120/516]), and carbamazepine (24.4% [126/516]).

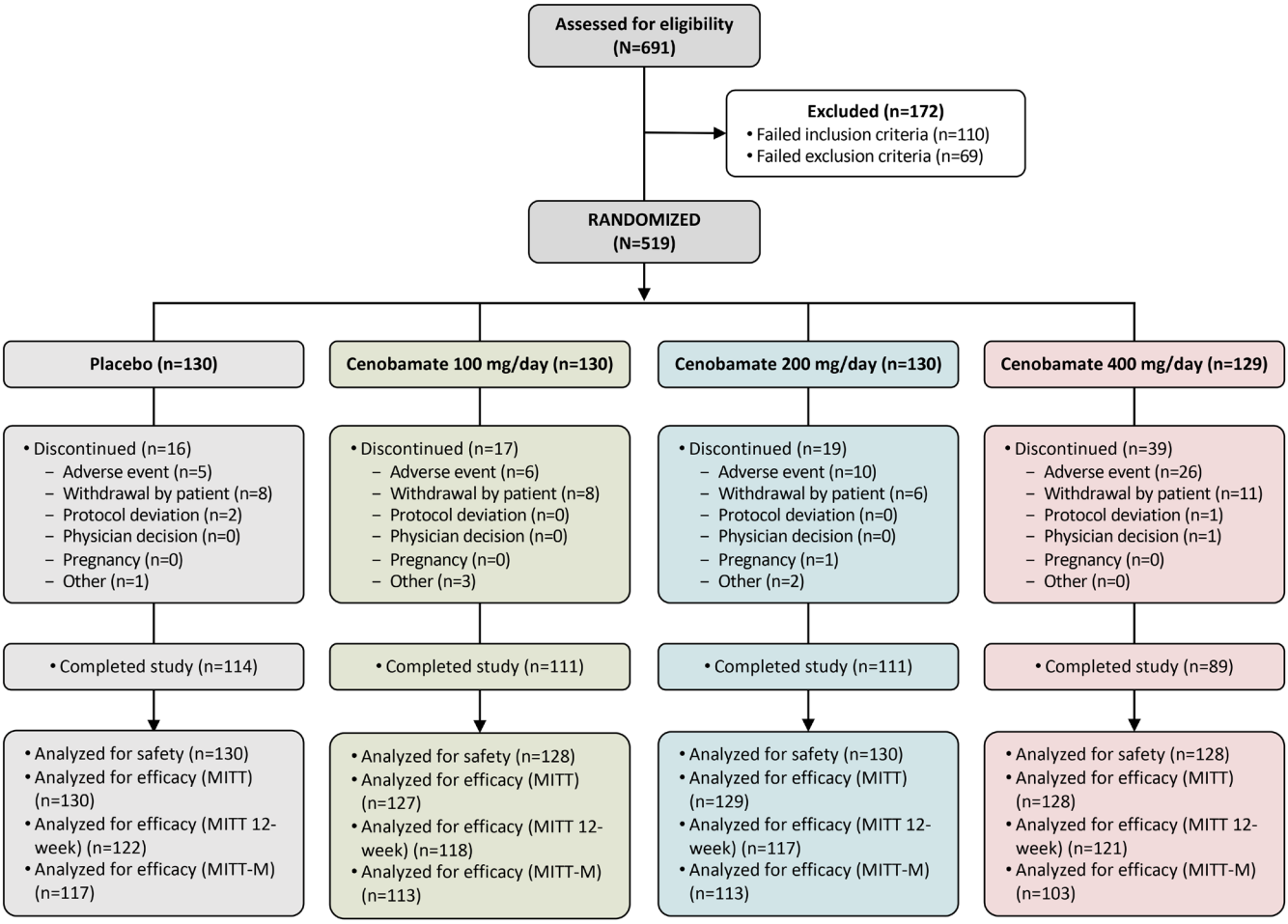

FIGURE 2 Patient disposition (across entire 24-week C035 main study). MITT, modified intent-to-treat population; MITT-M, modified intent-to-treat maintenance population; MITT 12-week, modified intent-to-treat 12-week population. Three patients (two in the 100 mg/day group and one in the 400 mg/day group) 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).

3.2 | Efficacy

During Weeks 1–2, 3–4, 5–6, and 7–8 of titration, patients treated with cenobamate experienced a median reduction in 28-day seizure frequency of 16.0% (vs 20.0% placebo, $p = .81$), 27.3% (vs 22.2% placebo, $p = .42$), 42.9% (vs 15.4% placebo, $p = .002$), and 55.6% (vs 20.0% placebo, $p < .001$), respectively. Statistically significant seizure frequency reductions vs placebo occurred in the cenobamate groups starting at Weeks 5–6 (42.9% for cenobamate 50 mg/day vs 15.4% for placebo [$p = .002$]) and continuing through Weeks 7–8 (55.6% for cenobamate 100 mg/day vs 20.0% for placebo [$p < .001$]) (Figure 3).

Cenobamate responder rates increased consistently with dose increases after the initial 12.5 mg/day dose. A placebo effect was observed in responder rates, which peaked at Weeks 5–6 and decreased at Weeks 7–8. Starting at Weeks 3–4 (cenobamate 25 mg/day), 50% responder rates for cenobamate were statistically significant vs placebo (36.5% of patients for cenobamate vs 25.6% for placebo, $p = .03$) (Figure 4). One hundred percent responder (seizure freedom) rates were statistically significant vs placebo at Weeks 7–8 (26.7% for cenobamate 100 mg/day vs 8.5% for placebo, $p < .001$).

During the remainder of the 18-week titration phase (Weeks 9–18), seizure frequency reductions with cenobamate in the MITT-M population were statistically significant compared with placebo ($p \leq .003$ for all cenobamate doses vs placebo; data not shown). Seizure frequency reductions were observed to be consistent between the MITT and MITT-M populations when assessed at 2-week intervals over the entire titration phase and during the 24-week double-blind treatment period. During the remainder of the 18-week titration phase (Weeks 9–18), increases in the percentage of ≥50%, ≥75%, ≥90%, and 100% responders with cenobamate in the MITT and MITT-M populations were statistically significant compared with placebo in the 200 and 400 mg/day cenobamate groups ($p < .001$ for 200 and 400 mg/day, all responder rates vs placebo; data not shown). Consistent ≥50% and 100% responder rates were observed

TABLE 1 Baseline demographics and clinical characteristics, MITT-M population ($n = 446$).

Characteristic	Placebo ($n = 117$)	Cenobamate		
		100 mg/day ($n = 113$)	200 mg/day ($n = 113$)	400 mg/day ($n = 103$)
Age at screening, years, mean (SD), range	34.3 (11.1), 18–64	36.8 (12.6), 18–67	35.5 (11.3), 18–65	34.5 (10.7), 18–65
Female, *n* (%)	57 (48.7)	43 (38.1)	53 (46.9)	51 (49.5)
BMI, kg/m^2, mean (SD)[a]	23.3 (4.2)	23.7 (3.7)	23.6 (3.9)	23.1 (4.2)
Country, *n* (%)				
China	50 (42.7)	48 (42.5)	50 (44.2)	47 (45.6)
Japan	33 (28.2)	30 (26.5)	28 (24.8)	27 (26.2)
Republic of Korea	34 (29.1)	35 (31.0)	35 (31.0)	29 (28.2)
Baseline 28-day seizure frequency, median (min, max)	11.0 (3.5, 1029.0)	9.0 (4.0, 617.5)	9.5 (3.1, 333.5)	12.2 (4.0, 616.5)
No. of concomitant ASMs[b], safety population ($n = 516$), *n* (%)				
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)

Abbreviations: ASM, antiseizure medication; BMI, body mass index; MITT-M, modified intent-to-treat maintenance; SD, standard deviation.

[a]This compares to mean BMIs of 27.4, 26.0, 26.1, and 25.8 for placebo and for cenobamate 100, 200, 400 mg, respectively, in Study C017 (Krauss et al.[6]) and to an overall mean BMI of 26.9 in Study C021 (Sperling et al.[7]).

[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.

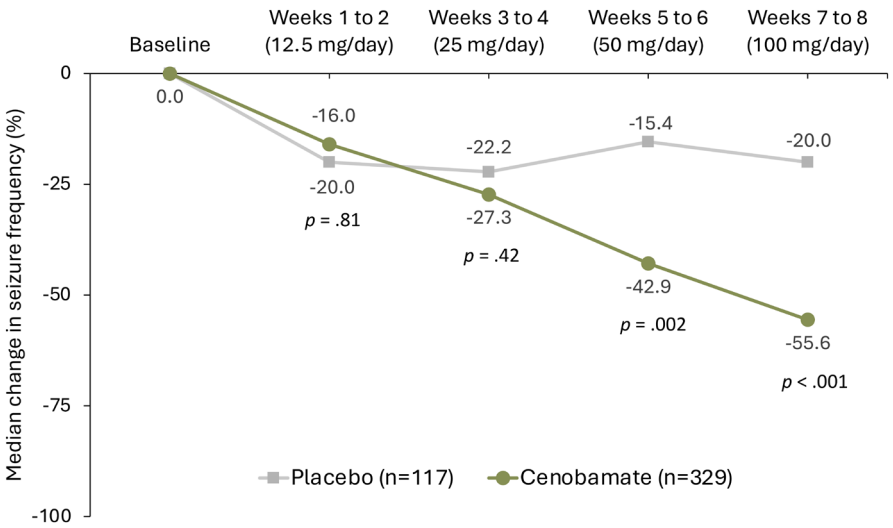

FIGURE 3 Median seizure frequency reductions from baseline during first 8 weeks of cenobamate titration (MITT-M population, $n = 446$). MITT-M, modified intent-to-treat maintenance. MITT-M population included patients taking ≥1 dose of study drug and with any postbaseline seizure data in the maintenance phase. *p*-values are vs. placebo.

between the MITT and MITT-M populations when assessed at 4-week intervals over the entire titration phase and during the 24-week double-blind treatment period.

3.3 | Safety

During the first 8 weeks of titration, patients achieved a maximum cenobamate dose of 100 mg/day (Figure 1). A post hoc analysis of the safety population ($n = 516$) determined that during the first 8 weeks of titration, TEAEs were reported in 57 of 130 patients (43.8%) in the placebo group and 228 of 386 (59.1%) in the cenobamate groups (Table 2). Most TEAEs were mild or moderate in severity. The most commonly occurring TEAEs during the first 8 weeks of titration were dizziness (cenobamate, 16.6% [64/386]; placebo, 5.4% [7/130]) and somnolence (cenobamate, 15.5% [60/386]; placebo, 10.0% [13/130]).

In comparison, during the entire double-blind treatment period, TEAEs occurred in 66.2% (86/130) of placebo-treated patients and 86.8% (335/386) of cenobamate-treated patients; most were mild or moderate

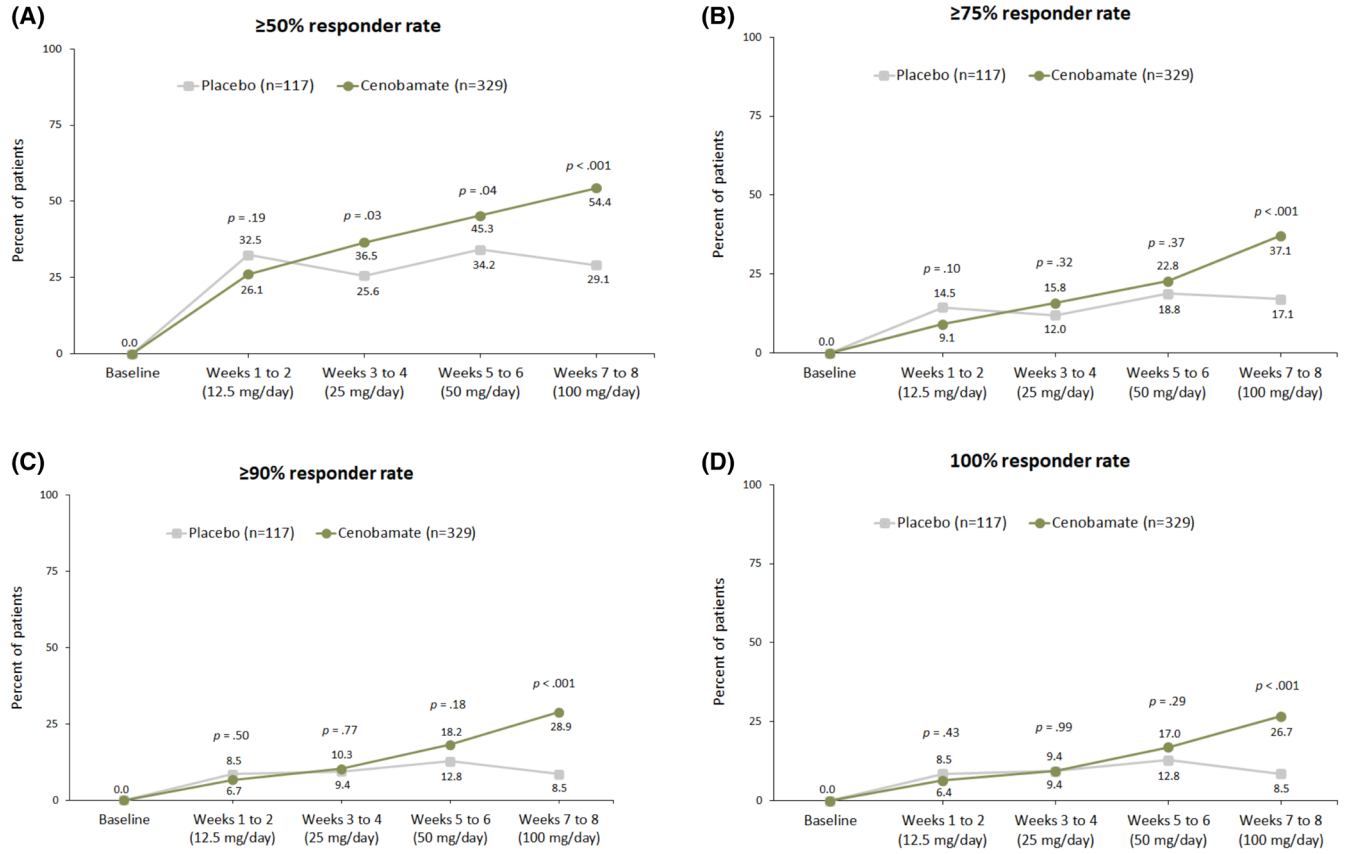

FIGURE 4 Responder rates during first 8 weeks of cenobamate titration (MITT-M population, $n = 446$): (A) ≥50%, (B) ≥75%, (C) ≥90%, (D) 100%. MITT-M, modified intent-to-treat maintenance. MITT-M population included patients taking ≥1 dose of study drug and with any postbaseline seizure data in the maintenance phase. *p*-values are vs placebo.

in severity (see Lee et al.[11]). The most frequently reported TEAEs (>10% of patients in any cenobamate treatment group) were dizziness, somnolence, gamma-glutamyl transferase (GGT) increased, diplopia, nausea, vomiting, and ataxia.

During the first 8 weeks of titration, TEAEs leading to study discontinuation occurred in 18 of 386 (4.7%) cenobamate-treated patients (maximum dose 100 mg/day) and 4 of 130 (3.1%) of patients in the placebo group. Over the course of the entire 18-week titration phase, the discontinuation rate for the cenobamate 100 mg/day group was 10.9%, and the discontinuation rate for the placebo group was 10.0%.

During the 24-week double-blind treatment period, a total of 91 patients discontinued the study (see Figure 2). Study discontinuations/study drug withdrawals due to TEAEs in the safety population ($n = 516$) were reported in a higher proportion of subjects 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.

Rash is an adverse event of interest with cenobamate, particularly among Asian patients who may be prone to idiosyncratic cutaneous reactions.[14] No serious or severe cutaneous adverse reactions were reported during the double-blind treatment period. Rash was reported as a TEAE by 1.6% (8/516) 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. Among cenobamate-treated patients, all cases of rash were mild in severity. One patient randomized to cenobamate 100 mg/day and two patients randomized to placebo discontinued the study due to rash. Drug eruption was reported by two patients (1.5%) in the placebo group. Both cases were mild and did not result in study discontinuation. There were no deaths and no cases of DRESS syndrome reported during the double-blind study.

4 | DISCUSSION

Study C035 was the first placebo-controlled study of cenobamate to assess the efficacy of cenobamate when administered according to the currently approved titration schedule, starting at 12.5 mg/day. The study design allowed the prospective assessment of efficacy

TABLE 2 Summary of adverse events in the safety population ($n = 516$) during the 8-week early titration phase (post hoc 8-week safety analysis).

	Placebo ($n = 130$)	All cenobamate ($n = 386$)[a]
Any TEAE	57 (43.8)	228 (59.1)
Treatment-related adverse events	34 (26.2)	157 (40.7)
Severe TEAEs	2 (1.5)	1 (0.3)
Serious TEAEs	3 (2.3)	4 (1.0)
TEAEs leading to discontinuation	4 (3.1)	18 (4.7)
Treatment-emergent adverse events ≥5% in either group		
Dizziness	7 (5.4)	64 (16.6)
Somnolence	13 (10.0)	60 (15.5)
COVID-19 infection	7 (5.4)	14 (3.6)

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

Abbreviation: TEAE, treatment-emergent adverse event.

[a]All patients were randomized 1:1:1:1 to placebo or one of the three cenobamate dose groups. During the first 8 weeks of titration, patients had achieved a maximum cenobamate dose of 100 mg/day and thus had not yet advanced to the higher doses.

trends during the first 8 weeks of titration, which is presented here. Of note, all dose groups during this time had received the same dose at each 2-week interval. Statistically significant reductions in median seizure frequency started at Weeks 5–6 (42.9% reduction for cenobamate 50 mg/day) and continued through Weeks 7–8 (55.6% reduction for cenobamate 100 mg/day). The earliest statistically significant response to cenobamate occurred during Weeks 3–4 (≥50% responder rate of 36.5% for cenobamate 25 mg/day). The placebo effect in responder rates peaked at Weeks 5–6 and decreased at Weeks 7–8. Thus, after Weeks 5–6, the responses to cenobamate became more clearly differentiated from placebo. The 17.0% seizure-free rate (vs 12.8% placebo, $p = .29$) observed at Weeks 5–6 (cenobamate 50 mg/day), was encouraging, although it is difficult to confirm how much of this short seizure-free interval can be attributed to the low cenobamate dose because patients continued to titrate up. The previous Phase 2 cenobamate studies that examined cenobamate efficacy at 4-week intervals using a higher starting dose (50 mg/day) and shorter titration period (weekly or faster) also found early efficacy, with median seizure frequency reductions of 40.6%–50.0% during the first 4 weeks of titration at cenobamate 50–200 mg/day.[5,6]

Direct comparisons of efficacy rates across studies with different assessment intervals and dosing regimens can be limited, but the 55.6% median seizure reduction and 26.7% seizure freedom rate occurring at Weeks 7–8 (cenobamate 100 mg/day) in the present study aligns with or exceeds the early efficacy demonstrated in the Phase 2 results. In a post hoc efficacy analysis conducted in a subset ($n = 240$) of patients from the Phase 3 cenobamate safety study,[7] which also used the currently approved titration regimen, ≥50% responder rates were 48.1% during Weeks 1–4 of titration (cenobamate 12.5–25 mg/day) and 61.7% during Weeks 5–8 of titration (cenobamate 50–100 mg/day). Of note, the post hoc efficacy analysis included patients with ≥1 focal seizure per 13 weeks at baseline compared to the current study, which included patients with ≥8 focal seizures per 8 weeks baseline.[10] In a separate post hoc analysis of patients from that $n = 240$ subset who had a higher baseline seizure frequency (median 8.4 seizures/28 days, $n = 113$), reductions of up to 78% occurred at cenobamate 50 mg/day.[15]

The results of this study reflect the largest placebo-controlled comparison performed in a cenobamate study to date, with 389 randomized cenobamate patients. These results were analyzed in a population that completed the first 8 weeks of titration and excluded dropouts (MITT-M population), similar to the analysis ($n = 113$ cenobamate patients) that examined early responses in the initial cenobamate Phase 2 study.[5] We acknowledge that exclusion of dropouts creates potential bias; however, during the entire 18-week titration phase, 10.9% of patients in the 100 mg/day group (the highest dose attained during the first 8 weeks of titration) were dropouts, a rate similar to the placebo group (10%). Moreover, analysis of the entire titration phase in the MITT population, which included dropouts, produced efficacy results similar to placebo. Taken together, these results suggest limited bias due to exclusion of dropouts during the first 8 weeks of titration.

The goal of this analysis was to examine trends in efficacy during the 2-week intervals of the early titration phase. The collection of seizure frequency data over short intervals poses a limitation, in that natural fluctuations in the course of the disease may result in decreased seizure frequency during a single 2-week period regardless of treatment. However, results from pivotal cenobamate efficacy studies also suggest that patients and prescribers may see responses with cenobamate at doses of 50 mg/day. The strong seizure-free rate demonstrated for cenobamate 100 mg/day in this analysis is encouraging, although it must be interpreted within the limited context of the early weeks of a clinical trial. Even so, patients who are seizure-free, even for a limited period, may experience improved physical and psychosocial outcomes.[16,17] The findings from the open-label extension of this study will provide more information regarding the maintenance of seizure freedom with cenobamate.

Consistent with the double-blind treatment period, dizziness and somnolence were the most commonly reported TEAEs during the first 8 weeks of titration. During early titration, the differences from placebo in dizziness and somnolence were less pronounced compared to the entire double-blind treatment period. This suggests that early treatment is well tolerated and reinforces that adverse events such as dizziness and somnolence are primarily dose-related. During the early titration period, dizziness, somnolence, headache, and coronavirus disease 2019 (COVID-19) infection occurred in at least 5% of patients treated with cenobamate. After the 8-week early titration phase, the frequency of TEAEs increased with increasing cenobamate dose and included increased GGT in the cenobamate 200- and 400-mg/day groups and diplopia, vomiting, headache, COVID-19 infection, ataxia, and nausea in the cenobamate 400-mg/day group. Dizziness, somnolence, headache, and COVID-19 infection were the most frequently reported TEAEs in the placebo group throughout the study.

Most of the study discontinuations that occurred during the titration period were due to adverse events. This is likely due to the restricted dose adjustments of concomitant ASMs and cenobamate allowed in the clinical trial setting. Because most patients (63.1%) were taking three concomitant ASMs during the double-blind study, it is possible that some discontinuations and adverse events were associated with patients' total drug burden during titration. When flexible dosing was employed in the cenobamate Phase 3 safety study, a post hoc analysis found that dose adjustments of concomitant ASMs most often occurred during titration and were associated with improved retention.[7,18] This highlights the importance of adjusting concomitant medications when initiating cenobamate in the clinical setting.[19] TEAE rates may have also been impacted by the length of the study, and the lower body mass index in Asian patients compared to previous cenobamate studies.[6] Based on cenobamate's initial efficacy, in clinical practice, patients may tolerate a reduction of concomitant ASMs during the titration schedule at low doses (50 and 100 mg/day) if tolerability issues arise.[19]

5 | CONCLUSIONS

Responses to cenobamate therapy in a population with uncontrolled seizures achieved statistical significance vs placebo at doses as low as 25 mg/day (≥50% responder rate), 50 mg/day (median seizure frequency), and 100 mg/day (seizure freedom). Median seizure frequency reductions continued to be statistically significant at 50 mg/day cenobamate onwards, and all responder rates had reached statistical significance vs placebo by Weeks 7–8. Thus, although cenobamate has a long titration schedule, in clinical practice patient responses to cenobamate may be seen during titration doses of 25–50 mg/day.

AUTHOR CONTRIBUTIONS

E.C., L.F., Y.H.J., J.J., M.K., M.W.K., J.P., P.P., and S.N.M. contributed to the study design. As study investigators, K.K., K.H., S.B.H., H.H., K.I., J.H.K., S.K.L., S.P., H.X., and T.Y. 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

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

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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

The authors confirm that they 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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