Seizure: European Journal of Epilepsy 133 (2025) 43–51

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Efficacy of adjunctive cenobamate by focal seizure subtypes: a randomized, double-blind, placebo-controlled, multicenter study in a multinational Asian population

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ARTICLE INFO

Keywords:
Focal seizures
Seizure subtypes
Cenobamate
Focal aware motor
Focal impaired awareness
Focal to bilateral tonic-clonic

ABSTRACT

Objectives: To assess the efficacy of adjunctive cenobamate by seizure subtype in Asian patients with uncontrolled focal epilepsy during a 24-week controlled study (NCT04557085 [C035]).
Methods: Adults 18–70 years old with ≥8 focal seizures (focal aware motor [FAM], focal impaired awareness [FIA], and/or focal to bilateral tonic-clonic [FBTC]) during an 8-week baseline, despite treatment with 1–3 antiseizure medications, were randomized 1:1:1:1 to receive placebo or cenobamate 100, 200, or 400 mg/day, starting at 12.5 mg/day and uptitrated at 2-week intervals. The study design included an 18-week titration phase and a 6-week maintenance phase. Median percent change from baseline in 28-day seizure frequency and responder rates for patients with FAM, FIA, and/or FBTC seizures were assessed during the maintenance phase and during a 12-week treatment period that combined the last 6 weeks of titration and the 6-week maintenance phase.
Results: $N = 519$ patients were randomized (maintenance phase $n = 446$, 12-week period $n = 478$). During both periods assessed, numerically greater reductions vs placebo occurred across all cenobamate doses and seizure subtypes. For cenobamate 200 and 400 mg/day, maintenance-phase median seizure frequency reductions were 76 %-100 % across all seizure subtypes; seizure-free rates were up to 52.4 % (FAM), 57.5 % (FIA), and 75.0 % (FBTC). The most common cenobamate-related treatment-emergent adverse events (≥20 %) were dizziness and somnolence.
Conclusions: Cenobamate reduced all focal seizure subtypes in a generally dose-response manner in adult Asian patients, including maintenance-phase seizure frequency reductions of 76 %-100 %. Notably high seizure-free

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https://doi.org/10.1016/j.seizure.2025.09.021
Received 10 July 2025; Received in revised form 26 September 2025; Accepted 29 September 2025
Available online 29 September 2025

rates were observed for patients with FBTC seizures, an important contributor to morbidity/mortality in focal epilepsy patients.

1. Introduction

Epilepsy is a common neurologic condition worldwide that affects the quality of life, morbidity, and mortality of affected individuals [1]. A significant proportion of this burden is due to focal seizures, which affect up to 61 % of people with epilepsy [1–3]. Subtypes of focal seizures (including focal aware motor, focal impaired awareness, and focal to bilateral tonic-clonic [FBTC]) carry varying degrees of morbidity and mortality. Focal seizure classification should be based on appropriate diagnostic criteria, including ruling out epilepsy imitators (ie, movement disorders, parasomnias) [4]. Historically, seizures have been classified according to level of awareness (when known) and earliest observable feature at onset [4,5]. If awareness is impaired at any point during the seizure, the seizure is designated as a focal impaired awareness seizure. Both impaired awareness seizures and seizures with motor features impact day-to-day patient safety and independence, including productivity at work or school, and may also result in social stigmatization [6,7]. Among the seizure subtypes, FBTC seizures are associated with significant morbidity and mortality, including a higher rate of sudden unexpected death in epilepsy (SUDEP) [7,8]. Of note, recent updates to International League Against Epilepsy (ILAE) seizure classifications replace “awareness” with “consciousness,” which encompasses awareness and responsiveness, and recommend describing seizures according to the chronological sequence of seizure semiology rather than solely by the initial sign [9].

Cenobamate, an antiseizure medication (ASM) approved in the United States and multiple other countries for the treatment of focal seizures in adults [10–13], has shown notable efficacy in focal seizures in phase 2 studies [14,15]. During the initial efficacy studies of cenobamate, reductions in seizure frequency vs placebo were shown in focal aware motor, focal impaired awareness, and/or FBTC seizures once maintenance dosing was reached [14,15]. A post-hoc analysis of the phase 2 dose-ranging study showed 100 % responder rates during the maintenance phase in the 100-, 200-, and 400-mg dose groups of 23.8 %, 12.5 %, and 30.0 % of patients, respectively, for patients with focal aware motor seizures (vs 0 % for placebo; $n = 82$); 5.3 %, 16.1 %, and 25.6 % of patients, respectively, for focal impaired awareness seizures (vs 2.3 % for placebo; $n = 355$); and 29.4 %, 56.3 %, and 52.8 % of patients, respectively, for FBTC seizures (vs 25.6 % for placebo; $n = 145$) [15]. In addition to these phase 2 results, a post-hoc efficacy analysis [16] of a cenobamate phase 3 safety study [17] showed sustained seizure frequency reductions among focal aware motor, focal impaired awareness, and FBTC seizure subtypes, including a seizure-free rate of 35.4 % for patients with FBTC seizures during the maintenance phase ($n = 48$) [16].

During cenobamate’s early clinical development, the serious adverse event of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was identified [10]. In order to evaluate the effect of a lower starting dose and slower titration rate on the occurrence of DRESS syndrome, the phase 3 open-label safety study noted above (Sperling 2020) was conducted [17]. Cenobamate was initiated at 12.5 mg/day for 2 weeks, 25 mg/day for 2 weeks, and 50 mg/day for 2 weeks, followed by subsequent increases in 50-mg/day increments every 2 weeks. Among 1339 patients exposed to cenobamate over a median duration of 29.5 months, no cases of DRESS syndrome were identified [17]. This dosing regimen is now standard in all countries where cenobamate is approved [10–13]. Since becoming available in 2020, cenobamate has been used to treat >220,000 adult patients worldwide, with no confirmed cases of DRESS syndrome [18,19].

The pivotal trials discussed above were primarily conducted in the United States and Europe. Cenobamate’s efficacy and safety in Asian populations had not been investigated. Therefore, a recent phase 3, multicenter, randomized, placebo-controlled dose-ranging study of adjunctive cenobamate 100, 200, and 400 mg/day (YKP3089C035 [C035]) was conducted in adult Asian patients with focal seizures [20]. The 24-week study, consisting of an 18-week titration phase and a 6-week maintenance phase, was the first randomized, controlled efficacy study to use the currently approved cenobamate titration schedule (ie, starting dose at 12.5 mg/day and uptitrated at 2-week intervals). The primary analysis assessed reductions in 28-day focal seizure frequency for each cenobamate dose vs placebo in patients who reached the maintenance phase. Median percent 28-day seizure frequency reductions in each cenobamate dose group during the 6-week maintenance phase (primary outcome) were 25.9 % for placebo vs 42.6 %, 78.3 %, and 100 % for cenobamate 100, 200, and 400 mg, respectively ($P < 0.001$ each vs placebo) [20]. Similar results were found for a secondary analysis of patients treated during a 12-week treatment period (last 6 weeks of titration phase plus 6-week maintenance phase). For this report we analyzed seizure frequency reduction and responder rates for focal aware motor, focal impaired awareness, and FBTC seizure subtypes by cenobamate dose during these two time periods of the study [20].

2. Methods

2.1. Study design and patients

Study C035 was a multicenter, randomized, placebo-controlled study (ClinicalTrials.gov NCT04557085) conducted at 70 sites in China, the Republic of Korea, and Japan. The 24-week study included an 18-week titration phase and a 6-week maintenance phase [20]. It was the first randomized efficacy study in focal epilepsy to use the currently approved cenobamate titration schedule (initiated at 12.5 mg/day and titrated at biweekly intervals). The study included adults 18–70 years old with a diagnosis of focal (partial-onset) seizures according to the ILAE’s 1981 Classification of Epileptic Seizures [21], with diagnosis confirmed by the Epilepsy Study Consortium. Patients were required to have ≥8 focal seizures (focal aware motor, focal impaired awareness, and/or FBTC seizures) during the 8-week baseline period despite receiving stable doses of 1–3 concomitant ASMs.

Patients with only focal non-motor seizures or primary generalized epilepsies, a history of Lennox-Gastaut syndrome, or use of phenytoin or phenobarbital were excluded. Vagus nerve stimulation (VNS) or deep brain stimulation (DBS) were permitted and did not count as an ASM. VNS/DBS 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 given orally in tablet form once daily. Randomization was carried out by the study investigator or designee at each site and was stratified by country. Patients, investigators, and study personnel were all masked to the randomized treatment assignment. To ensure adequate masking, study medications and packaging were visually identical. During the titration phase, patients received an initial dose of either 12.5 mg/day cenobamate or matching placebo. The dose of cenobamate was then increased at 2-week intervals to 25 mg/day and then 50 mg/day (or matching placebo) (Fig. 1). Thereafter, the cenobamate dose was titrated by 50 mg/day every 2 weeks to the target dose. After the first 6 weeks of titration, one 50-mg/day cenobamate dose adjustment was permitted for tolerability; the dose was increased

to the previous dose at the next visit. After 18 weeks, patients entered the maintenance phase, where they maintained their dose (100 mg/day, 200 mg/day, 400 mg/day, or placebo) for 6 weeks. Dose adjustments were not permitted during the maintenance phase. No changes to concomitant ASM total daily doses or dosing frequency were allowed during the entire double-blind treatment period.

The study was conducted in accordance with the International Council for Harmonisation's Guideline for Good Clinical Practice [22], 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. Outcomes

For this analysis, changes from baseline in 28-day seizure frequency and responder rates (≥50 %, ≥75 %, ≥90 %, and 100 % reduction from baseline) vs placebo among patients with focal aware motor, focal impaired awareness, or FBTC seizures were assessed 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. Based on these factors, it was determined that a 6-week maintenance phase (24-week double-blind treatment period) would be sufficient to initially demonstrate efficacy. To compensate for the relatively short maintenance phase, a prespecified analysis of the final 12 weeks of the double-blind treatment period (encompassing the last 6 weeks of titration plus the 6-week maintenance phase; see Fig. 1) was performed as a secondary efficacy endpoint. During the 12-week treatment period, patients randomized to cenobamate 100 and 200 mg/day received their respective dose for the entire 12 weeks, while patients randomized to cenobamate 400 mg/day received 250 mg/day for 2 weeks, 300 mg/day for 2 weeks, 350 mg/day for 2 weeks, and then 400 mg/day for 6 weeks.

2.3. Statistical analyses

The safety population included all randomized patients who received at least one dose of the study drug during the double-blind treatment period. 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 evaluation during the double-blind treatment period. The primary analysis of the study was the median percent change in 28-day focal seizure frequency in the MITT maintenance (MITT-M) population, which included all patients from the MITT population with ≥1 dose of study drug and ≥1 efficacy evaluation during the 6-week maintenance phase. A secondary efficacy analysis was performed in the 12-week treatment period population (MITT 12-week population), which included patients from the MITT population who had at least 1 efficacy evaluation during the 12-week treatment period. For inclusion in the focal aware motor, focal impaired awareness, and/or FBTC subtype analysis populations, patients must have experienced at least one of the seizure types during the 8-week baseline period. Patients may have had more than one seizure subtype and therefore could be included in more than one seizure subtype category. Seizure frequency for each seizure subtype during the baseline and treatment phase was 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. Median percent change in 28-day seizure frequency from baseline 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. For the analysis reported here, the same model was applied to outcomes by seizure subtypes. Responder rates were analyzed using the Cochran-Mantel-Haenszel test, unless otherwise specified. Safety data were analyzed descriptively. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.1 or higher).

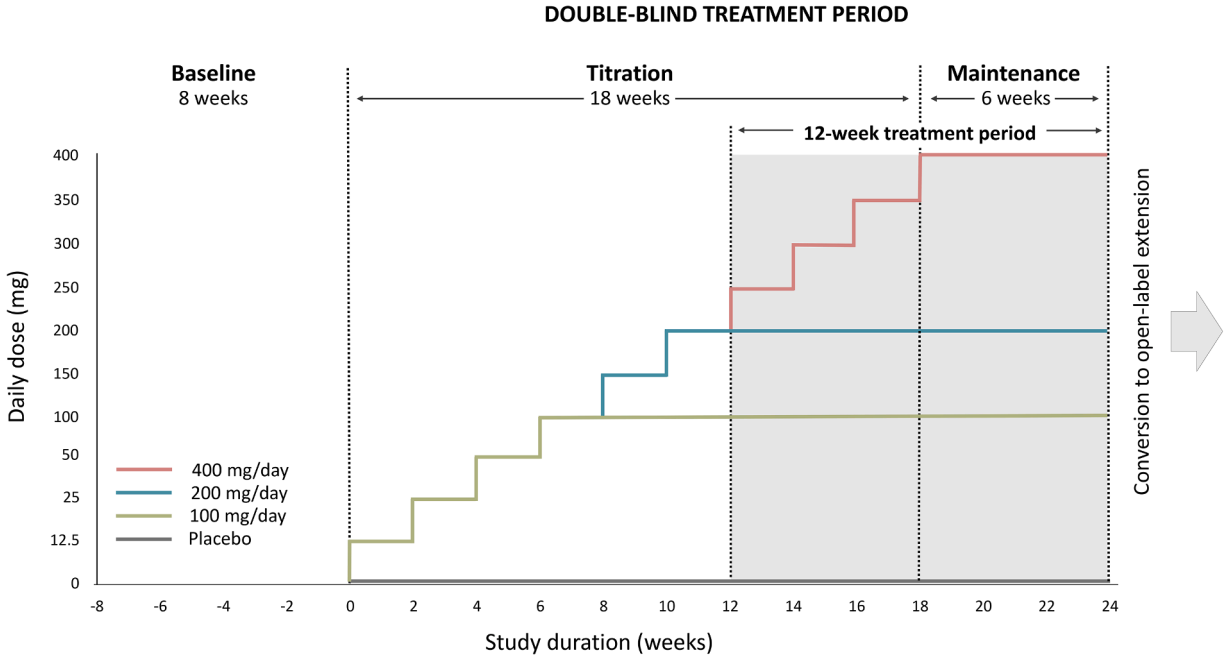

Fig. 1. Study design.
The 12-week treatment period combined the last 6 weeks of the titration phase and the 6-week maintenance phase. Reprinted from Lee SK, et al. Epilepsia 2025 (in press). Used with permission.

3. Results

3.1. Patient disposition

The main C035 study was conducted from April 27, 2021, to February 16, 2024. Among 519 patients 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 population (Fig. 2). At baseline, 79 (17.7 %), 375 (84.1 %), and 115 (25.8 %) patients in the MITT-M population had focal aware motor, focal impaired awareness, and/or FBTC seizures, respectively (Fig. 2, Table 1). The MITT 12-week population included 478 patients: 85 (17.8 %), 402 (84.1 %), and 120 (25.1 %) had focal aware motor, focal impaired awareness, and/or FBTC seizures at baseline, respectively; patients could have been included in more than one seizure subtype category. Most patients (63.2 % [326/516]) were taking 3 concomitant ASMs at the start of cenobamate therapy. The most frequently used concomitant ASMs (>20 % in the safety population) included levetiracetam (47.5 % [245/516]), valproate/valproic acid (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]).

3.2. Efficacy

3.2.1. Outcomes during the 6-week maintenance phase

During the 6-week maintenance phase, median percent reductions in 28-day seizure frequency were numerically greater than placebo in all cenobamate treatment groups for all seizure subtypes (focal aware motor, focal impaired awareness, and FBTC) (Fig. 3). Statistically significant median percent reductions in 28-day seizure frequency vs placebo were observed for the focal aware motor subtype at cenobamate 200- and 400-mg/day doses (placebo: 26.1 % reduction; cenobamate 200 mg/day: 100 % reduction, $P < 0.001$; cenobamate 400 mg/day: 95.4 % reduction, $P < 0.001$). In the focal impaired awareness group, maximum median percent reductions were observed in the cenobamate 400-mg/day group, followed by the cenobamate 200- and 100-mg/day groups (42.6 %, 76.0 %, and 100.0 % for cenobamate 100, 200, and 400

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 (years) at screening, mean (SD)	34.3 (11.1)	36.8 (12.6)	35.5 (11.3)	34.5 (10.7)
Female, n (%)	57 (48.7)	43 (38.1)	53 (46.9)	51 (49.5)
BMI (kg/m^2), mean (SD)	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 (all subtypes), 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)
Baseline 28-day seizure frequency by seizure subtype, median (min, max)				
FAM (n = 79)[a]	12.2 (0.5, 392.0)	13.5 (3.5, 617.5)	11.0 (1.5, 328.0)	37.5 (4.1, 616.5)
FIA (n = 375)[a]	10.0 (1.0, 1024.0)	7.3 (0.5, 158.0)	8.5 (0.5, 241.0)	9.4 (0.5, 163.5)
FBTC (n = 115)[a]	2.0 (0.5, 112.5)	3.6 (0.5, 43.5)	4.0 (0.5, 80.5)	3.8 (0.5, 44.0)

[a] Patients may have had been included in more than one seizure subtype category.

BMI, body mass index; FAM, focal aware motor; FBTC, focal to bilateral tonic-clonic; FIA, focal impaired awareness; MITT-M, modified intent-to-treat maintenance population; SD, standard deviation.

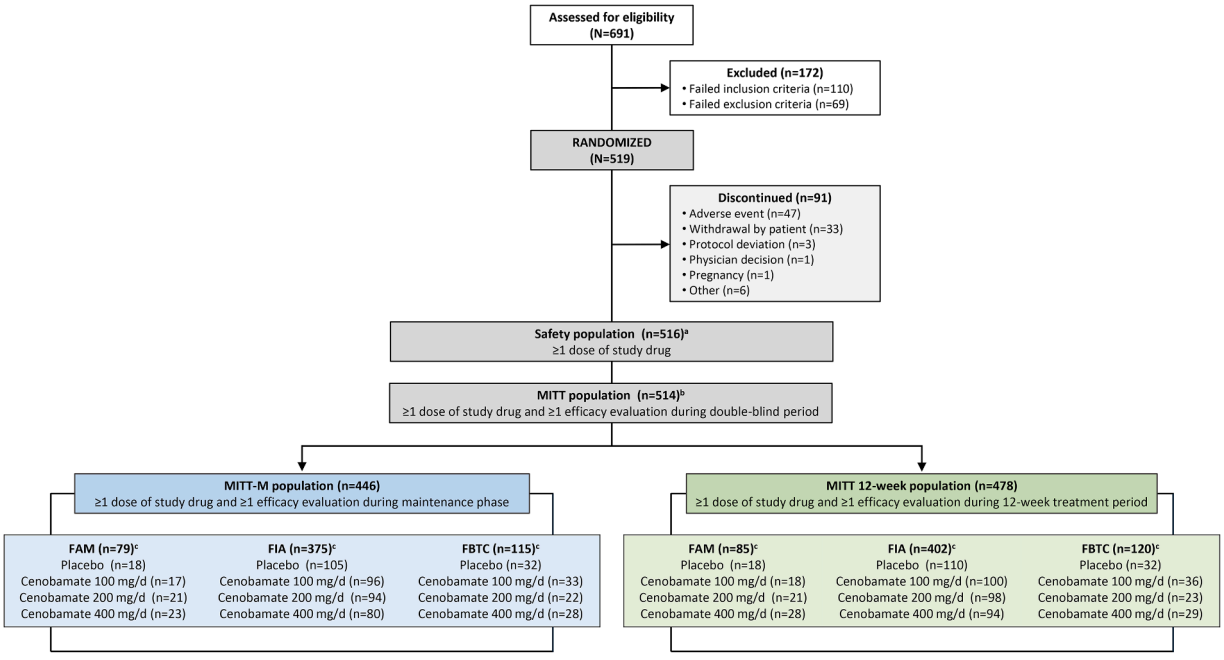

Fig. 2. Patient disposition.
[a]Three subjects were randomized to treatment but did not receive any dose of study drug.
[b]Two patients received study drug but had no efficacy evaluations.
[c]Patients may have had been included in more than one seizure subtype category.
FAM, focal aware motor; FBTC, focal to bilateral tonic-clonic; FIA, focal impaired awareness; MITT 12-week, modified intent-to-treat 12-week; MITT-M, modified intent-to-treat maintenance.

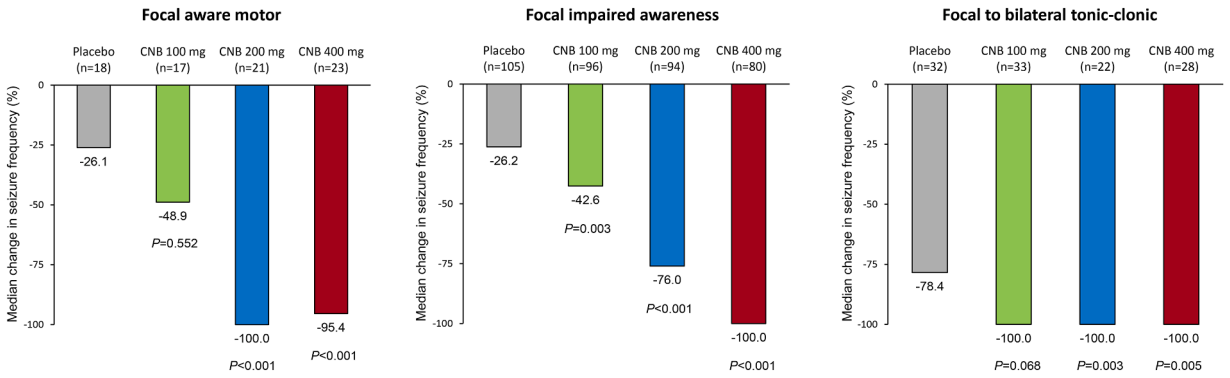

Fig. 3. Median change in 28-day focal seizure frequency during the 6-week maintenance phase by seizure subtype (MITT-M population, n = 446).
Patients may have had been included in more than one seizure subtype category.
CNB, cenobamate; MITT-M, modified intent-to-treat maintenance.

mg/day, respectively, vs 26.2 % for placebo; $P = 0.003$, $P < 0.001$, $P < 0.001$, respectively). For the FBTC group, median percent reductions of 100 % were observed across all cenobamate dose groups (vs 78.4 % placebo; $P = 0.003$, $P = 0.005$ vs placebo, respectively, for cenobamate 200 and 400 mg/day).

Responder rates of ≥50 %, ≥75 %, ≥90 %, and 100 % were observed in all cenobamate groups during the maintenance phase (Fig. 4). In the focal aware motor subtype, all responder rates were statistically significant vs placebo at cenobamate 200 mg/day, and ≥50 %, ≥75 %, and ≥90 % responder rates were statistically significant vs placebo in the cenobamate 400-mg/day dose group. In the focal impaired awareness group, all responder rates were statistically significant vs placebo at all cenobamate doses. For the FBTC group, statistically significant ≥75 %, ≥90 %, and 100 % responder rates occurred in the cenobamate 200- and 400-mg/day dose groups. Maintenance-phase seizure-free rates for patients with FBTC seizures were 72.7 % for cenobamate 200 mg/day and 75.0 % for cenobamate 400 mg/day (vs 43.8 % for placebo, $P < 0.05$ for both comparisons).

3.2.2. *Outcomes during the 12-week treatment period*

During the 12-week treatment period, median 28-day seizure frequency reductions were observed in all seizure subtypes (**Suppl. Fig. S1**). For the focal aware motor subtype, 12-week median seizure frequency reductions were consistent with those observed in the maintenance phase, with statistically significant reductions vs placebo occurring at cenobamate 200- and 400-mg/day doses. For the focal impaired awareness subtype, statistically significant seizure frequency reductions occurred at all cenobamate doses during the 12-week treatment period. Consistent with the maintenance-phase results, the greatest reductions in median seizure frequency occurred in the FBTC group, with a 91.7 % reduction for cenobamate 100 mg/day (not significant [NS] vs placebo) and 100 % reduction for cenobamate 200 mg/day and 400 mg/day, vs 66.7 % for placebo, $P < 0.05$ for both.

During the 12-week treatment period, responder rate analyses were similar to those observed during the maintenance phase (**Suppl. Fig. S2**). For the focal aware motor subtype, statistically significant ≥50 % and ≥75 % 12-week responder rates vs placebo were observed in cenobamate 200-mg/day dose group, and the ≥75 % responder rate was statistically significant vs placebo for the cenobamate 400 mg /day group. In the focal impaired awareness subgroup, 12-week responder rates were statistically significant vs placebo at all cenobamate doses and for all responder rates. In the FBTC group, statistically significant ≥90 % responder rates vs placebo occurred at cenobamate 100 mg/day, and all responder rates (≥50 %–100 %) were statistically significant vs placebo for cenobamate 200- and 400 mg/day, except the ≥50 % responder rate at 400 mg/day (see **Fig. S2**). In the FBTC group, 12-week seizure-free rates were 47.2 %, 65.2 %, and 65.5 % for cenobamate 100, 200, and 400 mg/day, respectively (vs 25.0 % for placebo, *P*=NS for 100 mg/day; $P < 0.05$ for 200 and 400 mg/day).

3.3. *Safety (24-week double-blind treatment period)*

In the placebo group, treatment emergent adverse events (TEAEs) were reported in 86/130 patients (66.2 %), while in the cenobamate groups, TEAEs were reported in 101/128 (78.9 %) patients in the 100-mg/day group, 111/130 (85.4 %) in the 200-mg/day group, and 123/128 (96.1 %) in the 400-mg/day group (Table 2). The most frequently reported TEAEs (>10 % of patients in any cenobamate treatment group) were dizziness, somnolence, gamma-glutamyl transferase (GGT) increased, diplopia, vomiting, headache, ataxia, COVID-19 infection, and nausea. Among patients receiving cenobamate, dizziness (21.9 %–70.3 % of patients) and somnolence (22.7 %–46.9 % of patients) were the most commonly reported TEAEs. In the safety population ($n = 516$), a higher proportion of patients in the cenobamate 400-mg/day group

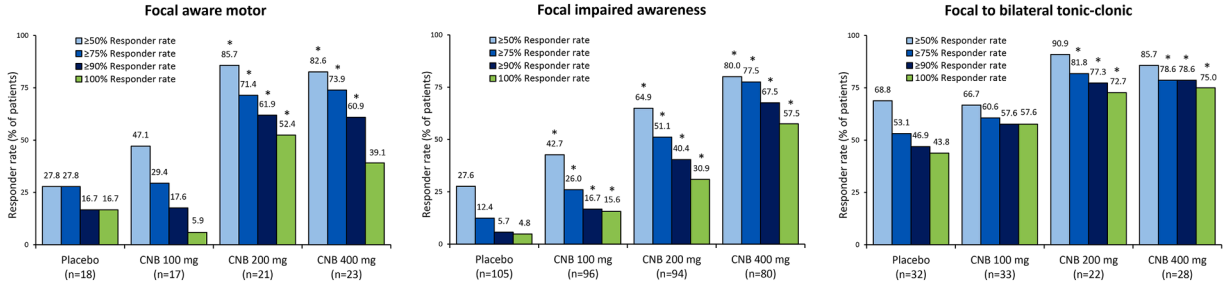

Fig. 4. Responder rates during the 6-week maintenance phase by seizure subtype (MITT-M population, n = 446).
Patients may have had been included in more than one seizure subtype category.
*P < 0.05 vs placebo.
CNB, cenobamate; MITT-M, modified intent-to-treat maintenance.

Table 2
Summary of adverse events during double-blind study, safety population (n = 516).

Event	Placebo (n = 130)	Cenobamate		
		100 mg/day (n = 128)	200 mg/day (n = 130)	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 (0.8)	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 (0.8)	5 (3.9)	4 (3.1)	7 (5.5)
Vision blurred	1 (0.8)	3 (2.3)	3 (2.3)	7 (5.5)
Muscular weakness	1 (0.8)	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)

Abbreviations: GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event.
Data are given as n (%). Safety population included all randomized patients who received ≥1 dose of study drug. Reprinted from Lee SK, et al. Epilepsia 2025 (in press). Used with permission.

(21.9 % [28/128]) reported TEAEs leading to drug withdrawal/study discontinuation vs those 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. In the placebo group the most frequently reported TEAEs were dizziness, somnolence, and COVID-19 infection. Treatment-related adverse events occurred in 53.9 % (69/128), 72.3 % (94/130), and 90.6 % (116/128) of patients in the cenobamate 100, 200, and 400 mg/day dose groups respectively, vs 39.2 % (51/130) for placebo. Most TEAEs were mild or moderate in severity.

Cutaneous adverse events are of interest in Asian populations, who may have a higher incidence of idiosyncratic cutaneous reactions compared with other populations [23]. No serious or severe cutaneous TEAEs were reported during the double-blind study. Rash was reported as a TEAE by 1.5 % (8/519) 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. In the cenobamate dose groups, all cases of rash were mild in severity. In the placebo group, one case of rash was of moderate severity. Study discontinuations due to rash were reported for 1 patient (0.8 %) in the cenobamate 100-mg/day dose group and 2 patients (1.5 %) in the placebo group. Two patients (1.5 %) in the placebo group reported drug eruption, which was mild and did not result in study discontinuation. Pruritus was reported by 1 patient (0.8 %) in the placebo group, 2 patients (1.6 %) in the cenobamate 100-mg/day group, 3 patients (2.3 %) in the cenobamate 200-mg/day group, and 1 patient (0.8 %) in the cenobamate 400-mg/day group. All cases were mild, and no study discontinuations occurred due to pruritus.

There were no deaths, and no cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome were reported [20]. No clinically meaningful changes from baseline were observed for vital signs or physical or neurologic examinations.

4. Discussion

Study C035 is the first randomized, controlled efficacy study to use the currently approved cenobamate biweekly titration schedule starting at 12.5 mg/day. In this study, seizure frequency reductions and responder rates were generally dose-related, and occurred in all cenobamate groups vs placebo with a similar magnitude of effect across focal aware motor, focal impaired awareness, and FBTC seizure subtypes during both the maintenance phase and the 12-week treatment period. Comparisons of ASM efficacy across clinical trials are limited by differences in study populations and design, and many pivotal studies are not powered to detect treatment effects based on seizure subtype, but consistent reductions across focal seizure subtypes, particularly focal aware motor seizures, have not been observed in studies of other widely used ASMs, including newer sodium channel agents [24–26]. The consistent efficacy observed across focal seizure subtypes with cenobamate may be related to the combined effects of its dual mechanism of action, which involves preferential inhibition of the persistent sodium current relative to the transient sodium current and positive allosteric modulation of gamma-aminobutyric acid type A ($GABA_A$) receptor-mediated tonic currents [27,28].

The results for focal aware motor and FBTC seizure subtypes are notable because focal aware motor seizures are traditionally difficult to treat and tonic-clonic seizures are associated with higher morbidity and mortality (including SUDEP) among patients with focal epilepsy [7,8]. Seizure-free rates for FBTC seizures of 65.2 %−75.0 % were observed during the 6-week maintenance phase and the 12-week treatment period at doses of 200 and 400 mg/day. For focal aware motor and focal impaired awareness seizures, maintenance-phase median seizure frequency reductions were generally similar between the cenobamate 200- and 400-mg/day groups (95.4 %−100 % for focal aware motor and 76.0 %−100 % for focal impaired awareness) and were higher compared with the cenobamate 100 mg/day group (48.9 % and 42.6 % for focal aware motor and focal impaired awareness respectively).

These results are generally comparable with seizure subtype responses observed during previous cenobamate phase 2 studies, which used higher starting doses (50 mg/day) and faster titration rates (weekly to every other week) than the currently approved schedule used in this study [14,15]. For example, during the phase 2 dose-ranging study, the highest maintenance-phase seizure frequency reductions occurred in the FBTC subtype (92.0 % and 83.0 %, respectively, for cenobamate doses of 200 and 400 mg/day [vs 51.0 % for cenobamate 100 mg/day and 33.0 % for placebo]) [15]. For the focal aware motor and focal impaired awareness seizure subtypes, seizure frequency reductions for the cenobamate 200- and 400-mg/day dose groups were generally similar and were higher vs the 100-mg/day group (focal aware motor seizure frequency reductions: 62.0 % and 69.0 % for cenobamate 200- and 400-mg/day dose groups vs 49.0 % for cenobamate 100 mg/day and 11.0 % increase for placebo; focal impaired awareness seizure reductions were 55.0 % and 61.5 % for the cenobamate 200- and 400-mg/day dose groups respectively vs 32.0 % for cenobamate 100 mg/day and 29.0 % for placebo) [15]. A post-hoc analysis of a phase 3 safety study, which used the current biweekly cenobamate titration schedule, also demonstrated substantial dose-related reductions to focal aware motor (47.8 % (11/23) 100 % seizure reduction Months 25–27), focal impaired awareness, and FBTC seizures, with the highest and earliest reductions occurring in the FBTC group [16,29].

Higher rates of dizziness and somnolence were reported in the 200- and 400-mg/day cenobamate groups compared to the previous randomized clinical studies [14,15]. This may have resulted from differences in the study design, which included a longer study duration (24 weeks vs 12 and 18 weeks), multiple dose transitions, and restricted dose adjustments of cenobamate and concomitant ASMs. Compared with the previous phase 2 studies [14,15], the Asian patient population

in this study was similar in terms of baseline demographics, including age, sex, baseline seizure frequency, and general distribution of seizure subtypes. In contrast to previous clinical studies, a higher proportion of patients in this study were taking three concomitant ASMs (65 % of patients randomized to cenobamate in Study C035 taking 3 concomitant ASMs vs 36.3 % and 24.9 % in Studies C013 and C017 respectively)[14,15]. Also, a lower body mass index (BMI) was observed compared to the previous cenobamate clinical study populations (23.1–23.8 kg/m^2 for cenobamate-treated patients in Study C035 vs 25.6–26.1 kg/m^2 for those treated with cenobamate in the previous randomized, double-blind studies [15,17]). This may also have contributed to the higher frequency of adverse events. In clinical practice, slowing the cenobamate titration rate and/or reducing concomitant ASM doses is recommended to mitigate dizziness or sedation [17,30–32]. Frequent elevations in GGT were noted during adjunctive cenobamate treatment. 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 [33]. Across cenobamate groups, the incidence of alanine aminotransferase (ALT) elevations >3 × ULN (~0.8 %) was comparable to placebo.

GGT levels were not examined in previous clinical cenobamate clinical studies. In this study, the presence of GGT elevation usually occurred without accompanying aspartate aminotransferase (AST)/ALT level increases. This suggests that elevations resulted from hepatic enzyme induction, akin to GGT increases observed with other enzyme-inducing ASMs, such as carbamazepine, valproate, phenytoin, and phenobarbital [33–37]. In addition, COVID-19 infection, which has been associated with transient elevations in liver enzymes [38–40], occurred in 30 patients in the three cenobamate dose groups. GGT is a sensitive but nonspecific liver function test and therefore it can be difficult to distinguish between viral and drug-induced GGT effects [41], although it is likely that GGT elevations with cenobamate are similar to those observed with other enzyme-inducing ASMs.

Limitations of this analysis include lack of balance in the number of patients in each seizure subtype group, the small number of patients in some of those subtype groups, and variability in baseline seizure frequency across seizure types. The low baseline frequency of FBTC seizures in the placebo group, for example (2 seizures/28 days), combined with the natural variability of epilepsy [42], may have contributed to the higher-than-expected placebo response rates observed in the FBTC subgroup. In addition, although the 24-week treatment duration was adequate for a randomized, placebo-controlled study, the 6-week maintenance duration may be considered a limitation to this study.

With any short-term trial, data may be biased by the "honeymoon effect," meaning that temporary response to an ASM can be followed by resistance with prolonged use. In the case of cenobamate, the strong efficacy and retention rates observed during the phase 2 and longer-term open-label studies [14,15,43] suggest that the honeymoon effect is not a significant issue. During the present study a secondary endpoint, efficacy during a 12-week treatment period combining the last 6 weeks of the titration phase and the 6-week maintenance, was evaluated as a comparator with results from the 6-week maintenance phase. Similar benefits to 28-day median seizure frequency reductions were observed for the maintenance phase and 12-week treatment period when assessed by focal seizure subtype. In general, FBTC seizure-free rates are not consistently reported in randomized clinical trials of ASMs, and comparisons of ASMs across studies with differing methodologies and patient populations should be undertaken with caution. Nonetheless, the FBTC seizure-free rates observed with cenobamate compare favorably with previously published individual and pooled clinical studies of other third-generation ASMs [15,24,44–48]. Results from 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

In this study of adjunctive cenobamate 100, 200, and 400 mg/day for the treatment of focal seizures in Asian patients, maintenance doses of cenobamate were associated with clinically significant seizure reductions across all assessed seizure subtypes (focal aware motor, focal impaired awareness, and FBTC) compared with placebo. These effects were observed at all doses. Seizure frequency reductions for focal aware motor and focal impaired awareness seizure subtypes occurred in an overall dose-related manner, and FBTC seizure frequency reductions were 100 % across all cenobamate doses. Cenobamate was generally well-tolerated, and the results were in line with existing data related to cenobamate's efficacy in focal aware motor, focal impaired awareness, and FBTC seizure subtypes. Given that FBTC seizures have a higher incidence of morbidity and mortality, the response rates observed here with cenobamate for FBTC seizures were notable.

Acknowledgments

This study was funded by SK Biopharmaceuticals Co., Ltd. and SK Life Science, Inc. Medical writing and medical editing assistance were provided by June Stevens, PharmD, and Don Fallon, ELS, of MedVal Scientific Information Servies, LLC (Princeton, NJ, USA), and were funded by SK Life Science, Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals' Good Publication Practice (GPP) guidelines for company-sponsored biomedical research: 2022 update [DeTora LM, et al. Ann Intern Med. 2022;175 (9):1298–1304].

CRediT authorship contribution statement

EC, YHJ, JJ, MK, MWK, SNM, JP, and LF contributed to the study design. As study investigators, XW, LC, KH, SBH, KI, KK, JHK, SKL, TW, TY, and PY provided patient data. All authors interpreted the results, contributed to the writing, and reviewed the manuscript. All authors reviewed and approved the final draft of the manuscript.

Data availability

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.

Role of funding source

This study was funded by SK Biopharmaceuticals Co., Ltd. and SK Life Science, Inc., which provided study drug and placebo. SK Biopharmaceuticals Co., Ltd., and/or SK Life Science, Inc., designed the study, provided financial support to the investigators' institutions for patient data collection, performed the data analysis, compiled the study report, and funded publication costs. The investigators had full control over data collection, interpretation of the results, drafting/revision of the manuscript, and the decision to publish.

Study registry

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

Previous presentations

Ferrari L, et al. Efficacy of adjunctive cenobamate by focal seizure subtypes: a randomized, double-blind, placebo-controlled, multicenter study in a multinational Asian population. Presented at the American

Epilepsy Society Annual Meeting, December 6–10, 2024 (Poster 1.405) and encored at the American Academy of Neurology Annual Meeting, April 5–9, 2025 (Poster P80.006).

Declaration of competing interests

XW: Nothing to disclose.
LC: Nothing to disclose.
EC, YHJ, JJ, MWK, JP: Employees, SK Biopharmaceuticals Co., Ltd.
KH: Nothing to disclose.
SBH: Nothing to disclose.
KI: Consultant/advisor: Eisai; Speaker: Daiichi-Sankyo, Eisai, UCB Japan; Research funding: Ricoh, UCB Japan, Zimmer Biomet.
MK, SNM, LF: Employees, SK Life Science, Inc.
KK: Consultant/advisor: EP Medical, UCB Japan, Zimmer Biomet; Speaker: Daiichi-Sankyo, Eisai.
JHK: Nothing to disclose.
SKL: Nothing to disclose.
WER: Consultant/advisor: SK Life Science, Inc.; Speaker: SK Life Science, Inc.; Research support: SK Life Science, Inc., UCB Pharma.
TW: Nothing to disclose.
TY: Consultant/advisor: Eisai, UCB Japan; Speaker: Daiichi-Sankyo, Eisai, LivaNova Japan, UCB Japan, Zimmer Biomet.
PY: Nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2025.09.021.

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