Efficacy and safety of adjunctive cenobamate: Post-hoc analysis of study C017 in patients grouped by mechanism of action of concomitant antiseizure medications

Christian Brandt, Juan Carlos Sánchez-Álvarez, Bernhard J. Steinhoff, Ivan Milanov, Jose M. Serratosa

ABSTRACT

Purpose: To assess how efficacy and safety outcomes were affected when cenobamate was co-administered with antiseizure medications (ASMs) that use either sodium channel blocker (SCB) or non-sodium channel blocker (non-SCB) mechanisms of action (MoAs) in patients with uncontrolled focal seizures.

Methods: An exploratory post-hoc analysis of a randomized, double-blind, placebo-controlled clinical study (YKP3089C017) was conducted. Baseline concomitant ASMs were grouped as either those that employed an SCB or non-SCB MoA. Efficacy was examined by cenobamate dose (100 mg, 200 mg, and 400 mg/day) and concomitant ASM group using responder rates (≥50%, ≥75%, ≥90% seizure reduction; 100% seizure reduction/seizure freedom) during the maintenance phase and median percentage seizure reduction during the double-blind period. Treatment-emergent adverse events (TEAEs) were examined in the double-blind period.

Results: When co-administered with SCBs or non-SCBs, significantly higher percentages of patients achieved ≥50%, ≥75%, and ≥90% responder rates with cenobamate 200 mg/day and/or 400 mg/day versus placebo. Additionally, significantly higher percentages of patients achieved seizure freedom with cenobamate 400 mg/day versus placebo (SCB group, 17.5% versus 1.2%; non-SCB group, 40.0% versus 0.0%). Patients receiving 200 mg/day and 400 mg/day and concomitant SCBs and all patients taking cenobamate combined with non-SCB concomitant ASMs had significantly greater median percentage reductions in focal seizure frequency versus placebo. TEAEs were similar across groups; however, dizziness was more frequently reported in the SCB group.

Conclusion: Cenobamate is a highly effective new treatment option for patients with uncontrolled focal seizures when co-administered with SCB or non-SCB ASMs.

1. Introduction

Cenobamate is a new antiseizure medication (ASM) indicated for the treatment of focal onset (partial-onset) seizures in adults [1]. The summary of product characteristics for Europe specifies the use of cenobamate as adjunctive treatment for focal onset seizures in adults whose epilepsy has not been adequately controlled with at least two ASMs [2]. The efficacy and safety of cenobamate were demonstrated in two double-blind, randomized, placebo-controlled, phase 2 clinical studies (NCT01397968; NCT01866111) in patients with uncontrolled focal seizures who were taking one to three concomitant ASMs [3,4]. In the 12-week (6-week titration plus 6-week maintenance phase) study (YKP3089C013), patients were treated with adjunctive cenobamate 200 mg/day or placebo. In the 18-week (6-week titration plus 12-week maintenance phase) study (YKP3089C017), patients were treated with 100, 200, or 400 mg/day adjunctive cenobamate or placebo. Both clinical studies resulted in significantly greater reductions in seizure frequency, greater percentages of patients achieving responder rates of...
ASM improves the percentage of patients achieving 1-year seizure freedom after two ASMs, and the addition of a third or fourth ASM treatment may result in pharmacodynamic synergism, shown as an increase in efficacy, or more adverse events (AEs), through increased toxicity [6, 7].

Cenobamate is an oral tetrazole carbamate derivative that is distinct from other carbamate-containing ASMs [8]. At clinically relevant concentrations, cenobamate acts both as a positive allosteric modulator of GABA_A receptors and as a sodium channel blocker by preferentially blocking the persistent sodium current, suggesting that cenobamate has the potential to both prevent seizure initiation and limit seizure spread [9-13]. Cenobamate potentiates the chloride current by interacting at a different GABA_A receptor site than benzodiazepines [14, 15].

In the phase 2 clinical studies, cenobamate was combined with one or more concomitant ASMs with varying MoAs including sodium channel blocking agents (SCBs) and non-sodium channel blocking agents (non-SCBs). The current exploratory post-hoc analysis of Study YKP3089CO17 (C017) assessed how treatment with cenobamate, when co-administered with either SCB or non-SCB ASMs, affected efficacy and safety outcomes. Efficacy was examined using the responder rates in the 12-week maintenance phase of C017 and using the median percentage reduction in focal seizure frequency during the double-blind period. Safety was examined in the double-blind period.

2. Methods

2.1. Study design

Details of the multicenter, randomized, double-blind, placebo-controlled, parallel-group C017 study design have been previously published [4]. Briefly, patients had a diagnosis of focal epilepsy as defined by the International League Against Epilepsy [16, 17], epilepsy had to be uncontrolled despite treatment with at least one ASM within the past two years, and patients had to be taking phenytoin or phenobarbital, vigabatrin within the past two years, and patients had to be taking one to three ASMs at stable doses for at least 4 weeks prior to screening. Patients were adults 18 to 70 years old with ≥8 focal seizures during the 8-week baseline period (including ≥3 focal seizures per 4 weeks) before randomization and no consecutive 25-day seizure-free period. Key exclusion criteria were: taking phenytoin or phenobarbital, vigabatrin within the past two years, and patients had to be taking one to three ASMs at stable doses for at least 4 weeks prior to screening. Patients were adults 18 to 70 years old with ≥8 focal seizures during the 8-week baseline period (including ≥3 focal seizures per 4 weeks) before randomization and no consecutive 25-day seizure-free period. Key exclusion criteria were: taking phenytoin or phenobarbital, vigabatrin within the past year, or intermittent rescue benzodiazepines more than once a month within the past month; and history of status epilepticus.

The 18-week double-blind treatment period of Study C017 included a 6-week titration phase and a 12-week maintenance phase. Patients were randomized to cenobamate 100 mg/day, 200 mg/day, or 400 mg/day or placebo. The starting dose of cenobamate in the initial titration phase was 100 mg/day and was up-titrated weekly by 100 mg to the target dose. The titration protocol was amended to improve tolerability and the starting dose of cenobamate was lowered to 200 mg/day with a slowed titration rate increase of 50 mg/week up to the target dose of 200 mg/day, followed by 100 mg/week up to the target dose of 400 mg/day. Concomitant ASMs were to be continued unchanged during the double-blind period.

Study C017 was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, as well as any applicable country-specific regulations. The study protocol was approved by an independent ethics committee or institutional review board according to local regulations at each site. Written informed consent was obtained from each patient before study participation.

2.2. Concomitant ASMs

Baseline concomitant ASMs included medications that started prior to and were ongoing at the time of the first dose of cenobamate. The baseline concomitant ASMs were grouped by MoA into two groups: sodium channel blockers (lamotrigine, carbamazepine, oxcarbazepine, lacosamide, and eslicarbazepine acetate) and non-sodium channel blockers (benzodiazepines, GABA_A modulators, and levetiracetam). Most patients were receiving two to three ASMs of varying MoAs at baseline [4].

2.3. Efficacy outcome

Efficacy was examined using responder rates and median percentage change in focal seizure frequency. Responder rates were calculated as the percentage of patients achieving ≥50%, ≥75%, ≥90%, and 100% (seizure freedom) reduction from baseline in focal seizure frequency during the 12-week maintenance phase. The median percentage change from baseline in focal seizure frequency was averaged over 28 days in the 18-week double-blind treatment period.

2.4. Safety outcome

Safety outcomes included incidence of treatment-emergent adverse events (TEAEs) and study discontinuations due to TEAEs. TEAEs were defined as AEs with onset after the start of study medication or onset before study medication that worsened after medication was started, up to the last dose date of study medication plus 30 days. Adverse events were coded with the MedDRA Dictionary Version 20.0.

2.5. Data analysis

The post-hoc exploratory analysis of responder rates within each ASM MoA group used Fisher’s exact tests for treatment comparisons versus placebo. Responder rate analyses examined the modified intention-to-treat maintenance phase population, which included patients who completed the 6-week titration phase, took at least one dose of study drug in the maintenance phase, and had maintenance phase seizure data. The post-hoc exploratory analysis of percentage change in seizure frequency per 28 days within each ASM MoA group used ANCOVA models fit to the ranked values of baseline seizure rate and treatment group. The percentage change in seizure frequency analyses examined the modified intention-to-treat population, which included all randomly assigned patients who had taken at least one dose of study drug and had any post-baseline seizure data. Seizure frequency per 28 days was calculated by summing the number of seizures in each period (baseline, double-blind, maintenance periods), dividing by the total duration exposed (days), and multiplying by 28. Safety was assessed by the frequency of TEAEs during the double-blind period using the safety population that included all randomly assigned patients. An additional analysis was completed by applying the data analysis strategies to those patients who had failed ≥2 prior ASMs.

3. Results

3.1. Patient disposition

The percentage of patients who completed the double-blind period in the pooled-dose cenobamate and placebo groups was similar across the ASM MoAs of SCBs (80.8%; 87.8%), and non-SCBs (81.0%; 88.2%) (Table 1).

3.2. Patient characteristics

Demographic characteristics were generally similar among ASM MoA groups and pooled-dose cenobamate and placebo groups (Table 2).
Among patients assigned to placebo, 84.1% (90/107) of patients were taking concomitant SCBs; among patients assigned to placebo, 84.1% (90/107) of patients were taking concomitant SCBs.

### 3.3. Efficacy

#### 3.3.1. Cenobamate with sodium channel blockers

Among patients on concomitant SCBs in Study C017, patients receiving cenobamate 100 mg/day had numerically greater ≥50%, ≥75%, ≥90%, and 100% responder rates than those given placebo (Fig. 1). Significantly higher percentages of patients achieved ≥50% and ≥90% responder rates with cenobamate 200 mg/day and ≥50%, ≥75%, and ≥90% responder rates with cenobamate 400 mg/day versus placebo (Fig 1). Co-administration of cenobamate resulted in significantly greater seizure freedom rates than with placebo, with a 100% seizure reduction in 9.3% (P < 0.05) of patients taking cenobamate 200 mg/day and 17.5% (P < 0.001) of patients taking cenobamate 400 mg/day versus 1.2% of placebo patients.

The median percentage reduction from baseline in focal seizure frequency per 28 days during the double-blind treatment period in patients receiving concomitant SCB ASMs was numerically greater with cenobamate 100 mg/day (28.2%) and significantly greater with cenobamate 200 mg/day (52.2%, P < 0.001) and 400 mg/day (54.3%, P < 0.001) versus placebo (23.7%) (Fig 2).

#### 3.3.2. Cenobamate with non-sodium channel blockers

Fewer patients in the cenobamate treatment arms received concomitant ASMs that did not employ an SCB MoA (Table 3). A significantly greater percentage of patients receiving cenobamate in all dose groups combined with concomitant non-SCBs had a ≥50% reduction in seizures compared to those given placebo combined with concomitant non-SCBs (100 mg, P = 0.009; 200 mg, P = 0.001; 400 mg, P = 0.011) (Fig 1). Responder rates of ≥75% were observed in a significantly greater proportion of patients receiving cenobamate 200 mg (47.8%, P = 0.012) or 400 mg/day (60.0%, P = 0.002) combined with concomitant non-SCBs versus those given placebo and concomitant non-SCBs. In patients receiving 400 mg/day cenobamate with concomitant non-SCBs, a significantly greater percentage achieved ≥90% responder rates compared to those given placebo (46.7%, P = 0.015). Finally, in the group of patients taking concomitant non-SCBs, a significantly higher percentage of patients receiving cenobamate 400 mg/day achieved seizure freedom (100% seizure reduction) compared to placebo (40% versus 0%; P = 0.007).

### 3.4. Safety

The percentage of patients receiving cenobamate with at least one TEAE was dose-dependent across both ASM groups (Table 3). The highest frequency of TEAEs at the concomitant dose levels of 100 or 200 mg/day occurred in the concomitant SCB group: 65.6% at 100 mg/day, and 76.5% at 200 mg/day. In the non-SCB group, the highest frequency of TEAEs occurred at the 400 mg/day dose level, with 100.0% (18/18) of patients reporting at least one TEAE. The percentage of patients receiving placebo with at least one TEAE ranged from 72.2% in the concomitant SCB ASM group to 64.7% in the non-SCB group.

TEAEs primarily involved the central nervous system. TEAEs occurring in ≥10% of patients in both the SCB and non-SCB concomitant ASM groups were somnolence, dizziness, fatigue, headache, and diplopia (Fig. 3). The percentage of patients reporting an adverse event that led to study discontinuation in the concomitant combined with SCB group increased in a dose-dependent manner, similar to that observed in the total patient population (Table 3); however, the percentage of patients who discontinued due to TEAEs when receiving cenobamate 400 mg/day was higher in the non-SCB ASM group.

The TEAEs that led to study discontinuation in ≥2 patients occurred in those receiving cenobamate 400 mg/day with concomitant SCBs; these included vertigo (n = 2), dizziness (n = 4), somnolence (n = 3), ataxia (n = 3), and nystagmus (n = 2). TEAEs that led to study discontinuation in ≥2 patients also occurred within the concomitant SCB 200 mg/day group, including dizziness (n = 3) and ataxia (n = 3). Of those

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### Table 1: Patient disposition by MoA of concomitant ASMs and pooled cenobamate dose (double-blind period safety population).

|Reasons discontinued| Placebo | Cenobamate |
|---|---|---|
|Completed, n (%)| 90 (92.9%)| 74 (88.1%)|
|Discontinued, n (%)| 11 (11.2%)| 12 (14.2%)|
|Patients with ≥2 failed ASMs Committed, n (%)| 4 (4.4%)| 6 (7.1%)|
|Patients with ≥2 failed ASMs Discontinued, n (%)| 2 (2.2%)| 2 (2.4%)|

### Table 2: Baseline demographics by MoA of concomitant ASMs and pooled cenobamate dose (double-blind period safety population).

|Race, n (%)| Placebo | Cenobamate |
|---|---|---|
|White| 77 (85.6%)| 228 (84.1%)|
|Black| 8 (8.9%)| 28 (10.3%)|
|Other| 2 (2.2%)| 9 (3.3%)|
|Hispanic or Latino, n (%)| 9 (10.0%)| 24 (8.9%)|
|Number of ASMs, mean (SD)| 2.4 (0.7)| 2.4 (0.7)|
|Epilepsy diagnosis duration, years, mean (SD)| 23.6 (14.4)| 24.6 (13.0)|
|Baseline seizure frequency/28 days, median| 8.8| 10.0|
patients in the non-SCB group, TEAEs leading to study discontinuation occurred in 2 or more patients in all cenobamate treatment groups (100 mg, n = 2; 200 mg, n = 2; 400 mg, n = 5), compared to just 1 patient in the placebo group; the majority of these events were generally nervous system disorder-related. There were no TEAEs leading to discontinuation in two or more patients receiving placebo in either concomitant ASM group.

3.5. Efficacy and safety in patients who previously failed \( \geq 2 \) ASMs

An additional analysis was conducted to evaluate the response of patients who had failed \( \geq 2 \) prior ASMs. Demographics and the
percentage of patients who completed the double-blind period were similar to the entire study population (Supplementary Table 1). Of those taking concomitant SCBs and non-SCBs, the percentages of patients who achieved ≥50%, ≥75%, and ≥90% responder rates were higher in all cenobamate-treated groups compared to placebo (Supplementary Table 2). The median percentage reduction from baseline in focal seizure frequency in patients taking concomitant SCBs was numerically greater with 100 mg/day cenobamate compared to placebo and was significantly greater in the 200 mg and 400 mg groups. In those taking concomitant non-SCBs, the median percentage reduction in baseline focal seizure frequency was significantly greater in all cenobamate-treated groups versus placebo. TEAEs leading to study discontinuation that occurred in 2 or more patients were mostly observed in those who received cenobamate 400 mg/day, and central nervous system adverse events and dose-dependent responses were similar to those reported for the entire study population.

4. Discussion

Cenobamate was highly effective in patients with uncontrolled focal seizures in Study C017, resulting in marked reductions in focal seizure frequency when co-administered with SCB or non-SCB ASMs [4]. In this post-hoc analysis of Study C017, adjunctive cenobamate achieved generally dose-dependent improvements in ≥50%, ≥75%, and ≥90%, and 100% (seizure freedom) responder rates when combined with SCB or non-SCB ASMs. In particular, cenobamate showed consistent and high responder rates in patients receiving concomitant ASMs with an MoA that overlaps with cenobamate (e.g., SCBs). Concomitant administration of cenobamate with ASMs resulted in a significantly greater percentage of patients achieving seizure freedom than ASMs administered with placebo. This occurred regardless of the MoA group of concomitant ASM. Similar patterns of response by cenobamate dose and ASM MoA group were observed in the ≥50%, ≥75%, and ≥90% responder rate analyses. The median percentage reduction in focal seizure frequency from baseline was significantly greater compared to placebo (SCB group, cenobamate 200 and 400 mg/day; non-SCB group, all cenobamate doses).

TEAEs occurring in ≥10% of patients were similar across groups. Patient reports of somnolence, dizziness, and fatigue were higher across cenobamate dose levels. This suggests that this TEAE may be driven by pharmacodynamic interactions occurring between cenobamate and SCB drugs, an effect which has been previously reported. Patients in study C017 were not allowed to adjust the dose of concomitant ASMs during the rapid titration of cenobamate, likely exacerbating adverse events [4]. Among the non-SCBs, clonazepam (a benzodiazepine) was the most commonly used ASM [4]. Increases in TEAEs seen in the non-SCB ASM group might be due to reports from patients on clonazepam. This analysis supports a potential pharmacokinetic interaction that may lead to increased plasma concentrations of desmethylclonazepam (the active metabolite of clonazepam) and would support lowering the dose of clonazepam when used concomitantly with cenobamate to mitigate the increased rate of side effects [2].

Efficacy and safety outcomes of combined treatment with ASMs of similar or differing MoAs, with potential for positive (increased efficacy) or negative (increased toxicity with more AEs or reduced efficacy) effects, have previously been examined for lacosamide [18–23], eslicarbazepine acetate [24,25], perampanel [26], brivaracetam [27], and levetiracetam [28]. Post-hoc or retrospective analysis of clinical trials or clinical practice is commonly used among these studies, as well as overlap in concomitant ASM MoA and small patient groups. A key finding with lacosamide is improved tolerability and reduced discontinuation due to AEs with down-titration of concomitant SCBs [18,19,21–23]. Similarly with eslicarbazepine acetate, concomitant SCBs led to
increased risk of TEAEs and lower efficacy versus a non-SCB [24,25]. The presence of multiple concomitant ASMs, not specific to a particular ASM MoA, was associated with reduced efficacy for perampanel and levetiracetam [26,28].

Patients enrolled in study C017 were evaluated based on the International League Against Epilepsy (ILAE) Guidelines and by definition were considered to have medically intractable epilepsy. Here, in patients who had previously failed ≥2 ASMs, adjunctive cenobamate conferred generally dose-dependent improvements in ≥50%, ≥75%, and ≥90% responder rates, and increased percentages of patients achieving seizure freedom were also observed. In addition, the median percentage reduction in focal seizure frequency from baseline was numerically (cenobamate 100 mg/day) or significantly (cenobamate 200 and 400 mg/day) greater than placebo. Taken together, these analyses of

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**Fig. 3.** Most common TEAEs (≥10% of patients) for (A) total patients and for cenobamate combined with (B) sodium channel blockers and (C) non-sodium channel blockers (double-blind period safety population). Abbreviations: TEAE: treatment-emergent adverse event.
clobazam treatment demonstrated clinically effective responses in a
dose-dependent manner along with an acceptable tolerability profile,
suggesting that adjunctive clobazam may offer intractable patients
hope for seizure reduction or freedom.

In general, dose-dependent and high levels of clinical response were
seen in the analyses of clobazam by concomitant ASM regardless of
SCB or non-SCB MoA. Clinical response was observed in a dose-
dependent manner with statistically significant results reported for
clobazam 200 mg/day and 400 mg/day. TEAEs observed in both the
SCB and non-SCB ASM groups were also similar in type and frequency
to those for the total study population in Study C017. It is important to note
that long-term safety and tolerability of clobazam were shown in a
large, international, open-label safety study in patients with uncon-
trolled seizures who were receiving one to three concomitant ASMs
[29].

4.1. Limitations

Most patients in this study were receiving 2 to 3 concomitant ASMs at
baseline with the possibility of different MoAs across their ASM regimen.
As this is a post-hoc analysis, P-values were not controlled for multiple
comparisons and should be interpreted as exploratory. Alternatively, a
strength of these post-hoc exploratory analyses is the replication of ef-
ficacy in responder rates and median percentage reduction in focal sei-
zures and of safety findings in Study C017 across concomitant ASMs
with SCB or non-SCB MoAs.

Declaration of Competing Interest

The authors declare that they have no known competing financial
interests or personal relationships that could have appeared to influence
the work reported in this paper.

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Data Statement

Data are available to qualified researchers from the authors or
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Author Contributions

All authors had access to the study data, were involved in the deci-
sion to submit this article for publication, contributed to data interpre-
tation, reviewed the manuscript, and approved the final version for
submission.

Declaration of Interests Statement

CB, JCSA, BJS, IM, JMS: study conceptualization, data curation,
formal analysis, investigation, methodology, validation, writing – orig-
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Supplementary materials

Supplementary material associated with this article can be found, in
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