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Long-term cenobamate retention, efficacy, and safety: outcomes from Expanded Access Programme

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ABSTRACT

Aim of the study. To evaluate the long-term retention rate, efficacy, and tolerability of adjunctive cenobamate (CNB) in patients with drug-resistant epilepsy within the Polish Expanded Access Programme (EAP).

Clinical rationale for the study. Long-term retention rate is a useful measure of effectiveness including efficacy, safety, and tolerability of antiseizure medications.

Material and methods. We conducted a multicentre retrospective analysis of consecutive patients with focal epilepsy treated with CNB in the EAP between January 2020 and May 2023. All patients who completed the open-label extension phases of the YKP3089C013 and YKP3089C017 trials were offered the opportunity to continue CNB treatment within the EAP. We analysed cenobamate retention, seizure outcomes, and adverse events.

Results. 38 patients (18 females; 47.3%) continued CNB treatment within the Expanded Access Programme for 41 months. The mean baseline age of patients was 39.3 years (range: 18–57). All patients were on polytherapy, with the most commonly used antiseizure medications being valproate, levetiracetam, and carbamazepine. Adjunctive CNB treatment resulted in a reduced mean seizure frequency from 8.1 seizures (range: 4–20) per month to 3 seizures (range: 0–8) per month. At the final follow-up, the median CNB dose was 200 mg/day (range: 50–350). Among the patients, 24 (63.1%) achieved ≥ 50% seizure reduction, and eight (21%) remained seizure-free for at least 12 months. One in three patients experienced adverse events, which resolved in half of the subjects. The most frequent adverse events were dizziness, somnolence, and headache. The retention rate after completing the open-label extension phase was 100%.

Conclusions and clinical implications. Long-term effectiveness, including ≥ 50% seizure reduction and a 100% retention rate, was sustained over 41 months of CNB treatment within the Expanded Access Programme. No new safety issues were identified. These results provide support for the potential long-term clinical benefits of cenobamate.

Keywords: cenobamate, retention rate, efficacy, safety, adverse events

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Introduction

Epilepsy is one of the most prevalent and serious neurological conditions, afflicting 70 million people worldwide [1]. While antiseizure medications (ASMs) serve as the primary therapeutic area for most patients with epilepsy (PWE), a smaller fraction of patients benefit from alternative approaches such as epilepsy surgery, brain stimulation, and ketogenic diets.

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Despite the introduction of c.20 new antiseizure medications with varying mechanisms of action over the last three decades, a significant proportion — about 1/3 — of PWE do not achieve seizure freedom [2–5]. The challenges of drug-resistant epilepsy extend beyond seizures, encompassing somatic and psychiatric comorbidities, an elevated risk of injuries and premature mortality, impaired psychosocial functioning, and a diminished quality of life. Effective seizure management not only mitigates morbidity and mortality within the PWE community, but also holds the potential to improve overall quality of life.

Cenobamate (CNB) is a novel antiseizure medication that gained approval from the US FDA in 2019 and from the EMA in 2021 for adjunctive treatment of focal onset seizures in adults. CNB is an oral tetrazole alkyl mono-carbamate exhibiting a dual mechanism of action: preferential blockade of persistent sodium currents, and positive allosteric modulation of the GABA-A receptor [6]. In randomised clinical trials, CNB demonstrated remarkable efficacy, with a responder rate (≥ 50% seizure reduction) reaching as high as 64%. Furthermore, one in five patients achieved complete seizure freedom with the highest dose [7, 8]. Indirect comparisons between CNB and several second- and third-generation ASMs (brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, lamotrigine, levetiracetam, and topiramate) have indicated that adjunctive CNB yielded a higher responder rate and a greater likelihood of achieving seizure freedom compared to all comparators [9, 10]. Although open-label studies have confirmed its long-term effectiveness and safety [11, 12], real-world experience with CNB remains limited [13, 14]. Cenobamate received approval for reimbursement by the Polish public health system on 1 March, 2023. Prior to this date, patients participating in open-label extension studies of the C013 and C017 trials were provided with the opportunity to access cenobamate through Angelini Pharma's Early Access Programme (EAP).

Clinical rationale for the study

The primary objective of this study was to outline the extended clinical experience with cenobamate among patients with epilepsy who were treated within the Expanded Access Programme in the Silesian Voivodeship of Poland.

Material and methods

This study followed a multicentre, retrospective, observational design, encompassing patients who chose to continue treatment after completing an open-label extension (OLE) of two separate randomised, double-blind, placebo-controlled trials: a 12-week study (YKP3089C013) and an 18-week study (YKP3089C017) [5, 6].

The investigation involved patients who had taken part in the aforementioned trials at all four study sites within the Silesian Voivodeship of Poland. All patients were provided cenobamate through Angelini Pharma's Early Access Programme (EAP), which was initiated in Poland in January 2020.

Upon completing the open-label extension (OLE) phase, every patient was given the opportunity to extend their treatment with CNB through the Early Access Programme (EAP). The decision regarding any subsequent dose adjustment was made by the attending neurologist on a case-by-case basis, taking into account the treatment's effectiveness and tolerability. The maximum allowed daily dose was 400 mg. Data was retrieved from patients' medical records and kept according to usual clinical practice at each centre by participating physicians. All enrolled patients had a history of drug-resistant focal epilepsy. The recorded demographic and epilepsy-related data encompassed age, gender, epilepsy duration, epilepsy treatment type (monotherapy or polytherapy, specific antiseizure medications used, and CNB dosage), monthly seizure frequency before initiating CNB and during the most recent follow-up, duration of CNB exposure, and any encountered adverse events. For the purposes of this analysis, data was collected until the cutoff date of 31 May, 2023.

This study was a retrospective analysis of existing clinical data, so ethics committee review and patient consent were not required.

Results

Patients

Initially, 45 adult patients with epilepsy were enrolled in the open-label extension (OLE) phase. Over the course of the study, three patients were lost to follow-up. Additionally, four patients had to be withdrawn from the OLE for the following reasons: lack of efficacy in one patient (at a CNB dose of 400 mg), psychomotor agitation in another patient (at 50 mg, which resolved after discontinuation of CNB), and dizziness in two patients (at 50 mg and 100 mg doses).

Finally, a total of 38 patients progressed to the Expanded Access Programme. The average baseline age of patients was 39.3 years, and 18 (47.3%) were females. All patients were on polytherapy, with the most frequently employed antiseizure medications being valproate (19/38; 50%), levetiracetam (15/38; 39.5%), and carbamazepine (12/38; 31.6%). The median count of previously unsuccessful antiseizure medication treatments was five (range 2–9). A summary of demographic, clinical, and therapeutic data is set out in Table 1.

Cenobamate treatment outcome

As of May 2023, the median duration of CNB exposure, encompassing both the Open-Label Extension (OLE) and Early Access Programme (EAP), was 96 months (range: 70–132). Within the EAP, the median CNB exposure duration was 41 months. The median dose of cenobamate during the last follow-up was 200 mg/day (with an interquartile range [IQR] of 100 mg, ranging from 50 to 350 mg/day). During the final visit, 34.2% of patients were receiving less than 200 mg of CNB per day.

The addition of cenobamate as an adjunctive treatment led to a significant reduction in mean seizure frequency from

Table 1. Demographics and clinical characteristics of patients treated with cenobamate within Poland's Expanded Access Programme

Variable	n = 38
Age; [years], mean (range)	39.3 (18–57)
Sex (female)	18 (47.3%)
Duration of epilepsy [years] median (range)	15.0 (4–33)
Daily dose of cenobamate [mg]; range	201.3 (50–350)
Number of concomitant ASMs — median	2
1	9 (23.7%)
2	18 (47.4%)
3	11 (28.9%)
Number of ASMs previously tried — median (range)	5 (2–9)
2	2 (5.1%)
3	8 (21%)
4	6 (15.8%)
5	5 (13.6%)
6	4 (10.5%)
7	5 (13.6%)
8	5 (13.6%)
9	3 (7.8%)

ASMs — antiseizure medications

Table 2. Adverse events in patients treated with cenobamate

Adverse event	n (%)
Somnolence	6 (15.8)
Dizziness	4 (10.5)
Elevation of liver enzymes	2 (5.2)
Headache	1 (2.6)
Nausea	1 (2.6)
Nystagmus	1 (2.6)
Balance disorder	1 (2.6)

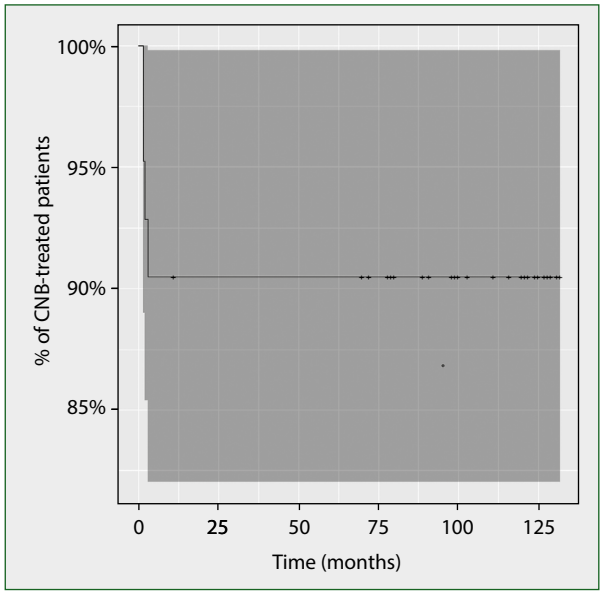

Figure 1. Kaplan–Meier plot presenting treatment retention in RCT and OLE phases. CNB — cenobamate; RCT — randomized controlled trial; OLE — Open-Label Extension

8.1 seizures per month (range: 4–20) to 3 per month (range: 0-8). By the end of the observation period, 24 (63.1%) patients achieved ≥ 50% seizure reduction, while 15 (39.5%) achieved ≥ 75% reduction. Eight (21%) patients experienced complete seizure freedom for at least 12 months. The median cenobamate dose associated with achieving seizure freedom was 200 mg (range: 100–300), while the same dose of 200 mg (range: 100–300) was linked to ≥ 50% seizure reduction.

One-third of patients (31.6%) reported experiencing at least one adverse event during their participation in the EAP. These events included drowsiness in six patients, dizziness in four, non-clinically significant elevation of liver enzymes in two, and nausea, headaches, balance disorder, and nystagmus in one patient each.

Drowsiness and dizziness occurred at CNB dose > 150 mg/day. Among patients encountering adverse events, an equal proportion (50%) were taking three concurrent antiseizure medications, while the remaining 50% were on two concomitant medications. In contrast, among the group without reported adverse events, 19.2% (5/28) were on three medications, 42.8% (12/28) on two, and 39.2% were being prescribed only one concurrent antiseizure medication. Adverse events were resolved during the study for half of the patients who experienced them. Side effects and their frequency are set out in Table 2.

All patients who successfully completed the Open-Label Extension (OLE) phase and transitioned to the EAP continued to receive CNB treatment until 31 May, 2023, resulting in a retention rate of 100%. Figure 1 shows a Kaplan–Meier plot illustrating the treatment retention in randomized controlled trial (RCT) and OLE phases.

Discussion

For the successful treatment of epilepsy, it is critical to find the right balance between obtaining adequate seizure control and avoiding adverse events. Randomised clinical trials are indispensable for assessing the safety and efficacy of new drugs. However, they have important limitations such as the short duration of intervention. Long-term retention rate is a useful measure of effectiveness including efficacy, safety, and tolerability.

In this retrospective study, we describe extensive long-term clinical experience with cenobamate among individuals with epilepsy who were treated under Poland's Expanded Access Programme (EAP). One key strength of our study is the exceptionally long observation period. The duration of cenobamate exposure was 3.5 years within the EAP and 4.5 years within the

Open-Label Extension (OLE), effectively resulting in patients receiving CNB treatment for an average of c.8 years (range: 70 to 132 months), all under the care of the same physician. In this analysis, the use of CNB was consistently linked to remarkable retention rates, ranging from 84.4% (38/45) in the OLE phase to an impressive 100% (38/38) in the EAP, serving as an additional indicator of its sustained long-term effectiveness. It is worth underlining that the retention rate observed in the Polish EAP remained steady across the span of 4.5 years of treatment, surpassing the rates reported in similar Spanish (87%) and Irish (89.5%) studies [11, 12]. It is important to note that both the Spanish and the Irish studies encompassed patients dealing with highly active and ultra-refractory epilepsy, a population more prone to discontinuing a medication due to lack of efficacy and adverse events.

The efficacy of cenobamate, as indicated by the achievement of ≥ 50% seizure reduction (63.1%) and seizure freedom (21%), closely paralleled the outcomes observed in randomised controlled trials. And this efficacy consistently endured over the 3.5-year observation period within the EAP [5, 6]. It is worth noting that the median cenobamate dose for both groups of patients was 200 mg, suggesting that further dose escalation could potentially lead to even higher reduction rates. Similar to other studies, adverse events such as dizziness, somnolence, and headache were observed; notably, these events were more frequent among patients taking a greater number of concurrent antiseizure medications [5, 6, 11, 12]. Encouragingly, in half of the patients experiencing adverse events, they resolved during the course of the study. Furthermore, the study's clinical observation did not identify any serious adverse events. Notably, our extensive long-term follow-up did not uncover any new safety concerns linked to the use of cenobamate.

One notable limitation of our study is the relatively small sample size. Additionally, due to its retrospective design, there was no available data on alterations in concomitant antiseizure medication (ASM) therapy.

Nevertheless, it is noteworthy that this study presents the most extensive follow-up of patients treated with cenobamate published to date. This extended observation period provides valuable insights for physicians regarding the enduring long-term efficacy and safety/tolerability profile of cenobamate.

Clinical implications/future directions

These findings from a long-term observation demonstrate the sustained efficacy and safety/tolerability of cenobamate in adult patients with uncontrolled focal epilepsy.

Article information

Authors' contributions: *ALB: conception and design of study, analysis and interpretation of data, critical revision of article, final approval of version to be published; BK, TZ, AKK, JK, BŻM, KM, KM, AWK: acquisition of data for work, final approval of version to be published; MB: conception and design of study, analysis and interpretation of data, drafting article, critical revision, final approval of version to be published.*

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References

1. Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology. 2020; 54(2): 185–191, doi: 10.1159/000503831, indexed in Pubmed: 31852003.
2. Nowak A, Rysz A, Dziedzic T, et al. Predictors of Class I epilepsy surgery outcome in tumour-related chronic temporal lobe epilepsy in adults. Neurol Neurochir Pol. 2019; 53(6): 466–475, doi: 10.5603/PJNNS.a2019.0061, indexed in Pubmed: 31793658.
3. Chen Z, Brodie MJ, Liew D, et al. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. JAMA Neurol. 2018; 75(3): 279–286, doi: 10.1001/jamaneurol.2017.3949, indexed in Pubmed: 29279892.
4. Wężyk K, Słowik A, Bosak M. Predictors of remission in patients with epilepsy. Neurol Neurochir Pol. 2020; 54(5): 434–439, doi: 10.5603/PJNNS.a2020.0059, indexed in Pubmed: 32757204.
5. Löscher W, Potschka H, Sisodiya SM, et al. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020; 72(3): 606–638, doi: 10.1124/pr.120.019539, indexed in Pubmed: 32540959.
6. Roberti R, De Caro C, Iannone LF, et al. Pharmacology of Cenobamate: Mechanism of Action, Pharmacokinetics, Drug-Drug Interactions and Tolerability. CNS Drugs. 2021; 35(6): 609–618, doi: 10.1007/s40263-021-00819-8, indexed in Pubmed: 33993416.
7. Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020; 19(1): 38–48, doi: 10.1016/S1474-4422(19)30399-0, indexed in Pubmed: 31734103.
8. Chung SS, French JA, Kowalski J, et al. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2020; 94(22): e2311–e2322, doi: 10.1212/WNL.0000000000009530, indexed in Pubmed: 32409485.
9. Lattanzi S, Trinka E, Zaccara G, et al. Third-Generation Antiseizure Medications for Adjunctive Treatment of Focal-Onset Seizures in Adults: A Systematic Review and Network Meta-analysis. Drugs. 2022; 82(2): 199–218, doi: 10.1007/s40265-021-01661-4, indexed in Pubmed: 35061214.
10. Privitera M, Richy FF, Schabert VF. Indirect treatment comparison of cenobamate to other ASMs for the treatment of uncontrolled fo-

cal seizures. Epilepsy Behav. 2022; 126: 108429, doi: 10.1016/j.yebeh.2021.108429, indexed in Pubmed: 34864380.
11. Klein P, Aboumatar S, Brandt C, et al. Long-Term Efficacy and Safety From an Open-Label Extension of Adjunctive Cenobamate in Patients With Uncontrolled Focal Seizures. Neurology. 2022 [Epub ahead of print]; 99(10): e989–e998, doi: 10.1212/WNL.0000000000200792, indexed in Pubmed: 35705501.
12. French JA, Chung SS, Krauss GL, et al. Long-term safety of adjunctive cenobamate in patients with uncontrolled focal seizures: Open-label extension of a randomized clinical study. Epilepsia. 2021; 62(9): 2142–2150, doi: 10.1111/epi.17007, indexed in Pubmed: 34254673.
13. Peña-Ceballos J, Moloney PB, Munteanu T, et al. Adjunctive cenobamate in highly active and ultra-refractory focal epilepsy: A "real-world" retrospective study. Epilepsia. 2023; 64(5): 1225–1235, doi: 10.1111/epi.17549, indexed in Pubmed: 36790345.
14. Villanueva V, Santos-Carrasco D, Cabezudo-García P, et al. Real-world safety and effectiveness of cenobamate in patients with focal onset seizures: Outcomes from an Expanded Access Program. Epilepsia Open. 2023; 8(3): 918–929, doi: 10.1002/epi4.12757, indexed in Pubmed: 37149853.