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ORIGINAL RESEARCH ARTICLE

Post-marketing Experience with Cenobamate in the Treatment of Focal Epilepsies: A Multicentre Cohort Study

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Abstract

Background In randomised controlled trials, adjunctive cenobamate (CNB) has been shown to reduce seizure frequency in patients with drug-resistant focal epilepsy. Studies conducted in real-world settings provide valuable complementary data to further characterise the drug's profile.

Objective To assess the efficacy, retention and tolerability of adjunctive cenobamate (CNB), and to identify factors that might predict these outcomes in the clinical treatment of focal epilepsies.

Methods This multicentre, retrospective cohort study included all patients who began CNB treatment between October 2020 and April 2023 at seven participating epilepsy centres. Baseline and follow-up data were collected from patients' medical records, covering clinical characteristics and outcome data such as seizure frequency, dosing of CNB, physician-assessed Clinical Global Impression of Change, treatment-emergent adverse events (TEAEs), CNB retention and reasons for discontinuation.

Results A total of 234 patients [mean age 40.7 ± 14 years, median 40 years, range 11–82 years; five adolescents under 18 years; 99 (42.3%) males] were analysed. The mean epilepsy duration at study entry was 23.2 ± 14.5 years (median 21 years, range 0.75–63 years), with the average age of epilepsy onset being 17.5 ± 13.0 years (median 17 years, range 0.1–71 years). The patients were taking a mean of 2.6 ± 0.8 (median 3) anti-seizure medications (ASMs) before starting CNB, and had failed a mean of 6 ± 3.3 (median 6) of further ASMs in the past. CNB exposure ranged from 5 to 1162 days, amounting to a total exposure time of 264.7 years. The retention rate was 92.6% at 3 months, 87.2% at 6 months and 77.8% at 12 months. At 3 months, 52.6% achieved a 50% seizure reduction, with 14.5% reporting seizure freedom; by 12 months, 47.7% maintained a 50% response rate and 11.9% were seizure-free. No significant differences in responder rates were observed based on sex, aetiology, seizure localisation, number of ASMs or target dose. The mean maximum CNB dose was 236.7 ± 97.4 mg (median 200 mg, range 12.5–450 mg), with 28 patients (12.0%) titrated up to 400 mg or above. During CNB treatment, 43.6% of patients were able to discontinue, and a further 24.4% were able to reduce the dose of a concomitant ASM. During CNB treatment, 144 patients (61.5%) experienced TEAEs. The most common TEAEs were sedation ($n = 84$, 35.9%), dizziness ($n = 58$, 24.8%) and ataxia ($n = 23$, 9.8%).

Conclusions CNB showed a relatively high and clinically useful 50% responder rate of 47.7% and an overall retention of 77.8% at 1 year. We were unable to identify specific predictors for response and retention, indicating that CNB may be beneficial for patients with a history of multiple failed ASMs, a high number of concomitant ASMs and any localisation or aetiology of focal epilepsy.

1 Introduction

Anti-seizure medications (ASMs) play a central and crucial role in the management of epilepsy, as most patients require long-term treatment. However, up to 30% of individuals with epilepsy do not respond to existing treatments [1, 2], highlighting the urgent need for new therapeutic options. Ongoing seizures in patients with drug-resistant epilepsy, compared with those with well-controlled seizures, contribute to higher rates of morbidity and mortality, social stigma, limited employment opportunities and a reduced quality of life (QoL) for both the patients and their caregivers [3–6]. The development of a new ASM provides an opportunity to achieve better seizure control for some of these patients.

Key Points

Long-term post-marketing data for cenobamate in 234 patients showed an overall retention rate of 77.8% at 1 year.

At 12 months, the 50% responder rate for cenobamate was 47.7%, with 11.9% reporting seizure freedom.

During cenobamate treatment, 43.6% of patients were able to discontinue a concomitant anti-seizure medication.

The most common adverse events were sedation (35.9%), dizziness (24.8%) and ataxia (9.8%).

No predictors of efficacy or retention could be identified.

Cenobamate (CNB) is a recently approved ASM for the treatment of focal-onset seizures, with or without secondary generalisation, in adult patients with epilepsy [7–9]. Clinical studies and meta-analysis have shown that cenobamate can achieve robust seizure reduction with good tolerability, and it has demonstrated potential for long-term seizure control in patients who have not responded to other therapies [9–13]. CNB is believed to enhance inhibitory signalling through modulation of voltage-gated sodium channels and potentiation of GABAergic transmission, offering a novel mechanism of action compared with existing ASMs [14, 15].

However, results from regulatory clinical trials are often difficult to translate to clinical practice, as these studies are limited by their short duration, strict inclusion and exclusion criteria and lack of dosing flexibility [16, 17]. When new ASMs are introduced, data on their efficacy and tolerability in real-world clinical practice are often limited. Therefore, it is crucial to evaluate the efficacy, tolerability, retention rates, impact on quality of life and long-term safety of new ASMs such as CNB in practical, everyday use.

Our multicentre study sought to evaluate the retention, efficacy and tolerability of CNB in a large group of patients with focal epilepsies. Additionally, we aimed to identify factors that might predict efficacy and tolerability and investigated outcomes and treatment-emergent adverse events (TEAEs).

2 Methods

2.1 Study Settings and Design

This retrospective, multicentre study was conducted across seven epilepsy centres in Germany (Düsseldorf, Erlangen, Frankfurt am Main, Freiburg i. Br., Greifswald, Marburg and Münster/Lingen). Ethics committee approval was obtained, and the need for informed consent was waived due to the retrospective methodology. The study adhered closely to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18]. No commercial sponsorship or funding was involved in the study.

The analysis included all patients with focal epilepsy who began treatment with CNB between October 2020 and April 2023. Data were collected from patients' medical records, covering information such as aetiology, sex, age at epilepsy onset, age at the initiation of CNB treatment, seizure frequency in the 3 months prior to CNB treatment (defined as baseline), prior and concurrent treatments with other ASMs and CNB dosing and titration. Follow-up data were also gathered from medical records and included target and maximum doses of CNB, seizure frequency, physician-assessed Clinical Global Impression of Change (CGI-C), TEAEs, CNB retention and reasons for discontinuation (categorised as due to TEAEs, lack of effectiveness, both or not reported).

Seizure reduction was analysed at 3, 6 and 12 months of follow-up for total seizures and generalised tonic–clonic seizures (GTCS), where they occurred. The 25% responder rate was defined as a reduction in seizures by 25% or more from baseline. Similarly, 50% and 75% responder rates were defined as seizure reductions of 50% and 75% or greater, respectively. No response was categorised as either no change in seizure frequency or a change (increase or decrease) of less than 25% compared with baseline. A seizure increase was defined as a 25% or greater rise in seizure frequency. Additionally, changes in seizure occurrence were recorded as the average number of seizure days per month, regardless of seizure type, from baseline to the last follow-up. Clinical change during CNB treatment was rated by physicians using the 7-point CGI-C scale, ranging from "very much improved" to "very much worse".

Retention rate was defined as the percentage of patients continuing CNB treatment at 3, 6 and 12 months and was presented using Kaplan–Meier survival curves. TEAEs were classified as central nervous system/ataxia, behavioural issues, skin reactions and other.

2.2 Data Entry and Statistical Analysis

Data were collected using standardised and anonymised reporting forms. Statistical analyses were conducted using IBM SPSS Statistics, Version 28 (IBM Corp., Armonk, NY, USA). Retention time for CNB between subgroups was compared using the log-rank test. Wilcoxon signed-rank and chi-squared tests were used for statistical analysis of the response to different clinical characteristics, and p values < 0.05 were regarded as statistically significant.

3 Results

3.1 Patients' Characteristics at Baseline

We report on 234 patients, with a median follow-up of 407.5 days (range 5–1162 days) and a total CNB exposure time of 264.7 years. At the start of CNB treatment, the mean age was 40.7 ± 14.0 years (median 40 years, range 11–82 years), and 99 patients were male (42.3%). Five patients (2.1%) were adolescents < 18 years old, while nine patients (3.8%) were older than 65 years of age. All 234 patients were diagnosed with focal epilepsy—115 temporal, 29 frontal, 63 multiregional and 27 with unknown localisation. Describing the epilepsy aetiology, 41 (17.5%) had cortical dysplasia, 33 (14.1%) hippocampal sclerosis, 23 (9.8%) cerebrovascular aetiology, 21 (9.0%) tumour aetiology, 17 (7.3%) post-infectious, 16 (6.8%) immune-mediated [6 GAD65, 1 Rasmussen encephalitis, 1 steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and 8 antibody-negative], 9 (3.8%) structural not otherwise specified, 6 (2.6%) traumatic brain injury and 68 (29.0%) unknown aetiology.

The patients had a mean epilepsy duration of 23.2 ± 14.5 years (median 21 years, range 0.75–63 years) with epilepsy onset at a mean age of 17.5 ± 13 years (median 17 years, range 0.1–71 years). The patients were taking a mean of 2.6 ± 0.8 ASMs (median 3 ASMs, range 1–6 ASMs) before starting CNB. Of these, those prescribed most frequently before initiation of CNB were lamotrigine (n = 103, 44%; mean dose 433.5 mg), brivaracetam (n = 102, 43.6%; mean dose 289.1 mg), lacosamide (n = 84, 35.9%; mean dose 425.5 mg), perampanel (n = 69, 29.5%; mean dose 8.8 mg), valproate (n = 39, 16.7%; mean dose 1478.2 mg), zonisamide (n = 38, 16.2%; mean dose 335.5 mg), oxcarbazepine (n = 31, 13.2%; mean dose 1374.1 mg) and levetiracetam (n = 28, 12.0%; mean dose 3026.7 mg); details are presented in Supplementary Fig. 1A. In the past, patients had a mean of 6 ± 3.3 failed ASMs, not including their current treatment (median 6, range 1–18). The 10 most common previously prescribed drugs were levetiracetam (n = 172, 73.5%), lacosamide (n = 115, 49.1%), valproate (n = 113, 48.3%), carbamazepine (n = 103, 44.0%), lamotrigine (n = 103, 44.0%), topiramate (n = 100, 42.7%), perampanel (n = 95, 40.6%), oxcarbazepine (n = 90, 38.5%), zonisamide (n = 86, 36.8%), brivaracetam (n = 64, 27.4%); details are presented in Supplementary Fig. 1B.

3.2 Treatment with CNB

Treatment with CNB was introduced at a mean dose of 12.47 ± 0.41 mg (median 12.5 mg, range 6.25–12.5 mg). In the majority of patients, the target dose was 100 mg (n = 55, 23.5%) or 200 mg (n = 161; 68.8%), with a mean target dose of 171.5 ± 45.3 mg (median 200 mg, range 50–225 mg) that was typically achieved in a median of 70 days. The maximal mean CNB dose was 236.7 ± 97.4 mg (median 200 mg, range 12.5–450 mg), with 26 patients (11.1%) titrated up to 400 mg and 2 (0.9%) treated with 450 mg per day, exceeding the upper recommended dose.

3.3 Seizure Outcome During the First Year of Treatment

During the first 3 months of follow-up, responder rates were available for 234 patients. Of these, 34 patients (14.5%) reported seizure freedom, 76 (32.5%) reported a 75% response rate, 123 (52.6%) reported a 50% response rate and 150 (64.1%) reported a 25% response rate. No change was reported by 60 patients (25.6%), 16 patients (6.8%) discontinued and 8 reported seizure increase (3.4%); details are presented in Table 1. There were no significant differences in response relating to factors such as sex, aetiology, localisation, number of current or previous ASMs or target dose. After 6 months, follow-up responder rates were available for 218 patients. Of these, 29 (13.3%) reported seizure freedom, 76 (34.9%) reported a 75% response rate, 121 (55.5%) reported a 50% response rate and 142 (65.1%) reported a 25% response rate. After 12 months of CNB treatment, responder rates were available for 176 patients, with 39 patients having discontinued CNB and 58 patients lacking follow-up. A 75% response rate was reported by 56 patients (31.8%), including 21 patients reporting seizure freedom (11.9%). A 50% response rate was reported by 84 patients (47.7%), and a 25% response rate by 103 patients (58.5%). In 30 patients (17%), no change in seizure frequency was reported, and 4 patients (2.2%) reported increased seizure frequencies; details are presented in Fig. 1A.

For changes in GTCS frequency, responder rates were available for 100 patients at 3 months. The other 134 patients had not experienced GTCS in the 12 months prior to starting CNB. Of the 100 who had previously suffered GTCS, 46 patients (46.0%) reported GTCS freedom, 55 (55.0%) reported a 75% GTCS response rate, 63 (63.0%) reported a 50% GTCS response rate and 66 (66.0%) reported 25% GTCS response rate after starting CNB. At 6 months' follow-up, responder rates were available for 95 patients. Of these, 41 (43.2%) reported seizure freedom from GTCS, 52 (54.7%) reported a 75% response rate, 60 (63.2%) reported a 50% response rate and 63 (66.3%) reported a 25% response rate. After 12 months of CNB treatment, responder rates were available for 77 patients, 36 of whom did not experience GTCS (46.7%). A 75% response rate was reported by 40 patients (51.9%), a 50% response rate was reported by 49 patients (63.6%) and a 25% response rate was reported by 50 patients (64.9%); details are provided in Fig. 1B.

Table 1 Clinical characteristics and total seizure outcome on follow-up of 3 months ($n = 234$)

	Patients *n*	Seizure free $n = 34$ (14.5%)	≥ 25% response $n = 150$ (64.1%)	No response $n = 84$ (35.9%)	*p* value*
Sex, % (*n*)					0.211
Male	99	17.2 (17)	68.7 (68)	31.3 (31)	
Female	135	12.6 (17)	60.7 (82)	39.3 (53)	
Epilepsy syndrome, % (*n*)					0.639
Temporal lobe epilepsy	115	18.3 (21)	62.6 (72)	37.4 (43)	
Extratemporal lobe epilepsy	119	10.9 (13)	65.5 (78)	34.5 (41)	
Aetiology, % (*n*)					0.469
Structural	166	14.5 (24)	62.7 (104)	37.3 (62)	
Cryptogenic or unknown	68	14.7 (10)	67.6 (46)	32.4 (22)	
Number of ASMs at start of CNB, % (*n*)					0.795
1–2 ASMs	106	15.1 (16)	63.2 (67)	36.8 (39)	
3 or more ASMs	128	14.1 (18)	64.8 (83)	35.2 (45)	
Previously failed ASMs (without current), % (*n*)					0.800
1–2 ASMs	33	12.1 (4)	60.6 (20)	39.4 (13)	
3–5 ASMs	76	21.1 (16)	67.1 (51)	32.9 (25)	
6 and more ASMs	123	11.4 (14)	62.2 (79)	35.8 (44)	
CNB target dose, % (*n*)					0.964
Below 200 mg/day	72	13.9 (10)	63.9 (46)	36.1 (26)	
200 mg/day and above	162	14.8 (24)	64.2 (104)	35.8 (58)	

ASM anti-seizure medication, *CNB* cenobamate

*Chi-squared test between at least 25% responders and non-responders (no change, increase, or discontinued)

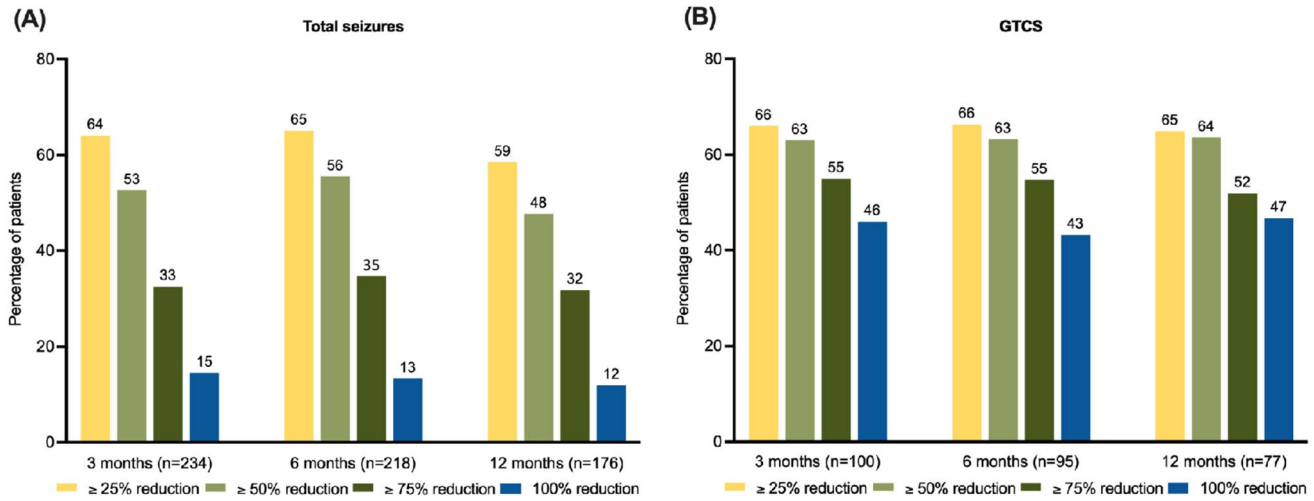

Fig. 1 Responder rates over time for (**A**) total seizures and (**B**) generalised tonic–clonic seizures (GTCS)

The patients had a mean of 12.2 ± 11.1 seizure days per month (median 7.25, range 0.17–30) during the 3-month baseline phase. Mean seizure days per month significantly decreased to 8.5 ± 10.9 (median 3.5, range 0–30) in the final three monitored months of CNB treatment ($p < 0.001$). Figure 2A shows the number of seizure days per month at baseline and final follow-up.

3.4 Impact of Cenobamate on Concomitant ASM Consumption

After starting treatment with CNB, 102 patients (43.6%) discontinued at least one concomitant ASM, and the dose of a concomitant ASM was reduced in a further 57 patients

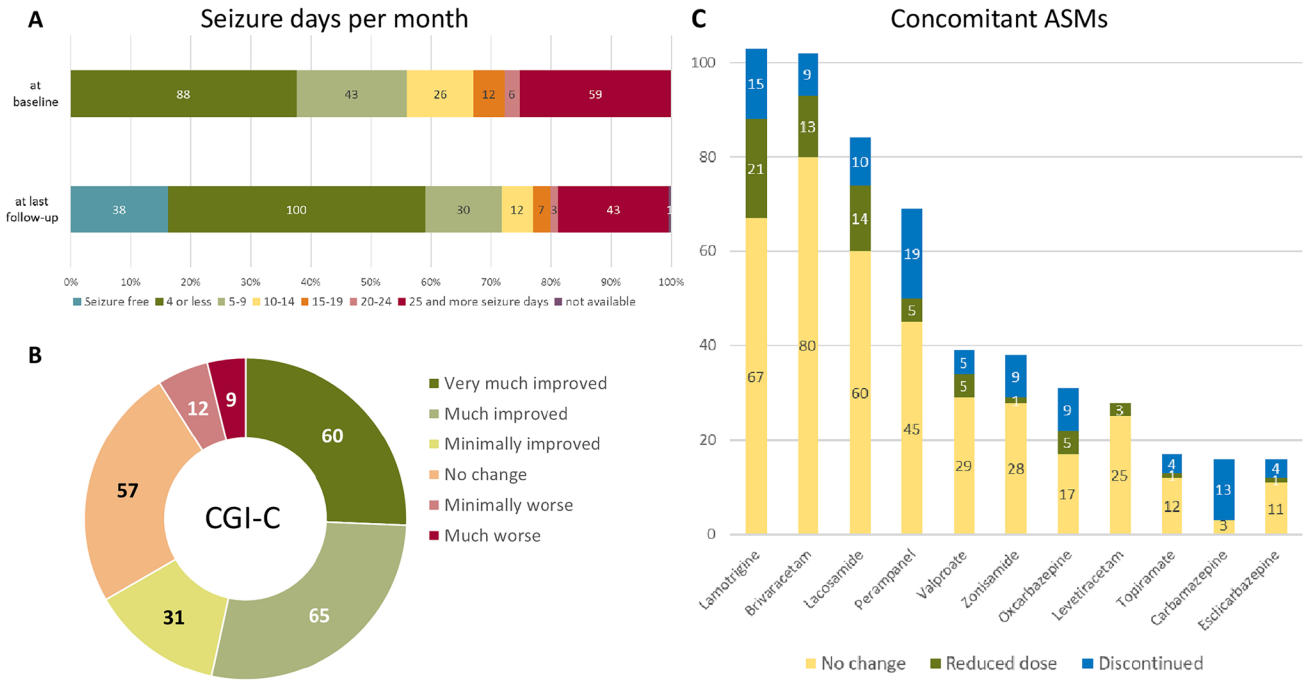

Fig. 2 **A** Percentage of patients according to seizure days per month across seven incremental categories at baseline and the final follow-up after initiation of cenobamate (CNB). **B** Physician-assessed Clinical Global Impression of Change (CGI-C). **C** Number of patients with concomitant antiseizure medications (ASMs) at baseline (represented as the entire stacked column), and no changes, discontinuations and dose reductions during CNB treatment

(24.4%). Frequently discontinued ASMs included perampanel (n = 19), lamotrigine (n = 15), carbamazepine (n = 13), lacosamide (n = 10) and brivaracetam, oxcarbazepine and zonisamide (each n = 9). Details of concomitant ASMs at baseline and changes during CNB treatment are presented in Fig. 2C.

3.5 Retention and Overall Change

In total, 48 patients (20.5%) discontinued CNB during the study period; Kaplan–Meier survival curves show the retention over time (Fig. 3A). The probability of remaining on CNB treatment for all patients was 92.6% at 3 months, 87.2% at 6 months and 77.8% at 12 months. The main reasons for discontinuation of CNB were TEAEs (n = 24, 10.3%), insufficient efficacy (n = 12, 5.1%), both (n = 10, 4.3%) or unknown (n = 2; 0.9%). There was no difference in retention associated with the number of concomitant ASMs (Fig. 3B; log-rank p value = 0.352), number of previously failed ASMs (Fig. 3C; log-rank p value = 0.277) or target dose of CNB (Fig. 3D; log-rank p value = 0.155).

Using the CGI-C, 60 patients (25.6%) were found to be very much improved at the final follow-up, 65 patients (27.8%) were much improved, 31 patients (13.2%) were minimally improved and 57 patients (24.4%) showed no change. In total, 12 patients (5.1%) were rated minimally worse, and 9 patients (3.8%) were rated much worse. No patients were rated as very much worse. Details are given in Fig. 2B.

3.6 Adverse Events

During CNB treatment, 144 patients (61.5%) experienced TEAEs. The most common adverse events (AEs) were central nervous system (CNS) symptoms (n = 121, 51.7%), including sedation (n = 84, 35.9%), dizziness (n = 58, 24.8%), ataxia (n = 23, 9.8%), cognitive deficits (n = 14, 6.0%), visual impairment (n = 12, 5.1%), tremor (n = 4, 1.7%), dysarthria (n = 3, 1.3%) and nystagmus (n = 2, < 1%). Behavioural AEs were observed in 13 patients (5.6%), specifically depressive mood (n = 9, 3.8%), aggression (n = 4, 1.7%), psychosis (n = 1, < 1%) and agitation (n = 1, < 1%). Skin (n = 13, 5.6%) and gastrointestinal (GI; n = 9, 3.8%) symptoms were also reported. In addition, 6 patients (2.6%) reported headaches, 5 patients (2.1%) showed changes in laboratory parameters such as elevated liver enzymes (n = 2, < 1%) or leukopenia (n = 1, < 1%), and 11 patients (4.7%) showed other AEs (Table 2).

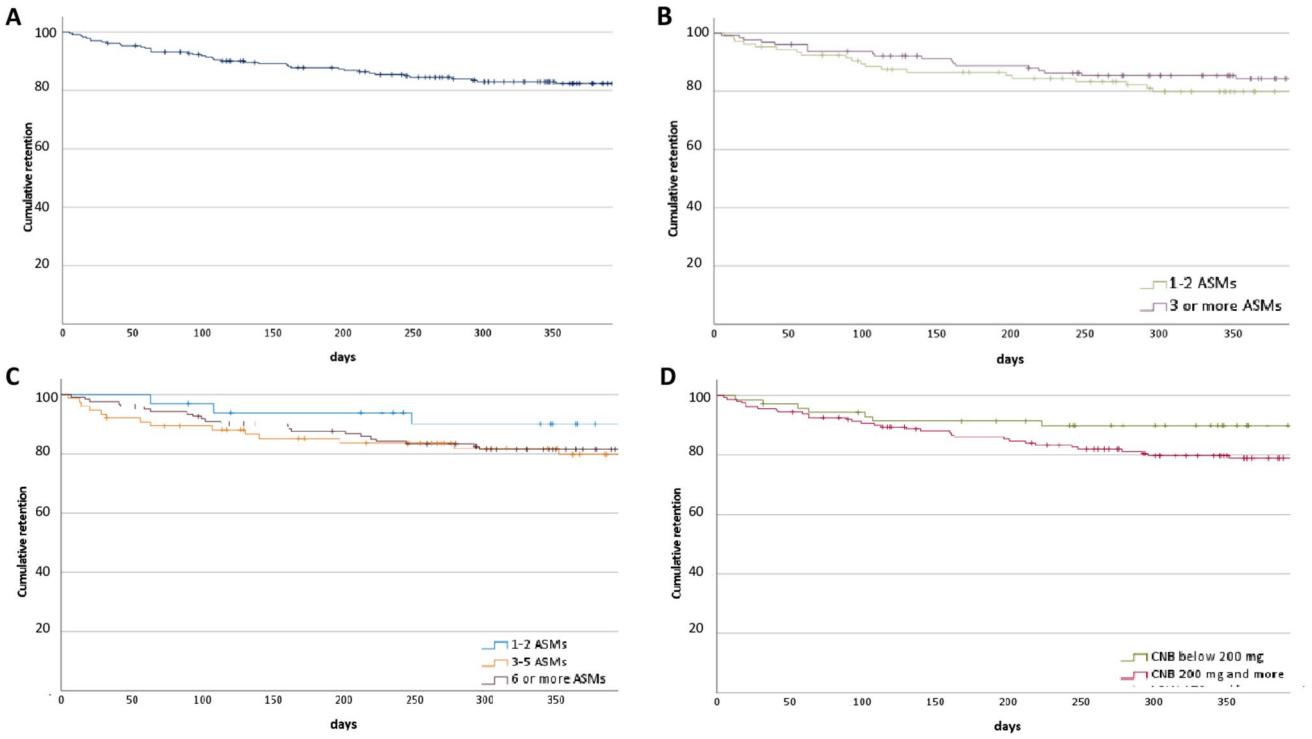

Fig. 3 Retention rate of cenobamate (CNB) in the complete cohort (**A**) and stratified for number of concomitant ASMs (**B**; long-rank *p* value = 0.352), number of previously failed ASMs (**C**; long-rank *p* value = 0.277), and low or high initial target dose of CNB (**D**; long-rank *p* value = 0.155). ASM, anti-seizure medication

4 Discussion

Our study reflects patient experience in the first year following the market introduction of CNB in a cohort of 234 patients with focal epilepsies. These patients were characterised by a high seizure burden and drug resistance, as indicated by the high number of concomitant and previously failed ASMs. Efficacy was demonstrated with 50% responder rates of 52.6% (14.5% seizure-free) at 3 months and 47.7% (11.9% seizure-free) at 12 months, which aligns closely with the outcomes reported in randomised, double-blind, controlled trials (RCTs) [10, 12, 13]. The slightly lower rate of seizure-free patients compared with the RCTs might be due to our drug refractory cohort with long epilepsy duration. The CNB phase III RCTs employed fixed-dose regimens ranging from 100 mg to 400 mg/day, while most patients in our and other post-marketing studies received daily doses between 100 and 200 mg (Table 3). Another observational study has shown that CNB is already effective at the low dose of 100 mg/day in refractory focal epilepsy [19]. In our data, the mean daily dose was titrated above 200 mg over the course of treatment, suggesting that under-dosing is unlikely. Physicians aimed primarily for 100 or 200 mg as the typical target dose. We could not determine any specific factors such as sex, aetiology, temporal versus extratemporal onset of seizures or the number of concomitant or previously failed ASMs to be associated with response and retention, so we cannot provide strong guidance for clinicians to assist in the determination of which patients will benefit from CNB use.

Few other studies examining the efficacy of CNB in real-world settings have extended to and beyond a 12-month follow-up period [19–22] (Table 3). The reported 50% response rate is between 46 and 50% at 3 months, with 9–18.4% achieving seizure freedom. While comparisons between studies should be approached with caution, as there might be differences in study populations, definitions of efficacy and the drug regimens assessed, CNB seems to perform at the higher end of efficacy outcomes for ASMs. Two studies [22, 23] compared CNB with other add-on ASM treatments, including brivaracetam, lacosamide, levetiracetam, perampanel, topiramate and valproate, and showed the highest retention rate for CNB in combination, with a good 50% responder rate. Our reported retention rates at 3 (95%), 6 (83%) and 12 (72%) months align with findings from other large post-marketing studies on CNB (78.8–80% at 12 months; Table 3 [20, 22]) and are in line or above other ASMs such as brivaracetam, eslicarbazepine, lacosamide lamotrigine, levetiracetam, perampanel, topiramate, valproate and zonisamide for focal or generalised epilepsies [24–34]. This is well in line with a prior systematic review

Table 2 Characteristics of reported adverse events during cenobamate treatment, their frequency and related discontinuation ($N = 234$)

Adverse events	Reported *n* (%)	Leading to withdrawal *n* (%)
Overall	144 (61.5)	34 (14.5)
CNS/symptoms	121 (51.7)	20 (8.5)
Sedation	84 (35.9)	14 (6.0)
Dizziness	58 (24.8)	8 (3.4)
Ataxia	23 (9.8)	3 (1.3)
Cognitive deficits	14 (6.0)	5 (2.1)
Visual impairment	12 (5.1)	2 (< 1)
Tremor	4 (1.7)	0
Dysarthria	3 (1.3)	2 (< 1)
Nystagmus	2 (< 1)	0
Behavioural	13 (5.6)	5 (2.1)
Depressive mood	9 (3.8)	3 (1.3)
Aggression	4 (1.7)	2 (< 1)
Psychosis	1 (< 1)	1 (< 1)
Agitation	1 (< 1)	0
Skin	13 (5.6)	9 (3.8)
Pruritus/rash	11 (4.7)	8 (3.4)
Acne	1 (< 1)	1 (< 1)
GI symptoms	9 (3.8)	0
Headache	6 (2.6)	3 (1.3)
Laboratory parameters	5 (2.1)	0
Elevated liver enzymes	2 (< 1)	0
Leukopenia	1 (< 1)	0
Other	11 (4.7)	6 (2.6)

CNS central nervous system, *GI* gastrointestinal

[35], which evaluated third-generation ASMs, including CNB, brivaracetam, eslicarbazepine acetate, lacosamide and perampanel, as adjunctive treatments for focal-onset seizures.

It is also notable that, during treatment with CNB in our study, 43.6% of patients were able to discontinue concomitant ASMs, and the dose was tapered in a further 24.4% of patients. Lauxmann et al. reported that at least one concomitant ASM was discontinued in 58.6% of cases during their observation period, with perampanel, lacosamide and phenytoin being the most commonly stopped [21]. This is consistent with our findings, where perampanel and the sodium channel blockers lamotrigine, carbamazepine and lacosamide were frequently discontinued. The reason for the high discontinuation rates of these drugs is unclear, although both CNB and perampanel are once-daily ASMs typically taken at bedtime. CGI-C was improved in more than half of the reported patients, indicating that CNB was generally well tolerated with few psychobehavioral side effects.

Overall, tolerability of CNB was favourable, with a TEAE rate of 61.5%; discontinuation due to such events was reported in 14.5% of patients. The most frequent TEAEs were sedation, dizziness and ataxia, consistent with findings from RCTs and other post-marketing studies [19–22]. Our study lacks stratification by severity and persistence of these TEAEs, limiting our ability to offer detailed guidance for their management.

In the early stages of clinical development, when initial treatment doses of 50 or 100 mg per day were used, three cases of drug reaction with eosinophilia and systemic symptoms (DRESS) were reported, including one fatality [10]. However, subsequent studies utilising a lower starting dose of 12.5 mg with biweekly titration in a safety population of 1339 patients reported no instances of DRESS [11]. This absence of DRESS cases is consistent with our analysis and other larger post-marketing reports [19–22]. Cases of rash were reported and resolved upon discontinuation of CNB.

This study has several strengths and some limitations. We evaluated a broad range of efficacy outcomes, and the population size was relatively large compared with other post-marketing studies. Due to the small number of adolescent patients ($n = 5$), the applicability of our findings to younger populations is limited. Larger, dedicated studies are needed to evaluate the efficacy and safety of CNB in children and adolescents. The prior and concomitant treatments spanned a wide variety of ASMs, reflecting the current treatment landscape for focal epilepsies. Therapeutic drug monitoring of CNB in such polytherapy regimens may aid in preventing TEAEs and guiding dosing adjustments. Recent advancements in volumetric absorptive microsampling (VAMS)-based liquid chromatography with tandem mass spectrometry (LC-MS/MS) methodology underscore its potential for accurate CNB quantification [36]. Integrating therapeutic drug monitoring into clinical practice could optimise dosing strategies and improve the overall safety and efficacy of CNB therapy. While we provide data on outcomes for the first year, a longer follow-up is necessary to assess the durability of seizure freedom rates and long-term safety. Additionally, as an observational study where clinicians were not blinded to the treatment, there is potential for bias in subjective outcomes such as responder rates, adverse events or CGI-C. Further studies are also required to explore the treatment's impact on overall QoL [37].

5 Conclusions

This study demonstrates that add-on CNB was well tolerated in a real-world clinical setting and improved seizure control in patients with focal epilepsies. The responder and seizure-free rates observed during the first 12 months of CNB therapy were consistent with those reported in previous RCTs, and the high retention rate of 77.8% after

Table 3 Efficacy data from post-marketing studies on cenobamate in focal epilepsies

	Strzelczyk et al. (current study)	Roberti et al., *Epilepsia* 2024 [20]	Lauxmann et al., *J Neurol* 2024 [21]	Steinhoff et al., *Epilepsia Open* 2024 [22]	Novitskaya et al., *Epilepsia* 2024 [9]
Study design	Multicentre, r	Multicentre, r	Multicentre, r	Monocentre, p	Monocentre, r
Country	Germany (7 centres)	Italy (21 centres)	Germany (Aachen, Tübingen)	Germany (Kork)	Germany (Freiburg)
Number of patients	234	236	116 (99 with focal epilepsy)	172	112
Mean age ± SD in years (range)	40.7 ± 14.0 median 40 (11–82)	Median 38 (Q1–Q3 = 27–49)	Median 38.5 (18–79)	40.5 ± 14.4, median 39 (18–76)	Median 38 (19–77)
Children included	Yes	Not reported	No	No	No
Female, *n* (%)	135 (57.7%)	130 (55.1%)	51 (44.0%)	91 (52.9%)	45 (40.2%)
Mean number of ASMs prior to CNB	6 ± 3.3 (median 6, range 1–18)	Median 7 (Q1–Q3 = 4–9)	Median 10.5 (2–24)	10.2 ± 4.2, (median 10, range 2–27)	Lifetime ASMs median 8 (2–23)
Mean number of concomitant ASMs	2.6 ± 0.8 (median 3, range 1–6)	Median 3 (Q1–Q3 = 2–4)	Median 3 (1–6)	2.6 ± 1 (median 3, range 1–6)	Not reported
Outcome report time period	3–12 months	3–12 months	6–18 months	12 months	3–12 months
Outcome data for CNB					
Maximum CNB dosage	Mean 236 mg median 200 mg (range 12.5−450 mg)	Median 200 mg (Q1–Q3 = 200–250 mg)	Median 200 mg (IQR 100 mg; range 25–400 mg)	Mean 261.9 mg (range 50–500 mg)	Median 250 mg (range 100–450 mg) at 12 months
50% responder rate at 3 months	123 (52.6%)	48.3%	50% (49/98) at 6 months	50% (*n* = 69) at 6 months	46% (46/101)
Seizure-free rate	34 (14.5%)	9.8%	18.4% (18/98) at 6 months	14% (*n* = 19) at 6 months	9% (9/101)
Retention rate at 12 months	77.8%	78.8%	Not reported	80%	Not reported
Adverse events					
Patients with adverse events, *n* (%)	144 (61.5%)	133 (56.4%)	35 (30.1%)	28 (18.7%) at 3 months	38% (38/101) at 3 months
Most common adverse events, *n* (%)	Sedation 84 (35.9%) Dizziness 58 (24.8%) Ataxia 23 (9.8%)	Somnolence 66 (29.6%) Vertigo 46 (20.6%) Balance disorders 22 (9.9%)	Fatigue 35 (30.1%) Dizziness 16 (13.8%) Gait disturbance 6 (5.2%)	Somnolence 42 (28.0%) Ataxia 22 (14.7%) Dizziness 18 (12.0%)	Daytime sleepiness 18 (18%) Dizziness 8 (8%) Blurred vision 7 (7%)

CNB cenobamate, *IQR* interquartile range, *SD* standard deviation, *r* retrospective, *p* prospective

1 year of treatment highlighted the good efficacy and tolerability of CNB. We could not determine specific factors associated with response and retention, suggesting that CNB might be beneficial for patients who have experienced numerous failed ASMs, are taking multiple concomitant ASMs or have various subtypes or aetiologies of focal epilepsy.

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Declarations

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Conflict of interest A. Strzelczyk has received personal fees and grants from Angelini Pharma, Biocodex, Desitin Arzneimittel, Eisai, Jazz Pharmaceuticals, Longboard, Neuraxpharm, Takeda, UCB Pharma and UNEEG Medical. F. von Podewils received personal fees and grants from Angelini Pharma, Desitin Arzneimittel, Eisai, Jazz Pharmaceuticals, UCB Pharma, Nutricia Milupa GmbH, Neuraxpharm and Bial. H.M. Hamer has served on the scientific advisory board of Angelini, UniQure, Eisai, GW/Jazz and UCB Pharma. He served on the speakers' bureau of or received unrestricted grants from Angelini, Ad-Tech, Alnylam, Bracco, Desitin, Eisai, Jazz, LivaNova, Nihon Kohden, Pfizer and UCB Pharma. S. Knake received speakers' honoraria from Bial, Destin Arzneimittel, Eisai, Jazz Pharma, Merck Serono and UCB. F. Rosenow has received personal fees from Angelini Pharma, Desitin Arzneimittel, Eisai GmbH, Jazz Pharma, Roche Pharma, Stoke Therapeutics and UCB Pharma and grants from the Detlev-Wrobel-Fonds for Epilepsy Research, the Deutsche Forschungsgemeinschaft (DFG),

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Ethics approval Ethics committee approval was obtained.

Consent to participate Consent was waived due to the retrospective nature of the study.

Consent for publication Not applicable.

Availability of data and material The data of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions A.S., F.R. and S.S.B. developed the idea for this study. A.S., F.v.P., H.M.H., S.K., F.R., K.A.K., G.K., N.M., E.B., C.M., L.M.W., J.P.Z., B.G., J.C., D.B., I.I. and S.S.B. participated in the recruitment of patients and data collection. A.S. supervised the study. A.S. and S.S.B. conceived the paper and performed the statistical analysis. A.S., E.B. and L.M.W. created the charts and figures. A.S., F.v.P., H.M.H., S.K., F.R., K.A.K., G.K., N.M., E.B., C.M., L.M.W., J.P.Z., B.G., J.C., D.B., I.I., L.K., A.B. and S.S.B. wrote the paper, discussed the results and contributed to the final manuscript. All authors have read and approve the final submitted manuscript, and agree to be accountable for the work.

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