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RESEARCH ARTICLE

Adjunctive cenobamate in people with focal onset seizures: Insights from the Italian Expanded Access Program

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Abstract

Objective: This study was undertaken to assess the effectiveness/tolerability of adjunctive cenobamate, variations in the load of concomitant antiseizure medications (ASMs) and predictors of clinical response in people with focal epilepsy.

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Methods: This was a retrospective study at 21 centers participating in the Italian Expanded Access Program. Effectiveness outcomes included retention and responder rates (≥50% and 100% reduction in baseline seizure frequency). Tolerability/safety outcomes included the rate of treatment discontinuation due to adverse events (AEs) and their incidence. Total drug load was quantified as the number of concomitant ASMs and total defined daily dose (DDD). Concomitant ASMs were also classified according to their mechanism of action and pharmacokinetic interactions to perform explorative subgroup analyses.

Results: A total of 236 subjects with a median age of 38 (Q_1–Q_3 = 27–49) years were included. At 12 months, cenobamate retention rate was 78.8% and responders were 57.5%. The seizure freedom rates during the preceding 3 months were 9.8%, 12.2%, 16.3%, and 14.0% at 3, 6, 9, and 12 months. A higher percentage of responders was observed among subjects treated with clobazam, although the difference was not statistically significant. A total of 223 AEs were recorded in 133 of 236 participants, leading to cenobamate discontinuation in 8.5% cases. At 12 months, a reduction of one or two concomitant ASMs occurred in 42.6% and 4.3% of the subjects. The median total DDD of all concomitant ASMs decreased from 3.34 (Q_1–Q_3 = 2.50–4.47) at baseline to 2.50 (Q_1–Q_3 = 1.67–3.50) at 12 months ($p < .001$, median percentage reduction = 22.2%). The highest rates of cotreatment withdrawal and reductions in the DDD were observed for sodium channel blockers and γ-aminobutyric acidergic modulators (above all for those linked to pharmacokinetic interactions), and perampanel.

Significance: Adjunctive cenobamate was associated with a reduction in seizure frequency and in the burden of concomitant ASMs in adults with difficult-to-treat focal epilepsy. The type of ASM associated did not influence effectiveness except for a favorable trend with clobazam.

KEYWORDS

antiseizure medication, cenobamate, clobazam, drug daily dose, epilepsy, focal seizures

1 | INTRODUCTION

The treatment of people with epilepsy is mainly symptomatic and aimed to reduce the risk of seizure recurrence.[1] Antiseizure medications (ASMs) represent the mainstay of treatment, and >20 new drugs have been approved in the past decades. Despite the increasing number of therapeutic options, approximately one third of people with epilepsy do not achieve freedom from seizures.[2] People with ongoing seizures may experience psychological and social dysfunction, carry an increased risk of injury and premature death, and have reduced educational and employment opportunities and impaired quality of life.[3,4] Of note, the burden of uncontrolled epilepsy has remained substantially stable over time, and there remains the need for new therapeutic options that are effective and safe.[2,5,6]

Cenobamate (CNB) is a novel tetrazole-derived carbamate molecule and one of the latest ASMs approved for the treatment of focal onset seizures. The drug is characterized

Key points

- Adjunctive CNB improved seizure frequency in adults with difficult-to-treat focal epilepsy.
- A higher but not statistically significant rate of responders was observed among subjects treated with clobazam.
- The most common adverse events included somnolence, vertigo, and balance disorders.
- Adjunctive CNB was associated with a reduction in the burden of concomitant antiseizure medications.
- The highest rates of cotreatment withdrawal and percentage reductions in the DDD were observed for sodium channel blockers and GABAergic modulators (above all for those whose serum levels were increased by CNB), and perampanel.

by a peculiar pharmacodynamic (PD) profile, which has not been completely understood and studied. The drug acts on voltage-gated sodium channels blocking persistent rather than transient currents (as most of other ASMs) and is a positive allosteric modulator of γ-aminobutyric acid type A ($GABA_A$) receptors independently from the benzodiazepine-binding site.[7]

In the European Union, CNB is indicated for the adjunctive treatment of focal onset seizures in adults with epilepsy who have not been adequately controlled despite a history of treatment with at least two ASMs.[8] In the USA, CNB is indicated for the treatment of focal onset seizures in adults.[9]

Randomized, double-blind, placebo-controlled trials provided evidence of the efficacy of adjunctive CNB to treat focal onset seizures in adults with uncontrolled epilepsy.[10,11] A remarkable finding in CNB-treated participants was the high rate of seizure freedom during the maintenance treatment, which compares very favorably with the rates observed in pivotal trials of other adjunctive ASMs.[12] Long-term effectiveness and tolerability of CNB have been confirmed in a phase 3, open-label study and throughout the open-label extension phase of the double-blind trials.[13–15]

Studies performed in a naturalistic setting provide the opportunity to complement the evidence obtained in clinical trials and further characterize the drug profile. The aim of this study was to assess the effectiveness and tolerability of adjunctive CNB and explore the variations in the daily drug load both overall and per concomitant ASM in a large population of people with focal epilepsy who were treated as part of the Italian Expanded Access Program (EAP). Furthermore, the potential value of the combination of CNB and different classes of ASMs according to their mechanisms of action and pharmacokinetic (PK) interactions has been analyzed.

2 | MATERIALS AND METHODS

2.1 | Participants

This was a retrospective, multicenter study conducted at 21 of the 22 centers that participated in the Italian EAP. Data collection included all the subjects who were prescribed adjunctive CNB within the national EAP (December 2020–May 2022). In detail, adult patients with drug-resistant epilepsy and focal onset seizures who had provided written informed consent (directly or by a legal representative) could be included in the EAP if the local ethics committee issued a favorable opinion. At the end of the EAP, follow-up data on patients who continued CNB as approved drug were also considered, until data collection stopped (February 2023).

CNB was started at 12.5 mg/day and uptitrated until the target dose of 200 mg/day (maximum allowed dose = 400 mg/day) according to the Summary of Product Characteristics.[8] The maximum titration rate was that recommended to avoid DRESS (drug rash with eosinophilia and systemic symptoms) syndrome,[8] but the physician could decide to go even more slowly according to the individual clinical response. Likewise, the target maintenance dose was individualized based on clinical judgment, and reaching 200 mg/day was not mandatory if subjects benefitted from lower doses.

Data on demographics, clinical history, type of seizures and epilepsy,[16] etiology, previous and concomitant ASMs, and baseline monthly seizure frequency (counted as the mean monthly number of seizures based on the total number that occurred during the 3 months before starting CNB) were collected.

Data on number of seizures, CNB dose, type and dose of concomitant ASMs, adverse events (AEs), and drug withdrawal were obtained from clinical records and seizures diaries, routinely used by participating centers. Subjects underwent clinical visits whenever deemed necessary (approximately every 3 months according to clinical practice).

Effectiveness outcomes included the retention rates of CNB at 3, 6, 9, and 12 months and the proportion of subjects with a ≥50% (responders), ≥75%, ≥90%, and 100% (seizure freedom) reduction and >25% increase (seizure worsening) in monthly seizure frequency relative to baseline at each time point. A more stringent definition of seizure worsening as a 100% increase in baseline monthly seizure frequency was also considered. Seizure freedom was defined as the occurrence of no seizures since at least the previous visit, that is, during at least the preceding 3 months. Subjects who discontinued CNB were considered to have no seizure frequency reduction at the time of discontinuation and onward. Sustained seizure response and sustained seizure freedom, which were defined as ≥50% and 100% reduction in baseline seizure frequency from the start of CNB throughout the 12-month follow-up, were also considered.[17,18]

Tolerability and safety outcomes included the rate of treatment discontinuation due to AEs and the incidence of AEs considered as related to CNB by participating physicians.

Changes in the concomitant drug load among subjects who were on CNB treatment at 12 months were evaluated. The total drug load was quantified as (1) the number of concomitant ASMs and (2) the cumulative or total defined daily dose (DDD). The DDD (Table S1) is the assumed average maintenance dose per day for a drug used for its main indication in adults as provided by the

Collaborating Center for Drug Statistics Methodology of the World Health Organization.[19] The daily dose of any ASM was related to the corresponding DDD by calculating the respective ratio (daily dose/DDD). The cumulative or total DDD was the sum of the ratio for any ASMs of the individual regimen. Data were provided by either including or not including CNB, to quantify the overall total DDD and that of all the concomitant ASMs. The DDDs for the different classes of ASMs were also calculated[20]; ASMs classes were divided according to their main mechanism of action and known PK interactions. Based on the main mechanism of action, ASMs were grouped into sodium channel blockers (SCBs; carbamazepine, eslicarbazepine acetate, phenytoin, lacosamide, lamotrigine, oxcarbazepine, rufinamide), GABAergic modulators (barbexaclone, benzodiazepines, phenobarbital, primidone, vigabatrin), synaptic vesicle protein 2A (SV2A) ligands (brivaracetam, levetiracetam), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist (perampanel), and valproic acid. Other ASMs with multiple mechanisms of action such as topiramate were not considered in the analysis according to the small sample size in this cohort and were not merged together, to avoid potential misleading findings. Based on known PK interactions,[8] we considered two subgroups; the first one, defined "PK interacting ASMs," included ASMs whose cytochrome P450 (CYP) metabolism (or that of their metabolites) is inhibited by CNB, leading to the increase in their serum concentrations (clobazam, phenobarbital, phenytoin, primidone); the second one, defined "no PK interacting ASMs," included all the other ASMs. These classifications were adopted to categorize DDDs over time and perform explorative subgroup analyses.

2.2 | Statistical analysis

Values were presented as number (percent) of subjects for categorical variables and mean (SD) or median (Q_1–Q_3) for Gaussian or skewed continuous variables, respectively. The Shapiro–Wilk test was used to verify the normality distribution of the continuous variables. Comparisons were made using the chi-squared or Fisher exact test, Wilcoxon matched-pairs signed-rank test, or marginal homogeneity test. Subgroup effectiveness analyses were carried out in the 12-month population to assess any difference in the frequency distribution of the following groups: (1) responders and nonresponders, (2) seizure-free and non-seizure-free subjects, and (3) seizure free and responders but non-seizure-free subjects, according to the concomitant class of ASM grouped by main mechanism of action (i.e., with and without SCBs, GABAergic modulators, SV2A ligands, perampanel, and valproic acid) and grouped by known PK interactions leading to CNB-mediated increase in serum levels of concomitant ASMs (i.e., with at least one among clobazam, phenobarbital, phenytoin, and primidone and without all of these). As there exist both PD and PK interactions between CNB and clobazam,[21] people treated with clobazam were further explored and also considered as a specific subgroup. Logistic regression was performed to identify baseline characteristics of participants associated with 12-month seizure freedom. Preselected independent variables included age, sex, number of previous ASMs, number of concomitant ASMs, and baseline monthly seizure frequency.[22,23] Results were considered significant for p-values $< .05$ (two-sided). Data analysis was performed using Stata/IC 13.1 (StataCorp). The study is reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[24]

2.3 | Ethics approval

The study was approved by the ethical committee at each participating site and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient or legal representative. Overall data collection has been approved by the ethics committee of Catanzaro, Italy (protocol no. 416/20).

3 | RESULTS

3.1 | Baseline characteristics of the study cohort

A total of 239 subjects were prescribed CNB. Three subjects had no follow-up data and were excluded from the analyses. The studied cohort had a median age of 38 (Q_1–Q_3 = 27–49) years, and 109 (46.2%) were males. The median duration of epilepsy was 27 (Q_1–Q_3 = 17–37) years, and the most frequent etiology was structural (123/236, 52.1%). The median number of prior ASMs was 7 (Q_1–Q_3 = 4–9), and 140 (59.3%) subjects had a history of at least six previous ASMs. The median number of concomitant ASMs was 3 (Q_1–Q_3 = 2–4), and the most frequent were carbamazepine (39.0%), clobazam (33.9%), and lacosamide (30.1%). Baseline characteristics of participants are summarized in Table 1, and details about the concomitant ASMs are provided in Table S2.

TABLE 1 Baseline characteristics of patients ($N = 236$).

Characteristic	Value
Age, years, median (Q_1–Q_3)	38 (27–49)
Male sex, *n* (%)	109 (46.2)
Age at epilepsy onset, years, median (Q_1–Q_3)	9 (3–15)
Duration of epilepsy, years, median (Q_1–Q_3)	27 (17–37)
Type of seizure, *n* (%)	
Focal onset only	115 (48.7)
Focal and focal to bilateral tonic–clonic	89 (37.7)
Focal and generalized onset	32 (13.6)
Etiology, *n* (%)	
Structural	123 (52.1)
Genetic	18 (7.6)
Immune	4 (1.7)
Infectious	8 (3.4)
Unknown	88 (37.3)
History of epilepsy surgery, *n* (%)	41 (17.4)
Number of previous antiseizure medications, median (Q_1–Q_3)	7 (4–9)
Concomitant antiseizure medications, median (Q_1–Q_3)	
n	3 (2–4)
Total defined daily dose[a]	3.46 (2.56–4.43)
Vagus nerve stimulation, *n* (%)	60 (25.4)
Baseline monthly seizure frequency, median (Q_1–Q_3)[b]	15 (6–31)

[a]Data available for 232 subjects.

[b]Based on the mean number of monthly seizures during the 3 months before starting adjunctive cenobamate and reported as median due to skewed distribution. Further details on the distribution of monthly seizure frequency at baseline are shown in Figure S1.

3.2 | Effectiveness, tolerability, and safety outcomes

All included participants had 3-month follow-up, and 6-, 9-, and 12-month follow-up was available for 221 (93.6%), 209 (88.6%), and 179 (75.9%) subjects. The median daily dose of CNB was 200 (Q_1–Q_3 = 150–200) mg at 3 months, 200 (Q_1–Q_3 = 200–200) mg at 6 months, 200 (Q_1–Q_3 = 200–250) mg at 9 months, and 200 (Q_1–Q_3 = 200–250) mg at 12 months.

The retention rate of CNB was 94.9% (224/236) at 3 months, 91.0% (201/221) at 6 months, 86.1% (180/209) at 9 months, and 78.8% (141/179) at 12 months. The proportion of patients experiencing a seizure frequency reduction of at least 50% was 48.3% at 3 months, 52.5% at 6 months, 57.9% at 9 months, and 57.5% at 12 months. The rates of seizure freedom during the preceding 3 months were 9.8%, 12.2%, 16.3%, and 14.0% at 3, 6, 9, and 12 months, respectively. There was no statistically significant difference in the rates of 12-month seizure freedom across CNB daily dosages (<200 mg, 200–300 mg, >300 mg; $p = .245$). The proportions of subjects with a reduction or worsening of baseline seizure frequency at each time point are displayed in Figure 1. At 12 months, the median percentage reduction in seizure frequency compared with baseline was 73.3% (Q_1–Q_3 = 36.1–93.7); 29.6% of the subjects had a sustained seizure frequency reduction of 50% or greater compared to baseline, and 6.2% were sustained seizure-free. An increase in baseline monthly seizure frequency by 100% or more was observed in .02% participants at 3 months, .05% at 6 and 9 months, and none at 12 months.

The number of concomitant ASMs (odds ratio [OR] = .57, 95% confidence interval [CI] = .35–.92; $p = .021$) was the only independent predictor of 12-month seizure freedom, a higher number of ASMs being associated with decreased odds of freedom from seizures.

There were no statistically significant differences between responders and nonresponders, seizure-free and non-seizure-free subjects, and seizure-free and responders but non-seizure-free subjects with and without SCBs, GABAergic modulators, SV2A ligands, perampanel, and valproic acid. A higher but not statistically significant percentage of responders was observed among subjects treated with PK interacting ASMs compared with those who were not (OR = 1.98, 95% CI = .94–4.14; $p = .09$). Similarly, percentages of responders were higher among subjects treated with clobazam compared with subjects taking any other GABAergic modulator (OR = 2.48, 95% CI = .85–6.46; $p = .125$) and all those without clobazam (OR = 2.02, 95% CI = .85–5.10; $p = .143$), although statistical significance was not reached. The median dose of clobazam did not differ between responders and nonresponders, being 10 mg/day in both the subgroups ($p = .216$). A total of 223 AEs were recorded in 133 of 236 (56.4%) participants and rated as mild in 52.9%, moderate in 39.0%, and severe in 8.1% cases. The most common AEs observed in the study cohort included somnolence, vertigo, and balance disorders (Table 2). AEs led to CNB discontinuation in 20 of 236 (8.5%) participants.

3.3 | Changes in concomitant drug load

A reduction of one or two drugs in the number of concomitant ASMs occurred in 60 of 141 (42.6%) and six of 141 (4.3%) of the subjects who were on CNB treatment at 12 months, respectively. The disposition of concomitant ASMs at baseline and at 12 months is shown in Figure S2.

Among subjects who were on CNB treatment at 12 months and for whom data about dosage of concomitant ASMs were available ($n = 137$), the median total DDD of all the concomitant ASMs decreased from 3.34

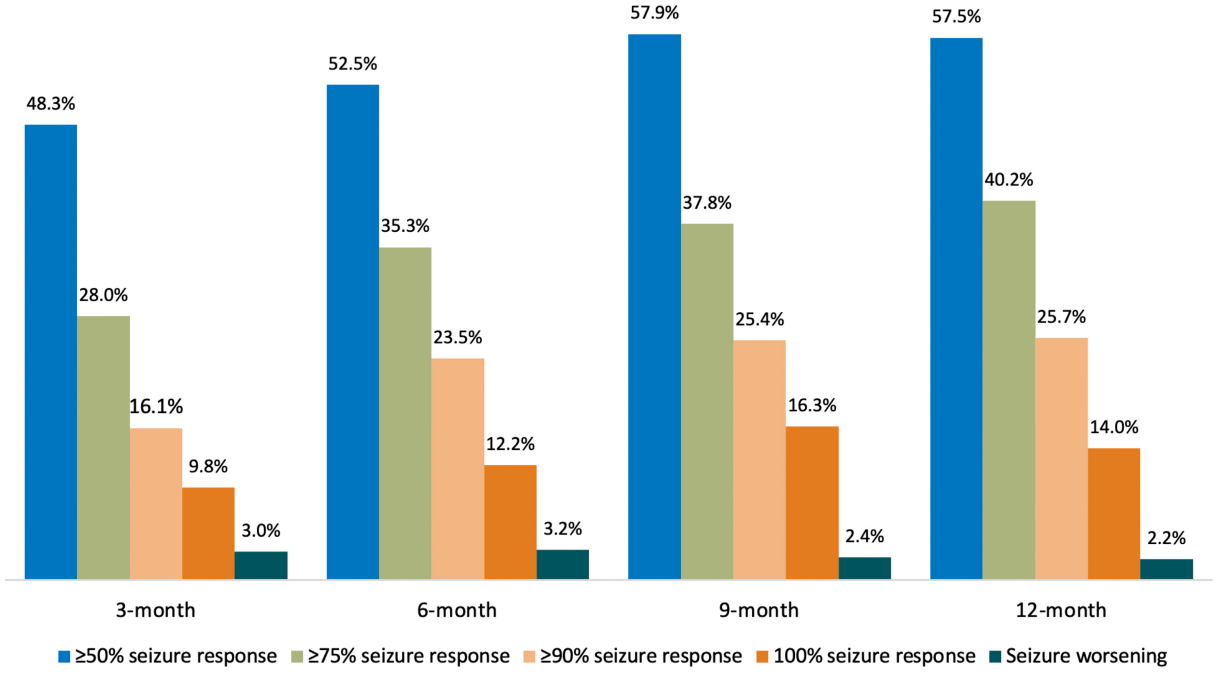

FIGURE 1 Clinical response to adjunctive cenobamate. Proportion of subjects with a ≥50%, ≥75%, ≥90%, and 100% (seizure freedom) reduction and >25% increase (seizure worsening) in monthly seizure frequency relative to baseline at 3, 6, 9, and 12 months is reported. Seizure freedom at each time point was defined as the occurrence of no seizures during at least the preceding 3 months.

(Q_1–Q_3 = 2.50–4.47) at baseline to 2.50 (Q_1–Q_3 = 1.67–3.50) at 12 months ($p < .001$); the corresponding median percentage reduction was 22.2% (Q_1–Q_3 = 8.9–34.8). According to the main mechanism of action, the highest rates of treatment withdrawal and the highest percentage reductions in the DDD were observed for perampanel, SCBs, and GABAergic modulators. There were no concomitant ASM withdrawals in the subgroup of subjects who were not taking PK interacting ASMs (Table 3). The percentage median changes from baseline in the total DDD (considering all the ASMs, including CNB) and by class of ASMs at 12 months are shown in Figure 2, in both the overall and the stratified population. The median total DDD at 12 months was 3.50 (Q_1–Q_3 = 2.75–4.80) in the overall population, corresponding to a median percentage change of 8.9 (Q_1–Q_3 = −7.1 to 26.9) compared with baseline ($p < .001$). In the stratified subgroups, the median percentage change of total DDD at 12 months was 20.7 (Q_1–Q_3 = −3.1 to 40), with a median absolute value significantly higher than baseline ($p < .0001$) in subjects who were not taking PK interacting ASMs, as well as in those who were treated with SCBs (median percentage change = 10, Q_1–Q_3 = −6.4 to 26.9; $p = .0001$) and perampanel (10.3, Q_1–Q_3 = −5.3 to 64.5; $p = .017$). No statistically significant differences were observed in the total DDD of the remaining subgroups (concomitant PK interacting ASMs: $p = .385$, GABAergic modulators: $p = .309$, SV2A ligands: $p = .264$, valproic acid: $p = .963$; Figure 2 and Figure S3). When the drug load was assessed for each class of ASMs, a statistically significant reduction was observed in the 12-month median values of all the subgroups compared with baseline (Figure 2 and Figure S4). The temporal trend of percentage changes from baseline in the drug load throughout the 12-month follow-up is shown in Figure 3.

4 | DISCUSSION

In this real-world analysis, the effectiveness of CNB was shown in subjects with uncontrolled focal onset seizures who were treated according to clinical practice. In the cohort of participants included in the Italian EAP, who have a long duration of epilepsy and a high number of prior and concomitant ASMs, the 12-month rates of ≥50% reduction in baseline seizure frequency and seizure freedom were 57.5% and 14.0%, respectively. In addition, 29.6% and 6.2% of the subjects were sustained seizure responders and sustained seizure-free at 12 months from the introduction of CNB. These findings support the efficacy of CNB to control seizures when added to current therapeutic regimens in everyday clinical practice in people with difficult-to-treat epilepsy, with more than half of the study cohort being represented by subjects with failure of six or more prior ASMs, representing so-called "absolute drug resistance."[18,25]

Notably, refractoriness was higher in this cohort compared to participants recruited in CNB clinical trials.

TABLE 2 Adverse events during cenobamate treatment.

Overall cohort	**236**
Subjects with adverse events	**133 (56.4)**
Total number of adverse events	**223**
Somnolence	66 (29.6)
Vertigo	46 (20.6)
Balance disorders	22 (9.9)
Diplopia	17 (7.6)
Confusion	11 (4.9)
Fatigue	11 (4.9)
Vomiting	8 (3.6)
Headache	8 (3.6)
Irritability	5 (2.2)
Mood change	5 (2.2)
Nausea	5 (2.2)
Blurred vision	3 (1.3)
Diarrhea	3 (1.3)
Dysarthria	3 (1.3)
Tremor	3 (1.3)
Cutaneous erythema	1 (.4)
Decreased appetite	1 (.4)
Erectile dysfunction	1 (.4)
Fever	1 (.4)
Nystagmus	1 (.4)
Xerostomia	1 (.4)
Hypotension	1 (.4)

Note: Data are given as *n* (%).

Subjects included in this study had a higher number of prior ASMs and a higher seizure frequency at baseline; of note, in the double-blind, randomized, placebo-controlled, dose–response clinical trial of Krauss and colleagues, the median number of ASMs taken at any time before the start of CNB was 3.[11] Furthermore, many of the subjects included in the EAP would have not been eligible for inclusion in the clinical trials due to the number and type of concomitant ASMs. Only subjects treated with 1–3 concomitant ASMs were eligible in randomized controlled trials, and those taking phenytoin or phenobarbital were excluded due to the potential for drug–drug interaction. Despite these differences, the effectiveness of CNB found in this analysis was consistent with outcomes from pivotal trials,[26] although negative predicting factors (e.g., number of previous ASMs and disease duration) could have forecast a lower response. Nevertheless, a post hoc analysis on randomized clinical trials supported the efficacy of CNB regardless of number of concomitant ASMs, baseline seizure frequency, and disease duration.[27]

Regulatory trials deviate markedly from standard practice, and the generalizability of their findings are hampered by the restrictive eligibility criteria, short follow-up, and rigid titration and dosing schedules.[28] Conversely, evidence produced in real-life settings can reflect daily experience and challenges, allowing further considerations and improving the use of each drug.

The outcomes in the current analysis consolidated data from the EAP conducted in other countries and findings from other real-world studies. The retrospective data collection of the Spanish EAP provided information on 170 subjects treated at 14 centers.[29] Among responders to treatment, the proportions of subjects achieving a ≥50%, ≥75%, ≥90%, or 100% reduction in seizure frequency since the previous visit increased with longer follow-up, and they were 74.4%, 56.4%, 38.5%, and 10.0% at 12 months. In a post hoc analysis, 18.1% of participants were continuously seizure-free during follow-up for at least 3 months, 19.5% for at least 6 months, and none for 12 months. The single-center, retrospective analysis of consecutive adults treated with CNB for at least 3 months within the Irish EAP included 57 subjects with ultraresistant epilepsy. A reduction in baseline seizure frequency by 50%–74%, 75%–99%, and 100% was observed in 42.1%, 28.1%, and 5.3% of the cohort.[30] Within the Polish EAP, 38 subjects were treated with CNB for a median time of 41 months; by the end of the observation period, 63.1% of the subjects achieved ≥50% seizure reduction, 39.5% achieved ≥75% reduction, and 21% experienced complete seizure freedom for at least 12 months.[31] Several series, which also included participants with highly active and ultrarefractory epilepsy, have overall confirmed the effectiveness of CNB in clinical practice.[32]

The 12-month retention rate observed in the cohort was 78.8%. The pooled data analysis from the clinical development program including 1844 participants also found long-term individual retention with CNB. The 1-year and 2-year retention rates were 80% and 72%, and they were reportedly higher compared with historical postmarketing retention estimates of commonly prescribed ASMs at a UK tertiary care center.[33]

AEs were observed in 56.4% of the participants throughout the 12-month follow-up, and most were mild in intensity. The most common AEs included somnolence, dizziness, and balance disorders, which are consistent with the PD properties of CNB and substantially overlap the tolerability profile of the majority of the ASMs.[34] These data matched the available evidence about the tolerability of adjunctive CNB obtained in both randomized and open-label studies.[26,29,32] No serious AEs occurred, and there were no cases of idiosyncratic drug reactions, further suggesting that the titration schedule with dose increments every 2 weeks represents a useful

TABLE 3 Withdrawal rates and changes in DDD of concomitant ASMs at 12 months.

ASM	Withdrawal rate, *n* (%)	Absolute change in DDD, median (Q_1–Q_3)	Percentage change in DDD, median (Q_1–Q_3)
Grouped by mechanism of action			
Sodium channel blockers, *n* = 121	18 (14.9)	−.33 (−.85 to .00)	−23.08 (−56.23 to .00)
GABAergic modulators, *n* = 87	12 (13.8)	.00 (−.75 to .00)[a]	.00 (−50.00 to .00)[a]
SV2A ligands, *n* = 52	6 (11.5)	.00 (.00–.00)	.00 (.00 to .00)
Valproic acid, *n* = 34	3 (8.8)	.00 (−.31 to .00)	.00 (−38.13 to .00)
Perampanel, *n* = 27	6 (22.2)	−.25 (−.50 to .00)	−25.00 (−50.00 to .00)
Grouped by known PK interactions			
PK interacting ASMs, *n* = 78	13 (16.7)	−.33 (−1.00 to .00)[b]	−25 (−66.67 to .00)[b]
No PK interacting ASMs, *n* = 59	0 (.0)	.00 (.00–.00)	.00 (.00 to .00)

Note: Data are obtained from subjects who were receiving the specific drug class agent at baseline. PK interacting ASMs included clobazam, phenobarbital, phenytoin, and primidone.

Abbreviations: ASM, antiseizure medication; DDD, defined daily dose; GABAergic, γ-aminobutyric acidergic; PK, pharmacokinetic; SV2A, synaptic vesicle protein 2A.

[a]GABAergic modulators were introduced in two subjects who were not receiving them at baseline (*n* = 89).

[b]PK interacting ASMs were introduced in two subjects who were not receiving them at baseline (*n* = 67).

strategy to avoid or minimize the risk of these adverse effects.

One major aim of the current study was to assess the variations of the load of concomitant ASMs. Among subjects who were on CNB treatment at 12 months, a decrease in the number of concomitant ASMs occurred in 46.9% cases and the median decrease in total DDD was 22%. The ASMs that have been mostly withdrawn or had their dosage reduced were ASMs whose metabolism is inhibited by CNB; among those there were both SCBs (phenytoin) and GABAergic modulators (clobazam, phenobarbital, primidone). The withdrawal/dose reduction of these two classes of ASMs was expected, also considering the PD properties of CNB. The temporal analysis of the variations in the DDD also showed how the reduction in the dosage of concomitant ASMs started early after the introduction of CNB and tended to continue throughout the 12 months. Of note, the highest reduction in the SCB dosage was observed after 6 months of follow-up, followed by an increase at 9 months and then a reduction at 12 months; such findings might reflect the complexity of balancing efficacy and tolerability issues during treatment. Additionally, these results highlight how the analysis of the drug load is merely an attempt to provide a quantifiable measure of changes in ASM management. ASM polytherapy is based on the combination of different therapeutic choices, in which PK and PD interactions can be exploited advantageously or not, and it cannot be reduced to a simple matter of amount of medication. Therefore, all the considerations about drug load should be made bearing in mind this perspective. The dose reduction of concomitant ASMs contributed to minimizing the global change in the total DDD to a median increase of <10% in the overall cohort. Critically analyzing these results, the total DDD did not change in the subgroups of patients who were treated with PK interacting ASMs, GABAergic modulators, SV2A ligands, and valproic acid. On one hand, it should be and usually is normal clinical practice to reduce the number of concomitant drugs when introducing a new ASM effective on seizure control. This phenomenon is likely to occur any time a new drug is introduced displaying efficacy. On the other hand, the reduction in the load of PK interacting ASMs and GABAergic modulators was likely linked to tolerability issues.

These two subgroups are partly overlapping, as the PK interacting group consisted mainly of GABAergic modulators (3/4) and there were 76 of 87 ASMs with known CNB-mediated increase in serum levels in the GABAergic subgroup. It is now well understood that the combination of CNB with GABAergic modulators mainly leads to the appearance of PD-related side effects. Therefore, it is difficult to establish how much the increase in serum levels of the concomitant drugs due to PK interactions (or their proactive reduction to prevent it) and PD-related side effects have contributed to reducing the drug load of these classes. However, we might hypothesize that PK interactions leading to the inhibition of CYP-mediated metabolism played a major role, because the overall drug load in

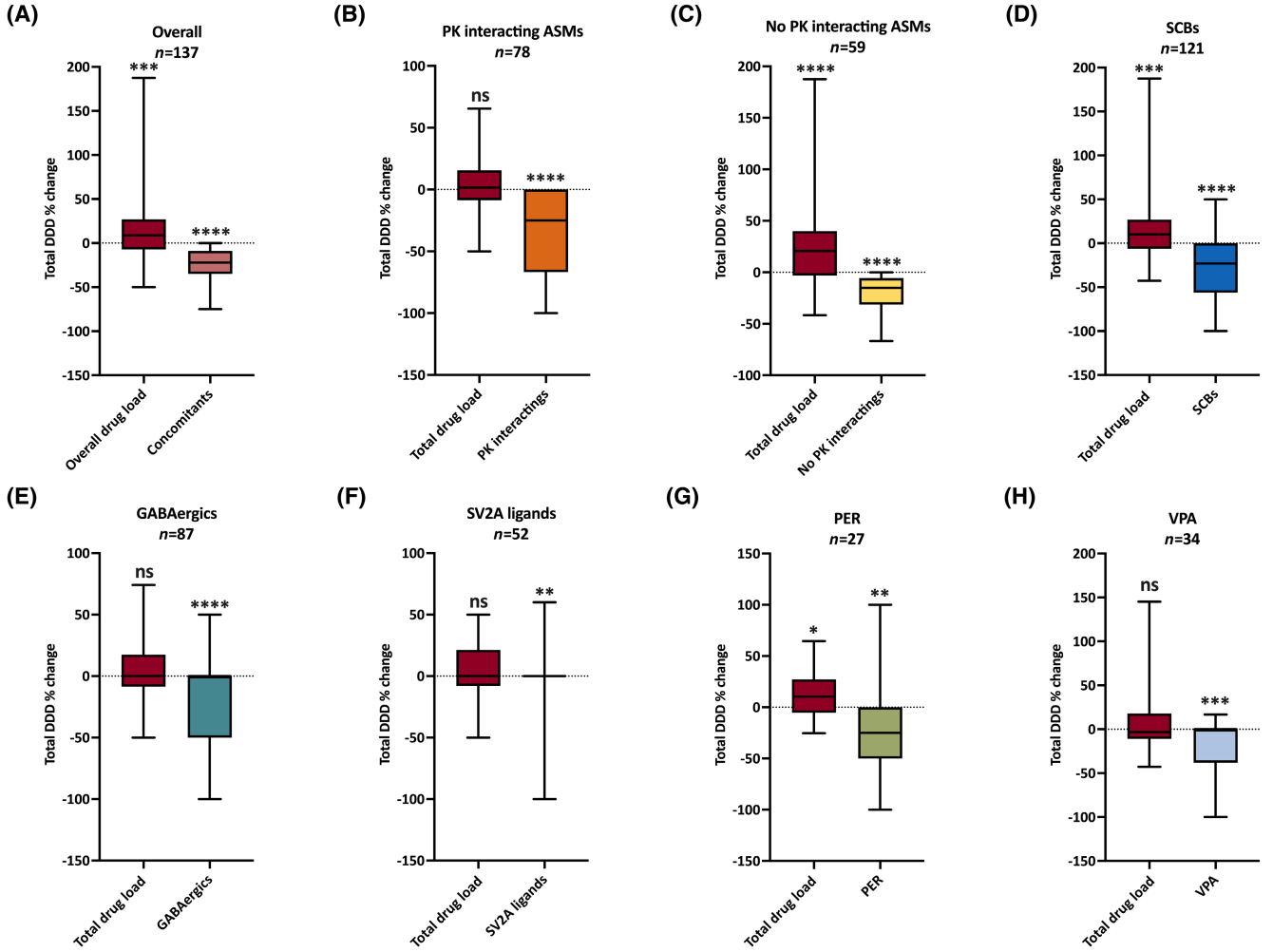

FIGURE 2 Percentage change in the total defined daily dose (DDD) and by class of concomitant antiseizure medications (ASMs) at 12 months in the overall and the stratified population. (A) Percentage changes in the total drug load and in the load of all concomitant ASMs compared with baseline in the overall 12-month population. (B) Percentage changes in the total drug load and in the load of PK interacting ASMs compared with baseline in the 12-month population taking at least one pharmacokinetic (PK) interacting ASM (i.e., clobazam, phenobarbital, phenytoin, primidone). (C) Percentage changes in the total drug load and in the load of ASMs without known PK interactions compared with baseline in the 12-month population taking no PK interacting ASMs. (D) Percentage changes in the total drug load and in the load of sodium channel blockers (SCBs) compared with baseline in the 12-month population taking at least one SCB. (E) Percentage changes in the total drug load and in the load of γ-aminobutyric acidergic (GABAergic) modulators compared with baseline in the 12-month population taking at least one GABAergic modulator. (F) Percentage changes in the total drug load and in the load of synaptic vesicle protein 2A (SV2A) ligands compared with baseline in the 12-month population taking at least one SV2A ligand. (G) Percentage changes in the total drug load and in the load of perampanel (PER) compared with baseline in the 12-month population taking PER. (H) Percentage changes in the total drug load and in the load of valproic acid (VPA) compared with baseline in the 12-month population taking VPA. Boxes limits indicate Q_1–Q_3 values, with a central line highlighting the median value. Lines extend from each box to show minimum and maximum values. Asterisks summarize *p*-values of the Wilcoxon matched-pairs signed-rank test comparing absolute 12-month values with baseline (see Figures S3 and S4). ns, not significant. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$; ****$p \leq .0001$.

the subgroups of patients without concomitant PK interacting ASMs increased compared with baseline, as well as in those who were taking SCBs, which are also known to cause PD-related side effects. In both cases, the overall drug load was not completely redistributed after the introduction of CNB, although the increase was counterbalanced by the improvement in seizure control. It should be kept in mind that drug adjustments follow the overall clinical outcomes. In other words, if CNB is showing efficacy, then the appearance of SCB-linked side effects supports the reduction of these concomitant drugs. The complexity of this management is highlighted by the oscillations in the doses used for SCBs in this study over time. The necessity of drug adjustments has been recently discussed in an expert consensus recommending that doses of clobazam, phenytoin, phenobarbital, and lacosamide should

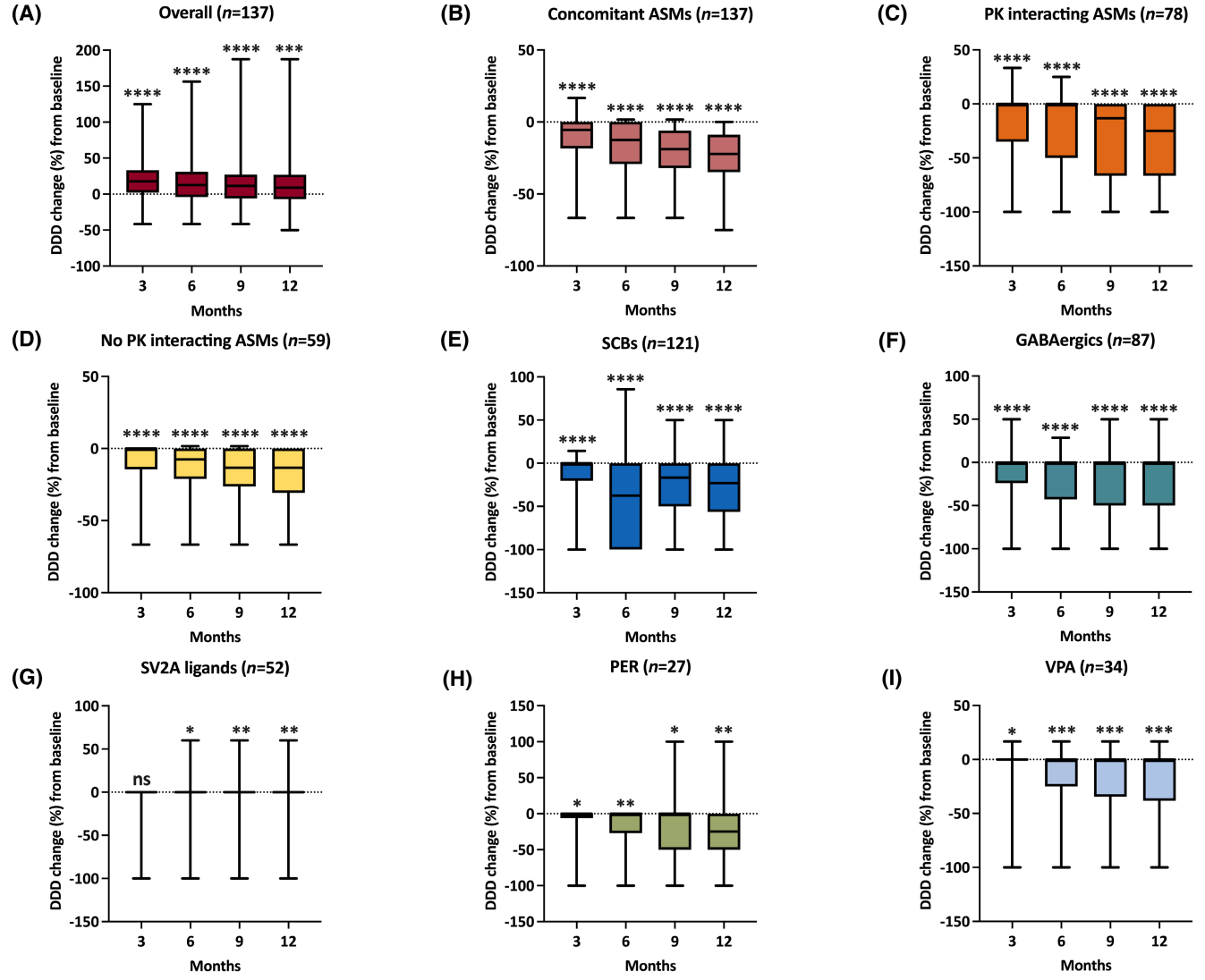

FIGURE 3 Percentage changes from baseline in the total defined daily dose (DDD) and by class of concomitant antiseizure medications (ASMs) during follow-up. Percentage changes from baseline are shown at 3, 6, 9, and 12 months in the total (including cenobamate) DDD (A) and in the DDDs of all the concomitant ASMs (B), ASMs with known pharmacokinetic (PK) interactions (i.e., clobazam, phenobarbital, phenytoin, primidone; C), ASMs without known PK interactions (D), sodium channel blockers (SCBs) (E), γ-aminobutyric acidergic (GABAergic) modulators (F), synaptic vesicle protein 2A (SV2A) ligands (G), perampanel (PER; H), and valproic acid (VPA; I). Boxes limits indicate Q_1–Q_3 values, with a central line highlighting the median value. Lines extend from each box to show minimum and maximum values. Asterisks summarize *p*-values of the Wilcoxon matched-pairs signed-rank test comparing absolute values of each time point with baseline. ns, not significant. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$; ****$p \leq .0001$.

be reduced proactively during CNB treatment due to PK and PD drug–drug interactions.[35] However, the definition of proactive must be intended as a clinically meaningful decision of adjusting both CNB and concomitant drugs in the safest way, personalizing the therapeutic approach. For example, it has been suggested that the concomitant use of clobazam may be relevant and the drug may not be completely withdrawn (see below for further discussion on this aspect).[36] The cohort of patients treated with perampanel had the highest withdrawal rate; it can be speculated that perampanel withdrawal was linked to the choice of reducing the DDD load, discontinuing an ASM whose efficacy could be reduced by the CNB-mediated CYP3A4 induction. However, this cohort was the smallest, being composed of only 27 subjects, and this made it difficult to draw definitive conclusions and generalize the results.

So far, only a few studies have explored the pharmacological burden after the introduction of CNB in the therapeutic regimen, and there are very limited data about the variations in DDD over time. Moreover, none of these studies has taken into account the contribution of CNB to the overall DDD. In the Spanish EAP cohort, the number of concomitant ASMs at the last visit was reduced in 44.7% of participants, and SCBs and clobazam were those most

frequently discontinued.[29] In a retrospective chart review of 90 subjects treated with CNB at a single US center, discontinuation and dose reduction of one or more concomitant ASMs occurred in 50% and 23.3% of the cohort. Furthermore, 14.4% of the subjects successfully transitioned from polytherapy to CNB monotherapy.[37] In a small retrospective, single-center study including 20 subjects within the Spanish EAP, the total DDD for concomitant ASMs decreased from 3.6 to 2.6 after 6 months of treatment and it was significantly lower for benzodiazepines, SCBs, and perampanel compared with baseline. Of note, the reduction in concomitant ASMs was the most important factor driving cognitive improvement.[38] In a post hoc analysis of a US phase 3, multicenter, open-label study of CNB, 24.6% of 240 participants discontinued one or more concomitant ASMs completely.[39] Subjects who benefitted from CNB reduced the doses of concomitant ASMs, these being SCBs and GABAergic modulators already reduced during the titration phase of CNB. Doses of some concomitant ASMs, like levetiracetam and brivaracetam, were adjusted latest in the maintenance phase to reduce the overall drug load rather than because of specific issues with tolerability.[39] According to a further post hoc analysis of the same open-label, phase 3 study, the mean concomitant ASM drug load was reduced by 29.4% at 12 months after CNB initiation and the greatest reduction was in benzodiazepines; reductions were observed regardless of age, prior surgery, and baseline seizure frequency.[40]

A further issue arising any time a new drug arrives on the market is linked to the best combinations. With CNB surely arises the question about its combination with SCBs. The knowledge of the mechanism by which sodium currents are influenced by the various ASMs[41,42] and the accumulated evidence already allow some speculations: (1) CNB is effective despite the failure of previous SCBs; and (2) the combination of CNB with SCBs generally leads to the appearance of side effects, which require dosage adjustments and optimization of the therapy on a personalized base.[43] Regarding the positive modulation of $GABA_A$ receptors by CNB, the combination with GABAergic drugs deserves further study.[44] We did not observe any difference in the effectiveness outcomes comparing the groups with or without a GABAergic drug. However, among subjects who were taking a GABAergic drug, the presence of clobazam suggested a higher probability of response to CNB and a similar trend was observed comparing responders with and without clobazam. The PK interaction between CNB and clobazam is well known; it is due to the inhibition of CYP2C19 by CNB and characterized by the increase in plasma levels of desmethyl-clobazam, the active metabolite of clobazam, which may at least partially explain the enhanced effect on seizure frequency reduction. A PD synergy that may further contribute to the higher efficacy of CNB when given in combination with clobazam has been also recently hypothesized[45] albeit not demonstrated. Because the lack of statistical significance could be due to a relatively small sample, this combination deserves to be further explored and considered a valuable choice when appropriate and tolerated. It is also clear that the concomitant use of CNB with GABAergic drugs is generally linked to the appearance of sedation.

4.1 | Strengths and limitations

The main strengths of this study include the recruitment at multiple sites and the large sample size. Of note, this analysis is based on the larger population among the studies that so far assessed the effectiveness of adjunctive CNB in real-world clinical practice. The study built up the currently available evidence about the impact of CNB treatment on the pharmacological burden by adopting the total DDD and providing information about its temporal variations. The DDD represents a more reliable measure of the actual changes in concomitant ASMs than solely the number of ASMs discontinued. In addition, the real-world setting offers a high degree of external validity and generalizability of the findings to everyday clinical practice. Some shortcomings also need to be acknowledged. Main limitations include the open-label and retrospective design, which may have introduced potential sources of biases, and the lack of a control group treated with an alternative option, which prevented comparison of the effectiveness of CNB with other ASMs. The small number of subjects receiving CNB doses of >300 mg/day did not allow fully exploring dose–response relationships with the outcomes. Furthermore, no therapeutic drug monitoring data were available to evaluate the effects of PK interactions on effectiveness and tolerability outcomes, and missing data on subtype of etiology and treatment response by seizure type did not allow further explorative subgroup analyses. Finally, no standardized questionnaires were used to collect AEs and to examine the effects of treatment on patient-reported outcome measures and quality of life.

5 | CONCLUSIONS

The data analysis of the Italian EAP provided the opportunity to expand the real-world evidence on the effectiveness of CNB in a large population of people with uncontrolled focal epilepsy and gain additional knowledge on its clinical use. Research is warranted to investigate the most advantageous therapeutic combinations, explore the actual

potential of CNB as early add-on treatment, and provide further practical guidance for clinical decisions.

AUTHOR CONTRIBUTIONS

Roberta Roberti, Emilio Russo, Simona Lattanzi: Conception and design of the study; acquisition and analysis of data; drafting a significant portion of the manuscript and figures; final revision of the manuscript. **Giovanni Assenza, Francesca Bisulli, Giovanni Boero, Laura Canafoglia, Valentina Chiesa, Carlo Di Bonaventura, Giancarlo Di Gennaro, Maurizio Elia, Edoardo Ferlazzo, Alfonso Giordano, Angela La Neve, Claudio Liguori, Stefano Meletti, Francesca Felicia Operto, Nicola Pietrafusa, Monica Puligheddu, Patrizia Pulitano, Eleonora Rosati, Ilaria Sammarra, Elena Tartara, Giampaolo Vatti, Flavio Villani:** Acquisition of data; critical revision of the manuscript. **Cenobamate Expanded Access Program Italy Study Group:** Significant contribution to data acquisition.

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CONFLICT OF INTEREST STATEMENT

R.R. has received consultancy fees from Eisai. F.B. has received consultancy fees from Angelini Pharma, UCB Pharma, Jazz Pharmaceuticals, and Eisai. L.C. has received travel support from Angelini Pharma. V.C. has received consulting fees from UCB Pharma. C.D.B. has received consulting fees and honoraria from GW Pharmaceuticals, UCB Pharma, Eisai, Angelini Pharma, and Bial. G.D.G. has served on advisory boards for or has received consultancy fees from Angelini Pharma, UCB Pharma, and Neuraxpharma, and has received speaker honoraria from Angelini Pharma, Eisai, LivaNova, and Lusofarmaco. E.Fe. has received speaker honoraria from UCB Pharma, Eisai, and Angelini Pharma. A.L.N. has received speaker or consultancy fees from Eisai, Mylan, Sanofi, Bial, GW, UCB Pharma, Arvelle Therapeutics, Angelini Pharma, and Neuraxpharm. C.L. has received research support and speaker honoraria from Angelini Pharma and has no other relevant conflict of interests related to this article. S.M. has received consulting fees or speaker honoraria from UCB Pharma, Eisai, Jazz Pharmaceuticals, and Angelini Pharma. P.P. has received consulting fees or speaker honoraria from Angelini Pharma, UCB Pharma, and Eisai. E.Ro. has received consultancy fees from Angelini Pharma, UCB Pharma, Jazz Pharmaceuticals, Ecupharma and Eisai. E.T. has received speaker fees from Angelini Pharma. F.V. has received speaker fees from Angelini Pharma, UCB Pharma, Eisai, Lusofarmaco, and Jazz Pharmaceuticals, and has

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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