Long-term Efficacy and Safety From an Open-Label Extension of Adjunctive Cenobamate in Patients With Uncontrolled Focal Seizures

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Abstract

Background and Objectives
To evaluate long-term efficacy (percent seizure frequency reduction and responder rates), safety, and tolerability of adjunctive cenobamate (CNB) in an open-label extension (OLE) of the randomized, double-blind, placebo-controlled study.

Methods
Patients (aged 18–70 years) with uncontrolled focal seizures despite treatment with 1–3 antiseizure medications who completed the 18-week double-blind study (n = 360) could enter the OLE, where they underwent a 2-week blinded conversion to CNB (target dose, 300 mg/d; min/max, 50/400 mg/d).

Results
Three hundred fifty-five patients were included in the OLE safety population (265 originally randomized to CNB, 90 originally randomized to placebo), and 354 were included in the OLE modified intent-to-treat population. As of July 2019, 58.9% of patients (209/355) were continuing CNB treatment and 141 had discontinued, including 16.6% (59/355) because of lack of efficacy, 8.7% (31/355) because of withdrawal by patient, and 7.6% (27/355) because of adverse events. The median (range) duration of OLE exposure was 53.9 (1.1–68.7) months. Retention rates at 12, 24, 36, and 48 months were 83%, 71%, 65%, and 62%, respectively. Median percent seizure frequency reduction over baseline increased with each 6-month OLE interval, up to 76.1% at months 43–48. Among observed patients, 16.4% (36/220) achieved 100% and 39.1% (86/220) achieved ≥90% seizure reduction during >36–48 months. Among the initial OLE modified intent-to-treat population, 10.2% of patients (36/354) achieved 100% and 24.3% (86/354) achieved ≥90% seizure reduction during >36–48 months. Similar to the double-blind study, adverse events (AEs) included dizziness, somnolence, fatigue, and headache. Serious AEs occurred in 20.3% of patients (72/355).

Discussion
Long-term efficacy, including 100% and ≥90% seizure reduction, was sustained during 48 months of CNB treatment, with 71% retention at 24 months. No new safety issues were identified. These results confirm the findings of the double-blind study and support the potential long-term clinical benefit of CNB.

Classification of Evidence

This study provides Class IV evidence that oral CNB 50–400 mg/d is effective as an adjunctive treatment for the long-term management of patients with uncontrolled focal seizures previously treated with 1–3 ASMs.

Trial Registration Information

ClinicalTrials.gov NCT01866111 (clinicaltrials.gov/ct2/show/results/NCT01866111).

Despite the introduction of more than 20 new antiseizure medications (ASMs) over the past few decades, the rate of patients with epilepsy achieving seizure freedom (defined as 100% seizure frequency reduction) has not improved.[1,2] Approximately 40% of patients with newly diagnosed focal epilepsy do not achieve ≥1 year of 100% seizure frequency reduction after 2 different ASMs.[3] Fewer than 1 in 10 patients with uncontrolled, drug-resistant focal epilepsy achieve 100% seizure frequency reduction with recently introduced ASMs in real-life outcome studies.[4] Patients with uncontrolled seizures experience poor quality of life, increased comorbidity and cognitive decline, higher health care costs, and are at increased risk of injuries and premature death, including deaths from status epilepticus, injuries, and sudden unexpected death in epilepsy (SUDEP).[5-10]

Cenobamate (CNB, XCOPRI; SK Life Science, Inc., Paramus, NJ) is a tetrazole alkyl carbamate derivative approved by the US Food and Drug Administration for the treatment of adults with focal seizures.[11] Two randomized controlled clinical trials have shown statistically significant reductions in seizure frequency, including 100% seizure frequency reduction, in CNB-treated adults with uncontrolled focal seizures.[12,13] One of these studies was an 18-week double-blind, dose-response phase 2 study with an optional open-label extension (OLE) (ClinicalTrials.gov NCT01866111).[12] In the 18-week double-blind period, the median percent reduction in focal seizure frequency per 28 days for the whole treatment period, including 6 weeks of titration and 12 weeks of maintenance treatment, was 35.5%, 55.0%, and 55.0% for CNB 100, 200, and 400 mg/d, respectively, compared with 24.0% for placebo (all $p < 0.01$ vs placebo).[12] During the 12-week maintenance phase, 3.9%, 11.2%, and 21.1% of patients treated with CNB 100, 200, and 400 mg/d, respectively, achieved 100% seizure reduction, compared with 1.0% for placebo.[12] The most common treatment-emergent adverse events (TEAEs) during double-blind treatment were CNS-related (e.g., somnolence, dizziness, and fatigue). Patients who completed the entire 18-week double-blind treatment period were eligible to continue CNB in the OLE. The purpose of this analysis was to assess the long-term efficacy, safety, and tolerability of CNB from the OLE of the phase 2 study in patients with uncontrolled focal seizures.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All patients provided written informed consent before study entry. The study was conducted according to the principles set forth by the International Conference on Harmonisation for Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by an independent ethics committee or institutional review board according to local regulations at each site.

Participants

Details of the 18-week, multicenter, double-blind, randomized, placebo-controlled study design (ClinicalTrials.gov NCT01866111) have been described elsewhere.[12] In brief, eligible patients aged 18–70 years with uncontrolled focal epilepsy and ≥8 seizures during the 8-week long baseline period who were taking 1–3 ASMs were included.

Study Design, Randomization, and Blinding

Patients in the double-blind study were randomized 1:1:1:1 to receive either placebo or CNB 100, 200, or 400 mg once daily, as previously reported.[12] The initial starting dose was 100 mg/d, which was uptitrated weekly by 100 mg/d. Owing to tolerability, the initial starting dose was later reduced to 50 mg/d (by protocol amendment), and the titration rate was slowed to 50 mg/day increments per week (up to 200 mg/d), then 100 mg/d increments per week (up to 400 mg/d). One case of drug reaction with eosinophilia and systemic symptoms (DRESS) also occurred during the initial faster titration protocol.[12]

The double-blind treatment period included a 6-week titration phase and a 12-week maintenance phase. Patients who completed the double-blind study and still met the inclusion criteria (except for seizure frequency) and met none of the exclusion criteria were eligible to enter the OLE. Patients who

Figure 1 Patient Disposition and Reason for Discontinuation (OLE Population)

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┌─────────────────────────────┐
│   Completed double-blind     │
│        (N = 360)             │
└─────────────────────────────┘
               │          ┌──────────────────────────────────────┐
               ├─────────▶│ Excluded; did not enter OLE (n = 4):  │
               │          │ • Adverse event (1)                   │
               │          │ • Withdrawal by patient (1)           │
               │          │ • Withdrawal by sponsor due to        │
               │          │   noncompliance (1)                   │
               │          │ • Reason unspecified (1)              │
               │          └──────────────────────────────────────┘
┌─────────────────────────────────────┐
│ Entered OLE (n = 356):               │
│ • Analyzed for safety (n = 355)      │
│ • Analyzed for efficacy (mITT, n = 354) │
└─────────────────────────────────────┘
               │
┌─────────────────────────────────────┐
│ Discontinued (n = 141):              │
│ • Lack of efficacy (59)              │
│ • Withdrawal by patient (31)         │
│ • Adverse event (27)                 │
│ • Lost to follow-up (7)              │
│ • Death (5)                          │
│ • Protocol violation (3)             │
│ • Other (9)                          │
└─────────────────────────────────────┘
               │          ┌──────────────────────────────┐
               ├─────────▶│ Completed OLE study[a]        │
               │          │         (n = 5)               │
               │          └──────────────────────────────┘
┌─────────────────────────────────────┐
│ Ongoing at data cutoff               │
│     (n = 209; 58.9%)                 │
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[a]Study completion as reported on the end-of-study subject disposition case report form. mITT = modified intent-to-treat; OLE = open-label extension.

chose to enter the OLE underwent a 2-week double-blind conversion to a target dose of CNB 300 mg once daily. During the 2-week conversion phase, patients received a blinded treatment ranging from placebo to 200 mg/d CNB (depending on the assigned dose) plus an open-label treatment. For patients originally assigned to placebo in the double-blind study, open-label treatment with CNB started at a target dose of 100 mg/d at week 1, followed by 200 mg/d at week 2 and 300 mg/d starting at week 3. During the 2-week conversion, the investigator could increase or decrease the open-label dose, if clinically indicated, to a minimum of 50 mg/d and maximum of 400 mg/d. Therefore, although the target open-label dose of CNB was 300 mg/d, patients may have been taking 50–400 mg/d at week 3 of the OLE. Doses of concomitant ASMs could be adjusted during the conversion phase. During the OLE treatment phase, concomitant ASMs could be added, removed, or adjusted (no CNB monotherapy allowed) and CNB dose could be adjusted.

Outcomes

Scheduled OLE study assessments occurred every 2 weeks for the first month and then every 3 months. Patients continued to record seizure frequency/type (patient diaries) in the OLE. For efficacy assessments, all focal seizures except focal aware nonmotor were counted. Efficacy assessments included median percent change in focal seizure frequency over baseline of the double-blind study, analyzed at consecutive 6-month intervals,

Table 1 Patient Demographics and Baseline Characteristics (Safety Population)

	All cenobamate (n = 355)
Age, y, median (IQR)	38 (17)
Female, n (%)	170 (47.9)
BMI, mean (SD), kg/m²	26.4 (6.19)
Race, n (%)	
Caucasian/White	306 (86.2)
Asian	32 (9.0)
Black/African-American	9 (2.5)
Other	8 (2.3)
Seizure type by history, n (%)[a]	
Focal aware nonmotor	75 (21.1)
Focal aware motor	77 (21.7)
Focal impaired awareness	275 (77.5)
Focal to bilateral tonic-clonic	209 (58.9)
Baseline seizure frequency/28 d[b]	
Median (IQR)	9.5 (15)
Mean (SD)	24.1 (56.9)
No. of background/concomitant ASMs[c] at baseline of double-blind, n (%)	
1	55 (15.5)
2	139 (39.2)
3	154 (43.4)
>3	7 (2.0)
Background/concomitant ASMs (≥10% of patients), n (%)	
Levetiracetam	153 (43.1)
Lamotrigine	118 (33.2)
Carbamazepine	97 (27.3)
Valproate[d]	87 (24.5)
Topiramate	63 (17.7)
Lacosamide	61 (17.2)
Oxcarbazepine	49 (13.8)

Abbreviations: ASM = antiseizure medication; BMI = body mass index; IQR = interquartile range.
[a] Patients may be reported in more than 1 category.
[b] Baseline seizure frequency = number of seizures over baseline period (56 days before study day 1) divided by number of days in the interval multiplied by 28.
[c] Defined as ASM started before and are ongoing at the time of first dose in the double-blind study.
[d] Valproate includes all forms of valproate, valproic acid, or divalproex sodium.

and the percent of patients with 100% seizure reduction, analyzed at consecutive 12-month intervals. The duration of 100% seizure reduction was also analyzed during any consecutive

Figure 2 Kaplan-Meier Plot of Time to Discontinuation During OLE
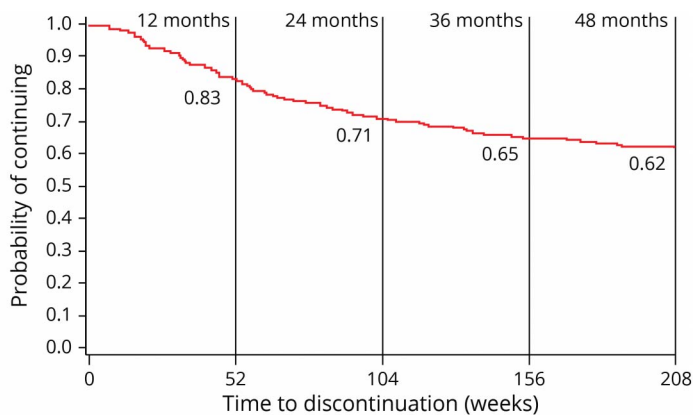
Event = early discontinuation from OLE. Patients who completed the study and patients ongoing at the date of data cutoff are considered as censored. OLE = open-label extension.

≥12-month or ≥24-month interval (i.e., interval did not have to include the last visit). Additional responder rates (≥50%, ≥75%, ≥90%) were also analyzed at 12-month intervals. Safety assessments, including frequency, seriousness, and timing of treatment-emergent adverse events (TEAEs); TEAEs leading to discontinuation; and the Columbia Suicide Severity Rating Scale (C-SSRS) were assessed at every OLE visit. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 20.0.

Statistical Analysis

This analysis used a data cutoff of July 1, 2019. The OLE safety population was defined as all patients who entered the OLE and had taken at least 1 dose of CNB. The OLE modified intent-to-treat (mITT) population was defined as all patients who had taken at least 1 dose of CNB and had any seizure data recorded in the OLE. Two different methods were used for the analysis of responder rates over time using the OLE mITT population: (1) The observed or active patient population at each 12-month interval was used as the denominator and (2) a more conservative approach that used the initial OLE mITT population at each 12-month interval was used as the denominator.

Data Availability

The data for the analyses described in this article are available by request from the corresponding author, investigators, or SK Life Science, Inc. (Paramus, NJ, USA), the company sponsoring the clinical development of CNB for the treatment of focal epilepsy. At the time of the request, the format and scope of the anonymized data to be disseminated will be determined by the authors and SK Life Science, Inc.

Results

Between July 31, 2013, and June 22, 2015, 437 patients were randomized and participated in the double-blind C017 study,

including 108 patients treated with placebo and 108, 110, and 111 patients treated, respectively, with 100, 200, and 400 mg/d of CNB; 360 patients completed the double-blind study.[12] Of the patients who completed the study, 356 (98.9%) entered the OLE (Figure 1). One patient did not have any dose data recorded, leaving 355 in the OLE safety population, including 265 who were originally randomized to CNB and 90 who were originally randomized to placebo and transitioned to CNB. One additional patient did not have any seizure data and was not included in the mITT population (n = 354). Baseline demographics of the OLE were similar to those of the double-blind study[12] regarding median age (38 years, interquartile range [IQR] 17), sex (47.9% female), and mean body mass index (26.4 kg/m^2) (Table 1). Most of the patients in the OLE population (82.5% [293/355]) were taking 2 or 3 concomitant ASMs at baseline of the double-blind study.

As of July 2019, 58.9% of patients (209/355) were continuing in the OLE; 141 patients discontinued, including 16.6% (59/355) because of lack of efficacy, 8.7% (31/355) because of withdrawal by patient, and 7.6% (27/355) because of adverse events (Figure 1). In the safety population, the median duration of CNB OLE exposure was 53.9 months (IQR 40.6 months; range 1.1–68.7 months); 82.8% of patients were treated for at least 12 months (eTable 1, links.lww.com/WNL/C130). At 12, 24, 36, and 48 months after OLE initiation, 83%, 71%, 65%, and 62% of patients, respectively, continued CNB treatment (Figure 2). The median modal daily CNB dose was 300 mg (IQR 100 mg; range 50–400 mg); the mean (SD) modal dose was 264.5 mg (89.1 mg).

Median percent reduction in seizure frequency during the first 6 months of the OLE for all CNB OLE patients was 65.4% (IQR 52.0%) and was similar among patients originally treated with CNB or placebo in the double-blind study (Figure 3). The median percent reduction in seizure frequency over baseline for all CNB OLE patients increased with

Figure 3 Median Percent Change in Seizure Frequency/28 Days by 6-Month Intervals During OLE (mITT Population)
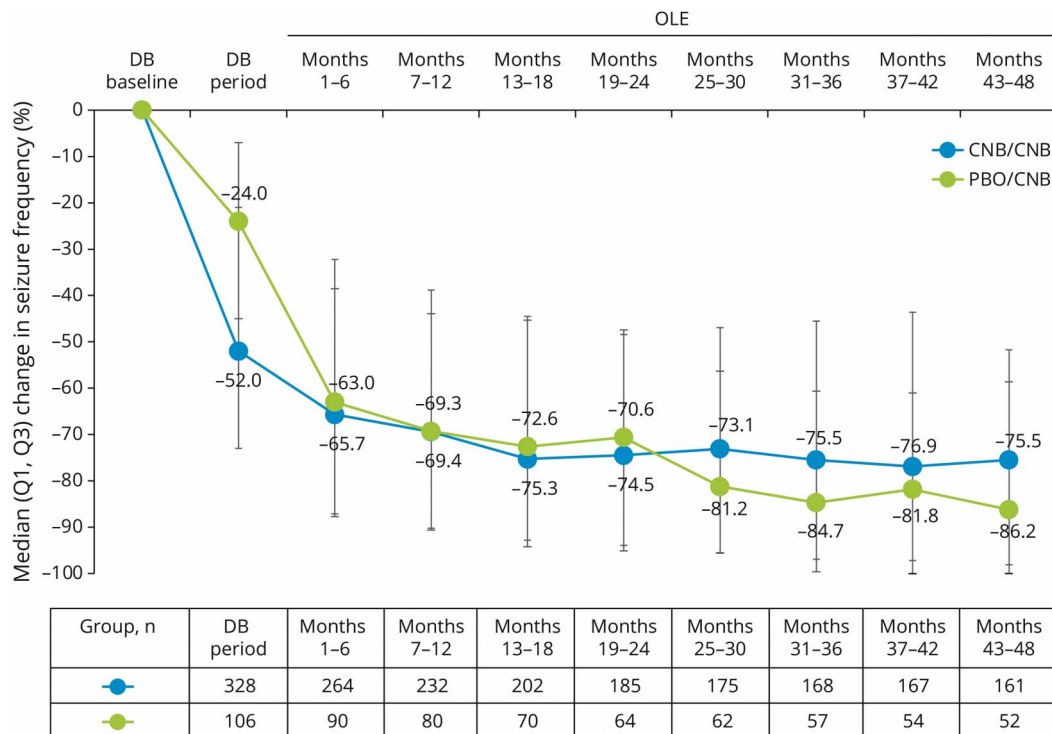

Median (IQR) baseline seizure frequency/28 days during the double-blind study for the 354 patients in the mITT population was 9.5 (16.0). CNB = cenobamate; DB = double-blind; IQR = interquartile range; mITT = modified intent-to-treat; OLE = open-label extension; PBO = placebo.

each 6-month OLE interval, up to 76.1% (IQR 44.8%) at months 43–48.

The percent of observed patients achieving 100% seizure reduction at consecutive 12-month intervals increased from 13.3% (36/271) during >12–24 months to 16.4% (36/220) during the last 12-month interval, >36–48 months (Figure 4). Among the patients in each 12-month interval group, the median (IQR) duration of 100% seizure reduction for the entire study was 48.0 (20.1) months, 47.2 (18.3) months, and 45.1 (27.4) months. The median modal daily dose for patients with 100% seizure reduction at each 12-month interval was 300 mg (IQRs ranging from 50 to 100 mg). When using the initial OLE mITT population (n = 354) as the denominator, 10.2% of patients (36/354) achieved 100% seizure reduction during the last 12 months of the 48-month treatment duration (Figure 4). In addition, 39.1% (86/220) of observed patients (24.3% of mITT, 86/354) had >90% seizure reduction during the last 12-month interval ending at month 48. Any consecutive ≥12-month duration of 100% seizure reduction occurred in 18.4% of patients (65/354), and any consecutive ≥24-month duration of 100% seizure reduction occurred in 11.9% of patients (42/354). Additional responder rates are shown in Figure 5. Seizure frequency reductions of ≥50% and ≥75% during >36–48 months were achieved in 76.4% (168/220) and 51.8% (114/220) of observed patients, respectively (Figure 5A).

At data cutoff, 6 deaths had been reported in the OLE (pneumonia/sepsis, septicemia, fatal injuries after being struck by a car, cardiogenic shock, myocardial infarction, and suicide). All were considered to be unrelated to the study drug by the investigator. The patient who experienced fatal cardiogenic shock was a 39-year-old man with no medical history of coronary artery disease, although an autopsy revealed underlying ischemic cardiomyopathy due to severe coronary arteriosclerosis. One patient (0.3%) completed suicide during the OLE. The patient, a 31-year-old man with no history of depression or psychiatric visit, committed suicide by hanging after 49.3 months of CNB treatment. He had argued with a family member 3 days prior. His medical history included a tumor in the right occipital lobe of unknown etiology since 2004. Concomitant ASMs included levetiracetam and lamotrigine. There was no indication for any suicidal behavior or ideation from the C-SSRS assessments during treatment. Serious TEAEs occurred in 20.3% (72/355) of patients (Table 2 and eTable 2, links.lww.com/WNL/C130). Overall, the most common serious TEAEs (≥0.5%) were seizure (1.4%, n = 5), vertigo (1.1%, n = 4), seizure cluster (0.8%, n = 3), dizziness (0.6%, n = 2), epilepsy (0.6%, n = 2), generalized tonic-clonic seizure (0.6%, n = 2), myocardial infarction (0.6%, n = 2), cholelithiasis (0.6%, n = 2), pneumonia (0.6%, n = 2), pyelonephritis (0.6%, n = 2), sepsis (0.6%, n = 2), accidental overdose (0.6%, n = 2), clavicle fracture (0.6%, n = 2), and concussion (0.6%, n = 2)

Figure 4 100% Reduction in Seizure Frequency by 12-Month Intervals During OLE (mITT Population)

mITT = modified intent-to-treat; OLE = open-label extension; SE = standard error.
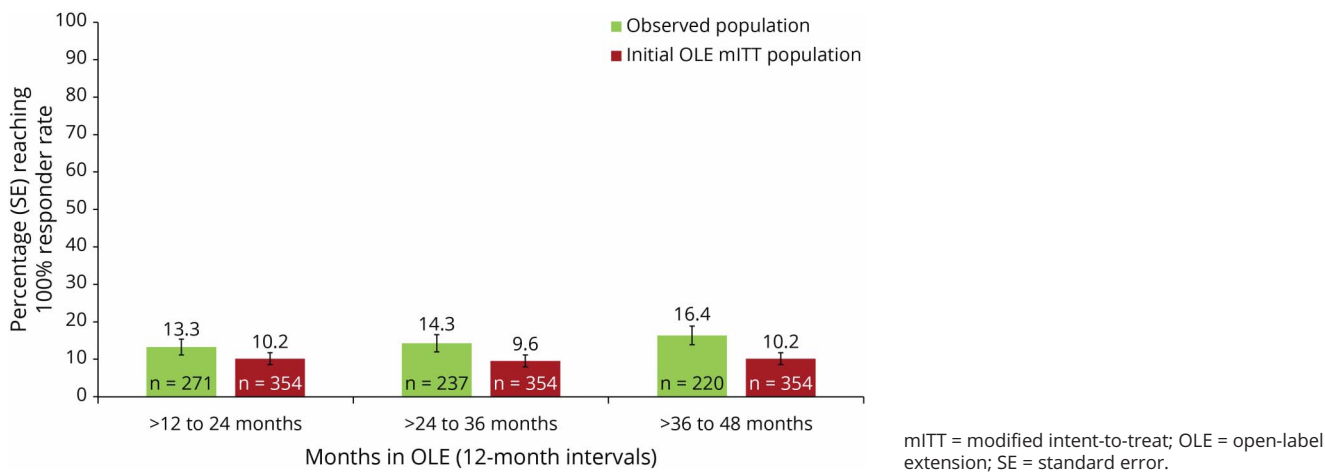
(eTable 2). Serious TEAEs considered to be related to CNB occurred in 5.4% of patients (19/355). There were no cases of DRESS or any serious skin and subcutaneous tissue disorder during the OLE.

TEAEs occurred in 88.2% of patients (313/355) during the OLE (Table 2) and were primarily mild (21.7%, 77/355) or moderate (45.4%, 161/355) in severity. The most common (≥10%) TEAEs reported in all patients were dizziness, somnolence, fatigue, headache, diplopia, gait disturbances, and upper respiratory tract infection.

Thirty-one patients (8.7%) had at least 1 TEAE leading to discontinuation, most frequently due to nervous system disorders (3.4%, n = 12); dizziness (0.8%, n = 3), somnolence (0.6%, n = 2), balance disorder (0.6%, n = 2), and depression (0.6%, n = 2) were the most frequently (≥0.5%) reported. Psychiatric disorders leading to discontinuation were reported in 6 patients (1.7%), including depression in 2 patients (at 8.1 and 12.0 months of treatment) and bradyphrenia, hallucination, persistent depressive disorder, and psychotic disorder in 1 patient each. Six patients (1.7%) reported skin and subcutaneous tissue disorders that led to discontinuation (n = 1 each of alopecia, angioedema, pruritus, maculopapular rash, skin lesion, and toxic skin eruption). Other categories of TEAEs leading to discontinuation that included more than 1 patient were infections and infestations (0.6%, n = 2) and eye disorders (0.6%, n = 2). In the OLE, commonly reported TEAEs (e.g., dizziness, somnolence, diplopia, and fatigue) most frequently occurred during the first month of treatment during the OLE conversion (eFigure 1, links.lww.com/WNL/C130).
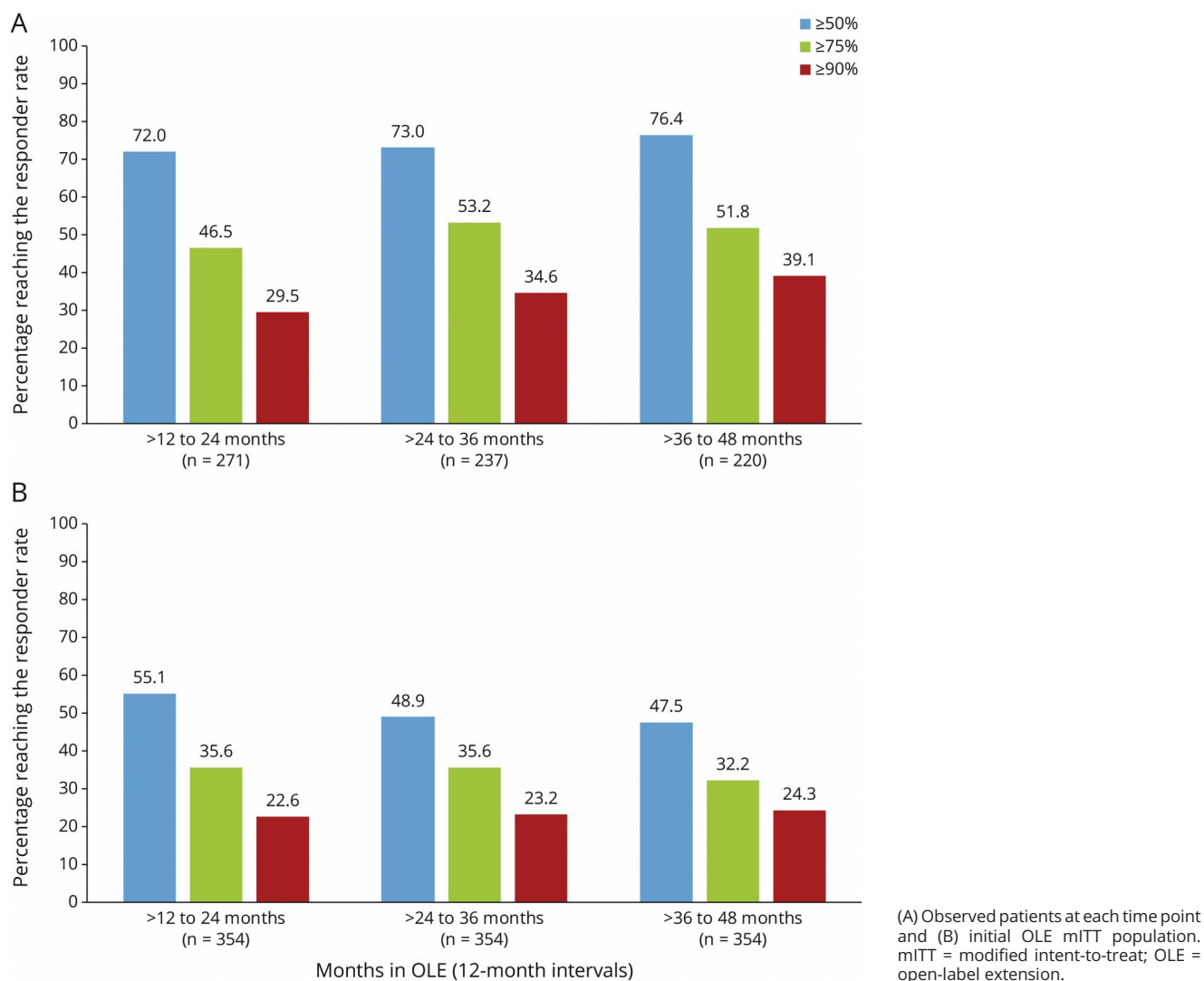
Classification of Evidence

This study provides Class IV evidence that oral CNB 50–400 mg/d is effective as an adjunctive treatment for the long-term management of patients with uncontrolled focal seizures previously treated with 1–3 ASMs.

Discussion

Epilepsy is a chronic neurologic condition treated primarily with ASMs, which must be administered over long durations of time. OLEs of clinical ASM studies provide an important opportunity to assess long-term effectiveness, safety, and tolerability. OLEs allow greater flexibility in dosing and adjustment of concomitant ASMs than randomized clinical studies, and thus, OLE findings may be more reflective of real-world clinical practice.

Previous results from 2 double-blind clinical trials of adjunctive CNB found significant reductions in median percent seizure frequency and high response rates, including 100% seizure frequency reduction.[12,13] Data from this OLE study demonstrate that the high response rates, including 100% and ≥90% seizure reduction, are sustained long-term. During the last 12-month interval (>36–48 months), 16.4% of observed patients achieved 100% seizure reduction for a median duration of 45.1 months. Although difficult to compare across studies because of different methodologies and study durations, the rates of 100% seizure reduction with adjunctive CNB were notable when considered in the context of other long-term OLEs of newer ASM studies.[14-20] For example, in OLEs of brivaracetam, 100% seizure reduction for the first 24 months was 3.0% for the ITT cohort (N = 1,836).[14] In OLEs of perampanel, yearly rates of 100% seizure reduction ranging from 0% (0/78) to 12.8% (10/78) were reported in observed patient cohorts treated for 1–4 years (0% [0/1,217] to 0.8% [10/1,217] for the ITT cohort).[15] For lacosamide OLEs, yearly rates of 100% seizure reduction were 3.0% (7/231), 3.1% (6/193), 1.8% (3/167), and 1.1% (1/88) in observed patient cohorts treated for 1–4 years (range 2.3% [7/307] to 0.3% [1/307] for the ITT cohorts).[21] Favorable comparisons using traditionally reported efficacy outcomes, including median percent seizure frequency reduction and ≥50% responder rates, were also observed.[14-16,18,19,21]

Figure 5 ≥50%, ≥75%, and ≥90% Reduction in Seizure Frequency by 12-Month Intervals During OLE (mITT Population)

(A) Observed patients at each time point and (B) initial OLE mITT population. mITT = modified intent-to-treat; OLE = open-label extension.

Also noteworthy in this OLE study of CNB was the ≥90% seizure reduction (39.1% of observed patients and 24.3% of mITT population at months >36 to 48). This response rate is not generally reported in OLE studies.[14,15,18,19] However, the sizeable ≥90% responder rate achieved with CNB suggests that it may include patients with seizures triggered by medication noncompliance only (i.e., patients who were seizure-free as long as they took the medication).

In this analysis, CNB was associated with high retention rates ranging from 83% at 12 months of treatment to 62% at 48 months, providing another measure of overall long-term effectiveness. Among patients who completed 12 months of CNB treatment (n = 294), 73% (215/294) were likely to remain on treatment through 48 months. High 12-month and 24-month retention rates have been reported in other OLE studies of newer ASMs, up to 80% and 68%, respectively.[14-20] However, the retention rates with CNB at 36 and 48 months

(both >60%) were particularly encouraging relative to other extension studies that have evaluated retention at similar treatment durations (reported retention rates up to 54% at 36 months and 39% at 48 months)[15,18,19,21] and further indicate the long-term tolerability and sustained efficacy of CNB.

The assessment of efficacy in the dose-ranging 18-week double-blind study period (doses of 100, 200, and 400 mg/d) demonstrated dose-related improvement but also showed greater discontinuations because of TEAEs in the 400-mg dose group (20%).[12] The target dose in the OLE was 300 mg/d with a maximum allowed dose of 400 mg. The median (mean) modal dose during the OLE was 300 (264.5) mg/d, which suggests that this may be a suitable target dose for patients with difficult-to-treat seizures (median baseline seizure frequency/28 days of 9.5 despite taking 1 to ≥3 ASMs). Of note, the median modal dose reported in the OLE was higher than the median modal dose reported in the phase 3 safety study (200 mg/d); however,

Table 2 Summary of TEAEs (Safety Population)

MedDRA preferred term	All cenobamate (n = 355)		Cenobamate/cenobamate (n = 265)		Placebo/cenobamate (n = 90)	
≥1 TEAE, n (%)	313 (88.2)		235 (88.7)		78 (86.7)	
≥1 serious TEAE, n (%)	72 (20.3)		55 (20.8)		17 (18.9)	
≥1 TEAE leading to discontinuation, n (%)	31 (8.7)		22 (8.3)		9 (10.0)	

TEAEs[a]	n (%)	Rate per 100 patient-years (events)	n (%)	Rate per 100 patient-years (events)	n (%)	Rate per 100 patient-years (events)
Dizziness	122 (34.4)	18.8 (208)	92 (34.7)	18.5 (152)	30 (33.3)	19.8 (56)
Somnolence	87 (24.5)	11.1 (123)	55 (20.8)	9.1 (75)	32 (35.6)	17.0 (48)
Fatigue	56 (15.8)	6.9 (76)	42 (15.8)	6.8 (56)	14 (15.6)	7.1 (20)
Headache	54 (15.2)	8.0 (88)	42 (15.8)	8.7 (72)	12 (13.3)	5.7 (16)
Diplopia	51 (14.4)	8.8 (97)	37 (14.0)	8.5 (70)	14 (15.6)	9.5 (27)
Gait disturbances	41 (11.5)	5.4 (60)	31 (11.7)	5.8 (48)	10 (11.1)	4.2 (12)
Upper resp. tract inf.	38 (10.7)	5.7 (63)	28 (10.6)	6.1 (50)	10 (11.1)	4.6 (13)
Vertigo	30 (8.5)	3.8 (42)	17 (6.4)	2.4 (20)	13 (14.4)	7.8 (22)
Fall	29 (8.2)	4.1 (45)	19 (7.2)	2.9 (24)	10 (11.1)	7.4 (21)
Viral upper resp. tract inf.	28 (7.9)	4.5 (50)	24 (9.1)	5.0 (41)	4 (4.4)	3.2 (9)
Seizure	24 (6.8)	2.9 (32)	17 (6.4)	2.9 (24)	7 (7.8)	2.8 (8)
Nausea	24 (6.8)	2.5 (28)	16 (6.0)	2.4 (20)	8 (8.9)	2.8 (8)
Nystagmus	22 (6.2)	2.4 (27)	14 (5.3)	2.1 (17)	7 (7.8)	3.5 (10)
Urinary tract inf.	22 (6.2)	2.4 (27)	14 (5.3)	2.2 (18)	8 (8.9)	3.2 (9)
Balance disorder	21 (5.9)	2.5 (28)	14 (4.5)	2.4 (20)	7 (7.8)	2.8 (8)
Back pain	21 (5.9)	2.1 (23)	17 (6.4)	2.3 (19)	4 (4.4)	1.4 (4)
Vision blurred	20 (5.6)	2.1 (23)	11 (4.2)	1.5 (12)	9 (10.0)	3.9 (11)
Vomiting	19 (5.4)	2.5 (28)	16 (6.0)	2.9 (24)	3 (3.3)	1.4 (4)
Ataxia	19 (5.4)	2.3 (26)	12 (4.5)	2.2 (18)	7 (7.8)	2.8 (8)
Weight decreased	19 (5.4)	2.1 (23)	14 (5.3)	2.2 (18)	5 (5.6)	1.8 (5)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
[a] Listed TEAEs are those reported in ≥5% of patients in the all cenobamate group.

the safety study had less stringent eligibility criteria regarding seizure frequency.[22]

CNB was generally well-tolerated during a treatment duration of up to 69 months. Assessment of adverse events during the OLE did not raise any new safety/tolerability signals. The safety profile of CNB during the OLE was generally consistent with that of the double-blind phase 2 clinical studies[15,19] and the phase 3 open-label safety study,[22] with most of the TEAEs CNS-related, primarily somnolence and dizziness. Furthermore, the results from the OLE showed that the most common CNS-related TEAEs occurred more frequently within the first 4 weeks of treatment (including the dose conversion period). Overall, discontinuations because of TEAEs were low

during the OLE (8.7%). Discontinuation because of TEAEs was generally within the range of discontinuation because of TEAEs reported from other ASMs, which have ranged from 8.8% to 19% with 4–5.5 years of follow-up.[15,18] The rate of serious TEAEs reported with CNB in this study (20.3%, see eTable 2, links.lww.com/WNL/C130) was also similar to the rates reported in these other ASM OLE studies (23.1% and 23.7%).[15,18]

Although there is a possibility of drug-drug interactions between CNB and several ASMs (i.e., phenytoin, clobazam), a post hoc analysis[23] from a subset of the long-term, phase 3 open-label study[22] showed that efficacy with CNB was generally similar among the frequently administered concomitant

ASMs.[23] The authors of the study noted that doses of some concomitant ASMs, particularly, phenytoin, phenobarbital, clobazam, valproate, and lacosamide, may be reduced early to mitigate potential tolerability issues.

Limitations of this study, as with all long-term follow-up analyses, include the uncontrolled study design and potential confounders, including the use of and changes in concomitant ASM therapy, and changes in CNB dose. Potential differences because of prior treatment with CNB in the double-blind period may also confound the reduction in seizures; however, when analyzed separately by randomized treatment arm, the results were generally comparable. Interpretation of OLE data should consider the reduced sample size over time and the potential selection bias for the remaining cohort. There is a need for standardization of long-term efficacy reporting to help reduce bias. A conservative analysis of efficacy over time using the initial mITT cohort also demonstrated relatively high rates of 100% and ≥90% seizure reduction during >36–48 months of treatment (10.2% and 24.2%, respectively, of initial mITT patients). Together these results, along with the robust retention rates, provide important evidence supporting the efficacy of CNB over time.

In summary, these findings from the OLE demonstrate the sustained long-term efficacy and safety/tolerability profile of CNB in adults with uncontrolled focal seizures previously treated with 1 to ≥3 ASMs.

Disclosure
P. Klein is a consultant/advisor for Abbott, Aquestive, Arvelle, Eisai, Engage, Neurelis, SK Life Science, Inc., and UCB Pharma; is a speaker for Aquestive, Eisai, Neurelis, Sunovion, and UCB Pharma; has received research support from Eisai and Lundbeck; and is a member of the Medical Advisory Board for Alliance-Stratus, a member of the Scientific Advisory Board for OB Pharma, and the CEO of PrevEp, LLC. S. Aboumatar is a consultant/advisor for Eisai and SK Life Science, Inc.; and is a speaker for Eisai and Sunovion. C. Brandt is a consultant/advisor for Arvelle, Desitin, Eisai, GW Pharmaceuticals, Idorsia, Novartis, and UCB Pharma; and is a speaker for Arvelle, Eisai, SK Life Science, Inc., UCB Pharma, Upsher-Smith, and Zogenix. F. Dong is an employee of SK Life Science, Inc. G.L. Krauss is a consultant/advisor for Adamas, Eisai,

Otsuka, and Shire; and has received research support from Biogen, SK Life Science, Inc., UCB Pharma, and Upsher-Smith. S. Mizne is an employee of MedVal Scientific Information Services, which was contracted by SK Life Science, Inc for medical writing services. J. Sánchez-Álvarez is a consultant/advisor for Arvelle, BIAL, Eisai, Esteve, GlaxoSmithKline, and UCB Pharma; is a speaker for BIAL, Eisai, Esteve, Sanofi, and UCB Pharma; and has received research support from BIAL, Eisai, and UCB Pharma. B.J. Steinhoff is a consultant/advisor for Arvelle, B. Braun Melsungen, Desitin, Eisai, GW Pharmaceuticals, UCB Pharma, and Zogenix; and has received research support from Eisai, GW Pharmaceuticals, SK Life Science, Inc., and UCB Pharma. V. Villanueva is a consultant/advisor for Arvelle, BIAL, Eisai, Esteve, GlaxoSmithKline, GW Pharmaceuticals, Novartis, Sandoz, UCB Pharma, and Zogenix; is a speaker for BIAL, Cevomed, Eisai, Esteve, GW Pharmaceuticals, Newbridge, and UCB Pharma; and has received research support from BIAL, Eisai, GW Pharmaceuticals, and UCB Pharma. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Pavel Klein, MD	Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Sami Aboumatar, MD	Austin Epilepsy Care Center, Austin, TX	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Christian Brandt, MD	Bethel Epilepsy Centre, Mara Hospital, Bielefeld, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Fang Dong, PhD	SK Life Science, Inc., Paramus, NJ	Analysis or interpretation of data
Gregory L. Krauss, MD, PhD	Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Sarah Mizne, PharmD	MedVal Scientific Information Services, Princeton, NJ	Drafting/revision of the manuscript for content, including medical writing for content; other

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