

# Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures

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## Abstract

### Objective

To evaluate the efficacy and safety of adjunctive cenobamate 200 mg/d in patients with uncontrolled focal (partial-onset) seizures despite treatment with 1 to 3 antiepileptic drugs.

### Methods

In this multicenter, double-blind, placebo-controlled study, adults 18 to 65 years of age with focal seizures were randomized 1:1 (cenobamate:placebo) after an 8-week baseline period. The 12-week double-blind treatment period consisted of a 6-week titration phase and a 6-week maintenance phase. The primary outcome was percent change in seizure frequency (from baseline) per 28 days during double-blind treatment.

### Results

Two hundred twenty-two patients were randomized; 113 received cenobamate and 109 received placebo; and 90.3% and 90.8% of patients, respectively, completed double-blind treatment. Median baseline seizure frequency was 6.5 in 28 days (range 0–237). Compared to placebo, cenobamate conferred a greater median percent seizure reduction (55.6% vs 21.5%;  $p < 0.0001$ ). The responder rate ( $\geq 50\%$  reduction in seizure frequency) was 50.4% for cenobamate and 22.2% for placebo ( $p < 0.0001$ ). Focal seizures with motor component, impaired awareness, and focal to bilateral tonic-clonic seizures were significantly reduced with cenobamate vs placebo. During maintenance, 28.3% of cenobamate-treated and 8.8% of placebo-treated patients were seizure-free. Treatment-emergent adverse events reported in  $>10\%$  in either group (cenobamate vs placebo) were somnolence (22.1% vs 11.9%), dizziness (22.1% vs 16.5%), headache (12.4% vs 12.8%), nausea (11.5% vs 4.6%), and fatigue (10.6% vs 6.4%).

### Conclusion

Adjunctive treatment with cenobamate 200 mg/d significantly improved seizure control in adults with uncontrolled focal seizures and was well tolerated.

### ClinicalTrials.gov identifier

NCT01397968.

### Classification of evidence

This study provides Class I evidence that, for patients with uncontrolled focal seizures, adjunctive cenobamate reduces seizures.

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Previous presentations: Chung SS, et al. Efficacy and tolerability of YKP3089 in patients with partial-onset seizures: results of a phase 2 randomized, double-blind, placebo-controlled study. Presented at the American Epilepsy Society Annual Meeting, December 5–9, 2013, Washington, DC. Abstract 3.306. Krauss G, et al. Seizure freedom with YKP3089 as adjunctive therapy for refractory partial-onset seizures in double-blind placebo-controlled trials. Presented at the American Academy of Neurology Annual Meeting, April 15–21, 2016, Vancouver, BC, Canada. Abstract P2.019.

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## Glossary

AE = adverse event; AED = antiepileptic drug; ITT = intention-to-treat; TEAE = treatment-emergent adverse event; VNS = vagus nerve stimulation.

Despite the increased availability of new antiepileptic drugs (AEDs) over the past 25 years, seizures remain uncontrolled in a substantial portion (>30%) of patients with epilepsy.<sup>1–4</sup> In addition, once an initial AED fails to suppress seizures, the likelihood of achieving seizure control with each subsequent AED regimen diminishes markedly (50.5% with the first AED, 11.6% with the second, and 4.1% with the third).<sup>1</sup> Thus, there is a need for new AEDs that can improve seizure control, particularly in patients with refractory epilepsy.

Cenobamate is a novel tetrazole alkyl carbamate derivative recently approved in the United States for the treatment of adults with focal (partial-onset) seizures.<sup>5</sup> The mechanism of action of cenobamate is thought to involve reduction of repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current.<sup>6</sup> It has also shown positive allosteric modulation of 6 subtypes of the GABA ion channel.<sup>7</sup> Cenobamate has demonstrated broad-spectrum anticonvulsant activity in animal epilepsy and seizure models,<sup>5</sup> including pentylenetetrazol kindling and maximal electroshock seizure models; a proof-of-concept study demonstrated suppression of the photoparoxysmal response in patients with photosensitive epilepsy.<sup>8</sup> A randomized, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of adjunctive cenobamate 200 mg/d in adults with uncontrolled focal seizures (YKP3089C013; clinicaltrials.gov NCT01397968).

## Methods

### Classification of evidence

The primary research question was to investigate whether adjunctive cenobamate would significantly reduce the percent seizure frequency per 28 days compared with placebo. This study provides Class I evidence that, for patients with uncontrolled focal seizures, adjunctive cenobamate reduces seizures.

### Standard protocol approvals, registrations, and patient consents

This study (clinicaltrials.gov identifier NCT01397968) was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, as well as any applicable country-specific regulations. The study protocol was approved by an independent ethics committee or institutional review board according to local regulations at each site. Written informed consent was obtained from each patient before study participation.

### Participants

Patients were adults 18 to 65 years of age with a diagnosis of treatment-resistant focal (partial-onset) epilepsy, as defined by the International League Against Epilepsy.<sup>9,10</sup> Patients must have had an EEG consistent with the diagnosis of focal epilepsy and a CT or MRI scan performed within the last 5 years. All seizure diagnoses were confirmed by an independent review from The Epilepsy Study Consortium. Patients must have been taking 1 to 3 AEDs at stable doses for at least 12 weeks before randomization. Within the 2 months before randomization (baseline period), patients were required to have  $\geq 3$  focal aware (simple partial) seizures with motor component, including aphasia and other observable symptoms; focal impaired awareness (complex partial); or focal to bilateral tonic-clonic (secondarily generalized) seizures per month, plus no consecutive 21-day seizure-free period. Vagus nerve stimulation (VNS) was permitted and was not counted as an AED. VNS had to have been implanted at least 5 months before randomization, and the stimulation parameters must have remained stable for at least 4 weeks before the screening (baseline) visit. Adjustment of VNS parameters was not permitted during the study.

Patients taking vigabatrin within the past year, felbamate for <18 continuous months, or intermittent rescue benzodiazepines more than once a month within the past month were excluded, as were patients taking phenytoin or phenobarbital because of the potential for drug-drug interaction with cenobamate inhibition of CYP2C19.<sup>11,12</sup> Patients with a history of status epilepticus within the past year, history of alcoholism or drug abuse within the past 2 years, clinically significant psychiatric illness, active suicidal ideation within the past 6 months or history of suicide attempt in the past 2 years, or >2 allergic reactions to an AED or 1 serious hypersensitivity reaction were also excluded.

### Study design, randomization, and blinding

This phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 40 centers in the United States, India, Republic of Korea, and Poland. Before randomization, patients underwent a screening visit and a baseline period (4 or 8 weeks, depending on availability of 4 weeks of adequate retrospective seizure diary at screening) to assess seizure frequency. Eligible patients were randomized (1:1) via an interactive web response system to receive placebo or cenobamate at a target dose of 200 mg once daily, stratified by country, and entered a 12-week double-blind treatment period that included a 6-week titration phase and a 6-week maintenance phase. Randomization codes were computer generated by a statistician with stratification for country. Patients, study personnel, and investigators

remained blinded to the randomized treatment assignment during the double-blind study.

During the titration phase, patients received an initial dose of cenobamate 50 mg once daily or matching daily placebo and were uptitrated by 50 mg/d every 2 weeks to a target dose of 200 mg/d at the beginning of the maintenance phase. If a patient could not tolerate the next higher dose, the patient was to continue on the current dose or have the dose reduced. During the 6-week maintenance phase, patients could not exceed the maximum dose level of study drug attained during titration. Dose reductions for tolerability could occur throughout the double-blind treatment period. No dose changes to concomitant AEDs were allowed during the double-blind study. Patients were to continue taking their allowed concomitant AEDs without any dose changes throughout the double-blind treatment period. At the end of double-blind treatment, patients either were tapered off study drug before transitioning to optional open-label treatment or were allowed to directly convert to open-label cenobamate without being tapered off if medically warranted (following protocol amendment).

### Study outcomes

Seizure frequency and type were recorded in patient diaries. The primary efficacy outcome was percent change from baseline in focal seizure frequency per 28 days during the double-blind treatment period (both titration and maintenance phases). Secondary outcomes included responder rate (response defined as a  $\geq 50\%$  reduction in seizure frequency) and assessment of seizure frequency by seizure type: focal aware with motor component, focal impaired awareness, or focal to bilateral tonic-clonic.

Safety outcomes included the incidence of treatment-emergent adverse events (TEAEs); serious adverse events (AEs); treatment discontinuations; and changes from baseline in vital signs, physical and neurologic examinations, clinical laboratory evaluations, and 12-lead ECGs. Any patient who reported a rash was evaluated for drug hypersensitivity. Columbia Suicide Severity Rating Scale questionnaires were also administered to monitor suicidality.

### Statistical analysis

The intention-to-treat (ITT) population included all randomized patients who had taken at least 1 dose of study drug and had at least 1 efficacy evaluation. The completer population included all ITT patients who completed the double-blind treatment period. The safety population included all randomized patients who took a single dose of study drug or placebo.

Assuming an SD of 40%, a sample size of 100 participants in each group would be required to detect a 16% treatment difference in percent seizure frequency at a 2-sided significance level of 0.05 with 80% power using a Wilcoxon rank-sum test. Seizure frequency during the baseline and 12-week treatment periods was calculated by summing the number of

seizures in each period and dividing by the total duration (days), excluding days with no available diary data, and multiplying by 28 to normalize to a monthly rate. The analysis of baseline seizure frequency used a total duration of 56 days; thus, some patients may have a calculated baseline rate of  $< 3$  seizures per 28 days despite meeting the inclusion criteria of  $\geq 3$  seizures per month. A prespecified model-fitting strategy was applied to examine and understand the distribution characteristics of the primary outcome data. Because of the nonparametric nature of the data, the percent change in seizure frequency from baseline was analyzed with a Wilcoxon rank-sum test. The  $\geq 50\%$  responder rate was analyzed with a logistic regression model including treatment, country, baseline seizure frequency, and treatment by study site interaction. Adjusted odds ratio and 95% confidence interval (Wald  $\chi^2$ ) for the estimated odds ratio were used to estimate treatment effect of cenobamate relative to placebo during the double-blind period. Post hoc analyses were conducted to determine additional responder rates at 75%, 90%, and 100% (i.e., seizure-free) during the maintenance phase. Seizure frequency over time was analyzed post hoc at sequential 4-week intervals (weeks 1–4, weeks 5–8, etc) with comparisons between treatment groups with a Wilcoxon rank-sum test.

Safety and tolerability were analyzed descriptively. AEs were coded according to the Medical Dictionary for Regulatory Activities (version 16.0).

### Data availability

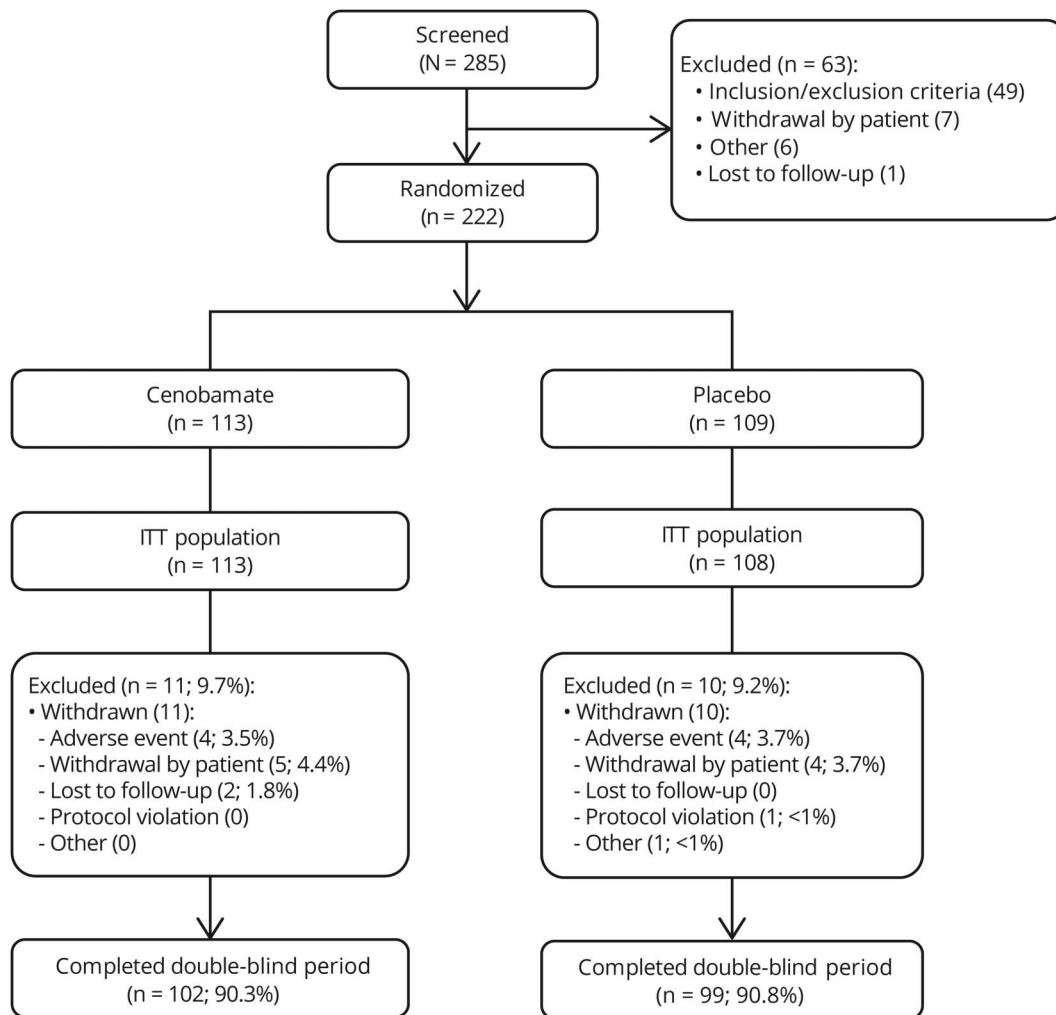
The data for the analyses described in this paper are available by request from the author, investigators, or SK Life Science, Inc, the company sponsoring the clinical development of cenobamate for the treatment of focal epilepsy.

## Results

### Patients

The double-blind study was conducted from July 2011 to June 2013. A total of 222 patients (median age 37 years, range 18–61 years) were randomized to receive cenobamate 200 mg/d ( $n = 113$ ) or placebo ( $n = 109$ ) (figure 1) and entered the titration phase. All patients received at least 1 treatment dose and were included in the safety population. All patients except 1 in the placebo group had at least 1 efficacy evaluation and were included in the ITT population; 201 patients completed the study, including 90.3% (102 of 113) of patients in the cenobamate group and 90.8% (99 of 109) of patients in the placebo group. The highest dose of cenobamate achieved during treatment by patients who completed the study was 200 mg/d (66.7%, 68 of 102), 150 mg/d (24.5%, 25 of 102), 100 mg/d (4.9%, 5 of 102), and 50 mg/d (3.9%, 4 of 102). Fifty-nine patients (57.8%, 59 of 102) completed the study on the 200-mg cenobamate target dose. Study discontinuation rates among all randomized patients were similar in the cenobamate ( $n = 11$ , 9.7%) and placebo ( $n = 10$ , 9.2%) groups, with AEs reported as the primary reason for withdrawal in 4 patients in each treatment group.

**Figure 1** Patient disposition



ITT = intention-to-treat.

Baseline patient demographics and epilepsy characteristics were similar in each treatment group (table 1). Although 9 patients had a history of generalized seizures, all patients had a diagnosis of drug-resistant focal epilepsy at the time of study enrollment. A substantial portion of patients were taking 2 (47.3%) or 3 (38.7%) concomitant AEDs. The most frequently used concomitant AED was levetiracetam (46.8%), followed by carbamazepine (36.5%), lamotrigine (33.8%), and oxcarbazepine (22.5%) (table 1).

### Efficacy

In the ITT population, median focal seizure frequency per 28 days during double-blind treatment decreased from 7.5 at baseline to 3.8 for the cenobamate group (n = 113) and from 5.5 at baseline to 5.0 for the placebo group (n = 108). The median percent reduction in seizure frequency per 28 days (primary outcome) was 55.6% and 21.5% for cenobamate- and placebo-treated patients, respectively ( $p < 0.0001$ ) (figure 2A). The  $\geq 50\%$  responder rate was also significantly

greater for patients treated with cenobamate (50.4%) vs placebo (22.2%) (odds ratio 3.94, 95% confidence interval 2.14–7.24;  $p < 0.0001$ ) (figure 2B).

Within each focal seizure subtype, the median percent reduction in 28-day seizure frequency from baseline for the cenobamate and placebo groups (ITT population) was 76.3% and 27.8% ( $p = 0.0448$ ), respectively, for patients with focal aware motor seizures, 55.6% and 21.1% ( $p = 0.0009$ ) for patients with focal impaired awareness seizures, and 77.0% and 33.0% ( $p = 0.0117$ ) for patients with focal to bilateral tonic-clonic seizures (figure 3).

During the 6-week maintenance phase, significantly greater percentages of patients (post hoc analysis) achieved seizure reduction rates of  $\geq 75\%$  (38.7% vs 20.6%;  $p = 0.0019$ ),  $\geq 90\%$  (34.0% vs 8.8%;  $p < 0.0001$ ), and 100% (28.3% vs 8.8%;  $p = 0.0001$ ) with cenobamate compared with placebo (figure 4A). Similar results were shown in the completer

**Table 1** Patient demographic and baseline clinical characteristics (safety population)

	<b>Cenobamate (n = 113)</b>	<b>Placebo (n = 109)</b>
<b>Age, median (minimum, maximum), y</b>	36 (18, 61)	38 (18, 59)
<b>Female, n (%)</b>	58 (51.3)	51 (46.8)
<b>Race, n (%)</b>		
<b>Caucasian/white</b>	57 (50.4)	58 (53.2)
<b>Asian</b>	49 (43.4)	45 (41.3)
<b>Black/African American</b>	3 (2.7)	2 (1.8)
<b>Other or unknown</b>	4 (3.5)	4 (3.7)
<b>Time since diagnosis, median (minimum, maximum), mo</b>	239.4 (28, 630)	252.8 (29, 729)
<b>Baseline focal seizure frequency (28 d),<sup>b</sup> median (minimum, maximum)</b>	7.5 (0, <sup>a</sup> 187)	5.5 (2, 237)
<b>Seizure types by history,<sup>c</sup> n (%)</b>		
<b>Focal seizures</b>	106 (93.8)	102 (93.6)
<b>Focal aware nonmotor</b>	18 (15.9)	16 (14.7)
<b>Focal impaired awareness</b>	83 (73)	92 (84)
<b>Focal aware motor</b>	31 (27.4)	25 (22.9)
<b>Focal to bilateral tonic-clonic</b>	73 (64.6)	67 (61.5)
<b>Generalized</b>		
<b>Nonmotor (absence)</b>	1 (0.9)	0
<b>Motor tonic</b>	1 (0.9)	2 (1.8)
<b>Motor tonic-clonic</b>	2 (1.8)	3 (2.8)
<b>Febrile</b>	6 (5.3)	5 (4.6)
<b>No. of background/concomitant AEDs, n (%)</b>		
<b>1</b>	19 (16.8)	12 (11.0)
<b>2</b>	53 (46.9)	52 (47.7)
<b>3</b>	41 (36.3)	45 (41.3)
<b>Background/concomitant AEDs (≥10% of patients), n (%)</b>		
<b>Levetiracetam</b>	51 (45.1)	53 (48.6)
<b>Lamotrigine</b>	41 (36.3)	34 (31.2)
<b>Carbamazepine</b>	38 (33.6)	43 (39.4)
<b>Lacosamide</b>	27 (23.9)	21 (19.3)
<b>Topiramate</b>	25 (22.1)	21 (19.3)
<b>Oxcarbazepine</b>	24 (21.2)	26 (23.9)
<b>Clobazam</b>	22 (19.5)	16 (14.7)
<b>Valproate sodium</b>	17 (15.0)	20 (18.3)
<b>Valproic acid</b>	13 (11.5)	11 (10.1)

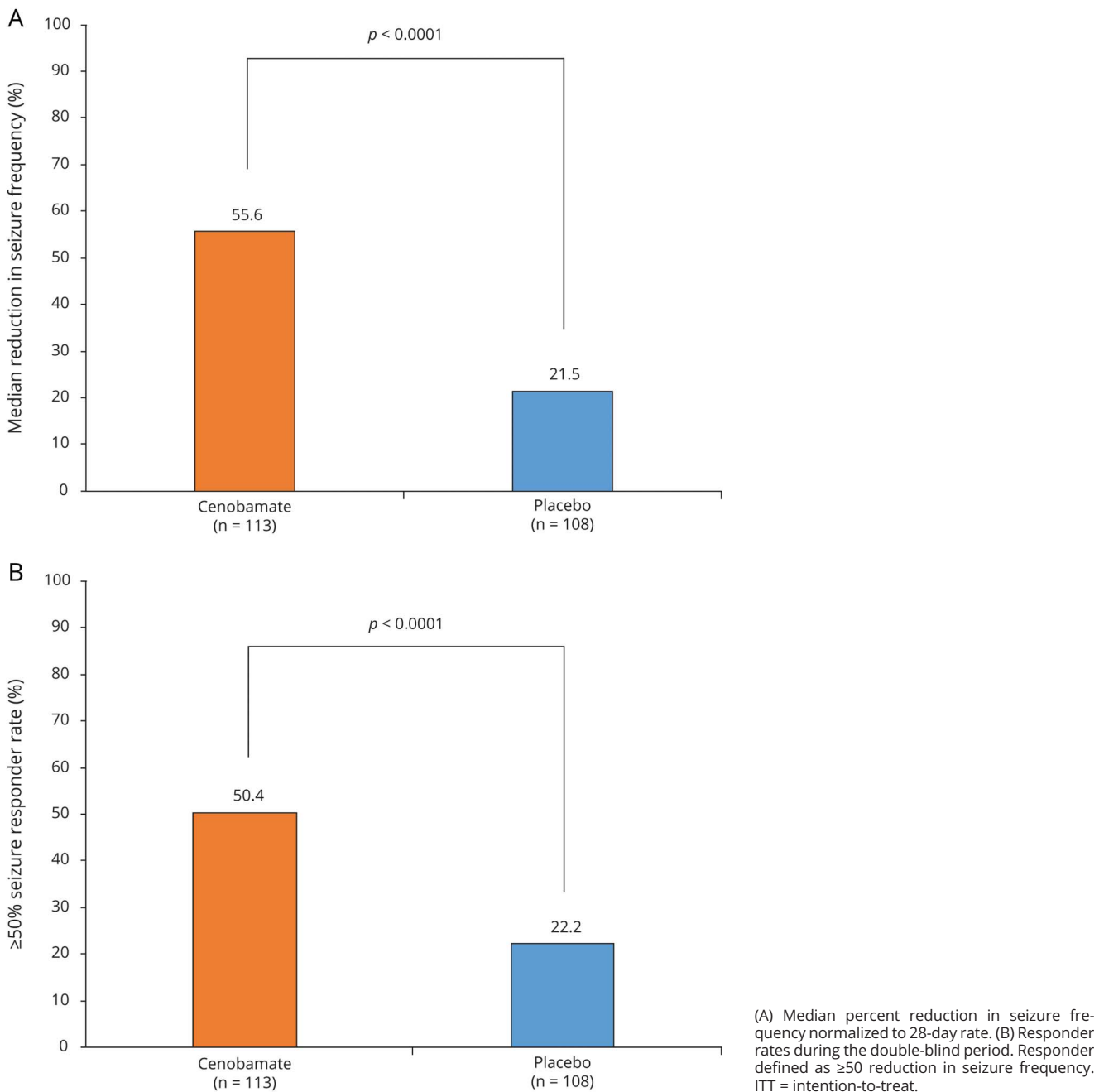
Abbreviation: AED = antiepileptic drug.

<sup>a</sup> One patient had only focal aware nonmotor seizures during baseline and was randomized and treated in error. This patient was counted in the intention-to-treat and safety populations.

<sup>b</sup> 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.

<sup>c</sup> Patients may be reported in >1 category.

**Figure 2** Median percent reduction in seizure frequency from baseline and  $\geq 50\%$  responder rates (ITT population)



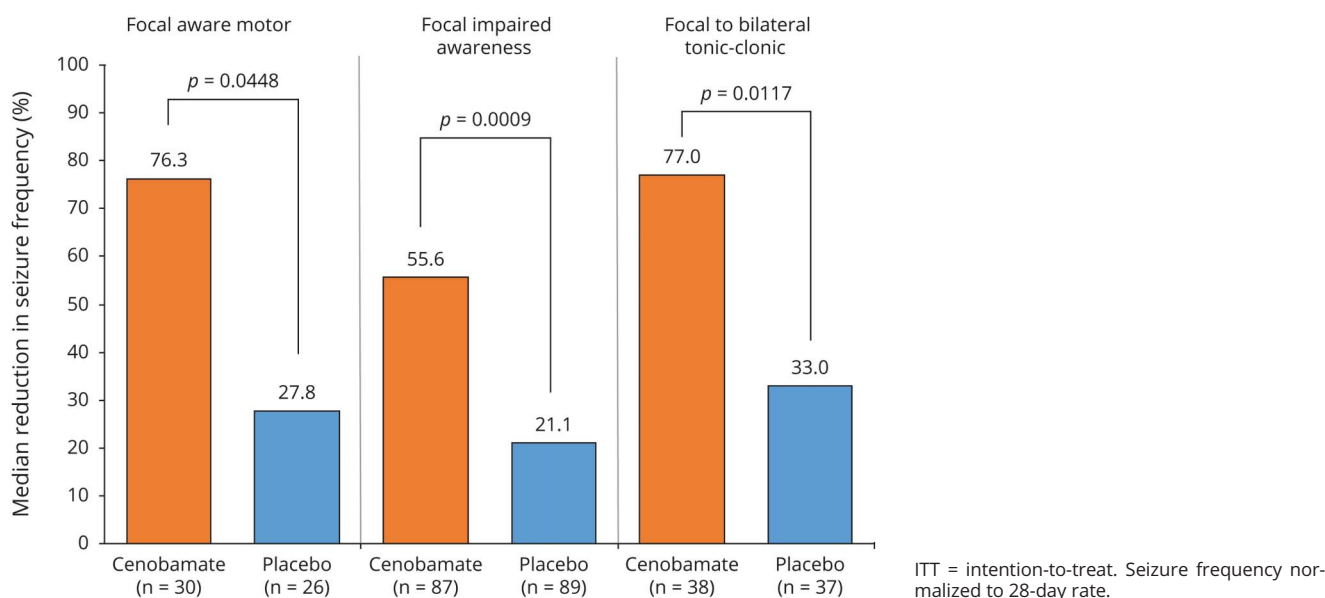
population (figure 4B). Among cenobamate-treated patients in the completer population, 27.5% (28 of 102) achieved 100% seizure reduction during the 6-week maintenance phase (post hoc analysis).

In the assessment of patients who completed the study, the median percent change in seizure frequency decreased during the first 4 weeks of titration by 40.6% from baseline compared with 14.3% for placebo ( $p = 0.001$ ) (figure 5). Significantly greater reductions from baseline occurred over each subsequent 4-week interval for cenobamate vs placebo.

### Safety

During the 12-week treatment period, TEAEs were reported in 86 of 113 cenobamate-treated patients (76.1%) and 69 of 109 placebo-treated patients (63.3%). TEAEs reported in at least 5% of patients in either treatment group are shown in table 2; all except anxiety and headache occurred more frequently in the cenobamate group. The most frequently (>10%) reported TEAEs for cenobamate were somnolence (22.1%), dizziness (22.1%), headache (12.4%), nausea (11.5%), and fatigue (10.6%). For placebo, they were dizziness (16.5%), headache (12.8%), and somnolence (11.9%),

**Figure 3** Median percent reduction for focal seizure types (ITT population)



(table 2). Most TEAEs were mild or moderate in severity (cenobamate: mild or moderate 74.3%, severe 1.8%; placebo: mild or moderate 56.9%, severe 6.4%). One TEAE of suicidal ideation was reported in each treatment group. Columbia Suicide Severity Rating Scale responses did not reveal any increases in suicidal ideation, intensity, or behavior from baseline with cenobamate. Among infectious TEAEs, only urinary tract infections (8.0% cenobamate vs 1.8% placebo) and nasopharyngitis (6.2% cenobamate vs 0.9% placebo) occurred with at least a 5–percentage point difference between groups. Treatment-related TEAEs occurring in >5% of cenobamate-treated patients with a  $\geq 5\%$  difference over the placebo group included somnolence (22.1% vs 10.1%), dizziness (20.4% vs 13.8%), balance disorder (7.1% vs 0.9%), and nystagmus (9.7% vs 0%).

In the cenobamate group, 5 patients experienced 8 AEs that led to a treatment discontinuation (tachycardia, gastroesophageal reflux disease, drug hypersensitivity, nystagmus, aggression, depression, and dyspnea). In the placebo group, 3 patients experienced 8 AEs that led to a treatment discontinuation (altered state of consciousness, ataxia, dyskinesia, grand mal convulsion, partial seizure, somnolence, status epilepticus, and tremor). Serious TEAEs were reported in 2 cenobamate-treated patients (n = 1 drug hypersensitivity reaction, n = 1 urinary tract infection) and 4 placebo-treated patients (n = 2 status epilepticus, n = 1 convulsion, n = 1 hospitalization for coronary angiography performed because of chest pain and ECG abnormalities). A drug hypersensitivity reaction of moderate intensity was reported in a patient who received a single dose of 50 mg cenobamate and was considered related to treatment. The reaction began on day 1 of treatment and was characterized by reddening of palms and soles and itching of

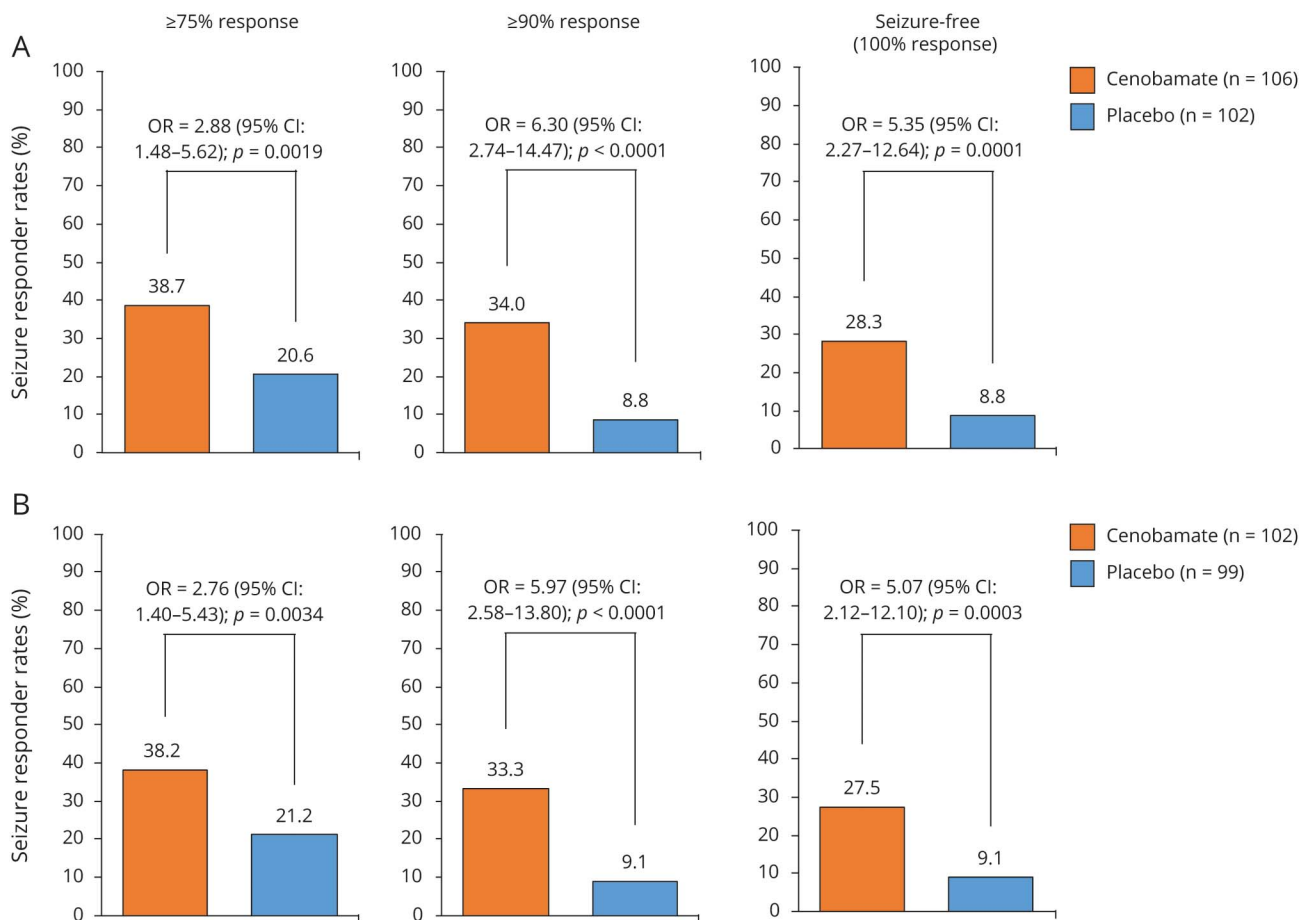
ears. Study treatment was discontinued; oral antihistamines and corticosteroids were administered; and the patient recovered after 22 days. No other serious dermatologic TEAEs, including cases of drug reaction with eosinophilia and systemic symptoms or Stevens-Johnson syndrome, were reported. No deaths occurred during the double-blind treatment period. One sudden unexplained death in epilepsy occurred in a patient before randomization.

There were no clinically meaningful trends in changes from baseline in mean laboratory values, physical and neurologic examinations, vital signs, or ECGs.

## Discussion

In this multicenter randomized study, treatment with adjunctive cenobamate led to statistically significant reductions in focal seizure frequency with few withdrawals due to AEs. Both the median percent reduction in seizure frequency relative to placebo per 28 days (55.6% vs 21.5%, primary outcome) and responder rates relative to placebo observed with cenobamate in this study compare favorably to published rates from individual and pooled randomized clinical studies of other adjunctive AEDs.<sup>13–28</sup> A significant positive benefit with cenobamate was observed in all assessed focal seizure types, with a large median percent reduction per 28 days noted among patients with focal to bilateral tonic-clonic seizures (77.0% vs 33% for placebo). The reduction in focal to bilateral tonic-clonic seizures is noteworthy given that persistent generalized tonic-clonic seizures are associated with an increased risk for sudden unexpected death in epilepsy.<sup>29</sup> Seizure reduction with cenobamate was observed relatively early, within the first 4 weeks of treatment during the titration

**Figure 4** Post hoc responder rates during the maintenance phase



(A) Responder rates during the 6-week maintenance phase (intention-to-treat population who took  $\geq 1$  dose of study drug during the maintenance phase  $n = 208$ ). (B) Responder rates during the 6-week maintenance phase (completer population  $n = 201$ ). Responder defined as  $\geq 75\%$ ,  $\geq 90\%$ , or  $100\%$  reduction in seizure frequency during the maintenance phase. CI = confidence interval; OR = odds ratio.

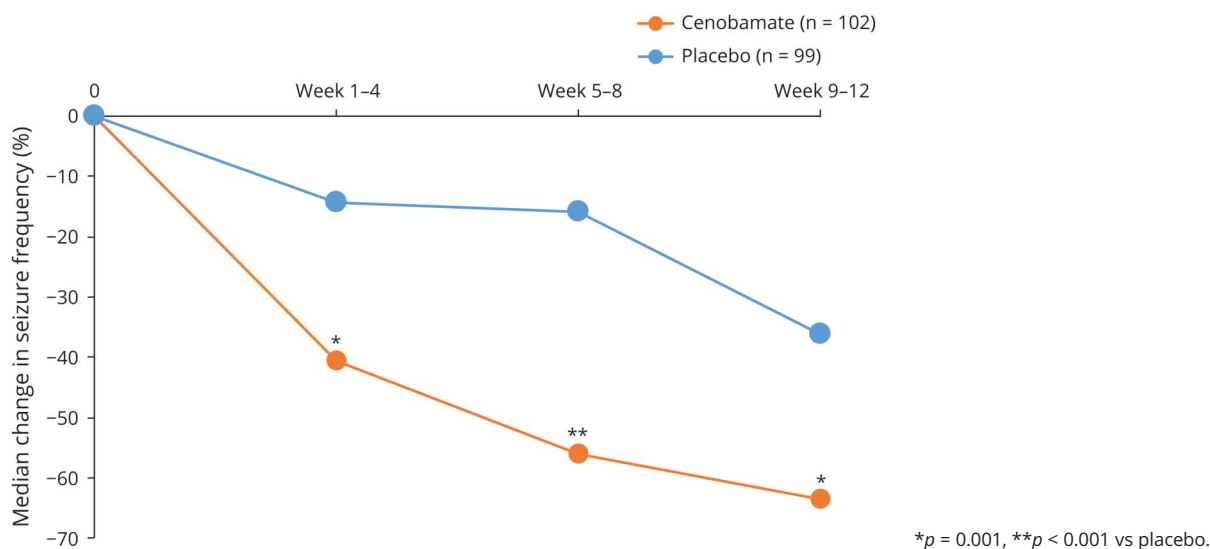
phase (dosages 50–100 mg/d), with a median percent reduction in seizure frequency of 40.6% during this time vs 14.3% for placebo.

Cenobamate was generally well tolerated as adjunctive therapy, as shown by the low (and similar) rate of withdrawals due to AEs between the cenobamate and placebo groups (only 4 patients in each group). Although the majority of patients tolerated the 200-mg/d target dose of cenobamate, approximately one-third (37%) did not reach this dose because there was no forced titration. Higher withdrawal rates have been reported with other AED studies, including those that used forced titration schedules.<sup>20,30,31</sup> The use of flexible titration may have contributed to the relatively low study discontinuation rate with cenobamate. This is an important aspect of the study in that a number of AED studies have demonstrated good efficacy at doses that were subsequently not tolerated in the clinic. The facts that patients in this study remained on the dose that they felt was tolerable and few dropped out mean, we hope, that the efficacy demonstrated can be recapitulated in the clinic.

Ongoing, even infrequent seizures, as few as 1 in the previous 5 years, have been shown to negatively affect patients,<sup>32</sup> underscoring the importance of reporting seizure freedom rates in AED clinical studies.<sup>33</sup> The post hoc analyses of additional seizure response rates, including 100% seizure reduction, used data from the maintenance phase. Reporting seizure responses during the maintenance phase more accurately reflects steady-state dosing levels at the target dose compared to using the entire treatment period, including the titration phase. This, however, does result in a relatively brief monitoring period (6 weeks) during the maintenance phase. Nevertheless, there were high  $\geq 75\%$ ,  $\geq 90\%$ , and 100% seizure reduction rates with cenobamate treatment compared with placebo. In particular, the percentage of seizure-free patients (28.3%) with cenobamate treatment was a noteworthy finding given that the percentage in the placebo group was 8.8% and  $>80\%$  of patients in this study were taking  $\geq 2$  concomitant AEDs. A similar percentage of seizure-free patients was also noted in the completer population. Analyses that include those patients who complete the study and do not allow study discontinuations resulting from AEs to count as seizure-free



**Figure 5** Median percent reduction from baseline in seizure frequency per 28 days over sequential 4-week intervals (completer population)



may be more informative.<sup>34</sup> When a previously suggested pragmatic ITT approach is used<sup>34</sup> that divides the number of seizure-free completers by the ITT population, 24.8% of patients (28 of 113) in the cenobamate group achieved 100% seizure reduction during the maintenance phase compared with 8.3% (9 of 108) in the placebo group.

The 6-week maintenance duration in the current study makes it difficult to directly compare rates across studies.<sup>17-26</sup> Furthermore, it is not yet known how long patients in this study will remain seizure-free or how long significant seizure control will be maintained because the open-label study is still ongoing. Nonetheless, these data offer an important first look at the clinical efficacy of cenobamate and can serve as a point of reference for future studies and analyses.

AEDs are commonly associated with AEs, most notably CNS-related AEs, and polytherapy can increase the risk of AEs.<sup>35</sup> In this study, the most common TEAEs associated with cenobamate were CNS related, including somnolence and dizziness; however, the majority were mild/moderate in severity and rarely led to treatment discontinuation. The rate of serious AEs during the double-blind treatment period was low, particularly in the cenobamate group. One serious drug hypersensitivity event was reported in a patient receiving cenobamate, which resolved with discontinuation. No other serious cutaneous reactions were reported during the double-blind treatment period in this study. Idiosyncratic AEs that have been reported with AEDs, including cutaneous reactions, can be severe and life-threatening.<sup>36,37</sup> During early clinical development, among the first 953 participants exposed to cenobamate, 3 confirmed cases of drug reaction with eosinophilia and systemic symptoms were reported.<sup>38</sup> A large ongoing multicenter phase 3 safety study is investigating the use

of adjunctive cenobamate at a lower starting dose (12.5 mg) and slower titration rate, with increases every 2 weeks (25, 50, 100, 150, and 200 mg) (clinicaltrials.gov NCT02535091).

While the precise mechanism of action of cenobamate is not fully known, assessments have characterized cenobamate as a modulator of voltage-gated sodium ion channels and GABA currents.<sup>6,7</sup> In particular, it has been shown to reduce repetitive neuronal firing by enhancing fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. Further investigation is needed to determine how the potentially unique combination of mechanisms of action may play a role in the clinical efficacy and manageable tolerability profile of cenobamate despite the use of various concomitant AEDs, including other sodium channel blockers. In this study, somewhat higher percentages of TEAEs occurred among cenobamate-treated patients taking sodium channel blockers compared to those not taking them. Among those taking sodium channel blockers, TEAEs occurred in 79.1% (68 of 86) of cenobamate-treated patients (relative to 62.5% [55 of 88] for placebo); among those not taking sodium channel blockers, TEAEs occurred in 74.1% (20 of 27) of cenobamate-treated patients (relative to 71.4% [15 of 21] for placebo). Given that the number of patients was small and unbalanced between groups (n = 86 vs n = 27), it is difficult to make definitive conclusions about tolerability in conjunction with sodium channel blockers. Data from the large phase 3 safety study, which allows dose adjustment of concomitant AEDs, should provide recommendations for the real-world management of patients taking cenobamate.

Study limitations include the relatively short treatment duration (12 weeks, with 6-week maintenance phase); however, analysis of patients in the ongoing open-label extension phase

**Table 2** Summary of TEAEs (safety population)

	Cenobamate (n = 113), n (%)	Placebo (n = 109), n (%)
<b>Any TEAE</b>	86 (76.1)	69 (63.3)
<b>Treatment-related TEAEs</b>	67 (59.3)	50 (45.9)
<b>Serious TEAEs</b>	2 (1.8)	4 (3.7)
<b>TEAEs ≥5%</b>		
<b>Somnolence</b>	25 (22.1)	13 (11.9)
<b>Dizziness</b>	25 (22.1)	18 (16.5)
<b>Headache</b>	14 (12.4)	14 (12.8)
<b>Nausea</b>	13 (11.5)	5 (4.6)
<b>Fatigue</b>	12 (10.6)	7 (6.4)
<b>Nystagmus</b>	11 (9.7)	0
<b>Balance disorder</b>	9 (8.0)	1 (0.9)
<b>Urinary tract infection</b>	9 (8.0)	2 (1.8)
<b>Upper respiratory tract infection</b>	8 (7.1)	5 (4.6)
<b>Tremor</b>	7 (6.2)	3 (2.8)
<b>Nasopharyngitis</b>	7 (6.2)	1 (0.9)
<b>Constipation</b>	6 (5.3)	0
<b>Diarrhea</b>	6 (5.3)	0
<b>Vomiting</b>	6 (5.3)	2 (1.8)
<b>Anxiety</b>	1 (0.9)	6 (5.5)

Abbreviation: TEAE = treatment-emergent adverse event. Adverse events that occur up to 7 days after the patient's last dose of double-blind study drug are included as TEAEs.

is anticipated and will provide additional insight into the long-term safety of adjunctive cenobamate. The treatment-refractory nature of the patient population, the use of flexible dosing, and concomitant medications present additional challenges to the interpretation of these data but also can be seen as strengths in terms of the generalizability of the results. Other strengths of the study include the use of an independent panel to confirm the appropriate diagnosis and classification of epilepsy and the inclusion of clinically important efficacy assessments.

Adjunctive cenobamate demonstrated statistically significant improvements from baseline in median percent seizure frequency reduction per 28 days compared with placebo in patients with uncontrolled focal seizures. Additional significant improvement in several focal seizure types and in seizure freedom rates was also shown with cenobamate, and the treatment appeared to be well tolerated.

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<b>Jacqueline A. French, MD</b>	NYU Comprehensive Epilepsy Center, New York	Major role in acquisition of data; interpreted the data; helped develop manuscript and revised manuscript for intellectual content
<b>Jacek Kowalski, MD</b>	NZOZ Vito-Med, Gliwice, Poland	Designed and conceptualized study; analyzed and interpreted the data; helped develop manuscript and revised manuscript for intellectual content
<b>Gregory L. Krauss, MD</b>	Johns Hopkins University School of Medicine, Baltimore, MD	Major role in acquisition of data; interpreted the data; helped develop manuscript and revised manuscript for intellectual content
<b>Sang Kun Lee, MD</b>	Adult Comprehensive Epilepsy Center, Seoul National University Hospital, Republic of Korea	Major role in acquisition of data; interpreted the data; helped develop manuscript and revised manuscript for intellectual content
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<b>William E. Rosenfeld, MD</b>	Comprehensive Epilepsy Care Center for Children and Adults, St. Louis, MO	Major role in acquisition of data; interpreted the data; helped develop manuscript and revised manuscript for intellectual content
<b>Michael R. Sperling, MD</b>	Thomas Jefferson University, Philadelphia, PA	Major role in acquisition of data; interpreted the data; helped develop manuscript and revised manuscript for intellectual content
<b>Sarah Mizne, PharmD</b>	MedVal Scientific Information Services, Princeton, NJ	Wrote initial manuscript draft based on input from the other authors and revised the manuscript for intellectual content under their guidance; drafted and revised the response to reviewers with the guidance of the other authors

## Appendix (continued)

Name	Location	Contribution
<b>Marc Kamin, MD</b>	SK Life Science, Inc, Paramus, NJ	Designed and conceptualized study; analyzed and interpreted the data; helped develop manuscript and revised manuscript for intellectual content

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