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Efficacy of cenobamate for uncontrolled focal seizures in patients with previous epilepsy-related surgery: Post hoc analysis of a phase 3, multicenter, open-label study

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ABSTRACT

Objective: This post hoc analysis of 10 US study sites from a long-term open-label phase 3 study of adjunctive cenobamate evaluated the efficacy of cenobamate in patients with prior epilepsy-related surgery.
Methods: Patients with uncontrolled focal seizures despite taking stable doses of 1–3 concomitant antiseizure medications (ASMs) received increasing doses of cenobamate (12.5, 25, 50, 100, 150, 200 mg/day) at 2-week intervals over 12 weeks (target dose, 200 mg/day). Further increases up to 400 mg/day using biweekly 50-mg/day increments were allowed during the maintenance phase. Dose adjustments of cenobamate and concomitant ASMs were allowed. Data were assessed until the last clinic visit on or after September 1, 2019.
Results: Of the 240 eligible patients, 85 had prior epilepsy-related surgery and 155 were nonsurgical patients. Baseline focal seizure frequency per 28 days was numerically higher among prior surgery (mean=25.9/median=4.1/range=0.3–562.3) versus nonsurgical (mean=13.8/median=2.4/range=0.2–534.2) patients. Among all patients, 100 % seizure reduction $\geq$ 12 months at any consecutive month interval occurred in 30.6 % (26/85) prior surgery and 39.4 % (61/155; $p > 0.05$) nonsurgical patients (cenobamate treatment median duration=32.9 months). Among the 177 patients still receiving cenobamate at the data cutoff, 29.2 % (19/65) of prior surgery and 36.6 % (41/112; $p > 0.05$) of nonsurgical patients had 100 % seizure reduction $\geq$ 12 months at the data cutoff. Cenobamate was well tolerated.
Conclusions: This post hoc analysis supports the efficacy of cenobamate in patients with refractory focal seizures despite prior surgery. These findings suggest cenobamate may be considered early in the treatment regimen, including, in some patients, before surgery is considered.

1. Introduction

More than one-third of patients with newly diagnosed epilepsy have continued seizures despite treatment with two or more antiseizure medications (ASMs), and the likelihood of additional patients achieving seizure freedom (100 % seizure reduction) diminishes with each added ASM (Chen et al., 2018). Epilepsy surgery can be an effective treatment option for selected patients following failure of adequate treatment trials with at least two ASMs; however, approximately half of these patients may continue to experience focal seizures at 5 years post-surgery (de Tisi

Abbreviations: ASMs, antiseizure medications; AVM, arteriovenous malformation; C021, ClinicalTrials.gov NCT02535091; DNET, dysembryoplastic neuroepithelial tumor; MedDRA, Medical Dictionary for Regulatory Activities; RNS, responsive neurostimulation; TEAEs, treatment-emergent adverse events; VNS, vagus nerve stimulation.

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et al., 2011; Mohan et al., 2018). Treatment options following failed surgery include consideration of additional surgery or adjustments/additions to the patient's ASM regimen. The percentage of patients achieving complete seizure freedom at 2 years post-surgery declines with each successive surgery (58 % at first surgery, 49 % at second surgery, 39 % at third or more surgeries) suggesting "surgical refractoriness" (Yardi et al., 2020). Studies examining further trials of ASM treatment following failed epilepsy surgery are limited but suggest fewer than 10 % of these patients may achieve long-term seizure freedom (Ma et al., 2020; Ryzí et al., 2015).

Cenobamate (SK Life Science, Inc.) is an ASM approved in the US (XCOPRI®) and Europe (ONTOZRY®) for the treatment of adults with focal seizures. Two randomized, double-blind, placebo-controlled phase 2 studies in patients with uncontrolled focal seizures who were taking stable doses of 1–3 ASMs showed significantly reduced focal seizure frequency with adjunctive cenobamate treatment (Chung et al., 2020; Krauss et al., 2020). In these studies, 28 % of patients receiving cenobamate 200 mg/day (vs 9 % placebo) and 21 % of patients receiving cenobamate 400 mg/day (vs 1% placebo) achieved 100 % seizure reduction (ie, zero seizures) during their 6-week and 12-week maintenance phases, respectively (Chung et al., 2020; Krauss et al., 2020). A large (N = 1347), global, phase 3, open-label safety study (NCT02535091; C021) showed that lowering the starting dose of cenobamate to 12.5 mg and titrating every other week resulted in good safety and tolerability, as shown in high long-term retention of patients (Sperling et al., 2020). Reporting of seizures was not required in the C021 safety study because long-term efficacy was not assessed; however, a protocol amendment permitted post hoc collection of seizure data from seizure diaries and clinic seizure records from 10 US C021 study sites that had high-quality, long-term seizure data recorded (Sperling et al., 2021). A post hoc analysis of this subset of patients from C021 found sustained seizure reduction and high rates of seizure freedom (~36 % of patients) for ≥ 12 months (Sperling et al., 2021).

The current post hoc analysis of the 10 US study sites within the global phase 3 C021 study examined the efficacy of cenobamate treatment in patients with uncontrolled focal seizures who had prior epilepsy-related surgery (ie, prior surgery). The surgeries included resection, corpus callosotomy, tumor removal, ablation, vagus nerve stimulation (VNS), and responsive neurostimulation (RNS). The efficacy of cenobamate in patients with prior surgery and uncontrolled focal seizures has not previously been reported. This post hoc analysis was performed to evaluate cenobamate treatment in this patient group with particularly treatment-resistant seizures.

2. Methods

2.1. Study design and participants

Details of the study design and patient eligibility for the C021 global, multicenter, open-label safety study have been reported (Sperling et al., 2020). Following a screening period of up to 21 days and a 12-week titration phase, the open-label maintenance phase continued for a total study duration of up to 43 months in the post hoc analysis efficacy subset of patients (Sperling et al., 2021). Eligible patients were 18–70 years old with a diagnosis of focal epilepsy (as defined by the International League Against Epilepsy seizure classification criteria (Fisher et al., 2017; Scheffer et al., 2017) and uncontrolled focal seizures despite treatment with 1–3 concomitant ASMs at stable doses (Sperling et al., 2020). Cenobamate treatment began at 12.5 mg/day for 2 weeks, followed by 25 mg/day for 2 weeks and 50 mg/day for 2 weeks. The dose was then increased by 50 mg/day at 2-week intervals to a target dose of 200 mg/day, and further increases up to 400 mg/day using biweekly increments of 50 mg/day were allowed during the maintenance phase. Cenobamate dose reduction was allowed (minimum dose was 50 mg/day) based on investigators' clinical judgment. Cenobamate monotherapy was not allowed. Patient visits occurred every 2 weeks for 16 weeks and then every 1–3 months (Sperling et al., 2021).

For the post hoc analysis, eligible sites were those in the US that enrolled ≥ 11 patients who had recorded high-quality seizure data (Sperling et al., 2021). To be included, patients had to have (1) ≥ 1 focal aware motor, focal impaired awareness, or focal to bilateral tonic-clonic seizure per 13 weeks baseline prior to the screening visit, (2) focal aware motor, focal impaired awareness, or focal to bilateral tonic-clonic seizure data for evaluation (if any seizures occurred) while on treatment, (3) raw seizure data consistently documented, and (4) seizure data of good quality for ≥ 85 % of time spent in the study. Focal seizure data were available for 240 patients from 10 eligible US study sites. The median duration of cenobamate exposure for all patients in the post hoc analysis was 30.2 months (range 0.10–43 months) and 177 patients were still receiving cenobamate as of the data cutoff on or after September 1, 2019 (Sperling et al., 2021).

The C021 primary study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines (Sperling et al., 2020). An independent ethics committee or institutional review board approved the study protocol, amendments, and post hoc analysis. Each patient provided written informed consent prior to participation in C021 and no new consent was required for the post hoc analysis.

2.2. Assessments and data analysis

The post-hoc analysis evaluated patients with prior epilepsy-related surgery or no surgery. Prior surgeries included resection, corpus callosotomy, lesionectomy/tumor removal, laser ablation therapy, VNS, and RNS. Patients with or without prior epilepsy-related surgery were examined for 100 % seizure reduction efficacy outcomes. Three efficacy outcomes were assessed: (1) the percentage of all patients achieving 100 % seizure reduction ≥ 12 months at the last clinic visit (ie, interval includes the last clinic visit for the patient prior to discontinuation or data cutoff); (2) the percentage of all patients achieving 100 % seizure reduction at any consecutive ≥ 12-month interval during exposure to cenobamate (ie, does not have to include the last visit); and (3) the percentage of patients who were still receiving cenobamate who achieved 100 % seizure reduction ≥ 12 months at the data cutoff visit (ie, interval includes the data cutoff visit). Patients with any missing seizure frequency data could not be counted as having 100 % seizure reduction. Safety was assessed by treatment-emergent adverse events (TEAEs) coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Demographic and clinical characteristics of patients with prior surgery versus nonsurgical patients were analyzed using two-sample *t*-tests ($\alpha = 0.05$, 2-sided) for comparisons of mean group differences and using Fisher's exact test for comparisons of group differences in percentages of patients. Patients with prior surgery and nonsurgical patients were compared on the efficacy outcomes using Fisher's exact test. All other numerical differences in efficacy and safety data were summarized descriptively.

3. Results

3.1. Patients

Of the 240 patients who were eligible to participate in the post hoc efficacy analysis of the C021 study, 85 (35.4 %) had prior surgery and 155 (64.6 %) had no prior surgery. The patients with prior surgery on average were younger than the nonsurgical patients ($p = 0.012$), had a slightly higher percentage of male patients ($p > 0.05$), and a higher percentage of White patients ($p = 0.023$) (Table 1). Patients with prior surgery had a numerically higher focal seizure frequency at baseline, with a mean (25.9 seizures/28 days) and median (4.1 seizures/28 days) monthly seizure frequency that was approximately double that of the nonsurgical patients (mean 13.8 and median 2.4 seizures/28 days) ($p > 0.05$). A numerically higher percentage of the patients with prior

Table 1
Demographic and clinical characteristics for cenobamate patients with and without prior epilepsy-related surgery.

	Prior surgery patients (n = 85)	Nonsurgical patients (n = 155)	*P*-value
Mean (min, max) age (years) at screening	38.6 (18, 69)	43.6 (18, 70)	0.012
Male/Female, n (%)	54 (63.5)/31 (36.5)	81 (52.3)/74 (47.7)	0.104
Race (n, %)			0.023
White	80 (94.1)	123 (79.4)	
Black or African American	3 (3.5)	18 (11.6)	
Hispanic	2 (2.4)	10 (6.5)	
Asian	0	4 (2.6)	
Seizure type[a], n (%)			
Focal aware motor	14 (16.5)	13 (8.4)	0.086
Focal impaired awareness	78 (91.8)	146 (94.2)	0.589
Focal to bilateral tonic-clonic	24 (28.2)	32 (20.6)	0.203
All patients mean/median (min, max) baseline seizure frequency/28 days	25.9/4.1 (0.3, 562.3)	13.8/2.4 (0.2, 534.2)	0.201
Patients with < 3 baseline seizures/28 days mean/ median baseline seizure frequency/28 days	1.6/1.5	1.5/1.4	0.452
Patients with < 3 baseline seizures/28 days, n (%)	35 (41.2)	92 (59.4)	0.010 [b]
Patients with ≥ 3 baseline seizures/28 days mean/ median baseline seizure frequency/28 days	43.0/9.9	31.8/7.9	0.515
Patients with ≥ 3 baseline seizures/28 days, n (%)	50 (58.8)	63 (40.6)	0.010 [b]
No. of concomitant ASMs at baseline (n, %)			0.002
1	3 (3.5)	26 (16.8)	
2	46 (54.1)	85 (54.8)	
3	36 (42.4)	44 (28.4)	
Concomitant ASMs at baseline > 15% (n, %)			
Lacosamide	37 (43.5)	61 (39.4)	0.583
Levetiracetam	26 (30.6)	63 (40.6)	0.128
Lamotrigine	23 (27.1)	43 (27.7)	1.000
Zonisamide	15 (17.6)	24 (15.5)	0.716
Clobazam	21 (24.7)	17 (11.0)	0.009

Comparisons of mean group differences were based on two-sample *t*-tests (α = 0.05, 2-sided). Comparisons of group differences in percentages of patients were based on Fisher's exact test.

[a] Patients may be reported in more than one category.

[b] The four-group comparison of baseline seizure frequency (ie, percentage of patients with prior surgery versus nonsurgical patients with <3 versus ≥3 baseline seizures/28 days) was based on Fisher's exact test.

surgery versus the nonsurgical patients also had focal aware motor (16.5 % vs 8.4 % of patients) and focal to bilateral tonic-clonic seizures (28.2 % vs 20.6 % of patients) (p-values > 0.05). A significantly greater percentage of patients with prior surgery had ≥ 3 baseline seizures per 28 days and a significantly greater percentage of nonsurgical patients had < 3 baseline seizures per 28 days (p = 0.010). A significantly greater percentage of patients with prior surgery were receiving 3 ASMs at baseline (42.4 % vs 28.4 % of patients, p = 0.002). Most notable among the concomitant ASMs at baseline was the higher percentage of patients with prior surgery receiving clobazam compared with the nonsurgical patients (p = 0.009).

Approximately half of the patients with prior surgery had VNS or RNS, 34.1 % had a temporal lobectomy, 15.3 % had an extratemporal resection, 9.4 % had a tumor-related resection, 7.1 % had a corpus callosotomy, and 2.4 % had an ablation (Table 2). Across these surgeries, 40 patients (47.1 %) had ≥ 1 procedure that was not VNS or RNS, 31 patients (36.5 %) had VNS (n = 30) or RNS (n = 2, including 1 patient with both VNS and RNS) only, and 14 patients (16.5 %) had both VNS and a resection or disconnection surgery.

Table 2
Type and location of prior epilepsy-related surgeries.

Surgery, n (%)	Prior surgery patients (n = 85)
VNS/RNS	45 (52.9)
Temporal lobectomy[a]	29 (34.1)
Right temporal	18 (21.2)
Left temporal	11 (12.9)
Extratemporal resection	13 (15.3)
Right	5 (5.9)
Left	8 (9.4)
Tumor-related resection[b]	8 (9.4)
Right frontal meningioma	1 (1.2)
Inferior right frontal and temporal oligodendroglioma	1 (1.2)
Calcified right parietal ganglioglioma	1 (1.2)
Left frontal neuroblastoma	1 (1.2)
Left frontal glioma	1 (1.2)
Left temporal ganglioma	1 (1.2)
Left temporal DNET	1 (1.2)
Hypothalamic hamartoma	1 (1.2)
Corpus callosotomy	6 (7.1)
Ablation	2 (2.4)
Right parietal AVM	1 (1.2)
Left frontal	1 (1.2)

Some patients had multiple procedures.
AVM, arteriovenous malformation; DNET, dysembryoplastic neuroepithelial tumor; RNS, responsive neurostimulation; VNS, vagus nerve stimulation.

[a] Some of the temporal lobectomy patients also had extratemporal resections that are not included in the table resection count.

[b] The tumor-related resections are not included in the temporal or extratemporal resection counts.

3.2. Patient retention

The percentage of patients who continued cenobamate treatment at data cutoff (retention rate) was 76.5 % (65/85) for patients with prior surgery and 72.3 % (112/155) for nonsurgical patients, with treatment up to 43 months (median duration of cenobamate treatment was 32.9 months). When patients who continued cenobamate were examined by type of surgery, retention rate was 72.5 % (29/40) for patients with prior resection, ablation, or disconnection surgery, 74.2 % (23/31) for patients with VNS or RNS, and 92.9 % (13/14) for patients with both resection or disconnection surgery and VNS.

3.3. Cenobamate dose

The mean dose of cenobamate was higher among patients with prior surgery who continued cenobamate treatment (n = 65; 313.8 mg/day) versus the nonsurgical patients who continued cenobamate treatment (n = 112; 270.5 mg/day) at data cutoff. Within subgroups of surgical procedures, the mean dose of cenobamate in patients continuing treatment was 329.3 mg/day in patients with prior resection, ablation, or disconnection surgery (n = 29), 302.2 mg/day in patients with prior VNS or RNS surgery (n = 23), and 300.0 mg/day in patients with both resection or disconnection surgery and VNS (n = 13).

3.4. Efficacy

In the patients with prior surgery, 23.5 % (20/85) had 100 % seizure reduction ≥ 12 months at the last clinic visit and 30.6 % (26/85) had 100 % seizure reduction at any consecutive ≥ 12-month interval (Fig. 1), compared with 27.1 % (42/155) and 39.4 % (61/155), respectively, of the nonsurgical patients (*p*-values > 0.05). Among the 177 patients still receiving cenobamate at the data cutoff, 29.2 % (19/65) of patients with prior surgery versus 36.6 % (41/112) of the nonsurgical patients had 100 % seizure reduction for ≥ 12 months at the data cutoff (p > 0.05). In a subgroup analysis, 100 % seizure reduction ≥ 12 months at data cutoff was examined by baseline seizure frequency in patients with prior

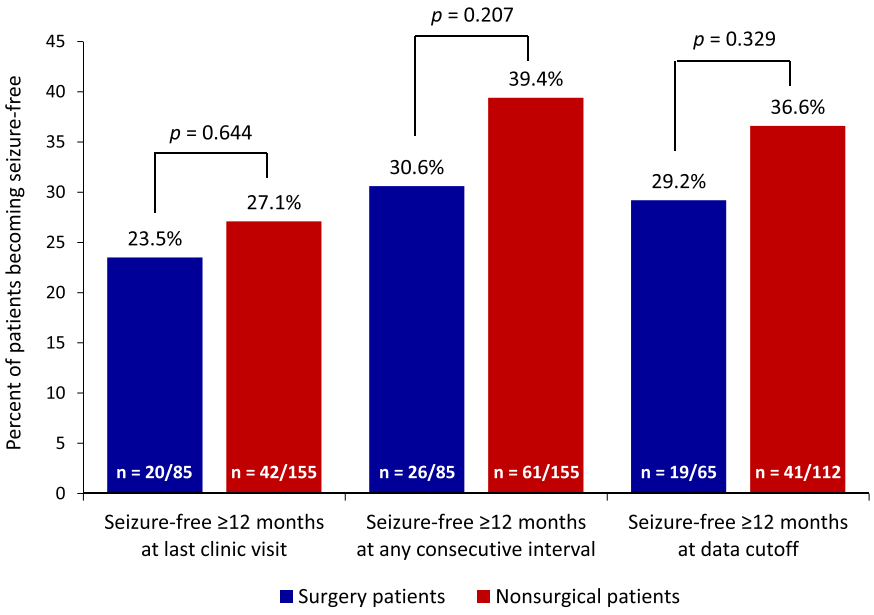

Fig. 1. . 100 % seizure reduction with cenobamate treatment in patients with prior epilepsy-related surgery and with no surgery. *P*-values are based on Fisher's exact test of patients with prior epilepsy-related surgery versus nonsurgical patients. **At last clinic visit:** interval includes the last clinic visit for the patient prior to discontinuation or data cutoff (includes all patients with prior surgery). **At any consecutive 12-month interval:** does not have to include the last visit (includes all patients with prior surgery). **At data cutoff visit:** interval includes the data cutoff visit (includes patients continuing on cenobamate at data cutoff).

surgery and nonsurgical patients. Among the patients with < 3 baseline seizures per 28 days, 41.7 % (10/24) of patients with prior surgery and 45.5 % (30/66) of nonsurgical patients had 100 % seizure reduction ≥ 12 months at data cutoff. Among the patients with ≥ 3 baseline seizures per 28 days, 21.9 % (9/41) of patients with prior surgery and 23.9 % (11/46) of nonsurgical patients had 100 % seizure reduction ≥ 12 months at data cutoff.

Seizure reduction was examined by surgery groups. In the first comparison, the group of patients with prior resection, ablation, or disconnection surgery was compared to the group of patients with prior VNS or RNS, and the 14 "overlapping" patients who had both resection or disconnection surgery and VNS were included in each of these two groups (Fig. 2A). The percentage of patients with prior resection, ablation, or disconnection surgery (with or without VNS) who had 100 % seizure reduction for ≥ 12 months with cenobamate treatment for any consecutive interval (35.2 %) was higher than the percentage of patients with prior VNS or RNS (with or without resection or disconnection surgery; 26.7 %) and slightly lower than the percentage of nonsurgical patients (39.4 %) (Fig. 2A). In the patients who continued cenobamate, the percentage of patients with 100% seizure reduction for ≥ 12 months at data cutoff was similar in the patients with prior resection, ablation, or disconnection surgery (with or without VNS; 28.6 %) compared with patients with prior VNS or RNS (with or without resection or disconnection surgery; 30.6 %) and was slightly lower than in the nonsurgical patients (36.6 %) (Fig. 2A). In the second comparison among surgery groups, the 100 % seizure reduction for ≥ 12 months at data cutoff among patients who continued cenobamate was similar for the group of patients with prior resection, ablation, or disconnection surgery only (27.6 % of patients), the group of patients with prior VNS or RNS only (30.4 %), and the group of patients with prior resection or disconnection surgery along with VNS (30.8 %) (Fig. 2B). The percentage of patients with 100 % seizure reduction for ≥ 12 months at any consecutive ≥ 12 months interval and at data cutoff when examined by the specific type of surgery are shown in Table 3.

3.5. Safety

Fatigue, dizziness, and somnolence were the most common TEAEs in patients with prior surgery (40.0 %, 38.8 %, and 25.9 %, respectively) and in nonsurgical patients (31.6 %, 28.4 %, and 31.6 %, respectively) (Table 4). Serious TEAEs were reported by 29.4 % of patients with prior surgery versus 16.1 % of nonsurgical patients. The serious TEAEs that occurred in more than 1 patient with prior surgery included 6 patients with seizure (7.1 %) and 2 patients each (2.4 %) with ataxia, mental status changes, urinary tract infection, and vomiting. The serious TEAEs that occurred in more than 1 nonsurgical patient included 2 patients each (1.3 %) with chest pain, pneumonia, post-traumatic epilepsy, postictal paralysis, postictal state, and pulmonary embolism. Discontinuation of cenobamate due to TEAEs occurred in 8.2 % of prior surgery patients and 15.5 % of nonsurgical patients (Table 4). TEAEs that led to discontinuation in more than 1 patient included somnolence (n = 2; 2.4 %) in prior surgery patients and ataxia, dizziness, and somnolence (each n = 2; 1.3 %) in nonsurgical patients.

4. Discussion

Patients with focal seizures that remain uncontrolled despite adequate trials with two or more ASMs and epilepsy surgery have particularly treatment-resistant seizures. Few studies have specifically examined whether adjusting/adding ASMs in patients for whom prior epilepsy-related surgery has failed can result in 100 % seizure reduction for these patients. In a retrospective review of medical records that examined the response to ASMs after surgery failure (ie, recurrence of seizures) in 103 consecutive patients with a minimum 2-year follow-up, patients tried an average of 4.02 ASMs; 9.7 % of patients attained seizure freedom and 72.8 % of patients had no change in focal seizures with ASM adjustments (Ma et al., 2020). Similarly, in a retrospective study of 34 patients who had no change in their seizures at 1 year following epilepsy surgery, long-term follow-up for an average of 7.6 years found that only 3 patients (8.8 %) achieved seizure freedom following a change in ASMs alone (4 others became seizure-free following resective reoperation and one after VNS) (Ryzí et al., 2015). The duration of 100% seizure reduction was not stated in these studies.

The current post hoc analysis of adjunctive cenobamate treatment in patients with prior surgery and uncontrolled focal seizures examined long-term (≥12 months) 100 % seizure reduction in patients treated in a subset of clinical sites from the C021 open-label study (Sperling et al., 2021; Sperling et al., 2020). Among all patients with prior surgery, 30.6 % had long-term 100 % seizure reduction at any interval of ≥ 12 consecutive months. In the patients with prior surgery who continued taking cenobamate until data cutoff, 29.2 % had long-term 100 % seizure reduction for ≥ 12 months before the data cutoff visit. These outcomes were slightly lower than those of the nonsurgical patients (39.4 % any interval and 36.6 % at data cutoff had long-term 100 %

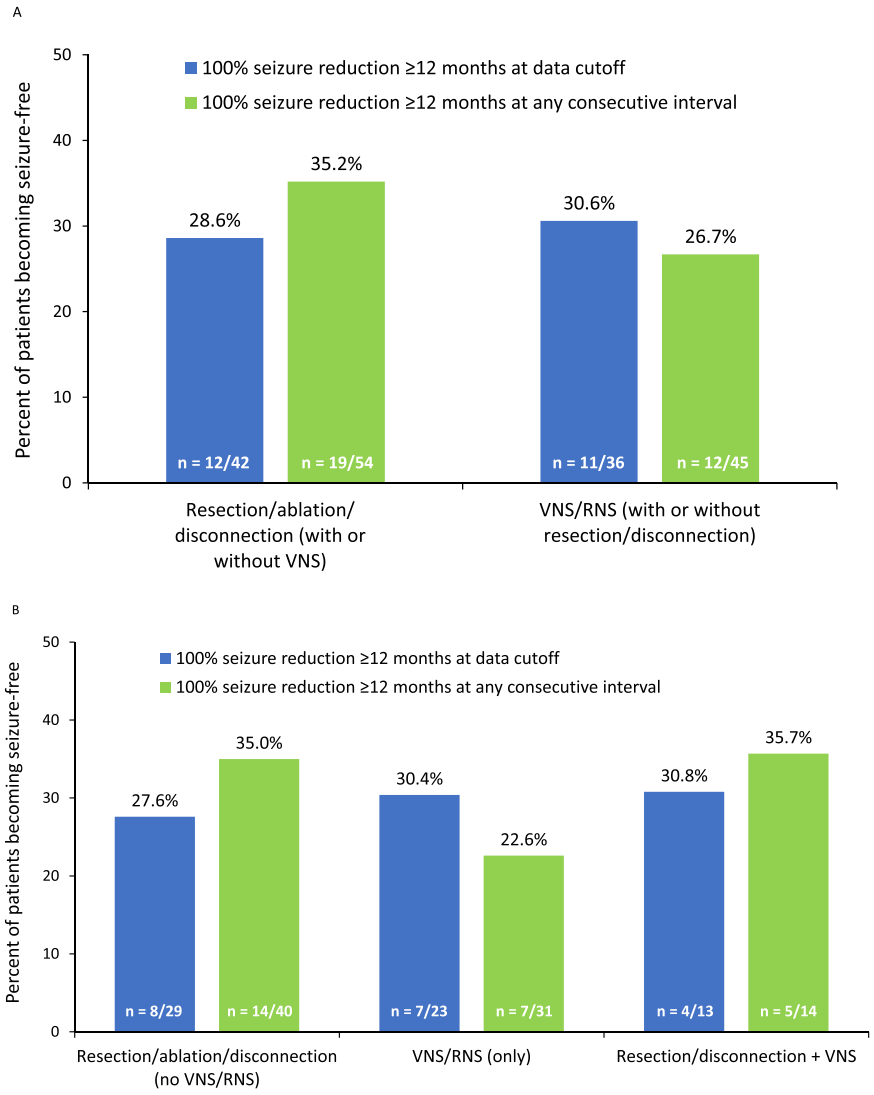

Fig. 2. 100 % seizure reduction with cenobamate treatment in patients with prior epilepsy-related surgery by (A) resection, ablation, disconnection (with or without VNS), or VNS/RNS (with or without resection or disconnection) surgery and (B) by resection, ablation, disconnection surgery versus VNS/RNS surgery versus resection/disconnection and VNS. RNS, responsive neurostimulation; VNS, vagus nerve stimulation.

seizure reduction for ≥12 months). However, the patients with prior surgery had a higher seizure burden, with on average double the frequency of seizures versus the nonsurgical patients at baseline.

These percentages of patients with prior surgery achieving long-term 100 % seizure reduction in response to cenobamate treatment are substantially greater than seen in previous reports of patients with failed epilepsy surgery who experienced seizure freedom (Ma et al., 2020; Ryzí et al., 2015). The percentage of patients with prior surgery who had 100 % seizure reduction ≥ 12 months with cenobamate treatment was also considerably higher than that reported with other ASMs, with < 13 % of patients achieving ≥ 12 months of seizure freedom, in open-label extension studies of phase 2 and phase 3 trials of lacosamide, perampanel, and brivaracetam in patients with focal seizures (Husain et al., 2012; Krauss et al., 2018; Toledo et al., 2016).

When evaluated by type of surgery, a higher percentage of patients in the current study with prior resection, ablation, or disconnection surgery (with or without VNS) had long-term 100 % seizure reduction at any interval compared with patients who had prior VNS or RNS (with or without resection or disconnection surgery; slightly more than a third of patients versus slightly more than a quarter of patients, respectively). Among the patients who continued cenobamate treatment at data cutoff, the percentage of patients with long-term 100 % seizure reduction at data cutoff was similar between patients with both prior resection or disconnection surgery and prior VNS and patients with VNS or RNS only, and the percentage of patients with prior resection, ablation, or disconnection surgery only was slightly lower. Altogether, these outcomes support the efficacy of cenobamate in achieving long-term 100 % seizure reduction in patients with highly refractory seizures.

Patients with prior surgery who continued cenobamate treatment were receiving a higher dosage of cenobamate than the nonsurgical patients at data cutoff. The highest average dose of cenobamate at data cutoff occurred in the group of patients who had prior resection, ablation, or disconnection surgery. Cenobamate treatment was well tolerated in patients with prior surgery, and the most common TEAEs were central nervous system-related, similar to the nonsurgical patients. Although the percentage of patients with TEAEs was slightly higher in the prior surgery patients than in the nonsurgical patients, discontinuation due to TEAEs was lower in the prior surgery patients. Clinicians were allowed to make adjustments to concomitant ASMs during the C021 study (Rosenfeld et al., 2021; Sperling et al., 2020), and dose reductions of concomitant ASMs may have mitigated TEAEs in prior surgery patients who on average received higher doses of cenobamate compared with nonsurgical patients. The most common serious TEAE in patients with prior surgery was seizure, reported by 6 patients, which is

Table 3
100 % seizure reduction ≥ 12 months by type of surgery.

	100 % seizure reduction ≥ 12 months (n/N, %)	
	Any consecutive ≥ 12 months	≥ 12 months at data cutoff
Temporal lobectomy[a]	12/29 (41.4)	8/29 (27.6)
Right side lobectomy	9/18 (50.0)	6/18 (33.3)
Left side lobectomy	3/11 (27.3)	2/11 (18.2)
Extratemporal resection	4/13 (30.8)	3/13 (23.1)
Right side resection	0/5 (0)	0/5 (0)
Left side resection	4/8 (50.0)	3/8 (37.5)
Tumor-related resection[b]	2/8 (25.0)	0/8 (0)
Corpus callosotomy	2/6 (33.3)	2/6 (33.3)
Ablation	0/2 (0)	0/2 (0)
VNS/RNS	12/45 (26.7)	11/45 (24.4)
VNS (no RNS)	11/43 (25.6)	10/43 (23.3)
RNS (no VNS)	0/1 (0)	0/1 (0)
RNS and VNS	1/1 (100.0)	1/1 (100.0)

Some patients had multiple procedures.
RNS, responsive neurostimulation; VNS, vagus nerve stimulation.
[a] Some of the temporal lobectomy patients also had extratemporal resections that are not included in the table resection count.
[b] The tumor-related resections are not included in the temporal or extratemporal resection counts.

Table 4
Most common TEAEs in patients with prior epilepsy-related surgery and with no surgery.

TEAEs, n (%)	Prior surgery patients (n = 85)	Nonsurgical patients (n = 155)
Patients with ≥ 1 TEAE	85 (100)	151 (97.4)
Patients with ≥ 1 TEAE leading to discontinuation	7 (8.2)	24 (15.5)
Patients with ≥ 1 serious TEAE	25 (29.4)	25 (16.1)
TEAEs in ≥ 10 % of patients		
Fatigue	34 (40.0)	49 (31.6)
Dizziness	33 (38.8)	44 (28.4)
Somnolence	22 (25.9)	49 (31.6)
Balance disorder	17 (20.0)	20 (12.9)
Upper respiratory tract infection	13 (15.3)	25 (16.1)
Headache	11 (12.9)	25 (16.1)
Seizure	10 (11.8)	7 (4.5)
Depression	10 (11.8)	9 (5.8)
Weight decreased	10 (11.8)	14 (9.0)
Constipation	9 (10.6)	12 (7.7)
Vomiting	9 (10.6)	13 (8.4)
Fall	8 (9.4)	17 (11.0)
Nausea	7 (8.2)	21 (13.5)

TEAEs, treatment-emergent adverse events.

not unexpected given the treatment-refractory seizures in this patient group. Treatment retention rates are an indicator of overall treatment satisfaction, including efficacy, safety, and tolerability, as each patient decides whether to continue treatment (Ben-Menachem et al., 2010; Chung et al., 2007). The high retention rate of 76.5 % for patients with prior surgery indicates cenobamate was an effective and tolerable treatment over a treatment period of up to 43 months.

One other ASM has been specifically evaluated in patients following failed epilepsy surgery. A retrospective study of levetiracetam, primarily as adjunctive treatment, in patients with recurrent focal seizures following epilepsy surgery examined seizure freedom in the last 3 months of treatment and found high short-term seizure freedom in patients with prior epilepsy surgery (10/21 patients; 47.6 %), considerably greater than in a comparison group of nonsurgical patients (9/61, 14.7 %) (Motamedi et al., 2003). Alternatively, a long-term follow-up study of epilepsy surgery reported 15.1 % of patients experienced seizure freedom (duration not reported) starting at 2 or more years after surgery that was associated with initiation of levetiracetam (de Tisi et al., 2011). A possible limitation of post-surgery treatment with levetiracetam is the greater incidence of psychiatric and behavioral adverse events in the patient group with failed epilepsy surgery as compared with nonsurgical patients (Habets et al., 2017; Motamedi et al., 2003).

Limitations of this study analysis include that the C021 study was an open-label safety study that was not designed to assess efficacy, and thus efficacy was analyzed post hoc. The C021 study was also not designed to evaluate efficacy in patients with prior epilepsy-related surgery. As a result, some details of patients' prior surgeries were not available, including pre-surgery magnetic resonance imaging and electroencephalogram findings and the extent of each patient's seizure reduction response to surgery prior to seeking additional ASM treatment. The study lumped together patients who had resective surgery, which is potentially curative, with patients who had palliative procedures, making the surgery group heterogeneous. Finally, because this post hoc analysis retrospectively evaluated patients from a subset of 10 clinical sites from the C021 study, there is the possibility of selection bias, although it should be noted that the subset cohort generally resembled the remaining C021 study sample (Sperling et al., 2021). Despite these limitations, a key strength of the C021 outcomes is their clinical practice relevance because the study was long-term and clinicians were allowed to make adjustments to the cenobamate dose as well as to concomitant ASMs (Rosenfeld et al., 2021; Sperling et al., 2020).

The decision to continue ASM trials or pursue epilepsy surgery in patients with treatment-refractory focal seizures requires evaluation of the benefits and risks of either choice (Kwan and Sperling, 2009). While surgery in appropriately selected cases may have significant benefits in seizure reduction, it has potential medical, neurologic, and psychiatric complications, some of which could be irreversible (Kwan and Sperling, 2009). The post hoc efficacy analysis of the C021 study has demonstrated sustained improvement in seizure control in adults with uncontrolled focal seizures who were treated with cenobamate (Sperling et al., 2021). High rates of sustained 100 % seizure reduction across focal seizure types and high retention of patients across the analysis period support long-term efficacy and tolerability of cenobamate (Sperling et al., 2021). This was demonstrated within the context of dose reduction and discontinuation of one or more concomitant ASMs to improve tolerability during the addition of cenobamate to an existing ASM regimen (Rosenfeld et al., 2021). Along with the current post hoc analysis showing long-term 100 % seizure reduction for any interval of ≥ 12 consecutive months in 30.6 % of patients with prior surgery, these outcomes support treatment with cenobamate early in the ASM treatment regimen. A trial of cenobamate may be considered before surgery (with the exception of tumor-related resections). The merits of this approach may be evaluated in a future trial of cenobamate in patients being considered for epilepsy surgery. It is probably appropriate to consider cenobamate prior to repeated epilepsy surgery, where the odds of achieving seizure freedom are reduced (Malmgren and Edelvik, 2017; Yardi et al., 2020).

5. Conclusions

In this post hoc analysis, high rates of sustained 100 % seizure reduction ≥ 12 months were achieved with cenobamate in adult patients with uncontrolled focal seizures who were refractory to prior epilepsy-related surgery as well as to 1–3 ASMs. These findings support the efficacy of cenobamate even in patients with very refractory seizures despite surgery. They suggest that cenobamate should be considered early in the treatment regimen, including, in some patients, prior to considering surgical treatment.

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Data availability

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

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References

Ben-Menachem, E., Sander, J.W., Privitera, M., Gilliam, F., 2010. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. Epilepsy Behav. 18 (1–2), 24–30. https://doi.org/10.1016/j.yebeh.2010.04.001.

Chen, Z., Brodie, M.J., Liew, D., Kwan, P., 2018. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 75 (3), 279–286. https://doi.org/10.1001/jamaneurol.2017.3949.

Chung, S., Wang, N., Hank, N., 2007. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure 16 (4), 296–304. https://doi.org/10.1016/j.seizure.2007.01.004.

Chung, S.S., French, J.A., Kowalski, J., Krauss, G.L., Lee, S.K., Maciejowski, M., et al., 2020. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology 94 (22), e2311–e2322. https://doi.org/10.1212/wnl.0000000000009530.

de Tisi, J., Bell, G.S., Peacock, J.L., McEvoy, A.W., Harkness, W.F., Sander, J.W., et al., 2011. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 378 (9800), 1388–1395. https://doi.org/10.1016/s0140-6736(11)60890-8.

Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., et al., 2017. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58 (4), 522–530. https://doi.org/10.1111/epi.13670.

Habets, J.G.V., Leentjens, A.F.G., Schijns, O., 2017. Serious and reversible levetiracetam-induced psychiatric symptoms after resection of frontal low-grade glioma: two case histories. Br. J. Neurosurg. 31 (4), 471–473. https://doi.org/10.1080/02688697.2016.1244255.

Husain, A., Chung, S., Faught, E., Isojarvi, J., McShea, C., Doty, P., 2012. Long-term safety and efficacy in patients with uncontrolled partial-onset seizures treated with adjunctive lacosamide: results from a Phase III open-label extension trial. Epilepsia 53 (3), 521–528. https://doi.org/10.1111/j.1528-1167.2012.03407.x.

Krauss, G.L., Klein, P., Brandt, C., Kun Lee, S., Milanov, I., Milovanovic, M., et al., 2020. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 19 (1), 38–48. https://doi.org/10.1016/S1474-4422(19)30399-0.

Krauss, G.L., Perucca, E., Kwan, P., Ben-Menachem, E., Wang, X.F., Shih, J.J., et al., 2018. Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: study 307. Epilepsia 59 (4), 866–876. https://doi.org/10.1111/epi.14044.

Kwan, P., Sperling, M.R., 2009. Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation. Epilepsia 50 (Suppl 8), 57–62. https://doi.org/10.1111/j.1528-1167.2009.02237.x.

Ma, J., Wu, J., Chen, H., Chen, Y., Xu, D., Tian, X., et al., 2020. Response to antiepileptic drugs after unsuccessful epilepsy surgery: a multivariate analysis of 103 patients. Seizure 81, 222–227. https://doi.org/10.1016/j.seizure.2020.08.014.

Malmgren, K., Edelvik, A., 2017. Long-term outcomes of surgical treatment for epilepsy in adults with regard to seizures, antiepileptic drug treatment and employment. Seizure 44, 217–224. https://doi.org/10.1016/j.seizure.2016.10.015.

Mohan, M., Keller, S., Nicolson, A., Biswas, S., Smith, D., Osman Farah, J., et al., 2018. The long-term outcomes of epilepsy surgery. PLoS One 13 (5), e0196274. https://doi.org/10.1371/journal.pone.0196274.

Motamedi, M., Nguyen, D.K., Zaatreh, M., Singh, S.P., Westerveld, M., Thompson, J.L., et al., 2003. Levetiracetam efficacy in refractory partial-onset seizures, especially after failed epilepsy surgery. Epilepsia 44 (2), 211–214. https://doi.org/10.1046/j.1528-1157.2003.26302.x.

Rosenfeld, W.E., Abou-Khalil, B., Aboumatar, S., Bhatia, P., Biton, V., Krauss, G.L., et al., 2021. Post-hoc analysis of a phase 3, multicenter, open-label study of cenobamate for treatment of uncontrolled focal seizures: effects of dose adjustments of concomitant antiseizure medications. Epilepsia 62 (12), 3016–3028. https://doi.org/10.1111/epi.17092.

Ryzí, M., Brázdil, M., Novák, Z., Hemza, J., Chrastina, J., Ošlejšková, H., et al., 2015. Long-term outcomes in patients after epilepsy surgery failure. Epilepsy Res. 110, 71–77. https://doi.org/10.1016/j.eplepsyres.2014.11.011.

Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., et al., 2017. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 58 (4), 512–521. https://doi.org/10.1111/epi.13709.

Sperling, M.R., Abou-Khalil, B., Aboumatar, S., Bhatia, P., Biton, V., Klein, P., et al., 2021. Efficacy of cenobamate for uncontrolled focal seizures: post-hoc analysis of a phase 3, multicenter, open-label study. Epilepsia 62 (12), 3005–3015. https://doi.org/10.1111/epi.17091.

Sperling, M.R., Klein, P., Aboumatar, S., Gelfand, M., Halford, J.J., Krauss, G.L., et al., 2020. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia 61 (6), 1099–1108. https://doi.org/10.1111/epi.16525.

Toledo, M., Whitesides, J., Schiemann, J., Johnson, M.E., Eckhardt, K., McDonough, B., et al., 2016. Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures. Epilepsia 57 (7), 1139–1151. https://doi.org/10.1111/epi.13416.

Yardi, R., Morita-Sherman, M.E., Fitzgerald, Z., Punia, V., Bena, J., Morrison, S., et al., 2020. Long-term outcomes of reoperations in epilepsy surgery. Epilepsia 61 (3), 465–478. https://doi.org/10.1111/epi.16452.