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Effectiveness and safety of adjunctive cenobamate for focal seizures in adults with developmental disability treated in clinical practice

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ABSTRACT

Effectiveness and tolerability of adjunctive cenobamate for uncontrolled focal seizures in adults living with a developmental disability are not defined. Retrospective medical record review included adults ≥18 years old living with a developmental disability, either in a group home or with parents, and experiencing uncontrolled focal seizures despite stable doses of ≥1 antiseizure medication (ASM). Effectiveness was examined as percentage change in focal seizure frequency per month from the 2-month average before cenobamate to the average of months 5 and 6 while receiving cenobamate. Percentages of patients achieving responder rates in focal seizure frequency at 6 months of cenobamate treatment were examined. Adverse effects and concomitant ASM dosage adjustments were assessed. Of the 28 included patients, 26 (92.9%) continued cenobamate beyond 6 months. The responder rate of 100% seizure reduction (seizure-free) occurred in 48.2% of the patients who continued cenobamate for 6 months. Ten adverse effects were reported in 9 patients (32.1%), and 80% (8/10) were resolved by reducing concomitant ASM dosages. Two patients (7.1%) discontinued cenobamate due to adverse effects. Cenobamate resulted in substantial reduction in focal seizure frequency and was well tolerated.

1. Introduction

There is an urgent need to identify effective and tolerable antiseizure medications (ASMs) for adults with epilepsy and intellectual and developmental disability. The lifetime prevalence of epilepsy in people with intellectual and developmental disability, at approximately 1 in 4, is higher than in the general population (global pooled lifetime prevalence = 7.60 per 1000 persons [1]), and treatment-resistant seizures occur in as many as two-thirds of those with epilepsy and intellectual disability [2]. Adults with intellectual and developmental disability and epilepsy have significantly lower health-related quality of life (QOL); among their self-reported critical priorities for improving QOL are preventing seizures and reducing seizure frequency and adverse effects of ASMs [3]. The recommended treatment approach for adults with intellectual and developmental disability and epilepsy, as in the general epilepsy population, is to select ASMs based on seizure type and standard practice [4–6]. There is a need for more ASM-specific efficacy and safety outcome data for these patients, especially regarding ASM tolerability related to cognition, behavior, and mobility [6,7].

Cenobamate is approved for patient use in the United States (XCOPRI®) and Europe (ONTOZRY®) as treatment of focal seizures in adults [8]. Patients with uncontrolled focal seizures who were taking stable doses of 1–3 ASMs had significant reductions in focal seizure frequency with adjunctive cenobamate treatment in two randomized, double-blind, placebo-controlled phase 2 studies [9,10]. In these studies, patients receiving cenobamate had a significantly greater median percentage seizure reduction, and significantly greater percentages of patients achieved the responder rates of ≥50%, ≥75%, ≥90%, and 100% (seizure reduction compared with placebo. Seizure freedom was achieved by 28% of patients receiving cenobamate 200 mg/day versus 9% of patients receiving placebo during a 6-week maintenance phase, and by 4% of patients receiving 100 mg/day, 11% receiving 200 mg/day, and 21% receiving 400 mg/day cenobamate versus 1% receiving placebo during a 12-week maintenance phase [9,10]. Long-term tolerability of cenobamate was demonstrated by a high patient retention rate (ie, 79% at 1 year) in a phase 3 open-label safety study [11]. A post hoc analysis of a subset of patients from this study found high rates

Abbreviations: ASM, antiseizure medication; NA, not applicable; QOL, quality of life.

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of 100% seizure reduction (~36% of patients) that was sustained for ≥12 months [12].

Examination of outcomes during routine clinical practice, such as through health records, can provide valuable information for clinicians in their decision-making about treatment selection for patients [13]. Described here is the first report of the effectiveness and tolerability of cenobamate during routine clinical practice in patients with a developmental disability and uncontrolled focal seizures despite treatment with at least one ASM. Using a retrospective medical chart review, the percentage focal seizure reduction, percentage of patients achieving seizure reduction responder rates, and tolerability of cenobamate treatment were evaluated. Adjustment of concomitant ASM dosages to mitigate adverse effects or polypharmacy was also examined.

2. Materials and methods

2.1. Participants

Among patients being seen in routine clinical practice in a neurology clinic, those eligible for inclusion in this retrospective medical record review were: (1) ≥18 years old; (2) living with a developmental disability in a group home or with parents; (3) experiencing uncontrolled focal seizures (as documented by electroencephalogram focal abnormalities or no generalized discharges) despite stable doses of ≥1 ASM; and (4) initiated on adjunctive treatment with cenobamate. All patients who met these criteria were included in the study. As this study was a retrospective medical chart review, IRB review and patient consent were not applicable.

2.2. Study design

This study used a retrospective medical chart review, including patient seizure diaries, to collect data on focal seizure frequency, cenobamate dose and duration, concomitant ASM dosages, and adverse effects. Standardized forms were used to report seizure frequency as part of standard clinic procedures. Seizure diaries consisted of the summation of these forms and were documented in patients' charts. The information within the medical charts could have been provided by the patient or by a proxy (ie, parent caregiver for patients living at home; group home caregiver for patients living in a group home). All patients were treated by one physician and the prescribing information guidelines for cenobamate titration were followed.

2.3. Outcomes

The effectiveness of adjunctive cenobamate was assessed by the percentage change in focal seizure frequency per month from the average of the 2 months prior to starting cenobamate (ie, baseline) to the average of Months 5 and 6 while receiving cenobamate treatment (ie, 6 months of adjunctive cenobamate treatment). Also examined was the percentage of patients achieving ≥50%, ≥75%, ≥90%, and 100% seizure reduction in focal seizure frequency at 6 months of cenobamate treatment. Safety was evaluated through report of adverse effects during treatment with cenobamate and discontinuation of cenobamate due to adverse effects. Adjustment of the dosing of concomitant ASMs during cenobamate treatment was assessed.

2.4. Data analysis

Data were summarized descriptively.

3. Results

Patients included 28 adults living with a developmental disability and living in a group home or with parents. The types of developmental disabilities were diverse, including cognitive, social, and physical disabilities. The mean age of patients was 38.4 years, 57.1% (16/28) were male, and mean epilepsy duration was 34.9 years (range, 15–62 years) at the start of cenobamate treatment (Table 1). On average, patients had 20.2 focal seizures per month (median = 3) prior to cenobamate treatment, including focal aware motor (*n* = 2 patients; 7.1%), focal impaired awareness (*n* = 11; 39.3%), and focal to bilateral tonic-clonic (*n* = 16; 57.1%) seizures. All patients were receiving ≥2 concomitant ASMs, and 53.6% (15/28) were receiving ≥4 concomitant ASMs. Prior epilepsy-related surgery had occurred in 28.6% of patients (8/28).

The most common seizure etiologies included cerebral palsy (*n* = 6; 21.4%), seizures with unknown etiology (*n* = 6; 21.4%), hydrocephalus (*n* = 4; 14.3%), Lennox-Gastaut syndrome (*n* = 4; 14.3%), and encephalitis (*n* = 3; 10.7%) (Table 2), and 4 patients also were diagnosed with autism.

3.1. Patient disposition

Twenty-six patients (92.9%) continued cenobamate treatment through 6 months. Mean cenobamate dose at 6 months of treatment was 156.7 mg/day (range, 50 mg/day to 300 mg/day), with 77% of patients receiving 100 to 200 mg/day (23.1% [6/26 patients] received 100 mg/day, 23.1% [6/26] received 150 mg/day, and 30.8% [8/26] received 200 mg/day). Slowed titration was used with one patient and two patients had a cenobamate dose reduction by 6 months. Two patients (7.1%) discontinued cenobamate prior to 5 months of treatment. One discontinuation occurred with cenobamate 25 mg/day due to ataxia. The patient's concomitant ASMs included lacosamide 400 mg/day and valproic acid 1500 mg/day. The lacosamide dose had been reduced to 200 mg/day to try to mitigate or resolve the ataxia, but ataxia continued. Before further adjustments could be made, the patient's parents chose to discontinue cenobamate. The other discontinuation occurred with cenobamate 50 mg/day due to dizziness. The patient's concomitant

Table 1
Patient demographics and clinical characteristics.

	All patients (*n* = 28)
Mean (min, max) age (years)	38.4 (19, 64)
Male/Female, *n* (%)	16 (57.1)/ 12 % (42.9)
Mean (min, max) epilepsy duration (years)	34.9 (15, 62)
Seizure type, *n* (%)*	
Focal aware motor	2 (7.1)
Focal impaired awareness	11 (39.3)
Focal to bilateral tonic-clonic	16 (57.1)
Mean (median) seizure frequency/month during the 2–3 months before starting cenobamate	20.2 (3)
No. of concomitant ASMs at start of cenobamate, *n* (%)	
1	0
2	5 (17.9)
3	8 (28.6)
4	5 (17.9)
≥5	10 (35.7)
Previous epilepsy-related surgery, *n* (%)	8 (28.6)
Vagus nerve stimulation	3 (10.7)
Vagus nerve stimulation and corpus callosotomy	3 (10.7)
Corpus callosotomy	1 (3.6)
Left temporal lobectomy	1 (3.6)

ASMs, antiseizure medications.
* One patient had both focal impaired awareness and focal to bilateral tonic-clonic seizures and was counted in both categories.

Table 2
Etiology of seizures.

Etiology, *n* (%)	All participants (*n* = 28)
Cerebral palsy*	6 (21.4)
Unknown seizure etiology	6 (21.4)
Hydrocephalus*	4 (14.3)
Lennox-Gastaut syndrome	4 (14.3)
Encephalitis	3 (10.7)
Cerebral dysgenesis	1 (3.6)
Febrile illness	1 (3.6)
Fetal alcohol syndrome	1 (3.6)
Head injury	1 (3.6)
Migrational disorder	1 (3.6)
Rett syndrome	1 (3.6)
7th chromosome deletion	1 (3.6)

* Two patients had both cerebral palsy and hydrocephalus and were counted in both categories.

ASMs included lamotrigine 600 mg/day and lacosamide 400 mg/day. Before dose reduction of concomitant ASMs could be made to try to mitigate or resolve the dizziness, the patient's parents discontinued cenobamate.

3.2. Effectiveness

Adjunctive cenobamate treatment through 6 months led to reduced mean focal seizure frequency from 20.9 seizures (median = 3.0) per month to 4.1 seizures (median = 0.5) per month. Mean focal impaired awareness or focal aware motor seizures were reduced from 11.7 (median = 3.0) to 3.4 (median = 0.5) seizures per month and mean focal to bilateral tonic-clonic seizures were reduced from 26.9 (median = 6.0) to 4.6 (median = 0.25) seizures per month (Fig. 1A). Among the patients who continued cenobamate treatment through 6 months, all but two patients achieved ≥50% responder rate (one patient showed no change in seizure frequency and one patient had <50% seizure reduction [33.3%]). 100% seizure reduction occurred in 48.2% of the patients (Fig. 1B). The seizure reduction responder rates within focal impaired awareness or focal aware motor seizures and within focal to bilateral tonic-clonic seizures were similar.

3.3. Safety

Ten adverse effects were reported in 9 patients (32.1%), and 80% (8/10) of the reported adverse effects were resolved by reducing concomitant ASM doses (Table 3). The most common adverse effect was dizziness, reported by 4 patients (14.3%), which resolved in 3 of these patients with reduction in lacosamide dose. Drowsiness was reported by 3 patients (10.7%) and was resolved in each of these patients with reduction of either brivaracetam, clobazam, or clonazepam dose. Ataxia was reported in 2 patients (7.1%) and resolved in 1 of these patients with reduction of the clobazam dose. Acting out was reported in 1 patient (3.6%) and resolved with reduction of the clobazam dose.

Dose reduction, including discontinuation of the ASM, occurred across 13 concomitant ASMs during cenobamate treatment. Concomitant ASM dose reduction was most common with lacosamide (45.5% of patients [10/22] taking lacosamide), clobazam (100%; 5/5), lamotrigine (30.8%; 4/13), and perampanel (50%; 3/6) (Table 4). Discontinuation of the ASM occurred with clobazam (4 patients), lacosamide (3 patients), perampanel (3 patients), cannabidiol (1 patient), clonazepam (1 patient), lamotrigine (1 patient), and topiramate (1 patient).

3.4. Patient well-being

Patient QOL was not systematically or formally assessed during routine patient care. However, medical record notes indicated family-reported improvement in patient well-being following cenobamate treatment for 5 patients. These patients were receiving 150–300 mg/day of cenobamate. Three patients with reduction in seizure frequency ranging from 67% to 78% were described as more alert and interactive and two patients with 100% seizure reduction were described as no longer using a helmet and using signals, being continent, and riding a horse. These patients were receiving 3–5 concomitant ASMs at the start of cenobamate and 4 of the patients discontinued 1 or 2 concomitant ASMs by 6 months of cenobamate treatment.

4. Discussion

Randomized controlled trials are necessary to demonstrate efficacy and safety of a new ASM. However, they are limited in their application to routine clinical practice because of an inability to adjust concomitant ASMs, short trial duration, and lack of focus on specific patient populations, such as patients with intellectual and developmental disabilities [14]. Outcomes during routine clinical practice can be a valuable complement to controlled clinical trials for clinicians in their treatment decision-making [13]. In the current study of adults living with a developmental disability either in a group home or with parents who continued to experience uncontrolled focal seizures despite treatment with two or more ASMs, treatment with adjunctive cenobamate for 6 months during routine clinical care resulted in substantial reductions in focal seizure frequency. Among the patients who continued cenobamate treatment through 6 months, almost half (48%) were seizure-free (100% seizure reduction) at 6 months of treatment. This seizure reduction response supports the effectiveness of cenobamate in these patients with highly refractory focal seizures, consistent with the significant seizure reduction responses in the adjunctive cenobamate phase 2 studies and in the post-hoc efficacy analysis of the open-label safety study [9,10,12]. The notable seizure reduction in these patients living with a developmental disability builds on the substantial seizure reduction seen with adjunctive cenobamate treatment in the single-center subset of patients from cenobamate open-label and long-term extension studies, of which approximately half had cognitive, neurodevelopmental, or other disabilities [15].

ASM treatment for patients with epilepsy and intellectual and developmental disability often involves polypharmacy due to treatment-resistant seizures and can be complicated by greater adverse effects [7]. The goal of ASM therapy is to improve patient QOL, with the best QOL achieved by seizure reduction without intolerable adverse effects [16]. Substantial seizure reduction, at the level of ≥90% or 100% seizure reduction, may be needed to improve QOL in patients with intellectual/developmental disability [15,17]. Tolerability of the ASM regimen is key to maintaining both effective treatment and QOL and reduction of adverse effects is a priority reported by patients and their caregivers [3]. Effective seizure control is also essential for reducing burden and improving QOL for caregivers [15,18]. The most common adverse effects reported during adjunctive cenobamate treatment within routine clinical care in the patients living with a developmental disability were dizziness and drowsiness, which is consistent with the cenobamate clinical trial program [9–11,19]. Discontinuations due to adverse effects were low (2/28 patients; 7.1%) during routine clinical care.

In line with the effectiveness and tolerability of adjunctive cenobamate in this group of patients, retention of patients through

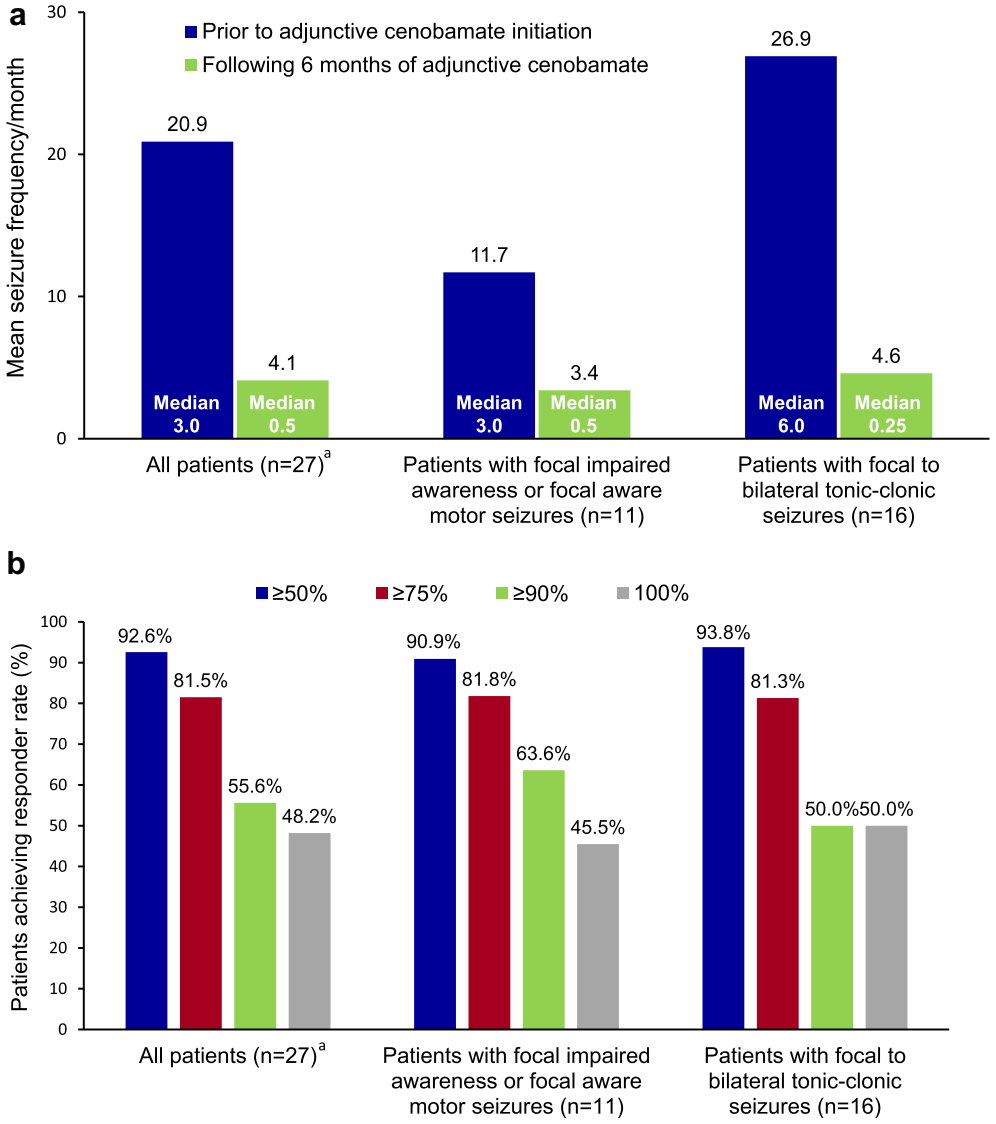

Fig. 1. (A) Seizure frequency/month and (B) ≥50%, ≥75%, ≥90%, and 100% seizure reduction with adjunctive cenobamate. Following 6 months of adjunctive cenobamate. * The patient with both focal impaired awareness and focal to bilateral tonic-clonic seizures was included in both categories. The two patients who discontinued prior to 5 months were excluded from all data.

Table 3
Summary of adverse effects and resolution with concomitant ASM reduction.

	All patients (n = 28), n (%)	Adverse effects resolved with concomitant ASM reduction, n (%)	Reduced concomitant ASMs
Patients with ≥1 adverse effect	9 (32.1)		
Discontinuations due to an adverse effect	2 (7.1)		
Adverse effects		8 (80) resolved of 10 reported	
Dizziness	4 (14.3)	3 (75)	• Lacosamide
Drowsiness*	3 (10.7)	3 (100)	• Brivaracetam • Clobazam • Clonazepam
Ataxia*	2 (7.1)	1 (50)	• Clobazam
Acting out	1 (3.6)	1 (100)	• Clobazam

ASM, antiseizure medication.
* One patient reported 2 adverse effects, ataxia and drowsiness, and both resolved with clobazam reduction.

6 months of cenobamate treatment was high (92.9% of patients). Long-term treatment retention during the cenobamate clinical trial program was evaluated up to 7.8 years, and, compared with the 6-month duration of the current study, ranged from 82.9% of patients for ≥6 months of treatment in the open-label safety study [11] to 73% and 83% of patients at 1 year in the phase 2 open-label extension studies [19]. In the single-center subset of patients, including those with cognitive, neurodevelopmental, and other disabilities, patient retention on long-term cenobamate treatment until the end of the study period, up to 8 years, was 78% [15].

In patients with intellectual and developmental disabilities, careful monitoring of the ASM cumulative load and potential for adverse effects, especially behavioral adverse effects, are recommended [20]. Unlike randomized controlled trials, adjustments can be made to concomitant ASMs during routine clinical care to mitigate or resolve adverse effects that may arise from drug interactions. This approach of adjusting ASMs is common when transitioning ASMs in clinical practice [21,22]. In these patients who were living with a developmental disability, adjustment of concomitant ASMs as needed for adverse effects during titration of

Table 4
Dose reductions of concomitant ASMs in patients who continued cenobamate.

Concomitant ASM	Patients taking ASM at start of cenobamate, *n* (%)	Patients with dose reduction, *n* (%)	Mean (median) % dose reduction	Patients who discontinued ASM, *n* (%)
Lacosamide	22 (78.6)	10 (45.5)	53.8 (47)	3 (13.6)
Lamotrigine	13 (46.4)	4 (30.8)	53.1 (43.8)	1 (7.7)
Brivaracetam	10 (35.7)	2 (20.0)	62.5 (62.5)	0
Clonazepam	8 (28.6)	1 (12.5)	100 (100)*	1 (12.5)
Levetiracetam	7 (25.0)	1 (14.3)	50 (50)*	0
Topiramate	7 (25.0)	2 (28.6)	75 (75)	1 (14.3)
Perampanel	6 (21.4)	3 (50.0)	100 (100)	3 (50.0)
Valproic acid	5 (17.9)	1 (20.0)	33 (33)*	0
Clobazam	5 (17.9)	5 (100)	92 (100)	4 (80.0)
Cannabidiol	3 (10.7)	2 (66.7)	54.4 (54.4)	1 (33.3)
Lorazepam	3 (10.7)	0	NA	0
Felbamate	2 (7.1)	1 (50.0)	80 (80)*	0
Rufinamide	2 (7.1)	0	NA	0
Zonisamide	2 (7.1)	1 (50.0)	50 (50)*	0
Carbamazepine	1 (3.6)	1 (100)	55 (55)*	0
Phenytoin	1 (3.6)	0	NA	0
Gabapentin	1 (3.6)	0	NA	0
Oxcarbazepine	1 (3.6)	0	NA	0
Phenobarbital	1 (3.6)	0	NA	0
Primidone	1 (3.6)	0	NA	0

ASM, antiseizure medication; NA, not applicable.
* Single patient value.

cenobamate contributed to tolerability, including the resolution of drowsiness, ataxia, and behavioral "acting out" with reduction of clobazam dosage, resolution of drowsiness with reduction of brivaracetam and clonazepam dosage, and resolution of dizziness with reduction of lacosamide dosage. Notably, 14 patients had discontinuation of an ASM involving 7 different concomitantly administered ASMs, helping to reduce the burden of polypharmacy in those patients. When possible, reduction of the number of ASMs in a patient's treatment regimen can help to reduce drug load and decrease adverse effects [23,24] without negatively affecting seizure control in patients with treatment-refractory seizures [25]. Adjustment of concomitant ASMs during treatment with cenobamate has been previously demonstrated [15,26].

The seizure reduction findings reported in this study should be interpreted within the limitations of retrospective medical chart data collection, the small patient sample, and the 6-month treatment duration. In the absence of large prospective and controlled studies that focus on the treatment of epilepsy in patients with intellectual and developmental disabilities, evaluation of outcomes using health records during routine clinical care has been reported [27–29]. Additionally, in this study the information within the medical records is from the parent or group home caregiver's report when a patient was unable to communicate directly, though this is the typical means of information gathering for this patient population [3]. Furthermore, the severity of the developmental disabilities was not formally assessed during routine clinical care, although no patient was living independently.

5. Conclusions

During routine clinical practice, the addition of cenobamate to existing ASM therapy for the treatment of uncontrolled focal seizures in patients living with a intellectual and developmental disability resulted in substantial reduction in seizure frequency and high responder rates, including some patients who attained seizure freedom. Adverse effects were reported in approximately one-third of patients and were generally mitigated or resolved by concomitant ASM drug or dose reduction or withdrawal.

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AW, an employee of SK Life Science, Inc., was involved in the collection, analysis, or interpretation of data; in the writing of the manuscript; and in the decision to submit the article for publication. SK Life Science, Inc. funded medical writing and editorial assistance, as noted below.

Ethical statement

This work was performed in accordance with the Declaration of Helsinki for experiments involving humans. Because this was a retrospective study, written consent to participate is not applicable.

Previous presentation

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Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **GSC:** Consultant/advisor, SK Life Science, Inc. **AW:** Employee, SK Life Science, Inc.

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