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RESEARCH ARTICLE

Cost-effectiveness of cenobamate for focal seizures in people with drug-resistant epilepsy

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Abstract

Objective: This study was undertaken to estimate the cost-effectiveness of add-on cenobamate in the UK when used to treat drug-resistant focal seizures in adults who are not adequately controlled with at least two prior antiseizure medications, including at least one used adjunctively.

Methods: We estimated the cost per quality-adjusted life-year (QALY) for cenobamate compared to brivaracetam, eslicarbazepine, lacosamide, and perampanel in the UK National Health Service over a lifetime time horizon. We used a Markov cohort structure to determine response to treatment, using pooled data from three long-term studies of cenobamate. A network meta-analysis informed the likelihood of response to therapy with brivaracetam, eslicarbazepine, lacosamide, and perampanel relative to cenobamate. Once individuals discontinued treatment, they transitioned to subsequent treatment health states, including other antiseizure medicines, surgery, and vagus nerve stimulation. Costs included treatment, administration, routine monitoring, event management, and adverse events. Published evidence and expert opinion informed the likelihood of response to subsequent treatments, associated adverse events, and costs. Utility data were based on Short-Form six-dimension form utility. Discounting was applied at 3.5% per annum as per National Institute for Health and Care Excellence guidance. Uncertainty was explored through deterministic and probabilistic sensitivity analyses.

Results: In the base case, cenobamate led to cost savings of £51 967 (compared to brivaracetam), £21 080 (compared to eslicarbazepine), £33 619 (compared to lacosamide), and £28 296 (compared to perampanel) and increased QALYs of 1.047 (compared to brivaracetam), 0.598 (compared to eslicarbazepine), 0.776 (compared to lacosamide), and 0.703 (compared to perampanel) per individual over a lifetime time horizon. Cenobamate also dominated the four drugs across most sensitivity analyses. Differences were due to reduced seizure frequency with cenobamate relative to comparators.

Significance: Cenobamate improved QALYs and was less costly than brivaracetam, eslicarbazepine, lacosamide, and perampanel. Therefore, cenobamate may be considered as a cost-effective adjunctive antiseizure medication for people with drug-resistant focal seizures.

KEYWORDS
adjunctive, antiseizure medicine, economic evaluation, QALY, quality-adjust life-year

1 | INTRODUCTION

There is an urgent unmet need for more effective seizure reduction strategies, as the proportion of people who become seizure-free has not changed in >30 years.[1] Currently, antiseizure medications (ASMs) are the mainstay of epilepsy treatment. Once an initial ASM fails to suppress seizures, the likelihood of achieving seizure control with each subsequent ASM regimen decreases markedly.[2]

If ASMs do not control seizures successfully, invasive nonpharmacological therapies such as surgery and vagus nerve stimulation may be considered for selected individuals.[3] Epilepsy is classed as drug-resistant when an individual has failed to become (and stay) seizure-free following two attempts with appropriately chosen ASMs.[4] Uncontrolled epilepsy is often disabling, with people having increased psychological and social dysfunction and an increased risk of premature death.[5]

The most recent National Institute for Health and Care Excellence (NICE) epilepsy guidelines state that first-line monotherapy treatment for newly diagnosed focal seizures should be lamotrigine or levetiracetam.[6] If three lines of monotherapy are ineffective or not tolerated, NICE guidelines recommend adjunctive treatment with carbamazepine, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, or zonisamide.

Between 2008 and 2016, several new ASMs, including brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel, were launched for adjunctive treatment of drug-resistant focal seizures. These newer drugs are likely better tolerated and have less potential for drug interactions than older ASMs.[7] They have longer half-lives that permit once-daily dosing, and some have novel mechanisms of action that may benefit people with drug-resistant epilepsy.[7] Lacosamide is recommended by NICE as either third-line monotherapy or first-line add-on, whereas brivaracetam, eslicarbazepine acetate, and perampanel are recommended as second-line add-ons.

In 2021, cenobamate was launched in the UK.[8] Cenobamate is a small molecule purported to have a dual mechanism of action thought to involve the enhancement of γ-aminobutyric acid type A receptor-mediated current and increase the inactivation of sodium channels.[5]

Key Points

- Cenobamate is highly effective for the treatment of focal seizures
- With significant seizure reduction, cenobamate may improve the quality of life of people with epilepsy
- Although cenobamate is more expensive than alternatives, it may lower the direct costs of epilepsy care due to seizures avoided

Cenobamate was assessed in NCT01866111, a multinational, double-blind, randomized, dose–response study in people with drug-resistant focal seizures followed by an open-label extension. A consistent dose–response for cenobamate was demonstrated; a significantly greater proportion of people treated with cenobamate achieved a ≥50% reduction in seizures than those treated with placebo (placebo: 25.5%; 200 mg: 56%, odds ratio [OR] vs. placebo = 3.74, 95% confidence interval [CI] = 2.06–6.80; 400 mg: 64%, OR = 5.24, 95% CI = 2.84–9.67).[5] Additionally, people treated with 200 and 400 mg of cenobamate achieved significantly greater levels of seizure freedom than placebo (200 mg: 11.2%, $p = .0022$; 400 mg: 21.1%, $p < .001$; placebo: 1.0%); these seizure freedom rates are notable compared to the pivotal studies of other ASMs.[9–16]

Cenobamate is recommended for treating focal seizures with or without bilateral tonic–clonic seizures in adults with drug-resistant epilepsy inadequately controlled with at least two ASMs if it is used as an add-on treatment after at least one other add-on treatment has not controlled seizures. In the UK, cenobamate has been recommended by NICE after a formal health technology appraisal of its clinical and cost-effectiveness, but treatment must be started in a tertiary epilepsy service.[17]

In this study, we aim to compare the cost-effectiveness of cenobamate in the UK by assessing the incremental cost-effectiveness ratio (ICER) associated with cenobamate compared to brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel.

2 | MATERIALS AND METHODS

2.1 | Analysis outline

We developed a cost-effectiveness model (CEM) to estimate the cost-effectiveness of cenobamate. Our target population included adults (≥18 years old) with drug-resistant focal seizures who have not been controlled despite a treatment history with at least two ASMs. The perspective considered the National Health Service (NHS) and Personal Social Services in England and Wales. A lifetime time horizon was chosen to capture the chronic nature of focal epilepsy, with a cycle length of 28 and 84 days to reflect the trial's double-blind and open-label phases. Costs and outcomes were discounted at 3.5% per annum, in line with the NICE reference case.[18]

Comparators were aligned with NICE clinical guidelines for managing people with epilepsy that were current at the inception of the model, that is, as adjunctive treatment after at least one adjunctive failure.[19] Clinical experts (including coauthors R.H.T. and J.W.S.) advised that newer ASMs are typically prescribed adjunctively in people with drug-resistant focal seizures. Due to a diminishing likelihood of response with further lines of therapy,[1] treatments with novel mechanisms of action are more likely to be prescribed in later treatment lines to increase the likelihood of response to treatment. Therefore, the comparators considered were brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel, which NICE accepted for the appraisal of cenobamate in the UK. Although other ASMs were recommended as adjunctive therapy after the failure of a first, these were excluded from the analysis due to their use as monotherapy ASMs.[19] Additionally, although treatments recommended for use in earlier lines may be used adjunctively, most people with drug-resistant epilepsy have epilepsy for many years, including numerous years of unsuccessful treatment. Therefore, people with drug-resistant epilepsy will likely have trialed several combinations of older ASMs and are more likely to be treated with newer ASMs compared to older generation ASMs. This decision was also supported by clinical experts (including R.H.T. and J.W.S.).

2.2 | Model structure

We adopted a Markov cohort structure allowing movement between response categories and subsequent treatments. The Markov structure (Figure 1) was intended to capture health states according to seizure frequency reduction and movement of individuals to subsequent ASM therapy, vagus nerve stimulation, and surgery. Clinical experts (including R.H.T. and J.W.S.) validated the model structure and the intervention's anticipated place in therapy.

People entered the model in the "no response" health state and could move between response health states aligned with the primary and secondary outcomes of the randomized controlled trial (RCT; NCT01866111)[5]:

- No response (<50% reduction in seizure frequency);
- Moderate response (≥50% to <75% reduction);
- High response (≥75% to <90% reduction);
- Very high response (≥90% to <100% reduction); and
- Complete response, that is, seizure freedom (100% reduction).

People could discontinue treatment from any of the response-based health states. Following treatment discontinuation, individuals entered the "subsequent ASM treatment" health state to receive further ASM treatment. Following no response to second-line adjunctive or subsequent ASM therapy, if eligible, people could transition to the surgery or vagus nerve stimulation health states to receive these invasive procedures. People stayed in the "surgery" or "vagus nerve stimulation" health states for one cycle, then transitioned to and remained in the "post-surgery" or "post-vagus nerve stimulation" health states until death. The likelihood of people undergoing invasive procedures was adjusted according to cycle length (i.e., 28 days during the double-blind phase or 84 days during the open-label phase). Those who did not undergo invasive procedures remained in "subsequent ASM therapy" until death. People could transition to the absorbing health state "death" from any health state.

2.3 | Clinical effectiveness

The clinical effectiveness of cenobamate was based on one RCT (NCT01866111), its open-label extension (NCT01866111), and one open-label study (NCT02535091).[5,20] Individuals in the cenobamate 200 and 400 mg treatment arms of the RCT and all those in the open-label long-term extension were considered in the CEM to reflect the target dose in clinical practice.

Baseline demographics (Table 1) in the CEM were aligned to people enrolled in NCT01866111; age and sex from the study informed mortality and societal productivity losses.[5] Individual-level data from this RCT and its open-label extension were used to parameterize transition probabilities for cenobamate. Transition probabilities were used to model the movement of people between response health states; data were available to parametrize movement among on-treatment people for the double-blind phase and 4 years of the open-label phase.

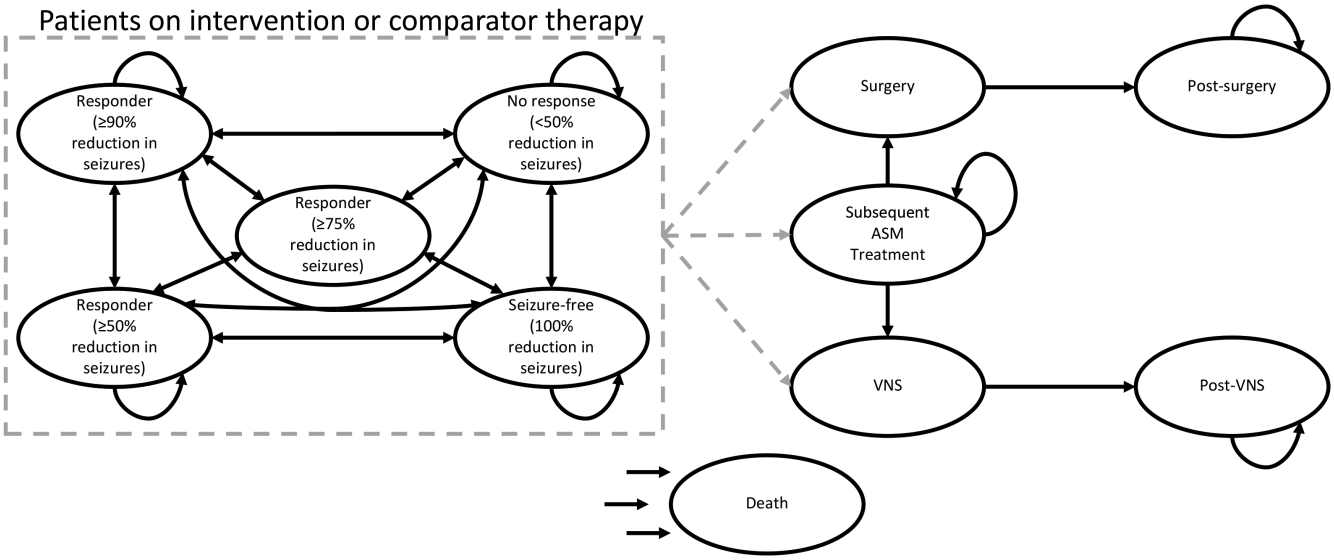

FIGURE 1 Markov cohort model structure. Responder health states are bounded above and below to ensure they are mutually exclusive and collectively exhaustive (e.g., the Responder [≥90% reduction in seizures] is bound above by the next health state, such that those residing in this health state have a reduction in seizures strictly <100%. ASM, antiseizure medication; VNS, vagus nerve stimulation.

TABLE 1 Trial C017: NCT01866111 baseline demographics used in cost-effectiveness model.

	Cenobamate				
	100 mg, *n* = 108	**200 mg, *n* = 110**	**400 mg, *n* = 111**	**Placebo, *n* = 111**	**Overall**
Age, mean years (SD)	39.0 (12.1)	40.9 (12.4)	39.6 (10.3)	39.6 (12.4)	39.8 (11.79)
Male, *n* (%)	57 (53)	54 (49)	52 (47)	58 (54)	221 (51)

After the open-label phase, transitions between response health states were extrapolated using the average of the open-label phase transition matrices. Safety data from the titration and maintenance phases of the RCT and its open-label study were used to model the likelihood of adverse events during the titration and maintenance phases of treatment. Safety data from the titration phase of the open-label study were also used to model the probability of adverse events during subsequent ASM therapy; adverse events that occurred in ≥5% of people during either the titration or maintenance phase were included.[5,20]

2.3.1 | Comparator efficacy

A systematic literature review identified clinical studies of cenobamate and comparator ASMs to treat drug-resistant focal seizures. Of 69 studies identified, 18 were included in a network meta-analysis to model the likelihood of brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel resulting in ≥50% reduction in seizure frequency, seizure freedom, or treatment-emergent adverse events relative to cenobamate (Appendix S1). As advised by the NICE Evidence Review Group, a joint synthesis, placebo-adjusted model was used for efficacy outcomes to avoid correlation between response health states and to correct for the placebo effect found in multiple studies. An independent analysis was performed for the likelihood of at least one treatment-emergent adverse event. The network meta-analysis was conducted adhering to NICE Decision Support Unit Technical Support Document 2.[21] The network meta-analysis parameterized the comparator transition matrices by applying risk ratios to the cenobamate transition matrices. Similarly, the probabilities of treatment-emergent adverse events for comparators were derived by applying ORs to the probability of adverse events for cenobamate (Table S2.1).

2.3.2 | Time to discontinuation

Individual-level data from the three cenobamate studies were used to extrapolate time to treatment discontinuation for the time horizon of the model (NCT01866111 and NCT02535091).[5,20] For comparators, Kaplan–Meier data for long-term retention rates were sourced from

published evidence. Kaplan–Meier data from the open-label studies were digitized using GetData GraphDigitiser to extrapolate time to treatment discontinuation data.[22] Kaplan–Meier data were extrapolated using methods recommended by the NICE Decision Support Unit (Technical Support Document 14).[23] Distributions for extrapolation were chosen based on statistical fit and clinical plausibility (Figure S2.1).

2.3.3 | Subsequent treatment

Published evidence informed clinical effectiveness of subsequent ASM treatment. The OR of having drug-resistant epilepsy with subsequent ASM treatment is reported relative to the previous line of therapy (OR = 1.73). Because people are less likely to respond to further lines of treatment, clinical effectiveness was derived by applying the OR to the likelihood of not being seizure-free to the least effective comparator (brivaracetam). Discontinuation was not applied, as there is a diminishing likelihood of response to subsequent ASMs with each line of treatment.

The proportion of people on subsequent ASM treatment eligible to undergo surgery or vagus nerve stimulation was sourced from clinical experts (including R.H.T. and J.W.S.). In the surgery and vagus nerve stimulation health states, people were assumed to have no response to treatment. In post-vagus nerve stimulation and post-surgery health states, the responses to invasive procedures were identified from published evidence.

The response distribution among each of the subsequent treatments was constant over time.

2.3.4 | Mortality

All-cause mortality, sourced from national life tables for England and Wales,[24] was adjusted for the greater risk of premature death associated with epilepsy. Published evidence informed hazard ratios for increased mortality and were applied to response health states for seizure freedom (hazard ratio = 1.6) and people who did not achieve seizure freedom (hazard ratio = 2.4). Hazard ratios for other health states were based on the proportion of seizure-free people in each health state.

2.4 | Cost and resource use

Cost inputs are summarized in Table S2.1. Cost categories consisted of treatment, administration, subsequent ASM therapy, routine monitoring, epilepsy event management, adverse events, and societal costs. Costs were incorporated into the model as values per health state per cycle and inflated using NHS Cost Inflation indices to year 2018/2019.[25]

2.4.1 | Treatment costs

Treatment costs were split into titration and maintenance costs. To reflect clinical practice, people taking cenobamate followed the titration schedule from the open-label study (NCT02535091). People uptitrated for 12 weeks to reach a target dose of 200 mg per day, leading to a titration cost of £518.70. The average cost per day of cenobamate was estimated for the maintenance phase according to the proportion of people on each dose and its associated pack price. This led to a maintenance cost of £7.37 per day.

For comparator ASMs, titration schedules were sourced from their Summary of Product Characteristics. The daily maintenance dose was sourced from studies in the network meta-analysis. Clinical expert opinion (including R.H.T. and J.W.S.) via a clinician survey informed background therapy use. Comparators and background ASM costs were sourced from the British National Formulary. Subsequent ASM therapy costs were modeled as a weighted average cost of the comparators to account for uncertainty in the treatment pathway beyond second-line adjunctive therapy. The compliance rate sourced from the RCT (NCT01866111) was applied to all treatments. Published evidence informed the cost of each surgery and vagus nerve stimulation procedure.

2.4.2 | Health state costs

Relative reduction of seizures by type and response category were generated from RCT (NCT01866111) individual data. Seizure frequency per 28-day cycle (sourced via the clinician survey) quantified resource use associated with event management according to response category; the frequency of seizures was adjusted based on the varying cycle length. Relative reduction of seizures per cycle in people who received subsequent ASM therapy or invasive procedures was derived from the distribution of treatment responses as presented in Table S2.1. The clinician survey determined the routine monitoring resource use per 28 days in people with drug-resistant focal seizures according to response to treatment; the frequency of routine monitoring was adjusted based on the varying cycle length. The clinician survey also determined the resource use per seizure (according to focal aware, focal impaired awareness, and focal to bilateral tonic–clonic seizures). The resource use was applied to costs sourced from the Personal Social Services Research Unit and NHS reference costs to derive the cost per 28-day cycle.[25,26]

TABLE 2 Assumptions underpinning the cost-effectiveness model.

Variable	Assumed value	Justification
Time horizon	Lifetime horizon (60 years)	Aligned with NICE reference case, to capture all differences in costs and outcomes[18] Shorter time horizons have been a concern in HTA submissions, including brivaracetam and retigabine[31,44] The C017 OLE: NCT01866111 has showed high retention rates for people on cenobamate (approximately 71% after 2 years and 60% after 4 years), providing data and rationale for this time horizon
Cycle length	28 and 84 days	28-day cycles align with the schedule of data collection and follow-up visits in the double-blind phase of C017: NCT01866111 (Cycles 1–5) 84-day cycles align with the schedule of follow-ups in clinical practice using C017 OLE: NCT01866111 (Cycle 6 onward)
Half cycle correction applied	Included in the base case	NICE reference case[18] and to align with conventional modeling standards
Health states	• No response • Moderate response • High response • Very high response • Complete response • Subsequent ASM therapy • Surgery • Postsurgery • Vagus nerve stimulation • Post-vagus nerve stimulation • Death	Alignment with the primary outcome of the pivotal study for cenobamate (C017: NCT01866111), where significance was achieved[5] QoL of epileptic people is driven by the occurrence of seizures, or lack thereof Use of subsequent ASM therapy and invasive procedures (i.e., surgery and vagus nerve stimulation) following lack of response to treatment were also considered to define response to treatment in the subsequent treatment pathway of people with FOS
Model approach	Markov cohort model	Markov models have been accepted by the SMC as an appropriate method to evaluate adjunctive treatments in epilepsy NICE review of retigabine suggested that a Markov model would be preferable to the manufacturer's use of a decision tree[31]
Cenobamate study arms for inclusion	200 and 400 mg from C017: NCT01866111	Recommended maintenance dose is 200 mg with the ability to titrate to 400 mg if required Cenobamate 100 mg is not considered in the analysis, as it is not used in UK clinical practice
Transition matrix for Cycle 1 and Cycle 2	Time between Visits 3 and 5 was split into two cycles	Time between Visits 3 and 5 was split into two cycles to reflect an extended titration period.
Transition matrix extrapolation	Transition probabilities for Cycle 26 onward based upon the average of the 21 cycles of the C017 OLE: NCT01866111	Cenobamate and comparator treatments from Cycle 26 onwards were extrapolated using the average transition probabilities over Cycles 6–26, which comprised the C017 OLE: NCT01866111 duration
TTD extrapolation	Individual parametric curves were used to model TTD	Long-term retention data were sourced from comparator open-label studies as a more appropriate estimate of treatment discontinuation for comparators and a better reflection of retention to treatment in clinical practice. TTD was extrapolated for all treatment individually. The following distributions were applied: • Cenobamate: generalized gamma • Brivaracetam: generalized gamma • Lacosamide: lognormal • Eslicarbazepine acetate: exponential • Perampanel: lognormal

TABLE 2 (Continued)

Variable	Assumed value	Justification
Subsequent ASM treatment: TEAEs	Subsequent ASM treatment AEs equal to TEAEs of second-line adjunctive ASMs during the titration period	Individuals on subsequent ASM therapy begin titration with an alternative second-line adjunctive ASM The individual distribution among these treatments is based on the current market share of second-line adjunctive ASMs (excluding cenobamate) based on clinical expert opinion via clinician survey
Subsequent ASM treatment: treatment cost	Treatment cost is a weighted average of cost per cycle of comparator treatments and market share	It is assumed that those in the subsequent ASM treatment health state will receive one of the key comparators as an alternative to their second-line adjunctive treatment The individual distribution among these treatments is based on the current market share of second-line adjunctive ASMs sourced from clinical expert opinion via clinician survey
Individual utility	Valued using SF-6D according to response to treatment	Valued using SF-6D due to shortcomings of the EQ-5D in people with epilepsy[45] Sourced from a mapping study of people with epilepsy and retrospectively applied in the C017: NCT01866111[29] QoL in other health states was derived from response to subsequent treatments Burden on individuals imposes a significant burden on carers[46–49] Carer QoL is correlated with the QoL of people with FOS[50]

Abbreviations: AE, adverse event; ASM, antiseizure medicine; EQ-5D, EuroQol five-dimensional form; FOS, focal seizures; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; QoL, quality of life; SF-6D, Short-Form six-dimension form; SMC, Scottish Medicines Consortium; TEAE, treatment-emergent AE; TTD, time to discontinuation.

The resource use associated with treatment-related adverse events was sourced from a past health technology assessment submission and the cost identified from the Personal Social Services Research Unit[25,27]; it was assumed that treatment-related adverse events would require treatment by a specialist nurse.[25] Adverse events costs for invasive procedures were also sourced from NHS reference costs from 2018/2019.[26]

Societal costs were included in a scenario considering productivity losses. Average full- and part-time salaries in England and Wales were sourced from the Office for National Statistics.[28] The average unpaid carer salary in England and Wales was assumed to be equivalent to the average full-time salary.

2.5 | Quality of life

Quality of life input values are displayed in Table S2.1. A mapping study was conducted to generate Short-Form six-dimension form utility values stratified by response health state.[29] The regression from the mapping study was applied to participants in the RCT (NCT01866111) to generate Short-Form six-dimension form values and was implemented in the CEM. Duration and disutility associated with treatment-related adverse events and accidents due to seizures were collected from published evidence to estimate total quality-adjusted life-year (QALY) decrement.

Carer disutility was sourced from a caregiver survey used to generate evidence on health-related utility for caregivers of people with ≥3 focal seizures per week according to the duration of seizure freedom.[29]

The assumptions considered in the CEM are provided in Table 2, with parameters and sources identified from published evidence summarized in Table S2.1.

2.6 | Cost-effectiveness analysis

2.6.1 | Base case results

Incremental costs and outcomes (QALYs) of treatments were estimated based on total costs and outcome values over the lifetime horizon. Incremental costs and QALYs were used to estimate the ICER.

2.6.2 | Sensitivity and scenario analyses

The probabilistic sensitivity analysis ran 10 000 simulations to explore the impact of parameter uncertainty using probabilistic distributions: gamma, beta, and lognormal distributions used for costs and resource use, probabilities and utilities, and ratios, respectively. Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane. A cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted. Within the distributions, one-way sensitivity analysis varied parameters between published (when available) or calculated 95% CIs assigned to each parameter. When CIs were not available,

TABLE 3 Results of the base case, probabilistic, and scenario cost-effectiveness analyses.

			Cenobamate	
Model setting tests	**Base case assumption**	**Scenario assumptions**	**Total costs**	**Total QALYs**
Base case	-	-	172 605	6.956
PSA	-	-	178 200	6.822
Time horizon	Lifetime	2 years	20 221	0.653
		15 years	106 805	4.027
Cenobamate arms for study inclusion in clinical data	Cenobamate 200 and 400 mg with mortality benefit applied	Cenobamate 400 mg	171 790	6.972
		Cenobamate 200 mg	173 393	6.941
Discount rate	3.5% for costs and outcomes	0.0% for costs and outcomes	299 408	12.599
Perspective	NHS and PSS	Societal	449 204	6.956
Cenobamate maintenance price	Maintenance £7.37 per day	£6.50	169 576	6.956
		£8.50	176 530	6.956
Accidents due to seizures	Excluded	Included	210 861	6.811
Costs of epilepsy event maintenance	Output from clinician survey	Cost per event 50% of base case	121 974	6.956
Costs of routine monitoring	Output from the clinician survey	Presentation to health care is halved in the no response and moderate response health states	160 643	6.956
ITC inputs	Risk ratios for treatment response applied	All comparators assumed to have risk ratios for moderate response and seizure freedom midway between the median values derived from the ITC and 1 (the threshold of equivalence)	171 102	6.997
Mortality	HRs applied	HRs not applied	189 339	7.705
Quality of life	Mapping study output	Per clinician opinion	172 605	7.211
		Utilities sourced from Phumart et al. 2018[43]	172 605	10.873
		Utilities sourced from Phumart et al. 2018,[43] with interpolation applied between health states	172 605	10.940

Abbreviations: HR, hazard ratio; ITC, indirect treatment comparison; NHS, National Health Service; PSA, probabilistic sensitivity analysis; PSS, personal social services; QALY, quality-adjusted life-year. [Correction added on 20 March 2023, after first online publication: The values under the "Cenobamate" column under "Total QALYs" have been changed from ".653" to "0.653" for the first row of "Time horizon" and from "6972" to "6.972" for the first row of "Cenobamate arms for study inclusion in clinical data"].

upper and lower 95% CI bounds were estimated, assuming the parameter has a standard error of 20% of the mean value. Inputs from the network meta-analysis were varied using their 95% credible intervals.

Multiple scenario analyses were performed to test structural uncertainty in the cost-effectiveness of cenobamate.

3 | RESULTS

Aggregated base case and mean probabilistic sensitivity analysis results for the cost-effectiveness of cenobamate compared with second-line adjunctive ASMs are presented in Table 3. Over the lifetime horizon, treatment with cenobamate was associated with 6.956 QALYs at £172 605 per person. With the lowest cost and highest QALY gain compared with the base case comparators, cenobamate dominates all ASM therapies. Mean probabilistic sensitivity analysis costs present a total cost of £178 200 and mean total of 6.822 QALYs, similar to the base case (Figure 2A).

The CEAC shows that at the willingness to pay thresholds of £30 000/QALY, the probability of cenobamate being cost-effective compared to all comparators was 99.7% (Figure 2B). The CEAF (Figure 2C) found that cenobamate was most likely to be the most-cost effective treatment considered at all willing to pay thresholds.

Eslicarbazepine		Perampanel		Lacosamide		Brivaracetam	
Incremental costs	Incremental QALYs	Incremental costs	Incremental QALYs	Incremental costs	Incremental QALYs	Incremental costs	Incremental QALYs
21 080	−0.598	28 296	−0.703	33 619	−0.776	51 967	−1.047
23 935	−1.162	31 155	−1.381	36 265	−1.529	55 109	−2.116
5931	−0.109	6217	−0.116	6 261	−0.113	6 113	−0.122
22 524	−0.495	26 353	−0.551	28 633	−0.578	36 265	−0.691
21 869	−0.612	29 097	−0.718	34 415	−0.790	52 777	−1.061
20 324	−0.584	27 529	−0.689	32 569	−0.762	51 190	−1.032
21 221	−0.827	34 473	−1.027	45 171	−1.185	83 047	−1.760
59 106	−0.598	74 222	−0.703	85 079	−0.776	123 026	−1.047
24 109	−0.598	31 324	−0.703	36 647	−0.776	54 995	−1.047
17 155	−0.598	24 371	−0.703	29 694	−0.776	48 041	−1.047
14 521	−0.635	40 456	−0.750	47 383	−0.828	71 578	−1.121
8046	−0.598	12 330	−0.703	15 550	−0.776	26 238	−1.047
18 018	−0.598	24 543	−0.703	29 363	−0.776	45 915	−1.047
15 238	−0.497	20 362	−0.575	23 929	−0.623	37 096	−0.828
20 754	−0.609	28 882	−0.718	35 129	−0.796	57 117	−1.092
21 080	−0.791	28 296	−0.931	33 619	−1.030	51 967	−1.388
21 080	−0.496	28 296	−0.580	33 619	−0.636	51 967	−0.583
21 080	−0.512	28 296	−0.599	33 619	−0.658	51 967	−0.883

Cenobamate dominated all comparators, so the tornado diagram presents the net monetary benefit results of the one-way sensitivity analysis (Figure 2D). Results are presented relative to eslicarbazepine acetate, the next most effective treatment option. In all variations of the one-way sensitivity analysis, the net monetary benefit of cenobamate relative to eslicarbazepine remained positive. Results were most sensitive to utility associated with no response, the average number of focal to bilateral tonic–clonic seizures per 4 weeks, and the proportion of people who achieved seizure freedom after surgery.

4 | DISCUSSION

Our analysis shows that cenobamate dominates comparator ASMs and is associated with the lowest cost and highest QALY gain for people with focal seizures. Sensitivity analyses also show that cenobamate dominates other ASMs. Scenario analyses found that estimates of response and seizure freedom for comparators relative to cenobamate had a moderate impact favoring cenobamate. When clinical expert-based utility values were applied, the incremental QALY gain was more significant with cenobamate than the other ASMs.

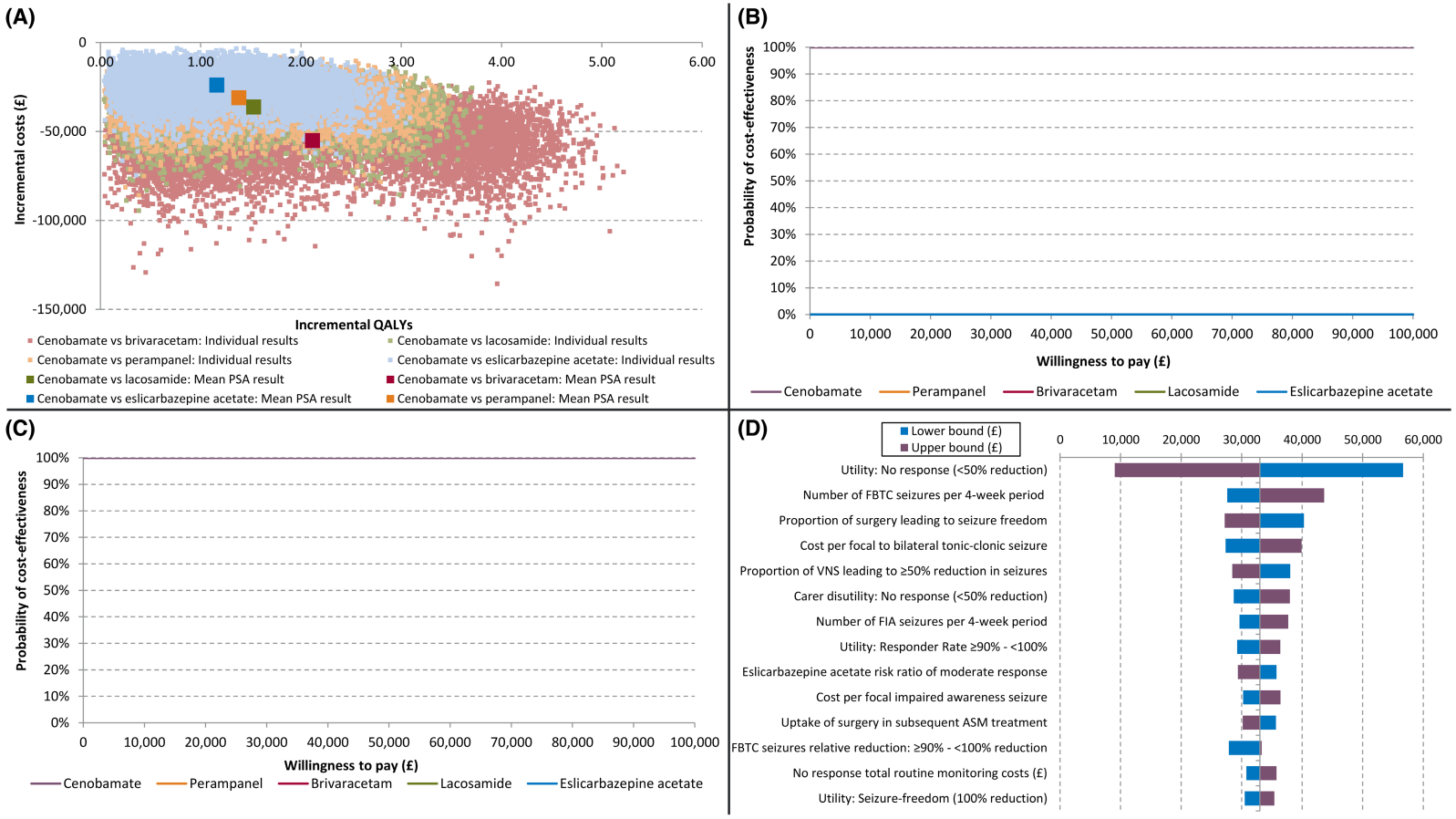

FIGURE 2 Results from the sensitivity analyses. (A) Incremental cost-effectiveness plane. (B) Cost-effectiveness acceptability curve (CEAC).* (C) Cost-effectiveness acceptability frontier (CEAF).* (D) One-way sensitivity analysis diagram. *The probability of cenobamate being cost-effective was very close to 100% at all willingness to pay thresholds assessed in the CEAC and CEAF (>99%). As such, cenobamate's probability of cost-effectiveness in the CEAC and CEAF appears along the graph axes. ASM, antiseizure medicine; FBTC, focal to bilateral tonic–clonic; FIA, focal impaired awareness; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; VNS, vagus nerve stimulation.

Epilepsy is a chronic condition often requiring long-term treatment, with a significant economic burden to individuals, which has not been considered in this cost-effectiveness analysis. Epilepsy also poses a significant societal burden, habitually due to restrictions on work and driving and limitations arising from comorbid conditions. Achieving seizure freedom is a primary goal for most people with epilepsy.[5] Over the past 20 years, evolving clinical practice guidelines have incorporated newer medications into recommendations for treating epilepsy.[19,30] Cenobamate offers a clinically significant therapeutic advancement, as it may enable more people to become seizure-free.

Following criticisms of a decision tree for a previous NICE appraisal of retigabine for the adjunctive treatment of partial seizures in epilepsy, we used a Markov model allowing flexible movement between response categories.[31–33] Clinicians endorsed the granularity of the model structure, as the costs and quality of life related to achieving at least a 75% or 90% reduction in seizures compared to baseline would differ compared to those achieved with only a 50% reduction.

The Markov model also allows for the modeling of subsequent treatments. In the UK, NICE recommends >20 adjunctive ASMs.[6] Following failure of adjunctive ASM treatment, there is an unmanageable number of possible subsequent treatment combinations. Our model conservatively assumes subsequent ASM treatments represent a single health state, applying a basket of treatments with a fixed cost. This underestimates the costs associated with routine monitoring and epilepsy management. In clinical practice, people likely have a diminishing probability of responding to successive lines of treatment, so the costs associated with routine monitoring and epilepsy event management increase as people experience new seizures.

Utility values were sourced from a de novo mapping study, based on the responses to a survey of 361 people with focal seizures,[29] as published data did not accurately quantify health-related quality of life in people with drug-resistant focal seizures in England and Wales. Utility data used in the clinical guidelines, Epilepsies: Diagnosis and Management, were considered inappropriate for this analysis due to a limited sample of 125 people.[34] Additionally, according to response to treatment, these utility values were based on a few eligible responses, with only 11 of the 125 individuals reporting seizure freedom and 25 of the 125 reporting ≥50% reduction in seizure frequency.

Caregiver disutilities were collected via a survey to incorporate all the direct health effects associated with focal seizures in the UK into the model. The role of a carer is vital for people with epilepsy; caregivers monitor medication adherence, offer support strategies for seizure management, and process and relay information about seizure symptoms to health care providers. Intense demand is placed on caregivers, including coping with psychological distress, dealing with frequent seizures, and addressing concerns about potential injury and even death.[35] In people with intellectual disabilities, many still live in the family home, where both parents are considered caregivers.[36–38] Therefore, the assumption that each individual has one caregiver is conservative; few people with epilepsy can live alone due to the risks associated with accidents due to seizures.

Our study has limitations. First, although the five-state model structure was deemed more appropriate than the three-state model, it was impossible to indirectly compare higher levels of response (≥75% and ≥90%) between cenobamate and comparators due to a lack of comparator data. Clinicians agreed that it is conservative to assume the OR for higher response levels was equal to the moderate response's OR.

Second, the model did not consider people in long-term remission who discontinued treatment.[2,5,20] The omission of this is conservative, as people treated with cenobamate are more likely to experience seizure freedom, and would therefore be more likely to discontinue due to terminal remission. Therefore, long-term costs associated with cenobamate are overestimated to a greater extent than the comparators.

Third, the network meta-analysis may introduce bias due to a lack of closed loops between treatments, because all included studies were placebo-controlled only. A placebo-adjusted model was developed to eliminate heterogeneity.

Additionally, there remains uncertainty about the long-term efficacy and safety of cenobamate and its comparators, given the lack of longer-term RCTs, rendering the network meta-analysis of outcomes infeasible. These data require a more complex methodology (such as matched-adjusted indirect comparisons) for evidence synthesis. Considering the lack of heterogeneity identified in the RCTs during the feasibility assessment, a more complex methodology would likely produce results consistent with the network meta-analysis. Data from the open-label studies for the comparators support the maintenance of benefits over the long term.[39–42] As noted by clinical experts (including R.H.T. and J.W.S.), cenobamate's long-term benefit is further supported by its longer half-life compared to comparator ASMs.

Other limitations included choice of ASMs that cenobamate was compared with, variation in the definitions of seizure freedom across studies, and efficacy outcomes being rarely reported for the entire treatment period. Results for the maintenance period were used where possible. Regarding comparators, they were selected in line with those that cenobamate is most likely to displace in clinical practice. However, there are several older, less

expensive ASMs that cenobamate has not been compared with. Therefore, conclusions about the cost-effectiveness of cenobamate relative to alternative ASMs cannot be made.

Lastly, the findings of the mapping study were discussed with clinicians, who indicated that the benefits in health-related quality of life associated with seizure freedom were underestimated. The incremental QALY gain between the seizure-free and ≥90%–<100% reduction in seizure frequency health states estimated by clinicians was approximately three times higher than the incremental gain identified in the mapping study, and far greater than the difference that has been published in other studies.[34,43] This is likely due to the subjectively estimated utilities for all health states, where all health states are subjective except seizure freedom, which is objective. This validates the use of the mapping study as a conservative choice.

Despite these limitations, this analysis shows that cenobamate may be considered a cost-saving and effective use of NHS resources, with an estimated lifetime savings of £22 340 per person compared to eslicarbazepine acetate, the next least expensive comparator. Future research comparing cenobamate directly with other ASMs, collecting long-term efficacy and safety evidence of cenobamate and its comparators via RCTs, and quality of life data measured directly in people treated with cenobamate, would help alleviate the limitations.

5 | CONCLUSIONS

Results from the base case analysis show that, over a lifetime, cenobamate is less costly and more effective when compared to brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel. In all analyses, cenobamate remained cost-effective and therefore can be considered a cost-effective treatment for people with drug-resistant focal seizures.

AUTHOR CONTRIBUTIONS

Vicki Laskier: Conceptualization (equal), formal analysis (supporting), investigation (equal), project administration (lead), supervision (supporting), writing–original draft preparation (supporting). Kenneth Agyei-Kyeremateng: Conceptualization (supporting), formal analysis (lead), investigation (equal), project administration (supporting), supervision (supporting), writing–original draft preparation (supporting). Alex E. Eddy: Conceptualization (supporting), formal analysis (supporting), investigation (equal), project administration (supporting), supervision (supporting), writing–original draft preparation (lead). Dilip Patel: Conceptualization (supporting), supervision (equal), writing–review & editing (supporting). Stuart Mulheron: Supervision (equal), writing–review & editing (supporting). Samuel James: Conceptualization (equal), writing–review & editing (supporting). Rhys H. Thomas: Validation (equal), writing–review & editing (equal). Josemir W. Sander: validation (equal), writing–review & editing (equal).

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CONFLICT OF INTEREST STATEMENT

V.L., K.K.A.K., and A.E.E. are employees of FIECON, a health economics outcomes research agency, which performed the analyses presented in the article, funded by Angelini Pharma. S.M. is currently an employee of Angelini. D.P. and S.J. are former employees of Angelini Pharma. R.H.T. reports personal fees from Angelini, Bial, Eisai, GW/Jazz, Sanofi, UCB Pharma, UNEEG, and Zogenix Pharma. J.W.S. reports personal fees from Angelini, Eisai, UCB Pharma, and Zogenix Pharma outside the submitted work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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

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