NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cenobamate for focal onset seizures in epilepsy [ID1553]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cenobamate for focal onset seizures in epilepsy [ID1553]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Arvelle Therapeutics

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Epilepsy Action

4. **Evidence Review Group report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**
   - **Company technical engagement response**
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7. **Technical engagement responses and statements from experts:**
   a. Prof Ley Sander – clinical expert, nominated by Arvelle Therapeutics
   b. Prof Rhys Thomas– clinical expert, nominated by Arvelle Therapeutics
   c. Daniel Jennings – patient expert, nominated by Epilepsy Action
   d. Rebecca Longley – patient expert, nominated by Epilepsy Action

8. **Technical engagement responses from consultees and commentators:**
   a. Eisai

9. **Evidence Review Group critique of company response to technical engagement** prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cenobamate for focal onset seizures in epilepsy [ID1553]

Document B

Company evidence submission

December 2020

File name	Version	Contains confidential information	Date
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Abbreviations

A&E	Accident and emergency
AE	Adverse event
AED	Anti-epileptic drugs
AEP	Adverse Event Profile
AIC	Akaike Information Criterion
ALDVMM	Adjusted limited dependent variable mixture model
ANCOVA	Analysis of covariance
ASM	Anti-seizure medication
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEDAC	Canadian Expert Drug Advisory Committee
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CNS	Central nervous system
CrI	Credible interval
CSR	Clinical study report
CT	Computer tomography
DBS	Deep brain stimulation
DDD	Daily defined dosages
DESM	Discrete event simulation model
DIC	Deviance Information Criterion
DRE	Drug-resistant epilepsy
DRESS	Drug-induced hypersensitivity syndrome
DSU	Decision Support Unit
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicines Agency
EMG	Electromyography
EQ-5D	EuroQol- 5 Dimension
EQ-5D-5L	EuroQol- 5 Dimension Five Level
ES	Epileptic Seizure
ESI-55	Epilepsy Surgery Inventory 55 Survey
EY51Z	Electrocardiogram Monitoring or Stress Testing
FOS	Focal-onset seizures
$GABA_A$	γ-Aminobutyric acid type A
GOS	Generalised onset seizures
GP	General practitioner
GTCS	Generalised tonic-clonic seizures
HEOR	Health economics outcomes research
HR	Hazard ratio

HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
ILAE	International League Against Epilepsy
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous therapy
KOL	Key opinion leaders
LOCF	Last observation carried forward
LSSS	Liverpool Seizure Severity Scale
LYG	Life years gained
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHC	Mental health condition
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimally important change
MITT-M	Modified intention-to-treat patients in maintenance phase
MOA	Mechanism of action
MRI	Magnetic resonance imaging
N/A	Not applicable
NA	Not available
NASH	National Audit of Seizure Management
NDDI-E	Neurological Disorders Depression Inventory in Epilepsy
NEWQOL-6D	Quality of Life in Newly Diagnosed Epilepsy 6 dimensions
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NICE CG137	NICE clinical guideline
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
OLE	Open-label extension
OLS	Ordinary-least squared
ONS	Office of National Statistics
OR	Odds ratio
OWSA	One-way sensitivity analysis
pD	Leverage
PIM	Promising Innovative Medicine
POS	Partial-onset seizures

PSA	Probability sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of Life
QOLIE-31-P	Quality of life in epilepsy- Problems
RCT	Randomised control trial
SAEs	Serious adverse events
SD	Standard deviation
SE	Safety evaluable
SF-36	Short-Form (36) Health Survey
SF-6D	Short Form-Six Dimension
SFD	Seizure free day
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SOC	System organ class
SOC	Standard of care
SUDEP	Sudden Unexpected Death in Epilepsy
TEAEs	Treatment emergent adverse events
TLE	Temporal lobe epilepsy
TLR	Targeted literature review
TSD	Technical Support Document
TTD	Time to death
VAT	Value added tax
VNS	Vagus nerve stimulation
WHOCC	World Health Organisation Collaborating Centres
WTP	Willingness to pay

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The anticipated marketing authorisation for cenobamate is for the [redacted].The submission covers cenobamate's full marketing authorisation for this indication.

The anticipated use of cenobamate in the third-line setting – in accordance with its anticipated marketing authorisation – is aligned with the NICE clinical guideline 137 (CG137), and confirmed by UK clinical experts as the anticipated place in therapy.[1]

The decision problem considered in this submission is summarised in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed.	[redacted]	Aligned with the anticipated EMA regulatory authorisation and the anticipated use of cenobamate in UK clinical practice.[1]
Intervention	Cenobamate	Cenobamate	N/A
Comparator(s)	Established adjunctive clinical management, including but not limited to: brivaracetam acetate, carbamazepine, eslicarbazepine acetate, lacosamide, levetiracetam and perampanel.	The comparators considered are brivaracetam acetate, eslicarbazepine acetate, lacosamide, and perampanel.	Carbamazepine and levetiracetam are not considered valid comparators for several reasons and are not included in the company decision problem: • According to NICE CG137, carbamazepine and levetiracetam are both indicated as first-line or second line treatment, in monotherapy or as an adjunctive ASM. As per the anticipated marketing authorisation for cenobamate, the technology is indicated after a patient has been inadequately controlled on 2 ASMs, therefore making cenobamate a 3rd-line therapy in accordance with NICE CG137. The anticipated licensed indicated for cenobamate excludes use in 1st line (monotherapy) and 2nd line (adjunctive) settings. • Additionally, clinical experts in the UK confirm that both carbamazepine and levetiracetam are commonly recommended and prescribed as first-line and second-line treatment options and therefore are not appropriate comparators to cenobamate.[1] • Finally, the clinical studies for cenobamate demonstrate that carbamazepine and levetiracetam were the two of the most

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			commonly used background therapies indicating that cenobamate is an adjunct to these rather than a comparator.[2–4]
Outcomes	The outcome measures to be considered include: • Change in seizure frequency • Seizure free rate • Time to first seizure • Response rate • Seizure severity • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures presented in the submission are the following: • Change in seizure frequency o Focal aware o Focal impaired awareness o Focal to bilateral tonic-clonic • Seizure-free rate • Time to first seizure • Response rate • Mortality • Adverse effects of treatment • Health-related quality of life	In line with the final scope. Please note that severity of seizures is captured according to the types of seizures experienced, considering that focal to bilateral tonic-clonic seizures are the most severe seizure type amongst patients with FOS.
Subgroups to be considered	No subgroups will be considered.	No subgroups are considered.	N/A
Special considerations including issues related to equity or equality	There are no equity or equality issues.	There are no equity or equality issues.	N/A

Abbreviations: EMA, European Medicines Agency; NICE, National Institute for Health and Care Excellence.

B.1.2. Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Cenobamate
Mechanism of action	Cenobamate's unique dual MoA suggests that is has the potential to both prevent seizure initiation and limit seizure spread.[5–9] As a mechanistically distinct ASM, cenobamate offers an important advancement in drug development for treatment of uncontrolled epilepsy.[10] Epilepsy has been generally associated with decreased neuronal inhibition via $GABA_A$ receptors and with increased persistent sodium current, both contributing to neuronal hyperexcitability, resulting in high risk of seizures.[5–7,11] Cenobamate is a novel small molecule that provides a unique, dual, complementary mechanism of action; it is the only ASM which, at clinically relevant concentrations acts both as a positive allosteric modulator of $GABA_A$ receptors at non-benzodiazepine binding sites and preferentially blocks the persistent sodium current.[12,13]
Marketing authorisation/CE mark status	The EMA is currently reviewing the regulatory submission for cenobamate and the anticipated date of CHMP positive opinion is [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated indication is for the [redacted]
Method of administration and dosage	Cenobamate is administered orally. The recommended initial dosage of cenobamate is 12.5 mg once daily, titrated to the recommended maintenance dosage of 200 mg once daily. The recommended titration schedule should not be exceeded. The maximum dosage is 400 mg once daily.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	Average cost of cenobamate is [redacted] per day during maintenance treatment, based on the anticipated NHS List price. Titration packs are available in the following doses at the following prices: 12.5 mg (x14)/25 mg (x14) [redacted] per pack 50 mg (x14) [redacted] per pack

	100 mg (x14) [redacted] per pack 150 mg (x14) [redacted] per pack 200 mg (x14) [redacted] per pack Maintenance packs are available in the following doses at the following prices: 50mg (x28) [redacted] per pack 100mg (x28) [redacted] per pack 150mg (x28) [redacted] per pack 200mg (x28) [redacted] per pack
Patient access scheme (if applicable)	N/A

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; $GABA_A$ receptors, γ-Aminobutyric acid type A; MoA, mechanism of action; NHS, National Health Service; SmPC, Summary of Product Characteristics

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Epilepsy

Overview

Epilepsy is a group of neurological disorders characterised by recurrent seizures which can be either focal or generalised. It is the most common neurological condition worldwide, and affects people across all ages, ethnicities, races, social classes and geographies.[14] It is estimated that epilepsy affects between 362,000 and 415,000 people in England.[15] In the UK, over 600 people are diagnosed with epilepsy per week.[16] Additionally, approximately 50% of adults with active epilepsy have one or more comorbid condition.[17]

The incidence of epilepsy has a bimodal distribution for age, with the highest risk in infants and older age groups.[18–20] Age-specific incidence rates of epilepsy have decreased with time in the youngest age groups, probably due to clinical improvements in care. In contrast, incidence has increased in the elderly, likely due to increased life expectancy (with parallel increase of age-related epileptogenic conditions, such as stroke, tumours and neurodegenerative disorders), and increased ascertainment of the disease in this age group.[21] Stroke is the leading cause of epilepsy in older adults, accounting for more than half of all new-onset cases.[22] In 2018, one in four diagnoses of epilepsy in the UK were in those aged over 65.[23]

Epilepsy is characterised by recurrent spontaneous seizures resulting from a disruption in the normal balance between excitation and inhibition in the brain. Clinical manifestation of epilepsy is recognised by epileptic seizure (ES) which can be defined as a rhythmic firing of neuron populations causing behavioural changes. It is characterised by seizures which can manifest in psychological and physical symptoms, negatively impacting day-to-day livelihood and quality of life, and increasing the likelihood of mortality.[24]

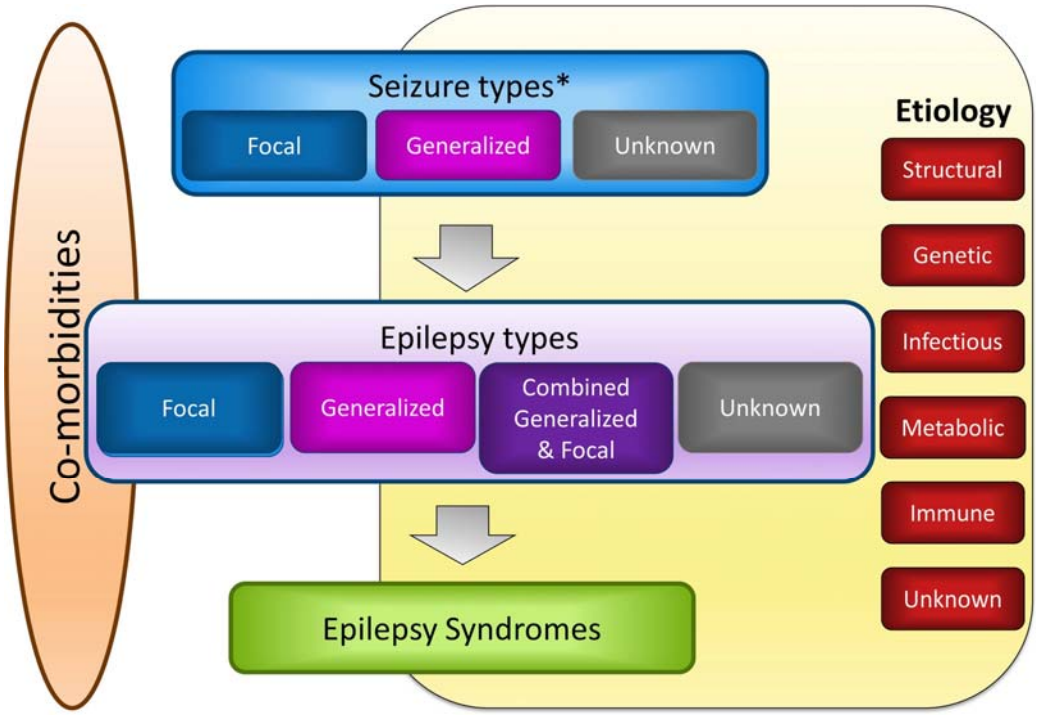
Classification

According to the International League Against Epilepsy (ILAE) updated classification of seizures from 2017, seizures can be allocated into one of three categories, according to how they begin in the brain[25]:

- Focal onset
- Generalised onset, and
- Unknown unset

The new framework for the classification of epilepsies can be seen in Figure 1.

Figure 1: Framework for classification of epilepsy[25]



*Denotes onset of seizure

There is limited data available measuring the incidence of focal onset seizures (FOS); however, it has been observed that FOS is generally more predominant than generalised epilepsy. The studies reported in a systematic review of epilepsy in Europe show that 33–65% cases are FOS, 17–60% generalised seizures and 2–8% unclassifiable seizures.[26]

FOS, previously known as partial onset seizures, are the most common type of seizure experienced by patients with epilepsy. Patients experiencing FOS account for over 60% of all patients with epilepsy.[27] FOS occur when electrical activity is localised to one side of the brain (although it may spread to the other side of the brain later in the seizure). The symptoms of FOS depend on the site of origin of the abnormal electrical discharge and their speed that they occur within the brain. FOS can be subdivided into three distinct types.

- Firstly, **focal aware seizures** where patients retain awareness of their seizure. Symptoms include: a general strange feeling that's hard to describe; a rising feeling in stomach; feelings of déjà vu; unusual smells or tastes; tingling in arms and legs; intense feeling of fear or joy; or stiffness or twitching in part of the body, such as the arms or hands.[28] During a focal aware seizure, patients remain awake, alert and are able to recall events during the seizure. Some people may be 'frozen' during the seizure, so may or may not be able to respond to others during the seizure. Typically, these seizures are brief, lasting less than two minutes.[29] Focal aware seizures are often a warning that another seizure may be about to happen, and so are often called 'warnings' or 'auras'.[28]
- Secondly, **focal impaired awareness seizures**, where patients experience-impaired awareness of their seizure. Symptoms include: lip smacking; hand rubbing; making random noises; random arm movements; picking at clothes or fiddling with objects; or chewing or swallowing.[28] During focal impaired awareness seizures, patients have a

change in their level of awareness during some or all of their seizure. During these seizures, patients are unable to respond to anyone else and will have no memory of it.

- Finally, **focal to bilateral tonic-clonic seizures** (previously known as a secondary generalised or a 'grand mal' seizure), seizures start in one side or part of the brain and spread to both sides, resulting in tonic-clonic seizures and represent the most severe type of focal seizure. They may begin with a focal aware or focal impaired awareness seizure.[30] These seizures are characterised by two stages – the tonic and the clonic phase. During the tonic phase, consciousness is lost and accompanied by generalised muscle stiffening which may cause patients to fall to the floor. During the clonic phase, there is rhythmical jerking of the limbs which may cause patients to lose control of their bladder or bowel, bite their tongue or cheek, or have difficulty breathing.[28] The active part of a focal to bilateral tonic-clonic seizure lasts for approximately one to three minutes; it is a medical emergency if the seizure lasts for more than five minutes.[30] Recovery of these seizures can take a long time – patients' consciousness slowly returns and they may be drowsy, confused, agitated or depressed for a while. Some patients may need to rest for a few hours. If individuals do not return to normal, or another seizure occurs before they return to normal, this may be a sign of status epilepticus which requires immediate medical attention.[30]

With regards to non-FOS, generalised onset seizures (GOS) occur when abnormal electrical activity originates from both hemispheres of the brain and spreads rapidly via bilateral neuronal networks. All GOS affect awareness or consciousness, and patients are not aware of their seizures.[31] GOS can be further sub-divided into motor or non-motor seizures. Motor seizures will have a change in muscle activity such as jerking (clonic), stiffness (tonic), loss of muscle tone (atonic) or automatisms (repeated or automatic movements). Non-motor seizures can have automatic symptoms (such as changes to heart rate and breathing), behavioural arrest, cognitive changes, emotional symptoms, or sensory symptoms.

Unknown onset seizures are cases where it is uncertain whether the seizure is generalised or focal; patients with these types of seizures may have varied states of awareness. Indeed, unknown onset seizures can vary in severity, with the most severe unknown onset seizures symptomatically resembling focal to bilateral tonic-clonic seizures.

B.1.3.2. Burden of epilepsy

Clinical burden

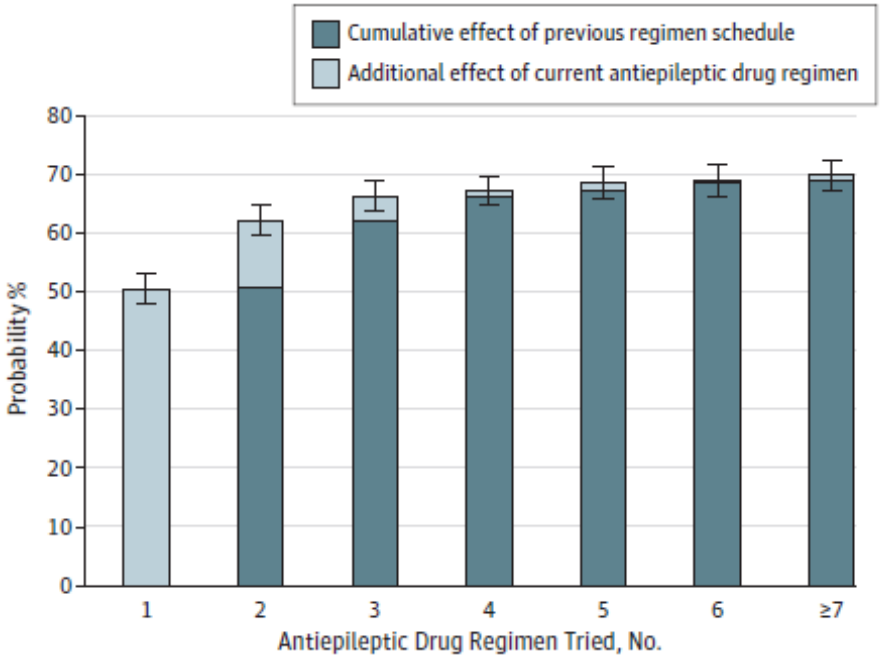
Drug-resistant epilepsy (DRE)

Although 60-70% of people with epilepsy will achieve remission, approximately 30% of epilepsy cases, particularly those with focal seizures, are drug-resistant – otherwise known as refractory to treatment or uncontrolled.[32,33] Epilepsy is classed as drug-resistant when a patient has failed to become (and stay) seizure free with adequate trials of two antiseizure medicines (ASMs).[34]

The likelihood of achieving a year of seizure freedom decreases with each successive ASM trialled, as shown in Figure 2.[32] The odds of remaining drug-resistant was 1.73 times higher with each successive ASM than on the previous ASM (confidence interval [CI], 1.56-1.91).[32]

Despite the introduction of more than 12 new ASMs over the past two decades, there remains no suggestion of improved treatment outcomes – or seizure control – in the data.[35]

Figure 2: Probability of 1-year seizure freedom for each additional antiepileptic drug regimen[32]



Patients with DRE experience comorbid illnesses, are at an increased risk of injury, premature death, psychological dysfunction and experience an overall reduced quality of life and as such account for most of the burden of epilepsy in the population.[32,36] It has been shown that compared to all patients with epilepsy, the risk of developing DRE is >50% in those with FOS.[37]

Morbidity and mortality

Adults with epilepsy have an increased risk of injury and premature mortality compared to the general population.[24,38–40] Epilepsy is associated with a two- to three-fold increased risk of mortality when compared to the age-matched general population, which can be due to the underlying cause of epilepsy, seizure related, or due to sudden unexpected death (SUDEP).[41] Several studies have shown an increased mortality risk in people who continued having seizures despite treatment when compared to people with epilepsy who are seizure free.[42] Additionally, SUDEP affects approximately 1 in 1,000 people with epilepsy; in drug-resistant patients, the rate of SUDEP has been reported as up to 9 per 1,000 patients.[43] The major risk factor of SUDEP is the occurrence and the frequency of generalized tonic-clonic seizures (GTCS).[44,45] The frequency of seizures can vary greatly in patients; some patients can experience multiple seizures per day.

In addition to the risk of death, seizures can reduce alertness and interfere with short-term information storage, whilst frequent, uncontrolled or night-time seizures can impair learning of new information, disrupt memory consolidation and affect language function.[46] Furthermore, seizures are associated with acute injuries such as burns, fractures and contusions. These injuries are more common in the most severe seizures: focal to bilateral tonic-clonic seizures.

Drug-resistant FOS, in particular, are associated with increased mortality compared with mortality in patients with controlled seizures. An Austrian study found standardised mortality ratios were higher for those without seizure freedom (3.3, 95% CI 2.6–4.4) compared to those who achieved seizure freedom (1.4, 95% CI 0.8–2.3) two years after diagnosis.[47]

Comorbidities

Approximately 50% of adults with active epilepsy have one or more comorbid condition. Comorbid conditions in epilepsy are associated with a range of body organ systems.[48] Several conditions, such as depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis are up to eight times more common in people with epilepsy compared to the general population.[17] Additionally, certain comorbidities, such as learning disabilities, neurological deficits and psychological problems, can often complicate assessments and treatment planning in patients.[49] Moreover, cognitive impairments, such as learning difficulties, behaviour change and memory impairment, can be induced or exacerbated by ASMs.[46] Therefore, consideration must be given to existing or potential comorbidities when deciding on the most appropriate treatment strategy for patients.

Psychiatric comorbidities are the most prevalent comorbidities in epilepsy with a reported prevalence of 29–40%, which is 7- to 10-fold higher than that of mental health conditions in the general population.[50] The lifetime prevalence rate for depression in people with epilepsy is reported to be in the 30–35% range.[51] Epilepsy is associated with an increased onset of psychiatric disorders before and after epilepsy diagnosis, and there is a two-way relationship between epilepsy and suicidality.[52] Additionally, some ASMs have been shown to induce symptoms of depression, while others are associated with mood stabilising properties and, in such cases, discontinuation may induce depression.[53]

Neurodegenerative conditions have been found to be present in 6% of patients who are newly diagnosed with epilepsy (although this can be as high as 10% in those older than 65 years of age).[54] In Alzheimer's disease patients, epilepsy usually occurs in the advanced stages of the disease, but can occur earlier, particularly where there are familial ties to the onset of Alzheimer's disease.[55] Importantly, most of these patients experience low seizure frequencies and respond well to treatment regardless of the stage of Alzheimer's disease.[54] Cognitive impairment in those with neurodegenerative disorders, however, may compromise recognition and monitoring of seizures, anti-epileptic treatment adherence, and patient education.[56]

Among people living with intellectual disabilities, approximately one in five will also have epilepsy, with prevalence increasing with increasing severity of intellectual disability.[57] Notably, epilepsy in adults with intellectual disability has a worse prognosis than epilepsy in the general population, with lower rates of seizure freedom and high rates of mortality, including SUDEP.[58]

Patient burden

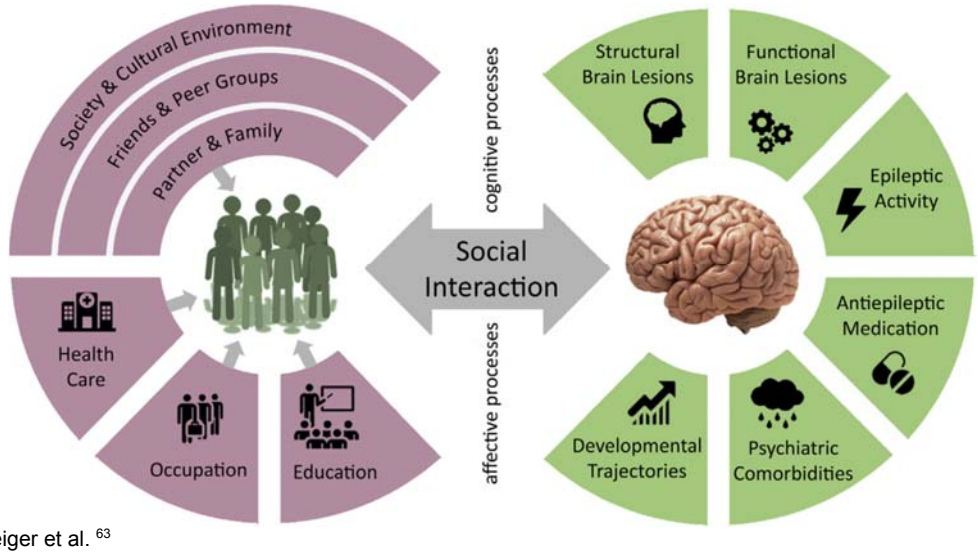
Independent living is often compromised for many adults with epilepsy, often due to restrictions on driving and limitations arising from comorbid conditions or aging.[59,60] In a survey carried out by the Neurological Alliance in 2019, 77% said that their epilepsy affected their day-to-day activities to either a great or moderate extent.[61]

Those with epilepsy also report a feeling a loss in sense of freedom, restrictions in physical activity and difficulties in the workforce when finding and maintaining a job.[59] Educational attainment, driving and job restrictions, and stigma may have a strong emotional impact and significant effects on self-esteem, relationships with peers and family members, and even personal finances.[59] Within the population with FOSs, those who are drug-resistant find themselves restricted from independent living, more so than those who are drug-responsive.[62]

In addition to restrictions to independent living, people with epilepsy are generally socially disadvantaged due to increased risk of loneliness, social exclusion and isolation.[59]

This can often lead to difficulties in developing relationships and maintaining employment. The causes of reduced social functioning in people with epilepsy are likely multifactorial and can be generally divided into individual and interpersonal determinants (as depicted in Figure 3). Regarding individual determinants, cognitive impairment may influence social difficulties, e.g. reductions in information processing speed due to brain lesions or side effects of ASMs may affect social encounters. Also, the increased prevalence of comorbid psychiatric conditions such as depression, anxiety, and psychosis, may further limit social engagement. Regarding interpersonal determinants, stigma and restrictions on experience, e.g. because of fear of seizures, this may impact social engagement.[63]

Figure 3: The individual and interpersonal determinant of social functioning in epilepsy



Source: Steiger et al. [63]

Patients with epilepsy have a lower QoL in comparison to that of the general population.[64] Seizure occurrence, in combination with the inability to live independently and social limitations, have a dramatically negative effect on patients' QoL. Given that the occurrence of seizures and the ability to live independently are intrinsically linked, alleviating seizure occurrence in patients with DRE would bring about significant improvements to their QoL. It was found that 81% of respondents to the survey carried out by the Neurological Alliance said that their epilepsy impacted the quality of their life to either a great or moderate extent.[61]

In a review of predictors of health-related quality of life (HRQoL) in adults with epilepsy, seizure frequency was found to be the most commonly reported predictor.[65] Seizure frequency and severity were found to be strongly associated with reduced HRQoL in 21 out

of 26 studies.[65] In addition to having a greater number of seizures, a number of additional risk factors for reduced QoL for people with epilepsy have been identified to date, including longer duration of seizures, the presence of tonic-clonic seizures, and earlier age of seizure onset.[59,66–68] Additionally, patients who fail to achieve seizure-freedom for ≥1 year show a significantly lower preference based HRQoL compared to those who do, suggesting that in order for significant improvement in QoL to be achieved, seizure-freedom must be achieved and maintained.[69]

Drug side effects have also been shown to negatively affect HRQoL. The most common types of adverse effects of ASMs include cognitive impairment, idiosyncratic effects (such as skin rashes), and chronic effects (weight gain).[70] The multicentre study conducted by Luoni, Bisulli investigated the relationship between adverse effects (AEs) and HRQoL. AEs (in terms of Adverse Event Profile [AEP] scores) were found to be one of the most important determinants of HRQoL.[71] Therefore, the choice of treatment for patient with epilepsy needs to balance the ability to reduce seizures with the incidence of untoward consequences of treatment.

HRQoL in patients with epilepsy is also often reduced due to the presence of comorbidities. Anxiety and depression have consistently been found to be negatively associated with HRQoL and, for depression, this negative association remains consistent both in ASM-managed patients and those with refractory epilepsy.[65] Alleviating the impacts of epilepsy on HRQoL in patients may also go some way to address further impacts caused by comorbidities to which epilepsy, or its treatment, has a causal or interdependent relationship.

Caregiver burden

Patients often require additional support, which is often provided as informal care by family members or spouses. The burden to patients described imposes significant burden to carers.[72–75]

Carers are often required to support patients with epilepsy in numerous ways, which includes:[76]

- Accompanying them in activities which might pose a safety risk if they were to have a seizure, such as cooking, hygiene, and leisure activities
- Providing transport
- Assisting with their treatment and disease management routine, e.g. taking ASMs, acting as a representative or advocate for the patients' care with doctors or other healthcare professionals
- Helping them to adapt their home
- Providing support during seizures, such as keeping them safe, calling for medical help when required, staying with them after seizures while they recover, and noting patterns or triggers to seizures.

Despite being the fourth most common neurological condition, the number of studies investigating caregiver burden in epilepsy is low, with most studies focusing on the paediatric population.

In a 2014 study, in which 92% of patients experienced FOS with or without secondary generalisation, higher caregiver burden in epilepsy was found to be associated with patients taking a higher number of ASMs, poorer neuropsychological performance, lower patient QOL score, and lower caregiver education level.[74] Additionally, it was found that on average 11.43 (±21.22) hours were spent for patient care per week, with the majority (58.34%) of caregivers being a spouse/partner.[74] A survey of caregivers of patients with DRE who have ≥3 FOS per week – conducted in 2020 – found that [redacted] of caregivers reported spending between 25 to 34 hours per week undertaking caring responsibilities; [redacted] of caregivers attended 1-3 medical appointments per week with patients with epilepsy.[77] It was also reported that [redacted] of respondents provided constant assistance, including support during seizures and help with everyday tasks.

Given the number of hours required to care, the impact to carers is notably higher in carers who are employed full- or part-time compared to retired. Moreover, carer QoL is also correlated with patient QoL;[78] improving quality of life in patients will also improve the quality of life in carers. Indeed, it was reported that depression in carers is negatively corelated with patients QOL. As found in the 2020 survey, amongst caregivers of patients with DRE who have ≥3 FOS per week, caregivers' had an age- and sex-adjusted EQ-5D-5L disutility of [redacted] compared to the general population.[77]

Economic burden

Epilepsy is a chronic condition that requires long-term treatment; as such, it is a major economic burden to individuals and societies.

Specifically, epilepsy imposes large direct costs which include the costs of healthcare (medicines, diagnostic investigations, surgery, hospitalisation). A recent review to assess the economic impact of epilepsy reported that nine out of 18 studies found drug and hospital costs are major sources of direct costs to health services and that costs of medications and outpatient consultations were higher for those with ongoing seizures.[79] Emergency admission costs are also high among those with epilepsy. In 2015, it was reported that approximately 1.4% of all emergency medical admissions for hospitals in England are epilepsy-related;[80] epilepsy is the most common neurological cause of hospital admission in England, with 47.1% of neurological admissions attributed to suspected seizures.[81]

Higher rates of hospitalisation or emergency department visits have been demonstrated among those with DRE compared to those who respond to treatment.[82] In 2019, there were 3,962 non-elective admissions for epilepsy in England.[83] The National Audit of Seizure Management (NASH) found that patients with emergency admissions due to a seizure had a mean length of stay of 5.7 days.[84] Moreover, in patients with an emergency admission due to a seizure, 43.2% were readmitted within a year; in the year preceding and following an emergency admission, patients had on average 2.2 and 2.9 emergency department visits, respectively. In 2019, the average cost per hospitalisation for epilepsy in England was £2,740.11.[83]

There are also indirect costs associated with epilepsy due to comorbidities, disabling side-effects and premature mortality that prevent a person from reaching their full potential in school, employment or household activities. Among focal drug-resistant patients in Europe,

high unemployment rates have been shown when compared to a matched control population (46% vs 19%).[85]

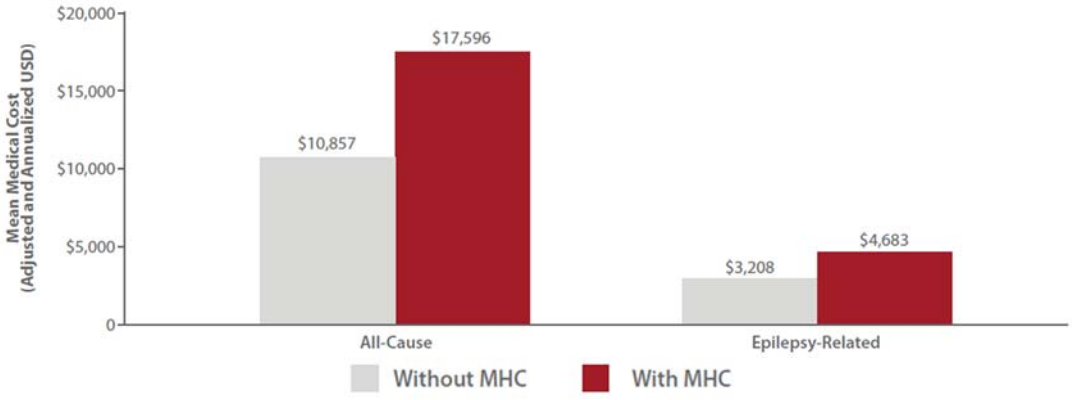
Additionally, indirect costs arise from out-of-pocket expenses associated with epilepsy and carer involvement due to their lost productivity. A 2018 study found that caregivers of patients on monotherapy had an average of 2.7 fewer days of work due to sick leave and short-term disability, whereas the caregivers to those on adjunctive therapy had an average of 5.1 fewer days of work due to the same reasons.[86] Given that adjunctive therapy is trialled in patients following failure of monotherapy, it can be concluded that the carer burden is greater in patients with DRE. Indeed, costs vary according to the severity of the condition, response to treatment, length of time since diagnosis and associated comorbidities.[21]

In 2010, the European Brain Council estimated the total annual societal cost (direct healthcare costs, direct non-medical costs and indirect costs) of epilepsy in Europe to be €13.8 billion (€5,221 per person) with large variations of expenditure across 35 countries.[87] In the UK, costs of epilepsy per patient were high - €6,143 per patient, totalling €1,638,000 per year across all patients with epilepsy.[87]

Relatively little research has focused on the economic burden of FOS in isolation. A French study of adults with FOS treated with a combination of ASMs estimated the mean annual direct epilepsy-related costs to be €3,850/patient/year (cost year 2010) with ASMs accounting for the main direct cost.[88] Drug-resistant patients had a mean extra cost of €2,560/patient/year, demonstrating the additional economic burden of DRE.

One study has compared direct and indirect costs between privately insured US patients with FOS and matched controls.[89] The study found direct annual costs for patients diagnosed with FOS were on average $7,190 higher than that of a control group without an epilepsy diagnosis (cost year 2005, US dollars). A further study in the US, assessed the economic burden of FOS in patients with and without comorbidities.[90] Medical costs, all-cause and epilepsy-related, were notably higher amongst patients with a comorbid mental health condition (Figure 4). Indeed, epilepsy related costs were $1,475 greater in patients who also had a mental health condition.

Figure 4: Medical costs associated with patients with epilepsy who do and don't have a mental health conditon



B.1.3.3. Clinical pathway of care

Guidelines

There are currently more than 30 different anti-seizure medicines (ASMs) that have been approved for the treatment of FOS, with 18 ASMs recommended by NICE;[15] these are commonly referred to as anti-epileptic drugs (AEDs) but the more recent terminology is ASMs.

The most recently updated NICE guidelines on the diagnosis and management of epilepsy from February 2020, states that first-line treatment for newly diagnosed focal seizures should be carbamazepine or lamotrigine.[91] If these treatments are not suitable, levetiracetam or oxcarbazepine or sodium valproate (except for women of childbearing potential) should be offered.

If first-line treatments are ineffective or not tolerated, the NICE guideline stipulates that carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, or sodium valproate should be offered as adjunctive treatment.[91]

If adjunctive therapy is not effective or tolerated, the treatment of patients with FOS should be discussed with, or referred to, a tertiary epilepsy specialist. Other therapies that may be offered by tertiary specialists include: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide.[91] Additionally, brivaracetam and perampanel are recommended in this positioning in NICE evidence summaries and local CCG formularies, though they are not explicitly referred to in NICE CG137 due to their more recent availability.[92]

Despite the numerous drug treatments available to patients in the UK, there is still an unmet need for patients with FOS as many patients remain drug-resistant.

Current management

Epilepsy is primarily managed with pharmacological interventions and, if ASMs are not successful at controlling seizures, non-pharmacological treatments are considered by NICE after the failure of pharmacological interventions.[93]

Antiseizure medicines (ASMs)

For adults with FOS, the recommended monotherapy ASMs according to the ILAE were carbamazepine, levetiracetam, phenytoin and zonisamide.[94] These represented the only drugs with robust efficacy and effectiveness evidence at that time to support their monotherapy use in newly-diagnosed focal onset patients. However, currently only carbamazepine and levetiracetam are recommended in this first-line position by NICE.

However, although ASMs are routinely given to adult patients with FOS, approximately just 45% of patients will achieve seizure-freedom with their first ASM regimen.[32] For patients who do not achieve seizure-freedom with their first ASM regimen, treatment options include other ASM monotherapies or if this fails, combination therapy using an additional ASM as adjunctive therapy.[32,95] Upon the failure of a second ASM, either as monotherapy or in combination, patients are considered to have DRE.[96]

In recent years, more treatments, known as 3rd generation ASMs, have been launched to treat patients with drug-resistant FOS as adjunctive therapy including brivaracetam,

lacosamide, perampanel and eslicarbazepine acetate. These new generation of drugs have fewer drug interactions, more mild adverse events and novel mechanisms of actions which can bring promise to patients with DRE.[97] These ASMs are recommended by NICE in the third-line as adjunctive treatments and are usually reserved for later lines of therapy in clinical practice.

Amongst currently approved 3rd generation ASMs, the highest seizure freedom rate reported across all RCTs (with varying population sizes and heterogeneity in study design) was 9.4% for brivaracetam 50 mg,[98] which exceeded seizure freedom reported in more commonly used, higher doses. Over maintenance phases for 3rd generation ASMs in their highest RCT doses, the highest response rate (≥50% reduction in seizures) observed was 43% for eslicarbazepine acetate 1,200 mg.[99] The highest relative reduction in seizure frequency observed in RCTs across 3rd generation ASM was 48.8% for lacosamide 400 mg.[100] Adverse events amongst 3rd generation ASMs tend to be mild to moderate.[101] Across studies for 3rd generation ASMs, typically less than 10% of adverse events were severe. Amongst lacosamide and eslicarbazepine acetate RCTs, TEAEs led to discontinuation in more than 25% of patients receiving 600 mg and 1,200 mg per day, respectively, likely due to higher doses for these ASMs.[102–104]

Although there are 18 ASMs recommended by NICE, after numerous trials of ASMs approximately 30% of patients will remain drug-resistant, defined as a failure of adequate trials of two or more tolerated and appropriately chosen and used ASM schedules (either monotherapy or in combination) to achieve sustained seizure freedom.[32,33,96]

Non-pharmacological treatments

Surgical procedures may be an option for patients with drug-resistant FOS. Epileptic surgery entails resective procedures whereby lesions or lobes in the brain causing seizures are removed. Despite its efficacy in reducing seizure activity over the long-term, surgery carries risks of permanent neurocognitive deficits.[105] The significant risks of complications, combined with high costs and strict eligibility criteria – for which eligibility can only be ascertained through extensive investigations and invasive procedures – mean that very few patients are considered candidates for surgery.

However, more than half of patients referred for resective surgery will not be suitable but rather would be suitable for implantation of a stimulator as a palliative treatment, known as vagus nerve stimulation (VNS); this involves the implantation of a stimulator, which is connected to left vagus nerve in the neck and sends mild electrical stimulations to calm the irregular electrical brain activity leading to seizures.[106] VNS is a palliative option for patients as it can offer modest benefits in reducing seizures, with similar rates of efficacy as adding a new antiseizure medications (ASMs).[107] Therefore, with VNS similar proportions of patients will gain seizure control. Although its efficacy is modest, VNS may also offer improvements in symptoms of depression amongst patients with DRE.[108]

Invasive treatments are not comparators to adjunctive ASM therapy. In the case of surgery, very few patients are eligible for surgery, with ever fewer proceeding. VNS is performed palliatively as a last resort, with its use reducing with time.

Unmet need

Over the last 20 years there have been major advances in ASM development as well as evolving clinical practice guidelines that incorporate newer medications into recommendations for epilepsy treatment.[15,94] Despite these advances, approximately one-half of patients fail the initial ASM treatment and nearly a third have DRE.[33,109]

Additionally, in patients with DRE pharmacological treatment options are limited; NICE gives recommendations for three lines of pharmacological therapy. Once patients have exhausted these three lines of treatment, there is not an established treatment pathway. Moreover, with very few patients suitable for resective surgery, a highly effective treatment option, there is a clear unmet need for newer, more effective medicines for patients with drug-resistant FOS.

Furthermore, the ultimate goal of treatment is seizure freedom and the probability of achieving it diminishes with each treatment failed.[32] This further reiterates the point that highly effective ASMs need to be made available as soon as possible in the treatment pathway to enable more patients the opportunity to have seizure freedom. Current standards of care for patients with drug-resistant FOS are inadequate, leaving patients cycling on rounds of ineffective ASMs whilst their seizures remain uncontrolled.

Cenobamate

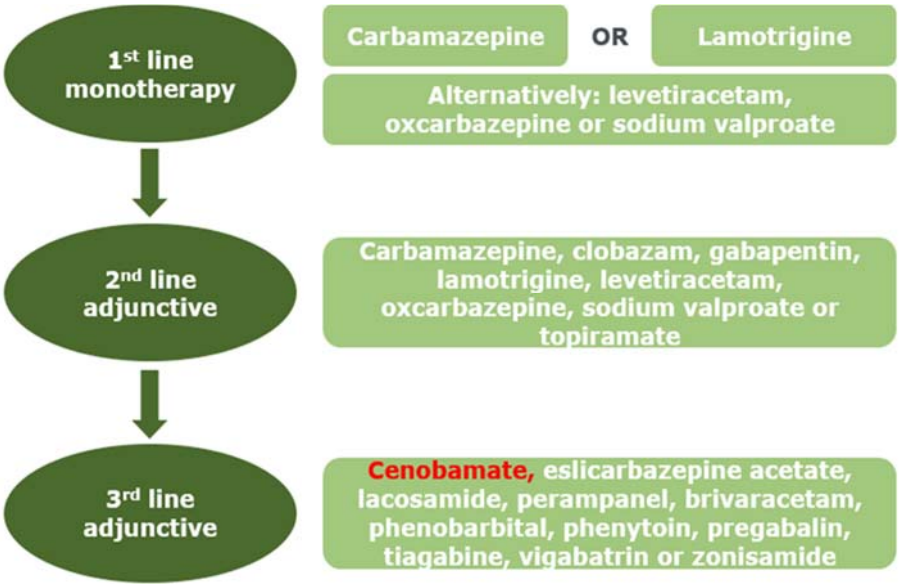
Cenobamate is a novel tetrazole alkyl carbamate derivative developed for the adjunctive treatment of FOS in adult epilepsy patients, including focal aware motor, focal impaired awareness, or focal to bilateral tonic-clonic seizures.

Cenobamate is the only ASM which, at clinically relevant concentrations, acts as a positive allosteric modulator of $GABA_A$ receptors at non-benzodiazepine binding sites and preferentially blocks the persistent sodium current.[12,13] Preclinical studies of cenobamate demonstrated that cenobamate is a mechanistically distinct ASM and its unique broad-spectrum antiseizure profile results from dual activity on excitatory and inhibitory paths in the brain.[10] Cenobamate's unique, dual MOA has the potential to both prevent seizure initiation and limit seizure spread,[5–9] offering an important advancement in drug development for the treatment of DRE.[10]

In the main clinical trials (described in Section B.2.2.1), patients with drug-resistant FOS treated with cenobamate experienced significant reductions in seizure frequency and high rates of seizure freedom compared to placebo,[2,3] which exceed rates seen for any other adjunctive treatment to date.[10,110–113] In a study to investigate the long-term tolerability of cenobamate, no significant safety or tolerability issues were found and patient retention rates remained high, suggesting good tolerability.[4]

Subgroup analysis demonstrated similar efficacy across all groups in the pivotal C017 study.[114] As such, this submission considers cenobamate as the [redacted]. This means that, once recommended, cenobamate would be available as a third-line, adjunctive treatment, alongside those summarised in Figure 5.

Figure 5: Proposed positioning of cenobamate in UK clinical practice



As there is an urgent need for new and more effective ASMs, cenobamate is a promising new therapy for patients with DRE and for patients who seek to achieve seizure freedom.[115] As a recognition of the potential of cenobamate to help the millions of people suffering from DRE, the MHRA has recently awarded cenobamate a Promising Innovative Medicine (PIM) designation.[115] Cenobamate addresses a clear unmet medical need, providing a more effective treatment option for patients with DRE, enabling them to attain levels of seizure-freedom not seen by any other ASMs to date.[10,110–113] Cenobamate would change the treatment paradigm for patients with epilepsy, by reducing – or eradicating - their seizure frequency and thus increasing their and their caregivers' quality of life whilst alleviating the burden of epilepsy to the NHS.

B.1.4. Equality considerations

Hospital admissions amongst patients with FOS are increased by seizure frequency and severity. In the context of the COVID-19 pandemic, there is further value in preventing hospitalisations as the NHS remains under pressure. Cenobamate can significantly reduce, or stop, seizure occurrence thus reducing hospitalisations amongst patients with FOS, alleviating the burden to healthcare and preventing the spread of infection.

Additionally, cenobamate is a once-daily medication and may help improve compliance in patients, especially those with co-morbidities and learning disabilities. There are studies that recognise that improved compliance is associated with improved outcomes.[116]

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

B.2.2.1. Cenobamate studies

The cenobamate clinical development program for the treatment of FOS includes 26 clinical studies: 22 phase 1 studies, three phase 2 studies and one phase 3 study. Amongst the phase 2 studies, one was a proof-of-concept study enrolling seven patients.

The efficacy of cenobamate as an adjunctive ASM was established in two randomised double-blind studies in patients with drug-resistant focal epilepsy (C017 and C013),[2,3] which formed the basis of evidence for the European Medicines Agency (EMA) regulatory filing. In both studies, the population enrolled were generalisable to that observed in UK clinical practice. The long-term efficacy of cenobamate was demonstrated in the C017 open-label extension (OLE). In addition, the safety profile of cenobamate has been well characterised in a large, ongoing open-label long-term safety study (C021).[4] These studies were also retrieved in a systematic literature review (SLR), as described in Appendix D.

Throughout the submission, evidence from the C017 study, its OLE and the C021 study are described and used in the economic evaluation. Data from the C013 study is not included in the main submission nor the economic evaluation as it had maintenance period of 6 weeks, which according to EMA guidance, is not sufficient to demonstrate long-lasting efficacy.[117] Findings from the study can be found summarised in Appendix D.

Study C017

Study C017 was a multinational, multicentre, double-blind, randomised, dose-response study in patients with drug-resistant FOS followed by an open-label extension (study C017 OLE) to provide additional insight into the long-term profile of adjunctive cenobamate. All enrolled patients (N=533) who completed screening (N=437) were randomly assigned (1:1:1:1) to receive their stable ASM regime at baseline with either cenobamate at 100 mg/day (N=108), 200 mg/day (N=110), 400 mg/day (N=111), or placebo (N=108). This study included a 6-week titration phase and 12-week maintenance phase.

Results from the C017 were reported by Krauss *et al.* (2019) and are summarised in the Clinical Study Report (CSR). There was a consistent dose-response observed for cenobamate in the EMA primary endpoint defined as a ≥50% responder rate during the 12-week maintenance phase; patients treated with cenobamate had a significantly greater response to treatment (defined as a ≥50% reduction in seizures) than those treated with placebo (placebo, 25%; cenobamate 100 mg, 40% [p=0.0365]; cenobamate 200 mg, 56% [p<0.0001]; cenobamate 400 mg, 64% [p<0.0001]).[2]

Moreover, cenobamate demonstrated significant benefits compared to placebo and demonstrated a dose response in the median relative reduction in seizures per 28 days during maintenance treatment (placebo, -27.0%; cenobamate 100 mg, -41.5% [p=0.0537]; cenobamate 200mg, -56.5% [p<0.0001]; cenobamate 400mg, -63.0% [p<0.0001]).[2]

Similarly, the proportion of patients achieving seizure freedom increased with dose and demonstrated significant improvements compared to placebo (placebo, 1%; cenobamate 100 mg, 4% [p=0.3688]; cenobamate 200 mg, 11% [p=0.0022]; cenobamate 400 mg; 21% [p<0.0001]). These seizure freedom rates are notably greater compared to the pivotal studies of other ASMs in the past 25 years.[118–124,124,125] Most of the adverse events were mild or moderate in severity, with serious adverse events occurring in between 4% (200mg group) and 9% (100 mg) of patients treated with cenobamate compared with 6% in the placebo group.

Study C017 safety and efficacy data were used in the economic model.

Study C017 OLE

The ongoing C017 OLE will provide further evidence of the long-term safety and the efficacy of adjunctive cenobamate in terms of seizure freedom and reduction. A total of 355 patients from C017 had enrolled into the OLE (265 were originally randomized to cenobamate and 90 were originally randomized to placebo and crossed over to cenobamate). As of July 2019, 58.9% (209/355) of patients were continuing in the OLE with 141 patients discontinued. All patients enrolled in the OLE were treated with a target dose of 300 mg of cenobamate per day after a 2-week blinded conversion from their randomised treatment in C017.

Results from the C017 OLE were summarised by Klein *et al*. (2019) and have been reported in post-hoc analyses; a CSR is not available for the C017 OLE. The median percent reduction in seizure frequency during the first 6 months of the OLE for all cenobamate OLE patients was 65.4% and was similar among patients originally treated with cenobamate or placebo in the double-blinded study.[126] Between years 4-5 of the OLE, seizure frequency reductions of ≥50%, ≥75%, ≥90%, and 100% compared to baseline were achieved in 8.1%, 54.9%, 42.2%, and 24.8% of patients, respectively. The percentage of patients achieving a period of 12 months and 24 months of consecutive seizure freedom at any point of the OLE was 23.2%, and 17.6%, respectively.

Study C017 OLE safety data were used in the economic model.

Study C021

The ongoing C021 study is a large phase 3, open-label study, designed primarily to assess the long-term safety of adjunctive cenobamate with their baseline ASM regime and to test the hypothesis that the rate of Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS) would be lower when initiating cenobamate at a low dose (12.5 mg/day) and titrating every 2 weeks. All patients enrolled (N=1,347) were treated with cenobamate at a target dose of 200 mg/day, and patients were able to up-titrate to 400 mg/day if required.

Interim results of the C021 safety study were reported by Sperling *et al.* (2020) and are also summarised in the C021 CSR.[4] There were three cases of DRESS observed in the clinical development program in studies with high initial dose and/or rapid titration.[4] Amongst the

1,340 patients exposed to cenobamate using a start-slow, go-slow titration approach, there were no additional cases of DRESS observed. The interim results of the study support the approach that initiating cenobamate at a lower dose and slowing the initial titration rate would lower the rate of DRESS. The ongoing study will provide additional long-term safety data.

Safety data from the ongoing Study C021 were used in the economic model.

Study C013

The C013 study was a randomised (1:1) study designed to evaluate the efficacy and safety of adjunctive cenobamate 200 mg/day in patients with drug-resistant FOS despite treatment with 1 to 3 ASMs. A total of 222 patients (median age 37 years, range 18-61 years) were randomised to receive their stable ASM regime at baseline with either cenobamate 200 mg/day (N = 113) or placebo (N = 109). The study included a six-week titration phase and a six-week maintenance phase.

The results reported by Chung *et al*. (2020) showed that, treatment with adjunctive cenobamate 200mg once daily led to statistically significant reductions in seizure frequency (including 100% reduction) compared to placebo with few withdrawals due to AEs.[3]

Compared to patients treated with placebo, cenobamate patients experienced greater median reduction in seizures frequency during double-blind treatment compared to the baseline (55.6% vs 21.5%, p<0.0001, the primary outcome) and high level of ≥50% responder rate (50.4% vs 22.2%, p<0.0001) – greater incremental results than seen with any other ASM to date.[111] A significant positive benefit with cenobamate was observed in all assessed focal seizure types, with a large median percent reduction per 28 days noted among patients with focal to bilateral tonic-clonic seizures (77.0% vs 33% for placebo, p=0.0117).[3] Additionally, post hoc analysis demonstrated that significantly greater percentages of patients achieved seizure freedom during the 6-week maintenance phase with cenobamate compared with placebo (28.3% vs 8.8%; p=0.0001).

Despite the significant evidence from this study supporting the clinical effectiveness of cenobamate, Study C013 is not further summarised in the main submission nor was it included in the economic analysis as the maintenance phase of the C013 study lasted 6 weeks, which according to EMA guidance, is not sufficient to demonstrate long-lasting efficacy.[117] Further details of the clinical effectiveness of cenobamate demonstrated in Study C013 can be found in Appendix D.2.1.4.

The key studies that provide clinical outcome data that are utilised in the economic model are the pivotal C017 study, and its open-label extension phase that patients who completed C017 could opt to participate in, and the ongoing open-label C021 safety study. Key characteristics of these studies are summarised in Table 3, Table 4, and Table 5, respectively; outcomes included in the economic model are indicated in bold. A summary of the C013 study can be found in Appendix D.

Table 3: Clinical effectiveness evidence – C017 study

Study	C017
Study design	A multicentre, double-blind, randomised, adjunctive placebo-controlled trial.

Population	Adult patients (aged 18–70 years) with drug-resistant focal seizures despite treatment with at least 1 ASM within the last 2 years and 1-3 concomitant ASMs at the baseline				
Intervention(s)	Cenobamate (100 mg, 200 mg and 400 mg)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	This study investigated cenobamate in the population to be treated as per the licensed indication and includes key outcomes that are utilised in the economic model.				

Reported outcomes specified in the decision problem	• **Change in seizure frequency**
	  o **Focal aware**
	  o **Focal impaired awareness**
	  o **Focal to bilateral tonic-clonic**
	• **Seizure-free rate**
	• Mortality
	• **Adverse effects of treatment**
	• Health-related quality of life determined via the Quality of Life in Epilepsy Questionnaire				

All other reported outcomes	• Clinical Global Impression of Change recorded by the physician at Visit 9 or Early Termination. • **Time on treatment** • Change from baseline in vital sign measurements • Physical and neurologic examination • Clinical laboratory evaluations • 12-lead electrocardiograms • Columbia-Suicide Severity Rating Scale				

Abbreviations: ASM, antiseizure medicine.
Bold outcomes indicate that they are included in the economic model

Table 4: Clinical effectiveness evidence – C017 OLE study

Study	C017 OLE				
Study design	A, single arm, open-label extension with a 2-week blinded conversion phase.				
Population	Adult patients (aged 18–70 years) who completed the double-blinded C017 study and were eligible to enter the OLE.				
Intervention(s)	Cenobamate (300 mg/day)				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	

Rationale for use/non-use in the model	This study investigated cenobamate in the population to be treated as per the licensed indication and includes key outcomes that are utilised in the economic model.

Reported outcomes specified in the decision problem	• Change in seizure frequency
	  o Focal aware
	  o Focal impaired awareness
	  o Focal to bilateral tonic-clonic
	• Seizure-free rate
	• Mortality
	• **Adverse effects of treatment**

All other reported outcomes	• Clinical Global Impression of Change recorded by the physician at Visit 9 or Early Termination • **Time on treatment** • Change from baseline in vital sign measurements • Physical and neurologic examination • Clinical laboratory evaluations • 12-lead electrocardiograms • Columbia-Suicide Severity Rating Scale

Abbreviations: OLE, open-label extension.
Bold outcomes indicate that they are included in the economic model

Table 5: Clinical effectiveness evidence – C021 study

Study	C021				
Study design	An ongoing open-label, multicentre safety and pharmacokinetic study				
Population	Patients 18-70 years old with drug-resistant focal seizures, despite treatment with at least 1 ASM in the last year, taking stable doses of one to three ASMs.				
Intervention(s)	Cenobamate (200-400 mg)				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	x	**Indicate if trial used in the economic model**	Yes	x
	No			No	
Rationale for use/non-use in the model	This study is investigating cenobamate in the population to be treated as per the licensed indication and includes key outcomes that are utilised in the economic model.				
Reported outcomes specified in the decision problem	**Frequency and severity of adverse events**				
All other reported outcomes	Safety: • **Time on treatment** • Clinical laboratory test values • 12-lead electrocardiogram recordings • Vital sign measurements, physical and neurological examinations				

	• Columbia Suicide Severity Rating Scale • Safety was also assessed for the occurrence of DRESS. • Pharmacokinetic Assessments: • Plasma samples for YKP3089, phenytoin, phenobarbital and other concomitant ASMs were obtained periodically using sparse sampling during the first 9 visits of the study.

Abbreviations: ASM, antiseizure medicine; DRESS, Drug-induced hypersensitivity syndrome.
Bold outcomes indicate that they are included in the economic model

They key publications for each of the studies are listed in Table 6.

Table 6: Publications reporting data from the clinical studies

Study	Title	Citation	Presented in submission
C017	Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial.[2]	Krauss GL, Klein P, Brandt C, *et al*. The Lancet Neurology 2020. 19(1):38-48	Yes
C017 OLE	Long-term efficacy and safety of adjunctive cenobamate in patients with uncontrolled focal seizures: open-label extension of a randomized clinical study C017.[126]	Klein P, Krauss G, Aboumatar S, *et al.* Neurology 2020. 94: 15 Supplement.	Yes
C021	Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study.[4]	Sperling MR, Klein P, Aboumatar S, *et al*. Epilepsia 2020. 61(6):1099-1108	Yes

B.2.2.2. Comparator studies

A systematic literature review was conducted to determine the efficacy and safety of cenobamate and other ASMs used, when given as an adjunctive therapy for adults with drug-resistant focal epilepsy. For details of the systematic literature review, see Appendix D.

Following the review process, there were a total of 54 RCTs and 15 OLEs identified, as summarised in Appendix D (Table 3). Of the studies identified, 18 were included in evidence synthesis with cenobamate. There were six, four, four and four placebo-controlled studies considered for brivaracetam, lacosamide, eslicarbazepine acetate and perampanel, respectively. The studies identified varied in size, ranging from 157 to 760 patients included. The methodology and results of the 18 studies are presented in Appendix D, Tables 7-13.

In the six brivaracetam studies identified, doses ranged from 5 mg/day to 200 mg/day, with rates of response to treatment with brivaracetam, defined by a ≥50% responder rate, ranging from 22% (5 mg/day) to 56% (50 mg/day). This compared to rates of 17%-24% for placebo. Outcomes for seizure-freedom were low, with seizure freedom reported in 1% (5 mg/day) to 9% (50 mg/day) of patients. This compared to rates of <1%-2% for placebo.

In the four lacosamide studies, doses ranged from 200 mg/day to 600 mg/day, with the rate of response to treatment with lacosamide, defined by a ≥50% responder rate, ranging from

33% (200 mg/day) to 49% (400 mg/day), compared to 18%-26% in patients treated with placebo. Seizure freedom was reported in 3% (400 mg/day) to 8% (600 mg/day) of patients treated with lacosamide, compared to 0%-2% of patients treated with placebo.

In the four eslicarbazepine acetate studies, doses ranged from 400 mg to 1200 mg, with the rate of response to treatment with eslicarbazepine acetate, defined by a ≥50% responder rate, ranging from 17% (400 mg/day) to 43% (1,200 mg/day), compared to 13%-23% of patients treated with placebo. 1% (400 mg/day) to 8% (1,200 mg/day) of patients treated with eslicarbazepine acetate reported seizure freedom, compared to 1%-2% of patients treated with placebo.

In the four perampanel studies, doses ranged from 4 mg to 12 mg, with the rate of response to treatment with perampanel, defined by a ≥50% responder rate, ranging from 23% (4 mg/day) to 43% (12 mg/day) with perampanel compared to 15%-26% of patients treated with placebo. Seizure freedom was reported in 2% (8 mg/day) to 5% (12 mg/day) of all patients treated with perampanel, compared to 0%-1% of patients treated with placebo.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Study methodology

C017 study

The C017 study involved a multicentre, double-blind, randomised, dose-response study at 107 epilepsy and neurology centres in 16 countries. Adult patients (aged 18–70 years) with drug-resistant focal seizures, despite treatment with at least 1 ASM in the last 2 years, were randomly assigned (1:1:1:1) to receive their stable baseline ASM regime with either adjunctive once daily oral cenobamate at doses of 100 mg, 200 mg, or 400 mg, or placebo following an 8-week baseline period.

Table 7: C017 Study Design

Trial number (acronym)	**C017**
Trial design	This was a multicentre, double-blind, randomized (1:1:1:1), placebo-controlled dose-response study in patients with focal onset seizures. There was an 8-week prospective baseline and an 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for patients leaving the study), with a final follow-up visit 2 weeks after the last dose of study drug.
Participants (Inclusion criteria)	• Males and females aged 18 to 70 years • Weight of at least 40kg • Diagnosis of partial epilepsy according to the International League Against Epilepsy's Classification of Epileptic Seizures. Diagnosis should have been established by clinical history and an EEG that is consistent with localisation related epilepsy; normal interictal EEGs were allowed provided the patient met the other diagnosis criterion (i.e. clinical history)

	• Drug-resistant focal seizures and required additional ASM therapy despite having been treated with at least 1 ASM within approximately the last 2 years • During the 8-week baseline period, patients must have experienced ≥8 seizures including only focal aware seizures with motor component, focal impaired awareness seizures, or focal to bilateral tonic-clonic seizures without a seizure-free interval of >25 days any time during the 8 weeks baseline. Patients must have had had ≥3 focal seizures during each of the 2 consecutive 4-week baseline periods and no consecutive 25-day seizure-free interval. • Currently on a stable antiepileptic treatment regimen. o Must have been receiving stable doses of 1-3 ASMs for at least 4 weeks prior to screening to be continued unchanged throughout the study. o VNS was not to be counted as an ASM; however, the parameters were to be stable for 4 weeks prior to baseline. The VNS must have been implanted at least 5 months prior to Visit 1. o Benzodiazepines taken at least once per week during the 1 month prior to Visit 1 for epilepsy, or for anxiety r sleep disorder, was counted as 1 ASM and had to be continued unchanged throughout the study. • Computed tomography (CT) or magnetic resonance imaging (MRI) scan performed within the past 10 years that ruled out a progressive cause of epilepsy • Use of an acceptable form of birth control by female patients of childbearing potential
Participants (Exclusion criteria)	The key exclusion criteria were: • History of serious systemic disease including hepatic insufficiency, renal insufficiency, a malignant neoplasm, any disorder in which prognosis for survival was less than 3 months, or any disorder that in the judgement of the investigator would have placed the patient at excessive risk by participation in a controlled trial. • History of nonepileptic or psychogenic seizures. • Presence of only non-motor focal aware seizures or primary generalized epilepsies • History of seizure clusters (episodes lasting less than 30 minutes in which multiple seizures occurred with such frequency that the initiation and completion of each individual seizure could not be distinguished) within 3 months prior to Visit 1 • Presence of Lennox-Gastaut syndrome. • Scheduled epilepsy surgery within 8 months after Visit 1. • Pregnancy or lactation. • Patients planning to have implantation of DBS. • Evidence of significant active hepatic disease. • A history of non-epileptic or psychogenic seizures • Active CNS infection • Any clinically significant psychiatric illness
Settings and location where	A total of 107 epilepsy and neurology centres in 16 countries were included in the study. Study sites were in the US, Australia, Europe, and Asia.

data were collected	
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	437 patients were enrolled into the study; 108, 110, 111 and 108 patients were randomised to cenobamate 100 mg, cenobamate 200 mg, cenobamate 400 mg and placebo, respectively. Both cenobamate and placebo were administered orally over the titration and maintenance phase of the study. **Titration phase** Enrolled patients first entered a 6-week titration phase, during which the initial dose for all patients assigned to receive cenobamate was 50 mg/day. All patients began an initial starting dose of cenobamate at 100 mg/day orally that was up-titrated by a weekly increment of 100 mg to the target dose, or a matching oral placebo daily. Following a blinded review of the first nine patients, the study protocol was amended to lower the starting dose to 50 mg/day and slow the titration rate increase to 50-mg/day/week increments until the target dose of 100 mg/day or 200 mg/day was reached. For patients randomized to 400 mg/day, the dose was increased by 100 mg/day/week after the dose of 200 mg/day was reached. **Maintenance phase** Patients were instructed to take the study drug once daily in the morning, with or without food. The investigator may have instructed the patient to take the dose of study drug in the evening if clinically indicated and consistent with other aspects of the protocol. In addition, the investigator could have altered the timing or amount of an individual dose of a concomitant ASM, but the total daily dose and dosing frequency of the concomitant ASM had to remain unchanged during the double-blind treatment period. No cenobamate dose adjustments were permitted after week 8. **Concomitant medications** Patients were required to be taking 1-3 concomitant ASMs for at least 12 weeks prior to randomisation which should remain unchanged throughout the entire double-blind period of the study. Intermittent benzodiazepines (other than diazepam) could be taken as rescue mediation once during the baseline period and twice during the treatment phase. Vigabatrin was prohibited for use during the study and in 1 year prior to the first visit. Clopidogrel, fluvoxamine, amitriptyline, clomipraminie, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz and natural progesterone were prohibited during the study and thirty days prior to the first visit. diazepam, phenytoin, phenobarabital or metabolites of these drugs were also prohibited during the study and thirty days prior to the first visit.
Primary outcomes (including scoring methods and timings of assessments)	Responder rate during the maintenance phase, defined as a ≥50% reduction from baseline in seizure frequency during the maintenance phase of the double-blind treatment period.
Other outcomes used in the economic model/specified in the scope	• The percentage change from the pre-treatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) for all seizures compared with the maintenance phase of the double-blind treatment period

	• Higher response rates (≥75%, ≥90%, and 100%) of all seizure types during the double-blind treatment period and during the maintenance phase compared with the baseline phase • Seizure rate over time (based on moving average over 4-week intervals). • QOLIE-31-P completed by the patient at Visit 3 and Visit 9 or Early Termination. • Safety during the double-blind treatment period was assessed by the nature, frequency, and severity of SAEs, TEAEs, discontinuations due to AEs, overall dropout rates,
Pre-planned subgroups	No pre-planned subgroups

Abbreviations: AEs, adverse events; ASM, anti-seizure medication; CNS, central nervous system; DBS, deep brain stimulation; EEG, electroencephalogram; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; VNS, vagus nerve stimulation.

C017 OLE

Participation in the OLE phase could continue if patients completed the 12-week maintenance phase of C017, and still satisfied all the inclusion criteria and none of the exclusion criteria (except for seizure frequency). The OLE phase is to continue indefinitely.

Table 8: C017 OLE Study Design

Trial number (acronym)	**OLE C017**
Trial design	Patients who completed the 12-week double-blind maintenance phase and who still met all inclusion criteria and none of the exclusion criteria (except for seizure frequency) were eligible to continue in an optional open-label extension phase.
Participants (Inclusion criteria)	Same as C017, except criteria on seizure frequency.
Participants (Exclusion criteria)	Same as C017.
Settings and locations where the data were collected	Same as C017.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients entering the OLE underwent a 2-week blinded conversion to a target dose of cenobamate 300 mg once daily. During the 2-week conversion, the investigator could increase or decrease the open-label dosage, if clinically indicated, to a minimum of 50 mg and maximum of 400 mg/day. Doses of concomitant ASMs could be adjusted during the conversion phase. During the OLE treatment phase, concomitant ASMs could be added, removed, or adjusted (no cenobamate monotherapy allowed). Scheduled study assessments occurred every 3 months
Primary outcomes (including scoring	See C017 for more details.

methods and timings of assessments)	
Other outcomes used in the economic model/specified in the scope	See C017 for more details.
Pre-planned subgroups	No pre-planned subgroups

Abbreviations: ASM, anti-seizure medication; OLE, open-label extension.

C021 study

The ongoing C021 study is a multicentre, open-label, phase 3 study at 137 epilepsy and neurology centres in 17 countries. Adult patients (aged 18–70 years) with drug-resistant focal seizures, despite treatment with at least 1 ASM in the last 2 years, are assigned to adjunctive once daily oral cenobamate at a target dose of 200 mg alongside their stable ASM regime. The purpose of the study is to characterize the rate of Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS) using a lower starting dose and a slower titration rate.

Table 9: C021 Study Design

Trial number (acronym)	**Study C021**
Trial design	This is an ongoing phase 3, multicentre, open-label study in patients with drug-resistant focal seizures consisting of a screening period, an open-label titration phase, an open-label maintenance phase, and for patients discontinuing, a taper period and a follow-up visit. The open-label treatment period consists of a 12-week titration phase followed by an open-label maintenance phase.
Participants (Inclusion criteria)	Enrolment to the C021 study was completed on 8th February 2018. As of July 1, 2020, a total of 1,340 patients received cenobamate and were analysed. The total includes 1,054 patients exposed for at least 12 months. Key inclusion criteria were: • Males and females aged 18 to 70 years • Weight of at least 40kg • Diagnosis of focal epilepsy according to the International League Against Epilepsy's Classification of Epileptic Seizures. Diagnosis should have been established by clinical history and an EEG that was consistent with localisation-related epilepsy; normal interictal EEGs were allowed provided that the patient met the other diagnosis criterion (i.e. clinical history) • Drug-resistant focal seizures and required additional ASM therapy despite having been treated with at least 1 ASM within approximately the last 2 years • Currently on a stable antiepileptic treatment regimen. o Patient must have been receiving stable doses of 1-3 ASMs for at least 3 weeks prior to Visit 2 o VNS or DBS were not counted as an ASM; however, the parameters must have remained stable for at least 4 weeks prior to baseline. The VNS or DBS must have been implanted at least 5 months prior to Visit 1.

	o Benzodiazepines taken at least once per week during the 1 month prior to Visit 1 for epilepsy, or for anxiety or sleep disorder, were counted as 1 ASM and must have continued unchanged throughout the study. • Computed tomography (CT) or magnetic resonance imaging (MRI) scan performed within the past 10 years that ruled out a progressive cause of epilepsy. • Use of an acceptable form of birth control by female patients of childbearing potential
Participants (Exclusion criteria)	Key exclusion criteria were: • History of any serious drug-induced hypersensitivity reaction or any drug-related rash requiring hospitalization • History of any drug-induced rash or hypersensitivity reaction with documented nature of the rash or hypersensitivity reaction • History of serious systemic disease, • Presence of only non-motor simple partial seizures or primary generalized epilepsies • Clinical evidence of phenytoin or phenobarbital toxicity. • Presence of Lennox-Gastaut syndrome. • Scheduled epilepsy surgery within 8 months after Visit 1. • Patients planning to have implantation of DBS. • Pregnancy or lactation. • Evidence of significant active hepatic disease. • Patients taking phenytoin must not have been taking phenobarbital or primidone; patients taking phenobarbital must not have been taking phenytoin or primidone. • Patients taking concomitant ASMs other than phenytoin or phenobarbital must not have been taking phenytoin, phenobarbital, or primidone • Patients with clinical evidence of phenytoin or phenobarbital toxicity. • History of non-epileptic or psychogenic seizures
Location	The study is being conducted at 137 study centres in 17 countries
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Patients are supplied with cenobamate 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily. Study drug can be taken with or without food. Treatment with cenobamate was initiated for 2 weeks at 12.5 mg/day and then for 2 weeks at 25 mg/day. Patients were then titrated upward at a rate of 50 mg/day every other week to a target dose of 200 mg/day. After reaching the target dose of 200 mg/day, patients are allowed to titrate up at 50 mg/day every other week to a maximum dose of 400 mg/day of cenobamate. If the investigator feels that a patient requires a dose lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day is reached. The downward dose adjustments may occur weekly by 100 mg/day or 50 mg/day. However, the downward rate of change may be more rapid or slow as clinically indicated. **Prior and Concomitant Therapy** Patients must have been on their current stable daily dosage of phenytoin or phenobarbital or any other concomitant ASMs for at least 3 weeks before Visit 2.

Permitted and disallowed concomitant medication	They must have continued taking the same brand of phenytoin or phenobarbital throughout the titration phase. Those patients taking phenytoin every 24 hours were instructed to take the dose at approximately 8:00 a.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase. On the day of Visit 2, patients were to delay the morning dose until the trough phenytoin plasma sample was obtained. Patients who were taking phenytoin every 24 hours at bedtime needed to switch to morning dosing at least 7 days before Visit 2. Patients who were taking phenytoin every 12 hours were instructed to take their doses at approximately 8:00 a.m. and 8:00 p.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase. Those patients taking phenobarbital every 24 hours were instructed to take the dose at approximately 8:00 a.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase. On the day of Visit 2, patients were to delay the morning dose until the trough phenobarbital plasma sample was obtained. Patients who were taking phenobarbital every 24 hours at bedtime did not need to switch to morning dosing. Patients who were taking phenobarbital every 12 hours were instructed to take their doses at approximately 8:00 a.m. and 8:00 p.m. beginning at least 7 days before Visit 2 and continue this regimen throughout the titration phase.
Primary outcomes (including scoring methods and timings of assessments)	Safety: Safety is assessed by the frequency and severity of adverse events, as well as by clinical laboratory test values, 12-lead EEG recordings, vital sign measurements, physical and neurological examinations, and the Columbia Suicide Severity Rating Scale. Additionally, safety is also assessed by the occurrence of DRESS. Pharmacokinetic Assessments: Plasma samples for cenobamate, phenytoin, phenobarbital and other concomitant ASMs were obtained periodically using sparse sampling during the first 9 visits of the study.
Other outcomes used in the economic model/specified in the scope	Time on treatment
Pre-planned subgroups	No pre-planned subgroups

Abbreviations: ASM, anti-seizure medication; EEG, electroencephalogram; DBS, deep brain stimulation; DRESS, Drug-induced hypersensitivity syndrome; VNS, vagus nerve stimulation

B.2.3.2. Baseline characteristics

C017 study

Patient demographics and baseline characteristics for the safety population are presented in Table 10. Overall, there were 221 males (50.6%) and 216 females (49.4%). The majority of patients were white (85.1%) and not Hispanic or Latino (91.5%). Overall, the mean age was 40 years of age with a range of 19 to 70 years of age. Age, height, weight, and BMI were similar across all treatment groups. Patients had, on average, been diagnosed with epilepsy at least 22 years ago and had trialled, on average, 3 different ASMs. During the screening

phase, patients experienced between 106-111 seizures per 28 days. The most common concomitant ASM was levetiracetam across all groups.

Table 10: Baseline characteristics of patients in the C017 study

Baseline characteristic	**Cenobamate 100 mg (N=108)**	**Cenobamate 200 mg (N=110)**	**Cenobamate 400 mg (N=111)**	**Placebo (N=108)**
Age, years, mean (SD)	39.0 (12.1)	40.9 (12.4)	39.6 (10.3)	39.6 (12.4)
Sex				
Male	57 (52.8)	54 (49.1)	52 (46.8)	58 (53.7)
Female	51 (47.2)	56 (50.9)	59 (53.2)	50 (46.3)
Race				
White	89 (82.4)	94 (85.5)	96 (86.5)	93 (86.1)
Black or African American	4 (3.7)	3(2.7)	1 (0.9)	4 (3.7)
Asian	10 (9.3)	11(10.0)	11 (9.9)	9 (8.3)
Other	5 (4.6)	2(1.8)	3(2.7)	2 (1.9)
Ethnic group				
Hispanic or Latino	8 (7.4)	7 (6.4)	13 (11.7)	9 (8.3)
Not Hispanic of Latino	100 (92.6)	103 (93.6)	98 (88.3)	99 (91.7)
BMI (kg/m2)	25.98 (5.42)	26.05 (5.36)	25.81 (4.87)	27.36 (7.90)
Time since diagnosis (years)	25.5 (13.4)	22.8 (13.2)	24.4 (14.2)	23.0 (14.2)
Seizure type by history*				
Focal aware non-motor	23 (21%)	20 (18%)	24 (22%)	24 (22%)
Focal aware motor	25 (23%)	25 (23%)	22 (20%)	22 (20%)
Focal impaired awareness	89 (82%)	84 (76%)	88 (79%)	84 (78%)
Focal to bilateral tonic-clonic	69 (64%)	61 (55%)	72 (65%)	60 (56%)
Baseline seizure frequency per 28 days †	108	109	111	106
Median (IQR)	9.5 (6.0-19.8)	11.0 (6.0-26.0)	9.0 (6.0-21.5)	8.4 (6.0–19.0)
Number of previous ASMs ‡	3 (2–4)	3 (2–4)	3 (2-4)	3 (2–4)
Number of concomitant ASMs §				

1	25 (23%)	39 (36%)	24 (22%)	27 (25%)
2	48 (44%)	47 (43%)	62 (56%)	54 (50%)
3	34 (31%)	24 (22%)	24 (22%)	27 (25%)
>3	1 (<1%)¶	0	1 (<1%)¶	0
Concomitant ASMs ‖				
Levetiracetam	47 (44%)	48 (44%)	50 (45%)	41 (38%)
Lamotrigine	44 (41%)	27 (25%)	50 (45%)	31 (28%)
Valproate or valproic acid	23 (21%)	28 (26%)	28 (25%)	31 (28%)
Carbamazepine	29 (27%)	29 (25%)	25 (23%)	39 (36%)
Oxcarbazepine	15 (14%)	17 (16%)	19 (17%)	13 (12%)
Clobazam	17 (16%)	12 (11%)	17 (15%)	5 (5%)

Data are mean (SD), n (%), or median (IQR), unless otherwise specified. *Patients might be reported in more than one category. †Calculated by the number of seizures over the baseline period divided by number of days in the interval multiplied by 28 (modified intention-to-treat population). ‡Antiepileptic drug medications taken any time before the start of the study; these might or might not have been ongoing during the study. §ASMs ongoing at the start of the study and continued during the study. ¶Patient received temporary treatment with a fourth ASM. ||ASM used in 10% or more of all patients.
Abbreviations: ASMs, antiseizure medications; IQR, interquartile range; SD, standard deviation.
Source: Krauss *et al.* 2020[2]

C017 OLE study

Patient demographics and baseline characteristics for the safety population are presented in Table 11. Overall, there were 185 (52.1%) males and 170 (47.9%) females. The majority of patients were white (86.2%) and ethnicity was classified as 'not Hispanic or Latino' in 92.1% of all patients. Overall, the mean age was 39.6 years of age. Patients were, on average, taking 2.3 ASMs each at baseline with 2% (7/355) of patients taking >3 ASMs.

Table 11: Baseline characteristics of patients in the C017 OLE study

Baseline characteristic	All Cenobamate (N=355)	Cenobamate DB to Cenobamate OLE (N=265)	Placebo DB to Cenobamate OLE (N=90)
Age, years, mean (SD)	39.5 (11.7)	39.6 (11.5)	39.6 (12.1)
Sex, n (%)			
Male	185 (52.1)	137 (51.7)	48 (53.3)
Female	170 (47.9)	128 (48.3)	42 (46.7)
Race, n (%)			
White	306 (86.2)	229 (86.4)	77 (85.6)
Black or African American	9 (2.5)	5 (1.9)	4 (4.4)
Asian	32 (9.0)	24 (9.1)	8 (8.9)
Other	8 (2.3)	7 (2.6)	1 (1.1)
Ethnic group, n (%)			
Hispanic or Latino	28 (7.9)	22 (8.3)	6 (6.7)

Not Hispanic of Latino	327 (92.1)	243 (91.7)	84 (93.3)
Mean BMI (kg/m^2)	26.43 (6.189)	26.11 (5.373)	27.39 (8.097)
Number of baseline ASMs per patient, mean (SD)	2.3 (0.75)	2.3 (0.76)	2.4 (0.74)
Number of baseline ASMs n (%)			
1	55 (15.5)	42 (15.8)	13 (14.4)
2	139 (39.2)	106 (40.0)	33 (36.7)
3	154 (43.4)	111 (41.9)	43 (47.8)
>3	7 (2.0)	6 (2.3)	1 (1.1)

Percentages are based on number of patients for each parameter (n). Date of data cut-off for analysis=01JUL2019. Baseline ASMs are ASMs started prior to and are ongoing at the time of the first dose in DB.
Abbreviations: ASMs, antiseizure medication; BMI, body mass index; SD, standard deviation.

C021 study

Patient demographics and baseline characteristics for the safety population of the ongoing C021 study are presented in Table 12. The mean age at baseline was 39.7 years, and 49.7% of patients were female and 50.3% of patients were male. At baseline, the majority of patients were white (79.4), while 3.5% were black or African American, 5.5% were Asian, 4.4% were American Indian or Alaska Native, and 7.2% were other. Patients had been diagnosed with epilepsy for an average of 22.9 years at baseline and were taking 2.3 ASMs – 82% of patients were receiving 2 or more ASMs at baseline.

Table 12: Baseline characteristics of patients in the C021 study

Baseline characteristic	**Cenobamate patients, N = 1,339**
Mean age, year (SD)	39.7 (12.8)
Female, n (%)	666 (49.7)
Race, n (%)	
White	1,063 (79.4)
Black or African American	47 (3.5)
Asian	73 (5.5)
American Indian or Alaska Native	59 (4.4)
Other	97 (7.2)
Mean BMI, kg/m^2 (SD)	26.93 (5.984)
Mean time since epilepsy diagnosis, y (SD)[a]	22.9 (14.35)
Current seizure type, n (%)[b]	
Focal aware non-motor	271 (20.2)
Focal aware motor/observable component	324 (24.2)
Focal impaired awareness	1036 (77.4)
Focal to bilateral tonic-clonic	786 (58.7)
Number of baseline ASMs, n (%)[c]	
0	3 (0.2)

1	238 (17.8)
2	510 (38.1)
3[d]	588 (43.9)
Concomitant ASMs in ≥10% of patients, n (%)[e]	
Levetiracetam	523 (39.1)
Lamotrigine	446 (33.3)
Valproic acid, all forms	412 (30.8)
Carbamazepine	369 (27.6)
Lacosamide	324 (24.2)
Clobazam	179 (13.4)
Topiramate	175 (13.1)
Oxcarbazepine	174 (13.0)

[a]n = 1336. [b]Patients could have >1 seizure type. [c]Baseline ASMs were defined as ASMs that started prior to and were ongoing at the time of first dose of cenobamate. [d]One patient taking four concomitant ASMs was enrolled into the study. [e]Concomitant ASMs were defined as ASMs that started prior to and were ongoing at the time of first dose of cenobamate or started after the first dose of cenobamate. Abbreviations: ASM, antiseizure medication; BMI, body mass index; SD, standard deviation.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the numbers of statistical analyses for each study are provided in Appendix D.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for each trial is provided in Appendix D.

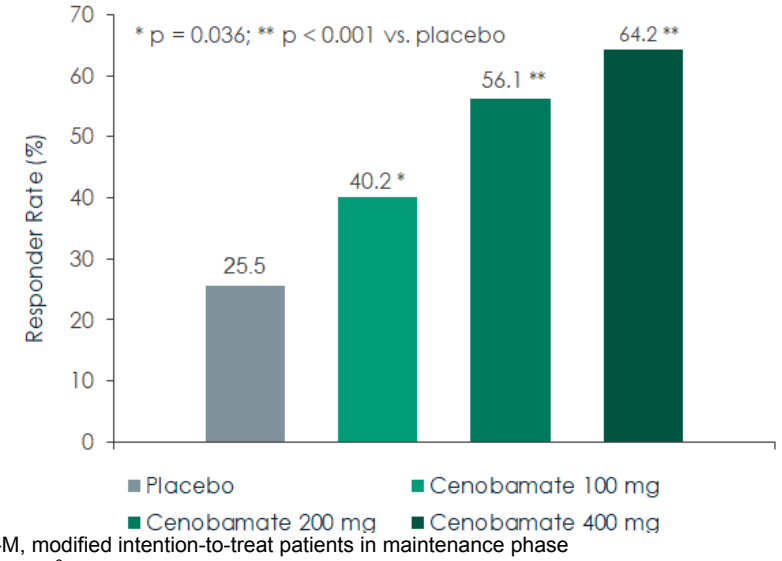
B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Study C017

Primary Efficacy Endpoint

The responder rate (proportion of patients achieving ≥50% reduction in seizure frequency from baseline) during the 12-week maintenance phase for the MITT-M population is summarised in Figure 6. Compared with placebo, there was a statistically significant difference in ≥50% responder rate for each of the cenobamate treatment groups during the maintenance phase. In the placebo group 25.5% (26 of 102 patients) of patients had ≥50% reduction in seizure frequency compared with 40.2% (41 of 102; p=0.0365) for the cenobamate 100 mg group, 56.1% (55 of 98; p<0.0001) for the cenobamate 200 mg group, and 64.2% (61 of 95; p<0.0001) for the cenobamate 400 mg.[2]

Figure 6: Primary Efficacy Endpoint: ≥50% responder rate in patients who received cenobamate (100mg, 200mg and 400mg) vs placebo in C017 (MITT-M Population)

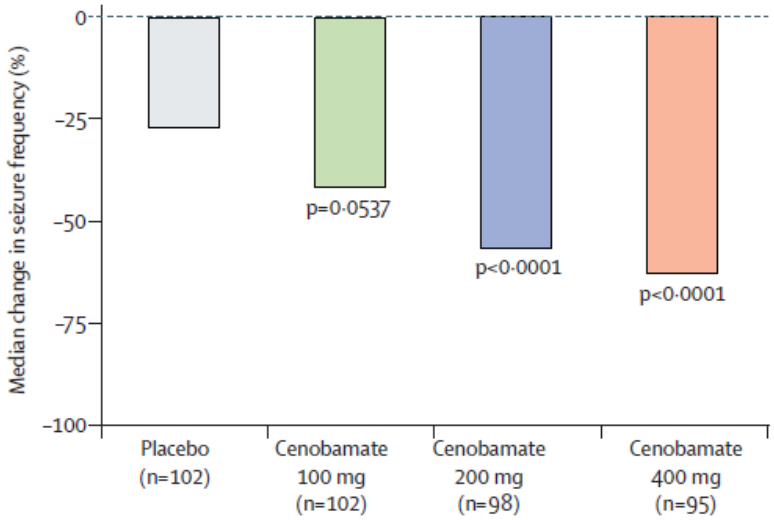


Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Krauss *et al*. 2020[2]

Secondary Efficacy Endpoints

The percentage change in seizure frequency during the maintenance phase for each of the study arms is shown in Figure 7. The median percentage change increased with dose of cenobamate, with reductions in seizure frequency of 27.0%, 41.5%, 56.5% and 63.0% in the placebo, cenobamate 100 mg, cenobamate 200 mg and cenobamate 400 mg, respectively. Compared with placebo, there were statistically significant reductions for both the 200 mg/day and 400 mg/day treatment groups (p<0.001 and p<0.001, respectively).

Figure 7:Median percent change in seizure frequency during the maintenance phase (MITT-M population)

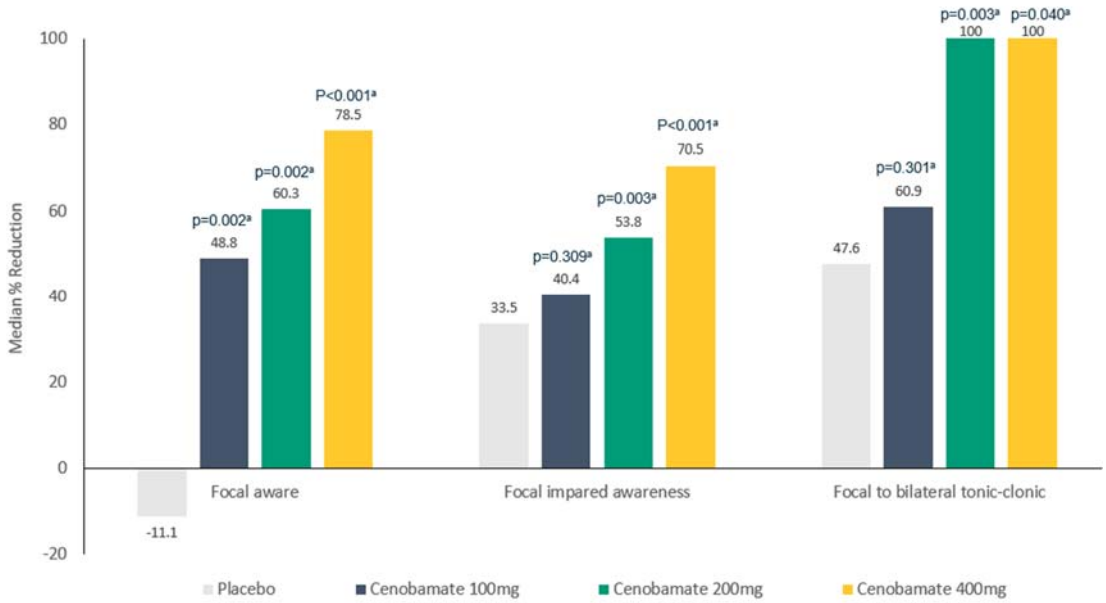


Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Krauss *et al*. 2020[2]

The percentage change in seizure frequency during the maintenance phase by seizure type (focal aware, focal impaired awareness and focal to bilateral tonic-clonic) in the MITT-M population is summarised in Figure 8. Across all seizure types, reduction in seizures

increased with dose of cenobamate. The reductions in focal to bilateral tonic-clonic seizures were larger than the reductions in focal aware seizures, which were also larger than focal impaired awareness seizures. In both the 200 mg/day and 400 mg/day treatment groups, patients achieved a 100% median reduction in seizure.

Figure 8: Reduction in seizure frequency by seizure type during maintenance in the C017 study (MITT-M)



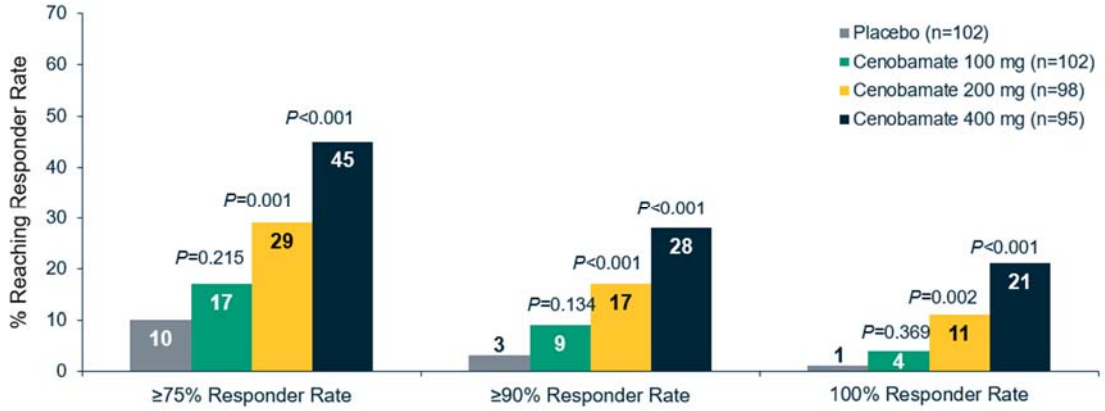
P-value vs placebo. [a]*P*-value based on Wilcoxon rank-sum test. [b]*P*-value is based on an ANCOVA model fit to the ranked values of percent change in seizure frequency from baseline period with terms for ranked baseline seizure rate and randomised treatment group.
Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase.
Source: Steinhoff *et al.* 2020[111]

Additional secondary prespecified endpoints

Additional responder rates – maintenance phase

The additional response rates (≥ 75%, ≥ 90%, = 100% [seizure free] reduction in seizure frequency) during the maintenance phase in the MITT population are summarised in Figure 9. At each of the additional responder thresholds, the proportion of patients achieving response increased with the dose of cenobamate. Compared with placebo, there were statistically significant differences in the number of patients with responder rates of ≥ 75%, ≥ 90%, and 100% in the 200 mg/day and 400 mg/day treatment groups during the 12-week maintenance phase in the MITT-M population. In the cenobamate 200 mg/day and 400 mg/day groups 11% of patients (n=11; p=0.0022) and 21% (n=20; p<0.001) , respectively, were seizure free compared to 1% of patients in the placebo group. The difference in responder rate at the seizure-free level between the 100 mg/day treatment group and placebo group did not reach statistical significance during the maintenance phase.

Figure 9: ≥75%, ≥90% and 100% Responder Rates maintenance phase (MITT-M) for C017 study

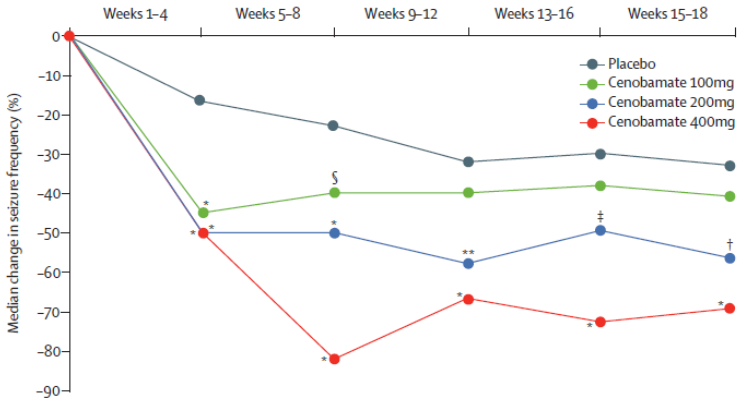


Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Steinhoff *et al.* 2020[111]

Post-hoc analysis

Post-hoc analyses were performed of the median percentage reduction in seizure frequency and the seizure free rate over time. Figure 10 demonstrates the median percentage reduction in seizure frequency over time. During the first 4 weeks of the double-blind treatment, the median seizure frequency reduction was 17.0% (IQR 8.0–47.0%) in the placebo group versus 45% (11.5–67.0%) for the cenobamate 100 mg group and 50.0% for both the 200 mg (IQR 17.0–75.0%) and 400 mg (15.0–78.0%) groups.[2] Sustained decreases in median seizure frequency were noted at each additional 4-week interval in the 200 mg and 400 mg cenobamate dose groups.

Figure 10: Post-hoc analyses of the median percentage reduction in seizure frequency over time for the C017



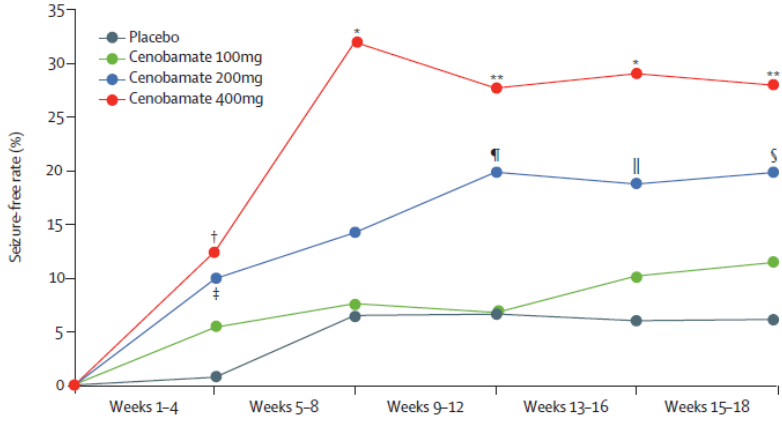
	Weeks 1–4	Weeks 5–8	Weeks 9–12	Weeks 13–16	Weeks 15–18
Placebo	106	104	101	97	95
Cenobamate 100 mg	108	103	101	97	96
Cenobamate 200 mg	109	104	95	90	90
Cenobamate 400 mg	111	103	90	86	82

Population = modified intention-to-treat patients in maintenance phase. Weeks 15-18 overlap in order to make the interval 4 weeks in duration. *p<0.0001, **p=0.0001,†p=0.0004, ‡p=0.0011, §p=0.0461, all vs placebo.
Source: Krauss *et al.* 2020[2]

Figure 11 shows high rates of seizure freedom in the 200 mg and 400 mg cenobamate dose groups within each 4-week interval starting at weeks 5–8. High rates of seizure freedom occurred within the 200 mg and 400 mg cenobamate dose groups from week 5 onwards.

Compared to placebo, the proportion of patients with seizure freedom in the 200 mg and 400 mg cenobamate arms was significant at the 5% level.

Figure 11: Post-hoc analyses of the proportion of patients seizure free over time for the C017



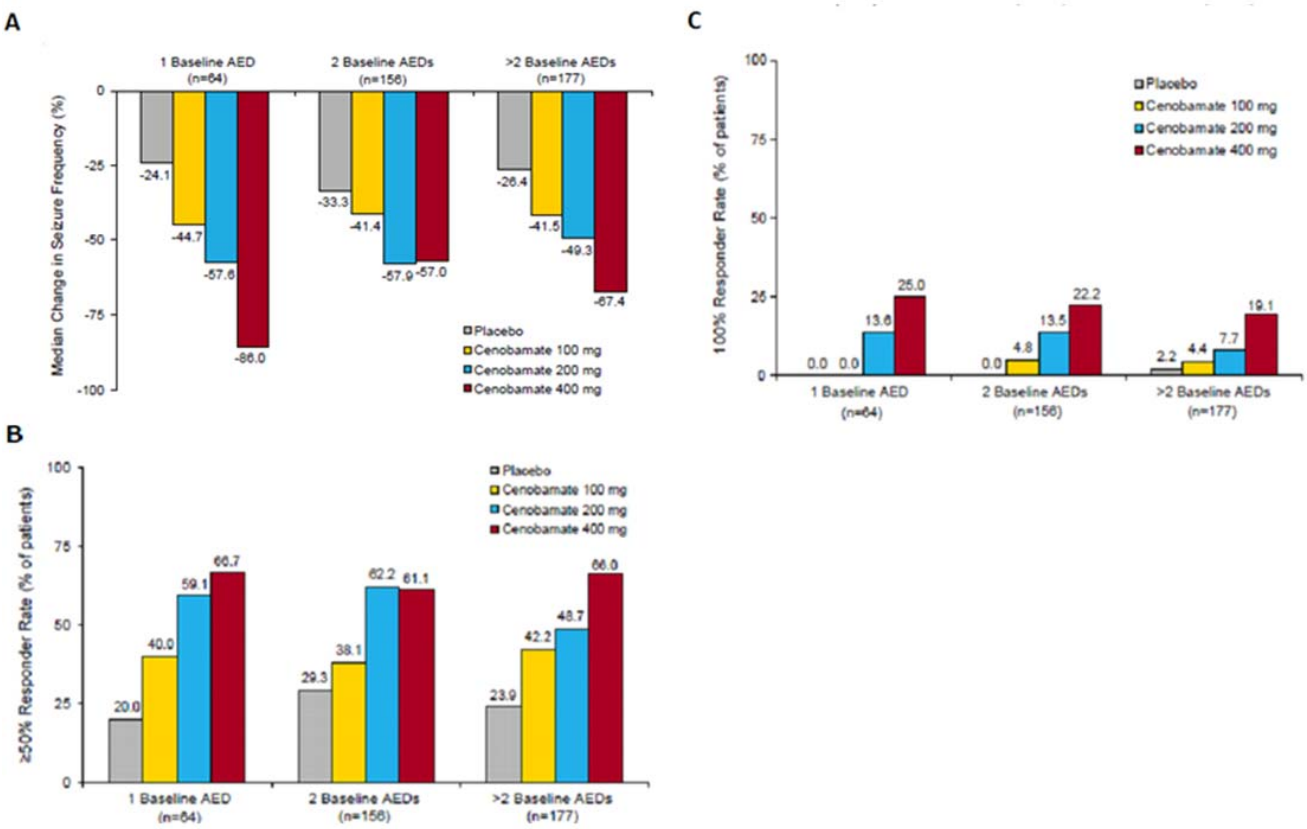
	Weeks 1–4	Weeks 5–8	Weeks 9–12	Weeks 13–16	Weeks 15–18
Placebo	106	104	101	97	95
Cenobamate 100 mg	108	103	101	97	96
Cenobamate 200 mg	109	104	95	90	90
Cenobamate 400 mg	111	103	90	86	82

Population = modified intention-to-treat patients in maintenance phase. *p<0.0001, **p=0.0002, †p=0.0007, ‡p=0.0051,§p=0.0078, ¶p=0.0105, ||p=0.0129, all vs placebo. All datapoints without a symbol were not significant.
Source: Krauss *et al*. 2020[2]

Post-hoc analyses were also performed to identify the efficacy of cenobamate according to disease characteristics of patients at baseline.

Figure 12 shows a post-hoc analysis demonstrating the efficacy of cenobamate according to the number of concomitant ASMs in the MITT-M population. Figure 12A, B and C demonstrates the median percent change in seizure frequency, the proportion of patients achieving a ≥50% response and the proportion of patients who achieved seizure freedom, respectively. Across all outcomes, there is a moderate dose-response relationship. In all outcomes, the greatest efficacy was observed in the cenobamate 200 mg/day and 400 mg/day arms, followed by cenobamate 100 mg/day and placebo. The levels of response to treatment attained across different numbers of concomitant medication were similar, with 66.7%, 61.1% and 66% of patients treated with cenobamate 400 mg/day taking 1, 2 and more than 2 concomitant medications, respectively, achieving ≥50% response to treatment.. Similarly, for seizure freedom, 25.0%, 22.2% and 19.1% of patients treated with cenobamate 400 mg/day taking 1, 2 and more than 2 concomitant medications, respectively, achieved seizure-freedom. The seizure-freedom outcome also demonstrated a clear dose-response relationship in seizure-freedom, with the proportions of patients achieving seizure freedom increasing with dose regardless of the number of concomitant ASMs they were receiving.

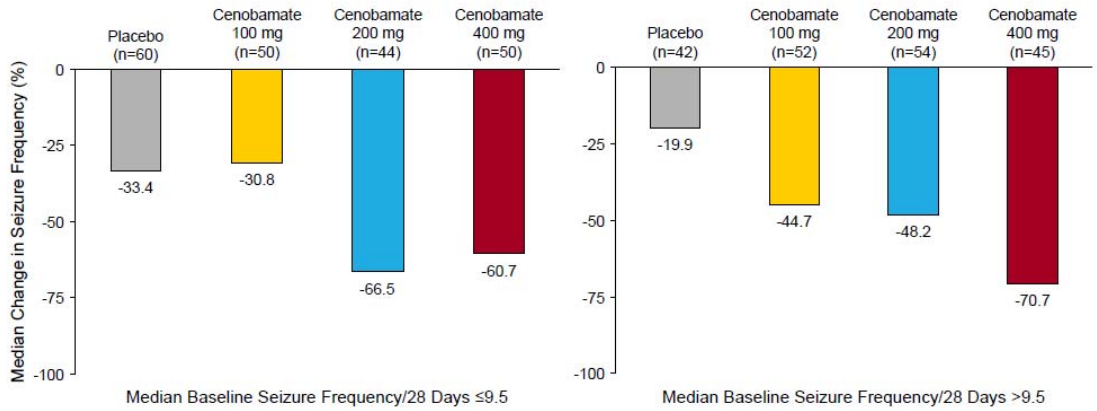
Figure 12: Efficacy by number of ASMs at baseline in the MITT-M population of the C017 study



A) Percent reduction in seizure frequency. (B) Percent of patients with ≥ 50% reduction in seizure frequency (C) Percent of patients with ≥ 100% reduction in seizure frequency
Abbreviations: ASMs, antiseizure medications; MITT-M, modified intention-to-treat patients in maintenance phase
Source: Rosenfeld *et al*. 2020[114]

Additional analyses presented in Figure 13 show the mean percent reduction in seizure frequency of patients experiencing a median of ≤9.5 seizures at baseline or >9.5 seizures at baseline. A moderate dose-response relationship was also observed, with the greatest reduction in seizure freedom experience by patients treated with cenobamate 200 mg/day and 400 mg/day, regardless of number of seizures per 28 days at baseline.

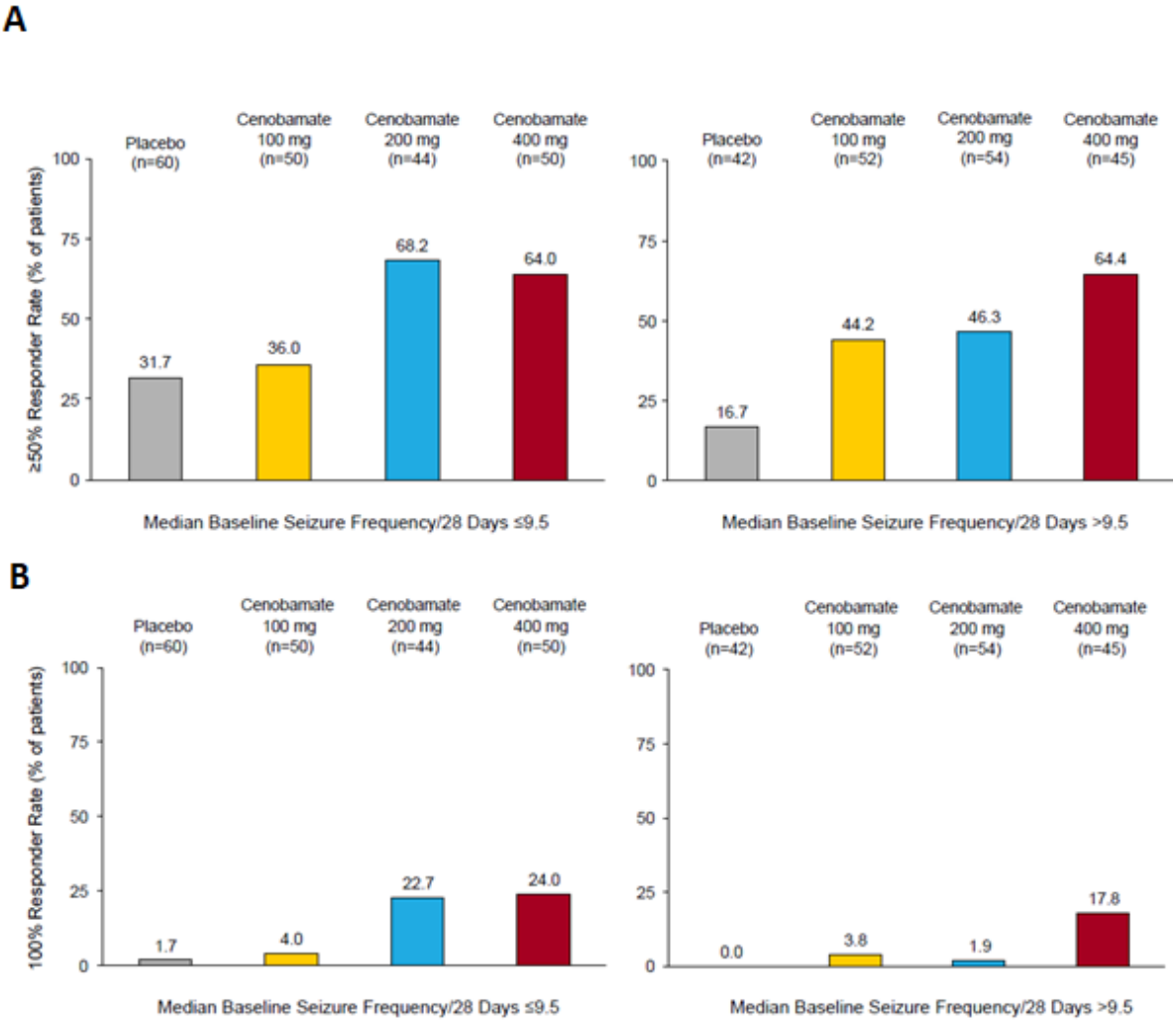
Figure 13: Efficacy by baseline seizure frequency (MITT-M): median percent reduction in seizure frequency



Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Rosenfeld *et al*. 2020[114]

The proportion of patients achieving ≥50%, ≥75%, ≥90% and 100% response to treatment according to frequency of seizures at baseline are presented in Figure 14. Similarly to the median reduction in seizures, the greatest proportion of patients achieving a ≥50%, ≥75%, ≥90% and 100% response to treatment were in the cenobamate 200 mg/day and 400/mg day groups. The likelihood of achieving a ≥50% response to treatment is similar according to frequency of seizures at baseline, with this level of response attained by 64.0% and 64.4% of patients with ≤9.5 and >9.5 seizures per 28 days, respectively, treated with cenobamate 400 mg/day.

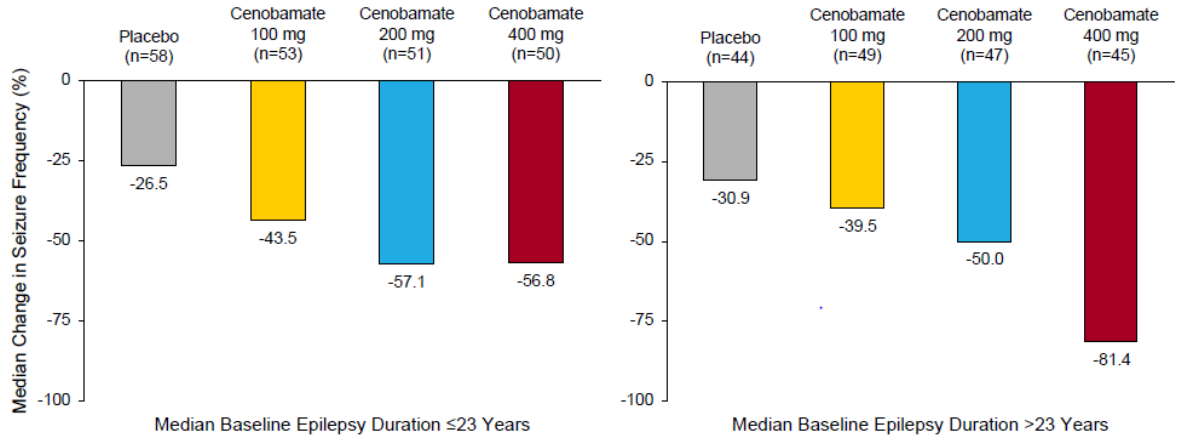
Figure 14: Efficacy by baseline seizure frequency (MITT-M): (A) ≥ 50% and (B) 100% responder rates



Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Rosenfeld *et al*. 2020[114]

Figure 15 presented the median percent reduction in seizure frequency amongst patients with a median baseline epilepsy duration of ≤23 years or >23 years. Similar reductions in seizure frequency were observed regardless of baseline epilepsy duration, though patients with a longer epilepsy treatment duration who were treated with cenobamate 400 mg/day saw the greatest reduction of 81.4%.

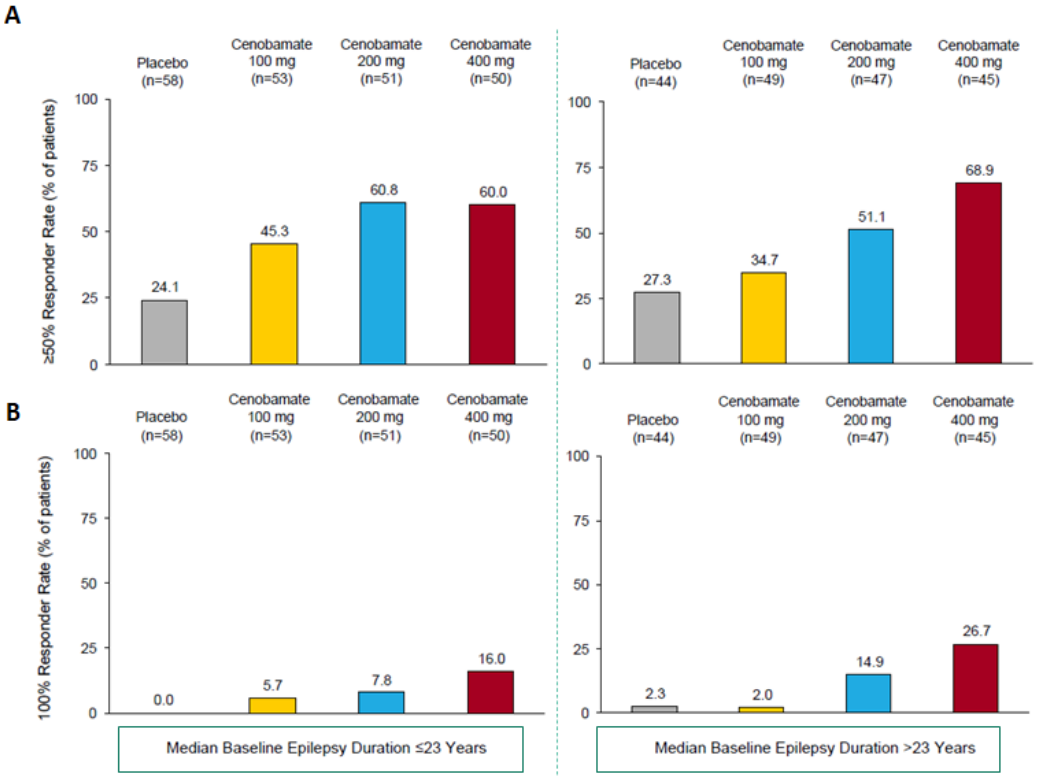
Figure 15: Efficacy by baseline disease duration (MITT-M): Percent reduction in seizure frequency



Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Rosenfeld *et al*. 2020[114]

Figure 16A proportion of patients achieving ≥50% and 100% response to treatment according to baseline epilepsy duration. There is a strong dose-response relationship at each level of response to treatment which is similar regardless of duration of epilepsy.

Figure 16: Efficacy by baseline disease duration (MITT-M): (A) ≥ 50% and (B) 100% responder rates

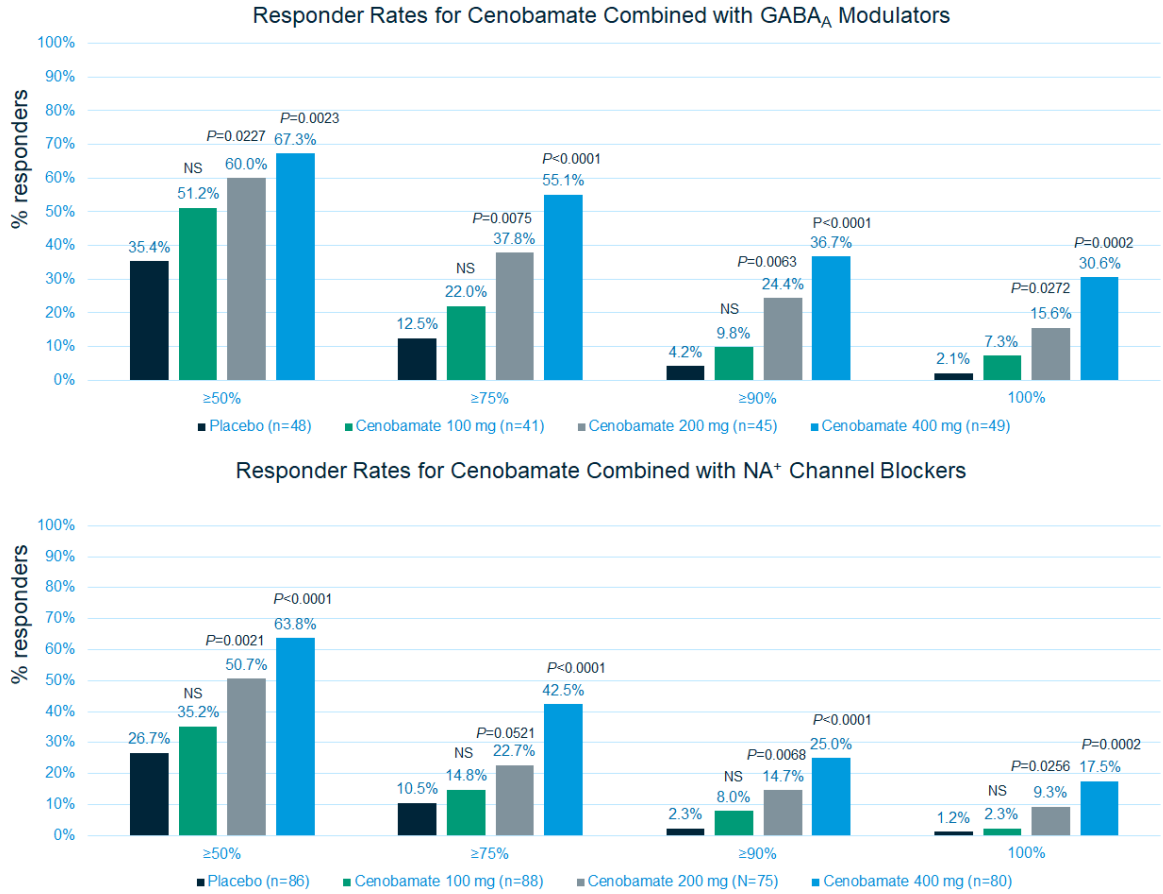


Abbreviations: MITT-M, modified intention-to-treat patients in maintenance phase
Source: Rosenfeld *et al*. 2020[114]

Additional post-hoc analyses showing the ≥50%, ≥75%, ≥90%, and 100% reduction in seizure frequency was performed when patients take cenobamate concomitantly with $GABA_A$ modulators or NA+ channel blockers. Figure 17 shows that patients treated with

cenobamate 200mg/day and 400mg/day achieved were statistically significantly more likely than placebo-treated patients to achieve ≥50%, ≥75%, ≥90%, and 100% reduction in seizure frequency. For both $GABA_A$ modulators and NA+ channel blockers, there is a consistent dose-response relationship and similar proportions patients achieved a ≥50% reduction in seizures when treated with cenobamate 400 mg/day (67.3% and 63.8%, respectively).

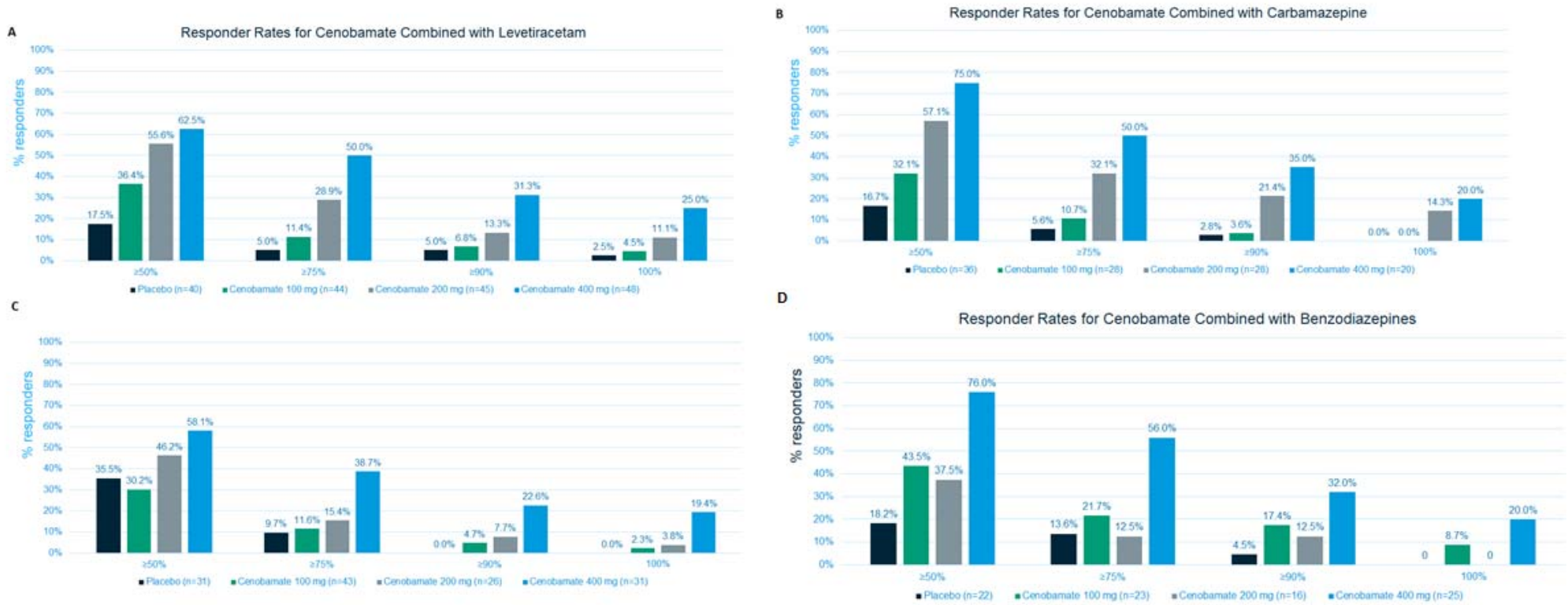
Figure 17: Efficacy with concomitant ASMs classified by MoA (A) GABAA modulators or (B) NA+ channel blockers.



Responder rates for cenobamate combined with (A) $GABA_A$ modulators, (B) NA+ channel blockers and (C) benzodiazepines
Abbreviations: ASMs, antiseizure medications; *P*-values vs placebo; MoA, mechanism of action; NS,not significant
Source: Data on file

Figure 18 presents the ≥50%, ≥75%, ≥90%, and 100% reduction in seizure frequency was performed when patients take cenobamate concomitantly with either levetiracetam, carbamazepine, lamotrigine and benzodiazepines. For carbamazepine and levetiracetam, the proportions of patients with response increase strictly with dose. For patients who received benzodiazepines or lamotrigine concomitantly, there is a pattern of increasing proportions of patients achieving response by dose, though it is not strict. All four graphs show the highest % responder rates at each threshold were seen in the 400mg/day arms; in patients treated concomitantly with levetiracetam or carbamazepine, 62.5% and 75.0% of patients achieved a ≥50% reduction in seizures, respectively.

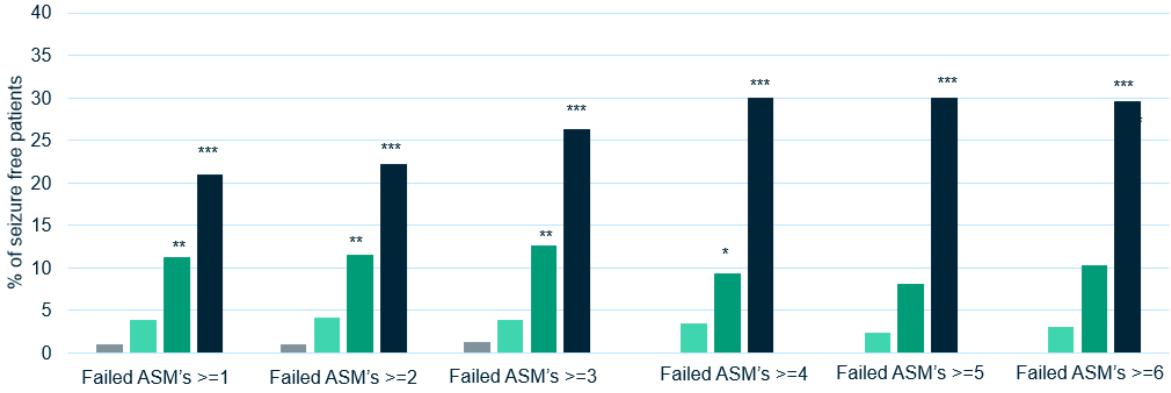
Figure 18: Responder rates according to concomitant background therapy (A) levetiracetam, (B) carbamazepine, (C) lamotrigine and (D) benzodiazepines



Source: Data on file

Figure 19 shows the number of seizure free patients by total number of drugs failed where failed ASMs are defined as the sum of ASMs received previously and baseline ASMs. At all number of failed ASMs, patients treated with 400mg/day were statistically significantly more likely than placebo-treated patients to achieve seizure freedom ($p<0.001$); amongst patients who had failed ≥5 ASMs, 30% achieved seizure freedom with cenobamate 400 mg/day. Patients treated with 200mg/day were statistically significantly more likely than placebo-treated patients to achieve seizure freedom after failing at least 1 ($p<0.01$) to 4 ASMs ($p<0.05$). At populations of this size, patients who have failed more than five ASMs require a dose of 400mg to achieve seizure freedom.

Figure 19: Percentage of seizure free patients by total number of drugs failed



Placebo	102	97	80	52	45	39
CNB 100 mg	102	95	78	57	46	31
CNB 200 mg	98	87	73	46	39	29
CNB 400 mg	95	90	74	45	33	37

* p < 0.05; ** p < 0.01; * p < 0.001

Placebo Cen 100 mg Cen 200 mg Cen 400 mg

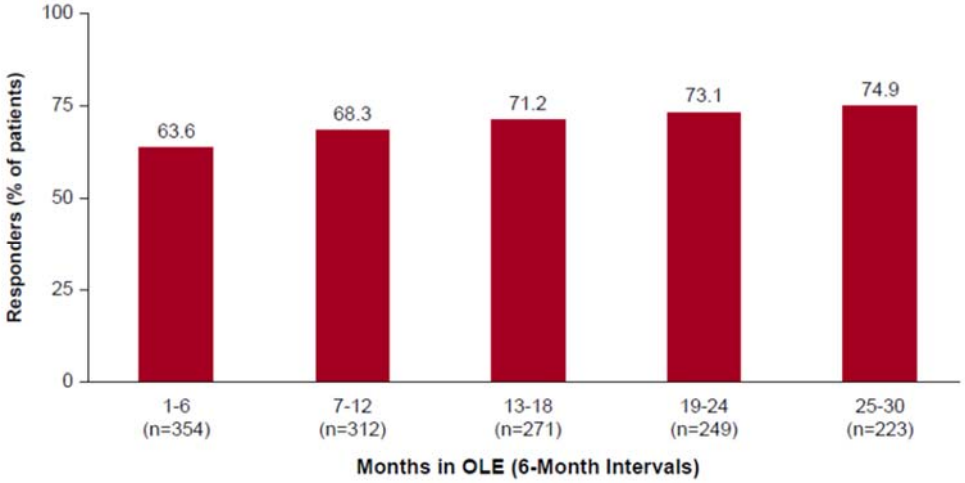
Abbreviations: ASMs, antiseizure medicines
Source: Data on file

B.2.6.2. Study C017 OLE

Responder rates

From the July 2019 data cut of the ongoing OLE, results in Figure 20 show that ≥50% responder rates (percentage of patients with ≥50% seizure reduction compared to baseline) increased with each 6-month interval during the OLE. The ≥50% responder rate during the first 6 months of the OLE for all cenobamate OLE patients was 63.6% and was similar among patients originally treated with cenobamate or placebo in the double-blinded study. At months 25-30, responder rate for all cenobamate OLE patients increased to 74.9%.[126]

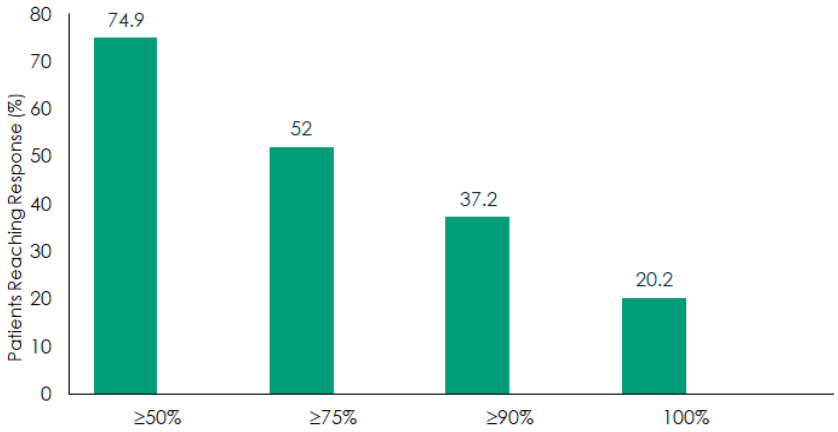
Figure 20: ≥50% Responder rate by 6-month intervals during C017 OLE



Abbreviations: OLE, open label extension
Source: Klein *et al*. 2020[126]

When analysed at months 25-30 (over a 6-month interval), seizure frequency reductions of ≥ 50%, ≥ 75% and ≥ 90%, were achieved in 74.9%, 52.0%, and 37.2%, of patients, respectively as shown in Figure 21.[126] At months 25-30, 20.2% (45/223) of evaluable patients were seizure-free. Among the 45 patients who were seizure-free (100% seizure reduction) at months 25-30, the median duration of seizure freedom achieved during the entire OLE was 33.2 months (range, 13.2-50.4 months).

Figure 21: ≥ 50%, ≥ 75%, ≥ 90%, and 100% reduction in seizure frequency at months 25-30 (6-month intervals) in C017 OLE



Abbreviations : OLE, open-label extension
Source: Klein *et al*. 2020[126]

The additional responder rates over each year of the OLE are presented in Figure 22. During the first year of the OLE, seizure frequency reductions of ≥50%, ≥75%, ≥90%, and 100% were achieved in 64.4%, 41.0%, 20.3%, and 4.8% of patients, respectively. Between years 4-5, seizure frequency reductions of ≥50%, ≥75%, ≥90%, and 100% were achieved in 81.1%, 54.9%, 42.2%, and 24.8% of patients, respectively.

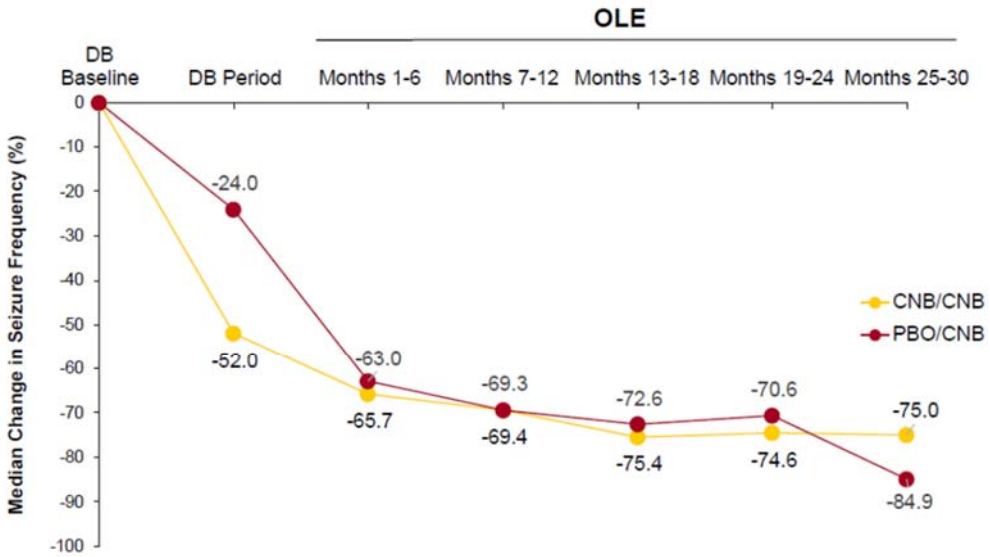
Figure 22: >=50%, >=75%, >=90%, and 100% Responder Rates During C017 OLE

Abbreviations : OLE, open-label extension
Source: Data on file.

Reduction in seizure frequency compared to baseline

Figure 23 shows the reduction in seizure frequency according to whether patients received cenobamate or placebo in the double-blind period. Once in the OLE, patients had similar reductions in seizure frequency regardless of treatment received during the double-blind period. During months 1-6, patients treated with cenobamate and placebo during the double-blind period experienced a median reduction in seizure frequency of 65.7% and 63% compared to baseline, respectively. By months 25-30, patients originally treated with cenobamate and placebo experienced reductions of 75.0% and 84.9% compared to baseline, respectively.

Figure 23: Median percent change in seizure frequency according to treatment received in the double-blind period



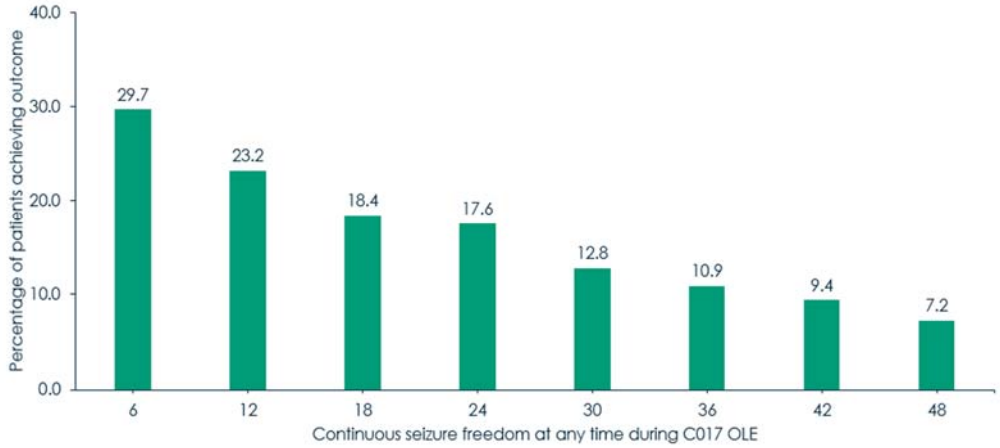
Group, n	DB Phase	Months 1-6	Months 7-12	Months 13-18	Months 19-24	Months 25-30
CNB/CNB	328	264	232	201	185	163
PBO/CNB	106	90	80	70	64	60

Abbreviations: CNB, cenobamate; DB, double-blind; OLE, open-label extension; PBO, placebo.
Source: Klein *et al*. 2020[126]

Seizure freedom

Figure 24 shows the long-term efficacy of cenobamate in terms of seizure freedom at any time point in the C017 OLE. According to this graph, 23.2% of patients were at least 12-months seizure free at any time point in the OLE. Similarly, 18.4% and 17.6% of patients were at least 18- and 24-months seizure free during at time point in the OLE, respectively.

Figure 24: Long-term efficacy of cenobamate in terms of seizure freedom at any point in the C017 OLE



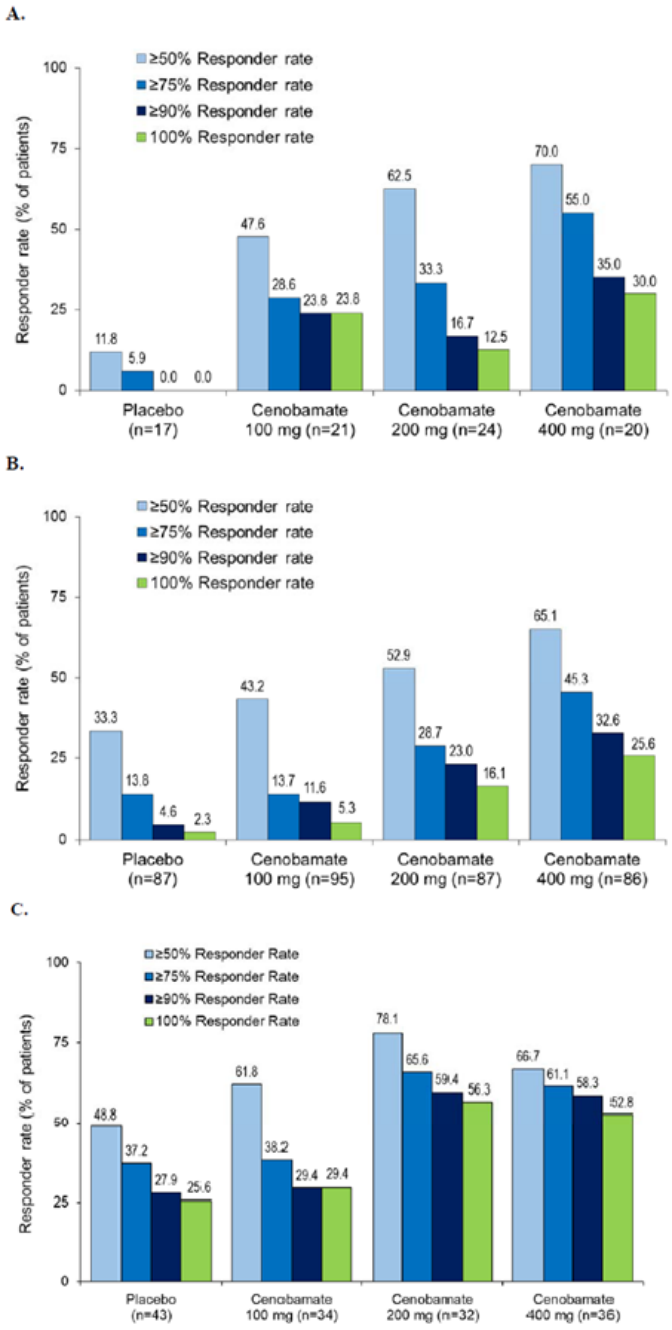
Abbreviations : OLE, open-label extension
Source: Data on file.

B.2.7. Subgroup analysis

B.2.7.1. Study C017

Post-hoc subgroup analyses were performed to identify the ≥50%, ≥75%, ≥90% and 100% responder rate according to type of seizure and the overall reduction in seizures. Results as presented in Figure 25 . Results show evidence of a consistent positive benefit with cenobamate compared with placebo in each dose group for all seizure subtypes.

Figure 25: Post-hoc responder rate for focal seizure subtypes (A) Focal aware motor. (B) Focal impaired awareness. (C) Focal to bilateral tonic-clonic



Source: Krauss *et al*. 2020[2]

Further post-hoc subgroup analyses were performed to identify the relative reduction in seizure frequency by seizure type and by responder category. The analysis is presented in Table 13.

Table 13: Relative reduction in seizure frequency by seizure type and overall responder rate

Treatment	Seizure type	Overall responder rate			
		<50%	50%-<75%	75%-<90%	90%-<100%

Cenobamate 100 mg	All focal aware seizures	11%	61%	84%	96%
	Focal aware	-8%	70%	75%	98%
	Focal impaired awareness	18%	60%	85%	90%
	Focal to bilateral tonic-clonic	-7%	68%	89%	N/A
Cenobamate 200 mg	All focal aware seizures	20%	55%	84%	93%
	Focal aware	-6%	61%	75%	N/A
	Focal impaired awareness	10%	57%	85%	94%
	Focal to bilateral tonic-clonic	18%	70%	78%	95%
Cenobamate 400 mg	All focal aware seizures	13%	57%	80%	92%
	Focal aware	6%	50%	88%	96%
	Focal impaired awareness	8%	55%	84%	96%
	Focal to bilateral tonic-clonic	-3%	67%	85%	91%

Abbreviations: N/A, not applicable.

B.2.8. Meta-analysis

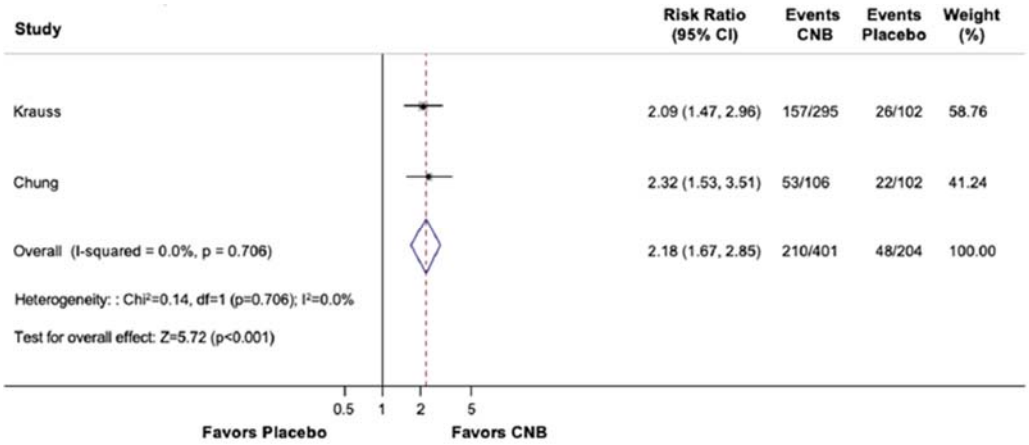
Lattanzi *et al*. 2020 reported a meta-analysis of the two cenobamate studies, C013 and C017.[110] Despite differences in the studies, namely the duration of the maintenance period, the methodology and results from the meta-analysis are presented here.

The χ^2 test was performed and the I^2 statistic were generated to assess heterogeneity. Where there was no heterogeneity present (p>0.10), meta-analysis was performed using a fixed-effect model. In the presence of heterogeneity (p≤0.10), a fixed- or random-effects model was chosen for I^2 <40% and ≥40%, respectively. The MITT-m data was used in the meta-analysis of efficacy. Results were presented according to the randomised cenobamate daily dose during the maintenance period – i.e. all randomised dosed combined on 200 mg/day only. Data analysis was performed using STATA/IC 13.1.

The results of the meta-analysis of the ≥50% responder rate in any dose of cenobamate is presented in Figure 26. This analysis considers 100 mg/day, 200 mg/day and 400 mg/day of cenobamate compared to placebo. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped. Results showed no significant heterogeneity amongst the two studies (p=0.76), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving a ≥50% response is 2.18 times more likely than compared to placebo.

This was statistically significant, as the CI demonstrated that, with 95% certainty, the risk ratio lies between 1.67 and 2.85.

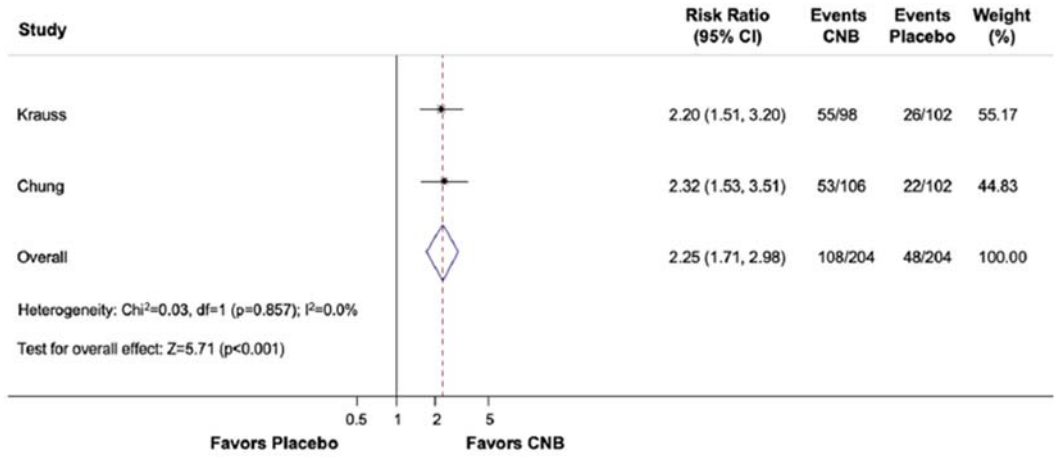
Figure 26: Meta-analysis of ≥50% responder rate in any dose of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the ≥50% responder rate in 200 mg/day of cenobamate compared to placebo are presented in Figure 27. The confidence intervals of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped. Results showed no significant heterogeneity amongst the two studies (p=0.857), so the analysis is presented using a fixed-effect model. The analysis found that, in 200 mg/day of cenobamate, the likelihood of achieving a ≥50% response is 2.25 times more likely than compared to placebo. This was statistically significant, as the confidence interval demonstrated that, with 95% certainty, the risk ratio lies between 1.71 and 2.98.

Figure 27: Meta-analysis of ≥50% responder rate in 200 mg/day of cenobamate

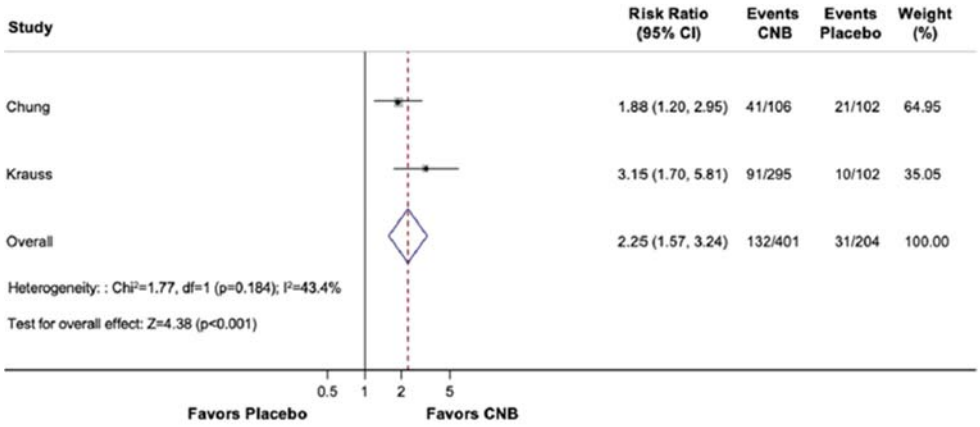


Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the ≥75% responder rate in any dose of cenobamate is presented in Figure 28. This analysis considers 100 mg/day, 200 mg/day and 400 mg/day of cenobamate compared to placebo. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped, though the mean estimate of the risk ratio from the C017 study did not fall inside the CI for the result from the C013 study. Results showed no significant heterogeneity amongst the two studies (p=0.184), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving a ≥75% response is 2.25 times more

likely than compared to placebo. This was statistically significant, as the confidence interval demonstrated that, with 95% certainty, the risk ratio lies between 1.57 and 3.24.

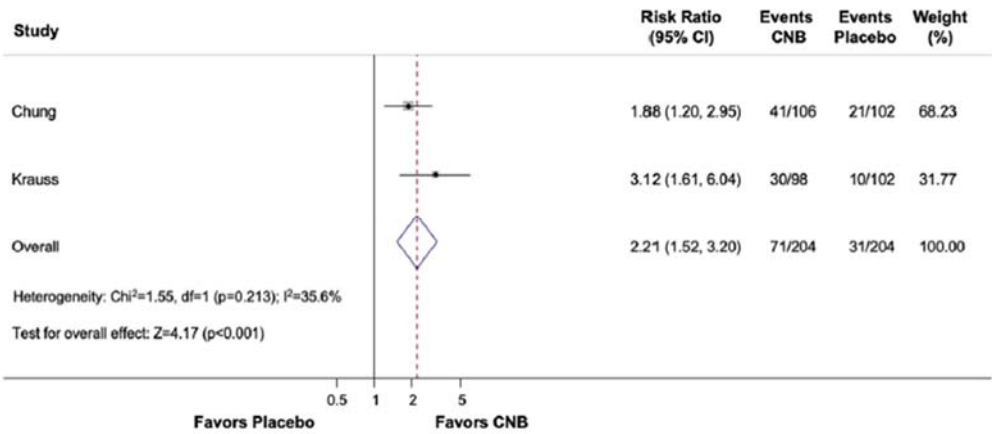
Figure 28: Meta-analysis of ≥75% responder rate in any dose of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the ≥75% responder rate in 200 mg/day of cenobamate compared to placebo is presented in Figure 29. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped. Results showed no significant heterogeneity amongst the two studies (p=0.213), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving a ≥75% response is 2.21 times more likely than compared to placebo. This was statistically significant, as the CI demonstrated that, with 95% certainty, the risk ratio lies between 1.52 and 3.20.

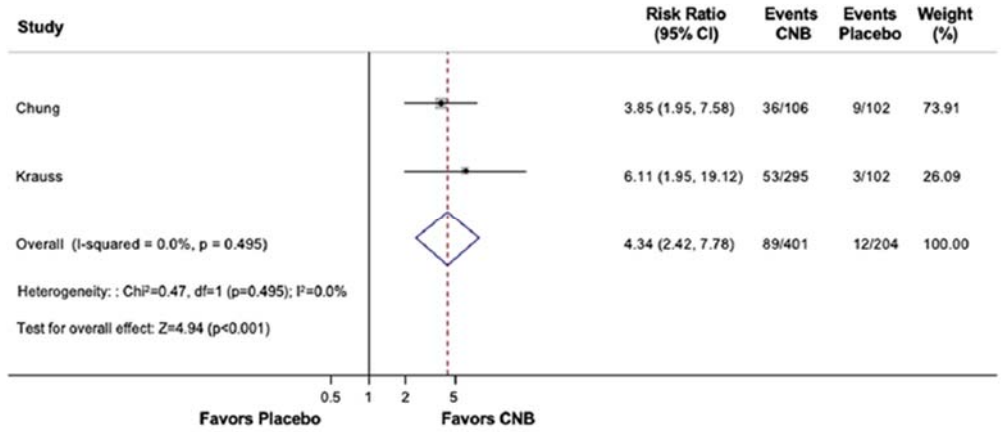
Figure 29: Meta-analysis of ≥75% responder rate in 200 mg/day of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the ≥90% responder rate in any dose of cenobamate is presented in Figure 30. This analysis considers 100 mg/day, 200 mg/day and 400 mg/day of cenobamate compared to placebo. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped. Results showed no significant heterogeneity amongst the two studies (p=0.495), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving a ≥90% response is 4.34 times more likely than compared to placebo. This was statistically significant, as the CI demonstrated that, with 95% certainty, the risk ratio lies between 2.42 and 7.78.

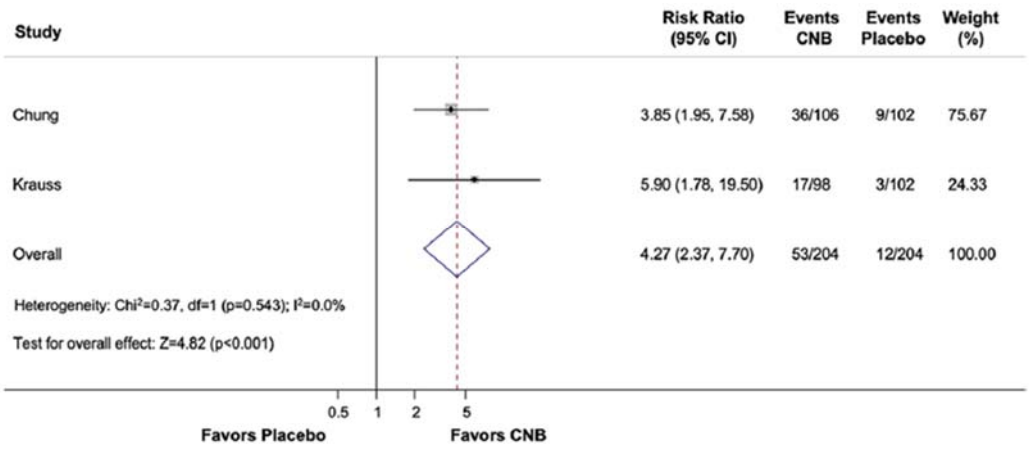
Figure 30: Meta-analysis of ≥90% responder rate in any dose of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the ≥90% responder rate in 200 mg/day of cenobamate compared to placebo is presented in Figure 31. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped. Results showed no significant heterogeneity amongst the two studies (p=0.543), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving a ≥90% response is 4.27 times more likely than compared to placebo. This was statistically significant, as the CI demonstrated that, with 95% certainty, the risk ratio lies between 2.37 and 7.70.

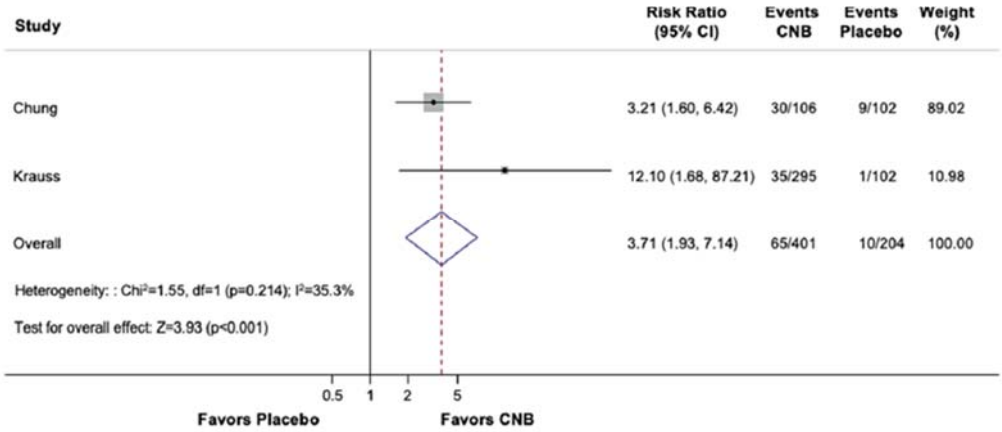
Figure 31: Meta-analysis of ≥90% responder rate in 200 mg/day of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the seizure freedom in any dose of cenobamate is presented in Figure 32. This analysis considers 100 mg/day, 200 mg/day and 400 mg/day of cenobamate compared to placebo. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped, though the CI was far broader in C017. Results showed no significant heterogeneity amongst the two studies (p=0.214), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving seizure freedom is 3.71 times more likely than compared to placebo. This was statistically significant, as the CI demonstrated that, with 95% certainty, the risk ratio lies between 1.93 and 7.14.

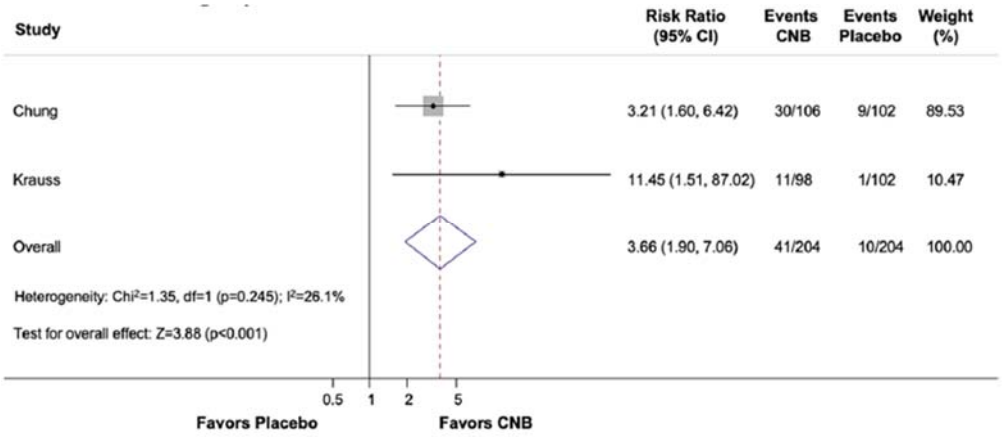
Figure 32: Meta-analysis of seizure freedom in any dose of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

The results of the meta-analysis of the seizure freedom in 200 mg/day of cenobamate compared to placebo is presented in Figure 33. The CIs of the risk ratio of response with cenobamate relative to placebo from C017 (Krauss) and C013 (Chung) overlapped, though the confidence intervals were far broader in C017. Results showed no significant heterogeneity amongst the two studies (p=0.245), so the analysis is presented using a fixed-effect model. The analysis found that, in any dose of cenobamate, the likelihood of achieving seizure freedom is 3.66 times more likely than compared to placebo. This was statistically significant, as the CI al demonstrated that, with 95% certainty, the risk ratio lies between 1.90 and 7.06.

Figure 33: Meta-analysis of seizure freedom in 200 mg/day of cenobamate



Abbreviations: CI, confidence interval; CNB, cenobamate.

Across the C017 and C013 study, it was reported that withdrawal was 1.34 times more likely with any dose of cenobamate compared to placebo, though this was not significant as the confidence intervals contained one (CI=0.85-2.09). When comparing 200 mg/day of cenobamate to placebo, withdrawal was more likely compared to placebo than with any dose of cenobamate, with an estimated risk ratio of 1.26 (CI=0.77-2.08).

Treatment withdrawal due to adverse events was 2.27 times more likely with any dose of cenobamate compared to placebo (CI=1.08-4.79). When considering 200 mg/day of cenobamate, there was not a statistically significant difference (CI=0.91-4.46).

Adverse events, in any dose of cenobamate, was 1.14 times more likely than with placebo however this was not statistically significant (CI=0.99-1.31). Serious adverse events were as likely with cenobamate as placebo (RR=0.99, CI=0.36-2.75).

The results of the meta-analysis demonstrate that cenobamate, when considered across all doses or when considering only 200 mg/day, is associated with significantly greater responder rates (at the 50%, 75% and 95% thresholds). The likelihood of achieving seizure freedom is also significantly greater with cenobamate than placebo. Moreover, cenobamate was shown to be a safe treatment, with no increase in the likelihood of serious adverse events. Moreover, this meta-analysis demonstrated the consistency of findings from the C017 and C013 studies.

B.2.9. Indirect and mixed treatment comparisons

In the absence of direct comparisons of cenobamate, brivaracetam, perampanel, lacosamide and eslicarbazepine acetate from the literature, an indirect treatment comparison (ITC) is required. An ITC is a method of statistical analysis that enables the estimation of relative comparative effectiveness and safety in the absence or direct clinical data.

The feasibility assessment for the ITC focused on assessing homogeneity across studies to conduct viable indirect treatment comparisons on the new anti-seizure medications: cenobamate, brivaracetam, lacosamide, eslicarbazepine acetate and perampanel for which there were 23 studies identified via the SLR, as described in Appendix D.

Within the feasibility assessment, Study C013 and three dose-escalation trials featuring newer ASMs were excluded from the networks. The dose escalation studies were excluded as they did not include outcomes reported over a sufficient duration of maintenance. C013 was not included due to the shorter maintenance duration examined in the study.

The feasibility assessment identified several key considerations, including combining different time periods in which outcomes are reported over and whether doses should be pooled and analysed separately. The period of reporting for efficacy outcomes, namely ≥50% responder rate and seizure freedom, varied. The ≥50% responder rate was generally reported over the maintenance period with the majority of the brivaracetam studies reporting it over the “treatment period”. However, most of these studies did not have a titration periods and instead patients were given a fixed dose immediately. Key opinion leaders (KOLs) feedback suggested that using the treatment period data in the absence of maintenance period data seemed reasonable for the ≥50% responder rate outcome.

The seizure freedom outcome was similar with most studies reporting the outcome over the maintenance period. KOL feedback was that the length of time may affect seizure freedom however it was noted that as much information should be included in the primary network given the limited availability of data overall. Safety outcomes were generally reported for the safety population, however a sizeable number were measured over the ITT population. This is not expected to introduce any clinically significant heterogeneity.

It was discussed with KOLs that that the length of baseline could impact the overall outcomes especially if these are short. All included studies had a baseline of between four and eight weeks and were deemed sufficient for no studies to be excluded from the network based on baseline duration.

Baseline characteristics were similar within and across studies. Any differences identified between studies were deemed to not have a clinically significant influence on outcomes and therefore no studies were excluded on this basis.

Inclusion and exclusion criteria were generally similar across studies and no studies were identified as introducing significant bias or heterogeneity into the analysis. Four perampanel studies recruited patients aged ≥12 years old. However, excluding studies featuring adolescents will result in exclusion of perampanel as a comparator in the analysis. One potential criticism is that some brivaracetam trials allowed concomitant levetiracetam use which may be unlikely to be administered in clinical practice. Many of these trials reported results by concomitant levetiracetam use but were often post-hoc analyses

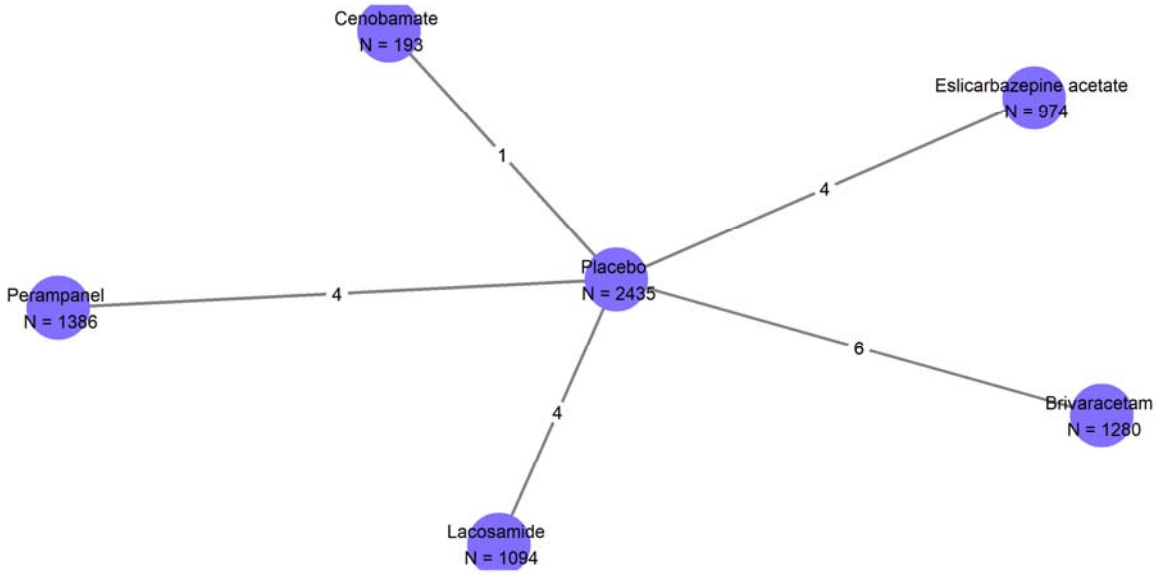
There were thus no significant sources of heterogeneity in the 19 remaining studies featuring 3rd generation ASMs: one cenobamate, six brivaracetam, four lacosamide, four eslicarbazepine acetate, and four perampanel. There were four remaining studies featuring levetiracetam. A quality assessment of studies included in the analyses was carried out according to criteria for assessment of risk of bias recommended by NICE. The tool used was the revise Cochrane risk-of-bias tool for randomised trials.

The outcomes of interest were the proportion of patients with ≥50% responder rate, the proportion of patients with seizure freedom, the proportion of patients experiencing at least one TEAE and the proportion of patients with TEAEs leading to discontinuation. Network meta-analyses (NMAs) were conducted under a Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[127] The same model framework was used for each outcome; it was assumed that data followed a Binomial likelihood distribution. Vague priors were fit to the treatment effects and, in the random effects models, between-study variation. All analyses were performed using random effects in the base case, with fixed effect analyses performed as a sensitivity analysis.

The results of the ITC random effects analyses are presented below. Full details of the quality assessment, methodology, the fixed effect analyses and sensitivity analyses can be found in Appendix D.1.1.4.

Figure 34 displays the number of trials and corresponding population numbers for each ASM included in the ≥50% responder rate analysis; there were no trials excluded from the ≥50% responder rate analysis.

Figure 34: Network of comparison for comparators included in the ≥50% responder rate analyses.



The results of the ≥50% responder rate random effects model are presented in Figure 35 showing the odds ratio (OR) and corresponding 95% credible interval (CrI) for each third generation ASM relative to cenobamate. The odds of achieving a ≥50% response rate during the maintenance period (or treatment period if not reported) was higher with cenobamate compared to all third generation ASMs (as the odds ratio relative to cenobamate is less than 1). The median estimates of the odds ratios were similar in the fixed effect model (Table 14).

Figure 35: Forest plot with 95% credible intervals of comparators versus cenobamate for ≥50% responder rate analyses

[redacted]

Random effects model was used with 300,000 iterations, 100,000 burn-in and a thinning factor of 80. The predictive mean and standard deviation used in the random effects from the baseline model was -1.43 and 0.205, respectively.

[redacted] in the random effects model, though all results were [redacted] in the fixed effect model (Table 14). [redacted] may be attributed to a relatively smaller population size in the cenobamate study and variation in the reported responder rates amongst patients in the studies treated with placebo– ranging from 10%-25%. Given that placebo is the common treatment for all indirect comparisons with cenobamate, this variation would have added uncertainty to the estimates of the treatment effect with each of the treatments considered.

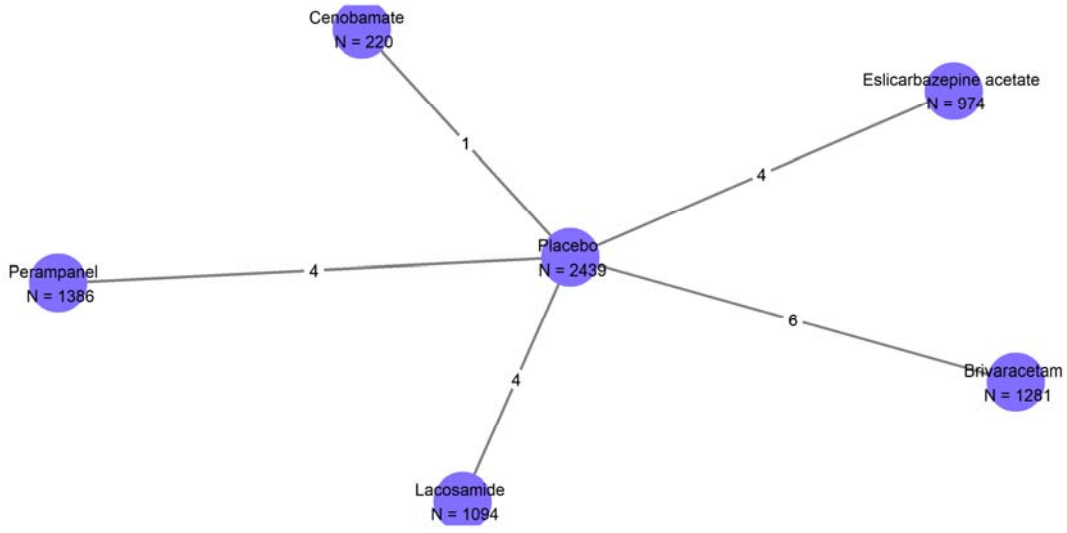
Despite the uncertainty contributing to the analysis from varying estimates of response with placebo, [redacted] CrIs in the random effects model indicate a [redacted] The comparison against perampanel, in particular [redacted]; the highest reported responder rate of amongst perampanel was 43.3% in patients treated with 12 mg/day in Study 335 compared to 64.2% in patients treated with cenobamate 400 mg/day in the C017 study.[2,128]

In the random effective model, the between study standard deviation was estimated to be [redacted] amongst the studies included. In the analysis, pD – the effective number of parameters - was estimated to be [redacted]; as there were 19 studies with at least two arms each, this indicates that the model is a good fit to the data. The DIC was [redacted] but not to an extent that would indicate that the [redacted].

A sensitivity analysis was performed whereby it was assumed that the 3rd generation ASM comparators were equivalent. This is supported by findings from literature whereby no significant differences in efficacy were found between brivaracetam, eslicarbazepine acetate, lacosamide and perampanel.[129] This was also supported by clinician opinion, where they report no significant differences in efficacy amongst these treatments. The findings of the sensitivity analysis are summarised in Table 14; in both the random and fixed effect analyses there was a [redacted] of achieving a ≥50% response to treatment with cenobamate relative to the alternative 3rd generation ASMs. This indicates that response to treatment is [redacted] likely with cenobamate than the alternative treatments considered.

Figure 36 displays the number of trials and corresponding population numbers for each ASM included in the seizure freedom analysis; there were no trials excluded from the seizure freedom analysis.

Figure 36: Network of comparison for comparators using the pragmatic ITT approach for Study C017 in the seizure freedom analyses.



The results of seizure freedom analyses using the pragmatic ITT approach and random effects model is presented in Figure 37; median estimates of the odds ratios were similar in

the fixed effect model (Table 14). The odds of achieving seizure freedom for Study C017 during the maintenance period (or treatment period for 3rd generation ASM studies if not reported) was higher with cenobamate compared to all third generation ASMs.

Figure 37: Forest plot with 95% credible intervals of comparators versus cenobamate for seizure freedom analyses using pragmatic ITT approach for Study C017

Random effects model was used with 400,000 iterations, 100,000 burn-in and a thinning factor of 150. The predictive mean and standard deviation used in the random effects from the baseline model was -4.96 and 0.543, respectively.

Abbreviations: ITT, intention to treat

Whilst [redacted] of the results are formally [redacted] in the random effects model, the CrIs indicate a [redacted] though the CrIs are [redacted]. When the results were performed using a fixed effect model, the CrI for the ORs were [redacted]. The breadth of the CrIs is due a relatively smaller population size in the cenobamate study and the rarity of seizure freedom amongst patients treated with placebo. Across the 23 studies included in the ITC, the maximum percentage of placebo-treated patients reporting seizure freedom was 2.0%, whilst in nine of the studies no placebo-treated patients reported seizure-freedom. Given the rarity of the outcome, the CrI for the true probability of achieving seizure freedom with placebo is [redacted]. As the estimates of treatment effect for all treatments considered in the ITC are anchored to placebo as the common treatment across studies, [redacted] for the range of treatment effect relative to placebo. This in turn has generated [redacted] estimates of the incremental effect between alternative treatments.

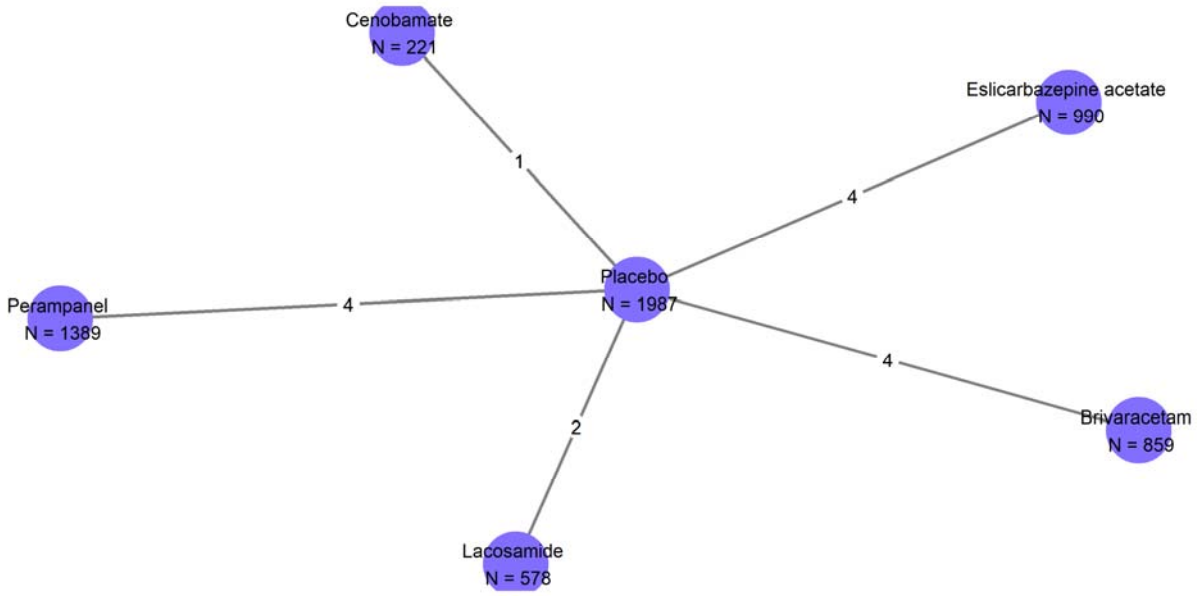
In the random effects model, the between study standard deviation was estimated to be [redacted] amongst the studies included. In the analysis, pD was estimated to be [redacted]; as there were 19 studies with at least two arms each, this indicates that the model is a [redacted]. The DIC was [redacted], but not to an extent that would indicate that the [redacted].

A sensitivity analysis was performed whereby it was assumed that the 3rd generation ASM comparators were equivalent. As for the ≥50% responder rate analysis, this is supported by findings from literature whereby no significant differences in efficacy were found between the 3rd generation ASMs,[129] which was also supported by clinician opinion. The findings of the sensitivity analysis are summarised in Table 14; the median estimates of the odds ratio of seizure freedom with other 3rd generation ASMs compared to cenobamate were [redacted] with the findings from the base case analysis. Whilst the results were [redacted]

[redacted], the reasons for [redacted] from the base case analysis pertain. However, the CrIs were much [redacted] than in the base case, adding support for the median estimates.

Figure 38 displays the number of trials and corresponding population numbers for each ASM in the analysis assessing the likelihood of experiencing TEAEs; two brivaracetam trials and two lacosamide trials were excluded as they did not report sufficient outcomes.

Figure 38: Network of comparison for comparators included in the safety analysis assessing the proportion of patients experiencing at least one TEAE.



The results of the analyses for the proportion of patients experiencing at least one treatment-emergent adverse event using a random effects model are reported in Figure 39. The median estimates of the odds ratios were similar in the fixed effect model (Table 14). In both the random and fixed effects models, there were [redacted] between cenobamate and third generation ASMs in terms of safety as measured by the proportion of patients experiencing at least one TEAE [redacted].

Figure 39:Forest plot with 95% credible intervals of comparators versus cenobamate for the proportion of patients experiencing at least one treatment-emergent adverse event analyses

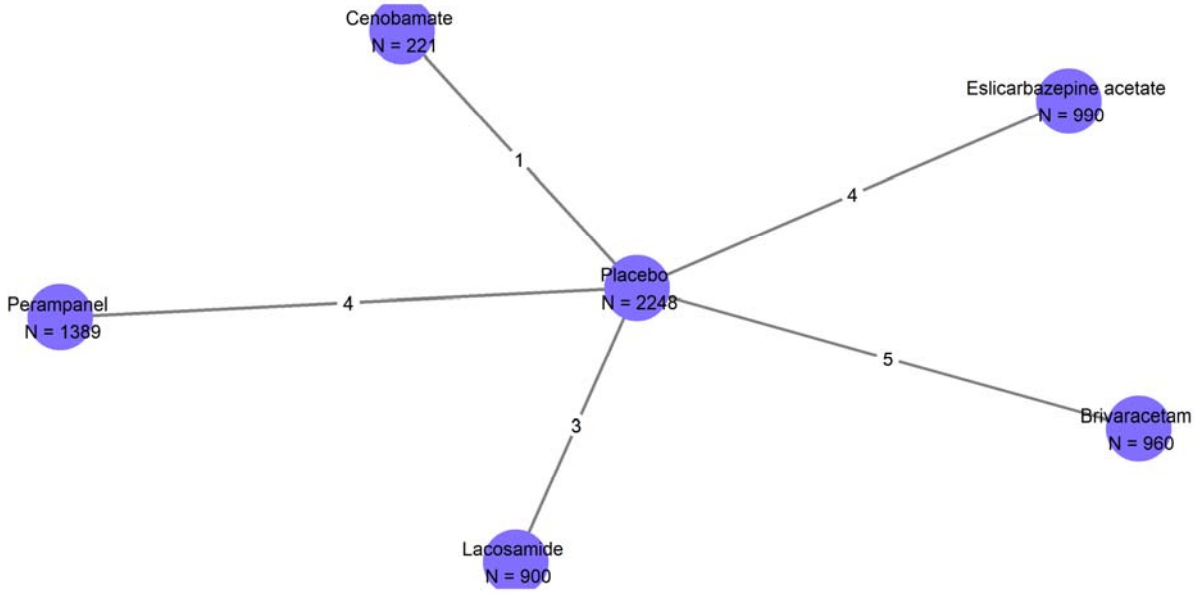
[redacted]

Random effects model was used with 300,000 iterations, 100,000 burn-in and a thinning factor of 100. The predictive mean and standard deviation used in the random effects from the baseline model was 0.47 and 0.642, respectively.

In the random effects model, the between study standard deviation was estimated to be [redacted] amongst the studies included. In the analysis, pD was estimated to be [redacted] there were 15 studies with at least two arms each, this indicates that the model is a good fit to the data. The DIC was [redacted], not to an extent that would indicate that [redacted].

Figure 40 displays the number of trials and corresponding population numbers for each ASM included in the analysis of the proportion of patients experiencing a TEAE that leads to discontinuation; two lacosamide studies were excluded from this analysis. Study 0754 reported data in combined arms only, whilst Study 1254 reported safety data for patients with generalised and focal seizures combined only.

Figure 40: Network of comparison for comparators included in the safety analysis assessing the proportion of patients experiencing at least one TEAE leading to discontinuation.



The results of the analysis of the proportion of patients experiencing at least one treatment-emergent adverse event leading to discontinuation using a random effects model is presented in Figure 41. The median estimates of the odds ratios were similar in the fixed effect model (Table 14). In both the random and fixed effects models, there were [redacted] between cenobamate and third generation ASMs for this outcome. The results of the analysis indicate that discontinuation due to TEAEs is numerically [redacted], though it should be noted that this comparison considers only cenobamate data from the C017 study which had higher rates of discontinuation due to inclusion of a forced titration which is much faster than anticipated in clinical practice.

The between study standard deviation was estimated to be [redacted], which indicates [redacted]. In the analysis, pD – the effective number of parameters - was estimated to be [redacted]; as there were 17 studies with at least two arms each, this indicates that the model is a [redacted]. The DIC was [redacted]

[redacted], but not to an extent that would indicate that the [redacted].

Figure 41: Forest plot with 95% credible intervals of comparators versus cenobamate for the proportion of patients experiencing at least one treatment-emergent adverse event leading to discontinuation analyses

Random effects model was used with 300,000 iterations, 100,000 burn-in and a thinning factor of 70. The predictive mean and standard deviation used in the random effects from the baseline model was -4.96 and 0.543, respectively.

A summary of the key random effects and fixed effect results from the ITC can be found in Table 14.

Table 14: Summary of the results from the ITC

Comparator	Odds ratio relative to cenobamate (95% CrI)							
	≥50% response		Seizure freedom		Occurrence of any TEAEs		Discontinuation due to TEAEs	
	RE	FE	RE	FE	RE	FE	RE	FE
Base case analysis								
Perampanel	0.48 [redacted]	0.48 [redacted]	0.21 [redacted]	0.21 [redacted]	0.91 [redacted]	0.91 [redacted]	0.56 [redacted]	0.57 [redacted]
Eslicarbazepine acetate	0.53 [redacted]	0.52 [redacted]	0.18 [redacted]	0.18 [redacted]	1.04 [redacted]	1.05 [redacted]	0.75 [redacted]	0.75 [redacted]
Lacosamide	0.54 [redacted]	0.54 [redacted]	0.21 [redacted]	0.21 [redacted]	0.63 [redacted]	0.62 [redacted]	0.49 [redacted]	0.49 [redacted]
Brivaracetam	0.50 [redacted]	0.49 [redacted]	0.28 [redacted]	0.28 [redacted]	0.62 [redacted]	0.63 [redacted]	0.39 [redacted]	0.41 [redacted]
Placebo	0.22 [redacted]	0.22 [redacted]	0.05 [redacted]	0.05 [redacted]	0.47 [redacted]	0.48 [redacted]	0.23 [redacted]	0.23 [redacted]
Sensitivity analysis of pooling all other 3rd generation ASMs								

Pooled 3rd gen ASMs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: ASMs, antiseizure medication; CrI, credible intervalFE, fixed effect; ITC, indirect treatment comparison; RE, random effects; TEAEs, treatment emergent adverse events. ***Bold credible intervals*** outcomes indicate statistical significance.

B.2.9.1. Uncertainties in the indirect and mixed treatment comparisons

The results of the ITC indicate that it's possible adjunctive treatment with cenobamate is more beneficial than the comparator treatments. The point estimates indicate [redacted]. However, there are several limitations that should be considered in the analyses presented.

Firstly, four out of six of the brivaracetam trials did not feature a titration period which may introduce some heterogeneity when comparing to the maintenance period of other ASM trials whose participants would have had more time on treatment to develop a response to the dose. Feedback from KOLs suggested that this may result in lower efficacy results for these studies, however exclusion would result in the majority of brivaracetam studies being omitted from the analyses. The maintenance periods of the brivaracetam trials featuring titration periods were also shorter (7–8 weeks) compared to the other ASMs (12–13 weeks). KOLs commented that although the length of follow up may affect seizure freedom outcome, as much information as possible should be included in the network. However, using random effects models in the base case, between study-variance has been accounted for. In some analyses, the between study standard deviation estimates were relatively high, which is reflected in the CrIs for the ORs of outcomes relative to cenobamate.

It is important to note that definitions of seizure freedom varied across trials. The majority of studies reported the “pragmatic ITT” definition, where only patients who completed the trial and were seizure free are classed as being seizure free in the numerator.[130] This is in contrast to a Last Observation Carried Forward (LOCF) approach whereby patients who were seizure free up to dropping out of a study can be classed as seizure free in the numerator. Reasons for drop-out varied across studies and were often due to tolerability issues or administration. Scenario analyses were conducted using both pragmatic ITT and LOCF approaches for cenobamate trial Study C017 to assess the influence on results. From the sensitivity analysis, it was seen that the pragmatic ITT produced much more conservative estimates of the effectiveness of cenobamate relative to other third generation ASMs with tighter CrIs. Therefore, the pragmatic ITT approach presented is likely to over-estimate the likelihood of achieving seizure freedom with the comparators relative to cenobamate, with seizure freedom with cenobamate relative to the comparators more likely than presented.

Additionally, it should be noted that the rates of discontinuation due to TEAEs reported in the C017 study overestimate the rate due to a forced titration that is faster than anticipated in

clinical practice. Given that faster titration is associated with more adverse events, a proportion of the patients discontinuing due to adverse events over all cenobamate arms would be averted over a slower titration. Reduced discontinuation was demonstrated in the C021 open-label study, where titration matched its anticipated use in clinical practice and 68% of patients remained on treatment for three years.[4] Similarly, long-term retention to treatment was high, with 60% of patients remaining on treatment six years after entering the OLE of C017.[126]

In terms of generalisability, clinical trials of epilepsy for regulatory purposes represent a more restrictive population, often with more drug-resistance epilepsy than what is observed in clinical practice.[131] Furthermore, in order to reduce the risk of heterogeneity, analyses were restricted to the maintenance phase of trials where ASM doses usually remain fixed, apart from where this was not reported for a trial and therefore the treatment period was used. It may be argued that the use of the full double-blind/treatment period in which titration periods are also included may be more reflective of clinical practice, although efficacy outcomes were mostly reported only for the maintenance period within publications. Contrastingly, maintenance periods with fixed doses may be less reflective of clinical practice since patients dose is adjusted by clinicians according to their response; therefore, if dose adjustments were permitted more patients could achieve better outcomes across the studies considered. Given that, in the cenobamate study, patients could not exceed their randomised dose, if dose adaptions were permitted much higher response rates could have been observed given the incremental difference seen between the 200 mg and 400 mg arms. Whilst this is also plausible for the comparator treatments, cenobamate demonstrated levels of response amongst the 400 mg arm that had not been observed by any available dose of the comparators; therefore, the results compared to cenobamate are likely conservative in nature.

Despite the uncertainties in the analysis, the results indicate improved clinical effectiveness with cenobamate compared to the alternative treatments considered; ≥50% responder rates and seizure freedom in patients treated with cenobamate 200 or 400 mg/day exceeding the reported values for the comparators investigated.

With regards to the ≥50% responder rates amongst comparators, the maximum reported outcome amongst comparators was 55.8% in patients treated with 50 mg/day of brivaracetam over seven weeks. Similarly, the highest ≥50% responder rates reported for lacosamide (400 mg/day), perampanel (12 mg/day) and eslicarbazepine acetate (1,200 mg/day) were 49%, 43% and 23%, respectively. This compares to 56.1% and 64.2% reported for cenobamate 200 mg/day and 400 mg/day, respectively in the C017 study.

With regards to seizure freedom, the data compared with cenobamate from comparator studies did not demonstrate the same level of benefit, In the four parampanel studies included in the ITC, seizure freedom rates ranged from 1% to 5% in patients treated with perampanel. Similarly, seizure freedom rates were achieved between 1% and 9% of patients in the brivaracetam trials, 2% to 8% of patients in the lacosamide trials and 1% to 8% of patients in the eslicarbazepine acetate trials. Contrastingly, 1% and 21% of patients treated with cenobamate 200 mg/day and 400 mg/day, respectively, achieved seizure freedom in the C017 study, highlighting the substantial improvement in seizure freedom that cenobamate offers patients with drug-resistant seizures.

B.2.10. Adverse reactions

B.2.10.1. Study C017

All ITT patients were evaluated for safety. The number and percentage of patients reporting AEs (including treatment-emergent laboratory abnormalities) were tabulated by randomized treatment group. The incidence of TEAEs in the SE population during the double-blind treatment period are summarised in Table 15.

Table 15: Summary of Treatment-Emergent Adverse Events (Safety Evaluable)

	Number (%) of patients			
	Cenobamate 100 mg (N=108)	**Cenobamate 200 mg (N=110)**	**Cenobamate 400 mg (N=111)**	**Placebo (N=108)**
Patients with TEAEs	70 (65)	84 (76)	100 (90)	76 (70)
Patients with treatment related TEAEs	62 (57)	72 (65)	92 (83)	46 (43)
Patients who died due to a TEAE	0	0	0	0
Patients discontinued due to a TEAE	11 (10)	15 (14)	22 (20)	5 (5)
Patients with serious TEAEs	10 (9)	4 (4)	8 (7)	6 (6)

TEAEs- Treatment-related adverse events.
Source: Krauss *et al*.[2]

At least 1 TEAE was reported for 70 patients (65%) in the 100 mg treatment group, 84 patients (76%) in the 200 mg treatment group, 100 patients (90%) in the 400 mg treatment group, and 76 patients (70%) in the placebo treatment group during the double-blind treatment period. There were no deaths during the double-blind treatment period. Nonfatal serious TEAEs were reported for 10 patients (9%) in the 100 mg treatment group, 4 patients (4%) in the 200 mg treatment group, 8 patients (7%) in the 400 mg treatment group, and 6 patients (6%) in the placebo treatment group during the double-blind treatment period.[2]

Treatment-related TEAEs (as assessed by the investigator) were reported for 62 patients (57.4%) in the 100 mg treatment group, 72 patients (65.5%) in the 200 mg treatment group, 92 patients (82.9%) in the 400 mg treatment group, and 46 patients (42.6%) in the placebo treatment group during the double-blind treatment period.[2] Treatment emergent AEs leading to discontinuation were reported for 11 patients (10.2%) in the 100 mg treatment group, 15 patients (13.6%) in the 200 mg treatment group, 22 patients (19.8%) in the 400 mg treatment group, and 5 patients (4.6%) in the placebo treatment group during the double-blind treatment period. [2]

The most common TEAE's occurring in more than 5% of patients in any treatment group in the SE population by system organ class (SOC) are summarised in Table 16. The SOCs with the most frequently reported TEAEs during the double-blind treatment period included nervous system disorders, general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders. Overall, somnolence, dizziness, and fatigue

were the most commonly reported PTs during the double-blind treatment period. Somnolence was reported in 20 (19%), 23 (21%), 41 (37%), and 9 (8%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively. Dizziness was reported in 19 (18%), 22 (20%), 37 (33%), and 15 (14%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively. Fatigue was reported in 13 (12%), 19 (17%), 27 (24%), and 9 (8%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively.[2] The majority of TEAEs were transient in nature.

Table 16: Treatment-Emergent Adverse Events (All Causalities) by System Organ Class and Preferred Term in at least 5% of patients in Any Treatment Group by Descending Order (Safety Evaluable Population, Double-Blind Treatment Period)

System Organ Class MedDRA Preferred Term	**Number (%) of patients**			
	Cenobamate 100 mg (N=108)	**Cenobamate 200 mg (N=110)**	**Cenobamate 400 mg (N=111)**	**Placebo (N=108)**
Patients with at least 1 TEAE	70 (64.8)	84 (76.4)	100 (90.1)	76 (70.4)
Somnolence	20 (19)	23 (21)	41 (37)	9 (8)
Dizziness	19 (18)	22 (20)	37 (33)	15 (14)
Headache	11 (10)	12 (11)	12 (11)	6 (6)
Balance disorder	3 (3)	2 (2)	10 (9)	0
Nystagmus	3 (3)	4 (4)	7 (6)	1 (<1)
Ataxia	2 (2)	4 (4)	7 (6)	1 (<1)
Dysarthria	2 (2)	3 (3)	7 (6)	0
Fatigue	13 (12)	19 (17)	27 (24)	9 (8)
Gait disturbance	1 (<1)	6 (6)	9 (8)	3 (3)
Diplopia	8 (7)	11 (10)	17 (15)	2 (2)
Constipation	2 (2)	3 (3)	10 (9)	1 (<1)
Nausea	7 (7)	1 (<1)	10 (9)	1 (<1)
Vomiting	2 (2)	3 (3)	6 (5)	0
Fall	2 (2)	4 (4)	4 (4)	6 (6)
Upper respiratory tract infection	3 (3)	4 (4)	3 (3)	6 (6)
Back pain	4 (4)	1 (<1)	6 (5)	3 (3)
Vertigo	1 (<1)	3 (3)	6 (5)	3 (3)
Decreased appetite	3 (3)	1 (<1)	6 (5)	1 (<1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse Event Notes: Percentages are based on the number of patients in each treatment group in the safety evaluable population
Source: Krauss *et al*.[2]

Table 17 shows that during the titration phase a total of 222 patients, 67.5%, throughout the three cenobamate arms reported at least one TEAE compared to 57.0% for placebo. Somnolence was reported in 15 (13.9%), 19 (17.3%), 40 (36.0%), and 97(6.5%) patients in

the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively. Dizziness was reported in 15 (13.9%), 18(16.4%), 32 (28.8%) and 11(10.3%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively.[132]

Table 17: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the titration phase of C017 study

	Number (%) of patients				
	All cenobamate (N=275)	**Cenobamate 100 mg (N=98)**	**Cenobamate 200 mg (N=92)**	**Cenobamate 400 mg (N=85)**	**Placebo (N=97)**
Patients with at least one TEAE	222 (67.5)	57 (52.8)	69 (62.7)	96 (86.5)	61 (57.0)
Vertigo	8 (2.4)	0 (0.0)	2 (1.8)	6 (5.4)	2 (1.9)
Diplopia	28 (8.5)	6 (5.6)	8 (7.3)	14 (12.6)	2 (1.9)
Vision blurred	6 (1.8)	1 (0.9)	2 (1.8)	3 (2.7)	0 (0.0)
Nausea	17 (5.2)	6 (5.6)	1 (0.9)	10 (9.0)	1 (0.9)
Constipation	10 (3.0)	1 (0.9)	3 (2.7)	6 (5.4)	1 (0.9)
Vomiting	9 (2.7)	0 (0.0)	3 (2.7)	6 (5.4)	0 (0.0)
Diarrhoea	5 (1.5)	0 (0.0)	1 (0.9)	4 (3.6)	1 (0.9)
Fatigue	54 (16.4)	12 (11.1)	16 (14.5)	26 (23.4)	8 (7.5)
Gait disturbance	14 (4.3)	1 (0.9)	6 (5.5)	7 (6.3)	2 (1.9)
Upper respiratory tract	5 (1.5)	1 (0.9)	3 (2.7)	1 (0.9)	1 (0.9)
Viral upper respiratory tract	5 (1.5)	1 (0.9)	3 (2.7)	1 (0.9)	4 (3.7)
Influenza	1 (0.3)	0 (0.0)	1 (0.9)	0 (0.0)	4 (3.7)
Fall	7 (2.1)	2 (1.9)	3 (2.7)	2 (1.8)	5 (4.7)
Laceration	1 (0.3)	0 (0.0)	1 (0.9)	0 (0.0)	4 (3.7)
Alanine aminotransferase increased	4 (1.2)	0 (0.0)	1 (0.9)	3 (2.7)	0 (0.0)
Decreased appetite	7 (2.1)	2 (1.9)	1 (0.9)	4 (3.6)	1 (0.9)
Back pain	5 (1.5)	3 (2.8)	1 (0.9)	1 (0.9)	2 (1.9)
Musculoskeletal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)
Somnolence	74 (22.5)	15 (13.9)	19 (17.3)	40 (36.0)	7 (6.5)
Dizziness	65 (19.8)	15 (13.9)	18 (16.4)	32 (28.8)	11 (10.3)
Headache	20 (6.1)	65 (4.6)	7 (6.4)	32 (28.8)	11 (10.3)
Ataxia	13 (4.0)	2 (10.9)	4 (3.6)	7 (6.3)	1 (0.9)

Balance disorder	13 (4.0)	2 (1.9)	4 (3.6)	7 (6.3)	1 (0.9)
Confusional state	7 (2.1)	2 (1.9)	2 (1.8)	3 (2.7)	0 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse
Source: C017 CSR[132]

Incidence of TEAEs, as shown in Table 18, rapidly decrease once patients enter the maintenance phase, with less than half of patients , 33.3%, throughout the three cenobamate arms reporting TEAE's during the first 6 weeks of the maintenance phase. During this phase, somnolence was only reported in 3 (2.9%), 4 (4.0%), 6 (6.3%) and 4 (3.9%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively. Dizziness was only reported in 3 (2.9%), 1 (10.0%), 2 (2.1%) and 1 (1.0%) of patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively.[132]

Table 18: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the first 6 weeks of the C017 maintenance phase

System Organ Class MedDRA Preferred Term	**Number (%) of patients**				
	All cenobamate (N=275)	**Cenobamate 100 mg (N=98)**	**Cenobamate 200 mg (N=92)**	**Cenobamate 400 mg (N=85)**	**Placebo (N=97)**
Patients with at least one TEAE	99 (33.3)	32 (31.4)	29 (29.3)	38 (39.6)	28 (27.5)
Diplopia	7 (2.4)	1 (1.0)	3 (3.0)	3 (3.1)	0 (0.0)
Constipation	7 (2.4)	2 (2.0)	0 (0.0)	5 (5.2)	0 (0.0)
Viral upper respiratory tract	2 (0.7)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)
Back pain	4 (1.3)	1 (1.0)	0 (0.0)	3 (3.1)	1 (1.0)
Arthralgia	3 (1.0)	0 (0.0)	1 (1.0)	2 (2.1)	0 (0.0)
Dizziness	13 (4.4)	3 (2.9)	4 (4.0)	6 (6.3)	4 (3.9)
Somnolence	6 (2.0)	3 (2.9)	1 (10.0)	2 (2.1)	1 (1.0)
Headache	10 (3.4)	5 (4.9)	4 (4.0)	6 (6.3)	4 (3.9)
Restless leg syndrome	2 (0.7)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse
Source: C017 CSR[132]

Once patients enter the last 6 weeks of the maintenance phase 84 patients (30.5%) reported at least one TEAE as shown in Table 19. During this phase, somnolence was only reported in 2 (2.0%), 4 (4.3%), 3 (3.5%) and 4 (4.1%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively. Dizziness was only reported in 2 (2.0%), 1 (1.0%), 3 (3.5%) and 0 (0.0%) patients in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively.[132]

Table 19: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the last 6 weeks of the C017 maintenance phase

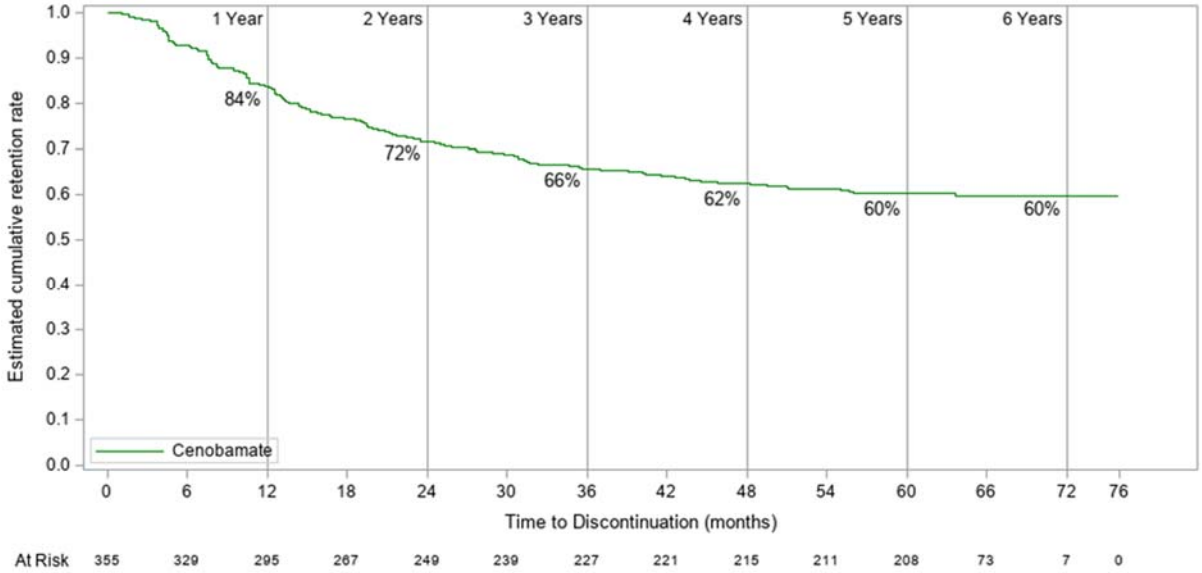
System Organ Class MedDRA Preferred Term	Number (%) of patients				
	All cenobamate (N=275)	Cenobamate 100 mg (N=98)	Cenobamate 200 mg (N=92)	Cenobamate 400 mg (N=85)	Placebo (N=97)
Patients with at least one TEAE	84 (30.5)	28 (28.6)	24 (26.1)	32 (37.6)	31 (32.0)
Diplopia	3 (1.1)	2 (2.0)	1 (1.1)	0 (0.0)	0 (0.0)
Fatigue	6 (2.2)	1 (1.0)	2 (2.2)	3 (3.5)	1 (1.0)
Bronchitis	3 (1.1)	1 (1.0)	2 (2.2)	0 (0.0)	1 (1.0)
Upper respiratory tract infection	2 (0.7)	1 (1.0)	0 (0.0)	1 (1.1)	4 (4.1)
Contusion	5 (1.8)	1 (1.0)	2 (2.2)	2 (2.4)	2 (2.1)
Fall	3 (1.1)	0 (0.0)	2 (2.2)	1 (1.2)	2 (2.1)
Decreased appetite	4 (1.5)	1 (1.0)	0 (0.0)	3 (3.5)	0 (0.0)
Back pain	2 (0.7)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
Pain in extremity	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.2)	3 (3.1)
Dizziness	11 (4.0)	5 (5.1)	3 (3.3)	3 (3.5)	3 (3.1)
Somnolence	9 (3.3)	2 (2.0)	4 (4.3)	3 (3.5)	4 (4.1)
Headache	6 (2.2)	2 (2.0)	1 (1.0)	3 (3.5)	0 (0.0)
Aphasia	3 (1.1)	1 (1.0)	0 (0.0)	2 (2.4)	0 (0.0)
Anxiety	4 (1.5)	1 (1.0)	2 (2.2)	1 (1.2)	0 (0.0)
Pollakiuria	2 (0.7)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)
Hiccups	3 (1.1)	0 (0.0)	2 (2.2)	1 (1.2)	0 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse
Source: C017 CSR[132]

B.2.10.2. Study C017 OLE

Of patients completing the double-blind study, 98.6% entered the OLE. One year after entering the OLE, 80% of patients continued cenobamate patients with 60% still receiving treatment after 6 years (Figure 42).

Figure 42: Kaplan-Meier plot of time to discontinuation during the C017 OLE



Source: Data on file.

Table 20 presents a summary of treatment-emergent adverse events (TEAEs). Serious TEAEs occurred in 20.3% (72/355) of patients; seizure (1.4%, n=5) and vertigo (1.1%, n=4) were the only serious TEAEs reported in >1% of patients. TEAEs reported in more than 10% of patients include dizziness (88.2%), somnolence (24.5%), fatigue (15.8%), diplopia (14.4%), headache (15.2%). The majority of TEAEs were transient in nature.

Table 20: Summary of Treatment-Emergent Adverse Events (Safety Evaluable)

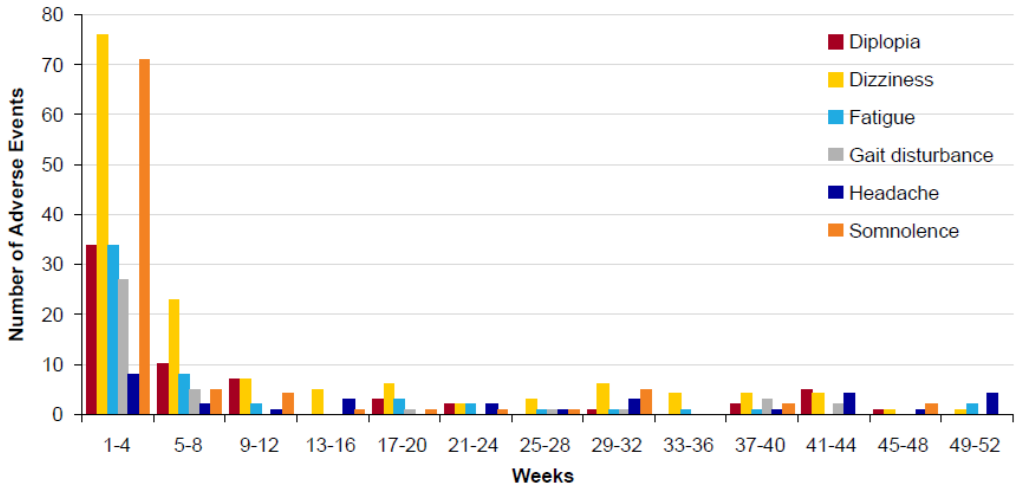
	Number (%) of patients		
	All cenobamate (n=355)	**Cenobamate-Cenobamate (n=265)**	**Placebo-Cenobamate (n=90)**
Patients with ≥1 TEAE	313 (88.2)	235 (88.7)	78 (86.7)
Patients with ≥1 serious TEAE	72 (20.3)	55 (20.8)	17 (18.9)
Patients with TEAEs leading to Treatment Discontinuation	33 (9.3)	23 (8.7)	10 (11.1)
Patients with Treatment-Related TEAEs	262 (73.8)	194 (73.2)	68 (75.6)
Patients with ≥ 10% in any group			
Dizziness	122 (34.4)	92 (34.7)	30 (33.33)
Somnolence	87 (24.5)	55 (20.8)	32 (35.6)
Fatigue	56 (15.8)	42 (15.8)	14 (15.6)
Headache	54 (15.2)	42 (15.8)	12 (13.3)
Diplopia	51 (14.4)	37 (14.0)	14 (15.6)
Gait disturbances	41 (11.5)	31 (11.7)	10 (11.1)
Upper respiratory tract infection	38 (10.7)	28 (10.6)	10 (11.1)

Vertigo	30 (8.5)	17 (6.4)	13 (14.4)
Fall	29 (8.2)	19 (7.2)	10 (11.1)
Vision blurred	20 (5.6)	11 (4.2)	9 (10.0)

Source: Arvelle data on file
Abbreviations: TEAEs, treatment emergent adverse events

Figure 43 shows that in the C017 OLE, TEAEs most frequently occurred during the first month of treatment.

Figure 43: Time of onset of the most common TEAEs during the C017 OLE treatment



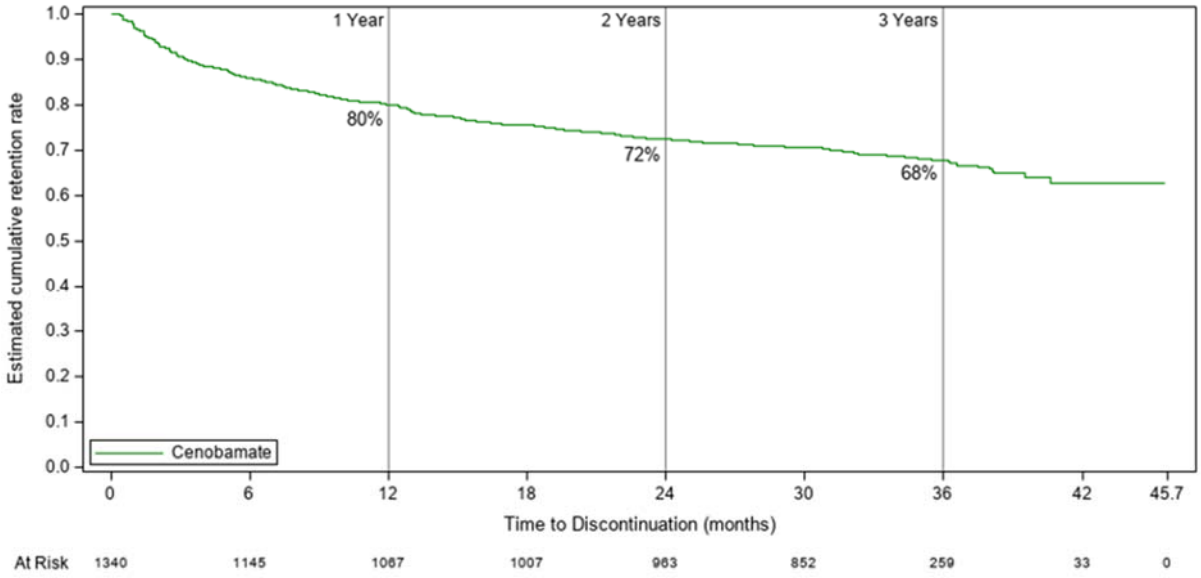
Abbreviations: OLE, Open label extension; TEAEs, treatment-emergent adverse events.
Source: Klein *et al*.[126]

At the data cut-off, five deaths had been reported in the OLE (pneumonia/sepsis, septicaemia, fatal injuries after being struck by a car, cardiogenic shock and myocardial infarction). All were considered unrelated to the study drug.

B.2.10.3. Study C021

As of the data cut-off date of June, 2020, the number (%) of patients exposed to cenobamate is summarised for the safety population in Table 21. Overall, treatment was received for at least one year in 80% of patients, and at least 3 years in 68% of patients (Figure 44). The median length of exposure across all cenobamate safety evaluable groups was similar. The overall mean modal daily dose was 225.4 mg (range: 50.0 to 400.0 mg).[133]

Figure 44: Kaplan-Meier plot of time to discontinuation during the ongoing Study C021 (safety population)



Source: Data on file.

The incidence of TEAEs in the safety population during the study is summarised in Table 21. Overall, at least 1 TEAE was reported by 1,185 (88.4%) of patients who received at least 1 dose of cenobamate. Overall, at least 1 treatment related TEAE (considered by the investigator to be related to study drug) was reported by 1,000 (74.6%) of patients who received at least 1 dose of cenobamate. [4]

Four patients (0.3%) reported a TEAE with an outcome of death during the study (sudden death with no autopsy, traumatic intracerebral haemorrhage after a fall, fatal injuries after being struck by a car, and respiratory failure in a patient with Angelman syndrome). All 4 TEAEs with an outcome of death during the study were considered unrelated or remotely related to study drug. Overall, a TEAE leading to study drug discontinuation was reported by 175 (13.1%) patients who received at least 1 dose of cenobamate.

Table 21: Summary of Treatment-Emergent Adverse Events (Safety Evaluable) in the C021 study

	Number (%) of patients
	Cenobamate patients (N=1,340)
Patients with TEAEs	1,185 (88.4)
Patients with treatment related TEAEs	1,000 (74.6)
Patients who died due to a TEAE	4 (0.3)
Patients discontinued due to a TEAE	175(13.1)
Patients with serious TEAEs	137 (10.2)

Abbreviations: TEAEs, treatment-emergent adverse events.
Source: Data on file.

TEAEs occurring in at least 5% of the patients in any safety evaluable group are summarized in Table 22. Overall, somnolence, dizziness, and fatigue were the most commonly reported treatment-related adverse events during the study. The majority of adverse events were transient in nature.

Table 22: Treatment-Emergent Adverse Events (All Causalities) in at least 5% of patients in Any Treatment Group by Descending Order

	Number (%) of patients
	Cenobamate patients (N=1,340)
Somnolence	405 (30.2)
Dizziness	359 (26.8)
Fatigue	252 (18.8)
Headache	208 (15.5)
Viral upper respiratory tract infection	118 (8.8)
Upper respiratory tract infection	104 (7.8)
Nausea	108 (8.1)
Diplopia	95 (7.1)
Balance disorder	89 (6.6)
Seizure	74 (5.5)
Diarrhoea	70 (5.2)
Fall	67 (5.0)

Abbreviations: TEAE, treatment-emergent adverse event. Notes: Percentages are based on number in analysis population. Source: Data on file.

There were no remarkable changes during the study in haematology, clinical chemistry, or urinalysis parameters; ECG readings; vital sign measurements; or physical examination or neurological examination findings. In addition, no cases of DRESS were identified.

Table 23 shows that during the titration phase, somnolence was reported in 295 (22.0%) of patients. Dizziness was reported in 222 (16.6%) and headache was reported in 101 (7.5%) of patients.

Table 23: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the C021 titration phase

System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Patients with at least one TEAE	960 (71.6)
Diplopia	48 (3.6)
Vision blurred	32 (2.4)
Nausea	48 (3.6)
Vomiting	30 (2.2)
Constipation	27 (2.0)
Fatigue	173 (12.9)
Gait disturbance	31 (2.3)
Viral upper respiratory tract infection	48 (3.6)
Upper respiratory tract infection	45 (3.4)
Dizziness	222 (16.6)
Somnolence	295 (22.0)

System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Balance disorder	40 (3.0)
Headache	101 (7.5)

Source: Data on file.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAEs, treatment emergent adverse events

Table 24 shows that during the maintenance phase, somnolence was only reported in 167 (14.0%) of patients. Dizziness was reported in 197 (16.5%) and headache was reported in 134 (11.3%) of patients.

Table 24: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the C021 maintenance phase

System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Patients with at least one TEAE	957 (80.4)
Diplopia	66 (5.5)
Vision blurred	35 (2.9)
Nausea	69 (5.8)
Diarrhoea	55 (4.6)
Vomiting	37 (3.1)
Constipation	45 (3.8)
Fatigue	113 (9.5)
Gait disturbance	42 (3.5)
Asthenia	34 (2.9)
Viral upper respiratory tract infection	76 (6.4)
Upper respiratory tract infection	67 (5.6)
Urinary tract infection	49 (4.1)
Influenza	39 (3.3)
Fall	51 (4.3)
Laceration	30 (2.5)
Weight decreased	47 (3.9)
Decreased appetite	31 (2.6)
Arthralgia	26 (2.2)
Back pain	26 (2.2)
Dizziness	197 (16.5)
Somnolence	167 (14.0)
Headache	134 (11.3)
Seizure	56 (4.7)
Balance disorder	53 (4.5)
Ataxia	40 (3.4)
Depression	37 (3.1)

System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Anxiety	30 (2.5)

Source: Data on file.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAEs, treatment-emergent adverse events

B.2.11. Ongoing studies

The C017 OLE, C013 OLE and C021 studies are still all ongoing. There are therefore three ongoing studies of cenobamate.

B.2.12. Innovation

Cenobamate represents an important development in drug-resistant FOS that can change the treatment paradigm, offering substantial health-related benefits to patients as well as carers and the NHS. The MHRA also designated cenobamate Promising Innovative Medicine (PIM) status in recognition of its potential to fulfil an unmet need drug-resistant patients with focal-onset seizures – a severe and debilitating condition.[115]

Currently approved third-line adjunctive ASM options offer insufficient improvements in seizure-freedom. Following the failure of two ASMs, only 15.0% of patients go on to achieve seizure freedom,[32] with the odds of remaining drug-resistant increasing with line of therapy. Moreover, the small improvements in seizure control offered by already available ASMs are met with tolerability issues and low retention rates. This clearly highlights that highly effective and tolerable ASMs need to be made available as soon as possible in the treatment pathway to enable more patients to achieve seizure freedom.

This disease imposes a substantial burden on individuals, their caregivers, and society as a whole. Seizure occurrence, in combination with the inability to live independently and social limitations, negatively affect patients' and carers' QoL. Moreover, seizure occurrence has been shown to exacerbate comorbidities, some of which occur 7-10 times more frequently in patients with epilepsy than the general population.[50] Several studies have shown an increased mortality risk in people who continued having seizures despite treatment when compared to people with epilepsy who are seizure-free.[42] Additionally, sudden unexpected death in epilepsy (SUDEP) affects approximately 1 in 1,000 people with epilepsy; in drug-resistant patients, the rate of SUDEP has been reported as up to 9 per 1,000 patients.[134] Drug side effects have also been shown to negatively affect HRQoL, with the intolerability of some treatments preventing the opportunity to attain a response. In DRE, patients are affected by increased morbidity and mortality, reduced employment opportunities, social stigma, and reduced quality of life for themselves and their carers.

Cenobamate is the only ASM which, at clinically relevant concentrations, acts as a positive allosteric modulator of $GABA_A$ receptors at non-benzodiazepine binding sites and preferentially blocks the persistent sodium current.[12,13] As a mechanistically distinct ASM, cenobamate offers an important advancement in drug development for treatment of DRE,[10] preventing seizure initiation and limiting seizure spread.[5–9] Investment has been made in cenobamate,[10] with more than 2,500 clinical patients exposed to the drug to date. Studies have demonstrated that patients treated with cenobamate are able to achieve seizure freedom in proportions that have not been possible with existing ASMs.[10, 110,111, 113,135]

Moreover, long-term data from open-label studies demonstrate high retention rates and efficacy with approximately 23.2% of patients achieving a seizure-free period of at least 12 months.[126] These are the highest reported in the published literature. By achieving seizure freedom or significant reductions in the frequency of seizures with cenobamate, patients with FOS have the potential to improve their quality of life.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Key findings of the clinical evidence

The pivotal C017 study is the first 18-week RCT to assess the efficacy, safety, and tolerability of adjunctive cenobamate across a range of doses (100 mg/day, 200 mg/day, and 400 mg/day) compared with placebo when added to a stable ASM regime in adult patients with drug-resistant focal seizures. In all cenobamate treatment groups, there were significantly more patients with a responder rate of ≥50% compared to placebo ($p=0.0365$, $p<0.0001$ and $p<0.0001$ for cenobamate 100 mg/day, 200 mg/day, and 400 mg/day, respectively). Moreover, in the cenobamate 200 mg/day and 400 mg/day treatment groups, there were statistically significant differences in the number of patients with responder rates of ≥ 75% ($p=0.0003$ and $p<0.0001$, respectively) and ≥ 90% ($p=0.0007$ and $p<0.0001$) compared to placebo during the 12-week maintenance phase. The greatest proportions of patients achieved seizure freedom in the 200 mg and 400 mg dose groups, with 11% (n=11; $p=0.0022$) and 21% (n=20; $p<0.0001$) of patients, respectively, seizure free compared to 1% of patients in the placebo group.[2]

Post-hoc analyses also provided evidence that seizure frequencies decreased relatively early during cenobamate titration; seizure reductions of 45–50% were evident across dose groups during the first 4 weeks of 50–100 mg/week titration. From week 5 onwards, high rates of seizure freedom occurred within the 200 mg and 400 mg cenobamate dose groups from week 5 onwards ($p<0.05$). Moreover, it was found that response to treatment and reductions in seizure frequency were consistent according to concomitant therapies, time since diagnosis and number of seizures at baseline. Attainment of seizure freedom was also consistent across number of failed ASMs in patients treated with 400 mg/day. This demonstrates that cenobamate is efficacious across the spectrum of severity amongst patients with FOS. Additionally, similar reductions in seizure frequency were consistent across the different FOS subtypes.

In the C017 OLE, the levels of response to treatment were sustained; 23% of patients had a seizure-free period that lasted for at least 1 year at any point during the OLE. Moreover, in patients who remained on treatment, the median reduction in seizure frequency increased over each six-month interval, demonstrating that benefit does not diminish with time.

The ITC demonstrated that cenobamate is associated with greater proportions of patients achieving a ≥50% response to treatment and seizure freedom. There was a strong numerical preference for cenobamate across the base case analyses with regards to seizure freedom and near-significant results for ≥50% response, with significant results across sensitivity analyses. In particular, the sensitivity analysis considering all 3rd generation ASMs to be equally effective found cenobamate to be associated with significantly greater odds of

response than alternative treatments in the fixed and random effects model. Similarly, the credible interval for odds of seizure freedom with 3rd generation ASMs compared to cenobamate was much narrower when they were assumed equivalent, demonstrating a move towards significant findings with greater statistical power. These findings demonstrate that it's highly likely adjunctive treatment with cenobamate is more beneficial than the comparator treatments, resulting in fewer seizures for patients than comparator treatments.

Most patients experienced adverse events during the C017 study and its OLE, with a dose-response relationship demonstrated. The rapid titration of 100 mg/week from 200 mg to 400 mg might have contributed at least in part, to the higher rates of treatment emergent adverse events in the 400 mg group.[2] The frequency of adverse events across all treatment arms in C017 was greatest during the titration period, which was accelerated due to the clinical study protocol. The ongoing C021 study demonstrated, that over a slower titration – in line with what is expected in clinical practice – the occurrence of adverse events is reduced.

Moreover, across C017, its OLE and C021, most TEAEs were transient in nature and the occurrence of serious adverse events was rare. The most common serious TEAEs associated with cenobamate were seizure and epilepsy, which are not unexpected in a patient population with DRE. In the C021 study, no cases of DRESS were identified in 1,339 patients initiating cenobamate using a start-low, go-slow approach of 12.5 mg/day and titrating every 2 weeks to a maximum of 400 mg/day.[4] These data combined, demonstrate that, when appropriately titrated, cenobamate is well-tolerated in patients with epilepsy.

During C017 which lasted 18 weeks, discontinuations due to adverse events increased in a dose-related manner, with 20% in the 400 mg group discontinuing treatment. Akin to the occurrence of TEAEs in the 400 mg arm, this may be attributed to rapid titration. Moreover, given that faster titration is associated with more adverse events, a proportion of the patients discontinuing due to adverse events over all cenobamate arms would be averted over a slower titration. Discontinuation over the first year was 20% in the ongoing C021 open-label study, where titration matched its anticipated use in clinical practice, supporting that in clinical practice retention is expected to be improved over titration. Moreover, long-term retention to treatment was demonstrated to be high with 60% of patients remaining on treatment 6 years into the OLE of C017. This finding was similar in the C021 study, where 68% of patients remained for 3 years.

The C013 study, reported in the appendices, are congruent to the efficacy and safety analyses demonstrated by the C017 study. Both the median percent reduction in seizure frequency relative to placebo (55.6% vs 21.5%, primary outcome) and responder rates relative to placebo observed with cenobamate in this study compare favourably to published rates from individual and pooled randomized clinical studies of other adjunctive ASMs. In particular, the percentage of seizure-free patients (28.3%) with cenobamate 200 mg treatment was a noteworthy finding given that the percentage in the placebo group was 8.8% and >80% of patients in this study were taking ≥2 concomitant ASMs.

B.2.13.2. Strengths and limitations of the clinical evidence base

Strengths of the clinical evidence base include two randomised, double-blind, placebo-controlled studies (C013 and C017), the use of an independent panel to confirm the

appropriate diagnosis, the inclusion of clinically important efficacy assessments and assessment of dose response.[136,137]

Other pivotal studies of ASM treatment in drug-resistant FOS over the past 25 years have been unable to demonstrate the levels of decrease in seizure frequency as well as seizure-freedom attained by cenobamate, providing new hope to patients suffering from drug-resistant focal epilepsy. The C017 study also demonstrated that the level of response increases with dose, with patients on higher doses (200 and 400 mg) of treatment more likely to observe the best outcomes. Though, it should be noted that on lower doses of cenobamate (100 mg) some patients observed a strong response to treatment. This indicates that patients may be able to elicit a strong response from treatment even at sub-therapeutic doses (i.e. titration dose and patients who cannot tolerate the target dose).

A number of other ASM studies have demonstrated good efficacy at doses that were subsequently not tolerated in the clinic. Higher withdrawal rates have been reported with other ASM studies, including those that used forced titration schedules.[138] The demonstration of mostly mild to moderate AEs that are transient in nature with AEs with a low rate of serious AEs in the ongoing C021 study demonstrates the safety of cenobamate when used over a slower titration, as anticipated in clinical practice. Moreover, patients treated with cenobamate remain on the dose tolerable to them with few dropouts indicating that the efficacy demonstrated can be replicated in clinical practice. Together, this demonstrates that cenobamate is a tolerable treatment option with high levels of retention.

Additionally, the design of the clinical trials has captured a population that is aligned to the patients with drug-resistant FOS in England and Wales; indeed, the C017 study included study sites in the UK. Their disease characteristics are aligned with the eligible population, which was broadly agreed with by two clinicians in the UK. The majority of patients were receiving two or three concomitant ASMs and had previously trialled 3 ASMs, aligning with the third-line adjunctive setting. Moreover, the medications received concomitantly with cenobamate were most commonly levetiracetam, lamotrigine, valproic acid and carbamazepine, which aligns with the most prescribed ASMs in England and Wales.

Limitations of the C013 and C017 studies, as with other controlled studies of adjunctive ASMs, include the short study durations. In particular, given guidance provided by the EMA, the 6-week maintenance duration of the C013 is too short in order to establish efficacy is long lasting. However, this is directly addressed via the C017 study and its OLE where long-term efficacy with cenobamate is demonstrated for up to four years.

Other limitations are related to the study design. Patients in the C013 study take 200mg/day of cenobamate whilst in the C017 study patients take either 100mg/day, 200mg/day or 400mg/day. Moreover, the C017 and C013 studies had different durations of maintenance treatment. These differences make conducting a meta-analysis to estimate the size of common effects problematic. However, in the network meta-analysis, which included only the C017 study as evidence for cenobamate, a compelling preference in favour of cenobamate was demonstrated compared to other 3rd generation ASMs with regards to seizure reduction and seizure freedom. Given that 3rd generation ASMs are the alternatives in clinical practice, rather than placebo, which was studied in C017 and C013, this

demonstrates the comparative improvements in seizure control with cenobamate relative to the alternative treatment options available in clinical practice.

The use of a placebo group in both C013 and C017, although still favoured in adjunctive ASM clinical studies for assessment of safety, precludes longer treatment durations for assessment of seizure freedom, because of ethical considerations. Further investigation is needed to determine how the potential unique combination of mechanisms of action may play a role in the clinical efficacy and manageable tolerability profile of cenobamate despite the use of various concomitant ASMs. The ongoing open-label extension phase of both studies and the ongoing C021 study provides additional insight into the long-term safety and efficacy profile of adjunctive cenobamate with different concomitant ASMs.

B.2.13.3. End of life criteria

Cenobamate does not meet the criteria for ‘life-extending treatment at the end of life'.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An economic targeted literature review (TLR) was conducted to identify economic evidence for cenobamate and other interventions, for the treatment of FOS seizures in adults, the methodology undertaken is summarised in Appendix G. Searches were performed in December 2019 and update searches performed in October 2020. The key objective was to identify cost-effectiveness studies of therapies available for the treatment of FOS in the adjunctive setting. The main review question that used to identify the studies was:

- What is the economic evidence for cenobamate and its comparators in the treatment of FOS?

Reviews of cost-effectiveness of cenobamate and its comparators in the treatment of FOS were assessed. Full details of the search strategy, eligibility criteria applied, and references identified can be found in Appendix G.

The economic SLR identified nine sources, including both published literature and HTA submission reports for therapies in the adjunctive setting, which are presented in Table 25.

Table 25: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population	Patient population (average age in years)	Incremental effectiveness	Incremental cost	ICER (per QALY gained)
Blais et al. 2005[139]	1999	• Levetiracetam with standard therapy versus standard therapy alone Dose escalation decision-tree model • 1-year time horizon	Patients with partial seizures, receiving a maximum of two classic ASMs	NR	19 SFDs◊	$CAD3924.76◊	$CAD80.70/ SFD gained◊
CEDAC 2011[140]	-	• Lacosamide (adjunctive) and standard therapy compared to standard therapy alone • Model structure was NR	Patients with drug-resistant POS, with or without	NR	-	-	$CAD39,156

			secondary generalisation				
Bolin et al. 2010[141]	2007	• Lacosamide compared to no adjunctive therapy • Decision-tree simulation model over • 2-year time horizon with 6-month cycles • Health states: seizure free, seizure reduction or withdrawal	Patients with drug-resistant POS, with or without secondary generalisation	NR	6 months: 24 QALYs 12 months: 33 QALYs 18 months: 37 QALYs 24 months: 38 QALYs	6 months: €777,227[Δ] 12 months: €1,060,072[Δ] 18 months: €1,168,501[Δ] 24 months: €1,164,470[Δ]	6 months: €30,254[Δ] 12 months: €29,305[Δ] 18 months: €28,651[Δ] 24 months: €27,641[Δ]
Simoens et al 2012[142]	2008	• Lacosamide with standard therapy compared to standard therapy alone • Decision-analytic model • 2-year time horizon with 6-month cycles • Health states: seizure reduction or withdrawal due to non-response	Patients with drug-resistant POS	NR	0.038 QALYs[◦]	€3,619	€4,754[◦] (NMB using a WTP of €30,000/QALY)
SMC 2009[143]	-	• Lacosamide compared to standard therapy alone • Decision-tree model based on pooled results of the two pivotal studies • 2-year time horizon	Patients with refractory epilepsy	NR	0.038 QALYs	-	£20,017
SMC 2010[144]	-	• Eslicarbazepine (adjunctive) compared to lacosamide (adjunctive) • Decision-tree analysis • 2-year time horizon	Patients highly refractory	NR	0.004 QALYs	-	£22,487[†]
Spackman et al. 2007[145]	2004	• Zonisamide and lamotrigine compared to levetiracetam and lamotrigine • Markov model • 15-year time horizon with 3-month cycles	Patients with partial epilepsy who are	NA	0.026 QALYs	Response: £543.99 No response: £582.11	£761

		• Health states: response (stay on treatment, no response (stay on treatment, treatment-limiting event, death	refractory to treatment			Treatment-limiting event: £597.75	
Vaatainen et al. 2019[146]	2019	• DESM • 5-year time horizon • Health states: seizure free, ≥50% seizure reduction, <50% reduction	Patients with FOS, with or without secondary generalisation	38.5	0.059 QALYs	€318 (ASMs, monitoring seizures, traveling)	€5,345
Sheikh et al. 2020[147]	2019	• Surgery compared to medical intervention • Markov decision-analytic model • Lifetime time horizon • One year cycle length	Patients with drug resistant TLE who are eligible for surgery	NR	-3.0 QALYs	Healthcare: -$95,000 Societal: -£185,000	Healthcare: -$31,667 Societal: -$61,333
			Patients with drug resistant TLE		-0.9 QALYs	Healthcare: $15,000 Societal: $3,000	Healthcare: -$16,667 Societal: -$3,333

Abbreviations: ASM, anti-seizure medication; DESM, discrete event simulation model; FOS, focal onset seizure; NA, not available; NR, not reported; POS, partial onset seizure; SFD, seizure-free day;; TLE, temporal lobe epilepsy; QALY, quality-adjusted life-year.
◊ Per patient per year, ∆ Per 1000 patients, ○ Over 24 months
†The base case estimated an average gain of 0.004 QALYs at an average cost of £75 to yield a cost effectiveness estimate of £16,099 per QALY. Applying dose escalation as observed within the one-year open-label study for ESL and an interim analysis of a lacosamide OLE of up to 5.5 years, patient exposure resulted in the net cost rising to £92, resulting in a cost-effectiveness estimate of £22,847/QALY

B.3.2. Economic analysis

An economic targeted literature review (TLR) of cost-effectiveness studies in treatments for FOS in adults was conducted, with searches performed in December 2019 and updated searches performed in October 2020. The studies identified compared levetiracetam, lacosamide and eslicarbazepine acetate with standard therapy. There was one comparison of zonisamide and lamotrigine compared to levetiracetam and lamotrigine, and another comparing brivaracetam as a third concomitant ASM with perampanel as a third concomitant ASM. There was also one study comparing surgical intervention with medical intervention. Patients were aged 38.5 years at baseline the economic analysis by Vaatainen (2019);[146] no other studies reported age at baseline.

Amongst the studies identified a decision tree was the most common model structure, followed by Markov model. Where health states were described in the studies, they focused on the response to treatment and whether patients had remained on treatment or not. None of the cost-effectiveness studies identified considered health states investigating subsequent treatment. Most of the cost-effectiveness studies identified by the SLR considered a time horizon of two years or less – just two studies considered a time horizon of 15 years or more.[145,147] Length of time horizon has been a concern in HTA submissions for treatments for FOS, including brivaracetam and retigabine.[148,149]

For the analyses from a UK perspective ICERs were all below £30,000 per QALY. Lacosamide was associated with an ICER of £20,017 compared to standard therapy alone per QALY gained – though this was assessed over a two-year time horizon. Similarly, eslicarbazepine acetate was associated with an ICER of £22,487 compared to lacosamide over a two-year time horizon. When assessed over a 15-year time horizon, zonisamide with levetiracetam was associate with a £761 ICER compared to lamotrigine when both were used concomitantly with lamotrigine. These results demonstrate that, though over relatively short time horizons, third generation ASMs (i.e. lacosamide and eslicarbazepine acetate) offer small incremental gains in HRQoL.

Given the preference of a lifetime time horizon to capture the full consequences of the disease and treatment benefit, in line with the NICE reference case,[150] as observed in the C017 study where response to treatment is sustained (Section 0) and the NMA found relative improvements compared to the available third generation ASMs (Section B.2.9), a lifetime time horizon is used in the base case to capture the long-term, chronic nature of the condition.

Decision trees historically have been deemed suitable but as it does not allow for flexible movement between response categories, modelling of response to subsequent treatments a Markov model is be preferable.[148] In light reported appropriateness of Markov model structures in previous submissions, a Markov model structure was employed with health states focusing on response to treatment, and expanding to consider subsequent treatment that may occur over a long time horizon.

B.3.2.1. Patient population

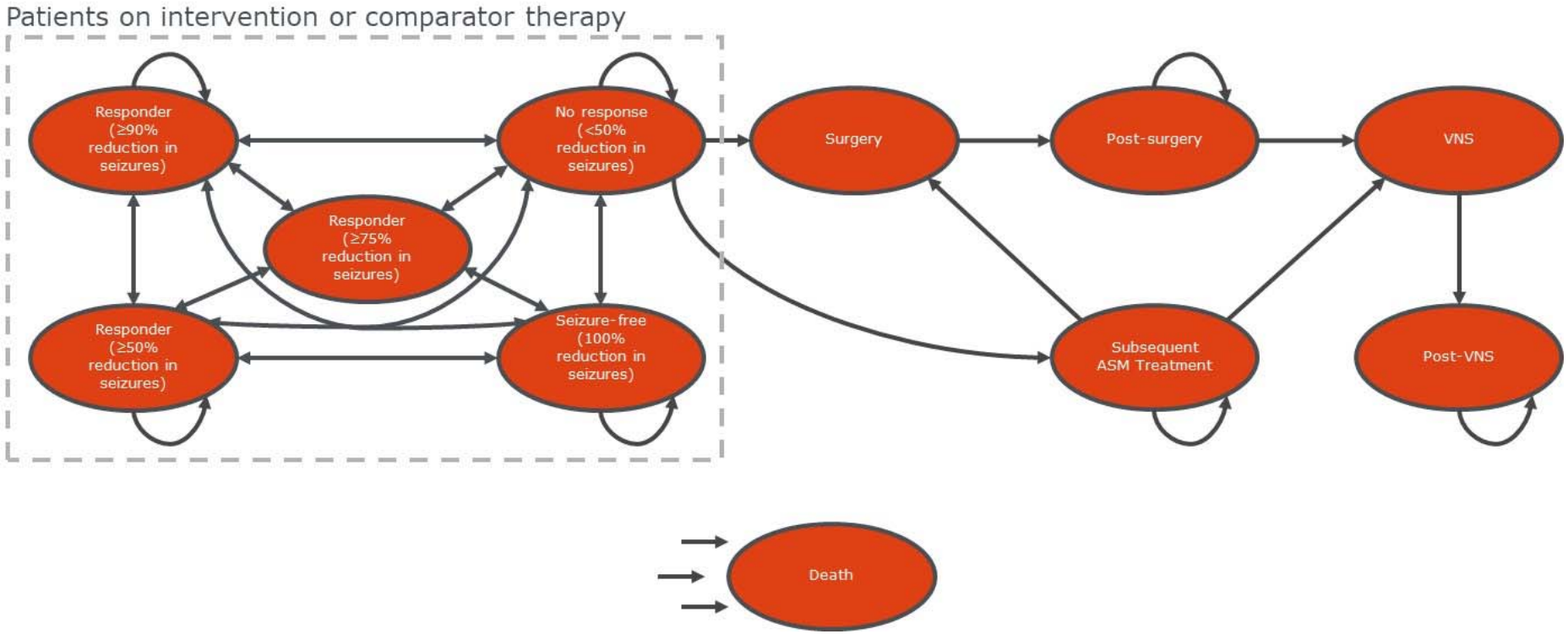
The population entering the CEM includes adult patients with epilepsy who have FOS and have not been adequately controlled despite a history of treatment with at least two ASMs, in line with the anticipated marketing authorization and the population considered in the decision problem (Section B.1.1).

B.3.2.2. Model structure

A *de novo* Markov cohort structure was adopted to capture the long-term, chronic nature of FOS. The model structure was influenced by committee comments in a previous NICE appraisals of ASMs that have suggested that a Markov model was preferable to a decision tree because it would have allowed more flexible movement between response categories, and modelling of response to subsequent treatments and consideration of the uncertainty around model inputs.[148] The choice of a Markov structure was also validated by clinical expert opinion.

The model structure, illustrated in Figure 45, simulates the movement of patients between the illustrated health states. The structure was intended to capture health states according to clinical response (i.e. seizure frequency reduction) to cenobamate and its comparators, including the proportion of patients achieving seizure freedom. The structure also captures the movement of patients to subsequent ASM therapy and invasive procedures (i.e. VNS and surgery).

Figure 45: Markov cohort model structure



Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.
*Responder health states have an upper bound such states are mutually exclusive e.g. the responder >=90% must also be <100%

Patients enter the model in the 'No response (<50% reduction in seizures)' health state where they initiate adjunctive ASM treatment. Whilst on treatment with cenobamate or another of the comparators, patients move between the response health states. The response rate health states are linked to the relative reduction in seizures compared to baseline, aligned with the primary outcome and secondary outcomes of the C017 study:

- 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)
- Complete response i.e. seizure freedom (100% reduction)

Following discontinuation of the intervention or comparator treatment, patients enter the 'subsequent ASM treatment' health state where they receive further combinations of ASM therapies to manage their condition. Patients may leave the subsequent ASM treatment health state if they are suitable for surgery or VNS and proceed to these health states. Patients ineligible for invasive procedures remain on subsequent ASM therapy for the remainder of the model time horizon or until death.

Patients who entered the 'surgery' health state remained there for one cycle to reflect the acute nature of the intervention. Thereafter, patients transitioned to a 'post-surgery' health state and remained there until death. Correspondingly, patients entered the 'VNS' health state on failure of subsequent ASM therapy and remained there for one cycle. Thereafter, patients transitioned to a post-VNS health state and remained there until death.

The NICE reference case states that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any difference in costs or outcomes between the medicines being compared.[150] Consequently, a lifetime horizon was adopted to reflect the high patient retention rates that cenobamate can attain over substantially longer periods of time. This was reflected in a 60-year time horizon with the expectation that no patient can live beyond 100 years.

Over the time horizon, the cohort accrues the costs and outcomes faced when patients transition between the health states based on response rates, uptake of subsequent ASM therapy, referral for invasive procedures or transitions to the 'death' state. A half-cycle correction is applied assuming patients enter/exit health states mid-way through a cycle.

For each cycle, total costs and QALYs are calculated based on the distribution of patients across all health states including 'death'. These are accumulated over the model time horizon to calculate total costs and QALYs for the cohorts from which incremental results and the cost per QALY are determined. Costs and outcomes are discounted at 3.5% per annum in line with the NICE reference case.[150]

The model adopts a UK NHS and PSS perspective on costs and in line with the NICE reference case. The perspective on outcomes considers all direct health effects for patients and carers, in line with the NICE reference case.[150] For this reason, carer disutility is considered in the base case.

Societal costs are included as a scenario analysis to broaden the perspective of the model. Societal costs are incorporated into the model as productivity losses i.e. the relative reduction in both full-time and part-time work in patients in the model compared to the UK general population per treatment cycle. The numbers of carer hours required by health state per cycle is also implemented in the CEM for this sensitivity analysis.

Table 26: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (60 years)	Length of time horizon has been a concern in HTA submissions, including brivaracetam and retigabine.[148,149] C017 OLE study has shown high retention rates for patients on cenobamate (approximately 71% after 2 years and ~60% after 4 years), providing data over this time horizon and rationale for the selected time horizon.
Cycle Length	28 days	28-day cycles align with the schedule of clinical data collection and patients visits to clinicians in the C017 study. The use of 28-day cycles was also validated by clinical experts.[1]
Discount of 3.5% for utilities and costs	Yes	This aligns with the NICE reference case. The impact of alternative discount rates has been tested in sensitivity analyses.
Perspective (NHS/PSS)	UK NHS and PSS	This aligns with NICE reference case which considers all direct health effects for patients and carers.
Treatment waning effect?	N/A	Given the results reported in the C017 OLE, response to treatment is sustained and therefore a treatment waning effect is not applied.[126] Therefore, in the absence of randomised data, transitions over the three maintenance cycles are averaged to extrapolate outcomes.

Abbreviations: HTA, health technology assessment; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OLE, open label extension; PSS, personal social services; UK, United Kingdom.

B.3.2.3. Intervention technology and comparators

Cenobamate is a new adjunctive ASM which has a dual mechanism (Section B.1.2) of action pairing $GABA_A$ positive allosteric modulation with effects on voltage gated sodium channels. C017, the pivotal study, showed that cenobamate achieved unprecedented levels of seizure freedom after 12 weeks of maintenance treatment (18.7% more patients on cenobamate were seizure free than placebo patients [$p<0.001$]).[2] This magnitude of difference has not been shown by any ASM to date (further details of the study are available in Section B.2.6.1).[10,110–113]

Whilst cenobamate has only been directly compared to placebo in the clinical trial setting, a 'do nothing' approach is not a reasonable alternative for patients with drug-resistant seizures. In patients who are drug-resistant, their treatment regime must be amended in order to prompt a reduction in seizures, with the hope of achieving seizure freedom.

There are several treatments available for the adjunctive treatment of patients with drug-resistant FOS (Section B.1.3.3). To align with the NICE scope and the proposed positioning of cenobamate, the comparators included in model are:

- Fycompa (perampanel)
- Briviact (brivaracetam)
- Vimpat (lacosamide)
- Zebinix (eslicarbazepine acetate)

It is important to note, that these comparators were ratified as the most relevant by clinical experts across different sites in the UK. [1] Moreover, these are the most commonly prescribed treatments in the third-line adjunctive setting, whereby packing data indicates they have the largest market share amongst ASMs available in the third line and beyond.

From the final scope, the comparators carbamazepine and levetiracetam have been excluded, as discussed in Section B.1.1. According to NICE CG137, carbamazepine and levetiracetam are both indicated as first-line or second line treatment, in monotherapy or as an adjunctive ASM (Section B.1.3.3). As per the anticipated marketing authorisation for cenobamate, the technology is indicated after a patient has been inadequately controlled on 2 ASMs, therefore making cenobamate a 3rd-line therapy in accordance with NICE CG137. The anticipated licensed indicated for cenobamate excludes use in 1st line (monotherapy) and 2nd line (adjunctive). Moreover, the patients in which cenobamate was studied commonly received these treatments concomitantly, highlighting their use earlier in the treatment pathway.

B.3.3. Clinical parameters and variables

As discussed in Section B.2.2.1, the evidence base for cenobamate comes from the C017 study, its OLE and the C021 study; the C013 study is excluded from the evidence base as it had a shorter maintenance period than the C017 study, lasting only 6 weeks compared to 12 weeks in C017.

The C017 study was used to model the clinical effectiveness of cenobamate. The C021 study also was used to inform the safety and tolerability of cenobamate in clinical practice with the slower titration that would be anticipated in clinical practice. Both the C017 OLE and C021 studies informed clinical effectiveness via sustained response to treatment and treatment discontinuation. Therefore, the clinical effectiveness of cenobamate, demonstrated by the response to treatment at different thresholds, as shown by key outcomes from the C017 study were used to inform the economic model.

Given the absence of clinical trials directly comparing cenobamate and its comparators, an ITC (described in Section B.2.9) was performed to accurately capture the effectiveness of comparator ASMs. The ITC informs the comparative clinical effectiveness of the alternative second-line adjunctive ASMs at their median modal dose relative to cenobamate with

regards to treatment response, likelihood of seizure-freedom and the occurrence of TEAEs (Section B.2.9).

Given the limited published data on the uptake of invasive procedures, UK clinical expert opinion was elicited via a survey to inform these parameters. The survey collected responses from 14 neurology consultants from the United Kingdom. Additionally, data to parametrise effectiveness of subsequent ASM therapy and invasive procedures was identified from published literature; given these effectiveness of these treatment options are not directly compared with cenobamate, an indirect comparison was not necessary.

B.3.3.1. Baseline characteristics

As per Section B.2.3.2, patient demographics at baseline from the C017 study were used to inform the characteristics of the population entering the model (Table 27). The mean age of randomised patients forming the ITT population was 40 years old.[2]

Table 27: Baseline characteristics of patients entering the model

	Value	Reference
Age (years) – mean (SD)	39.8 (11.79)	Krauss *et al*. (2020)[2]
Male – n (%)	50.6	Krauss *et al*. (2020)[2]

Abbreviations: SD, standard deviation

B.3.3.2. Treatment response

Response to treatment with cenobamate was parametrised according to the relative reduction in seizures compared to baseline using patient level data. Data were sourced from the C017 study; the 200 mg and 400 mg arms were included in the derivations as they reflect the anticipated dose range of cenobamate.

For each patient, their level of response over the last 28 days, as defined according to the health states in the Markov structure Figure 45, was identified by calculating the relative reduction in seizures over the last 28 days compared to the frequency of seizures observed during the screening period. A description of each response category and the distribution of patients amongst them after cycle 5 is shown in Figure 46.

Figure 46: Distribution and description of response categories amongst cenobamate patients

Type of Response	Distribution	Description
No response	37.8%	Drug-resistant epilepsy, less than 50% reduction in seizure rate after addition of adjunctive treatment
Moderate response	20.3%	50-75% reduction in seizure rate after addition of adjunctive treatment
High response	12.2%	75-90% reduction in seizure rate after addition of adjunctive treatment
Very high response	5.8%	90-100% reduction in seizure rate after the addition of adjunctive treatment

Complete response	23.8%	Seizure freedom – 100% reduction in seizure rate

Source: Data on file.

Transitions between the different rates of response were generated by observing the movement of patients between these health states at Visits 3, 5, 7, 8 and 9 of C017. Transition probabilities for the first five cycles of the model were parameterised using the time to respond between Visit 3 (initiation of titration) and Visit 9. The time between Visits 3 and 5 was split into two cycles to reflect an extended titration period, as is anticipated in clinical practice.

Patients were assumed to start treatment without having attained a response to treatment, as Visit 3 is when patients begin titration. All patients start from the 'no response (<50% reduction)' health state at baseline. The response rate transition probabilities for cenobamate and comparator treatments from cycle 6 onwards were extrapolated using the average transition probabilities over cycles 3-5, which comprised the maintenance period.

A scenario analysis is present in which, following the first five cycles which are derived from the C017 study, data from the C017 OLE is used to derive response rate transition probabilities over cycles of 84 days. Therefore, after the first five cycles, the model used a cycle length of 84 days. There are 22 cycles of data from the C017 OLE which are then extrapolated using the average over all OLE transitions. This demonstrates how response to treatment develops with time on treatment.

The transition matrices applied from baseline to cycle 5, and extrapolation from cycle 6 onwards can be found in Appendix J1.1 (Table 1). The transition matrices applied in the scenario analysis for extrapolation can also be found in Appendix J1.1.

Odds ratios from the ITC random effects models (Section B.2.9) informed the treatment response for comparators. Treatment response was defined as the reduction in epileptic seizures after three months. Outcomes considered in the ITC were the proportion of patients with ≥50% reduction in seizures (moderate response) and the proportion of patients with seizure freedom (complete response).

To apply the odds ratios to transition probabilities, the odds ratios were converted to risk ratios. The proportion of patients responding to treatment averaged over the 200mg and 400mg arms at the end of the double-blind phase of the C017 study were used to anchor the odds ratios of response relative to cenobamate. These values enabled the isolation of the odds of each level of response with the comparators, which were then converted to risks to identify the risk ratios of response with comparator treatments relative to cenobamate. Risk ratios relative to cenobamate were then applied to the transition probabilities for cenobamate to generate transition matrices for the comparator treatments.

B.3.3.3. Clinical effectiveness of subsequent ASM therapy and invasive procedures

The clinical effectiveness of subsequent ASM treatment was used to parameterise distribution of patients according to level of response to treatment (i.e. seizure reduction and seizure freedom) within the subsequent ASM treatment and invasive procedure health states. The clinical effectiveness of subsequent ASM treatment was captured through the

Chen *et al*. (2018) study which reported the odds ratio of having DRE with subsequent ASM treatment relative to the previous line of therapy (OR [95% CrI]= 1.73 [1.56, 1.91]).[32]

Clinicians estimated that, annually, 2.0% and 2.7% of patients on subsequent ASM treatment move on to surgery or VNS, respectively. This annual probability was adjusted to reflect the probability per cycle and was used to inform the transition probability for patients on subsequent ASM treatment who move on to either surgery or VNS.

The proportions of patients who had ≥50% reduction in seizures and seizure freedom following surgery were sourced from the study by Picot et al. (2016) with values of 5.2% (where "ILEA class 2" is assumed equivalent to a 50% reduction in seizure frequency) and 69%, respectively.[151] For patients undergoing VNS, the proportions of patients who had a ≥50% reduction in seizures and seizure freedom were sourced from the study by Hamilton et al. (2018) with values of 59% and 6%, respectively.[152]

The proportions of patients who experience death following either surgery or VNS were sourced from the studies by Sperling et al. (2016) and Granbichler et al. (2015) with values of 0.86 and 0.97, respectively.[153,154] Table 28 outlines the clinical inputs for subsequent ASM treatment and invasive procedures.

Table 28: Effectiveness of subsequent ASM treatment and invasive procedures

Characteristic of clinical effectiveness	Surgery	VNS
Proportion of patients on subsequent ASM treatment who move on to an invasive procedure, per cycle	0.15%	0.21%
Proportion of patients who experience death following the invasive procedure	0.86%	0.97%
Proportion of patients who achieve ≥50% and <100% responder rate with subsequent treatment, per cycle	5.20%	59.00%
Proportion of patients who achieved seizure freedom with subsequent treatment, per cycle	69.00%	6.00%
Subsequent ASM therapy – clinical effectiveness		
Odds ratio of remaining drug-resistant with subsequent ASM treatment relative to current ASM treatment	1.73	

Abbreviations: ASM, antiseizure medicine.

Table 42 shows the distribution of patients on subsequent ASM therapy and invasive procedures based on treatment response calculated using the inputs and responses gathered in Table 28. It was assumed that patients in the surgery and VNS health states would have no response.

Table 29: Distribution of patients among response states in subsequent ASM treatment and invasive procedures

Response to treatment	Post-surgery	Post-VNS	Subsequent ASM
No response	25.80%	35.00%	53.40%
Moderate response	2.56%	29.10%	16.81%
High response	1.84%	20.92%	12.08%

Very high response	0.79%	8.98%	5.19%
Complete response	69.00%	6.00%	12.51%
On subsequent treatment following invasive procedure	30.21%	85.02%	100%

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.

B.3.3.4. Seizure occurrence

The frequency of seizures over a 28-day cycle was used to quantify resource use associated with event management per year according to response category. Baseline seizure frequency rates were attained from expert clinical opinion.

Data on the relative reduction by split by seizure type and response category, in Table 30, were generated from the C017 study using patient level data.[155] The relative reduction of seizures per cycle in patients who receive subsequent ASM therapy or invasive procedures was derived from the distribution of patients' treatment responses as described in Table 29.

Table 30: Seizure frequency per 28 days at baseline and median seizure reduction, by seizure type and response to treatment

	Focal aware	**Focal impaired awareness**	**Focal to bilateral tonic-clonic**
Baseline seizure frequency			
Average number of seizures per 4-week period:	4.63	6.25	2.50
Average reduction in seizure type by response category			
No response	-18.57%	-7.06%	7.11%
Moderate response	68.26%	59.73%	60.75%
High response	80.53%	84.32%	83.11%
Very high response	95.96%	95.50%	95.11%
Complete response	100.00%	100.00%	100.00%

Source: Data on file.

B.3.3.5. Adverse events

For cenobamate, the occurrence of adverse events was sourced from the C021 study, for the titration phase, and the C017 study, for the maintenance phase. Only TEAEs that were reported in more than 5% of subjects taking cenobamate were used. It has been assumed that TEAEs occurring in less than 5% of subjects has a minimal impact on costs and HRQoL. The frequency of AEs was adjusted to reflect the cycle length, using methods described by Briggs et al. (2006).[156]

$$p_B = 1 - \exp\left(-\left[-\frac{\ln(1-p_A)}{n}\right]\right)$$

Where p_A is the probability of the event from the study, n is the number of cycles occurring over the period that the event was observed, and p_B is the probability of the event over a cycle.

During the titration phase, somnolence, dizziness, headaches, and fatigue were the most commonly reported TEAEs, whilst during the maintenance phase, somnolence, dizziness, and headache were the most commonly reported TEAEs. These adverse events, which were applied in the model using their probabilities per cycle, are described in Table 31.

Table 31: Rate of adverse events with cenobamate

Adverse event	**Rate during titration adverse events**
Somnolence	6.02%
Dizziness	4.44%
Headache	1.93%
Fatigue	3.39%
Adverse event	**Rate during maintenance treatment**
Somnolence	1.30%
Dizziness	2.09%
Headache	1.38%

Source: Data on file

For comparators, the output of the ITC (Section B.2.9) was used to generate the rate of adverse events. Table 32 presents the results of the ITC for the base case comparators.

Table 32: Odds ratio of adverse events relative to cenobamate (base case comparators)

	Brivaracetam	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
OR of adverse events relative to cenobamate	0.62	0.63	1.06	0.92

Abbreviations: OR, odds ratio.
Source: Data on file

Table 33 shows the resulting TEAEs during the titration and maintenance phase, derived from the cenobamate TEAE rates and ITC values for base case comparator treatments.

Table 33: Rate of adverse events during titration and maintenance phases

	Brivaracetam	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Rate of adverse events during titration				
Somnolence	4.05%	4.09%	6.30%	5.64%
Dizziness	2.98%	3.01%	4.64%	4.15%
Headache	1.30%	1.31%	2.02%	1.81%
Fatigue	2.28%	2.30%	3.55%	3.18%
Rate of adverse events during maintenance treatment				
Somnolence	0.87%	0.88%	1.36%	1.22%
Dizziness	1.41%	1.42%	2.19%	1.96%
Headache	0.93%	0.94%	1.44%	1.29%

Source: Data on file

Table 34 shows the rates of TEAEs for patients on subsequent ASM treatment. As it is assumed that patients on subsequent ASM treatment will try another second-line adjunctive ASM, the TEAE rates during the cenobamate titration period are assumed to be equal to the annual probability whilst patients are on subsequent ASM treatment. These values are then adjusted to per-cycle probabilities, as shown in the table below.

Table 34: Probability of adverse events during subsequent ASM treatment

Event	Probability
Somnolence	1.89%
Dizziness	1.38%
Headache	0.60%
Fatigue	1.05%

Abbreviations: ASM, antiseizure medication.
Source: Data on file

Table 35 shows the probability of TEAEs for patients who have undergone VNS. TEAE values were sourced from a study by Panebianco et al. (2015) from the Cochrane database of systematic reviews, assessing the rate of adverse events for patients on high stimulation for partial seizures.[157] These TEAEs were not adjusted since it was assumed that if they occurred, patients would experience them in the cycle during which they had the procedure.

Table 35: Probability of adverse events during VNS

Event	Probability
Voice alteration hoarseness	54.50%
Cough	31.70%
Dyspnoea	18.10%
Pain	24.10%
Paraesthesia	13.40%
Infection	5.00%

Abbreviations: VNS, vagus nerve stimulation.

Table 36 shows the probability of TEAEs for patients who have undergone surgery. TEAE values were sourced from the study by Hader et al. (2013), assessing the reported frequency of medical complications.[158] The adult population was used to inform the TEAEs in the table below. These TEAEs were not adjusted since it was assumed that if they occurred, patients would experience them in the cycle during which they had the procedure.

Table 36: Rate of adverse events during surgery

Event	Probability
Neurological complications	8.80%
Infection	1.90%
Aseptic meningitis	3.40%
Deep vein thrombosis/pulmonary embolus	0.70%
Intracranial hematoma	2.00%

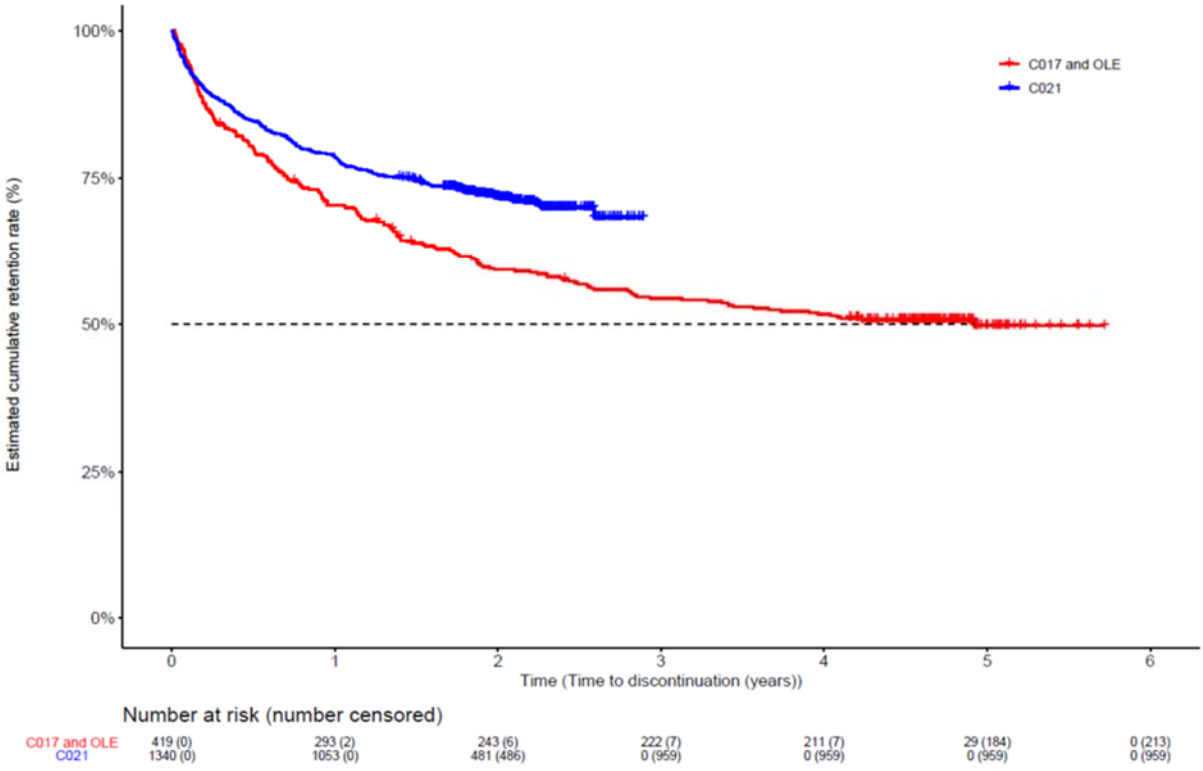
Pneumonia	1.50%
Cerebrospinal fluid leak	4.30%
Hydrocephalus	1.30%

B.3.3.6. Treatment discontinuation

Parametric distributions were used to extrapolate the proportion of patients continuing treatment beyond the study duration of the pivotal trials (C017 and C021). Estimates from the extrapolations were used to model the movement of patients from the treatment response health states to the 'subsequent ASM treatment' health state.

As shown in Figure 47, approximately 50% of patients remained on treatment five years after entry into the C017 OLE study. During the C017 study, 14% and 20% of 200 mg and 400 mg cenobamate-treated individuals discontinued, respectively. From entry to C017, approximately 59% of patients remained on treatment after two years. Conversely, in the C021 study, 68% of patients remained on treatment after three years. This reflects a reduced discontinuation frequency which may be attributable to slower titration, as anticipated in clinical practice and considered in the economic model. When considering the C017, C017 OLE and C021 studies together, after five years, approximately 57.6% of patients remained on treatment.

Figure 47: Time to discontinuation in the OLE studies



Abbreviations: OLE, open-label extension.

Data from the C017, C017 OLE and C021 study were used to inform the Kaplan Meier curve and the parametric distributions for TTD. The Kaplan Meier curve that was extrapolated using parametric distributions combines data from the C017, its OLE and C021. Table 37

shows the resulting parametric distributions along with their respective Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics.

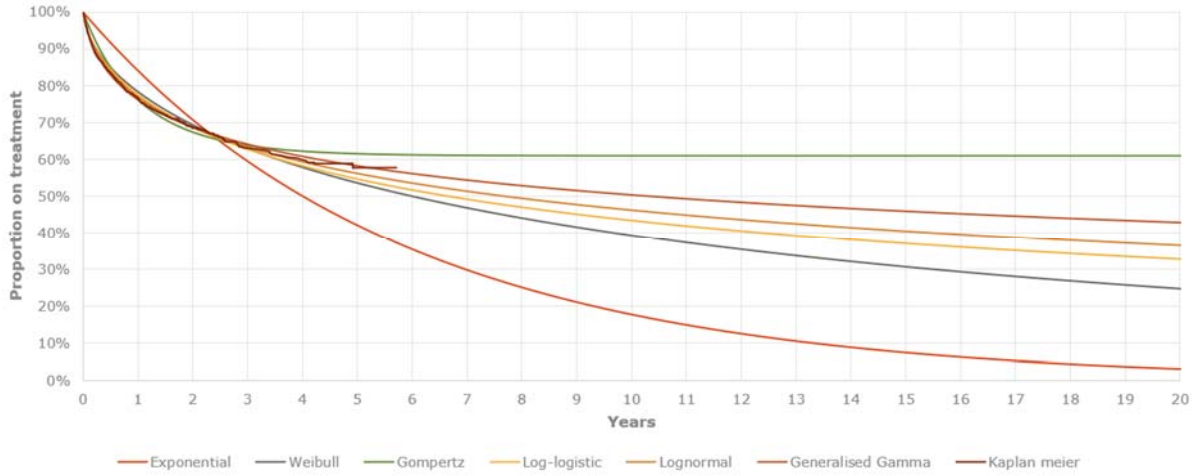
Table 37: AIC and BIC statistics from time-to-discontinuation parametric distributions

Distribution	AIC	BIC
Exponential	3236.42	3241.90
Weibull	2992.04	3002.98
Gompertz	2996.76	3007.71
Log-logistic	2974.38	2985.32
Lognormal	2946.74	2957.69
Generalised Gamma	**2939.36**	**2955.78**

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

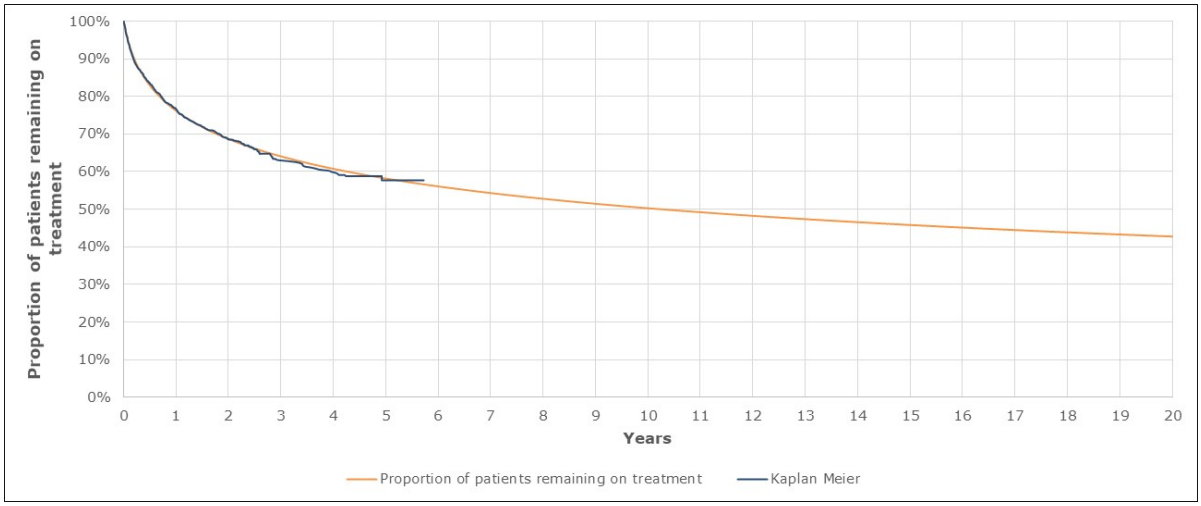
Figure 48 shows all parametric distributions and the Kaplan Meier curve. According to 4 UK expert clinicians, given the advantage that cenobamate has with regards to seizure freedom compared with other second-line ASMs, the most suitable parametric distribution to reflect treatment duration of cenobamate in a clinical setting is expected to be flatter compared to other distributions.

Figure 48: Time to discontinuation (cenobamate) - all distributions



The generalised gamma was the most appropriate curve for estimating treatment discontinuation, as shown in Figure 49. The selection was made after taking into account the flatter shape of the distribution, its AIC and BIC values being the lowest (AIC = 2939.36; BIC = 2955.78) and its consistency with treatment duration observed in the C017, C017 OLE and C021 studies (~69% of patient retention after two years). The TTD extrapolation demonstrates that the treatment benefit of cenobamate extends for many years as patients continue to respond to treatment.

Figure 49: Time to discontinuation - generalised gamma



Time-to-discontinuation extrapolations for comparator treatments were derived by generating naïve hazard ratio (HR) values based on published literature as shown in Table 38.

Table 38: Sources for discontinuation of comparators

Treatment	TTD source
Brivaracetam	O'Brien (2020a)[159]
Lacosamide	Rosenfeld (2014)[160]
Eslicarbazepine acetate	Halasz (2010) and Hufnagel study (2013)[161,162]
Perampanel	Krauss (2018)[155]

Abbreviations: TTD, time to discontinuation.

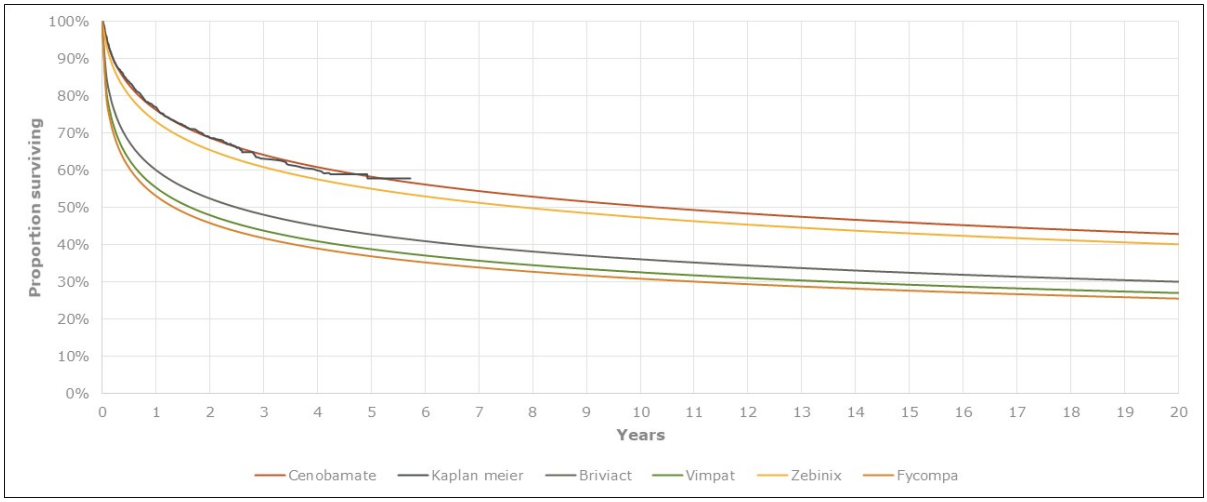
Time-to-discontinuation HRs for comparator therapies can be found in Table 43. The resulting time-to-discontinuation applied for all comparators is presented in Figure 50.

Table 39: Hazard ratio of discontinuation relative to cenobamate

Treatment	HR
Brivaracetam	1.56
Lacosamide	1.78
Eslicarbazepine acetate	1.10
Perampanel	1.89

Abbreviations: HR, hazard ratio

Figure 50: Time to discontinuation (generalised gamma) - all treatments



B.3.3.7. Mortality

Published literature has shown that treatment with adjunctive ASMs at efficacious doses is seven times more likely to reduce the incidence of definite or probable SUDEP compared with placebo.[163]

On this basis, the 'Death' health state accumulates patients who die due to all-cause mortality, adjusted for greater risk of death due to seizure occurrence. Hazard ratios attributed to greater risk of death due to seizure occurrence were sourced from the study by Trinka *et al*. (2013) which discloses HRs for subgroups of patients who achieve seizure freedom (HR = 1.6) and do not achieve seizure freedom (HR = 2.4).[47] The appropriateness of incorporate death in this way was validated by 2 UK clinical experts and a HEOR expert.[1]

HRs were applied to the treatment response health states. HRs attributed to subsequent ASM treatment and invasive procedure health states were derived from the distribution of patients' response. Hazard ratios applied to each health state are shown in Table 40.

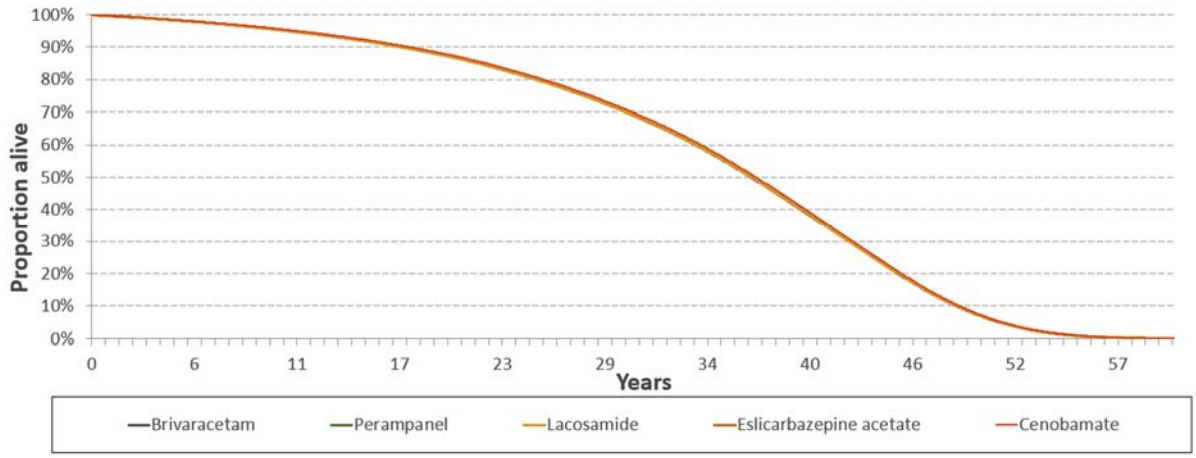
Table 40: Mortality hazard ratios by health state

Health state	HR
No response (<50% reduction)	2.40
Responder Rate ≥50% and <75%	2.40
Responder Rate ≥75% and <90%	2.40
Responder Rate ≥90% and <100%	2.40
Seizure-freedom (100% reduction)	1.60
VNS	2.40
Post-VNS	2.27
Surgery	2.40
Post-surgery	1.82
Subsequent ASM Treatment	2.30

Abbreviations: ASM, anti-seizure medicine; HR, hazard ratio; VNS, vagus nerve stimulation

The HRs for mortality are applied to mortality in the UK according to age and gender. This was sourced from the Office of National Statistics (ONS).[164] The resulting mortality applied in the model is illustrated in Figure 51.

Figure 51: Proportion alive over 20-year period



B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

Health-related quality of life (HRQoL) was measured in the C017 study via the disease-specific Quality of Life in Epilepsy (QOLIE-31-P) instrument. The instrument includes 31 questions about health and daily activities which is completed by patients. It is scored on a scale of 0 to 100, where a higher score indicates more favourable QoL.

QOLIE-31-P was measured in individuals in C017 following screening at initiation of treatment and again either when they completed the maintenance phase of the study or terminated early. A minimally important change (MIC) between baseline and the endpoint was predetermined to be 11.8.[165] HRQoL endpoints measured by the QOLIE-31-P were only included in a subpopulation of English-speaking patients from the US, UK and Australia. In total, 133 patients (across all treatment groups) were assessed at baseline, with 120 being assessed post-baseline. A summary of the outcomes reported in C017 is provided in Table 41.

Table 41: QOLIE-31 score as measured in the C017 study

	Cenobamate 100 mg (N=108)	Cenobamate 200 mg (N=109)	Cenobamate 400 mg (N=111)	Placebo (N=106)
Mean baseline score (SD)	65.6 (13.7)	57.3 (17.0)	61.5 (15.3)	59.3 (17.5)
Mean score at the endpoint (SD)	63.9 (14.8)	60.8 (16.9)	55.5 (14.3)	62.8 (12.7)
Mean change from baseline (SD)	-0.81 (9.7)	0.62 (12.0)	-6.21 (17.0)	3.76 (11.4)

MIC n (%)	3 (11.1)	3 (11.1)	5 (15.2)	7 (24.1)

Abbreviations: MIC, minimally important change; SD, standard deviation

The cenobamate 200 mg and placebo arms saw improvements in QOLIE-31-P score over the treatment period, though the statistical significance of this was not tested. Additionally, placebo patients saw the greatest proportion of patients achieving a MIC in QOLIE-31-P score.

However, given that the maximum time difference between baseline and the endpoint considered was 18 weeks, of which 6 weeks comprised titration, there was not sufficient time to demonstrate a meaningful benefit in QoL as measured by QOLIE-31-P. Indeed, the MIC of 11.8 was elicited from a study in which these changes in QOLIE-31-P score were observed over a 6-month period.[165] In a sensitivity analysis of the same study, the MIC was reduced to 4.4 over a time period of 9 months.

B.3.4.2. Mapping

Rationale

Given the absence of utility data available from the cenobamate clinical trials, a de novo mapping study was performed. This is supported by NICE clinical guidance (based on the development of five economic models) which states that where utility data is unavailable to inform the estimation of QALYs, the development of an algorithm to map epilepsy-specific quality of life outcome measure onto a preference-based generic measure could be very useful for economic work.[166]

The QOLIE-31-P data collected in the C017 study was not utilised in the mapping since a correlation was not observed between HRQoL and reduction in seizure occurrence, likely due to the limited follow-up time to demonstrate improved quality of life due to reduce seizure occurrence during the clinical trial. Moreover, it was found that seizure frequency is not an independent predictor of HRQoL, and seizure frequency overall was poorly correlated with QOLIE-31 scores.[71,167] At present there has only been one development of a mapping function to predict EQ-5D-5L values in people with epilepsy based on the general (non-preference based) condition-specific instrument QOLIE-31-P, for use in economic evaluations.[168] However, the results of the study highlighted the shortcomings of the EQ-5D-5L in people with epilepsy and, therefore, the overall limited use of the mapping function. Indeed, EQ-5D-5L considers the health of patients today only, and therefore does not consider the variation of HRQoL in patients with epilepsy over time given that there may be days in which drug-resistant patients have numerous seizures, and other days where they have no seizures at all. Therefore, the EQ-5D tool is an inappropriate choice to capture the changes in quality of life in patients with epilepsy as their seizure frequency change.

Contrastingly, the Short-Form (36) Health Survey (SF-36) is a 36-item patient-reported survey asking questions pertaining to a patient's HRQoL over time, with the majority of questions focusing on health over the last 4 weeks. The SF-36 generates scores on a 0-100 range, where a higher SF-36 score indicates greater HRQoL. This tool is much more suitable to reflect HRQoL in patients with DRE as it accounts for the variability in health– it does not consider HRQoL to be the same day by day. However, it does not produce a utility value.

The Short Form-Six Dimension (SF-6D) is derived from the SF-36 and covers six dimensions including physical functioning, role limitation, social functioning, pain, mental functioning, and vitality. Each dimension has four to six response levels. It is a preference-based measure of HRQoL that comes with a set of preference weights obtained from a sample of the UK general population using the recognised valuation technique of standard gamble. Totally, the SF-6D system defines 18,000 health states with a utility score ranging from 0.29 to 1.00.[169] Therefore, it was determined that the most appropriate tool to value HRQoL in patients with epilepsy would be the SF-6D obtained via the SF-36.

In order to determine how to parametrise quality of life, literature was reviewed to identify the explanatory variables for patients with epilepsy. Literature relating to the QoL and seizure frequency of people with FOS presents mixed results. As already noted, it was found that seizure frequency is not an independent predictor of HRQoL, and seizure frequency overall was poorly correlated with QOLIE-31 scores.[71,167] This can be explained by other domains such as depression, seizure worry and social functioning having a more profound impact on the patient's QoL than the frequency of their seizures. In contrast, Velez et al. and Cramer et al. observed further improvement in HRQoL with greater reductions in seizure frequency.[170,171] The main finding from the literature was that for a significant improvement in QoL to occur, seizure freedom is imperative.[172]

Published literature has shown that greater seizure severity was associated with lower overall QoL. Viteva (2014) demonstrated that patients with lower seizure severity – i.e. a lower Liverpool Seizure Severity Scale [LSSS] score – experienced higher QOLIE-89 scores than patients with higher seizure severity (QOLIE-89 score: 52.57, 47.84 and 42.64 in patients with LSSS of 1-20, 21-40 and ≥41, respectively).[173] Given that C017 also assessed three different seizure severity rates for each endpoint (including focal aware, focal impaired awareness, and focal to bilateral tonic-clonic seizures), seizure severity was also considered a key explanatory variable for HRQoL in patients with epilepsy.

The methodology employed to perform the mapping analysis can be found in Appendix H.

Results

A total of 361 individuals (males and females) with FOS were included in the final analysis set. The age of participants ranged from 18 to 69 years, with a mean age of 38 years. The majority of patients were from the United Kingdom (45%), followed by Spain (18%), Italy (18%), Germany (17%) and France (12%). A summary of the descriptive statistics, mapping analyses and model validation can be found in Appendix H.

The best fitting algorithm was the OLS regression model. This model is made up of one dependent variable (SF-6D utility index score), and four independent variables (seizure frequency, seizure freedom, seizure severity, and age). The final mapping algorithm is presented below and the details for each variable are displayed in Table 42.

[redacted]

Table 42. Variable details for the cenobamate mapping algorithm

Variable	Variable name in regression	Description

Predicted SF-6D utility index score	PrSF6D	The SF-6D scores are based on methods developed by Brazier and colleagues (16). In subsequent work, Brazier and colleagues updated the scoring algorithms for the SF-6D with the key objective of accurately dealing with missing SF-36/SF-12 item level data and these revised algorithms are incorporated into the model (29).
Seizure frequency	Seizures in 28days	The amount of seizures the person with FOS has experienced in the past 28 days.
Seizure freedom	Period seizure free	The longest amount of consecutive days the person with FOS has been seizure free for in the past 28 days.
Seizure severity	Tonic-clonic	Has the person with FOS experienced a focal to bilateral tonic clonic (secondary generalised) seizure in the past 8 weeks? Binary variable: Yes = 1 No = 0
Age	age	The age of the person with FOS.

Abbreviations: FOS, focal onset seizure, SF-6D, Short Form-Six Dimension

The predicted utilities from the OLS model estimated using seizure frequency, seizure freedom, seizure severity and age are presented in Table 43 and compared with the observed SF-6D utilities recorded in the patient sample. The results show that the mean value for OLS are identical to the observed SF-6D mean value. However, there was a difference in observed SF-6D estimates with predicted values for the minimum and maximum values, with the minimum being slightly greater and maximum lower for all models.

Table 43. Summary of observed and predicted values

	Observed SF-6D utilities	**OLS**
N	361	361
Mean	[redacted]	[redacted]
SD	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]

Abbreviations: ALDVMM. adjusted limited dependent variable mixture model; N/A, not applicable; OLS, ordinary-least squared; *Note that the AIC and BIC are not comparable to those for the other models due to the method of estimation for this model

Interpretation

This model assumes that the relationship between the dependent variable (SF-6D) and the independent variables are expressed as a linear function of the parameters. OLS models are usually reliable for predicting mean scores. A limitation to the OLS model is that it might be an inappropriate technique for mapping regressions onto SF-6D due to the bounded nature of the instrument. For instance, individuals cannot obtain a utility value higher than 1, which

represents ‘full health’. In this sample, no respondents reported full health and therefore this is not an issue for this mapping study. However, it should be noted that the mapping may underpredict the range of utilities amongst patients with epilepsy. Indeed, the minimum and maximum utility values fit were an over- and under-estimation, respectively. Therefore, the range of utilities generated by this mapping function are likely to be a conservative estimate of the true range.

Furthermore, it is noted that the UK based preference measure for SF-6D is bound below by 0.29; therefore, range of utility for HRQoL measured via SF-6D is censored below. Indeed, the EQ-5D makes it possible to estimate quality of life in states worse than death, whereby a utility less than 0 can be generated. For this reason, the mapping function may overestimate HRQoL in the worst health states.

B.3.4.3. Health-related quality-of-life studies

A TLR was undertaken to identify and summarise the best available HRQoL evidence available for the treatment of FOS, the methodology undertaken is summarised in Appendix H. Searches were performed in December 2019 and update searches performed in October 2020. The key objective was to identify utility values associated with FOS and associated treatments. The main review question that used to identify the studies was:

- What is the economic evidence for cenobamate and its comparators in the treatment of FOS?

The methods of the TLR are reported in Appendix H.

Five of the obtained citations from the review contained utility scores, one of which was hand-searched including a mixture of geographical locations and study populations as shown in Table 45.

However, the majority of the citations obtained from the searches contained mean scores from indirect, disease-specific QoL instruments. The most predominant instrument reported was the Quality of Life in Epilepsy inventory (QOLIE), with the QOLIE-31 being the most common tool used. The QOLIE-89 and QOLIE-10 tools were also reported. Other direct specific tools reported in the included citations were the Impact of Epilepsy, ESI-55, NDDI-E and LSSS, however only a small number were included. The results from the direct specific tools are summarized in Appendix H. Indirect generic tools were also reported in the included citations from the review, including data from the SF-36 survey, and are also summarised in Appendix H.

Amongst the utility values reported in literature, the majority simply reported the change in quality of life with treatment over time. Xu (2006) reported how HRQoL varied according to whether patients had sleep disturbance or not.[174] Fiest (2004) reported how quality of life changed according to whether patients were treated with ASMs or surgery.[175] Only Phumart (2018) reported QoL according to response to treatment, however the utility values did not sufficiently parametrise the intermediate response states in the Markov model.[176] Moreover, they could not characterise the QoL of patients in subsequent treatment.

A caregiver survey was also conducted to identify and quantify the burden of care for unpaid carers looking after patients with FOS who have ≥3 FOS per week. The EQ-5D-5L measure

assessed caregivers' HRQoL; Table 44 shows the mean age- and sex-adjusted disutility values stratified by patient characteristics, with caregivers experiencing a disutility of [redacted] on average. Caregiver disutility was [redacted]. Given the small population size of the survey, there was not power to detect differences between population groups.

Table 44: Summary of caregiver quality of life by patient disease characteristics

Variable	N	Percentage	Mean disutility (SD)
All caregivers	[redacted]	[redacted]	[redacted]
FOS number*	**N=85**		
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5 to 10	[redacted]	[redacted]	[redacted]
More than 10	[redacted]	[redacted]	[redacted]
Not sure	[redacted]	[redacted]	[redacted]
Seizure-free period (days)*	**N=83**		
0 to 5	[redacted]	[redacted]	[redacted]
6 to 15	[redacted]	[redacted]	[redacted]
16 to 20	[redacted]	[redacted]	[redacted]
21 to 27	[redacted]	[redacted]	[redacted]
Not sure	[redacted]	[redacted]	[redacted]
Seizure type	**N=83**		
Focal aware	[redacted]	[redacted]	[redacted]
Focal impaired awareness	[redacted]	[redacted]	[redacted]
Focal to bilateral tonic-clonic	[redacted]	[redacted]	[redacted]
Not sure	[redacted]	[redacted]	[redacted]
Number of seizures of disabling nature*	**N=83**		
1	[redacted]	[redacted]	[redacted]
2 to 5	[redacted]	[redacted]	[redacted]
6 to 10	[redacted]	[redacted]	[redacted]
More than 10	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; FOS, focal onset seizures.

Table 45: Identified studies reporting average utility scores

Study (year)	Country	Patient population (n)	Details of study arms, time point (n)	Average utility score (SD)
Mulhern (2017)[177]	UK	Newly developed focal epilepsy, Randomised to receive SOC i.e. carbamazepine or one of the other treatments (gabapentin, lamotrigine, oxcarbazepine, or topiramate) (n=1611)	Those completing the EQ-5D-3L, Baseline (n=1563)	0.735 (0.30)
			Those completing the EQ-5D-3L, Year 1 (n=1244)	0.769 (0.29)
			Those completing the EQ-5D-3L, Year 2 (n=1091)	0.789 (0.28)
			Those completing the NEWQOL-6D, Baseline (n=1508)	0.766 (0.13)
			Those completing the NEWQOL-6D, Year 1 (n=1156)	0.798 (0.13)
			Those completing the NEWQOL-6D, Year 2 (n=1023)	0.805 (0.13)
Mukuria (2017)[167]	UK	Patients treated with adjunctive brivaracetam for drug-resistant focal seizures (n=1095)**	Pooled analysis of N01252, N01253, and N0125 trials, Baseline (n=1095)	0.759 (0.232)
			Pooled analysis of N01252, N01253, and N01254 trials, Follow up (n=1095)	0.777 (0.230)
Fiest (2014)[175]	-	Patients with drug resistant TLE (n=80)	Patients treated with epilepsy drugs (n=40)	0.52 (0.32)
			Patients treated with surgery (n=40)	0.62 (0.25)
Xu (2006)[174]	US	Patients with partial-onset epilepsy receiving stable polytherapy regimens (at least two ASMs) * (n=200)	All patients (n=200)	0.64 (0.35)
			Diagnosed sleep disturbance (n=67)	0.49 (0.38)
			No diagnosed sleep disturbance (n=132)	0.71 (0.31)
Phumart (2018)[176]	Thailand	Focal seizure patients (n=225) who were categorised into: • Seizure-free • Seizure reduction • No improvement	Seizure-free (n=67)	0.82 (0.15)
			Seizure reduction (n=93)	0.79 (0.16)
			No improvement (n=64)	0.72 (0.21)

Abbreviations: ASM, antiseizure medicine; ED-5D-3L, EuroQol 5 Dimensions 3 Levels; NEWQOL-6D, Quality of Life in Newly Diagnosed Epilepsy 6 dimensions; SOC, standard of care; TLE, temporal lobe epilepsy. *The most common currently prescribed ASMs were phenytoin sodium (30%), levetiracetam (29%), carbamazepine (28%), and lamotrigine (22%) **Disutility scores (SD) reported for separate studies. N01252: >50% SFR, non-responder (226); 0.019 (0.24), >50%, responder (91); 0.016 (0.21). N01253: >50% SFR, non-responder (235); 0.000 (0.25), >50% SFR, responder (71); 0.103 (0.21). N01254: >50% SFR, non-responder (244); 0.01 (0.23), >50% SFR, responder (100); 0.036 (0.26).

B.3.4.4. Adverse reactions

The impact of adverse reactions to treatment as reported in C017 and C021 (Section B.2.10) were included to characterise the consequence on HRQoL for patients experiencing the events. Given that the occurrence of TEAEs are thought to drive QoL in patients with FOS ,[71] all events occurring in >5% of the population were included.

The duration of and disutility associated with adverse events of treatment were collected from published literature to calculate the total QALY decrement. These were then applied to the proportion of patients experiencing each event, according to their health state, as reported in Section B.3.3.5.

The TEAE disutility values and the disutility duration applied to patients receiving cenobamate or another of the comparators during titration, maintenance or subsequent ASM treatment are shown in Table 46. These inputs were obtained from a multivariate analysis conducted in the Kinderen (2016) study as a coefficient of the experience of side effects.[178] Disutility durations are user defined assumptions on the basis that the TEAEs are transient. The total QALY decrement is a product of TEAE disutility, disutility duration expressed in years.

Table 46: Disutility due to TEAEs

Adverse event	Disutility	Disutility duration (days)	Total QALY decrement
Somnolence	-0.06	28.00	-0.0047
Dizziness	-0.06	28.00	-0.0047
Headache	-0.06	28.00	-0.0047
Fatigue	-0.06	28.00	-0.0047

Abbreviations: QALY, quality-adjusted life-year.

TEAE disutility associated with VNS were sourced from the Oppong (2011) and Matza (2019) studies.[179,180] Disutilities associated with voice alteration, cough and dyspnoea were sourced from Oppong (2011). According to a review by Ben-Menachem, the proportion of patients with cough and dyspnoea was 65% and 16% and 3 months, respectively, 55% and 13% at 12 months, respectively and 1.5 and 2.3% at 5 years respectively.[181] Based on this, in most patients, these TEAEs took on average over a year to resolve and were conservatively assumed to last for one year. Similarly, 62% of patients had voice alteration at 3 months, reducing to 55% after 1 year and 18.7% after 5 years. Though the duration of this TEAE is on average longer than one year, it was assumed that the disutility would last 6 months on the basis that patients voice alteration is not limiting.

Disutilities associated with pain and paraesthesia (sourced from Matza [2019]) were calculated from difference in utility between the general population and those experiencing the AEs.[180] The disutility of infection was identified from Chotai (2015), and was calculated as the difference in digitised utility values over a 1-year period.[182]

Table 47: Disutility due to adverse events - vagus nerve stimulation

Event	Disutility	Disutility duration (days)	Total QALY decrement

Voice alteration hoarseness	-0.16	182.63	-0.08
Cough	-0.16	365.25	-0.16
Dyspnoea	-0.16	365.25	-0.16
Pain	-0.05	365.25	-0.05
Paraesthesia	-0.01	273.94	-0.01
Infection	-0.11	182.63	-0.05

Abbreviations: QALY, quality-adjusted life-year.

TEAE disutility and duration associated with surgery were sourced from the Chotai (2015), Utne (2016), McGill (2018) and Mangen (2017) studies.[182–185]

Disutilities sourced from Chotai (2015) (neurological complications, infection, intracranial hematoma, cerebrospinal fluid leak and hydrocephalus) were calculated as the difference in digitised utility values over a 1-year period using WebPlotDigitizer. Disutility duration was based on time taken for utility to plateau, which in most cases was 3 months (91.31 days). Neurological complications took longer to resolve, and there had a disutility duration of 6 months (182.63 days).[182]

The disutility of pulmonary embolism (PE)/ deep vein thrombosis (DVT) was sourced from, and averaged over, Chotai (2015) and Utne (2016).[182,183] As for other disutilites sourced from Chotai (2015), the disutility was generated by digitising utility over a 1-year period. Given that disutility associated with PE lasted 12 months in Chotai, and duration disutility associated with DVT was not reported, it was conservatively assumed that the disutility of either would last 3 months.[182]

Disutilities sourced from McGill (2018) (aseptic meningitis) were reported in the study; it was reported that patients experienced a QALY loss of 0.2 compared to the age-adjusted general population. Given the reporting on quality of life before and after meningitis, disutility duration was assumed to last 3 months (91.31 days).[184]

Disutilities sourced from Mangen (2017) (pneumonia) were also calculated as the difference in utility values for patients admitted to hospital and after being vaccinated for pneumonia. Disutility duration was based on the average time taken for patients' utility to plateau.[185]

Table 48 displays TEAE disutility, TEAE duration and total QALY decrement with surgery.

Table 48: Disutility due to adverse events – surgery

Event	Disutility	Disutility duration (days)	Total QALY decrement
Neurological complications	-0.20	182.63	-0.10
Infection	-0.11	91.31	-0.03
Aseptic meningitis	-0.20	91.31	-0.05
Deep vein thrombosis/ pulmonary embolus	-0.22	91.31	-0.06
Intracranial hematoma	-0.25	91.31	-0.06
Pneumonia	-0.64	91.31	-0.16

Cerebrospinal fluid leak	-0.28	91.31	-0.07
Hydrocephalus	-0.28	91.31	-0.07

Abbreviations: QALY, quality-adjusted life-year.

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

As the economic SLR was only able to identify a scarce number of studies containing relevant utility values, a mapping study was conducted to generate SF-6D utility values for inclusion in the CEM (Section B.3.4.2). The SF-6D was not mapped to EQ-5D due to shortcomings of the EQ-5D-5L in people with epilepsy.[168]

Data from all patients enrolled in the C017 study were used to retrospectively fit the mapping analysis to generate utility data from the C017 study; utility values were estimated according to patients at the end of the C017 study. Patients were then grouped according to their response rate health state in the last 28 days of the RCT. Averages of the SF-6D utility values by health state were then generated. As the mapping study did not produce statistically significant differences for the >75% and >90% response rates, most likely attributed to the there being just [redacted] patients in the ≥90% response rate in the last 28 days, HSUVs for their associated health states were assumed equal and averaged other both health states as shown in Table 49.

Table 49: Health state utility values according to response rate

	Mean utility (SD)
No response (<50% reduction)	[redacted]
Moderate Response (Responder Rate ≥50% and <75%)	[redacted]
High Response (Responder Rate ≥75% and <90%)	[redacted]
Very High Response (Responder Rate ≥90% and <100%)	[redacted]
Seizure-freedom (100% reduction in seizure frequency)	[redacted]

Abbreviations: SD, standard deviation

Utility values for subsequent ASM treatment, post-surgery and post-VNS were calculated as weighted averages of the response rate utility values and patients' distribution amongst different levels of response to treatment (e.g. proportion of patients undergoing surgery who achieved ≥50% or ≥75% response rate etc.). It was assumed that patients in the surgery and VNS health states would have the same utility as patients with no response to treatment. The resulting base case utility values for these health states are presented in Table 50.

Table 50: Health state utility values

	Utility
VNS	[redacted]
Post-VNS	[redacted]
Surgery	[redacted]
Post-surgery	[redacted]

Subsequent ASM Treatment	[redacted]

Abbreviations: ASM, anti-seizure medicine; VNS, vagus nerve stimulation

In light of the uncertainty that may arise from retrospective statistical analysis, the HSUV inputs were validated by four UK clinicians and a one HEOR expert to ensure that the HSUV inputs reflect what would be observed in a clinical setting.

Despite the HEOR expert agreeing with the method used to attain HSUV by health state, the clinicians advised that a larger increment in HSUV would be observed between patients with very high response and patients who achieve seizure freedom. Clinicians agreed that the HSUV associated with seizure freedom was under-estimated and should be closer to the HSUV of the general population. Conversely, clinicians also agreed that the HSUV associated with 'no response' was over-estimated. Therefore, clinicians indicate that the range of utility expressed from the mapping study may underestimates the value of improving response and seizure freedom; as such, the estimated QALY gains are likely conservative.

Carer disutility were sourced from a caregiver survey used to generate evidence on the quality of life and health-related utility of caregivers of patients with ≥3 FOS per week according to the duration of seizure-freedom. Carer disutility by response health state is shown in Table 51.

Table 51: Carer disutility by response health state

	Carer disutility
No response (<50% reduction)	[redacted]
Moderate Response (Responder Rate ≥50% and <75%)	[redacted]
High Response (Responder Rate ≥75% and <90%)	[redacted]
Very High Response (Responder Rate ≥90% and <100%)	[redacted]
Seizure-freedom (100% reduction in seizure frequency)	[redacted]

Carer disutility values for subsequent ASM treatment, post-surgery and post-VNS were calculated as weighted averages of the carer disutility values and patients' distribution amongst different levels of response to treatment (e.g. proportion of patients undergoing surgery who achieved ≥50% or ≥75% response rate etc.). It was assumed that patients in the surgery and VNS health states would have the same carer disutility as patients with no response to treatment. The resulting base case carer disutility values for these health states are presented in Table 52.

Table 52: Carer disutility values for Subsequent ASM therapy and invasive procedures

	Carer disutility
VNS	[redacted]
Post-VNS	[redacted]
Surgery	[redacted]
Post-surgery	[redacted]
Subsequent ASM Treatment	[redacted]

Abbreviations: ASM, antiseizure medication; VNS, vagus nerve stimulation

Disutilities due to adverse reactions

As mentioned in section B.3.4.4, the QoL decrement associated with adverse events of treatment were collected from published literature.

The disutility of accidents due to seizure occurrence was also captured in the model in sensitivity analyses. Disutility values were sourced from the Polinder (2009) study and calculated as the difference between the weighted average utility value for the general population and the average utility for patients who have experienced a given injury.[186] Disutility duration are assumed to be a month each based on the transient nature of acute injury.

B.3.4.6. Summary of utility values for cost-effectiveness analysis

Table 53: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Health state utility values				
Utility: No response (<50% reduction)	[redacted]	[redacted]	B.3.4.5	Generated from mapping study
Responder Rate ≥50% and <75%	[redacted]	[redacted]		
Responder Rate ≥75% and <90%	[redacted]	[redacted]		
Responder Rate ≥90% and <100%	[redacted]	[redacted]		
Seizure-freedom (100% reduction)	[redacted]	[redacted]		
VNS	[redacted]	[redacted]	B.3.4.5	Assumed equal to no response
Post-VNS	[redacted]	[redacted]	B.3.4.5	Weighted average of mapping study and distribution of clinical effectiveness
Surgery	[redacted]	[redacted]	B.3.4.5	Assumed equal to no response
Post-surgery	[redacted]	[redacted]	B.3.4.5	Weighted average of mapping study and distribution of clinical effectiveness
Subsequent Treatment	[redacted]	[redacted]	B.3.4.5	
TEAE disutility				
Somnolence	-0.06	N/A	B.3.4.4	
Dizziness	-0.06	N/A		

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Headache	-0.06	N/A		Adverse effects of treatment strongly contribute to HRQoL.
Fatigue	-0.06	N/A		
AE disutility: vagus nerve stimulation (VNS)				
Voice alteration hoarseness	-0.16	N/A	B.3.4.4	Sourced from published literature
Cough	-0.16	N/A		
Dyspnoea	-0.16	N/A		
Pain	-0.05	N/A		
Parathesis	-0.01	N/A		
Infection	-0.11	N/A		
AE disutility: surgery				
Neurological complications	-0.20	N/A	B.3.4.4	Sourced from published literature
Infection	-0.11	N/A		
Aseptic meningitis	-0.20	N/A		
Deep vein thrombosis/ pulmonary embolus	-0.22	N/A		
Intracranial hematoma	-0.25	N/A		
Pneumonia	-0.64	N/A		
Cerebrospinal fluid leak	-0.28	N/A		
Hydrocephalus	-0.28	N/A		
Disutility due to accidents during seizure occurrence				
Head contusions	-0.06	N/A	B.3.4.4	Sourced from published literature
Other contusions	-0.06	N/A		
Head lacerations	-0.07	N/A		
Other lacerations	-0.07	N/A		
Fracture (facial bone)	-0.06	N/A		
Fracture (vertebral)	-0.23	N/A		
Fracture (rib)	-0.09	N/A		
Fracture (scapula)	-0.09	N/A		
Fracture (clavicle)	-0.09	N/A		
Shoulder dislocation	-0.03	N/A		

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Burns	-0.02	N/A		
Carer disutility				
No response	[redacted]	N/A	B.3.4.5	Caregiver survey
Moderate Response	[redacted]	N/A		
High Response	[redacted]	N/A		
Very High Response	[redacted]	N/A		
Seizure-freedom	[redacted]	N/A		
VNS	[redacted]	N/A		
Post-VNS	[redacted]	N/A		
Surgery	[redacted]	N/A		
Post-surgery	[redacted]	N/A		
Subsequent ASM Treatment	[redacted]	N/A		

Abbreviations: N/A, not applicable; VNS, vagus nerve stimulation.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

A TLR was undertaken to identify and summarise the healthcare and resource use as a result of FOS, the methodology undertaken is summarised in Appendix I. Searches were performed in December 2019 and update searches performed in October 2020. The key objective was to identify healthcare resource utilisation as well as direct and indirect costs associated with FOS and associated treatments. The main review question that used to identify the studies was:

- What is the economic evidence for cenobamate and its comparators in the treatment of FOS?

The healthcare and resource use TLR did not yield any studies that could be used in the economic model. Only one study reported the costs and resource use associated with FOS and its treatment in the UK.[187] They reported the costs of AEs requiring hospitalisation, the costs associated with treatment of different ASMs and the costs of other healthcare and social services, though this was not split out to describe what the costs comprised. Full details of the SLR methodology and results can be found in Appendix I.

As such UK clinician expert opinion was obtained via the clinician survey to better understand the resource use of patients with epilepsy with FOS. The clinician survey was used to identify epilepsy event management resource use by seizure type (focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizures) and routine monitoring resource use per response category (no response, moderate response, high response, very high response and complete response).

Cost categories included in the CEM are treatment costs, administration costs, routine monitoring costs, epilepsy event management costs and treatment-emergent adverse events costs. UK costs were sourced from databases such as NHS reference costs, the British National Formulary (BNF) or from published literature.[188,189] In addition, accidents due to seizure occurrence costs and the societal perspective are included in sensitivity analyses.

B.3.5.1. Intervention and comparators' costs and resource use

Treatment costs

To assign treatment costs in the model, the cost per treatment period was calculated and applied to those who had not yet discontinued treatment.

Treatments were split into to the titration phase and the maintenance phase. Across both the titration and maintenance phases, compliance to treatment was considered. Compliance rates, as presented in Table 54 were sourced from the C017 study and assigned equally to both phases; it was assumed that comparators had the same level of compliance.

Table 54: Compliance rates for base case comparators

	Cenobamate	Perampanel	Brivaracetam	Lacosamide	Eslicarbaze-pine acetate
Compliance	96.6%	96.6%	96.6%	96.6%	96.6%

Cenobamate

Patients entering the C021 open-label study started treatment with cenobamate at a dose of 12.5 mg and then increased the dose every two weeks to further reduce the risk of many side effects, including hypersensitivity reactions. Patients were supplied with cenobamate 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily; each pack of tablets contains 14 tablets, enough to maintain the dose for two weeks.

During the 12-week-up-titration phase, patients titrated upward every other week to reach the target dose of 200 mg/day. Table 55 shows the initial up-titration schedule used to calculate treatment costs of cenobamate. Given that titration lasts 84 days for cenobamate, it was assumed that titration would last three cycles.

Table 55: Initial up-titration for subjects

	Weeks					
	Weeks 1 & 2	Weeks 3 & 4	Weeks 5 & 6	Weeks 7 & 8	Weeks 9 & 10	Weeks 11 & 12
Cenobamate dose (mg/day)	12.5	25	50	100	150	200

Abbreviations: mg, milligram

The distribution of patients amongst different doses of cenobamate during the maintenance phase of treatment is presented in Table 58. Data were sourced from the C017 study and used to determine the distribution of patients among different doses of cenobamate. Given that some patients discontinued treatment during titration, resource use in neither arm sums to 100% as not all patients progressed to the maintenance phase of treatment; allocation to

doses of cenobamate was weighted according to the proportion of patients on treatment during the maintenance phase of the study.

Table 56: Distribution of patients on different cenobamate doses, by dose during the maintenance phase

Maintenance dose (mg)	N (%) of Patients	
	200mg target dose	400mg target dose
50	2 (1.8)	1 (0.9)
100	1 (0.9)	4 (3.6)
150	9 (8.2)	17 (15.2)
200	86 (78.2)	5 (4.5)
250	-	2 (1.8)
300	-	14 (12.5)
350	-	2 (1.8)
400	-	49 (43.8)

Abbreviations: mg, milligram

Table 57 presents information on the pack prices of the technology being appraised.

Table 57: Technology being appraised

UK approved name and brand name	Cenobamate	
Indications and any restriction(s) as described in the SmPC	Patients are eligible for treatment with cenobamate if their condition has not been adequately controlled despite prior treatment with at least two anti-epileptic medicines.	
	Cost £	Source
Acquisition cost (including VAT as applicable)*	12.5mg (x14)/25mg (x14) [redacted] per pack 50mg (x14) [redacted] per pack 100mg (x14) [redacted] per pack 150mg (x14) [redacted] per pack 200mg (x14) [redacted] per pack 50mg (x28) [redacted] per pack 100mg (x28) [redacted] per pack 150mg (x28) [redacted] per pack 200mg (x28) [redacted] per pack Based on the proportion of patients on the 200 mg and 400 mg arm of the C017 study the average cost per pack is [redacted] during maintenance	Data on file.
Method of administration (including homecare provision)	Oral use	SmPC

Dosage	The recommended initial dosage of cenobamate is 12.5 mg once daily, titrated to the recommended maintenance dosage of 200 mg. The maximum dosage is 400 mg once daily.	SmPC
Average length of a complete course of treatment/cycle/dose	Cenobamate is provided until a clinical decision is made to discontinue treatment.	
Anticipated average interval between treatments/cycles/ doses	Treatment should be taken daily	
Anticipated number of treatments/cycles/ doses	N/A	
Dose adjustments	For patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200mg once daily.	SmPC
Administration costs and details of tariff(s) used (if applicable)	Titration phase The total cost is £531.00 per patient. Maintenance phase The total cost is £118.12 per patient per year.	The titration cost includes the cost of epilepsy outpatient visit during the titration phase of £177.00 sourced from NHS reference costs 2018.[190] Patients are assumed to have three outpatient visits. Includes the cost per repeat prescription of £29.53 sourced from PSSRU costs.[191] Patients are assumed to have four repeat prescriptions in one year of maintenance treatment.

Abbreviations: mg, milligram; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SmPC, summary of product characteristics; VAT, UK, United Kingdom.

Table 58 presents the pack prices for titration packs of cenobamate which contain 14 tablets per pack.

Table 58: Titration price of cenobamate

Titration pack prices of cenobamate	Cost £
12.5 mg/25 mg	[redacted]

50 mg	[redacted]
100 mg	[redacted]
150 mg	[redacted]
200 mg	[redacted]
Total	[redacted]

Abbreviations: mg, milligram.

Given that the total cost of titration is calculated according to the up-titration schedule explained in Table 55 – assuming that each patient takes each 2-week course starting at 12.5 mg per day and up-titrating every 2-weeks to the target dose of 200 mg per day - the total cost of titration is [redacted] per patient. This cost is applied in the model as an average over the three cycles of titration, costing [redacted] per cycle.

Table 59 shows the cost of each maintenance pack sourced from Arvelle. Each maintenance pack contains 28 tablets. The average cost per day during the maintenance phase of cenobamate is calculated by taking a weighted average of the proportion of patients on each dosage and its associated pack price.

Where patients are on a dose that is not available in daily tablets, they are assumed to table a combination of packs containing tablets of different sizes; for example, patients receiving 300 mg will receive a 200 mg pack of 28 tablets and a 100 mg pack of 28 tablets. The average daily cost of treatment is obtained by dividing the total cost of both packs through by 28. Then, the average cost per day, [redacted], is multiplied by 28 to achieve the cost of cenobamate per cycle, [redacted].

Table 59: Maintenance pack prices of cenobamate

Maintenance dose	Cost £
50 mg	[redacted]
100 mg	[redacted]
150 mg	[redacted]
200 mg	[redacted]

Abbreviations: mg, milligram.

Comparators

Duration of titration and up-titration schedules for base case comparators were sourced from the Summary of Product Characteristics (SmPC) of each comparator. Table 60 presents the titration schedule and any assumptions made in calculating costs during the titration period.

Table 60: Titration schedule and assumptions of base case comparators

Comparator	Titration schedule	Available pack size	Assumption
Brivaracetam[192]	No titration period is required.	N/A	N/A
Lacosamide[193]	Starting dose of 50 mg twice per day adjusted every week by 50 mg twice per	50 mg, 100 mg, 150 mg in pack sizes of 14 tablets.	Patients would use the entire pack of 50 mg, 100 mg and 150 mg tablets during titration, to reach an

	day to a target dose of 200 mg twice per day.		average maintenance dose of approximately 300mg per day. Given that titration lasts 21 days for Lacosamide, it was assumed that titration would last one cycle, with the remaining week including seven maintenance doses.
Eslicarbazepine acetate[194]	The starting dose is 400 mg once per day for one week and up titrated to 800 mg once per day for the following week. The dose is then increased to 1,200 mg once daily for a week.	200 mg and 800 mg in pack sizes which contain 60 and 30 tablets, respectively.	Patients have two 200 mg tablets per day for one week, before progressing to a single 800 mg tablet per day for one week. Thereafter, patients consume two 200 mg tablets and one 800 mg tablet per day for one week. Thus, patients consume a total of 28 tablets of 200mg dose and 14 tablets of 800mg dose over 21 days of titration. Given that titration lasts 21 days for eslicarbazepine acetate, it was assumed that titration would last one cycle, with the remaining week of the cycle including seven maintenance doses.
Perampanel[195]	Starting dose of 2 mg once a day, adjusted every 2 weeks from 2 mg/day to 8 mg once a day for 6 weeks.	2 mg - 10 mg in pack sizes of 28 tablets.	All pack sizes cost the same, allocation of doses was not calculated. It is assumed that patients consume one tablet per day. Given that titration lasts 56 days for perampanel, it was assumed that titration would last two cycles.

Abbreviations: mg, milligram.

Allocation of dosage employed in the model for each base case comparator during the maintenance phase was sourced from the ITC. Based on the weighted average daily doses, the daily resource use associated with each treatment during the maintenance phase was identified as presented in Table 61.

Table 61: Mean dose for base case comparators from ITC and assumption made

Comparator	Maintenance dose (average of doses within licensed range considered in ITC)	Available pack size	Assumption

Brivaracetam	110.64 mg/ day.	25 mg - 100 mg in pack sizes of 56 tablets.	All pack sizes cost the same, therefore allocation of doses was not calculated; it is assumed that patients consume two tablets per day.
Lacosamide	317.92 mg/ day.	50 mg, 100 mg, 150 mg, and 200 mg in pack sizes of 56 tablets.	82% of patients given lacosamide will have two doses of 150 mg per day and 18% of patients will have two doses of 200 mg per day, yielding an average daily dose of 317.92 mg/day.
Eslicarbazepine acetate	995.89 mg/ day.	800 mg (30 tablets per pack) or 200 mg (60 tablets per pack).	All patients would receive a tablet of 800 mg per day, with 98% of patients also receiving a 200mg tablet per day, reflecting a modal daily dose of 1,000 mg.
Perampanel	8.25 mg/ day.	2 mg - 10 mg in pack sizes of 28 tablets.	All pack sizes cost the same, therefore allocation of doses was not calculated; it is assumed that patients consume one tablet per day.

Abbreviations: ITC, indirect treatment comparison; mg, milligram.

The prices per pack of all base case comparators were taken from the BNF. Table 62 summarises the cost of treatment during the titration phase.

- The cost per pack of perampanel is £140 regardless of the dose containing 28 tablets (except the 2mg pack, with a cost of £35 containing 7 tablets at £5 per tablet). The cost per tablet is £5; this is used to calculate the total cost of titration over the 56-day period as £280; this results in a cost of £140 per titration cycle.
- There are no titration costs associated with brivaracetam.
- For lacosamide, packs are available at a price of £10.81, £86.50, and £129.74 for a 50mg, 100mg and 150mg pack, respectively. The 50mg pack contains 14 tablets and both the 100mg and 150mg packs contain 56 tablets. The cost per unit is used to calculate the total cost of titration over the 21-day period of £64.87. With the additional cost during titration of a week at maintenance dose, the cost of one cycle of titration is £97.95.

- For eslicarbazepine acetate, packs are available at a price of £68 and £136 for 200mg and 800mg tablets, respectively. Given that there are 60 and 30 tablets in the 200mg and 800mg packs, respectively, each has an average price per tablet of £1.13 and £4.53. Given the titration schedule of 400mg once a day for one week, followed by 800mg once a day for one week, then 1,200 mg once a day for one week, the average cost of titration was calculated as £95.20. With the additional cost during titration of one week at maintenance dose, the cost of one cycle of titration is £134.69.

Table 62: Base case intervention drug costs – titration phase

	Brivaracetam	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Duration of titration (days)	0.00	21.00	21.00	56.00
Daily dose	N/A	100 mg per day increased by 100 mg every week up to 300 mg	400 mg for one to two weeks then 800 mg, up to no more than 1,200 mg	2 – 8 mg
Pack size	N/A	42	68	28
Unit (mg)	NA	50, 100, 150	200 - 800	2 - 8
Units per pack (mg)	N/A	42	13,600	56-224
Cost of titration (£):	0	64.87	95.20	140.00
Cost per unit or dose (£):	0.00	3.50	4.81	5.00
Cost per cycle of titration (£):	0.00	97.95	134.69	140.00

Abbreviations: mg, milligram; N/A, not applicable.

Table 63 summarises the cost of comparator treatments during the maintenance phase. For the cost of base case comparators during maintenance, the cost of each comparator was calculated as follows:

- The cost of brivaracetam is £129.64 per pack, regardless of dosage. As each pack contains 28 tablets, the daily cost is calculated as £4.63. This is multiplied by 28 to obtain the cost per cycle of £129.64.
- 82% of patients given lacosamide will have two doses of 150 mg per day and 18% of patients will have two doses of 200 mg per day. Since packs of tablets of 150 mg and 200 mg doses of lacosamide, containing 56 tablets, cost £129.74 and £144.16, respectively, the cost per pack is £132.32. Therefore, the cost per day is calculated as £4.73. This is multiplied by 28 to obtain the cost per cycle of £132.32.
- A 200mg pack of 60 tablets and 800mg a pack of 30 tablets of eslicarbazepine acetate are priced at £68.00 and £136.00, respectively. These prices were adjusted to reflect the average dose of 995.89mg reported during the maintenance phase. As

all patients receive 800mg per day, and 98% of patients receive an additional 200mg to reflect an average dose per day of 995.89mg, the average cost per day is £5.64. This is multiplied by 28 to obtain the cost per cycle of £157.98.

- The cost per pack of perampanel is £140.00 regardless of the dosage required. As each pack contains 28 tablets, the daily cost is calculated as £5.00. This is multiplied by 28 to obtain the cost per cycle of £140.00.

Table 63: Base case intervention drug - maintenance phase (per cycle)

	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Daily dose (mg)	110.64	317.92	995.89	205.4
Pack size	56.00	56.00	30	28.00
Unit (mg)	25 - 100	150 - 200	800 - 1200	2 - 10
Cost per pack (£):	129.64	132.32	169.26	140.00
Cost per unit or dose (£):	4.63	4.73	5.64	5.00
Cost per cycle (£):	129.64	132.32	157.98	140.00

Abbreviations: mg, milligram.

Background therapy

It is assumed that all patients entering the model are also on background therapies defined as medications used concomitantly with adjunctive therapies. The proportion of patients receiving each background therapy was sourced from UK clinician experts via the clinician survey.[1] The survey identified the most prescribed background therapies in clinical practice as levetiracetam, lamotrigine and carbamazepine.

Table 64 presents the proportion of background therapies prescribed in clinical practice and their costs with the average cost per cycle of background therapy. The treatments administered in the background and the frequency of their use were identified in the survey. Daily defined dosages (DDDs) were sourced from the WHOCC.[196–202,202–208]

The costs per pack for each background therapy were sourced from the BNF and the average cost per DDD was identified and multiplied by 28 to get the total cost per cycle for each background strategy. Given that the DDD correlates well with the doses available, the calculation to obtain cost per DDD was simply, with units per pack were calculated as the product of number of tablets per pack and dose per tablet:

$$Cost\ per\ DDD = \frac{Cost\ per\ pack}{Units\ per\ pack} \times DDD$$

The cost per year cycle of each background therapy was then weighted by the percentage of therapy prescribed to patients to enable calculation of the total cost of background therapy per cycle of £10.18. This cost was applied as a one-off cost every cycle over the lifetime time

horizon as it was assumed that the use of background therapies is not affected by the adjunctive ASM patients are treated with.

Table 64: Background therapy resource use

	Levetiracetam	**Lamotrigine**	**Carbamazepine**	**Sodium valproate**	**Topiramate**
Dose (DDD) in mg:	1,500	300	1,000	1,500	300
Pack size (tablets):	60	56	84	100	60
Unit (mg):	750	100	200	500	100
Units per pack (mg):	45,000	5,600	16,800	50,000	6,000
Cost per pack (£):	8.02	3.12	3.83	22.76	15.63
Cost per unit or dose (£):	0.27	0.17	0.23	0.68	0.78
Cost per cycle (£):	7.49	4.68	6.38	19.12	21.88
% prescribed	34.58%	29.17%	16.25%	11.67%	4.17%
	Clobazam	**Zonisamide**	**Phenytoin**	**Oxcarbazepine**	**Pregabalin**
Dose (DDD) in mg:	20	200	300	1000	300
Pack size (tablets):	30	56	84	50	56
Unit (mg):	10	100	100	600	300
Units per pack (mg):	300	5,600	8,400	30,000	16,800
Cost per pack (£):	3.74	4.72	11.32	38.71	4.86
Cost per unit or dose (£):	0.25	0.17	0.40	1.29	0.09
Cost per cycle (£):	6.98	4.72	11.32	36.13	2.43
% prescribed	3.33%	3.33%	2.08%	2.25%	1.25%
	Phenobarbital	**Tiagabine**	**Clonazepam**		
Dose (DDD) in mg:	100	30	8		
Pack size (tablets):	28	100	100		
Unit (mg):	60	15	2		
Units per pack (mg):	1,680	1,500	200		

Cost per pack (£):	7.36	156.13	34.42	
Cost per unit or dose (£):	0.44	3.12	1.38	
Cost per cycle (£):	12.27	87.43	38.55	
% prescribed	0.42%	0.42%	0.42%	
Total cost of background therapy per cycle (£):	10.18			

Abbreviations: DDD, defined daily dose; mg, milligram.

Administration costs

The model assumes that some administration resource use is associated with issuing prescriptions for patients. It was assumed that during the titration phase, any prescription would be administered at epilepsy outpatient visits when escalation of the treatment is performed, and therefore there is no additional resource use during titration to administer prescriptions. Only patients who are on treatment incur administration of treatment costs within the model.

It is common for clinicians to conduct an electrocardiogram (ECG) for patients receiving lacosamide according to SmPC information.[193] Therefore, it is assumed that lacosamide patients will receive a single ECG. The cost per epilepsy outpatient visit and the cost of ECG monitoring were sourced from the NHS reference costs.[189]

During the maintenance phase, it was assumed that all patients would need to contact their GP for repeat prescriptions and that repeat prescriptions would be provided in a 15-minute GP telephone interview four times per year. The cost of a 15-minute GP telephone appointment was sourced from PSSRU 2018 and inflated using the NHSCII inflation indices.[191] Table 65 presents the total cost of administration during the titration phase and the maintenance phase for each base case comparator.

Table 65: Administration costs

	Cenoba-mate	**Brivaracetam**	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Cost per epilepsy outpatient visit during titration phase (£):	177.0	0.0	177.0	177.0	177.0
Number of epilepsy outpatient visits during titration phase:	3	0	2	2	3
Electrocardiogram monitoring (EY51Z) (£):	-	-	481.00	-	-
Cost per repeat prescription for responders during 1 year of maintenance phase (£):	29.53	29.53	29.53	29.53	29.53
Number of repeat prescriptions per 1 year of maintenance phase:	4	4	4	4	4
Total administration cost per cycle in titration phase: (£)	177.00	0.00	835.00	354.00	265.50
Total administration cost per cycle in maintenance phase (£):	9.06	9.06	9.06	9.06	9.06

Subsequent treatment

Subsequent ASM treatment

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 distribution of patients amongst these treatments is based on the assumed market share of cenobamate once it is available, as shown in Table 66.[209] The distribution of patients on background therapy was sourced from the clinician survey.

Table 66: Distribution of patients across available subsequent ASM treatment

	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Subsequent treatment distribution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASM, antiseizure medication

The total cost per cycle for subsequent ASM treatment is expressed as a weighted average of the cost per cycle of available subsequent ASM treatments. The acquisition cost per cycle were derived from the daily cost of subsequent ASM therapies sourced from the NICE British National Formulary (BNF).[188] The cost per day of subsequent ASM treatment in addition to the total weighted average cost per cycle is shown in Table 67.

Table 67: Subsequent ASM therapy - treatment cost

	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Cost per day	[redacted]	4.63	4.73	5.64	5.00
Cost per cycle	[redacted]				

Abbreviations: ASM, antiseizure medication

A background therapy cost comprising of the weighted average of all possible background therapy ASMs (sourced via the clinician survey) was added to the total acquisition cost per cycle to attain the total subsequent ASM therapy cost per cycle as shown in Table 68.[1]

Table 68: Total cost of subsequent ASM therapy

	Cost (£)
Background therapy	10.18
Subsequent intervention costs	[redacted]
Total subsequent ASM therapy cost per cycle:	[redacted]

Abbreviations: ASM, antiseizure medication

Invasive procedures

The unit cost of surgery was sourced from the Chilcott (1999) study as the marginal cost of surgery for epilepsy including both limbic and neocortical resections (£13,800). The unit cost of VNS was sourced from the Forbes (2003) study which comprised the cost of the VNS device, in-patient stay associated with the surgical procedure, the cost of theatre time for surgery and the cost of 1.1% of devices leading to infection (£7,271). Both costs were

inflated to 2018/2019 price using the NHS cost Inflation Index (NHSCII) to £23,125 and £10,222, respectively. The unit cost of surgery and VNS are shown in Table 69.

Table 69: Treatment Costs - Invasive procedures

Treatment cost	Cost per procedure (£)
Surgery	23,125.00
Vagus Nerve Stimulation	10,222.00

B.3.5.2. Health-state unit costs and resource use

Clinical expert opinion was elicited via a survey to inform understanding of the potential positioning of cenobamate in UK clinical practice and gather insights into how UK patients move through treatment options to help manage their disease. The survey collected responses from 14 neurology consultants from England, Scotland and Wales. The survey itself was double-blinded, i.e. client's name or name of product not revealed to participants and participant's name with specific answers not revealed to client.

Results of the survey were used to inform the occurrence of epileptic seizures and resource use associated with treating FOS, in particular for the frequency of seizures in drug-resistant patients, resource use associated with routine monitoring, and the resource use associated with acute management and treatment of seizures.

Routine monitoring costs

The survey was used to identify resource use associated with the routine monitoring of patients whilst on treatment. The survey identified that 93% of participants agreed that routine monitoring for patients with FOS varies according to the reduction in seizure frequency achieved by treatment and the addition of adjunctive treatments. As such, clinical experts were asked to identify hours of resource use per four-week period for patients with drug-resistant FOS and report how this changes according to response to treatment (i.e. moderate response [≥50% reduction in seizures], high response [≥75% reduction in seizures], very high response [≥90% reduction in seizures], complete response[seizure freedom]).[1] Results are presented in Table 70.

Table 70: Routine monitoring resource use per four-week period

Setting of care	Hours of resource use per four-week period				
	No response	Moderate response	High response	Very high response	Complete response
GP appointment	1.00	0.54	0.08	0.08	0.08
GP nurse appointment	0.29	0.14	0.07	0.07	0.07
Neurologist outpatient appointment	0.86	0.50	0.07	0.07	0.07
Outpatient nurse appointment	1.00	0.62	0.31	0.31	0.15

Abbreviations: GP, general practitioner

The following unit costs presented in Table 71 are sourced from the PSSRU 2019.[210] The cost of a GP appointment was £39, based on a consultation lasting 9.22 minutes including qualification costs and direct care staff costs. The cost of a general practice nurse appointment was identified as £37 per hour based on an appointment lasting 15 minutes the unit cost per appointment was £9.25. The cost of a neurologist outpatient appointment was obtained from the NHS reference costs.[189] The cost of an outpatient nurse appointment was based on a 15-minute appointment costing £46 per hour from the PSSRU 2019.[210]

Table 71: Unit costs of health services

Setting of care	Unit cost (£)
GP appointment[210]	39.00
General practice nurse appointment[210]	9.25
Neurologist outpatient appointment[190]	177.00
Outpatient nurse appointment[210]	11.50

Abbreviations: GP, general practitioner

Table 72 summarises the total cost per four-week period associated with routine monitoring split by response category.

Table 72: Routine monitoring costs by response

	No response	Moderate response	High response	Very high response	Complete response
Total cost	£205.40	£117.99	£19.72	£19.72	£17.88

Routine monitoring costs attributed to subsequent ASM treatment and invasive procedure health states were derived from the distribution of patients' response as summarised in (Table 29, Section B.3.3.2).

Epilepsy event management costs

Resource use associated with the management of epilepsy events (seizures) in drug-resistant patients over a four-week period were estimated via UK clinical expert opinion via the clinician survey.[1] In the extrapolation of outcomes relating to epilepsy event management over years, it was noted that frequency of seizures for which medical attention was sought and patients hospitalised were overestimated. These outcomes were revalidated with clinicians in the context of drug-resistant patients over a year, which yielded more realistic and conservative outcomes.

Epilepsy event management is comprised of two components: acute management of seizures and acute treatment of seizures.

The model splits resource use by seizure type (focal aware seizures, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures). These are presented in Table 73. Clinical experts identified the proportion of seizures of each subtype for which medical attention is required as 2.90%, 8.60% and 30.80%, respectively.[1] The resource use associated with a patient's initial presentation to a health care service was split by the proportion of patients presenting to a health service and the proportion of patients requiring treatment. For example, 26.76% of the 2.9% of all patients with focal aware seizures who

require medical attention present to accident and emergency (A&E) and of those, 9.25% require treatment following A&E attendance.

The proportion of patients who seek medical attention resulting in hospitalisation for focal aware seizures, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures is 22.9%, 21.4% and 36.3%, respectively. The average duration of hospital stay (days) is 1.67, 2.0, and 2.33, respectively. The proportion of patients who seek medical attention and are referred to other services is 28.6%, 18% and 21%, for these subtypes, respectively.

Table 73: Epilepsy management resource use

	Focal aware		**Focal impaired awareness**		**Focal to bilateral tonic-clonic**	
Proportion of seizures for which medical attention is required:	2.90%		8.60%		30.80%	
Costs by initial presentation to health care services	Proportion of patients presenting	Proportion of patients requiring treatment	Proportion of patients presenting	Proportion of patients requiring treatment	Proportion of patients presenting	Proportion of patients requiring treatment
A&E attendance in patients requiring medical attention	26.76%	9.25%	44.29%	19.76%	62.07%	37.47%
GP appointment in patients requiring medical attention	45.11%	8.85%	25.98%	8.51%	16.50%	3.88%
Primary care nurse appointment in patients requiring medical attention	7.70%	0.84%	6.40%	1.12%	5.50%	1.01%
Other	20.12%	8.45%	23.38%	8.48%	16.00%	5.07%
Hospitalisation resource:						
Proportion resulting in hospitalisation:	22.9%		21.4%		36.3%	
Average duration in hospital:	1.67		2.00		2.33	
Other resource:						
Proportion referred to other services:	28.6%		18%		21%	

Abbreviations: A&E, accident and emergency; GP, general practitioner.

The model accounts for treatment administered in each healthcare setting as shown in Table 74. It was assumed that patients with focal onset epilepsy who present to A&E are prescribed either/or clobazam 10mg/day, lorazepam 4mg IV single bolus, and midazolam 10mg/day. Similarly, patients who present to their GP are prescribed a short course of clobazam 10mg/day, or diazepam 10mg/day. GPs refer patients to either A&E (those with focal aware seizures) or to a neurologist (those with focal to bilateral tonic-clonic seizures).

Table 74: Acute treatment resource use

	Focal aware seizures	**Focal impaired awareness**	**Focal to bilateral tonic-clonic**
Resource use - A&E attendance:			
Clobazam (10 days)	0.5	0	0
Lorazepam 4 mg IV single bolus	0.5	0.5	0.5
Midazolam 10 mg IV single bolus	0	0.5	0.5
Resource use - GP appointment			
Clobazam (10 days)	0.5	1	0
Diazepam 10 mg (10 days)	0.5	0	0
Neurology appointment	0	0	1
Resource use -Primary care attendance:			
Neurology appointment	0	1	1

Abbreviations: A&E, Accident and Emergency; GP, General practitioner; IV, Intravenous therapy; mg – milligram.

Patients presenting to a primary care nurse appointment are referred to a neurologist. Treatments and services received during a hospital admission are presented in Table 75. Resource use relating to the proportion of patients receiving a magnetic resonance imaging (MRI) or electroencephalogram (EEG) was taken from a publication by Dixon et al.[80] It was assumed that all patients would use the resources associated with epilepsy event management regardless of whether they respond to their intervention treatment or not.

Table 75: Services and treatment received during hospital admission

Services and treatment received during hospital admission	**Resource use per admission**
Blood level of ASM	100%
Blood test for metabolic parameters	100%
Same Day Diagnostic Imaging Admission or Attendance[80]	22.4%
Conventional EEG, EMG or Nerve Conduction Studies, 19 years and over[80]	68.6%
Routine tests for underlying infection	100%

Abbreviations: ASM, Anti-seizure medication, EEG, Electroencephalogram; EMG, Electromyography

UK costs were obtained from standard databases, such as NHS reference costs, BNF, NHS drug tariff and PSSRU.[189,210,211] Table 76 presents the unit costs associated with the acute management of seizures.

Table 76: Acute management costs of seizures

Presentation to healthcare services	Unit cost £	Source
Costs by initial presentation to health care services		
A&E attendance in patients requiring medical attention	£168.00	Service code 180[190]
GP appointment in patients requiring medical attention	£39.00	Per surgery consultation lasting 9.22 minutes, with qualification costs, including direct care staff costs[212]
Primary care nurse appointment in patients requiring medical attention	£9.25	£37 per working hour, 15-minute duration assumed[212]
Other	£185.00	Service code 400, neurology outpatient appointment, consultant led[190]
Hospitalisation costs:		
Cost per night in hospital	577.98	Cost per night in hospital, HES data[213]
Referrals to neurology outpatient appointment	185.00	Service code 400, neurology outpatient appointment, consultant led[190]

Abbreviations: A&E, Accident and Emergency; GP, General practitioner.

Table 77 presents the unit costs of treatments received across the different healthcare settings.

Table 77: Cost of treatment and management given at healthcare providers

	Unit cost:	Total cost of treatment
Clobazam 10mg (10-day course)	£1.25	£1.25
Lorazepam 4mg IV single bolus	£0.35	£0.35
Diazepam 10mg (10-day course)	£0.33	£0.33
Cost of AE appointment	£168.00	£168.00
Referral to neurology appointment	£177.00	£177.00
Midazolam 10mg IV single bolus	£22.88	£22.88

Abbreviations: A&E, Accident and Emergency; IV,Intravenous therapy.

Table 78 summarises all costs associated with the acute treatment cost of seizures.

Table 78: Acute treatment cost of seizures

Treatment setting	Focal aware seizures	Focal impaired awareness	Focal to bilateral tonic-clonic
Treatments administered in A&E	£0.80	£11.61	£11.61

Treatments administered at GP appointment	£168.79	£1.25	£177.00
Treatments administered at primary care nurse appointment	£0.00	£177.00	£177.00
Treatments administered in other settings	£0.00	£0.00	£0.00
Cost of services and treatment received during hospital admission (£):	£235.08	£235.08	£235.08
Total acute treatment cost per seizure (£):	£2.00	£4.70	£30.28

Abbreviations: A&E, Accident and Emergency; GP, General practitioner.

Table 79 presents the overall cost per seizure when taking epilepsy management resource and cost data into account. Results show that the total cost per focal aware seizure is £12.86, per focal impaired seizure £39.87 and per focal to bilateral tonic-clonic seizure £236.36.

Table 79: Total cost per seizure

Total cost per seizure			
Cost category	**Focal aware seizures**	**Focal impaired awareness**	**Focal to bilateral tonic-clonic**
Acute management	£10.86	£35.16	£206.08
Acute treatment	£2.00	£4.70	£30.28
Total cost per seizure (£)	£12.86	£39.87	£236.36

Using the relative reduction data gathered from the C017 patient level data, Table 80 contains the epilepsy event management costs by health state. Event management costs associated with the 'VNS' and 'Surgery' health state are assumed to have the same event management costs as the 'no response' health state.

Table 80: Total epilepsy event management costs of seizures per cycle by health state

	Focal aware seizures	**Focal impaired awareness seizures**	**Focal to bilateral tonic-clonic seizures**	**Total**
No response	50.07	181.21	610.60	841.87
Moderate response	21.25	100.22	197.95	319.42
High response	9.15	38.96	102.42	150.53
Very high response	4.84	16.79	52.00	73.63
Complete response	0.00	0.00	0.00	0.00
Subsequent ASM treatment				525.31
VNS				841.87

Post-VNS				425.70
Surgery				841.87
Post-surgery				228.75

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.

Accidents due to seizure occurrence costs

The proportion of seizures that lead to accidents was utilised as a scenario analysis. The Kirby (1995) study reported that 15% of seizures lead to accidents; the resulting numbers of accidents per patient per cycle according to response are described in Table 81.[214] The frequency of accidents due to seizures attributed to subsequent ASM treatment and invasive procedure health states were derived from the distribution of patients' response to treatment.

Table 81: Number of seizures needing treatment by response and seizure type

Treatment response	Focal aware	Focal impaired awareness	Focal to bilateral tonic-clonic	Total
No response	0.02	0.06	0.12	0.19
Moderate response	0.01	0.03	0.04	0.08
High response	0.00	0.01	0.02	0.04
Very high response	0.00	0.01	0.01	0.02
Complete response	0.00	0.00	0.00	0.00
Subsequent ASM treatment	0.01	0.04	0.07	0.12
Surgery	0.02	0.06	0.12	0.19
Post-surgery	0.00	0.02	0.03	0.05
VNS	0.02	0.06	0.12	0.19
Post-VNS	0.01	0.03	0.06	0.10

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.

The possible accidents that could occur and the proportion of patients for whom accidents occurred per cycle were sourced from the study by Kirby and Sadler (1995) as shown in Table 82.[214]

Table 82: Proportion of patients for whom accidents of each type occur due to seizure occurrence, per cycle

Accident	Proportion of patients for whom accidents occurred per cycle
Head contusions	48.81%
Other contusions	10.71%
Head lacerations	27.38%
Other lacerations	1.19%
Fracture (facial bone)	2.38%

Fracture (vertebral)	3.57%
Fracture (rib)	1.19%
Fracture (scapula)	1.19%
Fracture (clavicle)	1.19%
Shoulder dislocation	1.19%
Burns	1.19%

Accidents due to seizure occurrence costs were sourced from the appropriate treatment codes from the 2018-2019 NHS national reference costs as shown in Table 83.[190]

Table 83: Accidents due to seizure occurrence costs

Accident Occurred	Unit Cost	Source codes[190]
Head contusions	£168.00	Accident and Emergency
Other contusions	£168.00	Accident and Emergency
Head lacerations	£3,777.04	Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury. Weighted average
Other lacerations	£277.91	Skin procedures, weighted average
Fracture (facial bone)	£3,765.48	Maxillofacial Procedures. CA90Z:CA95Z
Fracture (vertebral)	£2,486.09	HC20J:M Vertebral Column Injury without Interventions
Fracture (rib)	£1,461.11	HE71B:D Rib or Chest Fracture, without Interventions
Fracture (scapula)	£4,093.74	HT52A:HT55Z Shoulder procedures weighted average
Fracture (clavicle)	£4,093.74	Early Complications of Trauma or Injury of Non-Specific Joint Site
Shoulder dislocation	£4,093.74	Early Complications of Trauma or Injury of Non-Specific Joint Site
Burns	£5,820.41	Service code 161 Outpatient attendance
Total weighted average cost (£):	£1,548.83	

The total weighted average cost in Table 83 was applied to the number of seizures needing treatment by response and seizure type in Table 81 in order to ascertain the total cost of accidents due to seizure occurrence in Table 84.

Table 84: Total costs of accidents due to seizures per cycle according to health state

Health state	Total (£)
No response	301.91
Moderate response	121.29
High response	55.33
Very high response	26.69
Complete response	0.00
Subsequent ASM treatment	189.70

VNS	301.91
Post-VNS	154.93
Surgery	301.91
Post-surgery	82.24

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.

B.3.5.3. Adverse reaction unit costs and resource use

Only TEAEs that were reported in more than 5% of patients were used in the cost-effectiveness analysis. The C021 open-label study was used to inform TEAEs that occurred during the titration phase whilst the maintenance phase of the C017 study was used to inform TEAEs that occurred during maintenance treatment.

TEAEs were only considered when patients were on treatment with a third generation ASM. As such, once patients discontinue 2nd line treatment, it was assumed that there would be no further TEAEs.

The costs associated with TEAEs (Table 85) were sourced from NICE TA614; given that the most common TEAEs were aligned with the events reported in TA614, costs were also aligned with TA614.[215] It was assumed that all TEAEs would require treatment by a specialist nurse costing £44 sourced from PSSRU 2018/19.

Table 85: Treatment emergent adverse event costs

Event	AE cost £
Somnolence	£44
Dizziness	£44
Headache	£44
Fatigue	£44

Abbreviations: AE, adverse event.

Adverse events associated with VNS and surgery (Table 86 and Table 87, respectively) were sources from NHS Reference costs 2018/19 and PSSRU Unit Costs.[189,210]

Table 86: Adverse events costs associated with VNS

Event	HRG code	AE cost £
Voice alteration hoarseness	PSSRU 2019. Assumed one nurse visit. (Band 6)[210]	46.00
Cough	PSSRU 2019. Assumed one nurse visit. (Band 6)[210]	46.00
Dyspnoea	PSSRU 2019. Assumed one nurse visit. (Band 6)[210]	46.00
Pain	Service code 191: Pain management[190]	157.20
Paraesthesia	Service code 400: Neurology appointment[190]	177.00
Infection	Infections or Other Complications of Procedures, with Multiple Interventions: WH07A:G[190]	1,792.64

Abbreviations: AE, adverse event; HRG, healthcare resource group; VNS, vagus nerve stimulation

Table 87: Adverse events costs associated with surgery

Event	HRG code	AE cost £
Neurological complications	Service code 400 Neurology appointment[190]	£177.00
Infection	Infections or Other Complications of Procedures, with Multiple Interventions: WH07A:G[190]	£1,792.64
Aseptic meningitis	Infections or Other Complications of Procedures, with Multiple Interventions: WH07A:G[190]	£1,792.64
Deep vein thrombosis/pulmonary embolus	Average of Deep Vein Thrombosis, YQ51A:E, and Pulmonary Embolus, DZ09L:Q.[190]	£1,043.73
Intracranial hematoma	Intracranial procedure, AA50:57[190]	£5,712.65
Pneumonia	Lobar, Atypical or Viral Pneumonia, with Multiple Interventions. DZ11K:V[190]	£1,770.38
Cerebrospinal fluid leak	Headache, Migraine or Cerebrospinal Fluid Leak AA31C:E[190]	£603.34
Hydrocephalus	Headache, Migraine or Cerebrospinal Fluid Leak AA31C:E[190]	£603.34

Abbreviations: AE, adverse event; HRG, healthcare resource group

B.3.5.4. Miscellaneous unit costs and resource use

Societal costs

Societal costs are included as a scenario analysis to broaden the perspective of the model. Societal costs are incorporated into the model as productivity losses. The average full-time and part-time salary in the UK per 4-weekly cycle is £2,310.86 and £784.90, respectively.[216] The average unpaid carer salary in the UK is assumed to be equivalent to the average full-time salary (£2,310.86). These parameters are used to calculate the societal costs associated with patients with focal onset epilepsy.

The relative reduction in both full- and part-time work compared to the UK general population per treatment cycle is given in Table 88. The relative reduction to patients with epilepsy was derived from a published report that 46% of patients with DRE are unemployed, compared to 19% in the general population;[85] this translates to 54% of patients with DRE employed compared to 81% of the general population – a 33% relative reduction. It was conservatively assumed that the relative reductions to productivity were the same in full time and part time employment. The numbers of carer hours required by health state per cycle are given in Table 89. The average number of carer hours required per cycle were derived from a survey of caregivers of patients with epilepsy. Societal impacts to patients in the subsequent ASM treatment, post-surgery and post-VNS health states were calculated as weighted averages of the carer disutility values and patients' distribution amongst different levels of response to treatment. It was assumed that patients in the surgery and VNS health states would have the same societal impacts as patients with no response to treatment.

Table 88: Relative reduction in full-time and part-time paid work vs. England and Wales general population

Employment status	Relative reduction in paid work compared to the general population									
	No response	**Moderate response**	**High response**	**Very high response**	**Complete response**	**VNS**	**Post-VNS**	**Surgery**	**Post-surgery**	**Subsequent ASM treatment**
Full-time	33%	25%	13%	6%	0%	33%	22%	33%	10%	24%
Part-time	33%	25%	13%	6%	0%	33%	22%	33%	10%	24%

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation

Table 89: Number of carer hours required per week

No response	Moderate response	High response	Very high response	Complete response	VNS	Post-VNS	Surgery	Post-surgery	Subsequent ASM treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ASM, antiseizure medicine; VNS, vagus nerve stimulation.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A summary of the base case analysis inputs can be found in Appendix J.

B.3.6.2. Assumptions

Table 90: Assumptions underpinning cost-effectiveness model

Variable	*Assumed value*	*Justification*
Time horizon	Lifetime horizon (60 years)	• Aligned with NICE reference case, to capturing all differences in costs and outcomes[150] • Length of time horizon has been a concern in HTA submissions, including Brivaracetam and Retigabine.[148,149] • C017 OLE study has shown high retention rates for patients on cenobamate (approximately 71% after 2 years and 60% after 4 years), providing data over this time horizon and rationale for the selected time horizon.
Cycle length	28 days	28-day cycles align with the schedule of clinical data collection and patients visits to clinicians in the C017 study. This was also validated by clinical opinion.
Half Cycle correction applied	Included in the base case	• NICE reference case;[150] a half-cycle correction was applied to both costs and health outcomes in the Markov model to align with conventional modelling standards
Health states	• No response • Moderate response • High response • Very high response • Complete response • Subsequent ASM therapy • Surgery • Post-surgery • VNS • Post-VNS • Death.	• Aligned with the primary outcome of the pivotal RCT for cenobamate (C017), where significance was achieved.[2] • Furthermore, quality of life of epileptic patients is driven by the occurrence of seizures, or lack thereof. • The use of subsequent ASM therapy and invasive procedures (i.e. surgery and VNS) following lack of response to treatment is also considered to assess the changing treatment over a long time horizon.
Model approach	Markov Cohort Model.	• Treatment effectiveness is captured by distinct categories of response rates (≥50%,

Variable	*Assumed value*	*Justification*
		≥75%, ≥90% and 100% [i.e. seizure freedom]), which map to resource use, costs, and patients' quality of life. Therefore, a Markov cohort structure is appropriate to capture sustained response to treatment. • Markov models have been accepted by the SMC as an appropriate method to evaluate adjunctive treatments in epilepsy. • NICE review of retigabine which suggested that a Markov model would be preferable to the manufacturer's use of a decision tree.[148]
Cenobamate study arms for inclusion	200mg and 400mg from C017	• Recommended maintenance dose is 200 mg with the ability to titrate to 400 mg if required. • It is anticipated 100mg will be below the target maintenance dose in clinical practice. • In the 200 mg and 400 mg study arms, patients who are unable to tolerate the randomised dose were on a lower tolerable dose, reflecting anticipated use in clinical practice
Transition matrix for cycle 1 and cycle 2	The time between Visits 3 and 5 was split into two cycles.	• The time between Visits 3 and 5 was split into two cycles to reflect an extended titration period, as is anticipated in clinical practice.
Transition matrix extrapolation	Transition probabilities for cycle 6 onwards based upon the average of the last 3 cycles C017 trial	• Cenobamate and comparator treatments from cycle 6 onwards were extrapolated using the average transition probabilities over cycles 3-5, which comprised the maintenance period.
Subsequent ASM Treatment: Probability Adverse Event	Subsequent ASM treatment adverse events equal to adverse events of second-line adjunctive ASMs during titration period.	• 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 distribution of patients amongst these treatments is based on the assumed market share of cenobamate once it is available sourced from clinician survey.
Time to discontinuation extrapolation	Generalised gamma distribution was used to extrapolate TTD rates beyond trial duration	• The generalised gamma distribution was the most statistically efficient (AIC = 2939.36; BIC = 2955.78) • Generalised gamma distribution was also consistent with discontinuation rates observed in the C017 OLE trial (60% of patient retention after four years).

Variable	*Assumed value*	*Justification*
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 distribution of patients amongst these treatments is based on the assumed market share of cenobamate once it is available sourced from clinician survey.
Patient utility	No response: [redacted] Moderate response: [redacted] High response: [redacted] Very high response: [redacted] Seizure-freedom: [redacted]	• Valued using SF-6D due to shortcomings of the EQ-5D in patients with epilepsy.[168] • Sourced from a mapping study of patients with epilepsy and retrospectively applied to patients in the C017 study. • Quality of life in other health states derived from response to subsequent treatments.
Carer disutility	Included in the base case	• The burden to patients described imposes significant burden to carers.[72–75] • Carer QoL is correlated with patient QoL.[78]

Abbreviations: AIC, Akaike's Information Criterion; ASM, antiseizure medicine; BIC, Bayesian Information Criterion; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence, OLE, open-label extension; SMC, Scottish Medicines Consortium; TTD, time to discontinuation; VNS, vagus nerve stimulation.

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

Aggregated base case results for the cost-effectiveness of cenobamate compared with second-line adjunctive ASMs are presented in Table 91. Over the lifetime time horizon, treatment with cenobamate was associated with 6.937 QALYs at a total cost of [redacted]. With the lowest cost and the highest QALY gain compared with the base-case comparators, cenobamate dominates all ASM therapies in the base-case scenario.

Table 91: Base case results

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER versus baseline (£/QALY)**	**ICER incremental (£/QALY)**
Cenobamate	[redacted]	19.584	6.937					
Lacosamide	214,093	19.488	6.219	[redacted]	-0.096	-0.718	Dominated	Dominated
Perampanel	214,425	19.491	6.219	[redacted]	-0.093	-0.718	Dominated	Dominated
Brivaracetam	216,640	19.484	6.171	[redacted]	-0.100	-0.766	Dominated	Dominated
Eslicarbazepine acetate	230,621	19.458	5.988	[redacted]	-0.126	-0.948	Dominated	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

The PSA works by drawing a value for each parameter from their assumed probability distributions 10,000 times and evaluating the ICER obtained with each iteration. Where the standard errors for the parameters are unknown, they are assumed to be 20% of the parameter value for the purposes of defining the distributions for each parameter. Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

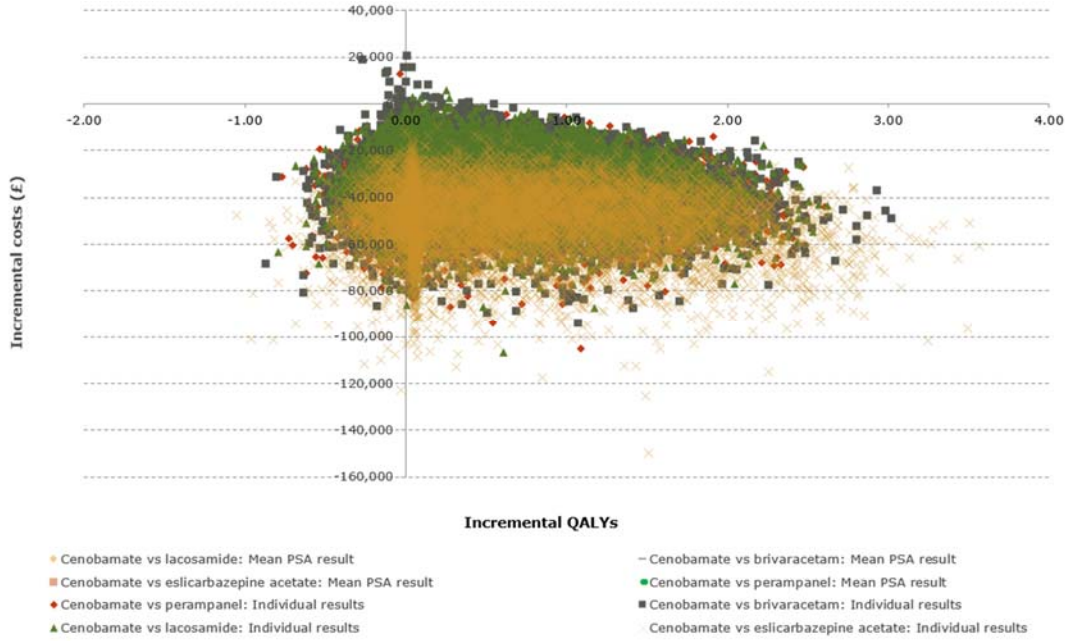
Table 83 shows the mean results of the PSA comparing cenobamate with relevant comparators respectively. With a mean probabilistic total cost of [redacted] and mean total QALYs of 6.562, mean probabilistic results are similar to the base case. With the lowest average cost and average QALYs, cenobamate dominates all comparators. The ICEP is illustrated in Figure 52.

Table 92: Probabilistic sensitivity analysis results

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Cenobamate	[redacted]	6.562	-	-	-
Lacosamide	223,481	6.043	[redacted]	-0.519	Dominated
Perampanel	224,880	6.026	[redacted]	-0.537	Dominated
Brivaracetam	226,004	6.005	[redacted]	-0.558	Dominated
Eslicarbazepine acetate	241,516	5.857	[redacted]	-0.706	Dominated

Abbreviations: QALYs, quality-adjusted life-years.

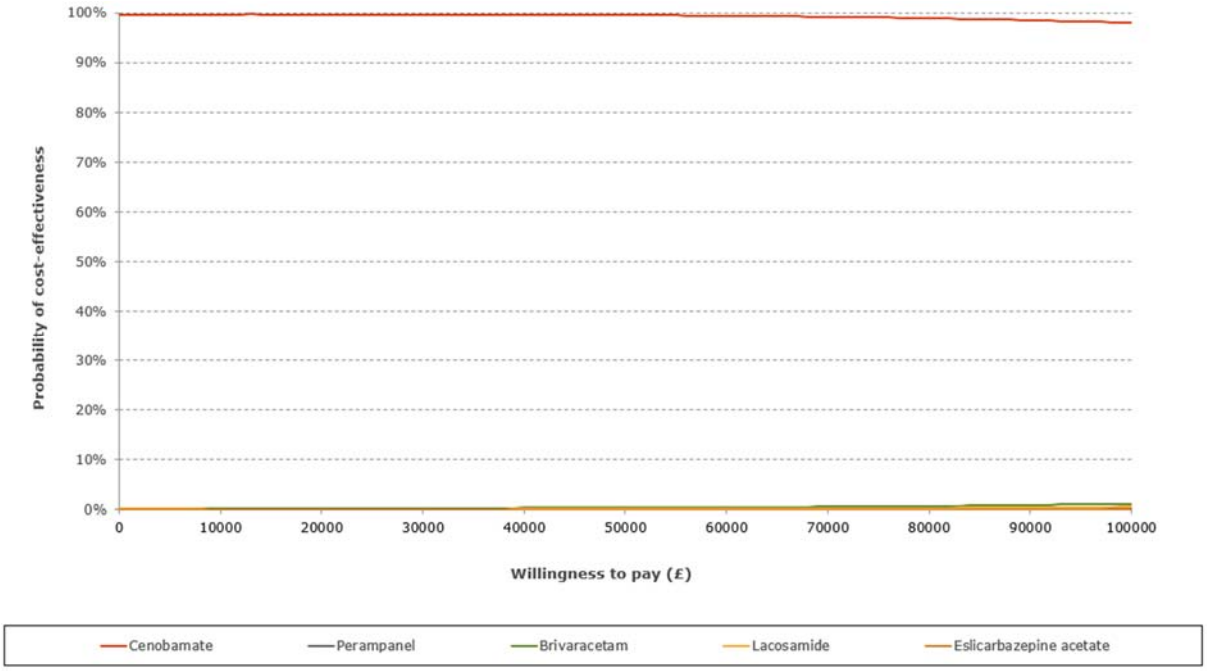
Figure 52: Incremental cost-effectiveness plane



Abbreviations: QALYs, quality-adjusted life years.

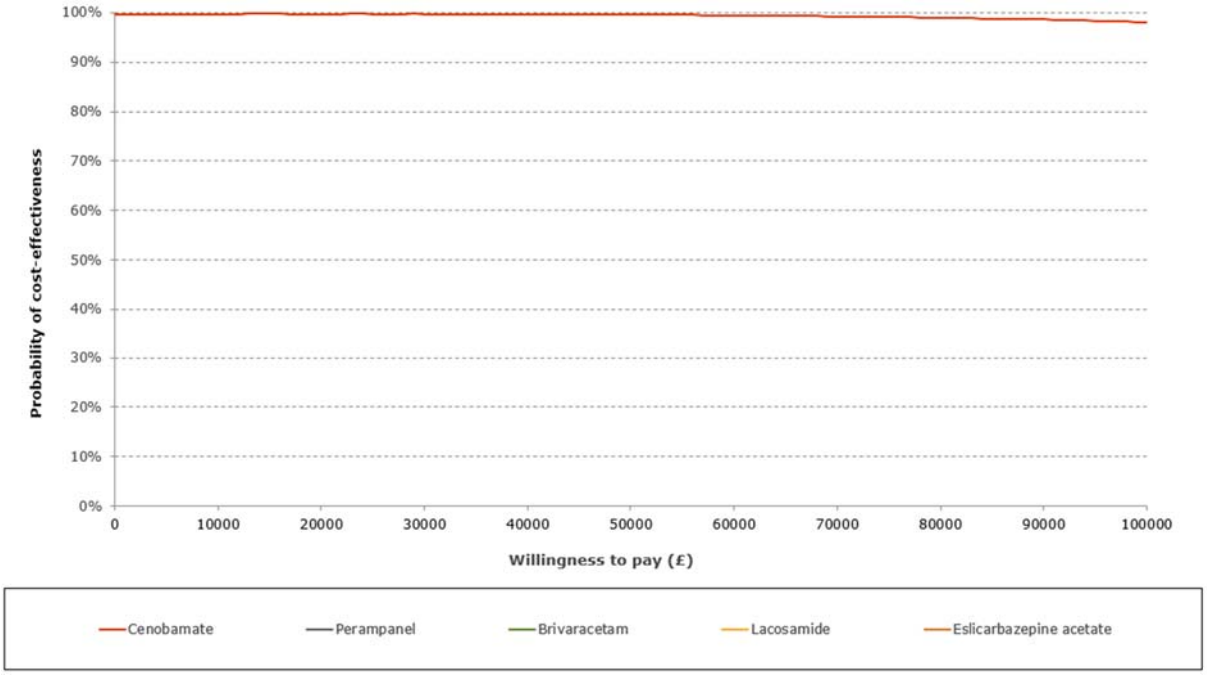
The CEAC is displayed in Figure 53 to illustrate the probability of cenobamate being cost-effective compared to base case comparators, at various willingness to pay thresholds. At thresholds of £0-£40,000/QALY the probability of cenobamate being cost-effective compared to all comparators is 99.7%. At a threshold of £100,000 per QALY, the probability that cenobamate is the most cost effective is 98.1%.

Figure 53: Cost-effectiveness acceptability curve



The cost-effectiveness acceptability frontier (CEAF) is shown in Figure 54 and found that cenobamate is most likely to be cost-effective compared to all comparators at all willingness to pay thresholds.

Figure 54: Cost-effectiveness acceptability frontier



B.3.8.2. Deterministic sensitivity analysis

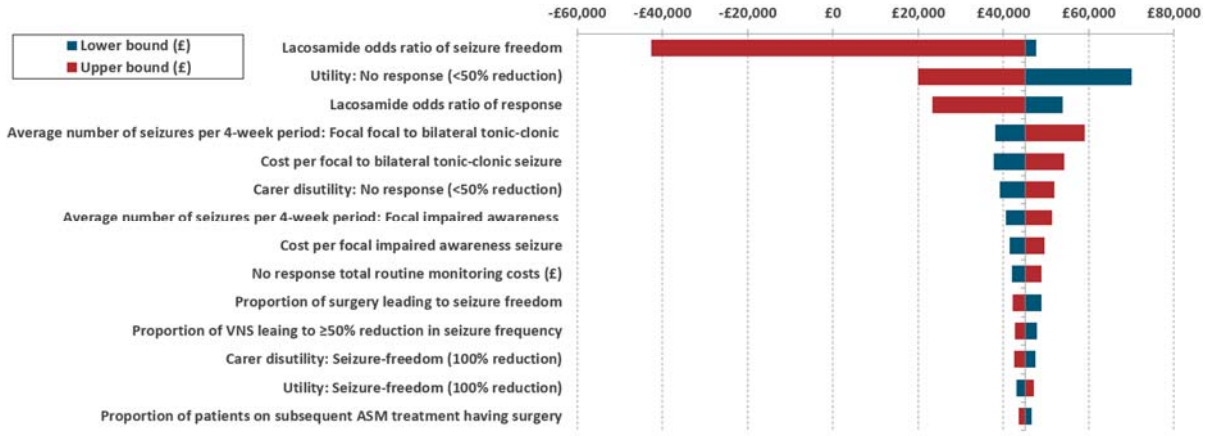
A one-way sensitivity analysis (OWSA) was used to assess the effect of parameter variation on the ICER and NMB. The OWSA was performed using a standard error approach. Where the standard error was not available for a parameter, the standard error was assumed to be 20% of the mean value. Based on its mean and the standard error, the parameter was then varied using a 95% confidence interval based on the distribution of the parameter.

The results of the model were then evaluated using the upper and lower bounds for each parameter, fixing all other parameters' values and recording the overall NMB value. This provides measures which variables have the largest impact on the overall cost-effectiveness analysis results and provides justification for estimates of the model's robustness to parameter variation. The results compared to lacosamide, the next cheapest comparator which is associated with the second most QALYs gained after cenobamate, are presented below. The results detailing the OWSA for other comparators can be found in Appendix J.

As cenobamate dominates lacosamide, Figure 55 displays the tornado diagram for the NMB results of the OWSA when compared with lacosamide. Results are most sensitive to the lacosamide odds ratio of seizure freedom where the lower and upper bounds produce an incremental NMB of £47,500 and -£42,627, respectively. However, it should be noted that the upper bound of the odd's ratio ([redacted]) is highly unlikely. In the C017 study, 21% and 11% of patients treated with 400 mg and 200 mg of cenobamate achieved seizure freedom, respectively, compared to just 1% of placebo-treated patients.2 In the ITC, data for lacosamide reported a range of 2.4%-8.1% of lacosamide-treated patients achieving seizure freedom compared to 0%-2.1% of placebo-treated patients.100, 138,217 Due to the rarity of seizure freedom amongst placebo-treated patients to which the comparison of cenobamate and lacosamide are linked, the estimate of the CrI is unrealistically broad for the odds ratio of seizure freedom with lacosamide relative to cenobamate.

Utility associated with no response, the odds ratio of seizure freedom and the odds ratio of response associated with lacosamide are the three parameters to which the NMB is most sensitive, highlighting these parameters as key drivers in the model.

Figure 55: NMB tornado diagram vs lacosamide



Abbreviations: NMB, Net monetary benefit

Results from the deterministic sensitivity analysis compared with lacosamide has been tabulated in Appendix J.

B.3.8.3. Summary of sensitivity analyses results

The results of sensitivity analyses showed that cenobamate is cost-effective at a threshold of £20,000/QALY at an average price of [redacted] per day and dominates all relevant comparator treatments. Cenobamate exhibited a positive incremental NMB compared with all comparator treatments. The most sensitive changes to the incremental NMB in the deterministic sensitivity analysis came from the treatment response odds ratios associated moderate response (≥50% reduction in seizure frequency), seizure freedom (100% reduction in seizure frequency) and the HSUV associated with no response.

The results from the probabilistic sensitivity analysis demonstrated that cenobamate dominated all relevant comparators with the lowest mean total cost ([redacted]) and highest mean QALYs (6.562). The majority of the iterations in the PSA (86.1%) were plotted in the south-east quadrant of incremental cost-effectiveness plane demonstrating the cost-effectiveness of cenobamate versus relevant comparators. The CEAC demonstrated a 99.7% probability of being cost effective at willingness-to-pay thresholds of £0-£40,000. At a threshold of £100,000 per QALY, the probability that cenobamate is the most cost effective is 98.1%. Additionally, the CEAF demonstrated cenobamate as most likely to be cost-effective at all willingness to pay thresholds.

The OWSA demonstrates cenobamate to have a positive NMB compared to lacosamide under all parameter variations except the upper bound of the odds ratio of seizure freedom with lacosamide relative to cenobamate. As previously noted, the upper bound is highly unlikely with the broadness of the CrI induced by the rarity of seizure freedom amongst placebo-treated patients.

B.3.9. Scenario analysis

Thorough sensitivity analysis of the model was performed, with results presented in Table 93. The scenario analysis found that the estimates of response seizure freedom for comparators had a relatively high effect on the cost-effectiveness and the utility values from the clinician validation have a moderate effect on the cost-effectiveness. In all scenarios presented cenobamate dominates relevant comparators exhibiting the lowest total cost and highest QALY gain.

Table 93: Scenario analysis of the base case model

Model setting tests	Base case assumption	Scenario assumptions	Cenobamate Incremental costs (compared to lacosamide)	Cenobamate incremental QALYS (compared to lacosamide)
Base case	-	-	[redacted]	0.718
Time horizon	Lifetime	2 years	-6,150	-0.110
		15 years	-23,928	-0.494
	Cenobamate 200mg and	Cenobamate 400mg with mortality benefit applied	-39,468	0.888

Model setting tests	Base case assumption	Scenario assumptions	Cenobamate Incremental costs (compared to lacosamide)	Cenobamate incremental QALYS (compared to lacosamide)
Cenobamate study arms for inclusion	400mg with mortality benefit applied	Cenobamate 400mg without mortality benefit applied	-43,251	0.916
		Cenobamate 200mg with mortality benefit applied	-23,003	0.566
		Cenobamate 200mg without mortality benefit applied	-25,035	0.588
Clinical data informing extrapolation of response to treatment	Average over the last three transition matrices derived from the C017 study.	Utilise the C017 OLE data to define transition matrices between response to treatment over cycles of 84-days	-49,528	0.962
Discount rate	3.5% for costs and outcomes	0.0% for costs and outcomes	-44,807	1.165
Perspective	NHS and PSS	Societal	-78,438	0.718
Cenobamate maintenance price	Maintenance £6.50 per day	£6.50	-33,705	0.718
		£8.50	-27,069	0.718
Accidents due to seizures	Excluded	Included	-43,746	0.767
	Per the Kirby 1995 reference	Per clinician validation	-42,425	0.763
Relative reduction in seizure frequency	Included, using median reduction	Included, using mean reduction	-34,404	0.718
Costs of epilepsy event maintenance	Output from clinician survey	Cost per event 75% of base case	-22,330	0.718
		Cost per event 50% of base case	-13,845	0.718
		Cost per event 25% of base case	-5,360	0.718
Costs of routine monitoring	Output from the clinician survey	Presentation to health care is halved in the no response and moderate response health states.	-26,872	0.718

Model setting tests	Base case assumption	Scenario assumptions	Cenobamate Incremental costs (compared to lacosamide)	Cenobamate incremental QALYS (compared to lacosamide)
ITC inputs	ORs for treatment response applied	All comparators assumed to have ORs for response midway between the median values derived from the ITC and 1 (the threshold of equivalence)	-18,259	0.512
Mortality	HRs applied	HRs not applied	-33,697	0.743
Quality of life	Mapping study output	Per clinician validation	-30,814	0.981
		Utilities sourced from Phumart et. al. 2018[176]	-30,814	0.591
		Utilities sourced from Phumart et. al. 2018,[176] with interpolation applied between health states	-30,814	0.600
		Beta-mixture mapping model	-30,814	0.619
		ALDVVM mapping model	-30,814	0.596
Discontinuation	Generalised gamma	Gompertz	-39,483	0.918
		Log-logistic	-26,348	0.612
	Different discontinuation with comparators	The same level of discontinuation as comparators	-46,731	0.970
Carer disutility	Included	Not included	-30,814	0.488

Abbreviations: ALDVVM, Adjusted limited dependent variable mixture model; HR, hazard ratio; ITC, indirect treatment comparison; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years.

B.3.10. Subgroup analysis

No subgroup analyses were performed.

B.3.11. Validation

B.3.11.1. Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation. The model was developed internally by a health economist and checked for accuracy by a further two health economists.

External validation of the model was performed in multiple stages with a HEOR expert (Michael Chambers), a statistician (Dr Kate Ren) and five clinical experts (Dr Rhys Thomas,

Dr Craig Heath, Phil Tittensor, Prof Ley Sander and one further clinician). The stages are detailed below.

Prior to the development of the cost-effectiveness model, a protocol was devised to outline the key modelling assumptions and inputs implemented. The model protocol was put forward to two clinicians (Dr Rhys Thomas and Dr Craig Heath) with the following objectives:

- To ratify the appropriateness and suitability of the model structure
- To ratify the appropriateness of population and comparators
- To ratify assumptions on quality of life and costs, including the cost categories that were implemented
- Validation and identification of data sources from the literature

At this stage, clinicians influenced the structure of the model, with both clinicians stating that it is incredibly rare that patients would undergo surgery if patients had already undergone VNS and vice versa. Clinicians also provided annual rates for patients who would undergo surgery or VNS after achieving 'no response' to subsequent ASM treatment. Clinicians supported the proposed methodology to parameterise the clinical effectiveness of cenobamate, including the omission of the 100 mg arm from the C017 study given its irrelevance to likely clinical practice, the omission of the C013 study, and its comparators.

A second round of validation interviews with four clinicians (not including Dr Craig Heath) took place to revalidate inputs in the context of the results they generated, to assess whether they reflected what would be observed practice. This included estimates of the effectiveness and safety of cenobamate and comparators, derived from the ITC, and the extrapolation of time on treatment.

An important finding from the validation was that all clinicians agreed that there should be a larger increase between the HSUVs in the patients achieving ≥90% reduction in seizures and seizure freedom. Reasons for this were focussed on patients' ability to perform everyday tasks e.g. ability to drive. As a result of this feedback, a scenario analysis – in which clinical opinion more closely reflects reality - was run using the average utility values provided by clinicians. This analysis demonstrated a much larger incremental QALY gain for cenobamate compared to all other treatments, indicating that the base case QALY estimates are conservative.

Additionally, some clinicians believed that the distribution of accidents due to seizures may vary in clinical practice. In particular, the proportion of events which were burns were thought to be underestimated. As accidents due to seizures were not included in the base case, this finding did influence the interpretation of the results.

Review of the CEM by the HEOR expert (Michael Chambers) validated the appropriateness and accuracy of the model and the use of a longer time horizon (of at least 20 years) to capture the long-term cost-effectiveness of the intervention. Additionally, feedback from the HEOR expert influenced the extrapolation of the transition matrices.

Assessment of the ITC was performed by a statistician (Dr Kate Ren) who sits on the evidence review group (ERG) at Sheffield University. KR's feedback supported the robustness of the methodology of the ITC. KR also supported conclusions that it's highly likely that adjunctive treatment with cenobamate is more beneficial than the comparator

treatments. The point estimates indicate a strong numerical preference for cenobamate. The wider CrIs for the clinical effectiveness of comparators relative to cenobamate likely arise due to the small sample size in the cenobamate trial and sparsity of data.

B.3.11.2. Interpretation and conclusions of economic evidence

The results from the base case analysis show that, over a lifetime time horizon, cenobamate is associated with 0.72-0.95 additional QALYs and cost savings when compared to brivaracetam, lacosamide, eslicarbazepine acetate and perampanel; cenobamate dominates all of the comparators considered.

Scenario analyses and an OWSA were performed to test the impact of parameter uncertainty on results. A range of sensitivity analyses have been explored to test structural and parametric uncertainty. In all but one of the scenario analyses and sensitivity analyses, cenobamate remained cost-effective at the cost per QALY of £20,000 threshold, demonstrating that it is robust to uncertainty in parametrisation. The results of the scenario analysis testing equivalent response to treatment with all 3rd generation ASMs and cenobamate, and the OWSA demonstrate that except at the extremes of the CrIs found in the NMA, there are very few instances where cenobamate may fail to be cost-effective. However, it is highly implausible that cenobamate is less effective than the treatments to which it is compared. The median results from the ITC demonstrate clear numerical preference for cenobamate, with unrealistically high upper bounds arising due to sparse data for placebo which anchors the indirect comparisons.

The results from the PSA confirm the deterministic results and show that in 99% of the 10,000 iterations conducted in PSA, cenobamate is less costly than the other 3rd generation ASMs. The CEAC demonstrated a 99.7% probability of being cost effective at willingness-to-pay thresholds of £0-£40,000. At a threshold of £100,000 per QALY, the probability that cenobamate is the most cost effective is 98.1%. This economic analysis shows that cenobamate may be considered a cost-saving and effective use of NHS resources.

B.4. References

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202. WHOCC - ATC/DDD Index Tiagabine. at <https://www.whocc.no/atc_ddd_index/?code=N03AG06&showdescription=yes>
203. WHOCC - ATC/DDD Index Oxcarbazepine. at <https://www.whocc.no/atc_ddd_index/?code=N03AF02&showdescription=yes>
204. WHOCC - ATC/DDD Index Phenytoin. at <https://www.whocc.no/atc_ddd_index/?code=N03AB02&showdescription=yes>
205. WHOCC - ATC/DDD Index Clonezapam. at <https://www.whocc.no/atc_ddd_index/?code=N03AE01>
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B.5. Appendices

Appendix C: Draft SPC

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix G: Published economic studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Confidentiality checklist

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cenobamate for focal onset seizures in epilepsy [ID1553]

Clarification questions

February 2020

File name	Version	Contains confidential information	Date
ID1553 Cenobamate ERG clarification letter 03022021_Arvelle response 28May2021_redacted	2.0	No	28.05.2021

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Decision Problem

A1. PRIORITY. The anticipated license for cenobamate as stated in the company submission is "[redacted]", while the NICE scope is for "Adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed."

a) **Please clarify the wording of the anticipated license for cenobamate as an adjunctive treatment, which could be interpreted in several ways. The wording could be interpreted as a treatment for adult patients with**

epilepsy that has not been adequately controlled despite a history of at least 2 anti-epileptic products as either:

(i) subsequent *monotherapies*, i.e., 1st line monotherapy anti-seizure medication (ASM), followed by 2nd line with an alternative ASM in monotherapy;

(ii) at least two ASMs used *adjunctively* in 1st line; or

(iii) one ASM used in *monotherapy*, followed by a second ASM used *adjunctively* in 2nd line.

b) Please clarify whether the anticipated license for cenobamate as a third line therapy deviates from the NICE scope, which implies that cenobamate could be a second line therapy if used adjunctively to two first line monotherapies (option (i) above).

(i) If yes, please explain and justify the proposed positioning of cenobamate as a second adjunctive treatment in UK clinical practice (Figure 5 of company submission).

a) The wording of the anticipated license for cenobamate as an adjunctive treatment means that patients should use cenobamate concomitantly with other antiseizure medicines (ASMs) as part of a treatment regime to manage their condition. Engagement with clinicians indicated that there would be a preference to add cenobamate to their current treatment regime rather than initiating an entirely new regime of treatment. Therefore, for patients who are not adequately controlled by their current treatment regime, adjunctive treatment with cenobamate would mean that cenobamate is added concomitantly to their existing treatment regime.

The [redacted] is at the interpretation of the clinician. Engagement with clinicians, as summarised in the 'Cenobamate Clinician Survey results' PowerPoint available in the 'Clinical expert opinion' reference pack, identified that given the anticipated license of cenobamate, they would likely prescribe cenobamate following the failure of two anti-epileptic regimes, ASM monotherapy and an ASM combination treatment. In

UK clinical practice, this is in line with the scenario described in option (iii). Therefore, when used following the failure of a first adjunctive treatment, cenobamate would place as a third-line treatment according to the NICE CG137.[1] In clinical practice the vast majority of drug-resistant patients have already cycled through many different treatments and lines of therapy. In reality, those patients suitable and likely to receive cenobamate would have already tried at least three lines of therapy including several adjunctive treatments.

b) The population considered in the final scope is “adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed.” The population for consideration in the final scope was discussed during the decision problem meeting; the Company highlighted that the anticipated licensed indication was narrower than the scope identified. However, the final decision by NICE was to keep the final scope broad and narrow it down in the company submission.

   As patients may have uncontrolled focal onset seizures following any number of lines of therapy, the population covered by the anticipated license for cenobamate is a subgroup of the population considered in the scope. Likewise, the population considered in the company submission, where cenobamate would be used as a second adjunctive treatment, is a subgroup of the anticipated licensed indication of cenobamate. However, in line with the anticipated license of cenobamate and the expected use in clinical practice, the population considered is as described in the response to question A1(a).

Comparators

A2. PRIORITY. The comparators included in the company submission are brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel. However, Figure 5 (page 30 in the company submission) shows phenobarbital,

phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide as alternative 3rd line treatment options based on clinical guideline 137.

a) **Please justify the exclusion of the third line adjunctive treatments listed in Figure 5 as relevant comparators.**

b) **Please clarify whether any specific evidence was used to justify the exclusion of treatments listed as 2nd line adjunctive therapy in Figure 5 that could also be used as 3rd line adjunctive treatments, such as topiramate and clobazam. If these decisions were based on clinical opinion only, please provide minutes of any meetings with clinical advisors.**

c) **Clinical advisors to the ERG highlighted that the following additional relevant comparators should be included in the economic model: clobazam, zonisamide and topiramate. Please provide an updated version of the economic model that comprises all these treatments options.**

a) The Company identified that brivaracetam, eslicarbazepine acetate, lacosamide and perampanel were the most relevant comparators to cenobamate during the decision problem meeting. The relevant comparators were identified via consultation with 14 neurology consultants from England, Scotland and Wales who treated, on average, 55 adult epilepsy patients with focal onset seizures per month. The consensus amongst these clinical experts was that cenobamate would be used as an adjunctive therapy in patients who are not adequately controlled with at least two previously prescribed ASMs and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies.[2] Additionally, the choice of comparators were verified during ratification of the economic model with two clinical experts.

   In addition, prescribing data demonstrates that very few patients are prescribed phenobarbital, pregabalin, tiagabine and vigabatrin . It has also been reported that phenytoin, phenobarbital and vigabatrin are not widely

used for adjunctive treatment due to a poor side effect profile and/or narrow therapeutic indication.[3]

Therefore, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide were not considered relevant comparators given that they are first- or second-generation adjunctive treatments

b) The likelihood of controlling seizure frequency with first and second-line adjunctive treatments, such as clobazam and topiramate, is low.[2] Clinicians advised, with a summary of findings provided in the PowerPoint 'Cenobamate Clinician Survey results' within the 'Clinical expert opinion' reference pack, that the majority of patients (62.14%) would be expected to fail to respond to, be intolerant to, or unsuitable for first generation therapies if they have not been adequately controlled despite treatment with at least two ASMs.[2] First generation therapies include second-line adjunctive treatments such as carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, and topiramate. Therefore, these second-line adjunctive treatments are not considered relevant comparators given their ineffectiveness and intolerability following treatment with two ASMs.

Additionally, many treatments indicated as a second-line adjunctive treatment are also indicated as first-line monotherapy treatments in NICE's clinical guideline (CG137).[1] Given their use earlier in the treatment pathway, they would not be appropriate comparators for those who are uncontrolled, or drug-resistant, as specified in the population of the NICE scope.[3] This includes carbamazepine, lamotrigine, levetiracetam, oxcarbazepine and sodium valproate.

Moreover, treatments indicated as a second-line adjunctive treatment would have been initiated prior to third-line adjunctive treatments. This is supported by evidence that levetiracetam, lamotrigine, carbamazepine, sodium valproate and topiramate are amongst the most commonly prescribed therapies that would be used as background medication.[2] As cenobamate is anticipated to be used as an adjunct to patients' existing treatment regime, rather than as part of a new regime, background therapies would not be considered as

appropriate comparators. This is because a large proportion of patients would receive cenobamate in addition to these first and second-generation therapies, rather than as an alternative to them.

Finally, whilst some of these medications are indicated as a second-line adjunctive treatment, their use is primarily for other purposes. For example, clinicians have advised that clobazam is mostly used for acute treatment to end status epilepticus rather than as an ongoing adjunctive ASM. As such, the uptake of second-line adjunctive treatments in the third-line setting is limited.

c) Clobazam, zonisamide and topiramate have not been included in the model as they are not valid comparators, according to clinical expert opinion, for the reasons listed above.

Meta-Analysis and Network Meta-Analysis

A3. PRIORITY. The following questions relate to the inclusion of study C013 in the network meta-analyses (NMAs).

a) Please explain why study C013 was not considered for the NMA given that: i) Lattanzi et al 2020 meta-analysis pooled evidence from both C017 and C013 studies; ii) study C013 provides potentially important evidence on effectiveness in the first 6 weeks of treatment; and iii) some studies included in the NMAs have similar maintenance periods to that of C013.

b) Please conduct the NMAs presented in the company submission including study C013 and present results.

a) Study C013 was included in the meta-analysis performed by Lattanzi 2020.[4] The meta-analysis was presented to demonstrate the consistency of findings across the two studies despite their difference in design.

Study C013 was not included in the NMA as it had a maintenance period of six weeks, which is not long enough to demonstrate sustained improvements in seizure control. Evidence on effectiveness over the first six weeks of treatment, from the C013 study, would aid interpretation of

the speed of response to treatment. However, sustained response to treatment over a longer maintenance period is more informative of the relative clinical effectiveness of treatments. Inclusion of the C013 study in the NMA would skew the results of the NMA towards the level of initial response to treatment in the first six weeks, and therefore the C013 study was excluded from the NMA.

Where reported, all but two studies of comparators included in the NMA had maintenance periods of at least 12 weeks. The two studies with shorter maintenance periods assessed brivaracetam; in these studies, maintenance lasted seven and eight weeks. These two studies had accompanying titration periods of three and eight weeks, respectively. However, in clinical practice brivaracetam does not require titration. Indeed, the remaining five studies for brivaracetam reported only the total treatment period, which ranged from seven to 16 weeks. Given that these two studies with shorter maintenance duration were within the range of the total treatment period of other studies, these were included in the NMA.

There were other RCTs identified in the SLR which had shorter maintenance periods; however, these were not included in the NMA as they were considered to be dose-escalation studies. These excluded studies were both for perampanel and had a maintenance period of four weeks.

b) The results for the sensitivity analyses including study C013 in ≥50% responder rate analysis are presented in Table 1. The inclusion of the C013 study demonstrates increased significance of the analysis as the odds of patients achieving a ≥50% responder rate with cenobamate are significantly higher than perampanel and brivaracetam in the random effects analysis. In the fixed effect analysis, the odds of patients achieving a ≥50% responder rate are significantly higher than all of the comparators considered. The inclusion of study C013 in the NMA has increased the point estimates of odds ratios; this is due to a larger placebo effect in study C013. The relative benefit of cenobamate compared to placebo was [redacted] However, the outcomes for cenobamate in study C013 were assessed

over six weeks, compared to maintenance periods of at least 12 weeks in all but two studies considered in the NMA. As noted by the EMA, six weeks is not sufficient to demonstrate long-lasting efficacy.[5] Indeed, due to fluctuations in seizure occurrence those treated with placebo are more likely to exhibit a placebo effect during a shorter maintenance period compared to studies with a longer maintenance period, from which demonstrations of efficacy are more robust.

Table 1. Odds ratios with 95% credible intervals of comparators versus cenobamate for ≥50% responder rate analyses (including Study C013)

Comparator versus cenobamate	Random effects	Fixed effect
Odds ratios, median (95% credible interval)		
Perampanel	[redacted]	[redacted]
Eslicarbazepine acetate		
Lacosamide		
Brivaracetam		
Placebo		
Model outputs		
Between-study SD, Median (95% CrI)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance Mean Median	[redacted]	[redacted]
Effective number of parameters	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

The results for the sensitivity analyses including study C013 in the seizure freedom analysis using the pragmatic ITT approach are presented in Table 2. Compared to the base case analysis, the credible intervals have [redacted] for all comparators whilst the odds of achieving seizures freedom with comparators has [redacted] relative to cenobamate. For brivaracetam, the odds of seizure freedom are now [redacted] compared to cenobamate. However, validation of the NMA outputs with clinicians during the CEM validation indicate that [redacted]; clinicians agreed that it would be expected for all comparators to have [redacted] of patients achieving seizure freedom. The results of this analysis are

[redacted] the validation that clinicians provided to the base case results.

Moreover, as previously noted, study C013 had a stronger placebo effect due to a shorter maintenance period; as such the data drawn from study C013 is less robust evidence for the likelihood of achieving seizure freedom with cenobamate relative to placebo. Indeed, the between-study standard deviation has increased in this analysis, from [redacted] in the base case to [redacted] in this sensitivity analysis, demonstrating that the inclusion of study C013 has increased heterogeneity amongst the studies included in the NMA.

Table 2. Odds ratios with 95% credible intervals of comparators versus cenobamate for seizure freedom analyses using pragmatic ITT approach for Study C017 and Study C013

Comparator versus cenobamate	Random effects	Fixed effect
Odds ratios, median (95% credible interval)		
Perampanel	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Model outputs		
Between-study SD Median (95% CrI)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance Mean Median	[redacted]	[redacted]
Effective number of parameters	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

The results for the sensitivity analyses including study C013 in the analysis assessing the odds of experiencing at least one TEAE are presented in Table 3. Compared to the base case analysis, the odds of experiencing at least one TEAE in this sensitivity analysis [redacted]. Moreover, the credible intervals have reduced from the inclusion of study C013 data. This demonstrates that though the

occurrence of TEAEs was slightly lower in study C013, safety results were consistent with study C017 as the direction of preference is unchanged.

Table 3. Odds ratios with 95% credible intervals of comparators versus cenobamate for the proportion of patients experiencing at least one treatment-emergent adverse event analyses (including Study C013)

Comparator versus cenobamate	Random effects	Fixed effect
Odds ratios, median (95% credible interval)		
Perampanel	[redacted]	[redacted]
Eslicarbazepine acetate		
Lacosamide		
Brivaracetam		
Placebo		
Model outputs		
Between-study SD Median (95% CrI)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance Mean Median		
Effective number of parameters	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

Random effects model was run with 300,000 iterations, 60,000 burn-in and a thinning factor of 50.
Fixed effect model was run with 80,000 iterations, 20,000 burn-in and a thinning factor of 10.The predictive mean and standard deviation used in the fixed effect and random effects from the baseline model was 0.470 and 0.608, respectively.

The results for the sensitivity analyses including study C013 in the analysis assessing the odds of discontinuing due to TEAEs are presented in *Table 4*. Compared to the base case analysis, the odds of discontinuing due to TEAEs in this sensitivity analysis is higher with the comparators relative to cenobamate. Indeed, in this analysis the likelihood of discontinuing due to TEAEs is higher with eslicarbazepine acetate than cenobamate. This demonstrates that the likelihood of discontinuing due to TEAEs is likely overestimated by study C017, where there was rapid titration to the 400 mg/day dose which did not feature in study C013. However, titration to the 200 mg/day dose was the same in both study C013 and study C017, which is faster than expected for clinical practice. Therefore, study C013 and study C017 combined still overestimate the odds of discontinuing due to TEAEs with cenobamate.

Table 4. Odds ratios with 95% credible intervals of comparators versus cenobamate for the proportion of patients experiencing at least one treatment-emergent adverse event leading to discontinuation analyses (including Study C013)

Comparator versus cenobamate	Random effects	Fixed effect
Odds ratios, median (95% credible interval)		
Perampanel	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Model outputs		
Between-study SD Median (95% CrI)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance Mean Median	[redacted]	[redacted]
Effective number of parameters	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

A4. PRIORITY. Please provide all electronic files required to reproduce the NMAs, including the data and initial values used.

All of the electronic files for the NMA are contained within the supplied zip folder named 'NMA – Electronic data and code files'.

A5. The flow charts in Appendix D of the company submission indicate that the systematic review (SR) for the NMAs included 23 studies (Figure 2, page 35) narrowed down from a total of 74 studies (Figure 1, page 15). Please provide all inclusion/exclusion criteria for the selection of studies included in the NMAs. Please provide a table of exclusions with reasons (as per table 5 in Appendix D) of all studies included in the SR that were excluded at feasibility assessment stage.

The inclusion/exclusion criteria for the selection of studies included in the NMA is the same as the criteria for the systematic literature review (see Appendix D, Table 1, p. 11), with the additional exclusion criteria of open-label extension (OLE) studies and treatments that are not relevant comparators to cenobamate. OLE studies were not included in the feasibility assessment as they are single arm studies which cannot be included in a NMA.

Following the exclusion of the OLE studies and studies assessing irrelevant comparators, there were three studies excluded from the network meta-analyses that were included within the clinical systematic literature review. These studies were dose escalation trials and were excluded from the networks for both efficacy and safety outcomes:

- Two perampanel trials, Study 206 (NCT00144690; Krauss *et al.* 2012a)[6] and Study 208 (NCT00416195; Krauss *et al.* 2012a)[6]
- One eslicarbazepine acetate study, Study 201 (NCT02170077; Elger *et al.* 2007).[7]

Dose escalation trials were excluded as patients did not receive a stable dose for a length of time that was comparable to other studies included in the analyses. This was evaluated during the feasibility assessment and validated by four key opinion leaders.[8] The three studies also had long titration and short maintenance periods (four weeks) and were limited in the outcomes reported. Furthermore, due to the study design in eslicarbazepine acetate Study 201 (NCT02170077; Elger *et al.* 2007), the trial did not feature a maintenance phase and all outcomes were measured over the 12-week titration phase.[7] Therefore, the study designs and outcome availability were not comparable to those reported in other studies.

A full list of studies that were included in the SLR that were excluded at feasibility assessment stage can be found in Table 1 of Appendix B, which is included alongside these responses to the ERG questions.

A6. Please clarify whether and to what extent the studies included in the NMAs may be generalisable to:

a) the anticipated licensed population;

b) the patient population in the NHS.

a) The studies included in the NMAs are generalisable to cenobamate's anticipated licensed population. The SLR inclusion criteria required the studies to include adult patients who receive adjunctive treatment for drug-

resistant focal onset seizures. As such, by design, all studies retrieved were aligned with the anticipated licensed population of cenobamate.

All studies included in the NMA included patients with drug-resistant focal onset seizures. Number of prior/previous ASMs were rarely reported among studies and where this was reported there was heterogeneity in the definition of prior ASMs (e.g. the period used to define prior ASM use). Therefore, it was not possible to assess this characteristic within this feasibility assessment. The number of concomitant ASMs at baseline could be considered as a proxy for failed treatment. Across the studies included in the NMA, the largest proportion of patients received two ASMs concomitantly, which would indicate a failure of at least two lines of therapy prior to the addition of the adjunctive treatment. This is therefore aligned with the anticipated licensed population.

b) The studies included in the UK align with the patient population in the NHS with most studies featuring predominately Caucasian patients. There were several studies included in the NMA that featured predominately Asian patients, but as verified with KOLs following the feasibility assessment, combining studies of mostly Caucasian patients with studies of mostly Asian studies would not have an effect on efficacy outcomes of the NMA.[8]

The majority of patients across the studies received one to three concomitant ASMs, which is aligned with the expected background ASM regime as advised by clinical expert opinion.[2] The majority of patients were receiving two concomitant ASMs. The reported number of concomitant ASMs varied with some reporting the exact number for all categories with some others, such as a brivaracetam trial,[9] giving the number for one and two concomitant ASMs and a greater or equal category for the remainder. In general, perampanel and lacosamide studies had a high proportion of patients taking three concomitant ASMs, whereas most of the brivaracetam and eslicarbazepine acetate trials included patients taking one to two concomitant ASMs only.

At baseline, the range of concomitant ASMs that were reported was similar across studies. The most commonly reported were levetiracetam, carbamazepine, lamotrigine, valproate/valproic acid, oxcarbazepine, topiramate and zonisamide. This aligned with the therapies that clinicians advised would be most commonly prescribed for background therapy.

A7. Section B2.9.1 (page 75 of the company submission) states that missing data in study C017 was informed using modified/pragmatic ITT analysis, for use in the NMA:

a) Please clarify how the modified/pragmatic ITT analysis was derived.

b) Please further explain the Last Observation Carried Forward (LOCF) approach.

c) Please provide results of the scenario analyses using both the pragmatic ITT and LOCF approaches.

a) The modified/pragmatic intention-to-treat (ITT) analysis was performed and presented in the base case analysis for seizure freedom. It is a more conservative approach where only patients that complete the study and are seizure-free can be classed as seizure free in the numerator and the mITT population in the denominator. In the feasibility assessment of the ITC, most studies used this approach as recommended by Gazzola *et al*. (2007).[10] There were no trials excluded from the seizure freedom analyses using the pragmatic ITT approach for study C017.

b) The last observation carried forward (LOCF) approach was performed and presented as a scenario analysis for seizure freedom. It classes patients who were seizure-free up to dropping out of a study as seizure free in the numerator and the mITT-maintenance population is used in the denominator. This approach has the potential to increase reported seizure-free outcomes in comparison to the modified/pragmatic ITT approach.[10]

c) The results of the base case and analyses for the pragmatic ITT and LOCF approaches, respectively, can be found in Tables 14 and Tables 23 of the Company submission and Appendix D, respectively. Both analyses are

replicated below for clarity in Table 5 and Table 6. The word “LOCF” is missing in the labelling of Table 23, which is corrected in Table 6 below.

Table 5: Summary of base case NMA results for seizure freedom (pragmatic ITT approach)

Comparator versus cenobamate	Random effects (base case)	Fixed effect (supportive analysis)
Odds ratios, median (95% CrI)		
Perampanel	0.21 [redacted]	0.21 [redacted]
Eslicarbazepine acetate	0.18 [redacted]	0.18 [redacted]
Lacosamide	0.21 [redacted]	0.21 [redacted]
Brivaracetam	0.28 [redacted]	0.28 [redacted]
Placebo	0.05 [redacted]	0.05 [redacted]
Model outputs		
Between-study SD (median)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance (median)	[redacted]	[redacted]
pD	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

Table 6: Summary of sensitivity analysis NMA results for seizure freedom (LOCF mITT- maintenance approach)

Comparator versus cenobamate	Random effects (base case)	Fixed effect (supportive analysis)
Odds ratios, median (95% CrI)		
Perampanel	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]
Placebo	[redacted]	[redacted]
Model outputs		
Between-study SD (median)	[redacted]	[redacted]
DIC	[redacted]	[redacted]
Total residual deviance (median)	[redacted]	[redacted]
pD	[redacted]	[redacted]

*Values highlighted in **bold** represent statistically significant results.
Abbreviations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

A8. For the NMAs included in the submission, please provide the following:

a) the 95% Credible Intervals for the between-study standard deviations reported for random effects model;

b) the mean total residual deviances (instead of the median).

The 95% credible intervals and mean total residual deviance for the NMA are provided below, in Table 7.

Table 7. Random effects between-study standard devidiation and mean total residual deviance from NMA analyses

Outcome	Mean total residual deviance		
	Random effects model	Fixed effect model	Random effects between-study SD, median (95% CrI)
Individual ASMs			
≥50% responder rate	[redacted]	[redacted]	[redacted]
Seizure freedom (pragmatic ITT for C017)	[redacted]	[redacted]	[redacted]
Seizure freedom (LOCF for C017)	[redacted]	[redacted]	[redacted]
All TEAEs	[redacted]	[redacted]	[redacted]
Discontinuation due to TEAEs	[redacted]	[redacted]	[redacted]
Pooled third generation ASMs			
≥50% responder rate	[redacted]	[redacted]	[redacted]
Seizure freedom (pragmatic ITT for C017)	[redacted]	[redacted]	[redacted]

Abbreviations: ASM, antiseizure medicine; CrI, credible interval; ITT, intention to treat; LOCF, last observation carried forward; SD, standard deviation; TEAE, treatment-emergent adverse event.

A9. For Appendix D of the company submission, Table 9, page 40 (Summary of baseline characteristics of studies included in the ITC), please provide the median number and range of previous ASMs for all trials.

The median number and range of previous ASMs of participants in the studies included in the ITC are presented in Table 2 of Appendix B, which is included in the zipped folder for this set of responses to the ERG questions.

A10. Please explore the inclusion of potential treatment effect modifiers to explain sources of heterogeneity in the different NMA analyses.

A feasibility assessment was conducted following the clinical systematic literature review which reviewed all studies with respect to study design, patient and clinical characteristics and outcome definitions and timings. There were no significant sources of heterogeneity identified across the studies which were validated by four key opinion leaders.[8] Baseline demographic and clinical characteristics, where reported, were similar across trials and therefore methods to adjust for differences in effect modifiers were not pursued. However, a random effects model was used to best account for any potential sources of heterogeneity across the studies.

A11. Please clarify whether evidence was available for response rates of ≥75%, ≥90% and 100% in the 19 studies included in the NMAs for ≥50% responder rate and seizure freedom outcomes (section B2.9, page 69 of the company submission). If results are available:

a) Please explain why it was not considered appropriate to inform the clinical effectiveness of the comparators based on response rates of ≥75%, ≥90% and 100%.

b) Please extract and present responder rate data at different response levels (≥50%, ≥75%, ≥90% and 100%) from the included studies in the company submission NMAs.

c) Please synthesise the extracted data using a single NMA model for ordered categorical data to quantitatively pool this evidence as explained in NICE Decision Support Unit Technical Support Document 2.

a) The most commonly reported response rate data in the studies included in the NMA was the ≥50% responder rate and seizure freedom – note that seizure freedom is equivalent to the 100% reduction in seizure frequency. Due to the limited availability of data for the ≥75% and ≥90% responder rates it was not possible to compare all of the comparators against cenobamate for these outcomes. There was only limited data for brivaracetam and eslicarbazepine acetate for the ≥75% response rate outcomes.

The choice of comparing ≥50% responder rates and seizure freedom was verified during protocol validation, the minutes of which are supplied in the reference pack for 'Clinical expert opinion'.

b) The responder rate data (≥50%, ≥75%, ≥90% and 100%) for the studies included in the NMA can be seen in Table 3 of Appendix B, which is included alongside these responses to the ERG questions. Amongst the 19 studies included in the NMA, few studies included ≥75% responder rate data, but only the C017 study included the ≥90% and 100% responder rate data.

c) As there is insufficient data for the ≥75% and ≥90% responder rate outcomes, no data synthesis has been conducted for the NMA.

A12. Please clarify the basis for the sensitivity analysis conducted on the NMA, pooling all 3rd generation ASMs (section B2.9, Table 14, page 74 of the company submission). Please clarify how this sensitivity analysis was implemented, providing the WinBUGS code and data used to inform it.

Bayesian network meta-analyses were conducted under a Bayesian framework using Markov Chain Monte Carlo sampling in accordance with NICE recommendations for the two efficacy outcomes: ≥50% responder rate and seizure freedom (using the pragmatic ITT data for Study C017).[11] This analysis was conducted whereby it was assumed that the third generation ASM comparators were equivalent in terms of efficacy and pooled into a single comparator. This was supported by findings from literature whereby no significant differences in efficacy were found between brivaracetam, eslicarbazepine acetate, lacosamide and perampanel.[12]

The data were modelled using a Binomial likelihood and the models were identical to those used in the main analyses assessing cenobamate against each individual ASM. For the pooled analyses, each study was created as a separate row in the data frame, where placebo was the reference treatment coded as 3, cenobamate coded as treatment 1 and all of the third generation ASM comparators were coded as 2. The data used was the same as that used in the analysis comparing cenobamate against each individual ASM, apart from the treatment coding

aforementioned. The code and data to perform this pooled analysis are provided in the aforementioned zipped folder, 'NMA – Electronic data and code files'.

Literature Searching

A13. Please provide the search strategies used for the update of the clinical effectiveness review carried out in October 2020 and referred to in Appendix D of the company submission (page 3, Section D1.1.1).

The search strategies used in the October 2020 update of the clinical effectiveness review can be found in Appendix A, which is included alongside these responses to the ERG questions.

A14. Please provide the search strategies for the Epistemonikos database which was listed as a resource that was searched for the following:

a) economic systematic literature review on page 2, Section G1.3 (Appendix G);

b) health related quality of life systematic literature review on page 23, Section H2.3 (Appendix H);

c) cost and healthcare resource use systematic literature review on page 2, Section I1.3 (Appendix I).

The Epistemonikos database was searched only for the clinical effectiveness systematic literature review but not for the economic, health related quality of life and cost and resource use systematic literature reviews as it is a database of systematic reviews. The Company apologise for the miscommunication.

Section B: Clarification on cost-effectiveness data

Economic Model

B1. PRIORITY. Figure 44 (page 97) of the company submission presents the model structure for the cost-effectiveness analysis.

a) **The company used five different response categories: "No response (<50% reduction in seizures)", "Responder (≥50% reduction in seizures)", "Responder (≥75% reduction in seizures)", "Responder (≥90% reduction in seizures)" and "Seizure-free (100% reduction in seizures)". Please explain why the response categories are disaggregated to this level when previous economic models, including that conducted for CG137, only used "No response (<50% reduction in seizures)", "Responder/not seizure-free (≥50% reduction in seizures)" and "Seizure-free (100% reduction in seizures)".**

b) **Please provide an updated version of the electronic model and corresponding cost-effectiveness results, where response is categorised as "No response (<50% reduction in seizures)", "Responder/not seizure-free (≥50% reduction in seizures)" and "Seizure-free (100% reduction in seizures)", as in CG137.**

c) Using the NMA results from question **A11**, please provide an updated version of the electronic model and corresponding cost-effectiveness results with the more granular response levels of ≥50%, ≥75%, ≥90% and 100% for the comparators.

a) The response rate health states are aligned with the primary and secondary outcomes of the C017 study. In this study, the primary endpoint was response rate to treatment, defined as the proportion of patients who achieve a ≥50% reduction in seizure frequency over the maintenance period compared to baseline. Higher response rates (defined by cut offs of ≥75%, ≥90%, and 100%) of all types of seizures during the maintenance phase of the double-blind treatment period were additional secondary endpoints.

Existing models, such as that developed for CG137 have looked at a simpler structure with health states defined as no response, response but not seizure free, and seizure freedom. However, they do not capture the incremental benefits of better seizure control. The granularity in the model structure developed was verified by clinicians during protocol validation, who agreed that the costs and quality of life associated with patients who achieved at least a 75% or at least a 90% reduction in seizures compared to baseline would differ to those who achieved only a 50% reduction.

The more granular response levels for cenobamate allows for a comprehensive assessment of the clinical effectiveness of cenobamate compared to 3rd generation ASM treatments. Additionally, a more granular selection of health states in the economic model allowed for more insightful analysis of costs that could be stratified by health state. Furthermore, quality of life of epileptic patients is driven by the occurrence of seizures. A more comprehensive selection of response health states allowed for a clearer view of the impact that reduction of seizures can have on health state utilities.

b) A scenario has been developed whereby the high (≥75% reduction in seizures) and very high (≥90% reduction in seizures) responder health states are combined into the moderate (≥50% reduction in seizures) response health state. Aggregated base case results for the cost-effectiveness of cenobamate relative to the comparators are presented in Table 8.

Table 8: Cost-effectiveness scenario analysis where the model is structure defined according to: no response, responder/not seizure-free, and seizure-free health states.

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.897			-
Lacosamide	205,532	6.237	[redacted]	-0.633	Dominated
Perampanel	206,187	6.233	[redacted]	-0.634	Dominated
Brivaracetam	207,896	6.195	[redacted]	-0.670	Dominated
Eslicarbazepine acetate	220,953	6.030	[redacted]	-0.830	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Over the lifetime time horizon, treatment with cenobamate was associated with 6.897 QALYs at a total cost of [redacted]. Cenobamate remains the treatment with

the lowest cost and the highest QALY gain amongst those considered in the economic model, and so cenobamate still dominates all comparators. Compared to the base case, the total cost of cenobamate decreases by [redacted]. The total cost associated with each of the comparators was also reduced compared to the base case, by £8,825 for perampanel to £9,728 to eslicarbazepine acetate. Cenobamate's total QALYs decreased by 0.036 compared to the base case as a result of this change. The scenario led to increased total QALYs compared to base case for the comparators; changes ranged from 0.015 for perampanel to 0.043 for eslicarbazepine acetate.

As the health state utility values were obtained from the mapping study applied to patients in the C017 study, combining the health states had diametrically opposed impacts to cenobamate and the comparators. Given the improved efficacy of cenobamate, there is a larger proportion of patients who have ≥75% and ≥90% reduction in seizure frequency compared to baseline. This biases the health state utility values as it will overestimate the QALY gains for comparators.

c) As updated analyses for question A11 have not been provided, an updated scenario has not been implemented in the economic model. As described in the response to A11, it was not feasible to perform the analysis requested.

B2. PRIORITY. Following discontinuation of the intervention or comparator treatments, the model includes a 'subsequent ASM treatment' health state.

a) Please justify why the full range of treatment sequences were not modelled to align with the treatment pathway and broad range of treatment options in UK clinical practice, where subsequent treatments are modelled using the average duration of treatment with ASMs over a patient's lifetime.

b) Please identify any relevant empirical evidence to inform the modelling of subsequent ASM treatments.

c) Please provide a more flexible cost-effectiveness model that allows for multiple lines of therapy following discontinuation of the intervention and comparators, where the choice of ASMs is fully flexible. Please use this

model to present cost-effectiveness results for alternative treatment sequences that are reflective of UK practice.

a) There is currently no guidance for treatment of patients with epilepsy in UK clinical practice beyond third-line. Moreover, there is not consensus amongst clinicians for what treatment would be used after cenobamate or the comparators considered in this appraisal. The approach taken to the modelling of subsequent ASM treatment and the rationale for this was discussed during the decision problem meeting.

Subsequent treatment strategies would be decided in discussion with clinicians to identify a treatment regime that delivers a reduction in seizures at a tolerable safety profile. With 14 ASMs recommended by NICE for the adjunctive treatment of focal onset seizures in addition to the comparators considered in this appraisal, there is an unmanageably large number of possible treatment combinations. If just two subsequent treatments were modelled, there are 91 possible treatment combinations. If this were extended to three subsequent treatments, there would be 364 possible subsequent treatment combinations.

Therefore, subsequent ASM treatment was represented in the economic model as a single health state and this was validated during the protocol stage with clinicians. Moreover, in lieu of established treatment pathways, a basket of treatments was applied which clinicians also agreed was appropriate. This approach is also reinforced by the general assumption amongst clinicians that efficacy is more or less equal between ASMs and highly dependent on patient tolerability.

The approach taken is conservative. As currently modelled, patients who discontinue treatment with cenobamate or the comparators move onto subsequent ASM treatment. Subsequent ASM treatment is assumed to be fixed in cost and effectiveness over the remainder of the model time horizon. However, in clinical practice, patients are expected to be increasingly less likely to respond to treatment with further lines of therapy. Therefore, over time, the proportion of patients who are classified as non-responders to subsequent ASM treatment is likely to increase. As such, the costs associated with routine monitoring and epilepsy event management are underestimated. Whilst the price of subsequent

ASM treatment is considered fixed in the economic model, it is plausible that the costs of treatment would reduce over time or indeed patients would come off treatment altogether. However, any overestimations in the price of subsequent ASM treatment is outweighed by the underestimated costs of routine monitoring and epilepsy event management.

Given that cenobamate patients are less likely to proceed to subsequent ASM treatment, the approach is likely to underestimate the incremental benefit of cenobamate. As presented in the scenario below, where costs of subsequent ASM treatment are reduced to £0, cenobamate remains dominant of the comparators.

Table 9: Cost-effectiveness scenario analysis where subsequent ASM treatment has no cost

	Total		Incremental		ICER (£) versus baseline (QALYs)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.933			-
Lacosamide	199,894	6.218	[redacted]	-0.715	Dominated
Perampanel	199,902	6.218	[redacted]	-0.715	Dominated
Brivaracetam	203,185	6.170	[redacted]	-0.763	Dominated
Eslicarbazepine acetate	219,428	5.987	[redacted]	-0.946	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

b) As mentioned above, the current approach to modelling subsequent ASM treatments was chosen after consultation with clinicians verified its appropriateness given the lack of evidence supporting a specific treatment sequence.

However, there is limited data available to parametrise the effectiveness of subsequent lines of treatment. Data from the Chen 2018 study reports that the odds of remaining uncontrolled with a subsequent treatment is 1.73 times the odds of being controlled with a current treatment.[13] Therefore, this value could be applied iteratively regardless of the specific intervention. However, it does not consider the differential effectiveness of alternative therapies. Using such data would assume all subsequent ASM treatments are as effective as each other, which is in line with the current modelling assumption.

Data to parametrise retention to treatment may be available from the SANAD study,[14] which reports time to discontinuation of lamotrigine, carbamazepine, oxcarbazepine, topiramate and gabapentin. However, there is no data available for all comparators that may be modelled.

Given the limitations of the available data, the Company believe that the most appropriate structure has been adopted.

c) Whilst acknowledging the ERG's suggestions of more flexible modelling approaches, given the lack of evidence to determine the subsequent pathway, this modelling approach has not been provided. Considering the evidence presented above, the current modelling approach adopted by the Company presents a conservative assessment of the cost-effectiveness of cenobamate relative to the comparators.

B3. Please compare the model predictions in terms of its key clinical outcomes with the corresponding results of the clinical trials for the % of patients by:

a) Response rate: No response (<50% reduction), ≥50% and <75%, ≥75% and <90%, ≥90% and <100%, Seizure-freedom (100% reduction)

b) Vagus nerve stimulation (VNS) and post-VNS

c) Surgery and post-surgery

d) Subsequent treatment

e) Survived

Please provide results for any other model validation processes that they may have been conducted.

a) Patient level data was available to directly parametrise the first 5 cycles of the economic model. Therefore, the predicted distribution of patients at the end of this period are aligned with the pivotal outcomes reported in the C017 study and are presented in Table 10.

Table 10: Patient response rate distribution - outcomes predicted by the model and actual published values

	Cenobamate		**Brivaracetam**		**Lacosamide**		**Eslicarbazepine acetate**		**Perampanel**	
	Predicted	Actual	Predicted	Actual[9, 15–20, 20,20,21]	Predicted	Actual[22–28]	Predicted	Actual[7,29–33]	Predicted	Actual[6,34–39]
≥50% reduction in seizures compared to baseline	52.2%	56.1% - 64.2%	12.9%	13.9%-55.8%	12.5%	32.7%-49.2%	15.1%	17.0%-54.0%	10.7%	20.6%-43.3%
≥75% reduction in seizures compared to baseline	34.1%	30.6% - 46.3%	4.9%	NA	4.3%	11.4%-24.6%	5.0%	2.1%-16.5%	3.7%	NA
≥90% reduction in seizures compared to baseline	24.4%	17.3% - 28.4%	2.3%	NA	1.6%	NA	1.7%	NA	1.5%	NA
100% reduction in seizures compared to baseline	21.3%	11.0% - 21.0%	1.9%	1.5%-9.4%	1.2%	2.4%-5.4%	1.3%	1.0%-8.0%	1.2%	1.5%-5.0%
Discontinued treatment	14.9%		28.4%		33.1%		16.6%		35.3%	

Abbreviations: NA, not available

The outcomes for all levels of response with cenobamate are well aligned with the values reported for the 200 mg and 400 mg arms of the C017 study. There is some variation in the outcomes for the comparators compared to the data published. There is no data available to compare the proportion of patients who had a ≥90% responder rate. There is only data available from brivaracetam and lacosamide to compare the proportion of patients with a ≥75% responder rate; for lacosamide there are fewer patients than typically reported whereas brivaracetam lies comfortably within the range reported by literature.

With regards to the proportion of patients with 100% reduction in seizure frequency, this is typically lower than reported in the literature for comparators. Similarly, the proportion of patients with a ≥50% reduction in seizure frequency is typically lower than reported in the literature for comparators. There are two reasons for this: (a) the placebo effect in studies of comparators was greater than the placebo effect observed for the cenobamate studies, and (b) the parameterisation of discontinuation in the economic model prevents some patients' response to treatment being assessed.

Due to the construct of NMA, the clinical effectiveness of comparators is determined via treatments that indirectly link the studies. The treatment indirectly linking all comparators to cenobamate is placebo. Therefore, the clinical effectiveness of comparators relative to cenobamate is identified according to the effectiveness of cenobamate relative to placebo and the effectiveness of the comparators relative to placebo. However, the comparator studies had a larger placebo effect, i.e. more patients treated with placebo in comparator studies achieved a ≥50% reduction in seizure frequency or seizure freedom compared to patients treated with placebo in the cenobamate studies. Therefore, the relative effectiveness of comparators relative to cenobamate was reduced.

Additionally, the parametrisation of discontinuation means that there are fewer patients in which response to treatment is reported in the economic model compared to the published studies. In Table 11, the response to treatment amongst patients on treatment at the end of cycle 5 is reported. These data are more closely aligned to the values reported in literature.

Table 11. Response to treatment at the end of cycle 5 in patients still on treatment

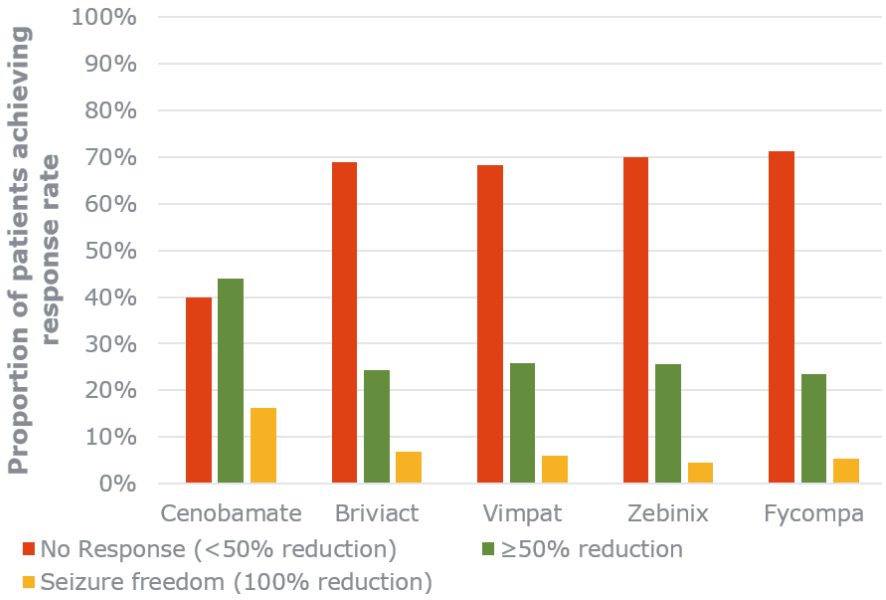
Responder rate	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
≥50% reduction in seizures compared to baseline	60.6%	18.0%	18.7%	18.1%	16.5%
≥75% reduction in seizures compared to baseline	39.6%	6.8%	6.4%	6.0%	5.7%
≥90% reduction in seizures compared to baseline	28.4%	3.2%	2.4%	2.1%	2.3%
100% reduction in seizures compared to baseline	24.8%	2.6%	1.9%	1.6%	1.8%

Finally, in the economic model, the distribution of patients is based on the frequency of seizures during the last 28 days relative to baseline, whereas

published data reports the frequency of seizures during the maintenance period compared to baseline.

The outcomes of the NMA were additionally validated with clinicians, who collectively agreed that the output of the NMA applied to the key clinical outcomes for the cenobamate studies was representative of the response to treatment for comparators. The distribution of response to treatment over the maintenance period for comparators derived from the NMA applied to the key cenobamate outcomes are presented in Figure 1.

Figure 1. Response rates to ASM therapy validated with clinicians



b) There is no available clinical data to compare the proportion of patients who would go on to receive vagus nerve stimulation (VNS) versus the predicted values in the model. Table 12 presents the predicted proportion of patients receiving VNS and the average time spent post-VNS across cenobamate and the comparators.

Table 12: VNS and post-VNS distribution – predicted outcomes from the model

	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Proportion of patients receiving VNS	24.8%	30.3%	31.7%	25.9%	32.3%

Average time (years) spent post-VNS	21.0	21.8	22.0	21.2	22.1

Abbreviations: VNS, vagus nerve stimulation

c) There is no available clinical data to compare the proportion of patients who would go on to receive surgery versus the predicted values in the model. Table 13 presents the predicted proportion of patients receiving surgery and the average time spent post-surgery across cenobamate and comparators.

Table 13: Surgery and post-surgery distribution – predicted outcomes from the model

	Cenobamate	**Brivaracetam**	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Proportion of patients receiving surgery	18.5%	22.6%	23.7%	19.4%	24.1%
Average time (years) spent post-surgery	22.7	23.6	23.8	22.9	23.8

d) There is no available clinical data to compare the proportion of patients who would go on to receive subsequent ASM treatment versus the predicted values in the model. Table 14 presents the predicted proportion of patients who discontinued treatment prior to cycle 5 i.e., the proportion of patients moving onto subsequent ASM treatment in addition to the average time spent on subsequent ASM treatment across cenobamate and 3rd generation comparators.

Table 14: Treatment discontinuation and subsequent ASM treatment – predicted outcomes from the model

	Cenobamate	**Brivaracetam**	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Proportion of patients who discontinued prior to cycle 5	14.0%	28.4%	33.1%	16.6%	35.3%
Average time (years) on subsequent ASMs	9.2	11.2	11.7	9.6	12.0

Abbreviations: ASM, antiseizure medicine

e) There is no available clinical data to compare the proportion of patients who would survive following adjunctive ASM treatment versus the predicted values in the model. Table 14 presents the predicted proportion of patients on cenobamate and comparators who have survived over 5 years, 10 years, 20 years 50 years and the entire length of the time horizon.

Table 15: Patient survival – predicted outcomes from the model

	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Proportion survived five years	98.3%	98.2%	98.2%	98.2%	98.2%
Proportion survived ten years	95.9%	95.7%	95.7%	95.7%	95.7%
Proportion survived twenty years	87.7%	87.2%	87.2%	87.1%	87.2%
Proportion survived fifty years	6.8%	6.5%	6.6%	6.3%	6.6%
Proportion survived time horizon	0.1%	0.1%	0.1%	0.0%	0.1%

Transition Probabilities

B4. PRIORITY. The company submission states that transition probabilities in the model were derived from patient-level data in study C017. In the model, they were derived from tables on the 'Clinical Inputs' sheet, cells BQ28 to BV95.

a) **Please clarify what the numbers in these tables represent, and how they were derived. If numbers in the said tables represent numbers of patients in each state in study C017, please explain why some entries have decimal points.**

b) **In the tables mentioned above, the number of patients transitioning from a state is often greater than the number of patients in that state in the previous cycle. For example, in cycle 2, the number of patients with no response is 53.5, while in cycle 3 the number of patients transitioning**

from 'no response' to other states is 93. In the model, transitions depend on the distribution of patients in the previous cycle (rather than at baseline), and so the number of patients transitioning from a state should never be greater than the number of patients who were in that state in the previous cycle. Please explain how these transition probabilities were derived and, if required, correct the calculations.

a) The numbers in the tables from cells BQ28:BV98 represent the number of patients in each state in study C017. Patients are allocated to a health state between cycles by the relative reduction in seizures that they experience over the cycle compared to the frequency of seizures that they experienced over the screening period (i.e., the eight weeks prior to initiation of treatment). That means, a patient would be in the health state moderate response (≥50% and <75% reduction in seizures) during any given cycle that they experience between ≥50% and <75% fewer seizures per 28 days than the average frequency of seizures per 28 days that they experienced before initiating treatment, in the screening phase of the study.

   The movement between cycles is defined according to the relative frequency of seizures compared to baseline during cycles. Therefore, if in one cycle a patient is a moderate responder (i.e. they have between ≥50% and <75% fewer seizures per 28 days than they did per 28 days at baseline) and in the subsequent cycle they are a non-responder (i.e. they have <50% fewer seizures than they did at baseline) they would move from the moderate response health state to the no response health state.

   The presence of decimals in the first two cycles arise as the two transition matrices were based on one 28-day period of data. As a faster titration was investigated in the C017 study than would be observed in clinical practice, it was assumed that half of patients made the transition from baseline to their health state by the end of Cycle 1, and the remaining half of patients made this transition by the end of Cycle 2. There are no other cycles that were adjusted and therefore there are no other cycles with decimals.

b) Many thanks for clarifying the discrepancy in the patient counts for the cycles. Cycle two is the only cycle in which there are fewer patients than in the cycle

that follows it; this is due to a typographical error entering the patient counts for patients remaining in the "No response" health state between the start and end of cycle two. The updated base case results are presented below in Table 16, and all analyses presented in this response take account of this error. Given that the impact to the base case is very minor, the scenario analyses presented in the company submission have not been rerun.

Table 16: Updated base case results with correction to the data defining transition matrices

	Total		Incremental		ICER (£) versus incremental (QALYs)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.933			-
Lacosamide	214,146	6.218	[redacted]	-0.715	Dominated
Perampanel	214,472	6.218	[redacted]	-0.715	Dominated
Brivaracetam	216,696	6.170	[redacted]	-0.763	Dominated
Eslicarbazepine acetate	230,681	5.987	[redacted]	-0.946	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

B5. Please clarify on what days after treatment initiation visits 3, 5, 7, 8 and 9 of the study C017 fell on and how response rates from these time points were used to inform transitions within the first 5 cycles of the economic model.

In study C017, baseline was set at Day 1 and treatment was initiated on Day 2. Visits 3, 5, 7, 8 and 9 fell on Day 1±2, 29±2, 71±2, 99±3 and 127±3, respectively. The visits were selected to be as closely aligned to 28-day periods as possible, the timeframe over which average seizure frequency relative to baseline were calculated.

The level of response to treatment between visits was defined as the reduction in frequency of seizures, between given time points, compared to the frequency of seizures over the screening phase of the study which defined the seizure frequency at baseline. Screening occurred over eight weeks prior to the study baseline.

The first two cycles use data from the movement of patients between health states at Visit 3 and Visit 5, i.e., between Day 1 and between Day 29 from baseline. As described in the response to question B4(a), the first cycle of data was augmented into two cycles as the speed of titration in the C017 study was much faster than anticipated in clinical practice.

The movement of patients in the third, fourth and fifth cycles were parametrised by the movement of patients between health states at Visit 5 and Visit 7, Visit 7 and Visit 8, and Visit 8 and Visit 9, respectively. Therefore, cycles three, four and five were parametrised by increments of 42, 28 and 28 days, respectively. Though the third cycle of data was based on more than 28 days of exposure to treatment, it was not split into two cycles since the time period included some of the maintenance treatment phase, which would not be appropriate to extrapolate.

B6. Please clarify where the "cenobamate risks at the end of the double-blind phase" estimates (excel model, "data store" worksheet) are sourced from. Please comment on how these compare to the estimates from the model, presented in Table 45.

Risks at the end of the double-blind phase were sourced from the pivotal C017 study. These values were used to convert the odds ratios to risk ratios for application to the cenobamate transition matrices to generate comparator transition matrices.

The values reported in the "Data Store" are the proportion of patients who, after completion of the C017 study, had a given response to treatment over the maintenance phase defined according to the relative reduction in seizures per 28 days over the maintenance phase of the study compared to the frequency of seizures per 28 days during the screening phase. A mean was taken across the cenobamate 200 mg and 400 mg arms. These proportions were identified from Krauss *et al.* (2020), where it was reported which proportion of patients had a response of *at least* the level described.[40] The calculations to generate the distributions of patients are presented in Table 17.

Table 17: Proportion of patients achieving level of response (cenobamate 200 mg, 400 mg, and average of 200 mg and 400 mg)

Response to treatment during maintenance phase	**Proportion of patients achieving *at least* the level of response described**			**Proportion of patients achieving the level of response described**
	200 mg	**400 mg**	**Average (mean of 200 mg and 400 mg)**	
No response (<50% reduction in seizures)	100.0%	100.0%	100.00%	39.9%
Moderate Response (≥50% and <75% reduction in seizures)	56.1%	64.2%	60.2%	21.7%
High response (≥75% and <90% reduction in seizures)	30.6%	46.3%	38. 5%	15.6%

Very high response (≥90% and <100% reduction in seizures)	17.3%	28.4%	22.9%	6.7%
Complete response (100% reduction in seizures)	11.2%	21.1%	16.2%	16.2%

The data was required to be reported over the entire maintenance phase for anchoring the odds ratios correctly, which compared to odds of achieving response to treatment during maintenance.

Table 45 in the company submission is not related to this data; Figure 45 in Document B refers to the distribution of patients across response health states after the final cycle in the maintenance period. The data in Figure 45 therefore refers to the relative reduction in frequency of seizures per 28 days during the last four weeks of the maintenance phase of the study whereas the data in the "Data Store" refers to the relative reduction in the frequency of seizures per 28 days during the entire maintenance phase of the study.

Clinical Effectiveness Model Inputs

B7. PRIORITY. Please provide an updated version of the electronic model and the corresponding cost-effectiveness estimates using the NMA results which include study C013, requested in question A3.

The economic model has been updated to include an option to include study C013 in the network meta-analysis. The results under this scenario are presented below in Table 18.

Table 18: Cost-effectiveness scenario analysis results where the NMA inputs are from the sensitivity analysis including study C013

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	10.873			
Brivaracetam	190,663	10.673	[redacted]	-0.200	Dominated
Lacosamide	201,596	10.484	[redacted]	-0.389	Dominated
Perampanel	202,986	10.468	[redacted]	-0.405	Dominated
Eslicarbazepine acetate	216,915	10.310	[redacted]	-0.563	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

As noted in the presentation of the results for the response to question A3, the efficacy of cenobamate is likely underestimated due to a larger placebo effect in study C013 which has been introduced by a shorter maintenance period. Indeed, six weeks is not sufficient to demonstrate long-lasting efficacy.[5] Given fluctuations in seizure occurrence, those treated with placebo are more likely to exhibit a placebo effect during a shorter maintenance period compared to studies with a longer maintenance period, from which demonstrations of efficacy are more robust.

B8. The model assumes that the maintenance dose of cenobamate is 200mg or 400mg (~50% each).

a) Please report the maintenance dose received by patients in studies C017 OLE and C021, including the proportion of patients that received 100mg, 200mg, 300mg and 400mg doses.

b) Please justify the split used in the model given the trials' maintenance dose and their generalisability to the UK. Please discuss the factors affecting the maintenance dose.

c) Please clarify if the treatment effectiveness and adverse events profiles of cenobamate 200mg and 400mg are equivalent, justifying also their combined use in the NMAs.

a) Table 19 presents patients' modal dose across the C017 OLE and C021 studies.

Table 19: C017 OLE & C021 OLE modal dose during maintenance phase

Study	Dose category								
	100 mg	**150 mg**	**200 mg**	**250 mg**	**300 mg**	**350 mg**	**375 mg**	**400 mg**	**Total**
C017 OLE n (%)	33 (9.09)	23 (6.53)	71 (20.17)	27 (7.67)	130 (36.93)	19 (5.40)	0 (0.00)	50 (14.20)	352
C021 n (%)	96 (8.07)	106 (8.91)	439 (36.89)	164 (13.7)	159 (13.36)	85 (7.14)	1 (0.08)	140 (11.76)	1190

Total n	128 (8.30)	129 (8.37)	510 (33.07)	191 (12.39)	289 (18.74)	104 (6.74)	1 (0.06)	190 (12.32)	1542

In the C017 OLE study, 33 (9.09%) patients were assigned to 100 mg/day, 71 (20.17%) patients were assigned to 200 mg/day, 130 (36.93%) patients were assigned 300 mg/day and 50 (14.20%) patients were assigned to the 400 mg/day dose. In the C021 study, 96 (8.07%) patients were assigned to 100 mg/day, 439 (36.89%) patients were assigned to 200 mg/day, 159 (13.36%) patients were assigned 300 mg/day and 140 (11.76%) patients were assigned to the 400 mg/day dose. Across both studies, the majority of patients were assigned to 200-400 mg/day.

b) The distribution of patients amongst different doses of cenobamate during the maintenance phase of the C017 study is presented in Table 20, as identified from patients randomised to 200 mg and 400 mg in the C017 study which was reported in the company submission. Given that the licensed dose of cenobamate will be a target dose of 200 mg/day with the ability to optimise their dose and up-titrate to 400 mg/day if required, it is expected that patients will be distributed across a spectrum of doses for cenobamate. Therefore, combining the allocation of doses across the 200 mg and 400 mg arms represents the anticipated allocation of doses in clinical practice.

Table 20: Distribution of patients amongst different doses of cenobamate during maintenance phase of C017

Maintenance dose (mg)	**% of Patients**
50	1.35%
100	2.25%
150	11.71%
200	40.99%
250	0.90%
300	6.31%
350	0.90%
400	22.07%

In clinical practice, dose is expected to be determined through identifying an optimal dose with the patient. Actual dose is influenced by tolerability and

efficacy. Some patients may be unable to tolerate cenobamate at higher doses, and therefore will receive a lower dose. Conversely, patients may not derive a response to treatment at the target dose of 200 mg/day and therefore they would require titration to a higher dose. On the other hand, some patients may respond to doses below the target dose.

As such, the distribution of doses across the 200 mg/day and 400 mg/day arms of the C017 study represents the likely distribution in UK clinical practice.

c) Please find the treatment-emergent adverse event (AE) profiles of cenobamate in the 200 mg and 400 mg arms presented in Table 21. In the 200 mg/day and 400 mg/day arm, treatment emergent adverse events were reported in 76% and 90% of patients, respectively. The higher rates may have been attributed to the rapid titration of 100 mg/week from 200 mg to 400 mg in the C017 study.

Table 21: Summary of Treatment-Emergent Adverse Events (Safety Evaluable population)

	Number (%) of patients	
	Cenobamate 200 mg (N=110)	**Cenobamate 400 mg (N=111)**
Patients with TEAEs	84 (76)	100 (90)
Patients with treatment related TEAEs	72 (65)	92 (83)
Patients who died due to a TEAE	0	0
Patients discontinued due to a TEAE	15 (14)	22 (20)
Patients with serious TEAEs	4 (4)	8 (7)

Abbrievations: TEAEs, Treatment-related adverse event.

When considering the TEAEs over titration as presented in Table 22, there are indeed higher rates for the 400 mg arm compared to the 200 mg. This further supports the fact that faster titration contributes to increased adverse events.

Table 22: : Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the titration phase of C017 study for the 200 mg and 400 mg arms

System Organ Class MedDRA Preferred Term	**Number (%) of patients**	
	Cenobamate 200 mg (N=92)	**Cenobamate 400 mg (N=85)**
Patients with at least one TEAE	69 (62.7)	96 (86.5)
Somnolence	19 (17.3)	40 (36.0)
Dizziness	18 (16.4)	32 (28.8)
Headache	18 (16.4)	32 (28.8)
Ataxia	7 (6.4)	32 (28.8)
Fatigue	16 (14.5)	26 (23.4)
Diplopia	8 (7.3)	14 (12.6)
Nausea	1 (0.9)	10 (9.0)
Gait disturbance	6 (5.5)	7 (6.3)
Balance disorder	4 (3.6)	7 (6.3)
Confusional state	4 (3.6)	7 (6.3)
Constipation	3 (2.7)	6 (5.4)
Vomiting	3 (2.7)	6 (5.4)
Vertigo	2 (1.8)	6 (5.4)
Diarrhoea	1 (0.9)	4 (3.6)
Decreased appetite	1 (0.9)	4 (3.6)
Vision blurred	2 (1.8)	3 (2.7)
Fall	3 (2.7)	2 (1.8)
Alanine aminotransferase increased	1 (0.9)	3 (2.7)
Upper respiratory tract	3 (2.7)	1 (0.9)
Viral upper respiratory tract	3 (2.7)	1 (0.9)
Influenza	1 (0.9)	0 (0.0)
Laceration	1 (0.9)	0 (0.0)
Back pain	1 (0.9)	1 (0.9)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
Source: C017 CSR[41]

Contrastingly, the occurrence of TEAEs during the maintenance as presented in Table 23 and Table 24 are much more similar in the 400 mg and 200 mg arms. Demonstrating that once titrated to treatment, tolerability is similar across the two doses.

Table 23: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the first six weeks of the C017 maintenance phase of the 200 mg and 400 mg arms

System Organ Class MedDRA Preferred Term	Number (%) of patients	
	Cenobamate 200 mg (N=92)	Cenobamate 400 mg (N=85)
Patients with at least one TEAE	29 (29.3)	38 (39.6)
Somnolence	1 (10.0)	2 (2.1)
Headache	4 (4.0)	6 (6.3)
Dizziness	4 (4.0)	6 (6.3)
Constipation	0 (0.0)	5 (5.2)
Diplopia	3 (3.0)	3 (3.1)
Back pain	0 (0.0)	3 (3.1)
Arthralgia	1 (1.0)	2 (2.1)
Viral upper respiratory tract	0 (0.0)	2 (2.1)
Restless leg syndrome	0 (0.0)	2 (2.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

Table 24: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the last six weeks of the C017 maintenance phase of the 200 mg and 400 mg arms

System Organ Class MedDRA Preferred Term	Number (%) of patients	
	Cenobamate 200 mg (N=92)	Cenobamate 400 mg (N=85)
Patients with at least one TEAE	24 (26.1)	32 (37.6)
Somnolence	4 (4.3)	3 (3.5)
Dizziness	3 (3.3)	3 (3.5)
Fatigue	2 (2.2)	3 (3.5)
Headache	1 (1.0)	3 (3.5)
Decreased appetite	0 (0.0)	3 (3.5)
Contusion	2 (2.2)	2 (2.4)
Back pain	0 (0.0)	2 (2.4)
Aphasia	0 (0.0)	2 (2.4)
Fall	2 (2.2)	1 (1.2)
Bronchitis	2 (2.2)	0 (0.0)
Anxiety	2 (2.2)	1 (1.2)
Hiccups	2 (2.2)	1 (1.2)
Pollakiuria	2 (2.2)	0 (0.0)

System Organ Class MedDRA Preferred Term	Number (%) of patients	
	Cenobamate 200 mg (N=92)	Cenobamate 400 mg (N=85)
Pain in extremity	0 (0.0)	1 (1.2)
Diplopia	1 (1.1)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (1.1)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
Source: C017 CSR[41]

In the C021 OLE, patients were titrated to 300 mg/day. The presented TEAEs in Table 25 over the maintenance period are comparable to those of the 200 mg and 400 mg arms in the maintenance period of the C017 study.

Table 25: Incidence of Treatment-Emergent Adverse Events (TEAEs) occurring in more than 2% of patients during the C021 maintenance phase

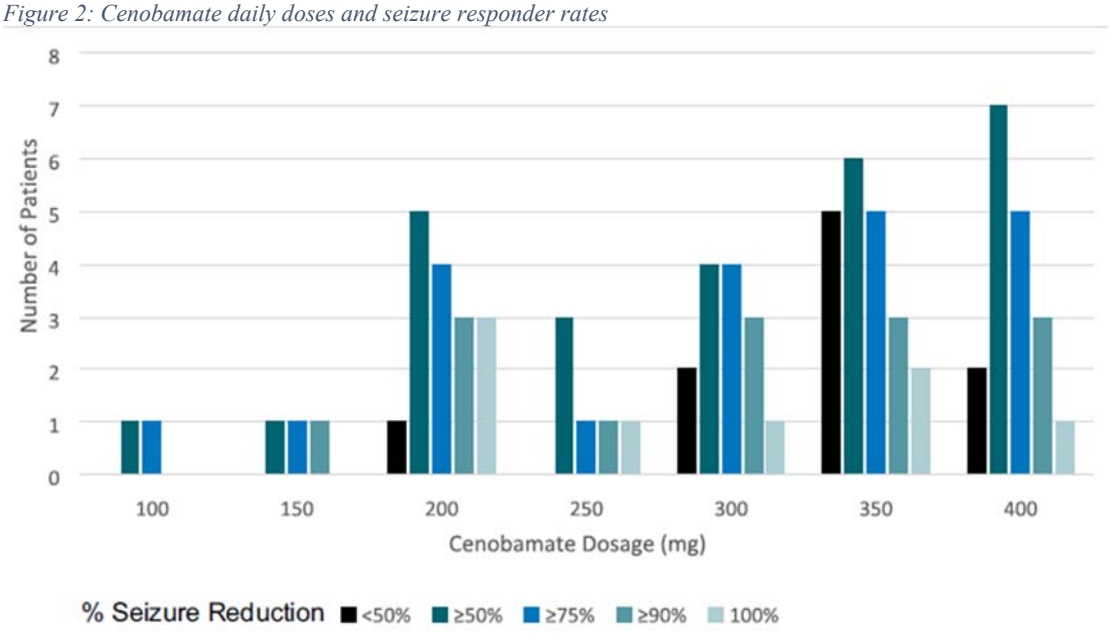
System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Patients with at least one TEAE	957 (80.4)
Dizziness	197 (16.5)
Somnolence	167 (14.0)
Headache	134 (11.3)
Fatigue	113 (9.5)
Viral upper respiratory tract infection	76 (6.4)
Nausea	69 (5.8)
Upper respiratory tract infection	67 (5.6)
Diplopia	66 (5.5)
Seizure	56 (4.7)
Diarrhoea	55 (4.6)
Balance disorder	53 (4.5)
Fall	51 (4.3)
Urinary tract infection	49 (4.1)
Weight decreased	47 (3.9)
Constipation	45 (3.8)
Gait disturbance	42 (3.5)
Ataxia	40 (3.4)
Influenza	39 (3.3)
Vomiting	37 (3.1)
Depression	37 (3.1)

System Organ Class MedDRA Preferred Term	All cenobamate (N=1,340)
Vision blurred	35 (2.9)
Asthenia	34 (2.9)
Decreased appetite	31 (2.6)
Anxiety	30 (2.5)
Laceration	30 (2.5)
Arthralgia	26 (2.2)
Back pain	26 (2.2)

Source: Data on file.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; TEAEs, treatment-emergent adverse events

With regards to efficacy, a recent publication by Elizabeth *et al.* (2021) reported response to treatment according to daily doses in the cenobamate extension studies.[42] There were 6, 3, 6, 11 and 9 patients treated with 200 mg, 250 mg, 300 mg, 350 mg and 400 mg per day, respectively. Figure 2 shows similar proportions of patients responding to treatment across doses in the range of 200 mg/day through to 400 mg/day with a trend for increased response to an increased dose. Additionally, a similar proportion of patients in the 400 mg/day and 200 mg/day arms experienced <50% reduction in seizures.

Figure 2: Cenobamate daily doses and seizure responder rates



Source: Elizabeth et al. (2021)[42]

Accordingly, both the 200 mg/day and 400 mg/day randomised arms were used in the NMA. This represents the safety and efficacy that would likely be observed in clinical practice according to patients being distributed across different maintenance doses.

B9. The treatment response estimates for cenobamate in figure 45 (page 101 of the company submission) do not match those in cycle 5 in the model. Please explain how these numbers were obtained.

Figure 45 in Document B describes the distribution of patients across the response health states after the final parametrised maintenance cycle. The data for Figure 45 is presented in Table 26. These numbers were calculated directly from the patient counts in the final parametrised transition matrix as the proportion of patients in each health state at the end of cycle 5.

Table 26: Cycle 5 patient count for transition matrix, including distribution of patients

Health state at the start of the cycle	**Health state at the end of the cycle**				
	No response (<50% reduction)	**Moderate response (≥50% and <75% reduction in seizures)**	**High response (≥75% and <90% reduction in seizures)**	**Very high response (≥90% and <100% reduction in seizures)**	**Complete Reponse (100% reduction in seizures)**
No response (<50% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Moderate Response (≥50% and <75% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High response (≥75% and <90% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very high response (≥90% and <100% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response (100% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sum of patients (by column)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient distribution by health state	**37.8%**	**20.3%**	**12.2%**	**5.8%**	**23.8%**

B10. The effect of cenobamate in the model was derived from the transition of patients in study C017. The derived effect may not reflect the possible placebo heterogeneity in the NMA, which was used to estimate the treatment effect of comparators. Please explain why the treatment effect of cenobamate was derived from study C017, and not the NMA like the effect of other comparators.

The possible placebo heterogeneity was eliminated from the NMA as the interventions assessed in each study were compared to different regimes of background therapy. That is, in the studies placebo was not a 'true' placebo as background therapy was maintained. Therefore, in eliminating the placebo heterogeneity due to differences in background therapy, the incremental effectiveness of the comparators relative to cenobamate, when used adjunctively to the same background regime, was described.

Indeed, were the clinical effectiveness of cenobamate in the economic model identified from the NMA, the clinical effectiveness would have been relative to the placebo arm of C017. This would have underestimated the clinical effectiveness of cenobamate when used adjunctively. Therefore, the clinical effectiveness of

cenobamate was derived from observed patient level data of the C017 study. This enabled the clinical effectiveness of cenobamate, when used as an adjunctive medicine, to be parametrised.

The application of the NMA to the clinical data for cenobamate from the C017 study described the incremental treatment benefit for each of the comparators relative to cenobamate when they are used with the same background regime concomitantly.

B11. Section B2.9.1 (page 75 of the company submission) states that missing data in study C017 was informed using modified/pragmatic ITT analysis, for use in the NMA. Please clarify whether the same method was used to inform missing data when deriving transition probabilities in the cost-effectiveness model.

Transitions between the different levels of response in the first five cycles were identified by calculating the movement of patients between these health states at Visits 3, 5, 7, 8 and 9 of the C017 study. Patients were included in the patient counts so long as they remained in the study during the period, therefore the LOCF approach was not necessary to use. As discontinuation was applied from the first cycle of the model, the response to treatment in discontinuers was not necessary to be captured as once they discontinued from treatment they progressed to subsequent treatments.

For patients who remained on treatment and were considered in the derivation of patient counts, their seizure diaries were used to identify frequency of seizures and therefore the response to treatment. Patients were required to complete seizure diaries to record the frequency of their seizures each day; any patients who had missing data for a day were assumed to have the same frequency of seizures on days that they did not complete their diary as they did on the days that they had completed during the cycle.

In the extrapolated transition matrices, an ‘average’ of cycles 3-5 was applied.

Subsequent ASMs

B12. PRIORITY. Costs and outcomes for subsequent ASMs were based on expected response to subsequent ASMs, assuming that the odds ratio of no response was 1.73 relative to cenobamate. As result, in the model, subsequent

ASMs are more effective than any of the comparators whose odds ratios are [redacted] to [redacted], since OR (no response) = 1/OR (response).

a) Please comment on the plausibility of this assumption

b) Please provide alternative scenarios for modelling effectiveness of subsequent ASMs. For example, apply the odds ratio (1.73) to the rate of no response in the least effective comparator, instead of that in cenobamate.

a) To avoid the bias that could be generated by making the effectiveness of subsequent ASM treatment as low as possible (and therefore enabling cenobamate to have the largest QALY gains from remaining on treatment), it was conservatively assumed that the effectiveness of subsequent ASM therapy should be calculated relative to cenobamate. Indeed, with the discontinuation of comparators quicker than cenobamate, reducing the effectiveness of subsequent ASM treatment would be biased in favour of cenobamate.

In consideration of the relative effectiveness of the comparator treatments and subsequent ASM treatment, shown in Table 27, subsequent ASM treatment is shown to be more clinically effective than brivaracetam, lacosamide, eslicarbazepine acetate and perampanel. Among 3rd generation ASM comparators, perampanel exhibited the largest proportion of patients who receive no response to treatment (72.7%). Conversely, lacosamide exhibited the smallest proportion of patients achieving no response (70.2%). These values are substantially higher than cenobamate, which provides a lower proportion of patients achieving no response (39.9%). For patients who are treated with these interventions, it is unlikely that subsequent ASM treatment would be more clinically effective. However, when patients are treated with cenobamate in the first instance, their likelihood of responding to subsequent treatments would be greater than those treated with comparators. As such, assuming the clinical effectiveness of subsequent ASM treatment is as effective for all comparators as they are for cenobamate is a conservative assumption.

Table 27: Distribution of patients: Cenobamate and comparators compared to subsequent ASM therapy

Response to treatment	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel	Subsequent ASM therapy
No response (<50% reduction in seizures)	39.9%	70.6%	70.2%	71.0%	72.7%	53.4%
Moderate Response (≥50% and <75% reduction in seizures)	21.7%	12.3%	13.0%	12.9%	11.8%	16.8%
High response (≥75% and <90% reduction in seizures)	15.6%	8.5%	9.1%	9.0%	8.2%	12.1%
Very high response (≥90% and <100% reduction in seizures)	6.7%	3.5%	3.7%	3.7%	3.4%	5.2%
Complete response (100% reduction in seizures)	16.2%	5.2%	3.9%	3.4%	3.9%	12.5%

Abbreviations: ASM, antiseizure medicine.

b) Table 28, Table 29, Table 30 and Table 31 provide the results of the scenario analysis where the effectiveness of subsequent ASM treatment is derived relative to brivaracetam, lacosamide, eslicarbazepine acetate and perampanel, respectively.

Table 28: Cost-effectiveness scenario analysis results where the odds ratio of being uncontrolled with subsequent ASM therapy is applied to brivaracetam

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.562		-	-
Lacosamide	246,376	5.722	[redacted]	-0.840	Dominated
Perampanel	247,242	5.700	[redacted]	-0.862	Dominated
Brivaracetam	247,424	5.712	[redacted]	-0.850	Dominated
Eslicarbazepine acetate	256,104	5.595	[redacted]	-0.967	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 29: Cost-effectiveness scenario analysis results where the odds ratio of being uncontrolled with subsequent ASM therapy is applied to lacosamide

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.567		-	-
Lacosamide	245,957	5.729	[redacted]	-0.838	Dominated
Perampanel	246,846	5.706	[redacted]	-0.861	Dominated
Brivaracetam	246,996	5.718	[redacted]	-0.849	Dominated
Eslicarbazepine acetate	255,774	5.600	[redacted]	-0.966	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 30 Cost-effectiveness scenario analysis results where the odds ratio of being uncontrolled with subsequent ASM therapy is applied toeslicarbazepine acetate .

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.566		-	-
Lacosamide	246,042	5.727	[redacted]	-0.838	Dominated
Perampanel	246,926	5.705	[redacted]	-0.861	Dominated
Brivaracetam	247,082	5.717	[redacted]	-0.849	Dominated
Eslicarbazepine acetate	255,841	5.599	[redacted]	-0.966	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 31: Cost-effectiveness scenario analysis results where the odds ratio of being uncontrolled with subsequent ASM therapy is applied to perampanel

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.559		-	-
Lacosamide	246,602	5.719	[redacted]	-0.841	Dominated
Perampanel	247,457	5.696	[redacted]	-0.863	Dominated
Brivaracetam	247,655	5.708	[redacted]	-0.851	Dominated
Eslicarbazepine acetate	256,283	5.593	[redacted]	-0.967	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

All scenarios lead to more costs and fewer QALYs for all treatments. When the odds ratio of being uncontrolled with subsequent ASM therapy is applied to perampanel, costs are highest and QALYs are lowest for all comparators. This demonstrates that the most conservative results are obtained when subsequent ASM treatment is compared to perampanel. In this scenario, costs are increased by

£24,218 to £32,985 compared to baseline. QALYs are reduced by 0.374 to 0.522 compared to the base case. For both costs and QALYs, cenobamate is impacted the least whereas perampanel is impacted the most.

However, as cenobamate is the least impacted by the treatment to which subsequent ASM treatment is compared, the base case scenario is conservative; the smallest incremental costs and QALYs relative to all comparators are demonstrated for cenobamate in the base case assumption for subsequent ASM treatment effectiveness.

B13. Please clarify if study C017 OLE could be used to obtain: a) the clinical effectiveness of subsequent ASM treatments; and b) the probability of moving on to surgery or VNS. If yes, please provide the derived estimates and a scenario that considers these in the model.

Unfortunately, these data are not available from the C017 OLE. Once patients discontinue treatment in the C017 OLE, they discontinue the study. Therefore, these long-term outcomes are not collected.

B14. Please explain how figures were obtained for table 29, page 103 of the company submission on the distribution of patients among response states in subsequent ASM treatment and invasive procedures.

Treatment response for the post-surgery, post-VNS and subsequent treatment health states were derived using data presented in Table 28 (Page 103 of the company submission) and the proportion of patients who achieved each level of treatment response with cenobamate (according to health state). This information has been replicated Table 32 and Table 33 below.

Table 32: Effectiveness of subsequent ASM treatment and invasive procedures

Characteristic of clinical effectiveness	Surgery	VNS
Proportion of patients on subsequent ASM treatment who move on to an invasive procedure, per cycle	0.15%	0.21%
Proportion of patients who experience death following the invasive procedure	0.86%	0.97%
Proportion of patients who achieve ≥50% and <100% responder rate with subsequent treatment, per cycle	5.20%	59.00%

Proportion of patients who achieved seizure freedom with subsequent treatment, per cycle	69.00%	6.00%
Subsequent ASM therapy – clinical effectiveness		
Odds ratio of remaining drug-resistant with subsequent ASM treatment relative to current ASM treatment	1.73	

Abbreviations: ASM, anti-seizure medicine; VNS, vagus nerve stimulation

Table 33: Distribution and description of response categories amongst cenobamate patients

Type of Response	Distribution	Description
No response	39.9%	Uncontrolled epilepsy, less than 50% reduction in seizure rate after addition of adjunctive treatment
Moderate response	21.7%	50-75% reduction in seizure rate after addition of adjunctive treatment
High response	15.6%	75-90% reduction in seizure rate after addition of adjunctive treatment
Very high response	6.7%	90-100% reduction in seizure rate after the addition of adjunctive treatment
Complete response	16.2%	Seizure freedom – 100% reduction in seizure rate

For the post-surgery health state, the proportion of patients with complete response (i.e., seizure freedom, 69%) was taken directly from Table 32.[43] The proportion of patients achieving moderate, high or very high response to surgery was 5.2%; the distribution of patients amongst these health states was assumed to proportionally relate to the distribution of cenobamate-treated patients amongst these health states as shown by Equation 1.

Equation 1: Calculating the proportion of patients who 'moderate', 'high' and 'very high' response in 'Post-surgery' health state.

$$Proportion\ with\ \boldsymbol{X}\ response = \frac{5.2\% \times Proportion\ of\ cenobamate\ patients\ with\ \boldsymbol{X}\ response}{\sum Proportion\ of\ cenobamate\ patients\ with\ moderate,\ high\ and\ very\ high\ response}$$

The proportion of patients who achieved no response was calculated as 100% less the sum of all other response rate categories.

For the post-VNS health state, the proportion of patients with complete response (i.e., seizure freedom, 6%) were taken directly from Table 32.[44] The proportion of patients achieving moderate, high or very high response to surgery was 59.0%; the distribution of patients amongst these health states was assumed to proportionally

relate to the distribution of cenobamate-treated patients amongst these health states as shown by Equation 2.

Equation 2: Calculating the proportion of patients who 'moderate', 'high' and 'very high' response in 'Post-VNS' health state.

$$Prop.with\ \boldsymbol{X}\ response = \frac{59.0\% \times Proportion\ \ of\ cenobamate\ patients\ with\ \boldsymbol{X}\ response}{\sum Proportion\ \ of\ cenobamate\ patients\ with\ moderate,\ \ high\ and\ very\ high\ response}$$

The proportion of patients who achieved no response was calculated as 100% less the sum of all other response rate categories.

The clinical effectiveness of subsequent ASM treatment captured through the Chen (2018) study which reported the odds ratio of having uncontrolled epilepsy with subsequent ASM treatment relative to the previous line of therapy (OR [95% CrI]= 1.73 [1.56, 1.91]).[13] The odds of having uncontrolled epilepsy with cenobamate were identified from the proportion of patients with no response to treatment converted to an odds using the following formula: $odds = \frac{risk}{1-risk}$.

The odds ratio were applied to the odds of having uncontrolled epilepsy after treatment with cenobamate to identify the odds of uncontrolled epilepsy in subsequent ASM treatment. The odds were then converted back to a probability value and was used to parameterise the probability of patients on subsequent treatment achieving no response. This meant that 53.4% of patients treated with a subsequent ASM treatment had no response to treatment. The proportion of patients in the remaining health states, i.e. ‘moderate response’, ‘high response’, ‘very high response’ and ‘complete response’ were calculated as described for post-surgery and post-VNS; i.e.,

Equation 3: Calculating the proportion of patients who 'moderate', 'high' and 'very high' response in the subsequent ASM treatment health state.

$$Proportion\ with\ \boldsymbol{X}\ response = \frac{(100\% - 53.4\%)\ \times\ Proportion\ of\ cenobamate\ patients\ with\ \boldsymbol{X}\ response}{\sum Proporti\ on\ of\ cenobamate\ patients\ with\ moderate,\ \ high, very\ high\ and\ complete\ response}$$

Treatment Discontinuation

B15. PRIORITY. Please explain how data from studies C017, C017 OLE and C021 were combined to inform the Kaplan Meier curve and the parametric

distributions for time to discontinuation of cenobamate (section B3.3.6, Figure 47, page 107).

The patient level data across the three studies were combined to a single dataset, it is weighted to reflect the relative sample sizes of each study. This was then used to create Kaplan Meier data and fit the parametric distributions for-time-to discontinuation of cenobamate.

B16. PRIORITY. Please justify the pooling of discontinuation rates from these studies given that the underlying reasons for discontinuation across studies could be different.

The company acknowledge that the underlying reasons for discontinuation between studies may be different, especially since the C021 study was designed primarily to assess the long-term safety of adjunctive cenobamate, thus not explicitly capturing discontinuation due to lack of response. However, there are similarities in the reasons for discontinuation across these studies, as presented in Table 34. Whilst discontinuation due to TEAEs was highest in the 400 mg arm of the C017 study, discontinuation in the C017 OLE is lower than in the C021 study, demonstrating that discontinuations primarily occur during titration.

Table 34. Reasons for discontinuation across the cenobamate studies

	C017		C017 OLE	C017 +OLE	C021
	200 mg N=110, n(%)	400 mg N=111, n(%)	All cenobamate N=355, n(%)	All cenobamate N=415, n(%)	All cenobamate N=1347, n(%)
Adverse event	15 (13.6)	23 (20.7)	27 (7.6)	78 (18.6)	137 (10.2)
Loss to efficacy	0	1 (0.9)	59 (16.6)	61(14.6)	NR
Withdrew consent, reason other than adverse event	4(3.6)	3 (2.7)	31 (8.7)	38 (9.1)	74 (5.5)
Lost to follow-up	0	1 (0.9)	7 (2.0)	7 (1.7)	11 (0.8)
Protocol deviation	1 (0.9)	1 (0.9)	3 (0.8)	5 (1.2)	6 (0.4)
Completed	0	1 (0.9)	5 (1.4)	NR	5 (0.4)
Pregnancy	0	0	0	1 (0.6)	1 (0.1)
Other	0	1 (0.9)	9 (2.5)	10 (2.4)	35 (2.6)
Deaths	0	0	5 (1.4)	5(1.2)	NR

Abbreviations: OLE, open-label extension.

Moreover, the rapid titration of 100 mg/week from 200 mg to 400 mg for six weeks in the C017 study may have overestimated the proportion of patients discontinuing due

to adverse events. The slower titration observed in the C021 study demonstrates reduced discontinuation due to TEAEs, highlighting that the high proportion of patients who discontinue due to TEAEs in rapid titration, as in the C017 study, would not be observed in clinical practice.

Nevertheless, the company would like to highlight that the pooling of discontinuation rates across studies is needed to capture the anticipated retention of cenobamate in clinical practice. Results from the C017 OLE show that approximately 60% and 57.70% of patients remained on treatment and maintained response after four and five years, respectively.[45] As such, pooling of discontinuation rates across the C021 study and the C017 OLE better support the long-term benefits of cenobamate.

B17. PRIORITY. Please comment on how the discontinuation rates sourced from studies C017 +OLE and C021 compare with treatment-specific discontinuation rates sourced from studies in Table 38, page 109 of the company submission.

A comparison of retention rates sourced from C017+OLE and C021 along with comparator treatment-specific retention rates is provided in Table 35. Retention rates over time are higher when combining data from C017+OLE and C021, highlighting the benefit slower titration has on reducing discontinuation frequency, thus representing what is observed in clinical practice.

In the C021 study, 80%, 72% and 68% of patients remained on treatment after one, two and three years, respectively. This was comparable to the C017+OLE, whereby 70.10% of patients remained on treatment one year from entering the OLE, followed by 59.00%, 54.30%, after two years and three years, respectively. The time to discontinuation from initiation of treatment is lower when considering the C017+OLE retention rates due to a quicker time to discontinuation during the RCT phase of the study which may be attributed to a forced titration.

The identified retention rates for cenobamate differ to comparator studies, as presented in Table 35. Retention rates for brivaracetam and perampanel are lower at all months compared to the combined retention in C017+OLE and C021, demonstrating the improved retention cenobamate has. Conversely, data for lacosamide indicates a marginally higher retention than cenobamate after one year;

however, in the long-term, retention to cenobamate was far higher than to lacosamide. Meanwhile there was only data available for the retention to eslicarbazepine acetate at 12 months from two studies; given the lack of long-term data the average of these two studies were combined for comparison with cenobamate. On average, the retention to eslicarbazepine acetate was lower than cenobamate after 12 months. These data demonstrate that retention to cenobamate is greater than the comparators in the long-term and short-term retention is greater with cenobamate than brivaracetam, perampanel and eslicarbazepine.

Table 35: A comparison of C017+OLE, C021 and comparator retention rates sourced from published literature.

Time (months)	C017 + OLE	C021*	C017 + OLE and C021	Brivara-cetam[46]	Peram-panel[38]	Lacos-amide[28]	Eslicarbaze-pine acetate[32,47]
0	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
12	70.10%	80.00%	76.60%	74.70%	73.50%	76.80%	72.60%
24	59.00%	72.00%	68.60%	63.30%	56.40%	NR	NR
36	54.30%	68.00%	63.10%	54.60%	46.20%	50.80%	NR
48	51.60%	NR	60.00%	49.20%	39.00%	NR	NR
60	49.70%	NR	57.70%	42.30%	36.19%	38.70%	NR
108	NR	NR	NR	12.40%	NR	NR	NR
120	NR	NR	NR	7.60%	NR	NR	NR

Abbreviations: NR, not reported; OLE, open-label-extension. *Data cut-off June 2020

B18. PRIORITY. Please clarify how time-to-discontinuation hazard ratios for comparator therapies (Table 39, page 109 of the company submission) were obtained using the published literature listed in Table 38 (page 109).

From the NMA, only a comparison of the odds of discontinuing treatment due to TEAEs was available. It is inappropriate to use this comparison to parametrise discontinuation with comparators relative to cenobamate.

Therefore, time-to-discontinuation was parametrised through the calculation of naïve hazard ratios for comparator therapies using the goal seek function in Excel. This identified the hazard ratio required for each comparator relative to cenobamate required to attain the specified retention rate at a given time point sourced from published literature. For example:

- The brivaracetam hazard ratio of 1.56 was required to ensure retention at five years matched the target rate of 42.30% sourced from O'Brien (2020)[46]
- The lacosamide hazard ratio of 1.78 was required to ensure retention at five years matched the target rate of 38.70% sourced from Rosenfeld (2014)[28]
- The eslicarbazepine acetate hazard ratio of 1.10 was required to ensure retention at year one matched the target rate of 72.60%, sourced from the Halasz (2010) and Hufnagel studies (2013)[32,47]
- The perampanel hazard ratio of 1.89 was required to ensure retention four year matched the target rate of 39.00% sourced from Krauss (2018)[38]

B19. PRIORITY. Given the differences between time to discontinuation in C017+OLE and C021, please fit parametric survival models to data from C017+OLE and to C021 independently, and provide options for using these as scenario analyses in the economic model.

Parametric survival models have been fit to data from C017+OLE and the C021 studies independently. Table 38 and Table 39 shows the resulting parametric distributions along with their respective Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics using data from C017+OLE and C021 study, respectively. The generalised gamma was the most appropriate curve for estimating treatment discontinuation for both studies. Like in the base case, the selection for each scenario was made after taking into account the flatter shapes of the distribution, the AIC and BIC values being the lowest (C017+OLE: AIC = 1008.754, BIC = 1020.868; and C021: AIC = 1906.991, BIC = 1922.592) and their consistency with treatment duration observed in the C017+OLE and C021 studies.

Table 36: AIC and BIC statistics from time-to-discontinuation parametric distributions using data from C017+OLE

Distribution	AIC	BIC
Exponential	1142.462	1146.499
Weibull	1048.663	1056.739
Gompertz	1017.127	1025.203
Log-logistic	1034.318	1042.394
Lognormal	1021.086	1029.162
Generalised Gamma	**1008.754**	**1020.868**

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 37: AIC and BIC statistics from time-to-discontinuation parametric distributions using data from C021

Distribution	AIC	BIC
Exponential	2095.908	2101.109
Weibull	1938.212	1948.613
Gompertz	1936.565	1946.966
Log-logistic	1929.952	1940.353
Lognormal	1911.961	1922.362
Generalised Gamma	**1906.991**	**1922.592**

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 3 and Figure 4 shows all parametric distributions and the Kaplan Meier curve for the C017+OLE and C021 studies, respectively.

Figure 3: Time to discontinuation (cenobamate) c017+OLE study - all distributions

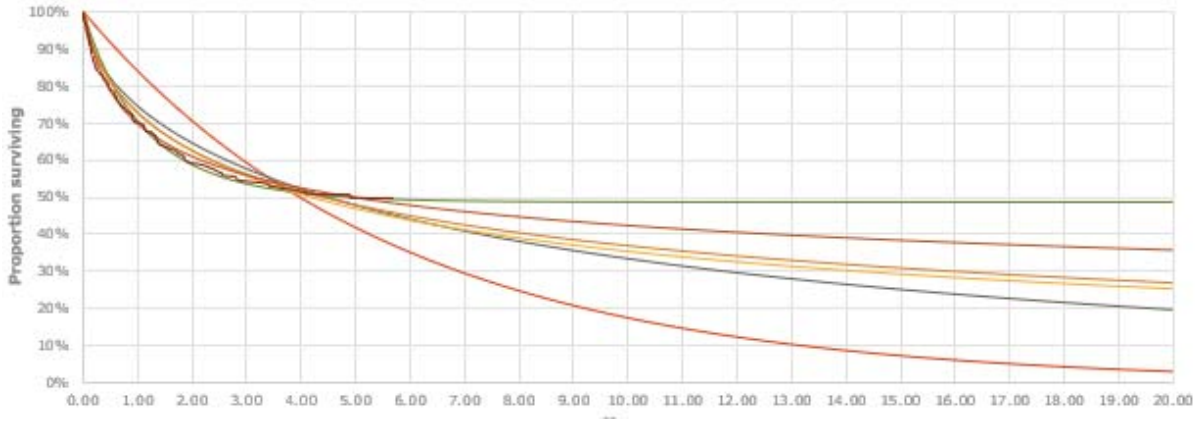
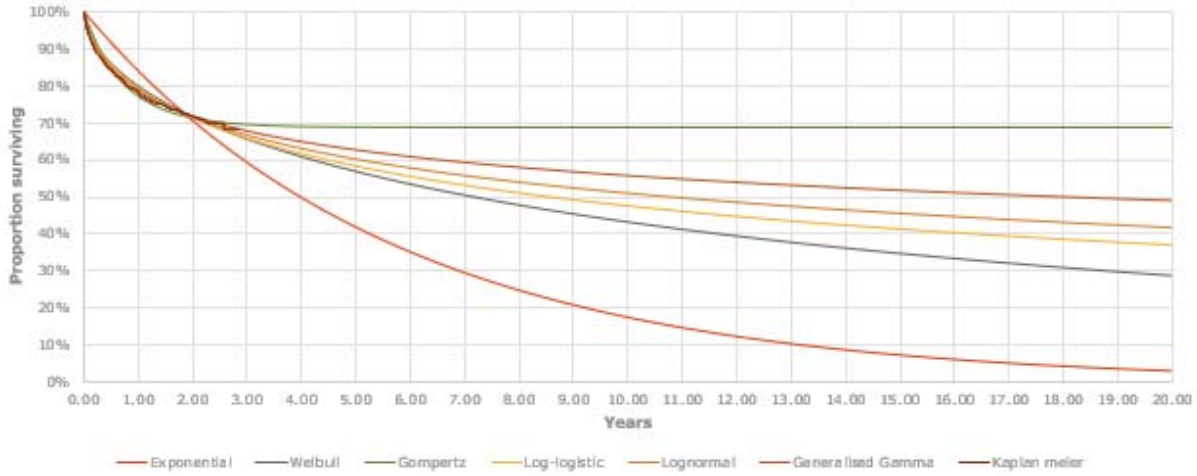


Figure 4: Time to discontinuation (cenobamate) C021 study - all distributions



Given time-to-discontinuation hazard ratios for comparator therapies are dependent on these parametric curves, the goal seek function (outlined in question B18) was used to identify the appropriate HRs relative to cenobamate. Table 38 outlines the revised hazard ratios for each comparator, dependent on the scenario chosen. The hazard ratio for eslicarbazepine acetate obtained from C017+OLE independently is now below one, which may be a result of the increased discontinuation frequency observed in the C017 due to rapid titration. Like in the base-case, all other hazard ratios for comparator therapies remain above one.

Table 38: HR's relative to cenobamate from C017+OLE and C021 independently

	C021	**C017+OLE**
Comparator	HR	HR
Brivaracetam	1.78	1.24
Lacosamide	2.01	1.40
Eslicarbazepine acetate	1.17	0.92
Perampanel	2.11	1.49-

Abbreviations: HR, hazard ratio; OLE, open-label-extension

The aggregated results for the cost-effectiveness of cenobamate relative to the comparators for each scenario in Table 39 andTable 40, respectively. As in the base-case, cenobamate dominates all comparators in both scenarios. When using time-to-treatment discontinuation data from C021 independently, over the lifetime time horizon, treatment with cenobamate was associated with 6.960 QALYs at a total cost of [redacted]. The lower cost of treatment with cenobamate compared to base-case scenario (cenobamate base case: [redacted], total QALYS: 6.933) highlights the

benefit of a slower titration observed in the C021 study. In comparison, when using TTD data from C017+OLE independently, over the lifetime time horizon, treatment with cenobamate was associated with 6.897 QALYs at a total cost of [redacted]. The increase in total cost of treatment with cenobamate and the decrease in total QALYs compared to base-case scenario reflects the impact of rapid titration observed in the C017 study, further supporting the Company's decision to pool discontinuation rates to better align with what is observed in clinical practice.

Table 39: Cost-effectiveness scenario results where discontinuation is based on data from the C021 study

	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.960			-
Lacosamide	214,685	6.208	[redacted]	-0.752	Dominated
Perampanel	215,275	6.205	[redacted]	-0.755	Dominated
Brivaracetam	216,946	6.165	[redacted]	-0.795	Dominated
Eslicarbazepine acetate	233,146	5.949	[redacted]	-1.011	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 40: Cost-effectiveness scenario results where discontinuation is based on data from C017+OLE study

	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.897			-
Lacosamide	214,563	6.212	[redacted]	-0.685	Dominated
Perampanel	214,858	6.213	[redacted]	-0.684	Dominated
Brivaracetam	216,713	6.170	[redacted]	-0.727	Dominated
Eslicarbazepine acetate	228,768	6.017	[redacted]	-0.881	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

B20. Please clarify whether a systematic literature review was undertaken to identify treatment-specific discontinuation rates from the studies in Table 38, page 109 of the company submission. Please explain how the studies in Table 38 were chosen.

A targeted literature review was performed to identify potential studies with treatment-specific discontinuation rates.

Figure 5 shows the four studies identifying retention rates for patients taking brivaracetam (Toldedo 2016[48], Arnold 2020[49], with data for two populations identified from O'brien 2020[46] for patients with focal seizures [a] and primary generalised

seizures [b]). The Toledo 2016 study only considered discontinuation due to AEs or lack of response whilst the remaining two studies did not adequately reflect the anticipated market authorisation. Ultimately, data from the O'Brien 2020 study for the focal seizure population was used because this is in line with the anticipated marketing authorisation.

Figure 5: Brivaracetam studies identified in targeted literature search.

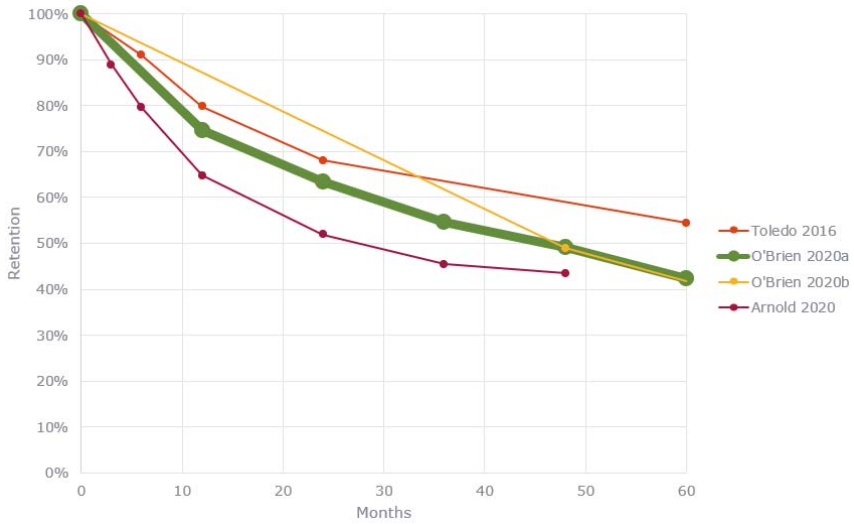


Figure 6 shows the two studies identifying retention rates for patients taking perampanel (Usui 2018[50] and Krauss 2018[38]). Retention rates from the Krauss study were chosen as the sample size was far smaller in the Usui study which would have created bias (Usui, N=21; Krauss, N=1,218).

Figure 6: Perampanel studies identified in targeted literature search.

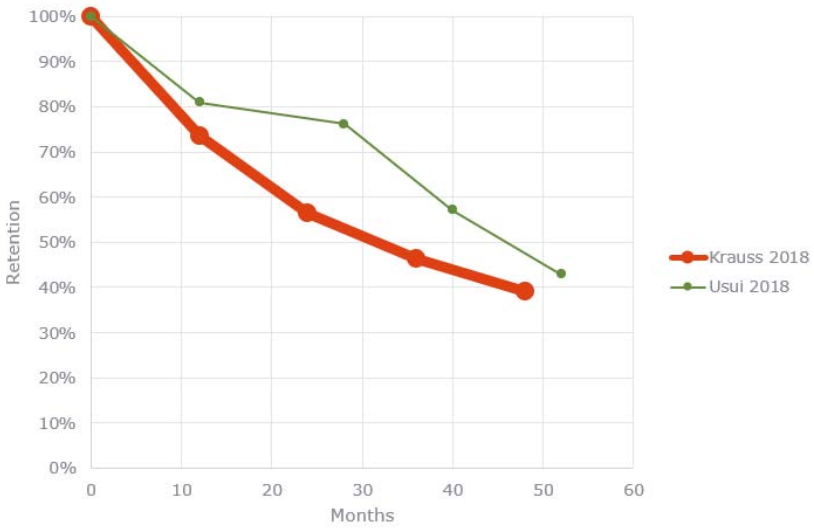
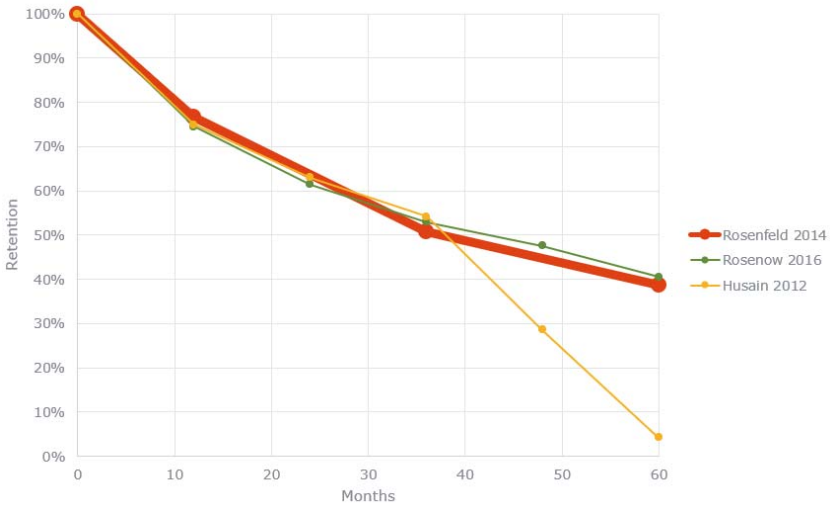


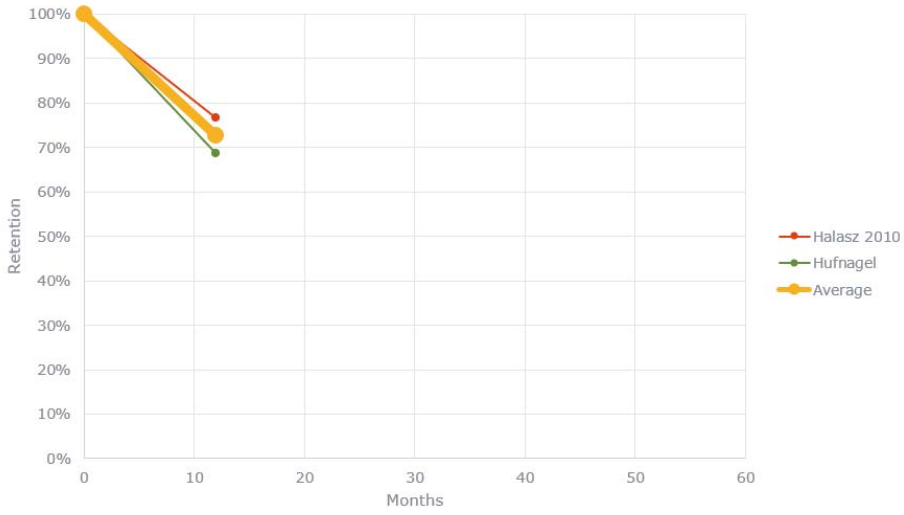
Figure 7 shows the three studies identifying retention rates for patients taking lacosamide. (Rosenfeld 2014[28], Rosenow 2016[26] and Husain 2012[27]). The Rosenfeld 2014 study includes adjunctive 100 mg/day to 600 mg/day and was chosen as it most closely reflects the licensed dose in clinical practice. In comparison the Rosenfeld and Husain studies included adjunctive 100 mg/day to 800 mg/day not, not reflective of clinical practice.

Figure 7: Lacosamide studies identified in targeted literature search.



Finally, Figure 8 shows the two studies identifying retention rates for patients taking eslicarbazepine acetate (Halasz 2010 and Hufnagel 2013[32,47]). Both studies assessed the same randomised dose and had similar patient numbers, therefore an average of both studies was taken.

Figure 8: Eslicarbazepine acetate studies identified in targeted literature search.



B21. The NMA provides odds ratios for experiencing at least one treatment emergent adverse event (TEAE) leading to discontinuation (section B2.9, page 73-74). Please provide a scenario where discontinuation rate is derived from the odds ratios in the indirect treatment comparison, instead of the hazard ratios in Table 39?

The NMA for odds ratios of discontinuation due to TEAEs was not suitable for use in the model. TEAE-related discontinuation rates in the C017 study were substantially higher across the cenobamate 200 mg and 400 mg arms (13.6% and 19.8%, respectively) compared to the TEAE-related discontinuation rates that are expected in clinical practice. Just 10.2% of patients discontinued due to TEAEs in the C021 study where titration is aligned with the expected use of cenobamate in clinical practice. In addition, discontinuation in the economic model also considers patients who have discontinued due to other factors (e.g. loss to follow-up, withdrawal of consent etc.). Implementing odds ratios of TEAE-related discontinuation to the economic model would not provide an accurate depiction of discontinuation rates of comparators.

An NMA analysis has been conducted to assess the odds ratios of discontinuation due to any reason with comparators relative to cenobamate. The methods performed are aligned with the base case analyses; analyses were conducted under a Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[11] It was assumed that data followed a Binomial likelihood distribution. Vague priors were fit to the treatment effects and between-study variation.

Results from the random effects analysis are presented in Table 41. The results indicate that patients treated with cenobamate have lower odds of staying on treatment compared to all comparators. Due to the high discontinuation rates in the C017 study, odds ratios from the ITC analysis underestimate the odds of discontinuing with comparators relative to cenobamate. This is due to the substantially higher TEAE-related discontinuation rates in the C017 study which are likely introduced from the rapid titration that would not be observed in clinical practice.

Table 41: 'All-cause' discontinuation ORs relative to cenobamate (random effects)

Comparator versus cenobamate	Random effects

Odds ratios, median (95% credible interval)	
Perampanel	[redacted]
Eslicarbazepine acetate	[redacted]
Lacosamide	[redacted]
Brivaracetam	[redacted]
Placebo	[redacted]
Model outputs	
Between-study SD Median (95% CrI)	[redacted]
DIC	[redacted]
Total residual deviance Mean Median	[redacted]
Effective number of parameters	[redacted]

*Values highlighted in **bold** represent statistically significant results.

Abbrveiations: DIC, Deviance information criterion; SD, standard deviation; CrI, credible interval.

[redacted]

The output of the NMA for the odds ratio of discontinuation due to any reason were implemented in the model for a scenario analysis; the incremental costs and QALYs are provided in Table 42. The scenario analysis did not change the total costs or QALYs for cenobamate. Costs for the comparators increased by £9,875-£34,302 whilst QALYs reduced by 0.15-0.54. The implementation of all-cause discontinuation ORs has the largest impact on the costs and the QALYs of eslicarbazepine acetate. With the lowest cost and the highest QALY gain compared with the 3rd generation comparators, cenobamate still dominates all comparators. However, this analysis is biased by the unrealistic discontinuation observed in the C017 study and should be interpreted with caution.

Table 42: Scenario analysis results – all-cause discontinuation ORs implemented in the model.

Treatment	**Total**		**Incremental**		**ICER (£)**
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Cenobamate	[redacted]	6.933	-	-	-
Lacosamide	239,161	5.817	[redacted]	-1.116	Dominated
Eslicarbazepine acetate	240,556	5.836	[redacted]	-1.097	Dominated
Brivaracetam	240,748	5.785	[redacted]	-1.149	Dominated
Perampanel	248,774	5.679	[redacted]	-1.254	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

B22. The model assumes that the probability of treatment discontinuation is independent of patients' level of response. Please discuss the plausibility of this assumption.

The probability of treatment discontinuation is independent of patients' level of response in the economic model. However, the time-to-treatment discontinuation curve applied does reflect the time-to-treatment discontinuation observed in clinical practice, regardless of response to treatment. The choice of curve was validated by clinicians who gave preference to a flatter curve which reflected that discontinuation would plateau as the remaining patients would have responded to treatment. Therefore, patients' level of response has indirectly been taken into account when choosing the most appropriate parametric curve.

Moreover, a conservative assumption has been made by applying discontinuation uniformly to all health states and therefore it is likely discontinuation of responders is overestimated. This is because in clinical practice, it is likely a higher proportion of non-responders would discontinue. Consequently, patients prematurely move onto less effective subsequent treatment options leading to underestimated incremental QALYs and overestimated incremental costs.

Adverse Drug Events

B23. Please clarify why Table 32 (page 105 of the company submission) estimates on the odds ratio of adverse events relative to cenobamate (base case comparators) do not match the estimates shown in the forest plot on Figure 40 (page 74 of the company submission).

Figure 40 and Table 32 of the company submission do not report the same data. Figure 40 reports the odds ratios of the comparators versus cenobamate for the proportion of patients experiencing a TEAE leading to discontinuation whereas Figure 38 reports the odds ratios for patients experiencing at least one TEAE.

The data in Table 32 represents the odd ratios for patients experiencing at least one TEAE and corresponds to the data in Figure 38 of the submission. There are two minor typographical errors in Table 32; the table should report odds ratios of 1.04 and 0.91 for eslicarbazepine acetate and perampanel, respectively (as in Table 14 of the company submission).

B24. The NMA suggests high levels of uncertainty in the relative risk of adverse events (Figure 38, page 72 of the company submission). This uncertainty was not reflected in the model, and only an arbitrary 20% uncertainty estimate in the costs and effects of adverse events was used. Please amend the model to include uncertainty in the occurrence of adverse drug reactions, and its subsequent effect on costs and outcomes.

The model has been amended to incorporate the uncertainty in the relative frequency of adverse events for comparators as identified from the NMA. The probabilistic and one-way sensitivity analysis results under this adjusted variation are reported in Appendix C.

The total costs and QALYs associated with each treatment under the upper and lower bounds of the credible intervals for the odds ratio of adverse events relative to cenobamate are presented in Table 43. As the total costs and QALYs of each treatment are only affected by the odds ratio for the likelihood of AEs of that treatment relative to cenobamate, the total costs and QALYs for cenobamate are unchanged. For comparators, total costs and QALYs are reduced under the upper bounds of the credible intervals and increased under the lower bound of the interval. Adopting the credible intervals for the odds ratios of adverse events with comparators presents slightly wider margins for total costs and QALYs compared to simultaneously varying the total costs and disutilities of adverse events in comparators by 20%, as done in the original company submission. However, the impact of this is minor as in all scenarios cenobamate remains dominant.

Table 43. Cost-effectiveness results under updated variance for relative likelihood of adverse evemts

	Lower bound of odds ratio of AEs relative to cenobamate			Upper bound of odds ratio of AEs relative to cenobamate		
Comparator	**Total costs**	**Total QALYs**	**ICER relative to cenobamate**	**Total costs**	**Total QALYs**	**ICER relative to cenobamate**
Cenobamate	[redacted]	6.933		[redacted]	6.933	
Lacosamide	214,089	6.224	Dominated	214,247	6.207	Dominated
Perampanel	214,401	6.226	Dominated	214,581	6.206	Dominated
Brivaracetam	216,637	6.176	Dominated	216,793	6.159	Dominated
Eslicarbazepine acetate	230,570	6.000	Dominated	230,855	5.968	Dominated

Abbreviations: AEs, adverse events; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Deriving the number of seizures

B25. Please clarify how the relative seizure reduction split by seizure type and response category in Table 30 (page 104 of the company submission) was derived. For example, over what period of time was the reduction observed?

a) Please include the uncertainty in the above estimates in the model.

Data for the relative reduction of seizures stratified by health state were identified from patient level data of the C017 study reported in Table 44. The frequency of seizures per 28 days are reported over the screening phase (baseline) and the maintenance phase of the study. The frequencies are further stratified according to response to treatment over the maintenance phase of the study (i.e., no response, moderate response, high response, very high response and complete response) and by seizure type (focal aware, focal impaired awareness, and focal to bilateral tonic-clonic).

Data included patients taking cenobamate at the 200 mg and 400 mg dose since it is the reduction demonstrated from treatment with the intervention at the therapeutic dose. The relative reduction in seizures by seizure type and response to treatment were identified from the percentage reduction in the median frequency of seizures during the maintenance phase compared to the screening phase. Naturally, the relative reduction of complete response across all three seizure types assumed a value of 100%.

a) As the relative reduction was calculated according to the median frequency of seizures, uncertainty was not evaluated in the relative reduction. Naturally, within health states the maximum and minimum reduction in seizure frequency are constrained by the definition of the health states (i.e., for high response, the relative reduction cannot be lower than 75% and cannot be equal to or higher than 90%).

   The variation in seizure frequency according to response to treatment over the screening phase and maintenance phase of the C017 study is reported in Table 44; the median, lower and upper quartiles, and the interquartile range

(IQR) are presented. This variation has not been implemented in the model as it is not possible to derive the variation in a quotient.

Table 44: Median seizure frequency, by seizure type and response to treatment

Response to treatment over the maintenance phase of the C017 study, study phase	Seizure frequency per 28 days: Q1, Median, Q2 (IQR)		
	Focal Aware	Focal Impaired Awareness	Focal to Bilateral Tonic Clonic
No response (<50% reduction in seizures), Screening phase	4.75, 10.50, 24.25 (19.50)	5.50, 8.50, 23.00 (17.50)	1.50, 2.25, 6.25 (4.75)
No response (<50% reduction in seizures), Maintenance phase	4.00, 12.45, 32.27 (28.27)	4.00, 9.10, 20.53 (16.53)	1.55, 2.09, 7.35 (5.80)
Moderate response (>=50% and <75% reduction in seizures), Screening phase	7.75, 35.00, 77.75 (70.00)	4.50, 7.50, 11.00 (6.50)	2.00, 4.00, 7.50 (5.50)
Moderate response (>=50% and <75% reduction in seizures), Maintenance phase	2.77, 11.11, 26.53 (23.77)	1.81, 3.02, 4.40 (2.59)	0.67, 1.57, 3.26 (2.59)
High response (>=75% and <90% reduction in seizures), Screening phase	6.50, 13.25, 34.62 (28.12)	5.50, 9.25, 11.00 (5.50)	2.25, 4.50, 6.50 (4.25)
High response (>=75% and <90% reduction in seizures), Maintenance phase	1.00, 2.58, 4.67 (3.67)	0.86, 1.45, 2.22 (1.36)	0.39, 0.76, 1.01 (0.62)
Very high response (>=90% and <100% reduction in seizures), Screening phase	13.50, 46.75, 80.00 (66.50)	4.75, 10.00, 34.00 (29.25)	2.50, 6.75, 20.50 (18.00)
Very high response (>=90% and <100% reduction in seizures), Maintenance phase	1.10, 1.89, 2.67 (1.57)	0.32, 0.45, 0.78 (0.47)	0.22, 0.33, 1.31 (1.09)
Complete response (=100% reduction in seizures), Screening phase	0.50, 2.25, 6.50 (6.00)	1.50, 4.00, 6.50 (5.00)	0.50, 1.00, 2.00 (1.50)
Complete response, (=100% reduction in seizures), Maintenance phase	0.00, 0.00, 0.00 (0.00)	0.00, 0.00, 0.00 (0.00)	0.00, 0.00, 0.00 (0.00)

Abbreviations: IQR, interquartile range.

B26. In the company submission, the number of seizures was derived from the baseline number of seizures (for each type of seizure) and the average magnitude of response in each transition state (no response, moderate, high and very high response, and seizure free). The company elicited the baseline number of seizures from clinicians. In Table 30 (page 104 of company submission), the average number of seizures per 4-week period were 4.63 focal aware + 6.25 focal impaired

awareness + 2.50 focal to bilateral tonic clonic = 13.38 seizures per 28 days. In trial C017 (Table 10), the baseline number of seizures was 8.4-9.5 seizures per 28 days.

a) Please explain why the number of focal aware and focal impaired awareness seizures on average increases with no response (-18.57% and -7.06% reduction seizures in Table 30), instead of remaining constant.

b) Please report baseline seizure rates (total and by type of seizure) in the baseline period of the clinical studies C013, C017 and C021.

c) Please present scenarios using the data from the trials to inform the baseline seizure rate and the number of seizures in the model.

d) Please clarify why clinical opinion was used to inform the model and discuss implications for the generalisability of the trials to the UK patient population.

a) The frequency of seizure in patients with no response to treatment was based on observed patient level data from the C017 as opposed to a user defined assumption that patient with no response will remain constant in seizure frequency. This would have underestimated the total costs in patients who do not respond to treatment as it is possible that ineffective treatment can exacerbate seizure occurrence.

   Utilising the patient level data provides an accurate reflection of the relative reduction in seizure frequency across all health states over a 28-day period. A scenario in which the frequency of seizures remains constant for non-responders would not reflect how seizure frequency is affected through treatment within studies or the real-world setting.

   Patient level data from the C017 trial (as shown in Table 45) indicated that patients with no response to cenobamate had an increase in seizure frequency of 18.57% and 7.06% in focal impaired awareness seizures and focal aware seizures, respectively.

Table 45: Median seizure frequency per 28 days over screening and maintenance phase in patients with no response

Response to treatment over the maintenance phase of the C017 study, study phase	Seizure frequency per 28 days: Median (IQR)		
	Focal Aware	Focal Impaired Awareness	Focal to Bilateral Tonic Clonic

No response (<50% reduction in seizures), Screening phase	10.50 (19.50)	8.50 (17.50)	2.25 (4.75)
No response (<50% reduction in seizures), Maintenance phase	12.45 (28.27)	9.10 (16.53)	2.09 (5.80)
Increase over screening and maintenance phase	2.45	0.6	-0.16
Relative increase over screening and maintenance phase	18.6%	7.1%	-7.1%

Abbreviations: IQR, interquartile range.

b) Table 46 presents the baseline seizure frequency per 28 days for focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizure types for the C017 study. Focal impaired awareness seizures were reported in the majority of patients, whilst focal aware seizures were reported in the fewest patients. The frequency of seizure types according to treatment arm were similar.

Table 46: Median baseline seizure frequency (by type of seizure) in the baseline period of C017 study

	Focal Aware	**Focal Impaired Awareness**	**Focal to Bilateral Tonic Clonic**	**Total**
Placebo (N=108)	12.5 (n=19)	8.0 (n=90)	2.5 (n=45)	8.4 (n=108)
Cenobamate 100 mg (N=108)	6.5 (n=22)	7.5 (n=101)	3.0 (n=37)	9.5 (n=108)
Cenobamate 200 mg (N=110)	11.0 (n=28)	8.0 (n=97)	3.0 (n=35)	11.0 (n=110)
Cenobamate 400 mg (N=111)	12.0 (n=22)	8.0 (n=100)	2.0 (n=43)	9.0 (n=111)

Table 47 presents the baseline seizure frequency per 28 days for focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizure types for the C013 study. As in the C017 study, focal impaired awareness seizures were reported in the majority of patients, whilst focal aware seizures were reported in the fewest patients. Again, the frequency of seizure types according to treatment arm were similar.

Table 47: Median baseline seizure frequency (by type of seizure) in the baseline period of C013 study

	Focal aware	**Focal impaired awareness**	**Focal to Bilateral Tonic Clonic**	**Total**
Cenobamate 200 mg (N=113)	5.1 (n=30)	6.5 (n=87)	3.3 (n=38)	7.5 (n=113)

Placebo (N=109)	3.5 (n=26)	5.5 (n=89)	2.0 (n=37)	5.5 (n=109)

Seizure frequency was not reported in the C021 study and is therefore not available.

c) Scenarios were conducted where the frequency of seizures was determined from the C017 and C013 studies. It was assumed that seizure frequency would be the average of the values reported for arms considered in the economic model (i.e., the 200 mg and 400 mg arm in C017, and the 200 mg arm in C013). As the frequency of seizure types was not reported in all patients, it was assumed that the frequency in patients was the same as in those who reported each type of seizure.

Table 48 presents the magnitude of seizure occurrence across all seizure types and ASM treatments using the baseline seizure frequency of 28 days from the C017 study.

Table 48: Seizure Occurrence (by seizure type) - Baseline seizure frequency from C017 study

	Cenobamate	**Brivaracetam**	**Lacosamide**	**Eslicarbazepine acetate**	**Perampanel**
Focal aware	2,832	3,747	3,668	3,970	3,669
Focal impaired awareness	1,847	2,411	2,363	2,550	2,363
Focal to bilateral tonic-clonic	515	665	652	702	652
Total	5,195	6,822	6,683	7,221	6,683

Utilising baseline seizure frequency from the C017 study, the total number of seizures experienced increased for all treatments. The largest increase was to focal aware seizures, whereas focal to bilateral tonic-clonic seizures remained the same.

Table 49 presents the incremental costs and QALYs resulting from baseline seizure frequency sourced from the C017 study. The total cost for all

comparators increased; QALYs were unaffected. In this scenario, cenobamate remains the dominant treatment.

Table 49: Cost-effectivness scenario analysis results where baseline seizure frequency is determined from C017 data

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.933	-	-	-
Lacosamide	242,524	6.218	[redacted]	-0.715	Dominated
Perampanel	242,876	6.218	[redacted]	-0.715	Dominated
Brivaracetam	245,650	6.170	[redacted]	-0.763	Dominated
Eslicarbazepine acetate	261,268	5.987	[redacted]	-0.946	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 50 presents the magnitude of seizure occurrence across all seizure types and ASM treatments using the baseline seizure frequency of 28 days from the C013 study.

Table 50: Seizure Occurrence (by seizure type) - Baseline seizure frequency from C013 study

	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Focal aware	1,256	1,661	1,626	1,760	1,627
Focal impaired awareness	1,501	1,959	1,920	2,071	1,920
Focal to bilateral tonic-clonic	680	878	861	927	861
Total	3,437	4,498	4,408	4,759	4,407

Utilising baseline seizure frequency from the C013 study, the frequency of all seizures increases. The largest relative increase is in the frequency of focal to bilateral tonic-clonic seizures whereas focal aware and focal impaired awareness seizures remain relatively close to the base case values.

Table 51 presents the incremental costs and QALYs resulting from baseline seizure frequency sourced from the C013 study. The total cost for all comparators increased; QALYs were unaffected. In this scenario, cenobamate remains the dominant treatment.

Table 51: Cost-effectiveness scenario analysis results where baseline seizure frequency is determined from C013 data

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.933	-	-	-
Lacosamide	245,735	6.218	[redacted]	-0.715	Dominated

Perampanel	246,069	6.218	[redacted]	-0.715	Dominated
Brivaracetam	248,875	6.170	[redacted]	-0.763	Dominated
Eslicarbazepine acetate	264,603	5.987	[redacted]	-0.946	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

d) Data from the C017 study did not indicate the frequency of types of seizures in all patients. Additionally, as the C017 study had a cohort of patients from a variety of countries, and that there are likely to be extremes in the observed values in clinical practice, clinician opinion was sought to inform the frequency of focal onset seizures in drug-resistant patients in the UK.

   Clinical expert opinion was sought on all aspects of the economic model to ensure that the cost-effectiveness of cenobamate was truly reflective of real-world clinical practice and to further validate the eligibility of cenobamate as a cost-effective ASM; given the impact that frequency of seizures have for the total costs it was important to ensure that this was accurately captured.

Costs

B27. In the up titration phase the target dose of cenobamate was 200mg, while in the maintenance phase 200mg and 400mg estimates were used. Please indicate how much additional up titration time is required for the 400mg dose.

An additional eight weeks is needed for patients to titrate to a dose of 400 mg/day of cenobamate. All patients initiate treatment at 12.5 mg per day and titration to a target dose of 200 mg takes 12 weeks. Patients who require their dose to be optimised beyond 200 mg per day will have their dose increased by 50 mg every two weeks. Therefore, it would take an additional eight weeks to titrate to a 400 mg/day dose, and 20 weeks in total to titrate from treatment initiation to a maintenance dose of 400 mg/day.

B28. Please model and present results for a scenario where cenobamate is removed from the drugs included in the costs of subsequent ASM health state.

The market shares of 3rd generation ASMs excluding cenobamate are based on the 'current' market uptake implemented in the budget impact analysis as shown in Table 52. It is conservatively assumed that cenobamate would be a treatment option in the subsequent ASM treatment pathway given that patients who are treated with

an alternative comparator initially would be eligible for its use if they do not derive a response to their allocated treatment.

Table 52: Market share of third generation ASMs excluding cenobamate

	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Subsequent treatment distribution	[redacted]	[redacted]	[redacted]	[redacted]

The aggregated results for the cost-effectiveness of cenobamate when cenobamate is excluded from subsequent ASM therapy are presented in Table 53. Over the lifetime time horizon, there are no differences in the QALYs gained. The scenario analysis results in a total cost of [redacted] for cenobamate, which is a [redacted] decrease compared to the base case. Costs for the comparators are also decreased, with the reductions ranging from [redacted] -[redacted]. Therefore, the exclusion of cenobamate in the subsequent ASM treatment options has the largest impact to cenobamate. With the lowest cost and the highest QALY gain compared with the 3rd generation comparators, cenobamate still dominates all comparators.

Table 53: Cost-effectiveness scenario results where cenobamate is excluded from subsequent ASM treatment basket

Treatment	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Heath related quality of life (HRQoL)

B29. PRIORITY. The C017 study collected data on HRQoL using the QOLIE-31-P instrument. The company submission states that the economic model does

not make use of QOLIE-31-P data because changes across treatment arms were not observed, arguing that the follow-up was too short.

a) **Please provide statistical test results for the differences in Table 41, clarifying if these differences are statistically significant or not.**

b) **Please provide a justification why HRQoL differences in terms of QOLIE-31-P were not observed. QOLIE-31-P differences have been found in trials of comparators (see https://www.sciencedirect.com/science/article/pii/S1525505016304590)**

c) **Please include a scenario where utilities derived from the C017 QOLIE-31-P data (mapped on to EQ-5D utility estimates) inform the economic model.**

a) Table 54 presents the number (and proportion) of patients who were able to achieve a minimally important change (MIC) (i.e., ≥11.8 points) in QOLIE-31-P score from baseline in the C017 study. Of the cenobamate arms, those randomised to 400 mg/day had the highest number of patients achieving a MIC in their QOLIE-31-P score (n=7 [7.1%]). However, results were not statistically significant compared to placebo for any dose of cenobamate.

Table 54: Patients achieving a minimally important change (≥11.8 points) in QOLIE-31 scores from baseline.

	Cenobamate 100 mg (N=108) (n=27)	Cenobamate 200 mg (N=109) (n=27)	Cenobamate 400 mg (N=111) (n=33)	Placebo (N=106) (n=29)
Patients achieving minimally important change in QOLIE-31-P score – n (%)	3 (11.1)	3 (11.1)	5 (15.2)	7 (21.1)
p-value	0.299	0.299	0.522	

Abbreviations: QOLIE-31, Quality of Life in Epilepsy – 31.
n within each group is used as the denominator for the calculation of the percentage.

Table 55 presents the number (and proportion) of patients who were able to achieve a MIC (at a lower threshold of >=5.19 points) in QOLIE-31-P scores from baseline in the C017 study. Of the cenobamate arms, those randomised to 400 mg/day arm had the highest number of patients achieving a MIC in their QOLIE-31-P score (n=10 [30.3%]). However, results were not statistically significant compared to placebo for any dose of cenobamate.

Table 55: Patients achieving a minimally important change (>=5.19 points) in QOLIE-31 scores from baseline.

	Cenobamate 100 mg (N=108) (n=27)	Cenobamate 200 mg (N=109) (n=27)	Cenobamate 400 mg (N=111) (n=33)	Placebo (N=106) (n=29)
Patients achieving minimally important change in QOLIE-31-P score – n (%)	6 (22.2)	8 (29.6)	10 (30.3)	12 (41.1)
p-value	0.158	0.412	0.430	

Abbreviations: QOLIE-31, Quality of Life in Epilepsy – 31.
n within each group is used as the denominator for the calculation of the percentage.

The change from baseline in QOLIE-31-P scores are presented in Table 56 with p-values reported compared to placebo.

Table 56. Summary of change from baseline in QOLIE-31-P score

Treatment	n (%)	Mean change from baseline (SD)	Change from baseline LS-mean (SE)	p-value
Cenobamate 100 mg (N=108)	27 (25.0)	-0.81 (9.66)	0.37 (2.21)	0.390
Cenobamate 200 mg (N=109)	27 (24.8)	0.62 (11.96)	0.02 (2.20)	0.329
Cenobamate 400 mg (N=111)	33 (29.7)	-6.21 (16.99)	-6.03 (1.99)	0.002
Placebo (N=106)	29 (27.4)	3.76 (11.37)	3.01 (2.12)	-

Abbreviations: LS, least squares; SD, standard deviation; SE, standard error

Only the cenobamate 400 mg/day arm observed a statistically significant change from baseline in QOLIE-31-P score, but this change indicated a worsening in condition. However, QOLIE-31-P was only recorded in participants of study C017 from Austalia, UK and the USA; therefore less than 30% of enrolled participants completed the questionnaire. Moreover, amongst the patients completing the questionnaire, the distribution of participants was skewed according to their response to treatment as demonstrated in Table 57. There are more patients without response data for the cenobamate 400 mg and 200 mg arms due to higher discontinuation of treatment due to fast titration. Given that few patients completing the questionnaire derived a high response to treatment, it is not possible to demonstrate statistically significant QOLIE-31-P improvements.

Table 57. Distribution of patients completing QOLIE-31-P questionnaire according to response to treatment in four weeks prior to study completion

Response to treatment in four weeks prior to the end of the study	N patients				
	Placebo	Cenobamate 100 mg	Cenobamate 200 mg	Cenobamate 400 mg	Grand Total
No response data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No response (<50% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate response (>=50% and <75% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High response (>=75% and <90% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Very high response (>=90% and <100% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response (100% reduction in seizures)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grand Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) As discussed in the Decision Problem Meeting proforma, there was not sufficient QOLIE-31-P data to derive a MIC from baseline scores. QOLIE-31-P was collected only in participants at English-speaking sites; therefore, only participants from the UK, USA and Australia completed the questionnaire. This represented less than a third of the population enrolled into the C017 study. This limited the statistical power of comparisons of the proportions of patients achieving MIC in QOLIE-31-P scores.

Moreover, the MIC in the C017 study was set to 11.8, in line with published recommendations for the MIC at nine months.[51] However, the C017 study did not collect QOLIE-31-P data after this period of time; therefore, there was not sufficient time considered to demonstrate meaningful improvements. In the study identified by the ERG, a MIC of 5.19 was considered which explains why the brivaracetam study was able to demonstrate significant

improvements in QOLIE-31-P. Additionally, the brivaracetam study had a much larger cohort size than the C017 study which enabled statistically significant differences to be identified.

An additional analysis has been performed and presented to the response to question B29(a) whereby a MIC threshold of 5.19 is considered.

c) There was a limited sample size in which QOLIE-31-P was collected in the C017 study; moreover, the duration of the C017 study was not sufficient to collect robust evidence for the long-term impacts to quality of life from treatment with cenobamate. Additionally, it has been acknowledged that the QOLIE-31-P does not map well to EQ-5D.[52] Therefore, a scenario considering health related quality of life parametrised by QOLIE-31-P from the C017 study has not been performed.

B30. PRIORITY. The state-specific utilities in the model were based on one trial of cenobamate.

a) Please clarify why state-specific QOLIE-31-P scores were not informed by the broader literature (Table 18 in appendix H).

b) Please use estimates from studies such as Mulhern (2017) and Velez (2017) to inform such utilities, assuming the same utilities for all 'response' categories if necessary.

a) State-specific QOLIE-31-P scores were not informed by broader literature due to a lack of available evidence. There is one reported mapping of QOLIE-31-P to EQ-5D-5L available from the literature.[52] However, this requires patients' age and scores according to the domains within the QOLIE-31-P instrument to calculate health state utility values.

Only three studies reported QOLIE-31-P score according to the level of response to treatment, Velez *et al.* (2017), Cramer *et al.* (2019) and Mukuria *et al.* (2017).[53–55] Mukuria *et al.* (2017) reported change in domain score according to response to treatment, and as domain scores at baseline score was not available, it was not possible to calculate total domain scores according to response to treatment.[55] Conversely, Velez *et al.* (2017) and

Cramer *et al.* (2019) reported QOLIE-31-P according to domains, however, age by response to treatment was not reported.[53,54] Therefore, across the three potential studies that could have yielded health-state utility scores from published QOLIE-31-P data, there was insufficient data to accurately calculate utilities. Assuming age was identical in the responder and non-responder health states generated illogical health state values whereby superior health states didn't generate superior utilities.

Additionally, the tool available to map QOLIE-31-P to EQ-5D is not reliable due to the shortcomings of EQ-5D for patients with epilepsy, which are acknowledged by the developers of the mapping.[52] As such, SF-6D was utilised due to its consideration of health over a longer time period which is relevant to patients with epilepsy.

b) The utility values identified from the HRQoL SLR are reported in Table 16 of Appendix H and are replicated here in Table 58. In the company submission, scenario analysis was performed using the utility values reported by Phumart *et al.* (2018). These utilities were reported according to the level of response to treatment and were identified as the best available published alternatives. Utility values reported in other studies gave results after treatment according to time since since baseline, as reported by Mulhern *et al.* (2017) and Mukuria *et al.* (2017).[55,56] In these studies, it was not clear whether baseline was the entry to the study or the initiation of treatment. Utilities according to time since baseline take no account of the level of response to treatment; the change in quality of life considers the quality of life of non-responders as well as those who derive a benefit from treatment, diluting the estimated incremental benefit from treatment. Therefore, the use of these alternative utility values would inaccurately capture the benefits from reduced seizure frequency. The remaining studies, Fiest *et al.* (2014) and Xu *et al.* (2006) did not report utilities that were suitable for use in the economic model as they described health states unrelated to the structure of the economic model, such as according to the presence of sleep disturbance.[57,58]

Table 58. Utility values identified from the HRQoL SLR

Study (year)	Country	Patient population (n)	Details of study arms, time point (n)	Average utility score (SD)
Mulhern (2017)[56]	UK	Newly developed focal epilepsy, Randomised to receive SOC i.e. carbamazepine or one of the other treatments (gabapentin, lamotrigine, oxcarbazepine, or topiramate) (n=1,611)	Those completing the EQ-5D-3L, Baseline (n=1563)	0.735 (0.30)
			Those completing the EQ-5D-3L, Year 1 (n=1244)	0.769 (0.29)
			Those completing the EQ-5D-3L, Year 2 (n=1091)	0.789 (0.28)
			Those completing the NEWQOL-6D, Baseline (n=1508)	0.766 (0.13)
			Those completing the NEWQOL-6D, Year 1 (n=1156)	0.798 (0.13)
			Those completing the NEWQOL-6D, Year 2 (n=1023)	0.805 (0.13)
Mukuria (2017)[55]	UK	Patients treated with adjunctive brivaracetam for uncontrolled focal seizures (n=1,095) **	Pooled analysis of N01252, N01253, and N0125 trials, Baseline (n=1095)	0.759 (0.232)
			Pooled analysis of N01252, N01253, and N01254 trials, Follow up (n=1095)	0.777 (0.230)
Fiest (2014)[57]	-	Patients with drug-resistant TLE (n=80)	Patients treated with epilepsy drugs (n=40)	0.52 (0.32)
			Patients treated with surgery (n=40)	0.62 (0.25)
Xu (2006)[58]	US	Patients with partial-onset epilepsy receiving stable polytherapy regimens (at least two ASMs) * (n=200)	All patients (n=200)	0.64 (0.35)
			Diagnosed sleep disturbance (n=67)	0.49 (0.38)
			No diagnosed sleep disturbance (n=132)	0.71 (0.31)
Phumart (2018)[59]	Thailand	Focal seizure patients (n=225) who were categorised into: Seizure-free Seizure reduction No improvement	Seizure-free (n=67)	0.82 (0.15)
			Seizure reduction (n=93)	0.79 (0.16)
			No improvement (n=64)	0.72 (0.21)

Abbreviations: ASMs, antiseizure medicines; EQ-5D-3L, EuroQol-5 Dimensions-3 Levels; NEWQOL-6D, Quality of Life in Newly Diagnosed Epilepst Instrument; SD, standard deviation; SOC, standard of care; TLE, temporal lobe epilepsy; UK, United Kingdom; US, United States

The scenario analysis which considers utilities according to those reported by Phumart *et al.* (2018) are replicated below in Table 59.

Table 59: Cost-effectiveness scenario results where utilities are defined from Phumart et al.(2018)

Treatment	**Total**		**Incremental**		**ICER (£)**
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	
Cenobamate	[redacted]	10.873	-	-	-

Lacosamide	214,146	10.284	[redacted]	-0.589	Dominated
Perampanel	214,472	10.283	[redacted]	-0.590	Dominated
Brivaracetam	216,696	10.245	[redacted]	-0.628	Dominated
Eslicarbazepine acetate	230,681	10.093	[redacted]	-0.780	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analyses are not presented for the additional studies since they do not characterise the benefits in quality of life that are associated with treatment.

B31. Please clarify how the baseline characteristics of the English-speaking subsample of the HRQoL survey compare to the UK's anticipated licensed population?

The HRQoL survey was conducted in patients from the UK, Germany, France, Spain and Italy. Therefore, participants from the UK are considered for the English-speaking subsample of the survey.

The baseline sociodemographic characteristics for participants from the UK are presented in Table 60. With [redacted] of the sample enrolled in the survey male, this is aligned with UK practice as reported by Kalilani *et al.* (2018).[60]

Table 60. Socio-demographic characteristics of UK respondents in the utility mapping survey

	Frequency	Percentage (%)
Age		
18-25	[redacted]	[redacted]
26-35	[redacted]	[redacted]
36-45	[redacted]	[redacted]
46-55	[redacted]	[redacted]
Gender	[redacted]	[redacted]
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Job status	[redacted]	[redacted]
Employed part-time	[redacted]	[redacted]
Employed full-time	[redacted]	[redacted]
Self-employed	[redacted]	[redacted]
Unemployed	[redacted]	[redacted]
Full-time student	[redacted]	[redacted]
Carer	[redacted]	[redacted]
Retired	[redacted]	[redacted]
University degree	[redacted]	[redacted]
Yes	[redacted]	[redacted]

No	[redacted]	[redacted]

Self-reported clinical data for participants from the UK are presented in Table 61 and Table 62. The sample included patients who had between 0 and 33 seizures in the last 28 days, on average, and seizure free periods of less than 29 days in the majority of patients. The sample also includes a mixture of patients who have and who have not experienced focal to bilateral tonic-clonic seizures in the last eight weeks. The sample includes a population with a broader spectrum of disease severity, which covers the extremities likely present in the anticipated licensed population. The breadth covered in the population enrolled is necessary to characterise how quality of life may be improved via treatment with cenobamate such that patients are able to control their seizure frequency. Indeed, the inclusion of patients with more than a year of seizure freedom enables the characterisation of the benefits associated with prolonged seizure freedom, such as regaining independence and the ability to drive.

Table 61. Self-reported clinical data of the UK respondents in the utility mapping survey

Variable	N	Mean	Median	SE (mean)	Std. Dev.	Min	Max
Years since diagnosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of seizures in the past 28 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Longest continuous seizure free period during the past 28 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Longest continuous seizure free period (if over 28 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of focal to bilateral tonic-clonic seizures in the past eight weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbrveiations: N, number of participants; SE (mean), standard error of the mean; Std Dev, standard deviation; Min, minimum; Max, maximum

Table 62. Self-reported clinical data of the UK respondents in the utility mapping survey

Experienced a focal to bilateral tonic-clonic seizure in the past eight weeks	**Freq.**	**Percentage (%)**
No	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Total	[redacted]	[redacted]
Number of focal to bilateral tonic-clonic seizures experienced in the last eight weeks		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
2-5	[redacted]	[redacted]
6-10	[redacted]	[redacted]
11-20	[redacted]	[redacted]
21-30	[redacted]	[redacted]
31-40	[redacted]	[redacted]
41-50	[redacted]	[redacted]
Unsure	[redacted]	[redacted]
Total	[redacted]	[redacted]
Type of seizure experienced	[redacted]	[redacted]
Focal aware seizure	[redacted]	[redacted]
Focal impaired awareness seizure	[redacted]	[redacted]
Focal to bilateral tonic-clonic seizure	[redacted]	[redacted]

B32. Please clarify if the SF-6D utility scores derived through mapping used the UK tariff.

The UK tariff was used to value the SF-6D utility scores to which disease characteristics were mapped.[61] In the mapping study for this submission, the UK SF-6D tariff was applied to the SF-36 data to generate patient utilities and then a mapping algorithm was used to predict the SF-6D utility values according to disease characteristics.

B33. Table 43 (Section B3.4.2, page 114) provides summary statistics of the observed SF-6D values and the predicted values for SF-6D using the mapping algorithm. Please provide a histogram of the observed and the predicted values.

The observed and fitted SF-6D values are presented in Figure 9 and Figure 10, respectively. The observed SF-6D values have a single peak at around [redacted], and they range from approximately [redacted] to [redacted]. The fitted SF-6D values two peaks, though one is much more pronounced than the other. The more prominent peak is approximately [redacted], with a minor peak at [redacted]. The fitted SF-6D values range from [redacted] to [redacted]. This

demonstrates that more extreme SF-6D values may not be predicted by the mapping, indicating that the utility values for patients with no response and complete response to treatment may be over- and under-estimated, respectively.

Figure 9: Observed SF-6D values in the utility mapping survey

Figure 10: Fitted SF-6D values in the utility mapping survey

Indeed, as summarised in Table 2 of Appendix H and replicated here in Table 63, the patients included in the survey covered a broad spectrum of severity. Seizure

frequency ranged from [redacted] per 28 days whilst the longest continuous seizure free period ranged from [redacted] (with an average of [redacted] days of consecutive seizure freedom in the[redacted] patients with more than 28 days of consecutive seizure freedom). As summarised in Table 10 of Appendix H (replicated here in Table 64), SF-6D is positively correlated with duration of seizure freedom, which supports that utility in those with the least and most severe disease is over- and under-estimated, respectively.

Table 63. Self-reported clinical data of the study sample in the utility mapping survey

Variable	N	Mean	Median	SE (mean)	Std. Dev.	Min	Max
Years since diagnosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of seizures in the past 28 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Longest continuous seizure free period during the past 28 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Longest continuous seizure free period (if over 28 days)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of focal to bilateral tonic-clonic seizure/s (secondary generalised) in the past eight weeks	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of participants; SE (mean), standard error of the mean; Std Dev, standard deviation; Min, minimum; Max, maximum

Table 64. Subgroup analysis: Longest amount of consecutive days seizure free in the past year

Longest amount of consecutive days seizure free in the past year	N	Mean	Std. Dev.	Min	Max	F-stat (Prob > F)	Bartlett's test: chi2(2) (Prob>chi2)
Gf+SF-6D							
1 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 to 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
31+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
QOLIE-31-P							
1 to 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 to 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
31+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Abbreviations: N, number of participants; Std Dev, standard deviation; Min, minimum; Max, maximum; F-stat, F-statistic

B34. Please adjust the mapped SF-6D estimates and all other mapped estimates obtained to account for the proportion of total variation explained by the mapping algorithms used (see Chan KK, Willan AR, Gupta M, Pullenayegum E. 'Underestimation of uncertainties in health utilities derived from mapping algorithms involving health-related quality-of-life measures: statistical explanations and potential remedies'. Med Decis Making. 2014;34(7):863–72).

The total variation in utilities has been updated to account for the total variation explained by the mapping algorithm, with the adjusted R^2 for the mapping being [redacted]. The variance of each utility estimate was adjusted using Equation 4.[62]

Equation 4: Formula to adjust

$$\sigma^2_{actual} = \frac{\sigma^2_{fitted}}{(1-\sqrt{R^2})^2}$$

The probabilistic and one-way sensitivity analysis results under this adjusted variation are reported in Appendix C.

B35. Please clarify if the economic model considers age-related reductions in HRQoL over time. If it does not, please justify the decision not to include it.

From the results of the utility mapping study, age had a positive coefficient in the best fitting model to describe HRQoL (summarised in Section B.3.4.2 of Document

B). Therefore, the mapping study indicated that, in patients with epilepsy, HRQoL increases with age. There are numerous hypotheses for why HRQoL increases with age in patients with epilepsy, including the increased likelihood of reaching seizure freedom and a better ability to manage their condition in increasing age.

For this reason, the economic model does not consider age-related reductions in HRQoL over time. The model considers HRQoL according to patients' age on the completion of the C017 study, which is conservative as gains in HRQoL with age are not considered. Given that the magnitude of the coefficients related to their disease status (number of seizures in the last 28 days, period seizure free and occurrence of tonic-clonic seizures in the last eight weeks) outweigh the coefficient for age by at least a factor of two, it is clear that age is less influential to quality of life in patients with epilepsy than the characteristics of their disease.

Section C: Textual clarification and additional points

Factual clarifications

C1. On page 32 of the company submission, for C017 OLE, the seizure frequency reduction of ≥50% is reported as **8.1%**, which is considerably lower than the seizure frequencies reductions reported for ≥75%, ≥90% and 100%. Please confirm that this value is correct.

This is a typographic error; the figure should be 81.1% for the seizure frequency reduction of ≥50% between years 4-5, as reported in Figure 21 (Page 59) of the company submission.

References

C2. PRIORITY. Please provide the results of the survey of clinicians as listed in Document B, Reference # 1 and minutes of all meetings with clinical advisers/ "key opinion leaders".

The results of the clinician survey, which is reference # 1, and the minutes of meetings with clinical advisers and key opinion leaders are included in the zipped folder named 'Clinical expert opinion' as submitted with the response to these clarification questions.

C3. Please check that all references have been submitted and are correctly referenced in the submission. Several appear to be missing, notably:

a) **PRIORITY. Reference #133: The clinical study report (CSR) for study C021**

b) **PRIORITY. The CSR for study C013**

c) Reference # 83 and #213: Health IQ: Arvelle Epilepsy HES Report

d) Reference # 4: Sperling et al. (2020), the file provided is different from the one referenced

e) Reference # 52: Hesdorffer et al. (2020), the file provided is different from the one referenced

f) Reference # 77: Quality of life study for caregivers of people with focal onset epilepsy- Preliminary UK Data Analysis

g) Reference # 103: Ben-Menachem et al. (2010)

h) Reference # 104: Sperling et al. (2015)

i) Reference # 141: Bolin et al. (2010)

j) Reference # 187: Marson et al. (2007), the file provided is different from the one referenced.

Thank you for highlighting these missing references. Upon review we found that the CSR for C021, and references # 4, # 77, # 103, # 104 and # 141 were provided. We have provided all references requested in a zipped folder named ‘Company submission - references’ to ensure access.

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ID 1553 – Cenobamate for focal onset seizures in epilepsy

Arvelle Therapeutics Response to ERG clarification question received on 2nd March 2021

1. The scenario considering aggregated health states was performed manually and presented; a switch for this was not incorporated into the model. This was because the base case model structure was built to align with the primary and secondary outcomes in the C017 study, the appropriateness of which was verified by clinicians during protocol validation. Clinicians agreed that there are important differences in costs and quality of life between the disaggregated health states.
   Additonally, as the health state utility values were obtained directly from patients enrolled in the C017 study, combining the health states would also have conflicting impacts to cenobamate and comparators. With the improved efficacy of cenobamate, there is a larger proportion of patients who have ≥75% and ≥90% reduction in seizure frequency compared to the comparators. This would cause bias in the health state utility values of comparators as the gains in quality of life for achieving ≥50% and <100% reduction in seizure frequency compared to baseline would be overestimated. For these reasons, we did not include an option to switch between the base case structure and this aggregated scenario. However, for transparency, the model has been provided with a switch to assess this scenario.
   To reiterate, the difference between achieving ≥50%, ≥75% and ≥90% reduction in seizures is clinically meaningful and all available clinical expert feedback indicates that a combination of these health states into one responder rate oversimplifies the real benefits gained in each of more specific health states.

2. We can confirm that no PAS is intended. If a pricing reduction is required then the company plan to modulate the NHS list price. This information has been provided to the PASLU team at NICE.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Cenobamate for focal onset seizures in epilepsy [ID1553]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Epilepsy Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Epilepsy Action is a patient-led charity representing the estimated 600,000 people living with epilepsy in the UK. We provide advice and information for people with epilepsy and their families, and also campaign for improvements to epilepsy services. We are mainly funded by donations from members and events, but also receive funding from researchers and other organisations.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	In December 2020 Epilepsy Action's Director of Epilepsy Services attended a patient advisory group exploring lived experience of epilepsy and epilepsy care. She arranged for people with focal epilepsy to attend and share experiences. This was conducted on behalf of Arvelle therapeutics. A £690 fee was paid to Epilepsy Action. We have been asked to help with a focus group date not set yet.

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Speaking directly with clinicians and patients with focal onset seizures, and existing knowledge from input at previous stages of appraisal, including consultation and scoping workshop.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Symptoms that may occur during a focal seizure include: • muscle contractions • odd sensations • abnormal head or eye movements • automatisms, or repetitive movements, such as skin-picking or lip-smacking • vision changes There are many different types of focal seizure, but they can be split into two main types according to the level of awareness during the seizure:

	• During a focal aware seizure, people stay fully aware of what's happening around them, even if they can't move or respond. Most focal aware seizures are brief, lasting between a few seconds and 2 minutes. • If their awareness of what's happening around you is affected at any time during your seizure, it's called a focal impaired awareness seizure. Focal impaired awareness seizures usually last between one and 2 minutes. What happens after a focal seizure varies from person to person. Some might feel fine after a focal seizure and be able to get back to what they were doing straight away. Others might feel confused or tired for some time afterwards and might need to sleep. Some people also find they have temporary weakness or can't move part of their body after they've had a seizure. Focal seizures can be debilitating, especially those people who do experience these further effects following a seizure. In addition, while some people may get a warning before a seizure, many do not. Even with a warning, the fear of experiencing a seizure, especially in public, can cause many people with the condition to be fearful of carrying out even simple daily tasks. People who are not aware of what they're doing might need help to guide them away from danger and keep them safe. For carers of people who experience multiple seizures in a day, this can be very demanding. In some cases carers will have to provide first aid, ensure that seizures do not lead to further injury, and administer emergency medication. Some people find that there are impacts on their daily life for example their ability to concentrate and the type of work they undertake or their confidence in travelling and under taking leisure activities. Receiving the initial diagnosis of epilepsy can be particularly overwhelming and distressing for people, given the impact it has on what you can and cannot do. Some people added that the diagnosis can affect how other people see and treat you, leading to a loss of social connections, as well as the way they view themselves. Some people have also mentioned that the condition can make them feel like a burden, due to not being able to drive and other limitations which mean they rely on family and/or carers for support.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatments for focal epilepsy include: • Pharmacological treatment • Psychological interventions • Ketogenic diet for children and young people • Vagus nerve stimulation (VNS) While there is increasingly a large choice of epilepsy medications, many cause side-effects, some of which can be severe and as debilitating as the seizures themselves. Only 52% of people with epilepsy are seizure free, either because their seizures are controlled by medication or due to surgery or other interventions. It is estimated that with the right treatment, the majority of people with epilepsy (70%) could be seizure free. Any new treatments that could address this gap would be welcome. Waiting times remain high in many areas, and have been exacerbated due to the ongoing pandemic. It is often difficult to access psychological interventions in many areas, a situation which again has been made worse by the current pandemic. For many people with epilepsy surgery is not a viable option. For those with a clearly identifiable area of the brain where seizures emanate surgery may be possible if damage to other parts of the brain can be avoided for some the risk of loss of function means surgery would be too high risk. Access to dietary therapies is limited as it requires close supervision by specifically trained HCPs

8. Is there an unmet need for patients with this condition?	Few Trusts and Health Boards are able to provide co-located mental health services people with epilepsy. Routine screening for mental health is not widely available. Many women with epilepsy are unable to access preconception counselling to discuss concerns about safety during pregnancy.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As Cenobamate has potential as an adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two epilepsy medicines, patients, especially those with uncontrolled epilepsy would welcome an alternate treatment option. It is felt that the drug could be a very useful addition where none of the currently licensed drugs have been efficacious
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Concerns about possible side effects. Many people with epilepsy already experience side effects from existing medication, and are worried about worsening side effects on new medication, and the potential for breakthrough seizures when switching medicines. Concerns about safety of use in pregnancy. People are increasingly aware of this issue due to sodium valproate. A recent CHM review highlighted that a number of epilepsy medications pose a risk of harm to the unborn baby if used in pregnancy. For many epilepsy medications there was not enough information about their safe use in pregnancy.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Older people are late onset seizures more likely to be focal? People with learning disabilities? Focal seizures can be difficult to diagnose in both these groups
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	We believe that people with both epilepsy and a learning disability should be given consideration as there is currently research proposed about ways of moving them from Carbamazepine to newer drugs. In addition, the STOMP campaign is about reducing additional drugs in that population
14. The company anticipates that cenobamate will be available as a second-line adjunctive antiseizure medicine in clinical practice. In this case, what will be the relevant comparators?	The most relevant comparators are brivaracetam, eslicarbazeline, lacosamide and perampanel.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- We welcome an additional treatment for people with focal onset epilepsy, specifically for people whose seizures have not been controlled by other medication
- It is important that concerns about safe use in pregnancy are addressed
- Possible side effects should be investigated and communicated to patients
- Consideration of people with learning disabilities and epilepsy

-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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CONFIDENTIAL UNTIL PUBLISHED
Evidence Review Group's Report
Cenobamate for adjunctive treatment of focal epilepsy

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Dina Jankovic critiqued and performed the economic analyses and wrote Sections 4, 5 and 6 of the report.

Alexis Llewellyn critiqued the clinical effectiveness review, wrote Section 2 and co-wrote Section 3 of the report.

Sumayya Anwer critiqued the clinical effectiveness review, co-wrote Section 3 and conducted additional analyses informing Section 3 of the report.

Melissa Harden critiqued the company search strategies and provided information support.

Rita Faria provided expert advice on the economic analyses and the report as a whole.

Claire Rothery provided expert advice and support for all aspects of the economic analyses and the report as a whole.

Alison Eastwood provided advice, commented on drafts of the report, led the overall clinical effectiveness sections and takes joint responsibility for the report as a whole.

Pedro Saramago Goncalves, critiqued and performed the economic analyses, provided advice, wrote and commented on drafts of the report, led the overall economic sections and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are [redacted].

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List of abbreviations

ADR	Adverse drug reactions
AE	Adverse event
AIC	Akaike Information Criterion
ASM	Anti-seizure medication
AWTTC	All Wales Therapeutic and Toxicology Centre
BIC	Bayesian Information Criterion
BGR	Brooks-Gelman-Rubin (convergence diagnostic)
BMI	Body Mass Index
BNF	British National Formulary
CC	Continuity-correction
CCG	Clinical Commissioning Groups
CI	Confidence interval
CNS	Central nervous system
Crl	Credible interval
CS	Company Submission
CSR	Clinical study report
CUA	Cost utility analysis
DES	Discrete Event Simulation
DIC	Deviance Information Criterion
DRE	Drug-resistant epilepsy
DRESS	Drug-induced hypersensitivity syndrome/ Drug reaction with eosinophilia and systemic symptoms
DSU	Decision Support Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
EQ-5D	EuroQol- 5 Dimension
EQ-5D-5L	EuroQol- 5 Dimension Five Level
ERG	Evidence Review Group
ESL	Eslicarbazepine acetate
FOS	Focal-onset seizures
HES	Hospital Episode Statistics
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
LOCF	Last observation carried forward
LYG	Life years gained
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
Mg	Milligram

MIC	Minimally important change
mITT	Modified intention of treat
mITT-M	Modified intention-to-treat patients in maintenance phase
N/A	Not applicable
NA	Not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG137	NICE Clinical Guideline 137
NMA	Network meta-analysis
NR	Not reported
OLE	Open-label extension
OLS	Ordinary-least squared
ONS	Office of National Statistics
OP	Outpatient
OR	Odds ratio
PFC	Points for clarification
PICOS	Population, Intervention, Comparison, Outcomes and Study
POS	Partial-onset seizures
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of Life
QOLIE-31-P	Quality of life in epilepsy- Problems
RCT	Randomised control trial
RE	Random-effects
RMSE	Root-mean-square error
RR	Risk Ratio/Relative Risk
SAEs	Serious adverse events
SD	Standard deviation
SE	Safety evaluable
SE	Standard error
SF-36	Short-Form (36) Health Survey
SF-6D	Short Form-Six Dimension
SLR	Systematic literature review
SOC	System organ class
SUDEP	Sudden Unexpected Death in Epilepsy
TEAEs	Treatment emergent adverse events
TSD	Technical Support Document
URTI	Upper respiratory tract infection
VNS	Vagus nerve stimulation
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of ERG's key issues

Table 1 Summary of key issues

ID1553	**Summary of issue**	**Report sections**
1	**Positioning of cenobamate in the treatment pathway** The anticipated marketing authorization places [redacted] The company's positioning of cenobamate is more restrictive, as it is only placed against a subset of 3rd generation 3rd line adjunctive therapy.	2.2, 2.3
2	**Generalisability of cenobamate and comparator trials to clinical practice** The design and populations of all cenobamate and comparator trials included in the company's model poorly reflect clinical practice. The applicability of the trial evidence to NHS practice is highly uncertain.	3.2.1, 3.2.2, 3.3.1, 3.3.2
3	**Long-term efficacy and safety of cenobamate and its comparators** The blinded evaluation periods of the RCT evidence supporting the company submission are too short to reliably inform clinical practice. Due to limited evidence, the long-term efficacy and safety of cenobamate against other relevant ASMs is highly uncertain.	3.2.3, 3.2.4, 3.3.3

4	**Relative safety and efficacy of cenobamate against relevant comparators** Due to the absence of head-to-head cenobamate RCTs, the company conducted an indirect treatment comparison (ITC) to estimate the efficacy and safety of cenobamate against other comparator treatments. The ITC is significantly limited by differences in trial populations and designs, and the limited evidence and exclusion of several relevant comparators means that the relative efficacy and safety of cenobamate compared with other adjunctive ASMs is highly uncertain.	3.4, 3.5
5	**Inappropriate model structure given the current evidence** The company considered five mutually exclusive health states that model the level of response to the intervention and comparators: no response (0 to <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 seizure freedom (100% reduction). This is more granular than previous models for FOS epilepsy, where three levels of response were used: no response (0 to <50% reduction in seizure frequency), partial response (50 to <100% reduction), and seizure freedom (100% reduction). The company justified the use of five different levels of response on the basis that higher response leads to better outcomes and lower healthcare costs, and that cenobamate is more likely to lead to higher levels of response (75 to <100%) than its comparators. The company did not provide evidence that cenobamate increases the probability of ≥75% and ≥90% reduction in seizure frequency compared to the comparators. Furthermore, the company did not provide evidence of important differences in costs and health-related quality of life between different levels of treatment response.	4.2.2

6	**Cost-effectiveness driven by cenobamate effectiveness** In the cost-effectiveness model, greater response to treatment is associated with higher QALYs and lower healthcare resource use. Cenobamate is estimated to be substantially more clinically effective than its comparators and, as result, it leads to better outcomes and lower costs, even though the treatment cost is higher. These results are fairly insensitive to changes in model parameters. However, the clinical trial used to measure clinical effectiveness of cenobamate (trial C017) shows poor generalisability to clinical practice (see issue 3.2). No direct evidence exists between cenobamate and the relevant comparators (see issue 3.3). Therefore, the results of the cost-effectiveness model are considered to be uncertain.	4.2.6.1, 4.2.6.2
7	**Subsequent treatment** In the model, discontinuing treatment with cenobamate or its comparators leads to treatment with subsequent anti-seizure medication (ASMs) – a homogenous health state where treatment effect is assumed to be independent of the previous line of treatment, and constant over time. In practice patients discontinuing third line adjunctive treatment could take one of many ASMs available in the UK. The cost-effectiveness model is a simplification of the treatment of FOS epilepsy in practice, as it does not reflect that subsequent ASMs could include numerous additional lines of treatment, and the potential effect of treatment sequencing.	4.2.6.3
8	**Uncertain rate of treatment discontinuation** Rate of treatment discontinuation affects costs and outcomes in the cost-effectiveness model, as subsequent lines of treatment are assumed to be less effective than cenobamate and its comparators. Data used to inform the rate of discontinuation for comparators implies that the risk of discontinuation in patients taking cenobamate is lower than that of comparators; however, these estimates are informed by non-comparative data and highly uncertain. Moreover, the same probability of treatment discontinuation is applied to all response states, assuming the risk is the same for all patients, irrespective of patients' level of response.	4.2.6.4

9	**Uncertain utility data** Study C017 disease specific QOLIE-31-P scores are not considered by the company on the basis that no meaningful benefits in terms of HRQoL was found in cenobamate trial arms. A highly uncertain mapping study is used to obtain utility estimates through a survey and the preference-based tool SF-6D.	4.2.10
10	**Uncertain resource use data** Resource use largely informed by clinical opinion and vastly different from previous evaluations such as those used in NICE CG137.	4.2.11

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are (i) the response levels modelled in the cost-effectiveness analysis; (ii) long term effectiveness estimate for cenobamate; (iii) the evidence used to inform baseline seizure frequency in the model; (iv) inclusion of study C013 in the estimate of the relative effects of comparators to cenobamate; (v) structure of the evidence synthesis model used to appropriately synthesise relevant outcomes; (vi) estimate of effectiveness for subsequent anti-seizure medication (ASM); (vii) estimate of the rate of treatment discontinuation for comparators; (viii) method used to model treatment discontinuation in the cost-effectiveness model; and (ix) exclusion of carer disutilities.

The ERG's preferred assumptions are more consistent with previous NICE guidelines for the diagnosis and management of epilepsies.(1) Where the company has not presented compelling evidence to support their assumptions, the ERG's preferred base case uses appropriate methodology to support the level of evidence available and is supported by the ERG's expert clinical advisors.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the probability of response to treatment (pre-defined reduction in seizure frequency)
- Decreasing the rate of treatment discontinuation that ultimately leads to receiving less effective treatment
- Effectiveness of subsequent ASM treatments

Overall, the technology is modelled to affect costs by:

- Reducing healthcare resource use by increasing response to treatment and decreasing the risk of treatment discontinuation
- Reducing the cost of managing epileptic events, by reducing the number of seizures
- [redacted]

The modelling assumptions that have the greatest effect on the ICER are:

- Average number of baseline seizures, by seizure type
- Treatment response, with a much higher response for cenobamate compared to comparator therapies

- Treatment-specific discontinuation rates, with a much lower discontinuation rate for cenobamate compared to comparator therapies

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Positioning of cenobamate in the treatment pathway

Report sections	2.2, 2.3
Description of issue and why the ERG has identified it as important	The company's placement of cenobamate is clinically appropriate, although it is more restrictive than the anticipated marketing authorization. The anticipated licence recommends that cenobamate is used as an [redacted] Given the comparator evidence presented in the submission, the company effectively places cenobamate as an adjunctive therapy in adult patients with focal onset seizures with or without secondary generalisation who are not adequately controlled with at least two previously prescribed ASMs and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies. The comparators included in the company submission only include four 3rd generation adjunctive therapies (brivaracetam acetate, eslicarbazepine acetate, lacosamide, and perampanel); this excludes clinically relevant treatment options recommended by NICE (CG137). Clinical advice to the ERG considers that eslicarbazepine acetate is not a relevant comparator, and that clobazam, topiramate and zonisamide adjunctive therapies should have been included in the decision problem.
What alternative approach has	The ERG suggests a scenario where all therapies being evaluated are equally efficacious, of equal discontinuation rates and equivalent adverse reaction profiles, i.e. a cost comparison analysis. From this analysis the cost-

the ERG suggested?	effectiveness of cenobamate could be inferred if cheaper than cenobamate adjunct therapies were to be included in the assessment.
What is the expected effect on the cost-effectiveness estimates?	Due to cenobamate [redacted], the ERG expects cenobamate to be dominated by remaining adjunctive therapies. This is true if adjunct therapies cheaper than cenobamate were to be included in the assessment.
What additional evidence or analyses might help to resolve this key issue?	An updated indirect treatment comparison and economic model that includes all relevant evidence for clobazam, topiramate and zonisamide would be better suited to inform the decision problem.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Generalisability of cenobamate and comparator trials to clinical practice

Report sections	3.2.1, 3.2.2, 3.3.1, 3.3.2
Description of issue and why the ERG has identified it as important	The design of all cenobamate and comparator trials included in the company's model poorly reflect clinical practice. In particular, dose titration periods were significantly shorter and more intense than would be seen in clinical practice, and four trials of brivaracetam did not report a titration period. Percentage reduction in seizure frequency, although reported in all trials, is not commonly used in clinical practice. ERG clinical advisers noted that the trial population was highly selected and did not reflect the population of patients with treatment-resistant focal onset seizures. In particular, the average baseline seizure rates of patients included in the ITC trials may be higher than would be seen in clinical practice. Exclusions of patients with progressive CNS disease further limits the generalisability of the trial populations to clinical practice. Overall, the applicability of the trial evidence to clinical practice is highly uncertain. Baseline seizure frequency is a key driver of the model.
What alternative approach has the ERG suggested?	See Issue 6 (Section 1.5)
What is the expected effect on the cost-effectiveness estimates?	See Issue 6 (Section 1.5)
What additional evidence or analyses might help to resolve this key issue?	Results from observational studies included in a recent published systematic review identified by the ERG indicated that the baseline severity of trial participants may have been overestimated, although evidence was limited to single centre studies. Pooling data from large specialist UK centres may provide more accurate baseline severity estimates for patients who would be eligible to receive cenobamate under its anticipated licence.

Issue 3 Long-term efficacy and safety of cenobamate and its comparators

Report sections	3.2.3, 3.2.4, 3.3.3
Description of issue and why the ERG has identified it as important	The blinded evaluation periods of all trials included the company submission ranged from seven to 19 weeks and are short to reliably inform clinical practice. ERG clinical advisers noted that in clinical practice, a treatment duration of one year was required to reliably assess treatment success. Although the company provided ongoing longer-term observational evidence for the safety of cenobamate and trial extension data for their main trial, due to limited evidence, the long-term efficacy and safety of cenobamate against other relevant ASMs is highly uncertain. The short and long-term effectiveness of cenobamate is a key driver of the model.
What alternative approach has the ERG suggested?	See Issue 6 (Section 1.5)
What is the expected effect on the cost-effectiveness estimates?	See Issue 6 (Section 1.5)
What additional evidence or analyses might help to resolve this key issue?	A systematic review and meta-analysis of the long-term safety and efficacy of cenobamate and all relevant comparators in patients who would be eligible for treatment in the proposed pathway may help to inform this issue. However, evidence may be sparse and comparisons between treatments at risk of confounding.

Issue 4 Relative safety and efficacy of cenobamate against relevant comparator treatments

Report sections	3.4, 3.5
Description of issue and why the ERG has identified it as important	Due to the absence of head-to-head randomised controlled trials (RCTs) comparing cenobamate against relevant comparators, the company conducted indirect treatment comparisons (ITCs) to estimate the efficacy and safety of cenobamate against other anti-seizure medications (ASMs). All trials included in the ITC were placebo-controlled, therefore the placebo comparator was used to connect cenobamate to the comparator ASMs in a star-shaped network. Due to the limited evidence, network consistency could not be checked, and only four outcomes were considered (≥ 50% responder rate, seizure freedom, the proportion of patients who experienced at least one treatment-emergent adverse event [TEAE], and discontinuation due to TEAEs). The ITC is significantly limited by differences in trial populations and designs. The limited evidence and exclusion of several relevant comparators means that the relative efficacy and safety of cenobamate compared with other adjunctive ASMs is highly uncertain. The ITC efficacy results are a key driver of the model.
What alternative approach has the ERG suggested?	To address some of the company's ITC limitations, the ERG re-ran analyses following a number of corrections and adjustments, notably to account for placebo response heterogeneity. However, some unexplained heterogeneity remains, and due to the limited evidence presented, no other adjustments could be made.
What is the expected effect on the cost-effectiveness estimates?	See Issue 6 (Section 1.5)
What additional evidence or analyses might help to resolve this key issue?	See Issue 6 (Section 1.5)

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 5 Inappropriate model structure given the current evidence

Report section	4.2.2
Description of issue and why the ERG has identified it as important	The model structure based on five levels of treatment response (no response, moderate response, high response, very high response and seizure freedom) may not be appropriate because there is insufficient data to inform the relative effectiveness of the intervention and comparators on each level of response.
What alternative approach has the ERG suggested?	The ERG suggests an aggregated response structure with health states of no response (<50% reduction in seizure frequency), response (≥50% to 99% reduction in seizure frequency) and seizure freedom (100% reduction in seizure frequency), largely because there is insufficient evidence that cenobamate increases the probability of ≥75% and ≥90% reduction in seizure frequency compared to the comparators.
What is the expected effect on the cost-effectiveness estimates?	Without sizeable impact on total costs and total QALYs across all treatments.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence for the intervention and comparators at a disaggregated level is required to inform a model structure with five levels of response. The company submission provides data for cenobamate for five levels of treatment response but only three levels for the comparators. It is unclear whether disaggregated data for five levels of response is available for all relevant comparators. Furthermore, additional evidence is required to support differences in costs and health-related quality of life between the various levels of treatment response.

Issue 6 Cenobamate and comparator effectiveness

Report sections	4.2.6.1, 4.2.6.2
Description of issue and why the ERG has identified it as important	Transition probabilities are directly derived from observed data in trial C017 which may overestimate response to treatment with cenobamate by failing to include all relevant evidence and account for any placebo effect. Transition probabilities may not reflect the slower cenobamate dose titration that will be used in UK clinical practice. The ERG considers that the approach to the extrapolation of cenobamate effect over time is highly uncertain as it assumes that patients will continue to improve (respond to treatment) over time. The ERG considers also that the approach taken by the company to estimate the effectiveness of comparators relative to cenobamate is uncertain as it excludes relevant evidence, performs independent modelling on a subset of response outcomes and does not control for existing between trial placebo heterogeneity.
What alternative approach has the ERG suggested?	The ERG suggests considering relevant evidence from study C013. Moreover, the ERG suggests to appropriately synthesise effectiveness evidence on comparators by reflecting the continuous nature (and correlation) of the response outcomes, together with accounting for placebo heterogeneity.
What is the expected effect on the cost-effectiveness estimates?	Without sizeable impact on total costs and total QALYs across all treatments.
What additional evidence or analyses might help to resolve this key issue?	Effectiveness evidence reflective of UK clinical practice is required.

Issue 7 Subsequent ASMs

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	In the company model, patients who discontinue treatment with cenobamate or its comparators move to subsequent ASM treatments - a homogenous health state where treatment effect is assumed to be independent of previous lines of treatment, and remains constant over time. The modelling of treatment sequences in a single health state does not reflect the range of treatment sequences seen in UK clinical practice.
What alternative approach has the ERG suggested?	The ERG suggests modelling of subsequent ASM lines of therapy instead of a single subsequent ASM treatment health state. However, the ERG recognises that there is unlikely to be a standardised approach to treatment sequencing in UK clinical practice and, therefore, identifying the choice of treatment sequences to model is challenging to address. Without modelling the full range of subsequent lines of therapy, the ERG highlights that the appropriateness of the model structure remains uncertain.
What is the expected effect on the cost-effectiveness estimates?	The ERG has not considered alternative treatment sequences due to the absence of a standardised approach and lack of evidence to inform the effectiveness of switching between active therapies. Effectiveness of subsequent ASMs could only impact the cost-effectiveness results in the unlikely scenario that subsequent lines of treatment are more effective than cenobamate and its comparators.
What additional evidence or analyses might help to resolve this key issue?	Evidence of effect of ASM switching

Issue 8 Treatment discontinuation rates of comparator treatments

Report section	4.2.6.4
Description of issue and why the ERG has identified it as important	The method employed to estimate the probability of treatment discontinuation for the comparators relative to cenobamate is highly uncertain as it relies on naïve hazard ratios obtained through inadequate methodology. All hazard ratios assumed implied that the risk of discontinuation in patients taking cenobamate was lower than that of comparators. Evidence from the NMA implied the opposite effect.
What alternative approach has the ERG suggested?	The ERG suggests the use of results from an NMA for 'all-cause' discontinuation as it considers this to be the best comparative evidence available for discontinuation, but highlights uncertainty in these estimates due to the limitations of the evidence used to populate the NMA.
What is the expected effect on the cost-effectiveness estimates?	Without sizeable impact on total costs and total QALYs across all treatments.
What additional evidence or analyses might help to resolve this key issue?	Longer-term trial data on discontinuation rates for cenobamate and comparator treatments is required to inform treatment-specific discontinuation rates. In the absence of this evidence, appropriate alternative assumptions relevant to expected discontinuation rates in UK clinical practice for cenobamate and comparators should be considered, in addition to the ones proposed by the company.

Issue 9 Utility data informing the economic model

Report section	4.2.10
Description of issue and why the ERG has identified it as important	A mapping study was developed by the company to convert seizure related epilepsy patients' characteristics into SF-6D index utility scores. Mapped utilities were directly obtained from patients in the cenobamate pivotal study C017. The mapping algorithm does not appropriately reflect the variability in observed SF-6D utility index scores, underestimating the range of predicted utilities. State-specific utilities in the cost-effectiveness model are highly uncertain. The company included a HRQoL disutility for caregivers. Carer utility values were obtained via a small, poorly reported caregiver survey aimed at carers of patients with ≥3 FOS per week according to the duration of seizure-freedom, where EQ-5D-5L was used to assess their HRQoL. The ERG has concerns regarding the caregivers' survey, the estimation of disutilities from the survey results and the magnitude of the values estimated.
What alternative approach has the ERG suggested?	The ERG suggests the use of utility data from previously published literature, such as the one from the NICE CG137, to assess the impact of the utility values used in the company's base case. The ERG suggests excluding caregiver utility from its base case.
What is the expected effect on the cost-effectiveness estimates?	The use of state-specific utilities from other sources is expected to have a small impact on outcomes, assuming the relative difference across health states is maintained (i.e. that higher level of response leads to better HRQoL). The exclusion of caregiver disutilities is expected to substantially increase total QALYs for all comparators, and decrease the estimated QALY gain of cenobamate relative to the comparators.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on state-specific and caregiver utilities, as well as evidence on the number of carers per patient is required.

Issue 10 Health resource use data informing the economic model

Report section	Section 4.2.11
Description of issue and why the ERG has identified it as important	In the company model, the vast majority of resource use was based on clinical opinion, due to a lack of empirical data. The resulting resource use is substantially different from estimates reported in the NICE CG137. The ERG highlights that there is substantial uncertainty in the resulting cost estimates. Furthermore, in the model, patients who discontinue 3rd line treatment for FOS are assumed to move onto one of the 3rd generation adjunctive treatments. The drug acquisition and administration cost of subsequent ASMs was the average cost of treatment with cenobamate and its comparators, weighted by their expected market share once cenobamate becomes available. The ERG considers the inclusion of cenobamate in the cost of subsequent ASMs to be inappropriate because cenobamate has not yet been approved. In addition, the market share estimates in which this analysis is based upon are uncertain and unknown for cenobamate.
What alternative approach has the ERG suggested?	The ERG suggests the use of cost data from previously published literature, such as the one from the NICE CG137, to assess the impact of the cost values used in the company's base case. The ERG also suggests excluding the cost of cenobamate from subsequent ASMs.
What is the expected effect on the cost-effectiveness estimates?	The use of state-specific costs from other sources is expected to have a small impact on outcomes, assuming the relative difference across health states is maintained (i.e. that higher level of response leads to lower healthcare resource use). Exclusion of cenobamate from the cost of ASMs is expected to decrease the incremental cost of cenobamate relative to its comparators, but the change is unlikely to be substantial.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on healthcare resource use at different levels of response to ASMs is required.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The results presented in Table 2 refer to the fully incremental cost-effectiveness analyses. When cenobamate is dominant to all other comparators, only the results of the next best treatment are shown.

Table 2 Summary of the ERG's preferred assumptions and ICERs

Preferred assumption	Comparator	Incremental cost	Incremental QALYs	ICER £/QALY
CS base case	[redacted]	[redacted]	[redacted]	[redacted]
1. Corrected typographical error in transition probabilities	[redacted]	[redacted]	[redacted]	[redacted]
2. Analysis 1 + cost-effectiveness model structure based on three levels of response	[redacted]	[redacted]	[redacted]	[redacted]
3. Analysis 2 + increased model cycle length to 84 days (starting in cycle 6) with transition probabilities informed by study C017 OLE	[redacted]	[redacted]	[redacted]	[redacted]
4. Analysis 3 + extrapolation of treatment effect adjusted – patients remain in the same state unless they discontinue treatment	[redacted]	[redacted]	[redacted]	[redacted]
5. Analysis 4 + baseline number of seizures informed by trial C013	[redacted]	[redacted]	[redacted]	[redacted]
6. Analysis 5 + inclusion of trial C013 in the NMAs	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Incremental cost	Incremental QALYs	ICER £/QALY
7. Analysis 6 + NMA model updated to account for correlation between outcomes	[redacted]	[redacted]	[redacted]	[redacted]
8. Analysis 7 + placebo adjustment added to the NMA	[redacted]	[redacted]	[redacted]	[redacted]
9. Analysis 8 + response to subsequent ASMs derived by applying the odds ratio of treatment resistance to the odds of no seizure freedom	[redacted]	[redacted]	[redacted]	[redacted]
10. Analysis 9 + effectiveness of ASMs calculated relative to the least effective comparator	[redacted]	[redacted]	[redacted]	[redacted]
11. Analysis 10 + time to treatment discontinuation for comparators informed by the NMA	[redacted]	[redacted]	[redacted]	[redacted]
12. Analysis 11 + time to treatment discontinuation for comparators in model cycles 6 onwards identical to C017	[redacted]	[redacted]	[redacted]	[redacted]
13. Analysis 12 + patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state	[redacted]	[redacted]	[redacted]	[redacted]
14. Analysis 13 + no carer disutility	[redacted]	[redacted]	[redacted]	[redacted]

Preferred assumption	Comparator	Incremental cost	Incremental QALYs	ICER £/QALY
15. Analysis 14 + cost of ASMs recalculated to exclude cenobamate ERG's preferred assumptions (base case)	[redacted]	[redacted]	[redacted]	[redacted]
ERG's base case + assuming equal efficacy, equal discontinuation rates and ADRs between cenobamate and comparators	[redacted]	[redacted]	[redacted]	[redacted]

Modelling errors identified by the ERG and corrected by the company and ERG are described in Section **Error! Reference source not found.** For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.1. All presented results are based on a deterministic analysis.

EVIDENCE REVIEW GROUP REPORT

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The company's description of the underlying health problem is broadly appropriate and relevant to the decision problem.

Epilepsy is a common condition affecting between 362,000 and 415,000 people in England.(2) It is characterised by recurrent spontaneous seizures caused by sudden bursts of electrical activity in the brain. The incidence of epilepsy has a bimodal age distribution, with infants and older age groups at highest risk. About of quarter of epilepsy diagnoses in the UK were in individuals aged over 65.(3) Approximately 50% of adults with active epilepsy have one or more comorbid condition.(4) Stroke accounts for more than half of all new-onset cases in older adults; other common causes include infection, brain injury, brain tumours and neurodegenerative disorders.

The International League Against Epilepsy (ILAE) classes seizures as either focal, generalised, or of unknown onset.(5) Focal onset seizures (FOS), previously known as partial onset seizures, are the most common type of seizure in patients with epilepsy. Patients experiencing FOS account for over 60% of all individuals with a diagnosis of epilepsy.(6) FOS occur when the onset of the seizure is located in one hemisphere of the brain, and may be subdivided into focal aware seizures (where patients retain awareness of their seizure), focal impaired awareness seizures (where patients experience impaired-awareness of their seizure), and focal to bilateral tonic-clonic seizures (where seizures start in one part of the brain and spread to both hemispheres). Focal to bilateral tonic-clonic seizures represent the most severe type of focal seizure and are associated with the highest morbidity and mortality risk. The frequency of seizures can vary greatly between patients; some patients with epilepsy may experience multiple seizures per day.

2.1.1 Treatment pathway

Epilepsy is primarily managed with anti-seizure medication (ASM). Approximately 60-70% of people with epilepsy do not achieve seizure freedom.(7) Drug-resistant epilepsy is defined as the failure of trials of two tolerated, appropriately chosen and used ASM schedules (as monotherapies or in combination), and account for approximately 30% of epilepsy cases.(8, 9) If ASMs are not successful at controlling seizures, resective procedures may be suitable for a very limited subset of patients. Implantation of a stimulator (vagus nerve stimulation (VNS)) may be considered as palliative treatment.

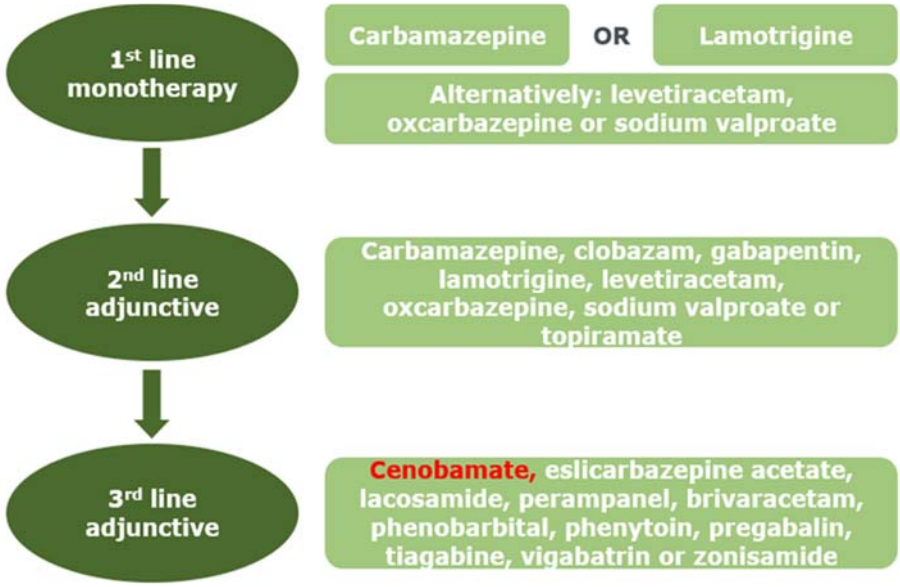
For newly diagnosed focal seizures, NICE clinical guideline on the diagnosis and management of epilepsy (CG137) recommend carbamazepine or lamotrigine as first-line treatment.(2) If these treatments are not suitable or not tolerated, levetiracetam or oxcarbazepine or sodium valproate (except for women of childbearing potential) should be offered. If first-line treatments are ineffective or not tolerated, carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, or sodium valproate as adjunctive treatments should be offered. If adjunctive therapy is not effective or tolerated, management should be discussed with, or referred to, a tertiary epilepsy specialist. Other therapies that may be offered in a tertiary setting include: eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide. Brivaracetam and perampanel are also recommended at this stage of the treatment pathway in NICE evidence summaries and local CCG formularies. Despite the range of drug treatments available to NHS patients, there is still an unmet need for individuals with FOS who remain drug-resistant.(7)

Current standard of care for epilepsy relies largely on a trial and error approach of sequential regimens of ASMs.(10) Clinical advisers to the ERG noted that most patients with drug-resistant FOS are managed with two to three ASMs at a time. Most ASMs are titrated to a maintenance dose, then increased to a maximum tolerated dose, with the aim to minimise adverse events and improve tolerability. Clinical advisers to the ERG noted that it may take approximately one year to confirm treatment failure before prescribing an alternative ASM. Clinical experts advising the company noted that the vast majority of drug-resistant patients have already cycled through many different treatments and lines of therapy. Clinical advisers to the ERG added that some patients may have treatments changed so frequently that they may return to a previously discontinued treatment. They also noted that there is significant heterogeneity in the choice of ASM and treatment sequences across clinicians and specialist centres in the UK, due notably to a paucity of comparative evidence and different clinician preferences.

2.2 Company's proposed positioning of cenobamate

The company stated that, if recommended, cenobamate would be available as third-line, adjunctive therapy, alongside other therapies listed in Figure 1.

Figure 1 Proposed positioning of cenobamate in UK clinical practice



Reproduced from CS Document B, figure 5

2.2.1 Interpretation of the anticipated licence

The anticipated licence recommends that cenobamate is used as

[redacted]

The wording of the anticipated licence for cenobamate could be interpreted in several ways. [redacted] can be understood as either:

(i) two monotherapies, i.e., 1st line monotherapy anti-seizure medication (ASM), followed by 2nd line with an alternative ASM in monotherapy;

(ii) at least two ASMs used adjunctively in 1st line; or

(iii) one ASM used in monotherapy, followed by a second ASM used adjunctively in 2nd line.

Following a request for clarification, the company replied that [redacted] was at the interpretation of the clinician. A survey of clinicians conducted by the company suggested that they would likely prescribe cenobamate following the failure of two anti-epileptic regimes, ASM monotherapy and an ASM combination treatment, which would be in line with option (iii) above.(11) However, they added that in practice, patients suitable

and likely to receive cenobamate would have already tried at least three lines of therapy including several adjunctive treatments. As such, the ERG agrees with the company that the population considered in their submission is a subgroup of the anticipated licensed indication for cenobamate.

2.2.2 Company positioning of cenobamate in the treatment pathway

The company stated that, if recommended, cenobamate would be available as third-line, adjunctive therapy, alongside other therapies as listed in Figure 1 above. However, the comparators considered in the company submission only include four adjunctive ASMs options: brivaracetam acetate, eslicarbazepine acetate, lacosamide, and perampanel. In response to a request for clarification, the company specified the choice of comparators was in line with a consensus statement from a survey of 14 UK based neurology consultants, according to which cenobamate was [redacted] *and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies*" (ERG italics). Therefore, the company excluded from its decision problem all older generation treatment options recommended by NICE (CG137). Clinical advisers to the ERG commented that this approach was not appropriate, and that clobazam, topiramate and zonisamide were also clinically relevant 3rd line options and should have been included in the decision problem. In addition, they noted that eslicarbazepine acetate was not a relevant comparator, as it is rarely used as adjunctive therapy. ERG clinical advisers also commented that levetiracetam may still be considered as a treatment option in combination with carbamazepine at this stage of the treatment pathway, and agreed that other 3rd line options (including phenobarbital, phenytoin, pregabalin and tiagabine) were less relevant due to their tolerability.

The exclusion of older-generation alternative therapeutic options from the decision problem means that the population considered in the CS is narrower than the anticipated licence, as it is restricted to a subgroup of patients suitable for a 3rd generation therapy used as 3rd line, second adjunctive treatment.

2.3 Critique of the company's definition of the decision problem

The population in the final NICE scope is "Adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed." As patients may have uncontrolled focal onset seizures following any number of lines of therapy, the population covered by the anticipated license for cenobamate is a subgroup of the population considered in the NICE scope. The population considered in the CS is also narrower than the anticipated licence, for reasons discussed in section 2.2 and summarised in Table 3.

Table 3 Summary of decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**	**ERG comment**
Population	Adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy in whom adjunctive therapy is needed.	[redacted]	Aligned with the anticipated EMA regulatory authorisation and the anticipated use of cenobamate in UK clinical practice.	The population considered in the CS is narrower than the anticipated licence. Clinical advisers to the ERG and to the company noted that patients suitable and likely to receive cenobamate would have already tried at least three lines of therapy including several adjunctive treatments. As such, the population considered in CS is a subgroup of the anticipated license.

				The exclusion of 1st and 2nd generation comparators effectively places cenobamate as an adjunctive therapy in adult patients with focal onset seizures with or without secondary generalisation who are not adequately controlled with at least two previously prescribed ASMs *and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies.*
Intervention	Cenobamate	Cenobamate	N/A	N/A

Comparator(s)	Established adjunctive clinical management, including but not limited to: brivaracetam acetate, carbamazepine, eslicarbazepine acetate, lacosamide, levetiracetam and perampanel.	The comparators considered are brivaracetam acetate, eslicarbazepine acetate, lacosamide, and perampanel.	Carbamazepine and levetiracetam are not considered valid comparators for several reasons and are not included in the company decision problem: According to NICE CG137, carbamazepine and levetiracetam are both indicated as first-line or second line treatment, in monotherapy or as an adjunctive ASM. As per the anticipated marketing authorisation for cenobamate, the technology is indicated after a patient has been inadequately controlled on 2 ASMs, therefore making cenobamate a 3rd-line therapy in accordance with	The comparators described in the company's submission only include a subset of four 3rd generation adjunctive therapies listed in the final scope. Clinical advisers to the ERG consider that the following comparators should be included in the decision problem: lacosamide, clobazam, zonisamide, brivaracetam, perampanel, topiramate; they also found that eslicarbazepine acetate was not relevant to the decision problem as it is rarely used as adjunctive therapy. Although levetiracetam is commonly prescribed as first and

			NICE CG137. The anticipated licensed indicated for cenobamate excludes use in 1st line (monotherapy) and 2nd line (adjunctive) settings. Additionally, clinical experts in the UK confirm that both carbamazepine and levetiracetam are commonly recommended and prescribed as first-line and second-line treatment options and therefore are not appropriate comparators to cenobamate. Finally, the clinical studies for cenobamate demonstrate that carbamazepine and levetiracetam were two of the most commonly used	second-line treatment, ERG clinical advisers stated it may also be used as an adjunct to carbamazepine in a third line setting and as such may be a relevant comparator.

			background therapies indicating that cenobamate is an adjunct to these rather than a comparator.	
Outcomes	The outcome measures to be considered include: • Change in seizure frequency • Seizure free rate • Time to first seizure • Response rate • Seizure severity • Mortality • Adverse effects of treatment • Health-related quality of life	The outcome measures presented in the submission are the following: • Change in seizure frequency o Focal aware o Focal impaired awareness o Focal to bilateral tonic-clonic • Seizure-free rate • Time to first seizure • Response rate • Mortality • Adverse effects of treatment • Health-related quality of life	In line with the final scope. Please note that severity of seizures is captured according to the types of seizures experienced, considering that focal to bilateral tonic-clonic seizures are the most severe seizure type amongst patients with FOS.	The outcomes are broadly consistent with the NICE scope. Although seizure type is a clinically relevant aspect of severity assessments, other dimensions (such as duration of seizure, time to return to normal from onset, or seriously disruptive automatisms) of severity were not captured in the evidence presented by the company.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The cost effectiveness of treatments is expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for estimating clinical and cost effectiveness was set	Same as the final scope issued by NICE.	The CS is in line with the final scope issued by NICE. The intervention is 3rd-line adjunctive treatment with cenobamate, as per the

	If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	to 60 years to be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs are considered from an NHS and Personal Social Services perspective.		decision problem. The comparators included in the company submission are brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel. The ERG considers the 2nd generation ASMs clobazam, zonisamide and topiramate to be used as part of 3rd line adjunctive treatment of FOS in UK clinical practice, and therefore should have been considered as relevant comparators.
Subgroups	No subgroups will be considered.	No subgroups are considered.	N/A	N/A

Special considerations including issues related to equity or equality	There are no equity or equality issues.	There are no equity or equality issues.	N/A	N/A

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company conducted a systematic literature review (SLR) to identify clinical evidence for cenobamate and relevant comparators for the treatment of focal onset seizures (FOS) in adults. Details of the SLR are reported in Appendix D of the CS. In absence of head-to-head comparisons, a feasibility assessment was conducted to identify potential analysis networks to compare the efficacy and safety of cenobamate to relevant comparators (Section D1.1.3 of CS Appendix D).

3.1.1 Searches

The search strategies were reported in CS Appendix D (p. 3-10) with further update search strategies provided in the company response to the points for clarification (see Appendix A). The ERG appraisal of the literature searching can be found in Table 4 below.

For the most part, the searches presented were appropriate to identify relevant trials of cenobamate or comparator therapies for the treatment of focal onset seizures. However, validated RCT study design search filters were not used in MEDLINE and Embase, and the searching for ongoing, unpublished studies was fairly limited.

Table 4 ERG appraisal of evidence identification

Topic	**ERG response**	**Note**
Is the report of the search clear and comprehensive?	YES	Update search strategies were not included in the original submission but were provided in the company response to the points for clarification. Full details of handsearching and internet searching were not reported.
Were appropriate sources searched?	PARTLY	Limited searching for ongoing, unpublished studies: - HTA database (https://www.crd.york.ac.uk/CRDWeb/) and the International HTA database (https://database.inahta.org/) were not searched. - Conference abstracts from EMBASE were removed from the search results. No further sources of conference abstracts were searched. WHO ICTRP was unavailable for the search update in October 2020.
Was the timespan of the searches appropriate?	YES	The searches covered the period 1999 to 9th October 2020.
Were appropriate parts of the PICOS included in the search strategies?	YES	Focal onset seizures (P) AND (cenobamate (I) OR relevant comparators (C))

		Searches were limited to RCTs in MEDLINE and Embase.
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	YES	Date limit applied – publication year 1999 onwards.
Were any search filters used validated and referenced?	NO	Searches were limited to RCTs in MEDLINE and Embase however validated RCT search filters were not used.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Study Selection

The study selection process is reported in the CS, Appendix D.1.1.2. The full eligibility criteria for the SLR are presented in Table 1 of CS Appendix D. RCT and open-label extension (OLE) studies conducted on adults who were receiving adjunctive treatment for uncontrolled FOS were included in the review. For the review FOS included focal aware seizures, focal impaired awareness seizures and secondary generalised tonic-clonic seizures. Patients in eligible studies could be receiving 3rd generation ASMs (i.e., cenobamate, lacosamide, brivaracetam, eslicarbazepine acetate, or perampanel) or 1st and 2nd generation ASMs (i.e., levetiracetam, carbamazepine, gabapentin, vigabatrin, zonisamide, topiramate, lamotrigine). The eligible efficacy outcomes were the number of patients achieving seizure-free status, the number of patients who achieved a 50%, 75%, 90% or 100% reduction in seizure frequency, and the median percentage reduction in total seizure frequency in 28 days. Eligible safety outcomes were the number of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), hypersensitivity reactions and psychiatric and behavioural adverse events (AEs). Only English language studies were included, and there were no search date restrictions.

A PRISMA flow diagram summarising the company's SLR selection process is presented in CS Figure 1, Appendix D. Seventy-four unique studies were included for analysis, which consisted of 56 RCTs and 18 OLEs. Two studies of cenobamate (12-14) and 72 studies of 13 distinct comparators were included. A summary of the included studies is presented in CS Table 4, Appendix D and excluded studies with the reasons for their exclusion are presented in CS Table 5, Appendix D.

In the absence of any direct comparisons of cenobamate with relevant comparators, the company conducted an indirect treatment comparison (ITC). A feasibility assessment was conducted to compare patient characteristics and study designs of the studies included in the systematic review, and to determine which studies were to be included in the ITC and identify possible analysis networks. In their points for clarification (PFC) response, the company explained that OLEs and studies of first- and second-generation comparators were excluded during the feasibility assessment. Out of the 56 RCTs and 18 OLEs included in the SLR, 23 placebo-controlled RCTs were included in the feasibility

analysis. A list of the studies considered in the feasibility assessment is presented in the CS Appendix D, Table 6; a list of studies excluded at feasibility assessment stage with reasons for exclusion is presented in the PFC response, Appendix B, table 1.

Of the 23 studies included in the feasibility assessment, four studies were excluded from the ITC efficacy studies, including one trial of cenobamate and three dose escalation studies. Cenobamate Trial C013(14) was excluded from the ITC analyses, as the six-week maintenance period was deemed insufficient to demonstrate long-lasting efficacy(15). Three dose escalation studies were excluded from the ITC for both efficacy and safety outcomes; two perampanel studies(16) were excluded as they had short maintenance periods (4 weeks) and reported limited outcomes data, and one (for eslicarbazepine acetate(17)) did not have a maintenance phase and was therefore not deemed comparable to other studies. A flow chart showing the flow of studies included in analyses is presented in CS Figure 2, Appendix D. A further five studies: two using brivaracetam(18, 19), two using lacosamide(20, 21), and one where the treatment is unclear (the study referenced is for levetiracetam(22)) were excluded from mixed treatment comparisons on safety outcomes. Reasons for exclusions from the ITC are detailed in Table 7, Appendix D.

Nineteen placebo-controlled RCTs of the following ASMs were included in the ITC: cenobamate (1 trial)(12), lacosamide (4 trials) (20, 21, 23, 24), brivaracetam (6 trials)(18, 19, 25-28), eslicarbazepine acetate (4 trials)(29-32), and perampanel (4 trials) (33-36); their characteristics are summarised in CS Appendix D, table 10.

3.1.2.1 Points for Critique

The SLR study selection process was broadly appropriate. The feasibility assessment led to the exclusion of most RCTs included in the SLR. Although justifications were provided for the inclusion of all studies, the ERG questions the company's rationale for a number of exclusions. In particular, the company excluded cenobamate trial C013 from the ITC, due to its short maintenance duration. The ERG agrees with the company that the six-week maintenance duration of trial C013 is insufficient to assess long-term efficacy. However, the decision to exclude it on these grounds is inconsistent with the evidence included in the ITC; the maintenance duration of trials included in the ITC ranged from 0 to 13 weeks, and treatment duration from seven to 19 weeks. Clinical advisers to the ERG noted that in clinical practice, a treatment duration of one year was required to reliably assess treatment failure. Therefore, the ERG believes that none of the RCT evidence included in the ITC had sufficient maintenance and treatment duration to assess the relative long-term efficacy of cenobamate and comparator ASMs reliably, and that the exclusion of trial C013 due to its short maintenance duration is not justified. The comparability of studies included in the ITC is further discussed Section 3.3.

3.1.3 Data Extraction

Data extraction methods are reported in Section D.1.1.2 (p13) of CS Appendix D. Data were extracted into data extraction tables and were checked and validated to identify and correct any extraction errors.

3.1.3.1 Points for Critique

The company did not clarify how many individuals were involved in the data extraction and whether they worked independently. Therefore, the risk of data extraction error and bias cannot be excluded.

3.1.4 Quality Assessment

The quality of RCTs was assessed using the Cochrane Risk of Bias (RoB) 2.0 tool(37) whereas OLE studies were assessed using the Cochrane ROBINS-I tool(38). Quality assessment of RCTs and OLEs were conducted by a single reviewer.

Results for the quality assessment for the RCTs included in the ITC are reported in Section D1.4 in CS Appendix D (Tables 30-32). Results of the ROBINS-I assessment were not reported.

3.1.4.1 Points for Critique

Only one reviewer performed the quality assessment, therefore the risk of error and bias cannot be excluded. The company used appropriate tools for assessing risk of bias, although other quality issues such as the clinical relevance of outcomes reported (e.g. percentage reduction in seizure frequency, which clinical advisers to the ERG found to be of limited relevance to clinical practice) or generalisability of the trial populations were not systematically assessed. Clinical advisers to the ERG noted that more recent trials may have more selected populations (due notably to the potentially higher number of previous therapies received); it is not clear whether this potential source of selection bias was captured in the risk of bias assessment. Justifications for risk of bias judgments were not provided, making their validity difficult to assess. It does not appear that risk of bias judgments were made at an outcome level. No results were reported for the quality assessments of non-RCTs. Due to a number of limitations, the ERG believes that the quality assessment conducted by the company may not be valid.

3.1.5 Evidence Synthesis

Although C013 was not included in the indirect treatment comparison or economic analysis because the 6-week maintenance phase was not considered long enough to demonstrate long-lasting efficacy(15) , the company reported the results of a meta-analysis combining two cenobamate studies: C013(14) and C017 (12).(Lattanzi et al. (2020) (39)).

Efficacy analyses were conducted in the modified intention-to-treat (ITT) population data for the maintenance phase (MITT-M), which included all randomized patients who had taken at least one dose of study drug and had any maintenance phase seizure data. The authors did not explicitly state which trial population informed the safety analyses. A fixed effect model was used except where there was evidence of substantial heterogeneity ($I^2 \geq 40\%$,), in which case a random effect model was preferred. No further descriptions of models used were provided. Efficacy outcomes were the proportions of patients with ≥ 50%, ≥ 75%, ≥ 90%, and 100% reduction in monthly seizure frequency during the maintenance treatment period compared with the pre-randomization baseline period. Safety and tolerability outcomes included the proportion of participants withdrawing from treatment for any reason and for adverse events (AEs) and who experienced any AE, any treatment-related AE, and any serious AE (SAE). Results for the efficacy outcomes were expressed as risk ratios (RR) with 95% confidence intervals (CIs) and presented in forest plots (see CS Figures 26-33). Results for safety outcomes were reported as RRs with 95% CIs. The meta-analysis results are discussed further below in Section 3.2.5. The methods and results of the ITC conducted by the company are discussed in section **Error! Reference source not found.**

3.1.5.1 Points for Critique

The methods of the meta-analysis combining trials C013 and C017 were broadly appropriate although the specific models used were not reported. Several analyses were not feasible due to lack of evidence (i.e. where only one trial reported an outcome). Although trials C013 and C017 had different maintenance periods (6 and 12 weeks respectively), the ERG believes that these are sufficiently similar for combining in a meta-analysis to assess the short-term efficacy and safety of cenobamate.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company presented the results of two published phase 2 double-blind placebo-controlled RCTs (C017 and C013), the open-label extension study for trial C017 (C017 OLE) and an ongoing open-label phase 3 non-randomised long-term safety study (C021). Trials C017 and C013 assessed the efficacy and safety of cenobamate as an adjunctive ASM in patients with drug-resistant focal epilepsy. Study C021 aimed to evaluate the safety and pharmacokinetics of cenobamate and concomitant ASMs, including interaction with phenytoin and phenobarbital. The company mentioned that the cenobamate clinical development programme also included 22 phase 1 studies and another small (n=7) phase 2 proof-of-concept trial in FOS, although results were not presented.

3.2.1 Trial Design and Methods

Details for the design and methodology for studies C017, C017 OLE, and C021 are reported in Section B2.2 of the CS. The design and methodology for study C013 is reported in CS Appendix D, section D2.1. CSRs were presented for C017, C013 and C021.

3.2.1.1 Study C017

Study C017 was a phase 2, placebo-controlled, dose-response study conducted in 107 epilepsy and neurology centres in 16 countries across the US, Australia, Europe, and Asia. A total of 437 adults (aged 18-70) with focal onset seizures were randomised in a 1:1:1:1 ratio to receive placebo, cenobamate 100 mg, cenobamate 200 mg, and cenobamate 400 mg. The trial consisted of an 8-week prospective baseline followed by an 18-week double-blind treatment period. The treatment period was divided into a 6-week titration phase (during which patients in the cenobamate arm were up-titrated to the target trial dose from a specified starting dose) and a 12-week maintenance phase (where patients continued taking cenobamate once a day). Patients leaving the study would be subject to a blinded taper period over a 3-week period, with a final follow-up visit scheduled 2 weeks after the last dose of the study drug.

Patients were required to be taking 1-3 concomitant ASMs for at least 12 weeks prior to randomisation which would remain unchanged throughout the study. During the 8-week baseline assessment, participants had to have eight or more FOS, with a seizure-free interval of less than 25 days; patients had to have at least three of these seizures during each of two consecutive 4-week segments of the 8-week pre-randomisation baseline assessment period. Central nervous system (CNS) disease deemed to be progressive during the course of the study, and "any clinically significant psychiatric illness, psychological, or behavioural problems that may have interfered with the subject's ability to participate in the study" according to the investigator were excluded. Further details are reported in CS document B, table 7 and in the study CSR(13).

Originally according to the study protocol, patients in the cenobamate treatment arms started the titration phase with an initial dose of 100 mg/day which was up-titrated by a weekly dose of 100 mg/day/week until they reached their target trial dose. After a blinded review of the first nine patients, the starting dose was lowered to 50 mg/day and patients in the 100 mg/day and 200 mg/day treatments were up-titrated by 50 mg/day/week increments whereas patients in the 400 mg/day treatment arm were up-titrated by 50 mg/day/week until they reached 200 mg/day whereupon the dose was increased by 100 mg/day/week. A total of 46 patients across all trial arms had received treatment prior to the protocol amendment.

Definitions of primary endpoints varied by trial centre location, due to different regulatory requirements. The primary efficacy endpoint for countries of Europe, Australia, New Zealand, and

South Africa was the responder rate during the maintenance phase, defined as a ≥ 50% reduction from baseline in seizure frequency during the maintenance phase of the double-blind treatment period. The primary efficacy endpoint for the United States and the rest of the world was the percentage change in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures during the double-blind treatment period, compared with the pre-treatment baseline phase. Efficacy was also assessed by measuring higher responder rates (≥ 75%, ≥ 90%, and 100%) of all seizure types as well as the change in seizure rate over time. Quality of life was assessed using the QOLIE-31-P tool for English speaking participants only (n=133).

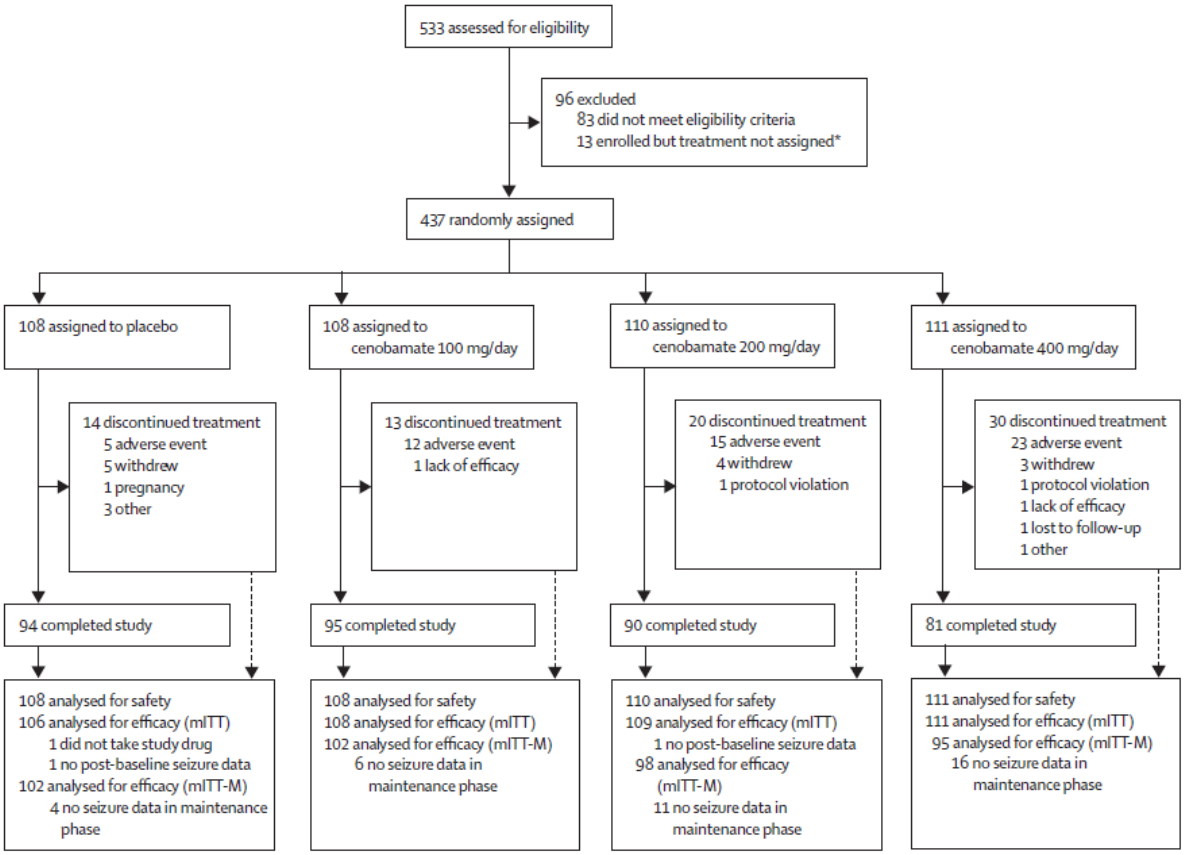
Key study populations are defined in Table 5 below, with further details reported in the C017 CSR Table S1.

Table 5 Trial C017: key population definitions

Population	Definition
Intention-to-treat (ITT) population Safety evaluable (SE) population	All randomised subjects
Maintenance-ITT (mITT) population	All randomised subjects with at least one dose of cenobamate or placebo and any postbaseline seizure data
mITT-M	All randomized subjects who completed the titration phase, took at least 1 dose of cenobamate or placebo in the maintenance phase and had maintenance phase seizure data

The flow of trial participants is presented in CS Appendix D and reproduced in Figure 2 below. This shows that, relative to the ITT population, the rate of patients with no maintenance phase seizure data (i.e. ITT patients excluded from the mITT-M population) was highest in the 400 mg arm (14.4%), compared with 200 mg (10.0%), 100 mg (5.6%) and placebo arms (3.7%).

Figure 2 Trial C017: participant flow



Source: CS Appendix D, figure 8

3.2.1.2 Study C017 OLE

Of the 437 patients randomised in trial C017, 355 patients who completed the 12-week maintenance phase of C017 and still satisfied the inclusion criteria were able to continue into the OLE phase. Of the 355 participants, 265 were originally randomized to cenobamate and 90 were originally randomized to placebo and crossed over to cenobamate). As of July 2019, [redacted] of patients were continuing in the OLE, and [redacted] patients had discontinued. Patients entering this study went through a 2-week blinded conversion period and were titrated to a target cenobamate dose of 300 mg/day. If clinically indicated, investigators could change the dosage from 50 mg/day to 400 mg/day. During this conversion phase, doses of concomitant ASMs could also be adjusted. Study assessments were scheduled to take place every three months indefinitely.

Outcomes for the OLE study were the same as those determined for the RCT C017. It appears that no adjustments were made for attrition in the efficacy analyses.

3.2.1.3 Study C013

Study C013 is a Phase 2, placebo-controlled trial conducted in adults (aged 18-65 years) with a diagnosis of treatment-resistant focal (partial-onset) epilepsy. This trial was conducted at 40 centres in four countries: The United States, Poland, India and South Korea.

Patients underwent an 8-week baseline period to assess seizure frequency followed by a 12-week treatment period (consisting of a 6-week titration phase and a 6-week maintenance phase). Patients who experienced at least three seizures over 28 days during the pre-randomisation baseline period with no 21-day seizure-free intervals were eligible. Participants must have been taking 1-3 concomitant ASMs, which they continued during the study.

A total of 222 participants (median age 37 years, range 18-61 years) were randomised in a 1:1 ratio to receive cenobamate 200 mg/day (N = 113) or placebo (N = 109). During the titration phase, patients in the cenobamate treatment group received an initial dose of 50 mg/day for two weeks. If patients exhibited good tolerability, they were up-titrated in increments of 50 mg/day every two weeks until they reached a dose of 200 mg/day or the highest dose they were able to tolerate. After the end of the double-blind period, patients were tapered off cenobamate over a 1-week period and then discontinued.

The primary outcome for the study was the percent change from baseline in seizure frequency per 28 days in the treatment period. Other outcomes included the responder rate, defined as the number of patients who experienced a ≥ 50% reduction in seizure frequency during the treatment period.

The flow of trial participants is presented as a flow diagram in Figure 7 in CS Appendix D.

3.2.1.4 Study C021

Study C021 is an ongoing Phase 3, non-randomised, single arm trial in adults (aged 18-70 years) with drug-resistant FOS who required additional ASM therapy despite having been treated with at least one ASM within approximately the last 2 years. Patients were enrolled at 137 centres in 17 countries. After an initial screening period, patients proceeded to a 12-week open label titration phase followed by an open label maintenance phase. Patients initiated the titration phase with a cenobamate dose of 12.5 mg/day for two weeks, followed by a dose of 25 mg/day for a further two weeks and then increased to a dose of 50 mg/day for another two weeks. Patients were then up-titrated at a rate of 50 mg/day every other week until they achieved a target dose of 200 mg/day. After reaching the target dose, patients were allowed to up-titrate at the same rate to the maximum cenobamate dose of 400 mg/day if needed. Patients must have been on their current stable dose of phenytoin or phenobarbital or any other concomitant ASM for at least three weeks before visit 2.

The primary outcome in this trial was the frequency and severity of AEs. Safety was also assessed through clinical laboratory tests, and physical and neurological examinations as well as the occurrence of DRESS. Interaction with phenytoin and phenobarbital was assessed in a subgroup of patients receiving either of these medications concomitantly. Further study design details are reported in CS Document B, Table 5. The flow of trial participants is presented as a flow diagram in CS Appendix D, Figure 9.

3.2.1.5 Points for Critique

The design of the cenobamate studies presented in the CS was generally well-reported. However, the ERG is concerned that the design of trials C017 and C013 poorly reflect clinical practice.

ERG clinical advisers noted that most patients with FOS who would be eligible for cenobamate in clinical practice would likely not meet the selection criteria of trials C017 and C013. In particular, they noted that the baseline seizure frequency requirements are significantly higher than the average treatment-resistant FOS population. Baseline disease severity selection criteria were somewhat more stringent for study C017, which required ≥8 FOS over the 8-week pre-randomisation period, compared with ≥3 seizures over 28 days in study C013. The exclusion of patients with progressive CNS disease or with "psychiatric illness, psychological, or behavioural problems", although standard in epilepsy trials, further limits the generalisability of the trial population to clinical practice.

Although commonly measured in ASM trials, ERG clinical advisers noted that percentage reduction in seizure frequency is not commonly used in clinical practice to inform treatments decisions, and its clinical relevance to patients may vary depending on a number of factors, such as individual preferences and individual treatment goals, as well as absolute baseline seizure frequency. For instance, the relevance to patients of a reduction from 100 to 50 seizures over a given period may differ from a reduction from 10 to five seizures.

The protocol change that led to reducing the initial starting dose from 100 mg/day to 50 mg/day and slowed the titration rate to improve tolerability in trial C017 is likely to be more reflective of clinical practice. No evidence was provided to evaluate the impact of this protocol change on cenobamate's tolerability and efficacy, although this is likely to be relatively marginal as only 46 patients across all trial arms initiated treatment prior to the protocol amendment. ERG clinical advisers noted that, even with this protocol change, the titration period for both trials (6 weeks) is shorter and the titration rate faster than would be expected in clinical practice; the extent to which the trial titration period may have affected the safety and efficacy of cenobamate compared to clinical practice is uncertain.

3.2.2 Population

The demographic and clinical characteristics of patients at baseline in all four cenobamate trials are presented in Table 6. Due to variations and gaps in reporting, comparisons between studies are somewhat limited.

Baseline demographics were broadly similar between the cenobamate studies, although the proportion of Asian patients in trial C013 was significantly higher due to the location and distribution of trial centres. Baseline median seizure frequency was higher in study C017 (ranging from 8.4 to 11.0 across trial arms) compared with trial C013 (5.5 and 7.5 in the placebo and cenobamate arm respectively); baseline mean seizure frequency was also significantly higher in trial C017 (from 21.0 to 30.6 across regions and arms) compared with C013 (15 and 16 for placebo and cenobamate respectively). Difference in mean baseline severity between C017 arms are a particular cause of concern, as they suggest that treatment arms may not have been balanced at baseline. Where reported, measures of variance indicated wide variation in baseline seizure frequency within study arms; for instance, in study C013, the number of seizures recorded over 28 days ranged from 0 to 237 across the two arms of trial C013, and standard deviations of baseline mean severity estimates were for C013 and C017 were large. Disease history (expressed as time since diagnosis of epilepsy and seizure types) appeared broadly comparable across the studies, although data were reported differently across studies. Most participants had 2 to 3 concomitant ASMs, the most common being levetiracetam, lamotrigine and carbamazepine.

Table 6 Baseline characteristics of studies C013, C017, C017 OLE and C021

Characteristic	C013		CO17				C017 OLE			C021
			Cenobamate			Placebo	Cenobamate OLE			
	Placebo	Cenobamate	100 mg	200 mg	400 mg		All participants	From Cenobamate	From Placebo	Cenobamate
N	**109**	**113**	**108**	**110**	**111**	**108**	**355**	**265**	**90**	**1339**
Age (years), mean (SD)	38 (11)	36 (11)	39.0 (12.1)	40.9 (12.4)	39.6 (10.3)	39.6 (12.4)	[redacted]	[redacted]	[redacted]	39.7 (12.8)
BMI (kg/m^2), Mean (SD)	NR	NR	25.98 (5.42)	26.05 (5.36)	25.81 (4.87)	27.36 (7.90)	[redacted]	[redacted]	[redacted]	26.93 (5.98)
Gender, n(%)										
Male	51 (47)	58 (51)	57 (52.8)	54 (49.1)	52 (46.8)	58 (53.7)	[redacted]	[redacted]	[redacted]	
Female	58 (53)	55 (49)	51 (47.2)	56 (50.9)	59 (53.2)	50 (46.3)	[redacted]	[redacted]	[redacted]	666 (49.7)
Race, n(%)										
Caucasian or White	58 (53.2)	57 (50.4)	89 (82.4)	94 (85.5)	96 (86.5)	93 (86.1)	[redacted]	[redacted]	[redacted]	1063 (79.4)

Characteristic	C013		CO17				C017 OLE			C021
			Cenobamate			Placebo	Cenobamate OLE			
	Placebo	Cenobamate	100 mg	200 mg	400 mg		All participants	From Cenobamate	From Placebo	Cenobamate
N	**109**	**113**	**108**	**110**	**111**	**108**	**355**	**265**	**90**	**1339**
African American or Black	2 (1.8)	3 (2.7)	4 (3.7)	3 (2.7)	1 (0.9)	4 (3.7)	[redacted]	[redacted]	[redacted]	47 (3.5)
Asian	45 (41.3)	49 (43.4)	10 (9.3)	11 (10.0)	11 (9.9)	9 (8.3)	[redacted]	[redacted]	[redacted]	73 (5.5)
Other	4 (3.7)	4 (3.5)	5 (4.6)	2 (1.8)	3 (2.7)	2 (1.9)	[redacted]	[redacted]	[redacted]	156 (11.6)
Baseline seizure frequency per 28 days[a]										
Mean (SD)	15 (29)	16 (25)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
			[redacted]	[redacted]	[redacted]	[redacted]				
Median (IQR)[†]	NR	NR	9.5 (6.0-19.8)	11.0 (6.0-26.00)	9.0 (6.0-21.5)	8.4 (6.0-19.0)	NR	NR	NR	NR
Median (Range)	5.5 (2, 237)	7.5 (0*, 187)	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR	NR
			[redacted]	[redacted]	[redacted]	[redacted]				
Time since diagnosis										
Median (min, max) (in years)	21.1 (2.4, 60.8)	20.0 (2.3, 52.5)	NR	NR	NR	NR	NR	NR	NR	NR
mean (SD) (in years)	NR	NR	25.5 (13.4)	22.8 (13.2)	24.4 (14.2)	23.0 (14.2)	NR	NR	NR	22.9 (14.35)[‡]
Seizure types by history[b], n(%)										
Focal Seizures	102 (93.6)	106 (93.8)	NR	NR	NR	NR	NR	NR	NR	NR
Focal aware nonmotor	16 (14.7)	18 (15.9)	23 (21)	20 (18)	24 (22)	24 (22)	NR	NR	NR	271 (20.2)
Focal impaired awareness	92 (84)	83 (73)	89 (82)	84 (76)	88 (79)	84 (78)	NR	NR	NR	1036 (77.4)
Focal aware motor	25 (22.9)	31 (27.4)	25 (23)	25 (23)	22 (20)	22 (20)	NR	NR	NR	324 (24.2)
Focal to bilateral tonic-clonic	67 (61.5)	73 (64.4)	69 (64)	61 (55)	72 (65)	60 (56)	NR	NR	NR	786 (58.7)
Generalised	5	4	NR	NR	NR	NR	NR	NR	NR	NR

Characteristic	C013		CO17				C017 OLE			C021
			Cenobamate			Placebo	Cenobamate OLE			
	Placebo	Cenobamate	100 mg	200 mg	400 mg		All participants	From Cenobamate	From Placebo	Cenobamate
N	**109**	**113**	**108**	**110**	**111**	**108**	**355**	**265**	**90**	**1339**
	(4.6)	(3.5)								
Nonmotor (absence)	0	1 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR
Motor tonic	2 (1.8)	1 (0.9)	NR	NR	NR	NR	NR	NR	NR	NR
Motor-tonic clonic	3 (2.8)	2 (1.8)	NR	NR	NR	NR	NR	NR	NR	NR
Febrile	5 (4.6)	6 (5.3)	NR	NR	NR	NR	NR	NR	NR	NR
Number of previous ASMs[c], Median (IQR)	NR	NR	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	NR	NR	NR	NR
No. of Baseline/Concomitant ASMs[d], n(%)										
1	12 (11)	19 (17)	25 (23)	39 (36)	24 (22)	27 (25)	[redacted]	[redacted]	[redacted]	238 (17.8)
2	52 (48)	53 (47)	48 (44)	47 (43)	62 (56)	54 (50)	[redacted]	[redacted]	[redacted]	510 (38.1)
≥ 2	45 (41)	41 (36)	NR	NR	NR	NR	NR	NR	NR	NR
3	NR	NR	34 (31)	24 (22)	24 (22)	27 (25)	[redacted]	[redacted]	[redacted]	588 (43.9)§
>3	NR	NR	1 (<1)	0	1 (<1)	0	[redacted]	[redacted]	[redacted]	
Background/concomitant ASMs[e], n(%)										
Levetiracetam	53 (48.6)	51 (45.1)	47 (44)	48 (44)	50 (45)	41 (38)	NR	NR	NR	523 (39.1)
Lamotrigine	34 (31.2)	41 (36.3)	44 (41)	27 (25)	50 (45)	31 (28)	NR	NR	NR	446 (33.3)
Carbamazepine	43 (39.4)	38 (33.6)	29 (27)	29 (25)	25 (23)	39 (36)	NR	NR	NR	369 (27.6)
Lacosamide	21 (19.3)	27 (23.9)	NR	NR	NR	NR	NR	NR	NR	324 (24.2)
Topiramate	21 (19.3)	25 (22.1)	NR	NR	NR	NR	NR	NR	NR	175 (13.1)
Oxcarbazepine	26 (23.9)	24 (21.2)	15 (14)	17 (16)	19 (17)	13 (12)	NR	NR	NR	174 (13.0)
Clobazam	16 (14.7)	22 (19.5)	17 (16)	12 (11)	17 (15)	5 (5)	NR	NR	NR	179 (13.4)

Characteristic	C013		CO17				C017 OLE			C021
			Cenobamate			Placebo	Cenobamate OLE			
	Placebo	Cenobamate	100 mg	200 mg	400 mg		All participants	From Cenobamate	From Placebo	Cenobamate
N	**109**	**113**	**108**	**110**	**111**	**108**	**355**	**265**	**90**	**1339**
Valproate sodium	20 (18.3)	17 (15.0)	23 (21)	28 (26)	28 (25)	31 (28)	NR	NR	NR	412 (30.8)
Valproic acid	11 (10.1)	13 (11.5)					NR	NR	NR	

† Values were not reported in the tables in the CS Document B, but were extracted from Table 6-1 of the CSR for C017 for the mITT population for patients in the United States and the rest of the world (population reported as N in this table). †† Values were not reported in the tables in CS Document B, but were extracted from Table 6-4 of the CSR for C017 for the mITT-M population for countries of Europe, Australia, New Zealand, and South Africa. * One patient in C013 only had focal aware nonmotor seizures during baseline and was randomised and treated in error. This patient was counted in the intention-to-treat and safety populations. ‡n=1336. § One patients taking four concomitant ASMs was enrolled into the study

[a] Calculated by the number of seizures over the baseline period divided by the number of days in the interval multiplied by 28. [b] Patients might be reported in more than one category. [c] ASMs taken at any time before the start of the study; these might or might not have been ongoing during the study. [d] For trials C013 and C017, this was the number of concomitant ASMs- there were ASMs that were ongoing at the start of the study and continued during the study. For trials C017 OLE and C021, this was the number of background ASMs- these were ASMs started prior to the trial and are ongoing at the time of the first dose of cenobamate. [e] Concomitant ASMs in ≥10% of the population

Abbreviations: ASM= anti-seizure medication, IQR= interquartile range, mITT= modified intention to treat, NR= Not reported (in data tables in the CS Document B) OLE=open label extension, SD= standard deviation

Source: Adapted from CS Document B: Tables 10-12 (pp.44-47), CS Appendix D: Table 35(pp.97-98), and C017 CSR

3.2.2.1 Points for Critique

The ERG has a number of concerns regarding the generalisability of the cenobamate trial population to clinical practice. As discussed in Section 3.2.1.5, ERG clinical advisers noted that the trial population was highly selected and did not reflect the population of patients with treatment-resistant FOS. In particular, they noted that the baseline seizure rates were higher than would be seen in clinical practice. The true incidence of seizures in patients with treatment-resistant FOS may vary substantially between patients and centres, as suggested by evidence from six observational studies (40-44) included in a recent systematic review of ASMs for FOS.(45) Data from a single Scottish centre for five consecutive prospective audits of newer ASMs, including topiramate (n = 135), levetiracetam (n = 136), zonisamide (n = 141), pregabalin (PGB; n = 135), and lacosamide (LCM; n = 160) in patients with uncontrolled partial-onset seizures reported a lower incidence of seizures prior to initiating treatment: a median of 4 seizures per month was reported in all cohorts except pregabalin (median=12), although the range of seizures within each cohort varied substantially (from 1 to 480 across all patients) and mean estimates were not reported.(41) To the ERG's knowledge, this is the largest published observational study providing seizure frequency data in uncontrolled FOS. Despite its single centre design and wide variation in estimates, it provides evidence that patients included in trials C013 and C017 may have had a significantly higher average incidence of seizures at baseline compared with UK clinical practice. Evidence from smaller (n=11 to 70) single centre non-UK studies

is more variable, with reported mean/median monthly seizure frequency ranging from 2.4 to 22.2.(40, 42-44)

As noted in Section 3.2.1.5, the lack of patients with progressive CNS disease or with "psychiatric illness, psychological, or behavioural problems" further limits the generalisability of the trial population to clinical practice. Differences and gaps in reporting limited the extent to which the cenobamate study populations could be compared.

3.2.3 Effectiveness

3.2.3.1 C017

Rates of reduction in seizure frequency

The clinical effectiveness results of study C017 are presented in Section B2.6.1 of the CS. Small discrepancies were identified between difference sources provided in the CS. Table 7 summarises responder rates by level of response (≥50%, ≥ 75%, ≥ 90%, and 100% reduction in seizure frequency from baseline) and by study arm for the mITT (treatment phase) and mITT-M (maintenance phase) populations from the study CSR. This shows significantly higher response rates for cenobamate compared with placebo overall. The largest effects were observed in the 400 mg arm, but the difference in response rates between the 100 mg and placebo arms were not statistically significant ($p<0.05$) except for the ≥ 50% response outcome. This suggests a dose response-effect, with higher doses of cenobamate being associated with higher rates of response. The largest effects were generally observed in the maintenance phase population, and differences in absolute rates of response between the mITT and mITT-M population were most notable for seizure freedom in the 400 mg arm ([redacted] in mITT population vs. 21.1% for mITT-M). As discussed in Section 3.2.1.1 above, the rate of patients in the ITT population who were excluded from the mITT-M population is higher in the 400 mg (14.4%) and 200 mg (10.0%) compared with placebo (3.7%); therefore, the risk of attrition bias favouring the results of the 400 mg and 200 mg arms in the mITT-M analyses cannot be excluded. A large placebo response was observed for the ≥ 50% endpoint ([redacted] in the mITT population).

Table 7 Study C017: Responder rate per study arm (mITT and mITT-M populations)

	mITT				mITT-M			
	Placebo (N=106)	**100 mg (N=108)**	**200 mg (N=109)**	**400 mg (N=111)**	**Placebo (N=102)**	**100 mg (N=102)**	**200 mg (N=98)**	**400 mg (N=95)**
Response ≥ 50%								
Response (%)	[redacted]	[redacted]	[redacted]	[redacted]	26 (25.5)	41 (40.2)	55 (56.1)	61 (64.2)
p (vs. placebo)		[redacted]	[redacted]	[redacted]		0.036	<0.001	<0.001

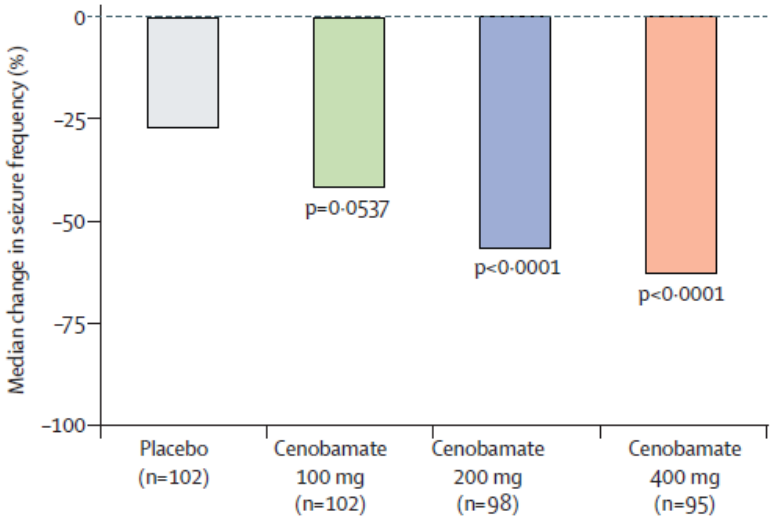
Response ≥ 75%								
Response (%)	[redacted]	[redacted]	[redacted]	[redacted]	10 (9.8)	17 (16.7)	30 (30.6)	44 (46.3)
p (vs. placebo)		[redacted]	[redacted]	[redacted]		0.215	<0.001	<0.001
Response ≥ 90%								
Response (%)	[redacted]	[redacted]	[redacted]	[redacted]	3 (2.9)	9 (8.8)	17 (17.3)	27 (28.4)
p (vs. placebo)		[redacted]	[redacted]	[redacted]		0.134	<0.001	<0.001
Response =100%								
Response (%)	[redacted]	[redacted]	[redacted]	[redacted]	1 (1.0)	4 (3.9)	11 (11.2)	20 (21.1)
p (vs. placebo)		[redacted]	[redacted]	[redacted]		0.369	0.002	<0.001

Source: Study C017 CSR

Percentage change in seizure frequency

The median percentage change in seizure frequency during the maintenance phase increased with an increase in the cenobamate dose. The median seizure frequency reduced by 27.0%, 41.5%, 56.5% and 63.0% in the placebo, cenobamate 100 mg, cenobamate 200 mg, and cenobamate 400 mg treatment arms respectively (Figure 3). The percentage change in seizures was significant in cenobamate 200 mg and cenobamate 400 mg when compared to placebo ($p<0.001$ for both comparisons). The reduction in seizure frequency in all seizure types was consistent with the trend observed overall (Figure 8, p49 of CS).

Figure 3 Median percent change in seizure frequency during the maintenance phase (mITT-M population)



Abbreviations: mITT-M, modified intention-to-treat patients in maintenance phase

Source: CS Document B, Figure 7 (p48)

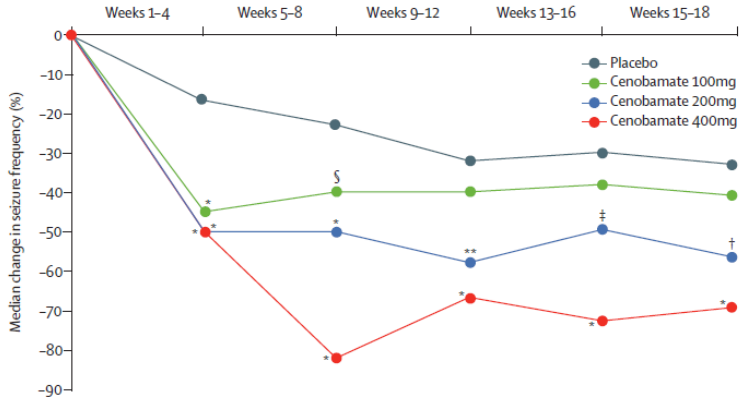
Post-hoc Analyses

Post-hoc analyses were performed for the median percentage reduction in seizure frequency and the seizure free rate over time (CS Document B, Section B.2.6.1). These are discussed below.

Reduction in seizure frequency over time

Figure **4** shows the median percentage reduction in seizure frequency across study arms. This suggests that, during the 18 weeks trial treatment phase, most of the average reduction in seizure frequency across the trial arms occurred during the first eight weeks of treatment (i.e. the entire titration phase and two weeks of maintenance therapy). This contrasts with the company's interpretation according to which, following the first four weeks of the double-blind period, a sustained decrease in median seizure frequency was observed at each additional four-week treatment interval in the 200mg and 400mg groups. The figure also indicates a greater reduction in seizure frequency with higher doses of cenobamate; there was no statistically significant difference in efficacy between the 100 mg arm and placebo during the 9-13 weeks period and subsequently.

Figure 4: Post-hoc analyses of the median percentage reduction in seizure frequency over time for C017



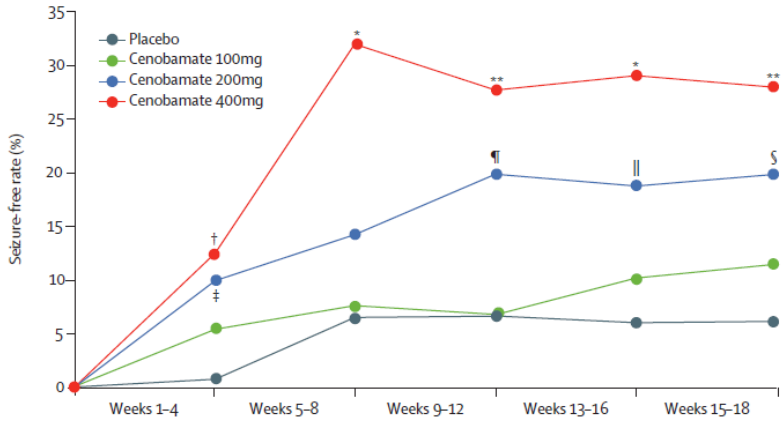
	Weeks 1–4	Weeks 5–8	Weeks 9–12	Weeks 13–16	Weeks 15–18
Placebo	106	104	101	97	95
Cenobamate 100 mg	108	103	101	97	96
Cenobamate 200 mg	109	104	95	90	90
Cenobamate 400 mg	111	103	90	86	82

Population = modified intention-to-treat patients in maintenance phase. Weeks 15-18 overlap in order to make the interval 4 weeks in duration. *p<0.0001, **p=0.0001,†p=0.0004, ‡p=0.0011, §p=0.0461, all vs placebo. Datapoints without a symbol were not significant.
Source: CS Document B, Figure 10 (p50)

Seizure-free rate over time

Figure 5 shows the proportion of patients who are seizure free over time during the treatment phase of study C017. Similar to Figure **4** above, this suggests that most of the improvements were observed during the first 8 weeks of treatment. The proportion of seizure-free patients increases more steadily in the 200 mg arm compared with the 400 mg group. There was no statistically significant difference in efficacy between the 100mg arm and placebo.

Figure 5 Post-hoc analyses of the proportion of patients seizure free over time for C017



	Weeks 1–4	Weeks 5–8	Weeks 9–12	Weeks 13–16	Weeks 15–18
Placebo	106	104	101	97	95
Cenobamate 100 mg	108	103	101	97	96
Cenobamate 200 mg	109	104	95	90	90
Cenobamate 400 mg	111	103	90	86	82

Population = modified intention-to-treat patients in maintenance phase.

*p<0.0001, **p=0.0002, †p=0.0007, ‡p=0.0051,§p=0.0078, ¶p=0.0105, ||p=0.0129, all vs placebo. Datapoints without a symbol were not significant. Source: CS Document B, Figure 11 (p51)

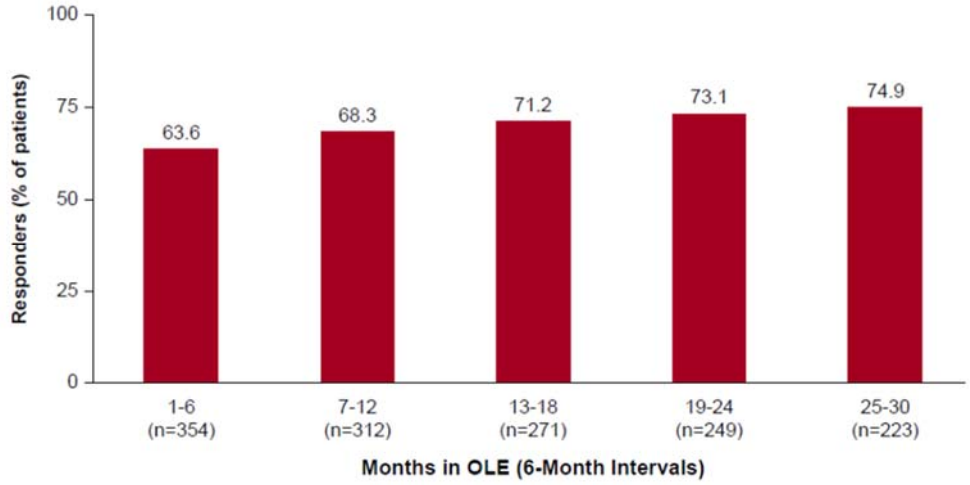
The results of a number of additional post-hoc analyses exploring the effect of baseline patient characteristics, including number and class of concomitant drugs, number of seizures at baseline, median epilepsy duration, and number of failed drugs, are presented in CS Document B, pp. 51-57. Overall, these analyses confirm the dose-response trends observed in the main analyses and did not show evidence that the relative efficacy of cenobamate compared with placebo may be confounded by patient baseline characteristics, although the results of these analyses should be interpreted with caution due to their nature and potential lack of adequate power.

3.2.3.2 C017 OLE

Figure 6 presents 50% responder rates at six-month intervals from the July 2019 data cut of the ongoing OLE for the 355 patients (or n=354 depending on figures provided by the company) who entered the extension phase of the trial. As of July 2019, [redacted] of patients had discontinued treatment. The ≥50% responder rate during the first 6 months of the OLE for all cenobamate OLE patients was 63.6%. The responder rate for all cenobamate OLE patients reached 74.9% at 25-30 months (n=223), and the percentage of patients achieving a period of 12 months and 24 months of consecutive seizure freedom at any point of the OLE was [redacted], and [redacted], respectively. Although they provide some evidence of long-term efficacy, these responder estimates

may be at high risk of attrition bias due to the high rate of discontinuation [redacted] at the latest cut-off. Due to the lack of comparator cohort, the OLE does not provide evidence for the long-term efficacy of cenobamate relative to other relevant ASMs.

Figure 6 ≥50% Responder rate by 6-month intervals during C017 OLE



Abbreviation: OLE= open label extension

Source: CS Document B, Figure 19

Further efficacy results of C017 OLE are presented in pp 57-60 of CS Document B.

3.2.3.3 C013

In the ITT population of study C013, the median seizure frequency during in the 200 mg cenobamate group decreased by 55.6% from baseline, whereas in the placebo group it decreased by 21.5%. The difference between these reductions was statistically significant ($p<0.0001$). The ≥50 % responder rate in the cenobamate arm was 50.4% (57/113) compared to 22.2% (24/108) in the placebo arm ($p<0.0001$). Post-hoc analyses for other responder rates (≥75%, ≥90% and ≥100% response) showed a statistically significant difference favouring cenobamate 200 mg compared with placebo. Further details are reported in CS Appendix D, Sections D.2.1.4 and D.2.1.5.

3.2.3.4 Points for Critique

Trials C017 and C013 provide promising evidence that cenobamate (at 200 mg and 400 mg doses) is effective at reducing seizure frequency in the short-term in patients with uncontrolled, treatment resistant FOS. There was no evidence that cenobamate administered at 100 mg doses was significantly more effective than placebo for 75%, 90% and 100% response outcomes. Due to the limited evidence, the efficacy of cenobamate compared with other relevant ASMs beyond 18 weeks of treatment is highly uncertain. Post-hoc analyses did not show evidence that baseline characteristics or concomitant treatments may have confounded efficacy results presented in the CS, although these findings should be interpreted with caution due to limited evidence. The reasons for the large placebo effect observed in both trials are unclear, although ERG clinical advisers noted that the risk of

regression to the mean associated with the high baseline frequency of seizures could not be excluded. Due to concerns about the generalisability of the study designs and trial population discussed in Sections 3.2.1.5 and 3.2.2.1, the applicability of the efficacy results to NHS clinical practice is highly uncertain.

3.2.4 Adverse Events

An adverse event (AE) was defined as any symptom, sign, illness, or experience that developed or worsened in severity during the study(13). A serious adverse event (SAE) was defined as any AE that was fatal, life-threatening, required or prolonged a hospital stay, resulted in persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event(13). No definition was provided for treatment emergent adverse events (TEAEs). Causality appears to have been assessed by the investigator only (rather than by an independent panel).

A summary of all TEAEs in the safety evaluable populations in studies C013, C017, C017 OLE and C021 is presented in Table 8.

Table 8 Summary of Treatment-Emergent Adverse Events (TEAEs) in the safety evaluable population

	Number of Patients (%)									
	CO13†		CO17†				C017 OLE			C021
				Cenobamate			Cenobamate OLE			
	Placebo	Cenobamate	Placebo	100 mg	200 mg	400 mg	All Cenobamate	Cenobamate-Cenobamate	Placebo-Cenobamate	Cenobamate
N	109	113	108	108	111	108	355	265	90	1340
Patients with ≥1 TEAE	69 (63.3)	86 (76.1)	76 (70)	70 (65)	84 (76)	100 (90)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with treatment-related TEAEs	50 (45.9)	67 (59.3)	46 (43)	62 (57)	72 (65)	92 (83)	[redacted]	[redacted]	[redacted]	[redacted]
Patients who died due to a TEAE	NR	NR	NR	NR	NR	NR	NR‡	NR‡	NR‡	[redacted]
Patients who discontinued due to a TEAE	3 (2.8)	5 (4.4)	5 (5)	11 (10)	15 (14)	22 (20)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with SAEs	4 (3.7)	2 (1.8)	6 (6)	10 (9)	4 (4)	8 (7)	[redacted]	[redacted]	[redacted]	[redacted]

† The safety-evaluable population is assessed during the double-blind treatment period.

‡ No deaths were reported in Table 20 in CS Document B (p82), but on p83 of the submission 5 deaths were reported for C017 OLE

Abbreviations: OLE= open label extension, SAE= serious treatment-emergent adverse event, TEAE= treatment-emergent adverse events.

Source: (Adapted from) CS Document B, Tables 15 (p77), 20 (p82), and 21 (p84), and CS Appendix D, Table 37 (p106)

3.2.4.1 Study C017

For study C017, all ITT patients (or all randomised patients) during the double-blind treatment period were included in the safety evaluable population. The most common TEAEs (occurring in at least 5% of the safety evaluable population) are reported in Table 9. As well as reporting commonly occurring TEAEs during the entire double-blind treatment period, the company also reported common TEAEs during the titration phase, the first six weeks of the maintenance phase and the last six weeks of the maintenance phase which are included in Table 9. No deaths were observed during the treatment phase.

TEAEs

Double-blind Period

During the double-blind period, 70 (65%) patients in the cenobamate 100 mg treatment group, 84 (76%) patients in the 200 mg treatment group and 100 (90%) patients in the 400 mg treatment group experienced at least 1 TEAE. 76 (70%) patients in the placebo treatment arm experienced at least 1 TEAE. The most commonly observed TEAEs were somnolence, dizziness, and fatigue.

Titration Phase

In the titration phase, for the three cenobamate arms combined [redacted] patients reported at least one TEAE compared to [redacted] in the placebo treatment group. The [redacted] group had the most patients who experienced at least one TEAE [redacted]), compared to [redacted] and [redacted] treatment groups, respectively.

Maintenance Phase

The incidence of TEAEs was lower in the maintenance phase compared to the titration phase. In all three cenobamate treatment groups combined, [redacted] of patients experienced at least one TEAE in the first six weeks of the maintenance phase compared to the placebo group [redacted].

Table 9. Treatment-emergent adverse events (TEAEs) reported in ≥ 5% of the safety evaluable population in the double-blind period in study C017.

	Number of Patients (%)																		
	Double-blind Period				**Titration Phase**					**Maintenance Phase (First 6 Weeks)**					**Maintenance Phase (Last 6 Weeks)**				
	Placebo	**Cenobamate**			**Placebo**	**Cenobamate**				**Placebo**	**Cenobamate**				**Placebo**	**Cenobamate**			
		100 mg	**200 mg**	**400 mg**		**All**	**100 mg**	**200 mg**	**400 mg**		**All**	**100 mg**	**200 mg**	**400 mg**		**All**	**100 mg**	**200 mg**	**400 mg**
N	**108**	**108**	**110**	**111**	**107‡**	**329‡**	**108‡**	**110‡**	**111‡**	**102‡**	**297‡**	**102‡**	**99‡**	**96‡**	**97**	**275**	**98**	**92**	**85**
Patients with ≥ 1 TEAE	76 (70.4)	70 (64.8)	84 (76.4)	100 (90.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	9 (8)	20 (19)	23 (21)	41 (37)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	15 (14)	19 (18)	22 (20)	37 (33)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	6 (6)	11 (10)	12 (11)	12 (11)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Balance disorder	0	3 (3)	2 (2)	10 (9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nystagmus	1 (<1)	3 (3)	4 (4)	7 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ataxia	1 (<1)	2 (2)	4 (4)	7 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysarthria	0	2 (2)	3 (3)	7 (6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	9 (8)	13 (12)	19 (17)	27 (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gait disturbance	3 (3)	1 (<1)	6 (6)	9 (8)														
Diplopia	2 (2)	8 (7)	11 (10)	17 (15)														
Constipation	1 (<1)	2 (2)	3 (3)	10 (9)														
Nausea	1 (<1)	7 (7)	1 (<1)	10 (9)														
Vomiting	0	2 (2)	3 (3)	6 (5)														
Fall	6 (6)	2 (2)	4 (4)	4 (4)														
URTI	6 (6)	3 (3)	4 (4)	3 (3)														
Back pain	3 (3)	4 (4)	1 (<1)	6 (5)														
Vertigo	3 (3)	1 (<1)	3 (3)	6 (5)														
Decreased appetite	1 (<1)	3 (3)	1 (<1)	6 (5)														

† Values provided have been extracted from CSR documents as they appeared to be reported incorrectly in the CS Document B. ‡ Safety evaluable populations reported are the ones provided in the CSR documents and not those reported in the CS.

Abbreviations: TEAE: treatment-emergent adverse events, URTI: upper respiratory tract infection

Source: (Adapted from) CS Document B, Tables 16-19 (pp78-81) and CSR for C017(13)

SAEs

During the double-blind period, 28 patients experienced at least one serious TEAE (Table 10). Ten patients (9%) in the cenobamate 100 mg group, 4 (4%) patients in the 200 mg group, 8 (7%) patients in the 400 mg group and 6 (6%) patients in the placebo group experienced SAEs. [redacted]

Table 10 Serious TEAEs in the double-blind period in C017

	Placebo (N=108)	Cenobamate 100 mg (N=108)	Cenobamate 200 mg (N=110)	Cenobamate 400 mg (N=111)
Patients with at least 1 serious TEAE	6 (6)	10 (9)	4 (4)	8 (7)
[redacted]				

[redacted]

† A subject who experienced multiple events within a preferred term was counted once for that preferred term.

Percentages of are based on the number of subjects in each treatment group in the safety population.

Includes TEAEs occurring during the double-blind treatment period from the first dose of study drug medication up to and including 30 days after the end of treatment for patients who completed the double-blind period and did not continue into the open-label phase or for subjects who discontinues early in the double-blind period, and TEAEs occurring up to Visit 9 date for subjects completing the double-blind period and not continuing in the open-label phase.

Abbreviations: ALT = alanine aminotransferase = AST, aspartate aminotransferase; DRESS = drug reaction with eosinophilia and systemic symptoms; TEAE = treatment-emergent adverse event.

Source: (Adapted from) C017 CSR(13) Table 8-7

Discontinuation due to TEAEs

During the double-blind treatment period, 11 (10.2%), 15 (13.6%) and 22 (19.8%) patients in the cenobamate 100 mg, 200 mg and 400 mg treatment groups discontinued due to AEs, respectively. 5 (4.6%) patients in the placebo group discontinued. [redacted]

Table 11 TEAEs that led to discontinuation in ≥2% in any treatment group by SOC during the double-blind period

	Number of Subjects (%)			
	Placebo (N=108)	**Cenobamate 100 mg (N=108)**	**Cenobamate 200 mg (N=110)**	**Cenobamate 400 mg (N=111)**
Patients with TEAEs that lead to discontinuation	**5 (4.6)**	**11 (10.2)**	**15 (13.6)**	**22 (19.8)**
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Ataxia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]

Nystagmus	[redacted]	[redacted]	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SOC= system organ class; TEAE = treatment-emergent adverse event.

Source: (Adapted from) C017 CSR(13)

3.2.4.2 Study C017 OLE

98.6% (n=355) of patients who completed the double-blind C017 study (N=360) started C017 OLE. The data cut-off used for the safety analysis was July 2019.

TEAEs

Commonly observed TEAEs in C017 OLE are summarised in Table 20 in the CS. The number of TEAEs observed was comparable irrespective of whether patients had been administered cenobamate or placebo during the double-blind phase of study C017. The most commonly reported TEAEs were dizziness [redacted]), somnolence [redacted] fatigue [redacted]), and headache [redacted]).

SAEs

[redacted]

Table 12 Common serious treatment-emergent adverse events (SAEs) reported in C017 OLE

SAEs, n(%)	All Cenobamate (N=355)	Cenobamate/Cenobamate (N=265)	Placebo/Cenobamate (N=90)
Patients with at least 1 TEAE	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]
Seizure cluster	[redacted]	[redacted]	[redacted]
Concussion	[redacted]	[redacted]	[redacted]
Generalised tonic-clonic seizures	[redacted]	[redacted]	[redacted]
Myocardial infarction	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]

Abbreviations: SAE= serious treatment-emergent adverse event, TEAE = treatment-emergent adverse event.

Source: (Adapted from) Table t04 in the company submitted files

Discontinuation due to TEAEs

[redacted] patients discontinued the trial due to TEAEs.

Deaths

Although deaths were not reported in Table 20 in the CS, at the July 2019 data-cut off, [redacted] were reported during the OLE. These deaths were due to [redacted]

3.2.4.3 Study C013

TEAEs

[redacted]. Further results are reported in Table 13 of the study CSR.

SAEs

[redacted]

Discontinuation due to TEAEs

[redacted]

Deaths

No deaths were observed during the double-blind period, although one patient died of SUDEP (sudden unexplained death in epilepsy) during the baseline period.

3.2.4.4 Study C021

As the trial is ongoing, the safety evaluable population in the CS was obtained from the June 2020 cut-off point. The overall mean modal daily dose of cenobamate was [redacted] (minimum dose: 50 mg, maximum dose: 400 mg) daily. Of the 1340 patients in the study, [redacted] received cenobamate for at least one year, and [redacted] for at least 3 years. Figure 7 presents the time to discontinuation in study C021. It appears that the rate of discontinuation was higher in the first year compared with the following two years, although findings should be interpreted with caution due to censoring between two- and three-years follow-up (number at risk dropping from 963 to 259).

Figure 7 Kaplan-Meier plot of time to discontinuation during the ongoing Study C021 (safety population)

Source: CS Document B, Figure 43

TEAEs

Overall, [redacted] of patients reported at least one TEAE during the study. In the titration and maintenance phases [redacted] and [redacted] of patients respectively reported at least one TEAE. Overall, [redacted] patients who received at least one dose of cenobamate reported a treatment-related TEAE. The most commonly observed TEAEs were somnolence [redacted]), dizziness ([redacted]), fatigue ([redacted]), and headache ([redacted]).

SAEs

[redacted] patients who received at least one dose of cenobamate experienced an SAE. No cases of DRESS were identified in the interim analyses.

Discontinuation due to TEAEs

[redacted] patients who received at least one dose of cenobamate discontinued the drug due to TEAEs.

Deaths

Four deaths were observed in C021 up to the data cut-off. One patient experienced a sudden death with no autopsy, and one person each died due to a traumatic intracerebral haemorrhage after a fall, fatal injuries after being struck by a car, and respiratory failure in a patient with Angelman syndrome. These deaths were deemed to be unrelated to cenobamate by the investigator.

Interactions with background therapies

In the overall study population, steady state cenobamate plasma levels were modestly lower (on average, 12% to 19%) at weeks 12 and 14 in the groups of subjects taking phenytoin or phenobarbital compared to the group taking any other concomitant ASMs, although. In the group of patients receiving other Concomitant ASMs group, mean plasma levels of clobazam, lamotrigine, oxcarbazepine, and perampanel were lower at weeks 12 and 14 compared to baseline; this indicated some induction of their metabolism by cenobamate as reported in **the C021 CSR**. Mean plasma levels of lacosamide, levetiracetam, and topiramate did not significantly change compared to baseline. Further results are reported in the study CSR.

3.2.4.5 Points for Critique

Safety outcomes were generally well reported. The most common TEAEs were somnolence, dizziness, headaches, and fatigue. Where reported, rates of adverse events were higher in the titration phase than the maintenance phase overall. Trial C017 showed evidence of a dose-response relationship for safety and tolerability, with a higher incidence of TEAEs and higher rates of discontinuation in treatment arms receiving stronger cenobamate doses. The duration titration phase of trials C017 and C013 (6 weeks for both studies) was significantly shorter than that of study C021 (12 weeks) and is not reflective of clinical practice. This may have led to a higher rate of TEAEs compared with clinical practice, and may at least partly explain differences in discontinuation rates between RCT evidence and C021. Evidence from study C021 suggested evidence of interaction with some background ASMs, notably phenytoin and phenobarbital.

3.2.5 Meta-analysis: Studies C017 and C013

Although the duration of the maintenance period was different in studies C013 and C017, the company reported a meta-analysis comparing the two studies(39). The meta-analysis was conducted on efficacy outcomes, using the mITT-M population. Two meta-analyses were conducted that compared any dose (100 mg/ day, 200 mg/day and 400 mg/day) of cenobamate and 200 mg/day dose of cenobamate in studies C013 and C017.

A χ^2 test was performed and the I^2-statistic was generated to assess heterogeneity. As there was no significant heterogeneity ($p>0.10$) in any of the meta-analyses, a fixed effect model was presented for all comparisons.

All analyses were performed in STATA/IC 13.1(46). The results of this meta-analysis are presented in CS Document B, Section 2.8. The outcome of the meta-analysis is the risk ratio (RR) of the response with cenobamate relative to placebo. A summary of results of the meta-analysis is presented in Table 13.The 95% confidence intervals (CIs) for the RRs in C013 and C017 overlapped for all meta-

analyses. C017 tends to be more favourable for cenobamate compared to C013 for all outcomes but the ≥ 50% responder rate.

Table 13 Summary of the results of the meta-analysis of C013 and C017

	Cenobamate 200 mg/day				Any Dose Cenobamate			
	RR (95% CI)	**χ^2**	**p†**	**I^2 (%)**	**RR (95% CI)**	**χ^2**	**p†**	**I^2 (%)**
≥ 50% Responder Rate	2.25 (1.71, 2.98)	0.03	0.857	0.0	2.18 (1.67, 2.85)	0.14	0.706	0.0
≥ 75% Responder Rate	2.21 (1.52, 3.20)	1.55	0.213	35.8	2.25 (1.57, 3.24)	1.77	0.184	43.4
≥ 90 % Responder Rate	4.27 (2.37, 7.70)	0.37	0.543	0.0	4.34 (2.42, 7.78)	0.47	0.495	0.0
Seizure Freedom	3.66 (1.90, 7.06)	1.35	0.245	28.1	3.71 (1.93, 7.14)	1.55	0.214	35.3
Withdrawal	1.26 (0.77, 2.08)	NR	NR	NR	1.34 (0.85, 2.09)	NR	NR	NR
Withdrawal due to AEs	NR (0.91, 4.46)	NR	NR	NR	2.27 (1.08, 4.79)	NR	NR	NR
AEs	NR	NR	NR	NR	1.14 (0.99, 1.31)	NR	NR	NR
SAEs	NR	NR	NR	NR	0.99 (0.36, 2.75)	NR	NR	NR

Values above 1 indicate a higher rate of events compared with placebo. Meta-analyses where

†For all meta-analyses, df=1 and all models were fixed-effect

Abbreviations: AE= adverse events, CI = confidence interval, NR= not reported, RR= risk ratio, SAE= serious adverse events. Source: CS CS Document B, Section 2.8

3.2.5.1 ≥ 50% Responder Rate

Forest plots for the results of the meta-analysis for the ≥ 50% responder rate outcome are presented in Figures 26 (all cenobamate) and 27 (200 mg/day cenobamate) of the CS Document B. Patients receiving any dose of cenobamate were 2.18 times more likely to achieve a ≥ 50% response compared to placebo (95% CI: 1.67-2.85), whereas patients receiving 200 mg/day of cenobamate were 2.25 times more likely to achieve a ≥ 50% response (95% CI:1.71-2.98).

3.2.5.2 ≥ 75% Responder Rate

Forest plots for the results of the meta-analysis for the ≥ 75% responder rate outcome are presented in Figures 28 (all cenobamate) and 29 (200 mg/day cenobamate) of the CS Document B. Patients receiving any dose of cenobamate were 2.25 times more likely to achieve a ≥ 75% response compared to placebo (95% CI: 1.57-3.24), whereas patients receiving 200 mg/day of cenobamate were 2.21 times more likely (95% CI:1.52-3.20).

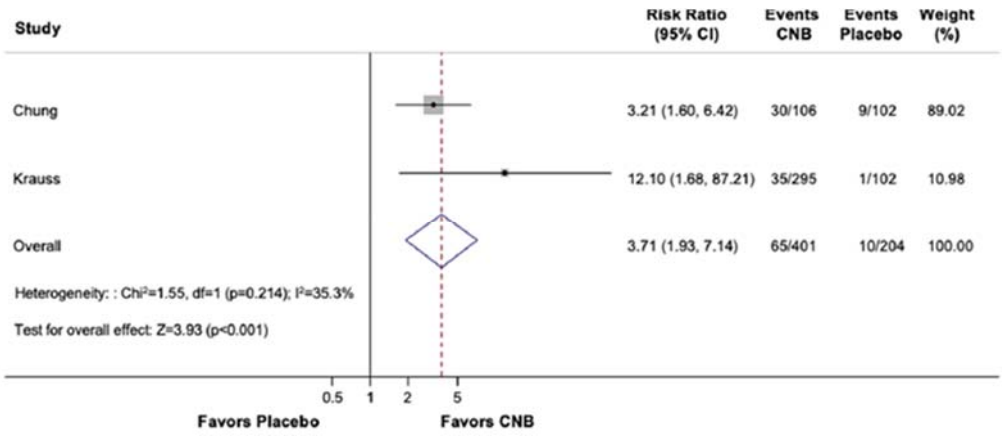
3.2.5.3 ≥ 90% Responder Rate

Forest plots for the results of the meta-analysis for the ≥ 90% responder rate outcome are presented in Figures 30 (all cenobamate) and 31 (200 mg/day cenobamate) of the CS Document B. The CI for C017 was wider than the one for C013, indicating greater uncertainty in the estimate for the RR for C017. Patients who received any dose of cenobamate were 4.34 times more likely to achieve ≥ 90% response compared to placebo (95% CI: 2.42-7.78), whereas patients who received 200 mg/day of cenobamate were 4.27 times more likely to achieve a ≥ 90% response (95% CI:2.37-7.70).

3.2.5.4 Seizure Freedom

Forest plots for the results for seizure freedom are presented in CS Document B, Figures 31 and 32. The meta-analysis of seizure freedom in any dose is reproduced below (Figure 8). The confidence interval for the RR was wider for C017 compared to C013 due to a lower event rate in both arms. Patients who received any dose of cenobamate were 3.71 times more likely to achieve seizure freedom compared to placebo (95% CI: 1.93-7.14), and patients who received 200 mg/day of cenobamate were 3.66 times more likely to achieve seizure freedom compared to placebo (95% CI: 1.90-7.06).

Figure 8 Meta-analysis of seizure freedom in any dose of cenobamate



Source: CS Document B, Figure 31

Meta-analyses were also conducted to compare withdrawal and adverse events between patients receiving cenobamate and placebo. According to RRs, patients receiving cenobamate (any dose and 200 mg/day) were more likely to withdraw, but this estimate was not significant (the CI contained 1). Patients receiving any dose of cenobamate were 2.27 times more likely to withdraw due to adverse events compared to placebo (95% CI:1.08- 4.79).

There was evidence suggesting a higher risk of AEs in the cenobamate arms (any dose vs. placebo: RR 1.14 (0.99, 1.31) although the estimate did not reach statistical significance. There was no

evidence of a difference in SAE incidence between all doses of cenobamate and placebo although the confidence interval was wide owing to the limited number of events (RR 0.99; 95% CI 0.36, 2.75). Subgroup results for the doses recommended in the anticipated licence [redacted] vs. placebo were not reported.

3.2.5.5 Points for Critique

The meta-analyses methods are generally appropriate (see Section 3.2.5), although results are limited by the small number of studies. Due to the limited evidence, pooling was not possible for a number of analyses, and pooled estimates were imprecise, as shown by the wide confidence intervals. Forest plots presented in the CS suggested that the magnitude of point estimates for some response outcomes and seizure freedom estimates tended to be larger for C017 compared with C013; there was some limited evidence of heterogeneity for ≥75% response and seizure freedom analyses (I^2 ranging from 26% to 43%), although confidence intervals overlapped in all analyses.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Due to the absence of head-to-head RCTs comparing cenobamate with other ASMs, the company conducted an indirect treatment comparison (ITC). Details of the SLR and feasibility assessment which identified comparator studies are outlined in Section 3.1.2. Nineteen RCTs of the following ASMs were included in the ITC: cenobamate (1 trial)(12), lacosamide (4 trials) (20, 21, 23, 24), brivaracetam (6 trials)(18, 19, 25-28), eslicarbazepine acetate (4 trials)(29-32), and perampanel (4 trials) (33-36). Details of the studies included in the ITC are reported in CS Appendix D.1.1.3. This section provides a summary and critique of these studies.

3.3.1 Study Design

All studies included in the ITC were placebo-controlled, and most studies were phase 3, international multi-centre trials, with sample sizes ranging from 157 to 768 participants. The duration of the baseline period ranged from four to eight weeks. Four brivaracetam studies did not report a maintenance period. Studies that had a titration period reported durations ranging from two to 12 weeks. Where reported, the maintenance period also varied in duration from four to 13 weeks, and treatment periods from seven to 19 weeks.

Table 14 Summary of designs of studies included in the ITC

Study (NCT number)	Phase	N*	Study period (month/year)	Study duration (weeks)				Location (number of centres)
				Baseline	Titration	Maintenance	Treatment	
Cenobamate								
Krauss et al. (2019) **C017(12)** (NCT01866111)	2	437	07/13 – 06/15	8	6	12	18	Global (107)
Brivaracetam								
Van Paesschen et al. (2013)(25) (NCT00175929)	2	157	05/05 – 03/06	4	3	7	10	Europe (inc. FR, DE, UK) (42)
French et al. (2010)(27) (NCT00175825)	2	210	11/05 – 06/06	4	0	0	7	Brazil, India, Mexico, US (41)
Ryvlin et al. (2014)(28) (NCT00490035)	3	399	09/07 – 02/09	8	0	0	12	Europe (inc. FR, DE, UK), India (88)
Biton et al. (2014)(18) (NCT00464269)	3	400	09/04 – 12/06	8	0	0	12	Australia, Brazil, Canada, Mexico, US (85)
Kwan et al. (2014)(19) (NCT00504881)	3	480	10/07 – 12/08	4	8	8	16	Global (74)
Klein et al. (2015)(26) (NCT01261325)	3	768	12/10 – 12/13	8	0	0	12	Global (142)
Lacosamide								
Hong et al. (2016)(23) (NCT01710657)	3	548	09/12 - 08/14	8	4	12	16	China, Japan (72)
Ben-Menachem et al. (2007)(24)	NR	418	02/02 – 05/04	8	6	12	NR	Europe, US (68)
Chung et al. (2010)(20) (NCT00136019)	3	405	03/04 – 08/06	8	6	12	18	US (72)
Halasz et al. (2009)(21) (NCT00220415)	3	485	06/04 – 01/06	8	4	12	NR	Australia, Europe (inc. FR, DE, UK), Russia (75)
Eslicarbazepine acetate								
Elger et al. (2009)(29) (NCT00957684)	3	402	07/04 – 11/05	8	2	12	14	Europe (inc. DE), Russia (40)
Ben-Menachem et al. (2010)(30) (NCT00957047)	3	395	09/04 – 12/06	8	2[b]	NR	14	Argentina, Australia, Brazil, Europe (inc. DE, UK), South Africa (45)
Gil-Nagel et al. (2009) (31) (NCT00957372)	3	253	12/04 – 01/07	8	2	12	18[c]	Mexico, Portugal, Spain (39)
Sperling et al. (2015)(32) (NCT00988429)	3	650	12/08 – 01/12	8	2	12	NR	Argentina, Australia, Brazil, Canada, Europe (inc. FR, DE), India, South Korea, South Africa, Ukraine, US (173)
Perampanel								
French et al. (2012)(33) (NCT00699972)	3	390	04/08 – 10/10	6	6	13	19	Argentina, Canada, Chile, Mexico, US (68)
French et al. (2013)(34) (NCT00699582)	3	386	05/08 – 01/12	6	6	13	19	Australia, Europe (inc. FR, DE, UK), India, Israel, Russia, US, South Africa (78)
Krauss et al. (2012b)(36) (NCT00700310)	3	706	08/08 – 05/10	6	6	13	19	Europe, Asia, Australia (116)
Nishida et al. (2018)(35) (NCT01618695)	3	710	05/12 – 09/14	6	6	13	19	Australia, China, Japan, Malaysia, Republic of Korea, Taiwan, Thailand (119)

*All randomised patients. [a]Dose-escalation trials, Study 201 (NCT02170077) featured a 12-week titration phase where doses were titrated every four weeks for 12 weeks over the "treatment period". [b]Two-week titration for 1,200 mg dose only. [c]The double-blind treatment phase also included a tapering off period. [d]No linked study name or NCT number. [e] add-on maintenance period, after this there is a monotherapy phase and down titration period of a concomitant ASM. Some studies did not report a treatment period despite having a titration and maintenance period. **Abbreviations:** NR= not reported, UK=United Kingdom, FR= France, DE =Germany, US = United States. Source; CS Appendix D, Table 10

3.3.1.1 Points for critique

Most trials included in the ITC were relatively large, multi-centre international studies. Clinical advisers to the ERG added that titration periods are significantly shorter and more intense than would be seen in clinical practice. This limits the applicability of the trial evidence. In addition, the duration of titration, maintenance and treatment periods varied significantly across the trials, and four trials (all of brivaracetam) did not report a titration period. This limits the comparability of the trials and the validity of the ITC.

3.3.2 Baseline Characteristics

The population of interest was adult patients (aged over 12 years) receiving adjunctive treatment for drug-resistant FOS in epilepsy. FOS included focal aware seizures, focal impaired awareness seizures, and secondary generalised tonic-clonic seizures. The baseline characteristics for the 19 comparator studies are presented in Table 15; baseline characteristics for study arms with doses outside the licenced dose range were excluded from the table.

The mean age of patients and sex in comparator studies were comparable to that of participants in C017. The majority of patients in comparator studies were Caucasian, with the exception of one lacosamide study(23) (where patients were either Chinese or Japanese), one brivaracetam study(27) (where 33% of patients were Caucasian), one eslicarbazepine acetate study(31) (where 34% of patients were Caucasian). Patient ethnicities were not reported in a perampanel study(35) that was conducted in Asia.

Where reported, the average duration of epilepsy in patients in most studies ranged from 17.3 to 25.3 years, one brivaracetam study(26) had a shorter duration of 13.7 years. Median/mean baseline seizure frequency ranged from 6.7 to 15.0 across all study arms, although measures of variance were not reported. Where reported, most patients were receiving two-to-three concomitant ASMs, although the proportion of patients receiving two or three ASMs varied between the trials arms, and some studies reported a significant minority of patients with one concomitant treatment; the most commonly reported included carbamazepine, levetiracetam and lamotrigine, although distributions were not reported.

Table 15 Summary of baseline characteristics of comparator studies

Study (NCT number)	**N**	**Daily treatment doses (mg)***	**Age (mean years)**	**% Caucasian**	**Sex (% male)**	**BMI (kg/m²)**	**Duration of epilepsy (years)**	**Seizure frequency/ 28 days at baseline (median)**	**No. of ASMs at baseline**	**Concomitant ASMs†**
Cenobamate										
Krauss et al. (2019) **C017(12)** (NCT01866111)	437	PBO, 100, 200, 400	39.8	84.8	50.8	26.3	23.9	8.4 – 11.0	1: 23 – 36% 2: 43 – 56% 3: 22 – 31%	LEV, CBZ, LTG, VPA, OXC, CLB
Brivaracetam										
Van Paesschen et al. (2013)(25) (NCT00175929)	157	PBO, 50, 150	37.5	99.4	44.6	24.7	22.0	7.0 – 11.8[a]	1: 14 – 25% 2: 66 – 83%	LEV, CBZ, TOP, LTG, VPA, OXC
French et al. (2010)(27) (NCT00175825)	210[b]	PBO, 50	32.3	32.9	44.4 – 53.8	NR	20.4	7.8 – 8.9[a]	1: 31 – 37% 2: 57 – 65% ≥3: 6%	LEV, CBZ, LTG, VPA, OXC, PHT, CLB
Ryvlin et al. (2014)(28) (NCT00490035)	399[b]	PBO, 50, 100	37.8	76.6	55.5	NR	21.6	7.2 – 8.3[a]	1: 14 – 20% 2: 77 – 83%	LEV, CBZ, LTG, VPA, OXZ
Biton et al. (2014)(18) (NCT00464269)	400[b]	PBO, 50	38.2	71.8	60.1	NR	25.3	10.4 – 11.6[a]	1: 13% 2: 81% ≥3: 5%	LEV, CBZ, LTG, VPA, PHT
Kwan et al. (2014)(19) (NCT00504881)	480	PBO and 50, 100, 150 (single arm)	36.5	57.5	53.2	NR	22.0	8.8 – 9.2[a]	1: 15 – 19% 2: 36 – 49% ≥3: 36 – 45%	LEV, CBZ, TOP, LTG, VPA
Klein et al. (2015)(26) (NCT01261325)	768	PBO, 100, 200	39.6	72.4	48.2	26.6	13.7	9.3 – 10.0	1: 28.1% 2: 71.3%	LAC, CBZ, TOP, LTG, VPA, OXC
Lacosamide										
Hong et al. (2016)(23) (NCT01710657)	548	PBO, 200, 400	32.4	None	54.9	22.7	17.7	10-11 over 8-week baseline	1: 20 – 22% 2: 39 – 45 3: 32 – 39%	LEV, CBZ, TOP, LTG, VPA, OXC
Ben-Menachem et al. (2007)(24)	418[b]	PBO, 200, 400	40.0	92.0	46.7	NR	24.8	11-13 over 8-week baseline	NR	NR
Chung et al. (2010)(20) (NCT00136019)	405[b]	PBO, 400	38.6	81.1	49.1	NR	24.4	11.5 – 15.0	1: 17.6% 2: 53.3%	LEV, LTG, CBZ, OXC, PHT, TOP, VPA

Halasz et al. (2009)(21) (NCT00220415)	485	PBO, 200, 400	37.8	99.2	43.4 – 55.8	25.5	22.3	9.9 – 11.5	1: 11 – 16% 2: 48 – 52% 3: 34 – 41%	NR
Eslicarbazepine acetate										
Elger et al. (2009)(29) (NCT00957684)	402	PBO, 400, 800, 1,200	38.6	100	43.1 – 55.1	24.5	21.0	6.7 – 7.5	1: 32 – 39 2: 60 – 68%	CBZ, TOP, LTG, VPA
Ben-Menachem et al. (2010)(30) (NCT00957047)	395	PBO, 400, 800, 1,200	36.9	87.6	40.6 – 53.1	25.0	23.9	8.0 – 9.0	1: 15 – 23% 2: 69 – 76% 3: 6 – 10%	LEV, CBZ, TOP, LTG, VPA, CBZ, PHT, PHB
Gil-Nagel et al. (2009) (31) (NCT00957372)	253	PBO, 800, 1,200	36.8	34.4	44.8	26.0	23.1	Mean: 11.3 – 11.6	1: 15- 26% 2: 68 – 79%	LEV, CBZ, TOP, LTG, VPA, PHT
Sperling et al. (2015)(32) (NCT00988429)	173	PBO, 800, 1,200	Median: 38.5	63.5	50.2	26.2	21.4	8.0 – 9.0	1: 28.2% 2: 71.1%	LEV, CBZ, LTG, VPA
Perampanel										
French et al. (2012)(33) (NCT00699972)	390	PBO, 8, 12	36.0	86.1	48.3	26.3	NR	12.0 – 13.7	1: 12 – 20% 2: 53 – 61% 3: 25 – 35%	LEV, CBZ, ZNS, TOP, LTG, VPA, OXC, CLB, PHT
French et al. (2013)(34) (NCT00699582)	386	PBO, 8, 12	35.5	83.4	48.0	NR	NR	11.8 – 13.7	1: 7 – 13% 2: 47 – 53% 3: 40 – 35%	LEV, CBZ, ZNS, TOP, LTG, VPA, OXC, CLB
Krauss et al. (2012b)(36) (NCT00700310)	706	PBO, 2, 4, 8	33.9	61.0 – 68.6	48.9	24.1	17.7	9.3 – 10.9	1: 11 – 16% 2: 49 – 51% 3: 36 – 39%	LEV, CBZ, TOP, LTG, VPA, OXC, CLB
Nishida et al. (2018)(35) (NCT01618695)	710	PBO, 4, 8, 12	33.4	NR	46.0 - 52.0	NR	17.3	NR	1: 5 – 9% 2: 34 – 42% 3: 51 – 55% 4: 0 – 1%	LEV, CBZ, TOP, LTG, VPA, OXC, PHT, CLB

Values reported are mean unless stated otherwise. Reporting of the duration of epilepsy varied across studies and included time from diagnosis, time from onset or was unclear in which period was considered. *Excludes unlicensed doses. †Occurring in ≥15% of patients in at least one arm. [a]Reported per 7 days and extrapolated over 28 days. [b]Includes patients in excluded study arms due to doses outside the licenced range. **Abbreviations:** BID, twice daily; BRB, barbiturates; CBZ, carbamazepine; CLB, clobazam; CP, complex partial; DE, dose escalation; EI, enzyme-inducing; IR, immediate release; LEV, levetiracetam; LTG, lamotrigine; NR, not reported; OXC, oxcarbazepine; PB, phenobarbitone; PBO, placebo; PGB, pregabalin; PHT, phenytoin; PHB, phenobarbital; PRD, primidone; QC, once daily; SG, secondary generalised; SP, simple partial; TOP, topiramate; VGB, vigabatrin; VPA, valproate/valproic acid; XR, extended release; ZNS, zonisamide. Source : CS Appendix D Table 9

3.3.2.1 Points for critique

Demographic characteristics of trials included in the ITC were comparable overall, with the exception of five studies with significantly different ethnicity distributions. Although most participants were receiving two-to-three concomitant ASMs, the distribution of the number of concomitant ASMs at baseline varied between the trials. Baseline median seizure frequency values were generally high compared with clinical practice (as discussed in section 3.2.2) and the ERG are concerned that these varied substantially across trial arms (from 6.7 to 15.0). Gaps in the reporting of baseline characteristics (notably mean and variance values for baseline severity, and the distribution of concomitant therapies) limits the extent to which the trial populations can be compared. Overall, the ERG believes that the evidence presented by the company is not sufficient to support the assumption that the trial populations are homogenous.

3.3.3 Outcomes

Table 16 presents the distribution of responder and seizure freedom endpoints reported in the ITC trials. This shows heterogeneity in reporting between trials of different ASMs. All trials of perampanel and lacosamide, and half of the eslicarbazepine acetate trials reported their efficacy outcomes over the maintenance period only, whereas all seizure freedom endpoints and most responder endpoints for brivaracetam trials were reported over the treatment period. There was significant variation in evaluation periods across the trials. Four brivaracetam trials did not report a maintenance period. For other trials, maintenance period duration ranged from seven to 13 weeks, and treatment periods from 12 to 19 weeks. The duration of the evaluation periods included in the ITC also varied across the trials, ranging from 7 to 14 weeks (CS Appendix D, table 13).

Table 16 Responder rate and seiure freedom outcomes reported by maintenance and treatment period in ITC trials

Study (NCT number)	Maintenance Period			Treatment period		
	≥50% responder rate	Seizure freedom	Time period (weeks)	≥50% responder rate	Seizure freedom	Time period (weeks)
Cenobamate						
Krauss et al. (2019) C017(12) (NCT01866111)	✓	✓	12	✓	✓	18
Brivaracetam						
Van Paesschen et al. (2013)(25) (NCT00175929)	✓		7	✓	✓	10
French et al. (2010)(27) (NCT00175825)			NA	✓	✓	7
Ryvlin et al. (2014)(28) (NCT00490035)			NA	✓	✓	12
Biton et al. (2014)(18) (NCT00464269)			NA	✓	✓	12
Kwan et al. (2014)(19) (NCT00504881)	✓		8	✓	✓	16

Klein et al. (2015)(26) (NCT01261325)			NA	✓	✓	12
Lacosamide						
Hong et al. (2016)(23) (NCT01710657)	✓	✓	12			16
Ben-Menachem et al. (2007)(24)	✓	✓	12			-
Chung et al. (2010)(20) (NCT00136019)	✓	✓	12			18
Halasz et al. (2009)(21) (NCT00220415)	✓	✓	12			-
Eslicarbazepine acetate						
Elger et al. (2009)(29) (NCT00957684)	✓	✓	12	✓		14
Ben-Menachem et al. (2010)(30) (NCT00957047)			-	✓	✓	14
Gil-Nagel et al. (2009) (31) (NCT00957372)	✓	✓	12			18
Sperling et al. (2015)(32) (NCT00988429)	✓	✓	12			-
Perampanel						
French et al. (2012)(33) (NCT00699972)	✓	✓	13			-
French et al. (2013)(34) (NCT00699582)	✓	✓	13			-
Krauss et al. (2012b)(36) (NCT00700310)	✓	✓	13			-
Nishida et al. (2018)(35) (NCT01618695)	✓	✓	13			19

Source: CS Appendix D, table 11

3.3.3.1 Points for Critique

ERG clinical advisers estimated that in clinical practice, one year follow-up is generally required to assess treatment failure. With a treatment period ranging from seven to 19 weeks, the trials may not have a sufficient follow-up to provide clinically meaningful efficacy results.

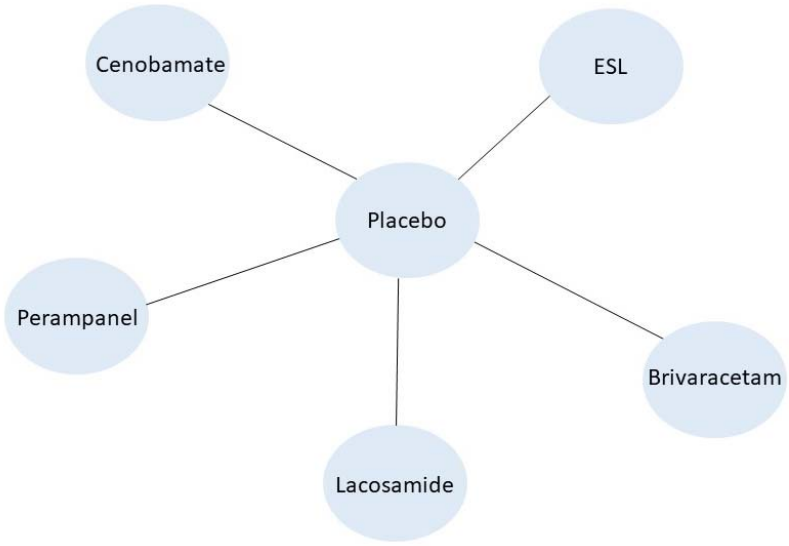
Variations in maintenance and treatment period durations limit the comparability of the trials included in the ITC. The maintenance periods of the brivaracetam trials featuring titration periods are shorter (seven to eight weeks) compared to the other active comparators (12 to 13 weeks). In addition, the shorter maintenance periods of the brivaracetam trials may penalise this comparator against other ASMs, as noted by clinical advisers to the company. Therefore, the safety and efficacy of brivaracetam compared with other ASMs are likely to be underestimated.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Due to the absence of head-to-head comparisons between cenobamate and other adjunctive ASMs, the company conducted an indirect treatment comparison (ITC) to compare efficacy and safety outcomes of cenobamate with the following third generation ASMs: brivaracetam, perampanel, lacosamide, and

eslicarbazepine acetate. As there were no trials that compared treatments directly the placebo comparator was used to connect cenobamate to the comparator ASMs in a star-shaped network. ITCs were conducted for four outcomes: ≥ 50% responder rate; seizure freedom; the proportion of patients who experienced at least one TEAE; and the proportion of patients who discontinued due to a TEAE. These outcomes were selected because they were commonly reported across comparator trials and were deemed by the company to be the most clinically meaningful and relevant for market access purposes. The overall network is presented in Figure 9, and the number of comparator studies for each outcome assessed is presented in Table 17.

Figure 9 Network of comparators for ITCs



Abbreviations: ITC= Indirect Treatment Comparisons, ESL=Eslicarbazepine acetate

Table 17 Number of studies comparing comparator to placebo by outcome

	Number of Studies per outcome			
Comparator	**≥ 50 Response**	**Seizure Freedom**	**Occurrences of any TEAEs**	**Discontinuations due to TEAEs**
Cenobamate	1	1	1	1
Brivaracetam	6	6	4	5
Lacosamide	4	4	2	3
Eslicarbazepine acetate	4	4	4	4
Perampanel	4	4	4	4

Abbreviations: TEAE= Treatment emergent adverse events

CS Appendix D, Table 12 shows that all studies included in the ≥50% responder rate analyses used a mITT denominator (individual definitions were not provided), except for the cenobamate trial, which only included the mITT-M population. The company did not justify this decision. The table also shows that, due to limited data, responder rates were extracted over different time periods: data for

four out of six brivaracetam trials and one of four eslicarbazepine acetate trial were available over the treatment period, rather than the maintenance period. As mentioned in Section 3.3.3, the duration of the evaluation periods informing the ITC also varied across the trials, ranging from 7 to 14 weeks.

The ITC was conducted within a Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling following the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 (47). As all four outcomes were dichotomous, all analyses assumed that data followed a binomial likelihood distribution. Random effects models were fit for all outcomes, and fixed effect models were fit as sensitivity analyses. In the company's ITC, the ≥50% response outcome for cenobamate trial C017 was estimated for the mITT-M population, whereas all other studies used the mITT population. The company also conducted a sensitivity analysis where they assumed that all 3rd generation ASMs were equivalent. This assumption was supported by literature where no significant differences in efficacy were observed between brivaracetam, lacosamide, perampanel, and eslicarbazepine acetate (48).

Analyses were conducted in WinBUGS(49) through R using the R2WinBUGS (50) package. The company provided code and data tables to allow the analyses to be reproduced. A summary of the key results is presented below in

Table 18. Results are presented for analyses that did not include cenobamate trial C013 (which was part of the company submission) as well as analyses that included C013 (provided in the company's response to PFCs). The results for seizure freedom in

Table 18 are estimated using the pragmatic ITT approach. Further details on the methods and results of the ITC are presented in CS Document B Section 2.9 and Appendix D Section 1.1.3.

[redacted]

[redacted]

Table 18 Summary of the company's main results for the RE model (Adapted from CS and company response to PFCs)

	C017 only				C017 and C013			
Comparator	**≥ 50% Response†**	**Seizure Freedom‡**	**Occurrence of any TEAEs**	**Discontinuation due to TEAEs**	**≥ 50% Response†**	**Seizure Freedom‡**	**Occurrence of any TEAEs**	**Discontinuation due to TEAEs**
[redacted]								
Odds Ratios relative to cenobamate (95% CrI)								
Perampanel	0.48 [redacted]	0.21 [redacted]	0.91 [redacted]	0.56 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	0.53 [redacted]	0.18 [redacted]	1.04 [redacted]	0.75 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	0.54 [redacted]	0.21 [redacted]	0.63 [redacted]	0.49 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	0.50 [redacted]	0.28 [redacted]	0.62 [redacted]	0.39 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	0.22 [redacted]	0.05 [redacted]	0.47 [redacted]	0.23 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model Outputs								
Between-study SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total residual deviance (Mean)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
Odds Ratios relative to cenobamate (95% CrI)								
Pooled 3rd Generation ASMs	[redacted]	[redacted]	[redacted]	[redacted]				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]				
Model Outputs								
Between-study SD	[redacted]	[redacted]	[redacted]	[redacted]				
DIC	[redacted]	[redacted]	[redacted]	[redacted]				
Total residual deviance (Mean)	[redacted]	[redacted]	[redacted]	[redacted]				

† For C017, the mITT-M population was used for this outcome, the other studies used the mITT population

‡ Pragmatic ITT (only patients that complete the study and are seizure-free can be classed as seizure free in the numerator and the mITT population in the denominator).

Odds ratios (OR) <1 indicate patients in the cenobamate treatment group are more likely to experience an event. Therefore, OR<1 favour cenobamate for seizure freedom and responder rates, but favour comparators for TEAEs and discontinuations due to TEAEs.

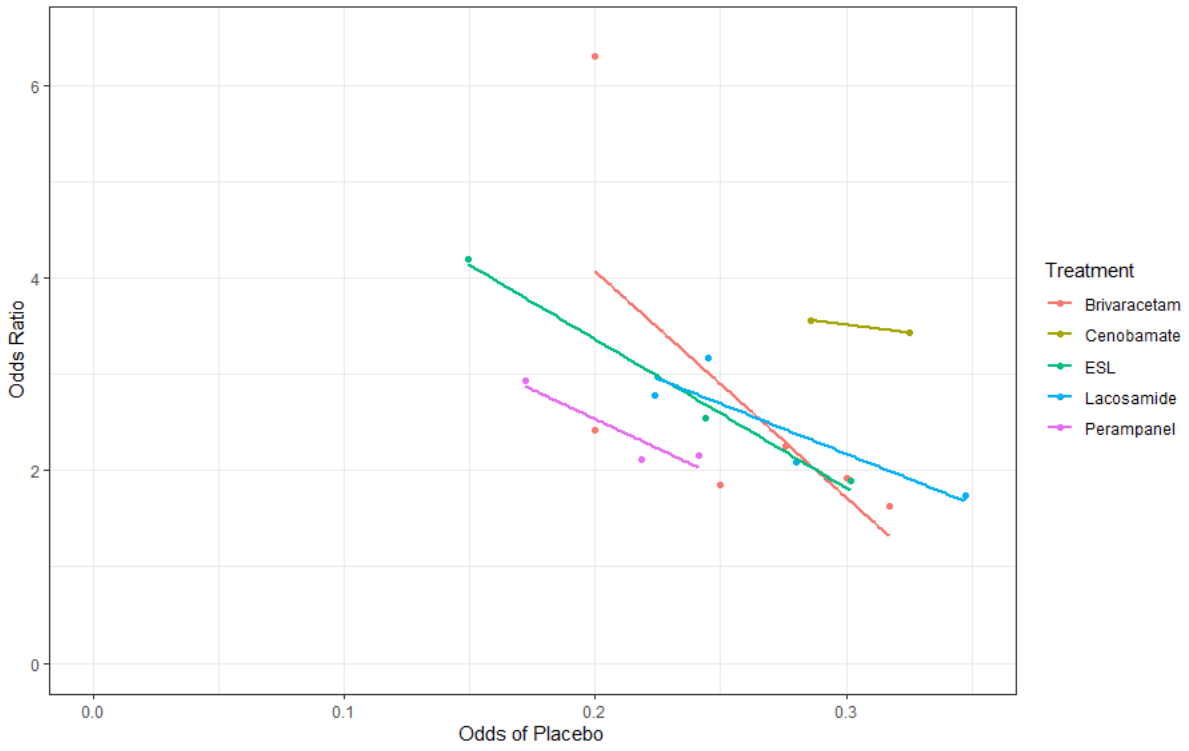
Abbreviations: ASM= antiepileptic drug, CrI= credible interval, ITT=intention to treat, NR= not reported, RE=random effects SD=

standard deviation, TEAE= treatment-emergent adverse event. Source: (Adapted from) CS Document B Table 14 (p74) and company response to PFCs

A large placebo effect was observed in all studies included in the ITCs, and this varied substantially between trials. The ≥ 50% response observed in the placebo arm in all the trials ranged from 13% (in Ben-Menachem (2010) (30), which was an eslicarbazepine acetate trial) to 26.4% (in French (2012)(33), a perampanel trial). Seizure freedom is a rarer outcome than ≥ 50% response, so the responder rate was lower in the placebo arms (ranging from 0% observed in one perampanel trial(33) and three trials each for lacosamide(14, 23, 24) and brivaracetam(18, 19, 28) to 8.3% in the cenobamate C013 trial (14). However, even in treatment arms, the seizure freedom response in trials ranged from 1.5% in Kwan (2014) (19) to 11.8% in C017 (12).

To demonstrate the impact of the placebo-effect on treatment effects, odds ratios for the ≥50% response for all trials by comparator were plotted against the odds of achieving ≥50% response in the placebo arm (Figure 10). The figure shows the heterogeneity of the placebo effect. For all treatments, a downward trend is observed, suggesting that lower placebo odds correspond to higher trial ORs and higher placebo odds correspond to lower trial ORs.

Figure 10 Trial odds ratios versus odds of placebo for the ≥ 50% response by treatment



The regression line was estimated using the linear model. For Cenobamate trial C017, the mITT population was used.

3.4.1 Points for Critique

The ERG identified a number of important limitations in the ITC presented by the company. The network of comparator therapies consisted of only placebo-controlled trials. As there were no head-to-head comparisons, consistency could not be checked which is an essential assumption of any network meta-analysis.

Only one study of cenobamate was included in the ITC. The company excluded trial C013 from all ITCs and subsequent economic evaluations due to the short 6-week maintenance phase in the trial. However, brivaracetam studies with 7–8-week maintenance periods were included in the ITC so that all available evidence was used. As ITCs included other trials with maintenance phases shorter than 12 weeks, the ERG believes that C013 should also be included. In their response to PFCs, the company repeated their analyses adding C013 to the ITCs. The ERG has also included C013 in their analyses. This is discussed in Section 3.5. The ITC is also limited in its scope as it excludes a number of older generation ASMs deemed to be relevant by ERG clinical advisers (see Sections 2.2 and 2.3).

No adjustments were made in the ITC analyses, despite a number of potential differences in patient characteristics between the trials included in the ITC, as discussed above in Section 3.3, and heterogeneity in placebo responses. The high placebo effect and differences in placebo responses may contribute to high between-study heterogeneity, which can be a source of bias when comparing treatment effects. Some differences in evaluation periods and population definitions between studies may have introduced bias favouring cenobamate. In particular, only the mITT-M population of the cenobamate trial was included in the responder analyses, and the evaluation period for most brivaracetam studies was the treatment period rather than the maintenance period only.

For the seizure-freedom outcome, the company conducted an ITC using pragmatic ITT and last observation carried forward (LOCF) methods. Seizure-freedom is relatively rare and for some studies no patients achieved the outcome (i.e. there were zero counts). The company added 0.5 to studies with zero cells as a continuity correction. This is unnecessary and incorrect in a Bayesian framework where binomial and Poisson likelihoods are permitted to have the occasional zero cell if the model being sampled is numerically stable (47), as is the case for the company's ITC.

3.5 Additional work on clinical effectiveness undertaken by the ERG

As mentioned in 3.4.1, the company incorrectly added a continuity correction to the ITCs for seizure freedom, the ERG repeated the pragmatic ITT analysis without the continuity correction (Section 3.5.1). The ERG also explored alternative models where responder data could be modelled simultaneously (Sections 3.5.2 and 3.5.3) and made adjustments for the placebo-effect (Section 3.5.3.2)

3.5.1 Continuity correction

The ERG repeated the pragmatic ITT ITC for seizure freedom (including C013) without the continuity-correction and present the results compared to those estimated with the continuity correction to demonstrate the extent of the inconsistencies in the results that can be attributed to the addition of 0.5. Results are presented in Table 19. The point estimates for the model without continuity correction are higher (i.e. less favourable to cenobamate) than those observed when a continuity correction was added. The continuity correction also reduced the between-study SD considerably.

Table 19 Results for the pragmatic ITT analysis (including C013) for seizure-freedom with and without continuity correction for zero counts

Comparator versus cenobamate	No Continuity Correction	Continuity Correction	Studies with CC	Total Studies
Odds Ratio, median (95% credible interval)				
Perampanel	[redacted]	[redacted]	1	4
Eslicarbazepine acetate	[redacted]	[redacted]	0	4
Lacosamide	[redacted]	[redacted]	3	4
Brivaracetam	[redacted]	[redacted]	3	5
Placebo	[redacted]	[redacted]	0	2
Model outputs				
Between-study SD, Median (95% CrI)	[redacted]	[redacted]		
DIC	[redacted]	[redacted]		
Total residual deviance (Mean)	[redacted]	[redacted]		

Odds ratio<1 favour cenobamate versus comparators

Abbreviations: CC= continuity correction, CrI= credible interval, SD=standard deviation

3.5.2 Joint synthesis models description

In the ITC and subsequent economic evaluation, the company synthesised ≥50% response and seizure freedom (100% response) as independent outcomes in separate synthesis models. However, the dichotomous outcomes are generated from the same continuous data by categorising at different cut-off points (i.e., 50% and 100%). Ordered categorical data can be synthesised simultaneously so that all available data are included, assuming that the treatment effect is the same irrespective of response level. Seizure freedom and ≥50% response are the most commonly reported endpoints in the published literature, and evidence for these was available for all trials included in the ITC. For some studies included in the ITC, responder rates for ≥75% and ≥90% responses were also available. There were insufficient data to conduct an independent ITC for these outcomes, but they can be included in a combined synthesis model.

The ERG implemented Bayesian network meta-analysis (NMA) models using a probit model for categorised multinomial outcomes of seizure response rates. As the company used random-effects models as their base-case models in their ITCs, the ERG only explored random-effects models as

well. The NMA models used follow the methodology for ordered categorical data described in the NICE DSU TSD 2 (47). Models were implemented considering all responder rates included in the company submission (≥ 50%, ≥75%, ≥90% and 100%), as well as aggregated responder rates of ≥50% and 100%. The results of these models are presented in Section 3.5.3.

In order to adjust for the placebo response, the ERG fit NMA meta-regression models on the placebo response(51, 52). A common interaction effect was imposed between the placebo response and relative effectiveness that accounted for variation in the placebo response across trials. The common interaction assumption is the least data demanding (only one additional parameter is needed), but it imposes the strongest assumption namely that the placebo effect is the same across the interventions(53).

All models were implemented in a Bayesian framework using MCMC sampling in WinBUGS(49). All models were sampled across 200,000 iterations across 3 chains with a burn-in of 100,000 iterations. Convergence was checked by trace plots and Brooks-Gelman Rubin (BGR) diagnostic(54).

3.5.3 Joint synthesis models' results

The results for the joint synthesis models, unadjusted for placebo effect are presented in Table 20 and Table 21.

3.5.3.1 Placebo unadjusted model

The simultaneous analysis of the ≥50 % and 100% responses indicated that patients receiving cenobamate are more likely to achieve ≥ 50% and 100% response compared to the other ASMs (Table 20). The absolute treatment effects (Table 21) also suggested that cenobamate is the most effective ASM, although the 95% credible intervals for all treatments are very wide and overlap significantly. The results for the simultaneous analysis of all available response data were consistent with the results for the model synthesising ≥ 50% and 100% responses.

Table 20 Relative treatment effects and model fit parameters for joint synthesis models (unadjusted for placebo effect)

Comparator	**Model 1**[†]		**Model 2**[‡]			
Relative Risk relative to cenobamate, median (95% CrI)						
	≥ 50 %	100%	≥ 50 %	≥ 75 %	≥ 90 %	100%
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Model Outputs						
Between-study SD, Median (95% CrI)						
DIC						
Total Residual Deviance, mean						

† Model 1 synthesises the ≥ 50% and 100% responses simultaneously

‡Model 2 synthesises the ≥ 50%, ≥75%, ≥90% and 100% responses simultaneously

Table 21 Absolute treatment effects and ranks for joint synthesis models (unadjusted for placebo effect)

	Model 1†			**Model 2‡**				
	Probability of seizure response (%)		**Rank**	**Probability of seizure response (%)**				**Rank**
Treatment	**≥ 50 %**	**100%**		**≥ 50 %**	**≥ 75 %**	**≥ 90 %**	**100%**	
Placebo								
Cenobamate								
Brivaracetam								
Lacosamide								
Eslicarbazepine acetate								
Perampanel								

† Model 1 synthesises the ≥ 50% and 100% responses simultaneously

‡Model 2 synthesises the ≥ 50%, ≥75%, ≥90% and 100% responses simultaneously

3.5.3.2 Placebo adjusted models

Results for the joint synthesis models, adjusting for the placebo effect are presented in Table 22 and Table 23.

Model parameters for the adjusted and unadjusted models were comparable for both the model synthesising the ≥ 50% and 100% responses and the model synthesising all available responses. The differences between the DIC and total residual deviance were minimal and not sufficient to suggest that one model was superior to the other (Table 20 and Table 22). Between-study heterogeneity in the placebo-adjusted model for the ≥ 50% and 100% response model was 54% lower than in the unadjusted model. For the model including all responses, the between-study heterogeneity for the

adjusted model was 42% lower than in the adjusted model. Moreover, the 95% CrI for the bias parameter, β, in the placebo adjusted model did not include 0, indicating that there is sufficient evidence against using the unadjusted model for both synthesis models (Table 22)(52).

Results for the placebo-adjusted models were consistent with those of the unadjusted models, although the relative treatment effects in the placebo-adjusted models tended to be more favourable to cenobamate than those observed in the unadjusted model.

Table 22 Relative treatment effects and model fit parameters for joint synthesis models (adjusted for placebo effect)

Comparator	**Model 1†**		**Model 2‡**			
Relative Risk relative to cenobamate, median (95% CrI)						
	≥ 50 %	100%	≥ 50 %	≥ 75 %	≥ 90 %	100%
Brivaracetam	[redacted]					
Lacosamide	[redacted]					
Eslicarbazepine acetate	[redacted]					
Perampanel	[redacted]					
Model Outputs						
B	[redacted]					
Between-study SD, Median (95% CrI)	[redacted]					
DIC	[redacted]					
Total Residual Deviance, mean	[redacted]					

† Model 1 synthesises the ≥ 50% and 100% responses simultaneously

‡Model 2 synthesises the ≥ 50%, ≥75%, ≥90% and 100% responses simultaneously

Table 23 Absolute treatment effects and ranks for joint synthesis models (adjusted for placebo effect)

	Model 1†			**Model 2‡**				
	Probability of seizure response (%)		**Rank**	**Probability of seizure response (%)**				**Rank**
Treatment	**≥ 50 %**	**100%**		**≥ 50 %**	**≥ 75 %**	**≥ 90 %**	**100%**	
Placebo	[redacted]							

Cenobamate	[redacted]							
Brivaracetam	[redacted]							
Lacosamide	[redacted]							
Eslicarbazepine acetate	[redacted]							
Perampanel	[redacted]							

† Model 1 synthesises the ≥ 50% and 100% responses simultaneously

‡Model 2 synthesises the ≥ 50%, ≥75%, ≥90% and 100% responses simultaneously

3.6 Conclusions of the clinical effectiveness section

The trials presented by the company provided promising evidence that cenobamate (at 200 mg and 400 mg doses) is more effective than placebo at reducing seizure frequency in the short-term in patients with uncontrolled, treatment resistant FOS. Trial C017 suggested that 100 mg doses may not be effective. Evidence from trials and observational studies did not raise significant safety concerns.

Due to the absence of head-to-head cenobamate RCTs, the company conducted an ITC to compare the efficacy and safety of cenobamate against other comparator ASMs. A feasibility assessment led to the inclusion of eighteen trials of four 3rd generation adjunctive ASMs: brivaracetam, lacosamide, eslicarbazepine acetate and perampanel. All other ASMs relevant to the decision problem defined in the final scope were excluded. Trial C013 was originally excluded from the ITC due to its short maintenance duration, but was subsequently added to analyses conducted by the company and the ERG.

All trials included in the ITC were placebo-controlled, therefore the placebo comparator was used to connect cenobamate to the comparator ASMs in a star-shaped network. As there were no head-to-head comparisons, network consistency could not be checked. ITCs were conducted for four outcomes: the ≥ 50% responder rate, seizure freedom, the proportion of patients who experienced at least one TEAE, and the proportion of patients who discontinued due to a TEAE. Due to limited evidence, no other outcomes included in NICE's final scope were considered. All ITCs presented were unadjusted.

The company's ITC analyses [redacted] There was also [redacted]

[redacted]

The company did not provide evidence for a number of older generation comparators deemed relevant by ERG clinical advisers (topiramate, zonisamide and clobazam), and only provided short-term evidence for all comparators, with treatment/follow-up periods ranging from seven to 19 weeks.

The ERG believes that the design of all trials included in the ITC poorly reflect clinical practice. In particular, titration periods were significantly shorter and more intense than would be seen in clinical practice, and four trials of brivaracetam did not report a titration period. A number of issues regarding the generalisability of the trial populations were identified. Trial participants appeared to be highly selected, although selection criteria were only presented for cenobamate studies. In particular, the average baseline seizure rates of patients included in the ITC trials may be higher than would be seen in clinical practice. Exclusions of patients with progressive CNS disease further limits the generalisability of the trial populations.

Due to a number of differences in trial participant populations and limited reporting, the ERG believes that the evidence presented by the company does not support the assumption that the populations included in the ITC are homogenous.

Some differences in evaluation periods and population definitions between studies included in the ITC may have introduced bias favouring cenobamate against active comparators. In particular, only the mITT-M population of the cenobamate trial was included in the responder analyses, and the evaluation period for most brivaracetam studies was the treatment period rather than the maintenance period only. However, due to the limited evidence, the overall magnitude and direction of bias due to confounding is uncertain.

Despite a number of differences in trial design and patient characteristics between the trials included in the ITC, and significant heterogeneity in placebo response, no adjustments were made in the company ITC analyses.

To address some of the ITC limitations, the ERG re-ran the ITC analyses following a number of corrections and adjustments, including correctly accounting for zero cells, modelling seizure responses simultaneously, and an adjustment for placebo response heterogeneity. Due to the limited evidence presented, no other adjustments were deemed possible. Although the ERG analyses reduced some of the heterogeneity seen in the company's ITC analyses, the limited evidence means that the relative efficacy and safety of cenobamate compared with other adjunctive ASMs, remains highly uncertain.

Overall, the validity and generalisability of the evidence supporting the company submission, and the extent to which the submitted evidence reflects the decision problem defined in the final scope are significantly limited.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company's methods for reviewing the cost-effectiveness literature are outlined in Appendix G of the company submission. The company did not identify any studies that evaluated the cost-effectiveness of cenobamate for the treatment of FOS. However, the company identified 12 studies that evaluated alternative treatments or combinations of treatments with levetiracetam, lacosamide, eslicarbazepine acetate, zonisamide, lamotrigine, brivaracetam and perampanel for FOS. The results of the identified publications are described in section 1.5.2 in Appendix G. A summary of 9 of the cost-effectiveness studies is shown in Table 25 in document B of the CS. The three studies identified in the systematic review in Appendix G but not reported in Table 25 of document B were submissions to the All Wales Therapeutics and Toxicology Centre (AWTTC). Six of the twelve studies had analyses presented from a UK perspective, where three were used to inform a population in Scotland, and three in Wales.

The nine publications reported in Table 25 varied in their approach to modelling the cost-effectiveness of treatment of FOS, and included decision tree models (n=5) with 1 and 2-year time horizons (n=1 and n=4, respectively), Markov models (n=2) with 15-year and lifetime horizons, and a discrete event simulation model (n=1) with a 5-year time horizon. One publication did not report how the cost-effectiveness of the treatment was modelled. Four of these publications reported the model structure. Two decision trees modelled 'seizure-free' and 'seizure reduction', one Markov model modelled 'response', 'no response (stay on treatment)', 'treatment-limiting events' and 'death', and one discrete event simulation (DES) model modelled '<50% reduction in seizures', '50 to <100% reduction in seizures' and 'seizure freedom'. Three publications that were identified in the review but excluded from Table 25 used a DES model, a Markov model and a decision tree, each with a 2-year time horizon. All three models modelled '<50% reduction in seizures', '50 to <100% reduction in seizures' and 'seizure freedom'.

4.1.1. Points for critique

The search strategies presented were generally appropriate to identify economic evaluations of cenobamate or comparator therapies for the treatment of focal onset seizures. However, the sources searched for published and unpublished studies were limited and some extra comparators were included in the search strategies which did not match those stated in the inclusion criteria. The search strategies did not identify the NICE CG137 (1) that includes a cost-effectiveness analysis of the treatment of FOS. It was likely excluded because the searches described in Appendix G only included cost-effectiveness analyses of adjunctive therapy for FOS, while NICE CG137 was primarily an economic evaluation of ASMs used as monotherapy in the treatment of adults with newly diagnosed

focal seizures. Nonetheless, the ERG considers this publication to be relevant for the evaluation of cenobamate because NICE CG137 models the first three lines of treatment and subsequent 'maintenance' treatment for FOS epilepsy, where the third line of treatment is adjunctive and, therefore, applicable to cenobamate and its comparators. Furthermore, subsequent 'maintenance' therapy in NICE CG137 is comparable to subsequent ASMs in the CS. Therefore, the ERG considers that the cost-effectiveness model in NICE CG137 provides a useful insight into the clinical pathway of FOS in England. NICE CG137 used a Markov model with 6 months cycles to model three levels of response to treatment (<50% reduction in seizures, 50 to <100% reduction in seizures and seizure freedom). In the first cycle on adjunctive therapy (6 months after starting the treatment), patients could discontinue treatment due to ADRs or due to treatment failure. In subsequent cycles, any treatment discontinuation was assumed to be due to treatment failure only. All patients who had no response or discontinued treatment moved to subsequent 'maintenance' therapy.

Table 25 in the main report contains information about the publications identified in the review; however, the company did not report the perspective of the reported analyses. Furthermore, the company excluded three publications identified in the literature review from Table 25(55-57); reasons for the exclusion are unclear. The excluded publications were submissions to AWTTC that included model-based cost-effectiveness analyses of brivaracetam, perampanel and eslicarbazepine as adjuncts to therapy for FOS. The ERG considers all three studies relevant as they described model-based cost-effectiveness analyses of the relevant comparators.

The company refers to an appraisal of the included studies in Table 5, Appendix G. However, the appraisal is incomplete – it includes very brief appraisals (e.g. 'minor limitations') of four of the 12 studies and does not describe the criteria used to appraise the studies.

The company did not explicitly use the results of the SLR to guide the development of their model. This is discussed in further detail in section 4.2.2. The ERG considers the following four publications to be of relevance to this appraisal:

- NICE CG137 (1) , a model-based cost-effectiveness analysis of the treatment of FOS epilepsy (including 3rd line adjunctive treatment);
- AWTTC (56) model-based cost-utility analysis (CUA) comparing brivaracetam with eslicarbazepine acetate, lacosamide, perampanel, and zonisamide in the treatment of patients aged 16 years and over with partial onset seizures (POS) who have not responded to monotherapy and require adjunctive therapy;
- AWTCC (55) model-based CUA of perampanel as a second-line adjunctive treatment for POS with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older;

- AWTCC (57) model-based CUA of eslicarbazepine acetate 800 mg once-daily compared to lacosamide 200 mg twice-daily for adjunctive treatment of adults with partial seizures with or without secondary generalisation.

The publications are considered relevant as they model the cost-effectiveness of adjunctive treatment for FOS in the UK setting. The methods employed in the appraisals are described and discussed in further detail in upcoming sections, when relevant.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

The company's economic evaluation is positioning cenobamate as a 3rd-line adjunctive therapy in accordance with NICE CG137(1), i.e., cenobamate is not evaluated as a first-line monotherapy or in the second line (adjunctive) setting. This means that the model is only evaluating cenobamate as adjunctive treatment in adult patients who have not been adequately controlled despite a history of treatment with at least two anti-epileptic products.

The Markov model submitted by the company tracks patients with FOS epilepsy eligible for cenobamate over their lifetime. Upon starting treatment with cenobamate, or one of its four comparators, patients can have five different levels of treatment response, where higher levels of response are associated with fewer seizures, lower mortality, higher Health Related Quality of Life (HRQoL) and lower healthcare resource use. Patients move to the next line of therapy if they discontinue treatment, where the probability of discontinuation is treatment-specific. After discontinuing treatment patients move onto subsequent pharmacotherapy with ASMs, which is modelled as a fixed state with constant effectiveness, independent of the previous line of treatment. A small proportion of patients on subsequent ASMs go on to receive vagus nerve stimulation (VNS) or surgery, which improves their outcomes but caries a small risk of mortality and adverse events.

4.2.1 NICE reference case checklist

Table 24 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS base case is appropriate. Societal perspective was adopted in scenario analysis – this is inconsistent with the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes	The CS is appropriate. Patients enter at the age of 39.8 years old and a maximum age of 100 is assumed.

	between the technologies being compared	
Synthesis of evidence on health effects	Based on systematic review	The CS is generally appropriate. Synthesis was implemented on 2 independent outcomes (>50% and % seizure free) while the whole distribution of proportion of patients observing seizure reduction could have been synthesised.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate. EQ-5D not considered sensitive to HRQoL in patients with epilepsy and SF-6D considered instead. HRQoL is expressed in QALYs.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate. Disease specific estimates from pivotal trial C017 not considered. A mapping study was developed to convert seizure related epilepsy patient' characteristics into SF-6D index utility scores. Mapped utilities were directly obtained from patients in the cenobamate pivotal study C017.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a *de novo* Markov model based on the outcomes reported in trial C017. The model cycle length was 28 days and a half-cycle correction was applied to all costs and outcomes. The model simulates the long-term outcomes from 3rd line treatment of patients with FOS, over their lifetime. Patients receive either cenobamate or one of the four 3rd generation comparators: perampanel, brivaracetam, lacosamide or eslicarbazepine acetate. Outcomes are assumed to be independent of treatment received prior to starting cenobamate or its comparators.

The model has five mutually exclusive health states that model the level of response to the intervention and comparators: no response (0 to <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 seizure freedom (100% reduction). All patients start the model in the 'no response' state, then move between the five states until they discontinue treatment or die. Higher levels of response are associated with higher HRQoL and lower healthcare resource use (discussed in detail in sections 4.2.10 and 4.2.11, respectively). The risk of mortality in all five response states was assumed to be higher than in the general population. Excess mortality was assumed to be lower in 'seizure-free' state (hazard ratio = 1.6), than in remaining response states (hazard ratio = 2.4), this is discussed in detail in section 4.2.8. Patients who discontinue treatment move to the 'subsequent ASM' state, representing subsequent pharmacotherapy with ASMs, VNS or surgery. VNS and surgery are both one-off treatments provided to a small proportion of patients with DRE. VNS and surgery are modelled as tunnel states to ensure patients can only spend one cycle in each (due to the one-off nature of the treatments), followed by death from VNS or surgery, or 'post-surgery' and 'post-VNS' states where patients stay until they die. Patients in 'subsequent ASMs' state may also move onto VNS or surgery. Patients in 'subsequent ASM', 'post-surgery' and 'post-VNS' states can have no, moderate, high and very high response, or seizure freedom (the distribution across the levels of response is described in section 4.2.6.3). The proportion of patients with each level of response is assumed to be independent of the previous line of treatment, and it is assumed to be constant, indefinitely. After surgery or VNS, patients with no, moderate and high response are assumed to continue taking ASMs.

The proportion of patients in each health state was used to derive utilities, cost of treatment, cost of monitoring patients with epilepsy, and the expected number of seizures in each cycle. The latter was used to estimate the cost of managing seizures and treating accidents caused by seizures, described in further detail in sections 4.2.7 and 4.2.11. Adverse drug reactions (ADRs) are accounted for using treatment-specific utility decrements and cost increments in every cycle the patient spent on that treatment. The impact of ADRs on HRQoL and costs (discussed in sections 4.2.10 and 4.2.11) is assumed to be independent of their level of response.

4.2.2.1 Points for critique

The ERG has concerns regarding three elements pertaining to the model structure: (i) the response levels, (ii) the treatment pathway following discontinuation of cenobamate or its comparators, and (iii) the cycle length.

Model structure: response levels

The model structure is different to all models for FOS epilepsy identified in the company's review or in NICE CG137. Previous models largely distinguish between three levels of response to treatment:

no response (<50% seizure reduction), partial response (50% to < 100% seizure reduction) and seizure freedom (ref three AWTTC models and NICE CG137(1). The model structure in the company submission is more granular, as it models five different levels of response: no response, moderate, high and very high response, and seizure freedom. Following request for clarification, the company explained that the more granular model structure was used to capture the incremental benefits of better seizure control for cenobamate. The company indicates that among patients achieving ≥50% seizure reduction, a larger proportion of patients will achieve ≥75% and ≥90% seizure reduction with cenobamate compared to the comparators. The company argued that resource use and HRQoL in patients who achieved ≥75% or ≥90% reduction in seizures would differ to those who achieved only a 50% to 75% reduction, and therefore, using a less granular model structure, where only three levels of response are modelled, may underestimate the benefits of cenobamate, relative to its comparators.

The ERG recognises that resource use and HRQoL in patients who achieve sustained ≥75% or ≥90% seizure reduction could differ to those who achieve only a 50% to 75% reduction. However, the company did not provide evidence that cenobamate increases the proportion of patients who achieve ≥75% and ≥90% seizure reduction compared to the comparators. The NMA used to inform the effectiveness of comparators relative to cenobamate (see section 3.4) did not synthesise the relative effect of comparators on ≥75% and ≥90% reduction in seizure frequency due to a lack of data, creating a mismatch between model requirements and availability of effectiveness evidence. Due to the lack of trial data, the relative effect of comparators on ≥75% and ≥90% seizure reduction was derived from their effect on ≥50% reduction estimated in the NMA, assuming that the relative effect (odds ratio) was the same in all three levels of response (for details see section 4.2.6.2). Furthermore, the estimates of HRQoL and healthcare resource use in different levels of response are highly uncertain (see sections 4.2.10 and 4.2.11 for details).

Considering the lack of evidence for ≥75% and ≥90% seizure reduction with comparator treatments, and the uncertainty in resource use and HRQoL associated with different levels of response, the ERG believes that the more granular model structure is not appropriate because there is not sufficient evidence to populate the additional levels of response for the comparators. In addition, the use of the more granular model structure means that any relevant data from previous economic evaluations in FOS, such as state-specific costs and utilities, could not be used in this submission. As result, the company model is largely populated using estimates derived from clinical opinion and single trial data (see sections 4.2.10 and 4.2.11 for details).

In response to clarification questions, the company provided an alternative scenario where moderate, high and very high response states were aggregated to match the structure of previous FOS epilepsy models. The new model structure did not significantly impact the results: the incremental costs and QALYs change in favour of the comparators (e.g. incremental costs and QALYs for cenobamate

relative to lacosamide reduced from [redacted] to [redacted] and from -0.715 to -0.660, respectively) but cenobamate remained dominant. The ERG considers the aggregated model structure to be the preferred model structure, and uses it in their base case.

Item 1: The model structure based on five levels of treatment response (no response of <50% seizure reduction; moderate response of 50 to <75% reduction; high response of 75 to <90% reduction; very high response of 90 to <100% reduction; and seizure freedom of 100%) as opposed to three levels (no response of <50% seizure reduction; partial response of 50 to <100%; and seizure freedom of 100%) may not be appropriate because there is insufficient data to inform the relative effectiveness of the comparators for the more granular structure.

Model structure: treatment following discontinuation of cenobamate and comparators
In the company model, patients who discontinue treatment with cenobamate or its comparators move to subsequent ASMs – a homogenous health state where treatment effect is assumed to be independent of previous lines of treatment, and remains constant over time. Patients with no response following subsequent ASMs are assumed to remain drug resistant.

According to ERG clinical advisors, patients with FOS epilepsy who discontinue third line adjunctive treatment can be prescribed one of many ASMs available in the UK, and will likely cycle through many more lines of therapy. The ERG highlights that the company model is a simplification of the treatment of FOS epilepsy in practice. Following request for clarifications (question B2), the company explained that the simplified version of the model was used because there is currently no UK guidance for treatment of FOS beyond third-line, and there is no consensus amongst clinicians for what treatment would be used after cenobamate or its comparators. The company highlighted that there are 14 ASMs recommended by NICE for the adjunctive treatment of FOS in addition to the comparators in this appraisal, and modelling all possible treatment sequences with multiple lines of therapy was practically infeasible. Homogenisation of subsequent ASMs in one health states assumes that efficacy is broadly comparable between all ASMs.

The ERG recognises the challenges around modelling all possible treatment sequences for multiple lines of therapy, and the likely challenge of finding evidence to populate such a model, but highlights the limitations of the simplified representation of subsequent lines of treatment. The model assumes that subsequent treatment is independent of previous lines of therapy and ignores the effect of treatment sequencing. It is unclear whether this is appropriate, and if effectiveness of subsequent treatments is conditional on the comparator, the model could result in biased estimates of incremental costs and QALYs. Furthermore, the model assumes that patients who do not respond to 4th line treatment remain drug resistant indefinitely. While each subsequent line of treatment is less likely to be effective than the last, there may be a proportion of patients who would not respond to 4th line but

may respond to further lines of treatment. Therefore, the model structure could be underestimating the effect of subsequent ASMs.

Methods for modelling subsequent treatment in previous FOS models varied. NICE CG137 (1), modelled 4th line treatment in the model as a homogeneous 'maintenance therapy' state where patients were maintained on monotherapy with an older ASM. Of the three AWTTC appraisals, one did not specify how they modelled subsequent lines of treatment (55). One AWTTCS submission (56) modelled five lines of adjunctive therapy, where in each line, the drug was selected randomly and its' effectiveness was assumed to be independent of the line of therapy or previous treatment used. One AWTTC submission (57) assumed that patients who discontinue treatment due to ADRs and those with no response enter a six-month 'switch' state (with down-titration of their adjunctive treatment), before entering a 'no adjunctive therapy' state, in which they are assumed to receive an unspecified form of treatment for six months or until death.

The ERG considers that none of the previous approaches accurately represent treatment following cenobamate and its comparators, or address the limitations highlighted in the company model. Without modelling the full range of subsequent lines of therapy, the ERG highlights that the appropriateness of the model structure remains uncertain.

Item 2: The approach to modelling subsequent ASMs following treatment discontinuation with cenobamate and its comparators does not reflect the range of treatment sequences seen in UK clinical practice.

Cycle length

The company used a 28-day cycle length in this model, which is lower than the cycle length used in previous cost-effectiveness models for FOS epilepsy identified in the company's review or NICE CG137(1). For example, CG137 and all three AWTTC submissions used a cycle length of 6 months. Clinical advisors to the ERG indicated that the cycle length used in the company model is too short to determine subsequent events in the model, such as treatment discontinuation, as assessment time point of 28 days is too short. The advisors indicated that a more appropriate assessment time point would be 6 to 12 months.

The company provided an additional scenario where, after the trial C017 end point, the cycle length was increased from 28 to 84 days (corresponding to cycle 5 in the model), and transition probabilities were informed by the C017 OLE trial instead of C017 trial alone. This scenario increased the incremental costs of cenobamate relative to the comparators from between [redacted] and [redacted] to between [redacted] and [redacted], and decreased the incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166, however, this change in cost-effectiveness results is likely to

reflect the different transition probabilities used in this scenario, rather than the change in cycle length alone.

The ERG considers the optimal cycle length in FOS epilepsy to be uncertain, but believes that 28 days is too short to appropriately assess treatment response in clinical practice. For this reason, the ERG used the scenario with the longer cycle length after cycle 5 (and transition probabilities informed by trial C017 OLE) in their base case.

Item 3: The model cycle length may be too short to appropriately assess treatment response in clinical practice and capture a meaningful change in resource use and HRQoL from subsequent events.

4.2.3 Population

The population in the decision problem is adults with uncontrolled focal onset seizures with or without secondary generalization in epilepsy, who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products. In the company's model, the population corresponds to the characteristics of the patient population in trial C017 in terms of age and sex. At model entry (that is, at the start of third line treatment with cenobamate), patients were assumed to be 39.8 years old and 50.6% of the sample was male. Further characteristics of patients in C017 trial are shown in Table 10 of the CS.

A key difference between the population in trial C017 and the modelled population is the baseline number of seizures. In the trial, patients had between 8.4 and 11 seizures per 28 days (with the average varying between trial arms), whereas in the model, the average number of baseline seizures is assumed to be [redacted] (Table 10 in document B of the CS), based on clinical opinion.

4.2.3.1 Points for critique

The ERG considers the modelled population age and sex to be broadly appropriate for an average UK population. However, the number of seizures at baseline is likely to be an overestimate of the numbers expected to be seen in UK practice. In trials C017 and C013, patients had 8.4 to 11 and 5.5 to 7.5 seizures per 28 days, respectively. Clinical advisors to the ERG highlighted that the baseline number of seizures in trials is likely to be greater than the general population treated with cenobamate because clinical trials tend to recruit patients with a greater number of seizures to ensure a seizure reduction can be detected within the trial follow up period. Indeed, in trials C017 and C013, having less than 8 and 3 seizures, respectively, in the 8-week baseline period was one of the exclusion criteria. In the model, the average number of seizures is assumed to be [redacted] based on clinical opinion. The ERG considers this number to be an overestimate of the baseline number of seizures.

The number of seizures at baseline is a key parameter in the model, because the number of seizures determines the impact of response to treatment on downstream healthcare costs. For example, increasing the baseline seizure rate means that a 50% reduction in the rate of seizures will lead to a greater reduction in the absolute number of seizures, and consequently lower cost of treating seizure-related accidents. Therefore, overestimating the number of seizures at baseline leads to an overestimation of the cost savings associated with treatment with cenobamate.

In their response to clarifications (question B26d), the company clarified that the number of seizures in the model was informed by clinical opinion because data on seizure type and frequency in trial C017 was incomplete, and because trial C017 had a cohort of patients from a variety of countries. The ERG believes that trial C017 is a more appropriate source of data, as the reported baseline number of seizures was considered to be sufficiently complete when used to measure response to treatment in the trial. Table 47 in the company's response to clarification questions suggests that all patients reported at least one type of seizure (as the number of patients who reported the number of seizures in each trial arm was the same as the number of patients in that arm).

In their clarification points (question B26c), the company provided alternative scenarios where the baseline number of seizures was informed by study C017 and C013, separately. The company used the baseline number of seizures in cenobamate 200mg and 400mg arms only, reported in Tables 46 and 47 in the company's response to clarification questions. The ERG believes that exclusion of other trial arms was inappropriate given that the baseline seizure rates were measured pre-treatment. In the ERG base-case, the baseline number of seizures was estimated using a weighted average from both arms in trial C013. Trial C013 was used by the ERG because the trial participants were less likely to be excluded on the basis of seizure frequency (trial C017 had a stricter exclusion threshold of 8 seizures per 28 days, compared to 3 seizures per 28 days in C013), and so it is considered to be more representative of patients eligible for treatment with cenobamate in the UK. The ERG also included an analysis exploring the effect of the baseline number of seizures on incremental cost of cenobamate.

In their response to clarification questions, the company did not provide the additional scenarios (as described above) in their updated model, and so the ERG could not validate their methods or results for deriving the baseline number of seizures from trial data. More specifically, the number of seizures used for these scenarios was unclear. The company indicated that not all patients reported the number seizures for each type of seizure, and that, where patients did not report the number of seizures, they assumed that data was missing at random (MAR). However, this is contrary to the C017 trial analysis where only non-missing seizure data were included to estimate treatment response, assuming that patients who did not report the number of seizures for a particular type of seizure did not experience any.

Inclusion of only non-missing seizure data – the assumption made when deriving response rates in trial C017 - leads to the number of seizures shown in Table 25 (for details on how values were derived see Appendix 1). The ERG used these numbers in their base case (trial C013).

Table 25. Number of seizures derived assuming all seizures were reported.

	Focal Aware	Focal Impaired Awareness	Focal to Bilateral Tonic Clonic	Total (derived)	Total number of seizures in C017
C017, Placebo (N=108)	2.2	6.7	1.0	9.9	[redacted]
C017, Cenobamate 100 mg (N=108)	1.3	7.0	1.0	9.4	[redacted]
C017, Cenobamate 200 mg (N=110)	2.8	7.1	1.0	10.8	[redacted]
C017, Cenobamate 400 mg (N=111)	2.4	7.2	0.8	10.4	[redacted]
C013, Placebo (N=113)	1.4	5.2	1.2	7.8	[redacted]
C013, Cenobamate 200 mg (N=109)	0.8	4.5	0.7	6.1	[redacted]

The ERG considers that both trials C013 and C017 are likely to overestimate the number of seizures typical of the relevant UK patient population because both excluded patients on the basis of low seizure frequency. For example, a prospective audit for new ASMs in focal epilepsy reported that the median number of seizures at baseline, before starting treatment with lacosamide was 4, although the number of seizures ranged between 1 and 300. Therefore, the ERG explored the effect of varying the number of seizures on the cost-effectiveness of cenobamate – details are provided in section 6.

Item 4: The baseline number of seizures of [redacted] may represent an overestimate of the average number of seizures in UK patients eligible for cenobamate and its comparators.

4.2.4 Interventions and comparators

The intervention is 3rd-line adjunctive treatment with cenobamate, as per the decision problem. Treatment with cenobamate involves a ≥12-week titration period, followed by maintenance treatment with 200mg or 400mg dose. The comparators are 3rd generation ASMs recommended for adjunctive treatment of FOS by NICE: perampanel, brivaracetam, lacosamide and eslicarbazepine acetate. As discussed in section 4.2.2, after discontinuation of cenobamate or its comparators, patients were assumed to switch to subsequent pharmacotherapy with ASMs, which is modelled as a fixed state with constant effectiveness, independent of previous line of treatment.

4.2.4.1 Points for critique

The comparators included in the company submission are brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel. However, Figure 5 (document B) of the CS shows phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin and zonisamide as alternative 3rd line treatment options based on NICE CG137 (1). Clinical advisors to the ERG indicated that treatment of epilepsy in the UK varies widely, and choice of ASM tends to be tailored to individual patients, based on their characteristics, response to previous treatment, and adverse events. Our clinical advisors suggested that some treatment options listed in Figure 5 would not often be considered as 3rd line treatment options (including phenobarbital, phenytoin, pregabalin and vigabatrin), but added that clobazam, zonisamide and topiramate would be relevant comparators.

In their response to clarification questions (question A2), the company argued that clobazam, zonisamide and topiramate were not relevant comparators because they are 2nd generation ASMs. However, the ERG considered these three 2nd generation ASMs to be used as part of 3rd line adjunctive treatment of FOS in UK clinical practice, and therefore are relevant comparators. The ERG discusses the implications of including the three additional comparators in section 6.1.2.

Item 5: All relevant comparators may not be appropriately included in the company submission for 3rd line adjunctive treatment of FOS because 2nd generation ASMs (namely, clobazam, zonisamide and topiramate) were excluded as relevant comparators.

4.2.5 Perspective, time horizon and discounting

In the company's base case analysis, the model adopts an NHS and Personal Social Services perspective. Outcomes included direct health effects to both patients and carers. The model discounts costs and outcomes at 3.5%, in line with the NICE reference case, and adopts a lifetime time horizon. Sensitivity analyses were conducted to exclude carers' disutility, and to adopt a societal perspective, including the cost of productivity loss due to epilepsy. The company did not make a case for lower discount rates to be applied, but they used a lower discount rate (0%) in a scenario analysis.

4.2.5.1 Points for critique

The ERG considers the company's approach to the time horizon and discounting to be appropriate and in line with the NICE reference case. No discounting used in scenario analysis is not in line with the NICE reference case, and justification for its use was not provided. This scenario is therefore not considered further.

The perspective in the base case (NHS and Personal Social Services) is broadly appropriate but it is unclear whether carers' disutility should be included. The NICE reference case (section 5.1.7) states that "the perspective on outcomes should be all direct health effects, whether for patients or other

people". The company made the case that patients with epilepsy often need support from carers (page 24, document B of the CS), and that carers' HRQoL is correlated with patients' HRQoL. Clinical advisors to the ERG indicated that caring for patients with epilepsy can indeed impact on carers' HRQoL. The ERG recognises the potential need to reflect carers' HRQoL in the analysis but evidence provided by the company does not support its inclusion. Methods for estimating and including carers' disutility in the model are further critiqued in section 4.2.10. The ERG also notes that previous evaluations of treatment for FOS (1) did not include carers' disutility in the analysis.

Section 5.1.7 in the NICE reference case states that 'the perspective adopted on costs should be that of the NHS and personal and social services. The scenario analysis reporting the cost-effectiveness of cenobamate from a societal perspective is not in line with the NICE reference case, and therefore, is not considered further.

4.2.6 Treatment effectiveness and extrapolation

This section considers the following aspects of treatment effectiveness: (i) effectiveness of cenobamate, (ii) effectiveness of comparators, (iii) treatment discontinuation, and (iv) effectiveness of subsequent lines of treatment.

4.2.6.1 Effectiveness of cenobamate

In the model, the treatment effect of cenobamate is reflected in the probabilities of moving between response states in the model (described in section 4.2.2). In the first five model cycles, transition probabilities were derived from the C017 trial directly, specifically the pooled effect of 200mg and 400mg dose arms. The proportion of patients with different levels of response in the cenobamate and placebo arms at the end of the maintenance period of trial C017 is shown in Table 26.

Table 26. Distribution of patients across response levels at the end of model cycle 5.

Treatment	No response (<50% reduction)	≥50% seizure reduction	≥75% seizure reduction	≥90% seizure reduction	Seizure-freedom (100% seizure reduction)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cenobamate 200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cenobamate 400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In the model, the transition probabilities were derived by tracking patients' level of response at approximately 28-day intervals. Patients who did not complete the trial were excluded from the calculations, assuming that trial drop-out was independent of treatment response. Model cycles 1-2 correspond to treatment titration, while cycles 3-5 correspond to maintenance treatment, as observed in trial C017. Following points for clarification (question B4), the company explained that transition

probabilities in the first two model cycles were derived from the first 28 days of treatment in C017, assuming that the rate of transition is half of that observed in the trial, in order to reflect a longer titration period expected in practice. The distribution of patients across response levels at the end of model cycle 5, conditional on being alive and not discontinuing treatment, is shown in Table 27. After 20 weeks (starting in model cycle 6), transition probabilities are assumed to remain constant and equal to the mean transition probabilities observed in the maintenance phase of trial C017, derived by averaging transition probabilities in cycles 3-5 (shown in Table 28).

Table 27. Distribution of patients across response levels at the end of model cycle 5.

Treatment	No response (<50% reduction)	Moderate response (≥50% to <75% reduction)	High response (≥75% to <90% reduction)	Very high response (≥90% to <100% reduction)	Seizure-freedom (100% reduction)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 28. Transition probabilities in model cycles 6 to 240 for cenobamate.

To → / From ↓	No response (<50% reduction)	Responder Rate ≥50% and <75%	Responder Rate ≥75% and <90%	Responder Rate ≥90% and <100%	Seizure-freedom (100% reduction)
No response (<50% reduction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder Rate ≥50% and <75%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder Rate ≥75% and <90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responder Rate ≥90% and <100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seizure-freedom (100% reduction)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company provided an additional scenario where transition probabilities after cycle 5 were informed using trial C017 OLE results. This scenario did not significantly impact the cost-effectiveness results – it changed incremental costs for cenobamate relative to the comparators from between [redacted] and [redacted] to between [redacted] and [redacted] and incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166.

Points for critique

The ERG has concerns regarding five elements pertaining to effectiveness of cenobamate used in the company's model: (i) the methods used for deriving transition probabilities, (ii) the evidence used to inform the transition probabilities, (iii) the duration of the titration phase in the model, (iv) the dose of

cenobamate used in the model, and (v) the extrapolation of treatment effect over the lifetime time horizon of the model.

Methods for deriving transition probabilities

Following request for clarification (question B4), the company highlighted a typographical error in the numbers used to derive transition probabilities and provided a model with corrected numbers. The error did not significantly impact the model results – incremental costs for cenobamate relative to the comparators decreased from between [redacted] and [redacted] to between [redacted] and [redacted], and incremental QALYs decreased from between -0.718 and -0.948 to between -0.715 and -0.946. The ERG used the corrected figures in the ERG base case.

Evidence informing transition probabilities

Effectiveness of cenobamate was estimated from trial C017 only, results from trial C013 were excluded from the analysis. In the CS (section B2.2.1), the company stated that trial C013 was excluded from the economic analysis because it had a shorter maintenance period than trial C017, lasting only 6 weeks compared to 12 weeks in trial C017. The ERG highlights that trial C013 could have been used to estimate transition probabilities during titration and the first 6 weeks of maintenance treatment. Trial C013 results suggest that response to cenobamate treatment is lower than that reported in C017, and so its exclusion from the estimation of transition probabilities may overestimate treatment response for cenobamate, and consequently overestimate the QALY gain and underestimate the resource use in the cost-effectiveness model.

Furthermore, transition probabilities derived from C017 directly do not account for the placebo effect. The probability of response (≥50% seizure reduction) after 12 weeks of taking 200mg and 400mg maintenance dose in the trial was 56.1% and 64.2%, respectively, while in placebo arm the probability was 25.5% (Figure 6, document B of the CS). In their response to clarification questions (question B10), the company argued that the placebo effect in the trial was caused by background therapy, and that adjustment for the placebo effect would have underestimated the effect of adjunctive treatment of cenobamate. The ERG highlights that the placebo effect in C017 could be caused by factors other than background therapy. Cenobamate is added in adjunction to ongoing therapy when response to this background treatment is suboptimal. At the start of trial C017, patients' response to background therapy, and therefore their rate of seizures, may be stable and captured in the baseline number of seizures. Clinical advisors to the ERG confirmed that the placebo effect in the trial can be caused by a range of factors other than background therapy, including regression to the mean, where a minimum number of seizures in the trial inclusion criteria means that patients may enter the trial during a seizure cluster (higher than usual rate of seizures). After baseline observations, patients' condition can improve spontaneously, reducing the number of seizures and creating the placebo effect. Failing to

account for the placebo effect may overestimate response to cenobamate, and consequently overestimate the QALY gain and underestimate the resource use in the cost-effectiveness model.

In addition, the ERG wishes to highlight that the response to treatment for the comparators was derived by applying the relative effect from the NMA to the response for cenobamate. Therefore, overestimating response to cenobamate, by failing to include trial C013 or to adjust for placebo, may also overestimate its response relative to the comparators. The effect on incremental QALYs and resource use in the cost-effectiveness model is unclear.

Item 6: Deriving transition probabilities directly from the observed data in trial C017 may overestimate response to treatment with cenobamate by failing to include all relevant evidence (specifically, trial C013), and to account for the placebo effect.

Duration of titration phase

The titration phase in the model is likely to be shorter than in clinical practice. Treatment titration in the model was assumed to last 8 weeks - slightly longer than the C017 protocol to reflect the expected titration rate in practice. In study C021 titration lasted between 10 and 12 weeks, according to the study protocol (12.5, 25, 50, 100, 150, and 200 mg per day doses increased at 2 weeks intervals, with additional 50mg increases allowed biweekly to reach 400mg dose) (58). It is possible that some patients were titrated up to 400mg per day dose over a longer period. Figure 6 in document B of the CS suggests that there is a dose-response relationship, where higher doses of treatment lead to better outcomes. Therefore, underestimating the length of the titration phase in the model could overestimate response to cenobamate until the maintenance dose is reached, thus overestimating the QALY gain and underestimating resource use in the model.

Item 7: Transition probabilities may not reflect the slower cenobamate dose titration that will be used in UK clinical practice.

Dose of cenobamate

The transition probabilities were derived from two arms of trial C017 - 200mg and 400mg per day dose. The resulting transition probabilities thus reflect those achieved when approximately 50% of patients takes each dose. Figure 6 in document B of the CS suggests that there is a dose-response relationship, where higher doses of treatment lead to better outcomes.

In their response to clarification (question B8), the company provided the distribution of doses in trials C017, C017 OLE and C021, to allow comparison of doses in the study used to derive transition probabilities (C017), and those likely to be administered in practice (C017 OLE and C021). The distribution of doses is summarised in Table 29. In C017 patients were more likely to receive a full 400mg dose ([redacted] in C017 compared to [redacted] and [redacted] in C021 and C017 OLE, respectively),

but less likely to receive more than 200mg ([redacted] in C017 compared to [redacted] to [redacted] in C021 and C017 OLE, respectively). Overall, the ERG is unable to judge whether the cenobamate dose in trial C017 is generalisable, and thus whether transition probabilities derived from C017 data are likely to over- or underestimate the effect of cenobamate. The ERG highlight that the estimated transition probabilities are uncertain, but unlikely to impact the model results. In the original submission, the company provided two additional scenarios where each trial arm was used to derive transition probabilities separately, and the scenarios did not impact on the overall conclusion of the analysis provided the relative effect of cenobamate to the comparators is the same.

Table 29. Percentage of patients taking different doses during maintenance period of three studies for cenobamate.

Study	Dose category							
	100 mg	150 mg	200 mg	250 mg	300 mg	350 mg	375 mg	400 mg
C017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C017 OLE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C021	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Extrapolation of treatment effect

In the CS, transition probabilities are assumed to remain constant after 20 weeks (starting in model cycle 6). The transition probabilities (shown in Table 29) result in an increasing response to treatment in those patients who are still alive and continue to receive cenobamate. To demonstrate, Table 30 shows the distribution of patients who are still alive and taking cenobamate across different levels of response, at different time points in the model. After cycle 17, the distribution of patients across the response states remains constant.

Table 30. Distribution of patients across response states, conditional on being in one of the response states.

Model cycle	0% to <50% reduction	50% to <75% reduction	75% to <90% reduction	90% to <100% reduction	100% reduction
5 (0.4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17 (1.3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The company provided an alternative scenario where transition probabilities in cycles 6 to 26 were informed using data from trial C017 OLE (for the duration of its follow-up), and in cycles 27 to 462 using the average probability of transition in cycles 6 to 26. In this scenario, the cycle length in cycles 6 to 462 was 84 days (instead of 28-days used in the company base case). In the additional scenario, the ERG identified an error, where some transition probabilities for comparators were not adjusted for the longer cycle length. Once the error was corrected, the additional scenario did not significantly impact the results. The distribution of patients across response states in this scenario is shown in Table 31. In this scenario, fewer patients had seizure freedom after 1.3 years, although the distribution of patients across the states varied between the cycles. The variation could be due to the granularity of the model and the length of model cycles, where a slight month-on-month variation in the number of seizures leads to high variation in patients' level of response.

Table 31. Distribution of patients across response states, conditional on being in one of the response states when transition probabilities are informed by study C017 OLE.

Model cycle	0% to <50% reduction	50% to <75% reduction	75% to <90% reduction	90% to <100% reduction	100% reduction
5 (0.4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 (0.6 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7 (0.8 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 (1.1 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9 (1.3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26 (6.4 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48 (10.3 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The method employed by the company differs to that used in previous FOS models. In NICE CG137 (1) , patients who responded to treatment (>50% or 100% seizure reduction) after the first model cycle (6 month) remained in the same response state, unless they had treatment failure. The probability of treatment failure was not drug-specific, and decreased over time (further details provided in 'Treatment discontinuation' section below). In a Markov model submitted to AWTTC (55), the probability or response to treatment (>50% seizure reduction) and seizure freedom were derived from an NMA and applied in the first six-month cycle. Response to treatment in subsequent cycles was assumed to be independent of treatment received and based on probabilities obtained from a published study of the cost-effectiveness of other ASMs (59). The probabilities of complete seizure freedom were applied in all subsequent cycles. In two additional submissions to AWTTC (56, 57) , it is not clear how the treatment effect was extrapolated.

The ERG considers that the assumption in the company base case, i.e. that patients will continue to improve (respond to treatment) over time, is highly uncertain. For this reason, the ERG's base case adopts the approach taken in NICE CG137 (1). In model cycle 6, patients discontinue treatment if they have no response. The model cycle length is changed to 3 months to reflect that one month of no response would not lead to treatment discontinuation. Thereafter, patients stay in the same response health state unless they have treatment failure. Treatment failure is informed by time to discontinuation in studies C017 OLE and C021, as discussed in further detail in section 'Time to discontinuation' below.

Item 8: Response to treatment over time for cenobamate is highly uncertain.

4.2.6.2 Effectiveness of comparators

The treatment effect for the comparators relative to cenobamate was derived from two independent NMAs of two measures of effectiveness: the odds of having partial response (≥50% reduction in seizures) and the odds of having a complete response (seizure freedom). The NMAs reported the odds ratio of each of the two levels of response in comparator treatments relative to cenobamate, results are presented in section 3.4. The NMA results were used to derive relative risks of response via the odds of response to cenobamate at the end of trial C017. The resulting distribution of patients across different levels of response in the model (cycle 5) is shown in Table 32. In the model, the relative risks were applied to transition probabilities for cenobamate throughout the analysis time horizon, by assuming that the relative effect of each drug would be sustained indefinitely.

Table 32. Distribution of patients across levels of response in model cycle 5, conditional on patients being alive and continuing treatment.

Level of response	<50%	50 to <75%	75 to <90%	90% to <100%	100%
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Relative effect of comparators is a key parameter in the economic model because an increase in treatment response increases subsequent QALYs, and decreases healthcare resource use and costs.

Points for critique

The ERG's critique considers four aspects of the methods used to derive the effect of comparators: (i) the evidence used to estimate the relative effect of comparators, (ii) the evidence included in the

NMA, (iii) the NMA model used to estimate the relative effect, and (iv) the implementation of the treatment effect in the cost-effectiveness model.

Evidence used to estimate the relative effect of comparators

The evidence used to estimate the relative effect of the comparators in the NMA does not include any direct comparisons with cenobamate, and so the estimates of relative effect are highly uncertain (the only indirect link is through the placebo arms of the trials). The clinical advisors to the ERG suggested that there are likely to be systematic differences between the studies included in the NMA. As discussed in section 3.1.1, the trial inclusion criteria, the shorter and more intense titration periods in trials (compared to the UK practice), and the relatively short follow ups limit the generalisability of the trial evidence. In addition, significant variation in the duration of titration, maintenance and treatment periods across the trials, limits the comparability of the trials and the validity of the ITC. The ERG cautions that there is considerable uncertainty in the derived estimates, and presents an analysis in section 6 with alternative estimates of relative effect for the comparators.

Item 9: The trial inclusion criteria, the shorter and more intense titration periods (compared to the UK practice), and the relatively short follow up limit the generalisability of the trials used to inform the effectiveness of comparators. Furthermore, the significant variation in the duration of titration, maintenance and treatment periods across the trials in the ITC, limits the comparability of the trials and the validity of the ITC. As result, there is considerable uncertainty in the estimate of the effectiveness of comparators relative to cenobamate derived from the NMA.

Evidence included in the NMA

The relative effect for the comparators was derived from the NMA that did not include trial C013. In their reply to points for clarification (question A3), the company provided results of a NMA with trial C013 included for four outcomes: ≥50% responder rate, seizure freedom, experiencing at least one TEAE and for discontinuation due to TEAE. However, the company argued that trial C013 should not be included in the NMA on the basis of (i) a shorter maintenance period than the C017 study, lasting only 6 weeks compared to 12 weeks in C017, (ii) exclusion of the 400mg dose from trial C013, and (iii) validity of the results. Table 1 in appendix D indicates that the length of follow up was not used as exclusion criteria in the systematic review of clinical effectiveness. The company response to points for clarification indicates that two comparator studies with a shorter follow up (4 weeks) were excluded, however, they were not excluded on the basis of their follow up, but because they were dose-escalation studies. Furthermore, page 67 of document B of the CS states that, while the length of time may affect seizure freedom, the clinicians advised the company that 'as much information should be included in the primary network given the limited availability of data overall'. On that basis, the ERG believes that trial C013 should not be excluded from the NMA in section B2.9 in the CS on the

basis of length of follow up. The NMA includes all licensed doses of comparators. The dose used in C013 is licensed, and so the ERG considers that, for consistency, C013 should not be excluded from the NMA on the basis of dose. Regarding validity of the results, the company argued that inclusion of trial C013 [redacted]*The company argued that this is implausible because, according to their clinical advisors, none of the comparators should lead to more than 10% seizure freedom. The company did not specify which analysis predicted seizure freedom in more than 10% of patients, and so the ERG is unable to comment on why it may occur. However, the ERG considers that a reduction in relative effectiveness of cenobamate is not a valid reason to exclude study C013.

The ERG considers C013 to be an important source of evidence for the effectiveness of cenobamate, despite its shorter follow up and lower dose than trial C017. For this reason, the ERG includes C013 in the NMA in their base case.

Item 10: Exclusion of trial C013 from the NMA fails to take account of all relevant evidence on the effectiveness of cenobamate and comparators.

Outcomes synthesised in the NMA

The NMA was performed on two measures of effectiveness only: partial and complete response (≥50% seizure reduction and seizure freedom). The results of the NMA did not fulfil the requirements of the cost-effectiveness model, where moderate (≥50 and <75%), high (≥75% and <90%) and very high (≥90% and <100%) response were modelled separately. As result, the odds ratio of moderate, high and very high response in the cost-effectiveness model was assumed to be identical to the odds ratio of ≥50% seizure reduction reported in the NMA. For each level of response, the odds ratio and the probability of response observed at the end of trial C017 were used to derive the relative risk of response that was applied in the model. The derived relative risks are shown in Table 33. The relative risk of response for the comparators depend on the baseline probability (and odds) of response to cenobamate. The probability of high and very high response to cenobamate is lower than the probability of moderate response, and so the treatment effect for the comparators relative to cenobamate decreases with the level of response, in favour of cenobamate (i.e. the relative risk decreases). The plausibility of this assumption is unclear. In points for clarification (question A11), the ERG requested an updated NMA model that included the relative effect on moderate, high, very high response and seizure freedom. However, the company did not update the model, due to the lack of evidence (availability of evidence for the ≥75% and ≥90% response rates is provided in Table 3, appendix B in clarifications).

Table 33. Risk ratio for response to comparators, relative to cenobamate.

Risk ratios relative to cenobamate (median)				
Comparator	Moderate response	High response	Very high response	Seizure freedom
Brivaracetam	0.565	0.546	0.522	0.320
Lacosamide	0.601	0.583	0.559	0.242
Eslicarbazepine acetate	0.594	0.576	0.551	0.211
Perampanel	0.545	0.527	0.501	0.243

The ERG emphasises that evidence of the relative effect of comparators on high and very high response is very sparse. The relative effects presented in Table 33 are underpinned by the assumption that the odds ratio is identical for the three levels of response. As discussed in section 4.2.2, the ERG recognises the potential benefit of modelling five different levels of response, but due to the lack of evidence that cenobamate increases the probability of a high or very high response relative to its comparators, the ERG used the aggregated version of the cost-effectiveness model in their base case. However, the ERG included an additional NMA model where moderate, high, very high response and seizure freedom are synthesised separately, where distribution of patients among different levels of response in comparators is informed by borrowing information from cenobamate studies C013 and C017.

Item 11: The NMA model does not synthesise all outcomes required in the cost-effectiveness model.

NMA model used to estimate the relative effect

As described above, the NMA was performed on two measures of effectiveness only: partial and complete response (≥50% seizure reduction and seizure freedom). The two outcomes were synthesised independently. The ERG considers the two outcomes to be correlated, as patients who experience seizure freedom also experience >50% reduction in seizures, as these belong to the same continuous outcome measure (proportion of patients achieving a certain *pre-defined* cut-off) that has now been categorised. According to NICE DSU TSD2 (47), correlation between outcomes should be reflected in evidence synthesis. Furthermore, patients who experience seizure freedom are included in both outcomes, potentially biasing the relative effect on ≥50% to <100% seizure reduction.

Furthermore, the NMA model in the company base case does not adjust for the placebo effect. Section 3.4 highlights that trials included in the NMA had a considerable placebo effect. The placebo effect can be caused by a range of factors, potentially reflecting heterogeneity between the trials. The placebo effect in the studies included in the NMA is negatively correlated with the relative effect, as

shown in Figure 10. Trials C013 and C017 had a higher than average placebo effect, and so failing to adjust for this, could bias the relative effect of comparators in favour of the comparators.

In order to address the issues outlines above, the ERG base case used an updated version of the NMA model to derive two levels of response: ≥50% to <100% seizure reduction and seizure freedom, where the two outcomes were correlated and the probability of response was adjusted for the placebo effect.

Item 12: The NMA fails to take into consideration the correlation between the two outcomes, and potentially double counts patients with seizure freedom.

Item 13: The NMA model does not adjust for the placebo effect, potentially biasing estimates of relative effect.

4.2.6.3 Effectiveness of subsequent treatment (ASMs, VNS and surgery)

After discontinuing treatment with cenobamate or its comparators, the model considers three treatment options: ASMs, VNS and surgery (see section 4.2.2 for details). The effectiveness of all three options was assumed to be independent of previous line of treatment.

All patients first received subsequent ASMs. The probability of response to subsequent ASMs was derived from Chen et al. (2018). Chen et al. (2018) measured response, defined as seizure-freedom in the preceding 12 months, to each line of ASMs in epilepsy, and found that the odds of treatment failure (no response) increased 1.73 times with each line of treatment with ASM. The company applied the odds ratio to the odds of no response observed in trial C017, where response was defined with <50% reduction in the rate of seizures. The distribution of patients across the different levels of response (moderate, high, very high response and seizure freedom) was assumed to be the same as in trial C017. As result, the distribution of patients after receiving ASM compared to cenobamate and other comparators at the end of cycle 5 is shown in Table 34.

VNS and surgery are offered to a small proportion of patients in the model. The proportion of suitable patients is informed by the company's clinical advisors, and estimated at 2.7% of patients on subsequent ASMs per year for VNS and 2% for surgery (or 0.21% and 0.15% per model cycle, respectively). Both VNS and surgery are assumed to carry a small mortality risk - 0.86% per model cycle for VNS and 0.97% for surgery. The subsequent response to treatment, and the mortality risk were derived from the literature. The response to subsequent treatment in the literature was reported in terms of >50% seizure reduction and seizure freedom, so distribution of patients across moderate, high and very high response was assumed to be the same as that in trial C017.

Table 34. Distribution of living patients across levels of response, for different treatment options. Distribution for subsequent ASMs, VNS and surgery assumed to be constant over time. Distribution for cenobamate and comparators represents that at the end of cycle 5 in the model.

Level of response	<50%	50 to <75%	75 to <90%	90% to <100%	100%
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent ASM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VNS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Points for critique

Relative effect of ASMs

The appropriateness of the study used to inform the relative effect of subsequent ASMs is uncertain. The study used to inform the reduction in response to subsequent treatments (Chen et al., 2018) was not conducted in FOS only but in all types of epilepsy. The odds ratio of 1.73 reported in the study represents the effect of subsequent treatment on treatment resistance, where treatment resistance is defined as seizure freedom for 12 months or longer. This outcome was not reported in C017, as the trial follow up was too short. Instead, in the model, the odds ratio was applied to the odds of having no response (<50% seizure reduction for 12 weeks). Trial C017 results (e.g. Figure 6 in document B of the CS) suggests that levels of response tend to differ between outcomes, and so extrapolating the relative effect of seizure-freedom after 12 months to partial response after 12 weeks is not appropriate. In the absence of an alternative source, the ERG's base case applied the odds ratio reported by Chen et al. (2018) to the probability of not achieving seizure freedom in trial C017 to derive response in subsequent ASMs, but consider the odds ratio estimate to be highly uncertain due to the disparity in the length of follow up between Chen et al. (2018) and trial C017.

Furthermore, the 1.73 odds ratio reported by Chen et al. (2018) was applied to the probability of no response in trial C017. The relative effect estimated by Chen et al. (2018) was lower than that of the comparators, indicating that the effectiveness of subsequent ASMs ($\geq 4^{th}$ line treatment) is greater in the model than the effectiveness of the comparators. Specifically, the odds of no response was 1.73 in subsequent ASMs (Chen et al., 2018), compared to 1.85 to 2.07 for partial response and 3.54 to 5.46 for seizure freedom for the comparators, reported in the company NMA (Figures 34 and 36 in document B of the CS), assuming that OR of no response = 1/OR of response. The effect is apparent in Table 34, where response to treatment with subsequent ASMs is greater than with comparators. The

ERG considers this to be implausible, as subsequent ASMs are assumed to be a combination of the comparators in the model, and their effectiveness is expected to be lower than that of comparators, as drug resistance is expected to be higher with each subsequent line of treatment (Chen et al., 2018). In their response to points for clarification (question B12), the company provided four alternative scenarios where effectiveness of subsequent ASMs is derived relative to the comparators, rather than cenobamate, to ensure that they are less effective than the comparators. The ERG considers this to be the preferred approach to model response to ASMs, and in their base case, the effectiveness of subsequent ASMs is derived relative to the least effective comparator – brivaracetam.

Item 14: Deriving the response to subsequent ASMs relative to cenobamate is likely to overestimate the effectiveness for subsequent ASMs.

Item 15: Applying the odds ratio of treatment resistance to the odds of no response likely to bias the response rates for subsequent ASMs.

Item 16: The clinical effectiveness of subsequent ASMs is highly uncertain.

The effect of VNS and surgery

The model assumes that surgery and VNS would not be offered before 4th line ASMs. This may not be the case, as some patients in C017 had had VNS before cenobamate (12). However, the proportion of patients who undergo VNS and surgery before 3rd line treatment with ASMs is likely to be very small, and so unlikely to impact the model results.

The frequency and outcomes of VNS and surgery are uncertain. The probability of undergoing VNS or surgery is based on clinical opinion, while their outcomes are derived from non-comparative studies. According to the ERG clinical advisors, the proportion of patients who would undergo VNS and surgery would be very small and comparable for all comparators. The ERG highlights uncertainty in the estimates of the probability and outcomes of VNS and surgery, but highlight that the direction of effect is generally plausible and identical for all comparators, and therefore it is unlikely to have a substantial effect on model results.

4.2.6.4 Treatment discontinuation

In the cost-effectiveness model, the probability of transitioning from the 'treatment response' health states to the 'subsequent ASM treatment' health state is time dependent, and applied to all response states, assuming the probability is the same for all patients independent of their level of response. Probability of treatment discontinuation is derived from treatment-specific time to discontinuation data.

For cenobamate, time to discontinuation was obtained by combining Kaplan Meier (KM) curves derived from studies C017 and its OLE, and C021 (shown in Figure 46 of CS), and fitting parametric survival curves to them. Study C017 OLE is a long term (>5 year follow up) study of the safety and efficacy of adjunctive cenobamate treatment (n=355). Study C021 is a phase 3, open-label study, designed primarily to assess the long-term safety of adjunctive cenobamate with baseline ASM regime (n=1,347); its follow up to date is less than 3 years. Overall, the discontinuation rate was higher in C017 OLE. The company argues that the difference in discontinuation is caused by the slower treatment titration, and therefore fewer adverse events, in C021. Following points for clarification (question B19), the company provided two alternative scenarios where each study is used to inform treatment discontinuation independently. The alternative scenarios did not significantly impact the cost-effectiveness model results - the incremental costs for cenobamate relative to the comparators ranged between [redacted] and [redacted] with C021 data only and between [redacted] and [redacted] and with C017 OLE data only, while QALYs ranged between -0.752 and -1.011, and between -0.684 and -0.881, respectively.

For the comparators, time to discontinuation was derived from drug-specific single-arm studies that report time to treatment discontinuation. The studies are listed in Table 38 of the CS. In their response to points for clarifications, the company explained that time to discontinuation was derived by: (1) extracting the probability of discontinuation at a particular time point (it is not clear how the time point was chosen), (2) using the goal seek function in Excel to derive the hazard ratio (relative to cenobamate) required to attain the probability of discontinuation at that particular time point, and (3) applying the derived hazard ratio to the time to discontinuation model for cenobamate. The derived hazard ratios are reported in Table 39 in document B of the CS, and imply that the probability of treatment discontinuation is lower in cenobamate than the comparators. The proportion of patients remaining on treatment in the first five model cycles is shown in Table 35. Treatment discontinuation is a key parameter in the economic model. Lower treatment effectiveness leads to earlier treatment discontinuation, decreasing QALYs and increasing costs of cenobamate and comparators.

Table 35. Probability of treatment retention in model cycles 1 to 5.

Model cycle	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Points for critique

Methods to derive time to discontinuation of cenobamate

The company's approach to fitting parametric survival curves to the KM data is considered broadly appropriate. However, the ERG is not certain whether data from C017 OLE and C021 should be combined to derive a single parametric curve, as the two study populations may be very different. The ERG notes that when comparing the hazards of discontinuation over time for these two studies, these do not converge, suggesting that detected differences are not purely due to titration at the start of the model. However, populating the model with data from each study separately had little impact on the cost-effectiveness results, and so the ERG do not consider this to be a critical issue.

Methods to derive time to discontinuation of comparators

The ERG has concerns regarding the methods used to identify literature used to inform time to discontinuation for the comparators, the methods used to extrapolate treatment discontinuation in the cost-effectiveness model, and the use of naïve comparisons to inform treatment discontinuation of the comparators.

In the CS, the company did not specify how they identified studies to inform the treatment-specific discontinuation rates in Table 38, page 109. Following points for clarification (question B20), the company clarified that the studies were identified using targeted searches, although did not provide a search strategy. The ERG believes that the searches may have excluded relevant studies, such as the study by Novy et al. (60), recommended by the clinical advisors to the ERG.

The ERG has concerns regarding the methods employed to derive the probability of discontinuation for the comparators. It is not clear why the company did not fit parametric survival models directly to digitised curves reported in the literature (Table 38 in document B of the CS), instead of deriving estimated hazard ratios by applying the discontinuation rate at a single time point to the cenobamate

survival function.

Figure 11 below shows the treatment retention rate reported in the studies in Table 38 (document B of the CS) and the rate used in the cost-effectiveness model. On visual inspection of

Figure 11, the retention rate used in the model appears to be a very poor fit to the data used to inform it.

Figure 11 Retention to treatment in the model and in the literature.

The ERG has concerns regarding the use of naïve comparisons to inform time to discontinuation of comparators relative to cenobamate. The naïve comparisons have no common comparator between studies, and so fail to take account of heterogeneity between studies that can confound outcomes, potentially biasing the estimate of relative effect (in this case, time to discontinuation of comparators relative to cenobamate). In points for clarification (question B21), the ERG requested an additional scenario where the time to discontinuation of comparators is derived from the time to discontinuation of cenobamate and the odds ratio of discontinuation estimated in the NMA in section 3.4. The company provided the additional scenario - the relative risk of discontinuation is shown in Table 36, suggesting that, contrary to their base case, the probability of discontinuation is higher for cenobamate relative to the comparators. The company argues that the use of NMA is not appropriate, as it includes discontinuation in studies C013 and C017, where more rapid titration may lead to higher discontinuation than is expected in practice.

Table 36. 'All-cause' discontinuation ORs relative to cenobamate (random effects).

Comparator versus cenobamate	Odds ratios, median (95% credible interval)
Perampanel	[redacted]
Eslicarbazepine acetate	[redacted]
Lacosamide	[redacted]
Brivaracetam	[redacted]
Placebo	[redacted]

In the absence of other comparative evidence, the ERG used the ORs from the NMA to inform the probability of discontinuation in their base case. The estimates from the NMA imply that discontinuation rate with cenobamate is higher than with comparators. This is consistent with the findings that cenobamate is more likely to leads to ADRs – one of the key reasons for discontinuation when first starting treatment with a new ASM. However, the ERG recognises that the resulting estimates may underestimate the probability of treatment discontinuation with comparators, and so explore alternative scenarios where their discontinuation rate is the same as cenobamate's after a fixed number of cycles.

Item 17: The method employed to estimate the probability of treatment discontinuation for the comparators relative to cenobamate is likely to overestimate discontinuation rates.

4.2.7 Deriving the number of seizures

In the cost-effectiveness model, the proportion of patients in each health state was used to derive the expected number of seizures in each model cycle. The number of seizures was used to estimate the cost of managing seizures and treating accidents caused by seizures, described in further detail in section 4.2.11. The number of seizures was based on point estimates of the baseline number of seizures informed by clinical opinion, and the average percentage reduction in seizures in each response category observed in trial C017 (both presented in Table 30, document B of the CS). The number of seizures estimated in each state is shown in Table 37.

Table 37. The number of seizures in each Markov state per 28-day cycle.

	Total number of seizures
No response - pre-treatment	[redacted]
No response	[redacted]
Moderate response	[redacted]
High response	[redacted]
Very high response	[redacted]
Complete response	[redacted]

Subsequent ASM treatment	[redacted]
Post-surgery	[redacted]
Post-VNS	[redacted]

Following points for clarification, the company provided an alternative model structure, where moderate, high and very high response health states were aggregated – see section 4.2.2 for details. In the new model, the number of seizures was derived by assuming that patients with focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizures on average have a [redacted], [redacted], [redacted] seizure reduction on average, resulting in [redacted] seizures per 28 days, on average, in patients who have ≥50% to <100% reduction in seizure frequency. In their response to clarification points, the company did not state how the seizure reduction in the aggregated state was informed.

4.2.7.1 Points for critique

The ERG believes there is uncertainty in the estimated number of seizures per health state. The number of seizures is based on clinical opinion, while seizure reduction for each level of response is derived from the results of one clinical trial (C017). In the trial, the number of seizures in patients with no response was, on average, higher than before starting treatment (in Table 37 the number of seizures increases with no response), suggesting the symptoms worsen after starting treatment. However, the increase could be due to random variation between the two time points, highlighting the uncertainty in the estimates.

The company did not propagate uncertainty in the estimated number of seizures per health state in the model. In points for clarification (question B25), the ERG requested estimates of uncertainty in the state-specific number of seizures. In response, the company provided the median, and upper and lower quartile for the number of seizures observed in trial C017 (Table 44, question B26), at different levels of response. However, the data could not be used to derive the change in seizure frequency in the model.

The ERG base case used an alternative number of seizures at baseline (derived from trial C013, as discussed in section 4.2.3) and highlights uncertainty in the percentage reduction in the number of seizures per level of response. A change in the number of seizures per level of response would not alter the ranking of cenobamate and its comparators because an increase in response decreases resource use, while QALYs are unaffected by the number of seizures. Thus, the higher the response to treatment, the higher the reduction in resource use will be observed. However, the magnitude of the incremental healthcare resource use (and consequently costs) may be overestimated if the percentage reduction in seizure frequency is overestimated, and vice versa.

4.2.8 Mortality

In the model, patients experience an increased risk of mortality compared to the general population, due to their condition. Mortality in the model is based on age and gender specific mortality in the UK population (61), and hazard ratios (attributed to greater risk of death) reported by Trinka *et al*. (62). Patients with seizure freedom are at lower risk of death than patients who do not achieve seizure freedom, regardless of their level of response (HR = 1.6 in seizure freedom, HR = 2.4 in no, moderate, high and very high response). In 'subsequent ASMs', 'post-VNS' and 'post-surgery' states, hazard ratios were derived by weighting the hazard ratios above by the probability of having seizure freedom in those response states. The resulting state-specific HRs are presented in Table 40 in document B of the CS, and in Table 38 below.

Table 38. Mortality hazard ratios, per health state.

Health state	**HR**
No response (<50% reduction)	2.40
Moderate response (≥50% and <75%)	2.40
High response (≥75% and <90%)	2.40
Very high response (≥90% and <100%)	2.40
Seizure-freedom (100% reduction)	1.60
VNS	2.40
Post-VNS	2.27
Surgery	2.40
Post-surgery	1.82
Subsequent ASM Treatment	2.30

Points for critique

The ERG is satisfied that patients with epilepsy are likely to have higher risk of mortality than the general population. However, the model assumes that the excess mortality risk is the same for all patients with seizures, regardless of their level of response. The ERG considers the excess mortality in response states to be uncertain, but unlikely to impact the model results.

4.2.9 Adverse drug reactions

For cenobamate, the cost-effectiveness analysis accounted for all Treatment-Emergent Adverse Events (TEAEs) occurring in ≥ 5% of the C021 cohort during the titration period, or the C017 cohort during the maintenance period. The included ADRs and their incidence are reported in Table 31 in document B of the CS. For comparators, the adverse event profile is assumed to be comparable to

cenobamate. The probability of adverse events was derived from the probability of adverse events with cenobamate, and the relative probability of adverse events with comparators relative to cenobamate, derived from the NMA in section 3.4. Disutility and cost of ADRs were applied in all model cycles assuming they will last indefinitely.

4.2.9.1 Points for critique

The ERG broadly agrees with the methods for accounting for adverse drug reactions in the cost-effectiveness model. The ERG notes that the decision to exclude ADRs with <5% prevalence is arbitrary but unlikely to impact the model results. Furthermore, it is possible that ADRs may resolve over time – this is not reflected in the model as prevalence of ADRs is assumed to be constant. However, the impact of ADRs is not explored in further detail because it is expected to have minimal impact on the cost-effectiveness results, particularly when future costs and outcomes are discounted.

4.2.10 Health related quality of life

4.2.10.1 HRQoL data from clinical trials

The CS presents data on HRQoL measured in the C017 study via the disease-specific Quality of Life in Epilepsy (QOLIE-31-P) instrument. QOLIE-31-P measurements were performed in English-speaking patients only following screening at initiation of treatment and again either at maintenance phase completion or early termination. Improvements in terms of change from baseline were observed only in the placebo (mean(Δ)=[redacted], SD(Δ)=[redacted]) and cenobamate 200 mg (mean(Δ)=[redacted], SD(Δ)=[redacted]) arms, though the statistical significance of these gains was not tested. Placebo patients saw the greatest proportion of patients achieving a minimally important change (MIC) of 11.8 in QOLIE-31-P score as established in Wiebe et al (63). The company considered the period of assessment in C017 to be too short to demonstrate a meaningful benefit in HRQoL, as measured by QOLIE-31-P, and chose not to utilise this evidence to inform the economic model.

In the response to clarification questions, the company provided statistical test results for the number of patients achieving ≥11.8 and ≥5.19 MIC points between placebo and the cenobamate arms in the C017 trial. The results were not statistically significant. Statistical tests were also performed for the change from baseline in QOLIE-31-P scores compared to placebo. The results were also not statistically significant, except for the 400mg/day arm. This statistically significant result for this trial arm versus placebo was justified by the small number of individuals in the subsample and the skewed distribution of participants in terms of their response to treatment.

4.2.10.2 Points for critique

The company highlights that study C017 measured HRQoL via the disease specific QOLIE-31-P instrument and not a generic instrument such as EQ-5D. It was not clear to the ERG whether relevant HRQoL data were collected in C013 or within the ongoing studies of C017 OLE, C013 OLE or C021.

The ERG is satisfied with the approach used for the statistical analysis undertaken by the company indicating that no statistical differences exist between cenobamate and placebo, for the MIC thresholds used. However, the ERG wishes to highlight that there is evidence in the literature to suggest that the QOLIE-31 tool is sensitive to measuring a seizure frequency reduction over 14 weeks' follow-up (64, 65).

4.2.10.3 Mapping

The company indicates that due to the absence of studies with utility data for cenobamate, a mapping study was performed. The company highlights the shortcomings of the EQ-5D instrument in adequately depicting changes in HRQoL in patients with epilepsy as their seizure frequency changes over time. This is mainly down to the fact that EQ-5D reflects the health of patients on a particular day, not being able to reflect the variations of HRQoL over time. Thus, the EQ-5D tool is not considered in the mapping study implemented by the company. The SF-36 and its derivation SF-6D, however, considers the patients' HRQoL over time, and thus, was deemed by the company to be more suitable to reflect HRQoL in patients with drug-resistant epilepsy, as it accounts for the variability in health over time.

The company followed the MAPS (MApping onto Preference-based measures reporting Standards) checklist. The mapping study involved designing a survey, which included the SF-36 and the QOLIE-31-P questionnaires, applying it to individuals with FOS across 5 countries (including the UK) recruited for this purpose, statistically analysing the data collected and performing the mapping analyses.

Socio-demographic characteristics of the [redacted] individuals ([redacted]) from the UK) with FOS included in the final analysis set can be found in Table 1 of Appendix H of the CS. Inclusion of participants with less severe focal epilepsy relative to those included in the cenobamate clinical trials, was deliberate, so that improvements in HRQoL of people with FOS following treatment are picked up in the mapping.

Survey results indicated that participants had, on average, poor HRQoL. A moderate to strong correlation between values obtained from SF-6D and QOLIE-31-P was found. Survey data identified that the HRQoL was statistically significantly lower for participants that reported experiencing the most severe type of focal seizure, compared to those that did not. Similarly, survey data identified that the HRQoL was statistically significantly higher as the number of days being seizure free increased.

Covariates included in the mapping algorithm were subject to a selection process. The selection process was purely statistical and anchored on assessing the statistical significance of covariates and their impact on the overall model goodness of fit via AIC and BIC values. Seizure frequency, seizure

freedom, seizure severity and age were selected as the observed covariates that best performed in explaining variability in SF-6D utility index scores. Different model estimation methods were tested and selected on how good they fitted the data, based on statistical indicators (e.g. RMSE). The OLS model provided the best fitting algorithm. Validation methods indicated that all models tested provided a good fit and that the chosen model – the OLS - demonstrated no or low multicollinearity.

The mapping algorithm indicated that increases in seizure frequency and experiencing the more severe type of seizures results in a decrease in SF-6D predicted utilities while increases in the number of days with seizure freedom and age corresponded to an increase in SF-6D predicted utilities. Observed and predicted SF-6D utility scores for the survey participants were compared (Table 43 in document B of the CS), which showed identical mean scores but with predictions at half of its true variability, denoted by a narrower range (maximum - minimum) of values ([redacted] vs [redacted], for observed and predicted, respectively). The company notes that the mapping algorithm underestimates the range of predicted utilities in the relevant population. Furthermore, that the mapping algorithm overestimates HRQoL for epilepsy patients in a worst health state given that the SF-6D is bounded at the lower level of 0.29.

In the response to clarification questions the company clarified that the baseline characteristics of the English-speaking subsample of the HRQoL survey are aligned with the UK's anticipated licensed population and that a UK tariff was used to value the SF-6D utility scores to which disease characteristics were mapped. The company complied with the ERG request of adjusting the variance of mapped utility estimates to account for the proportion of total variation explained by the mapping algorithm (66).

The ERG requested in points for clarification, a mapping of QOLIE-31-P scores from the C017 study onto EQ-5D utility. However, the company did not provide this mapping because of the limitations of the QOLIE-31-P data, as discussed above, and the company highlighted that it has been acknowledged in the literature that the QOLIE-31-P does not map well to EQ-5D (67).

4.2.10.4 Points for Critique

The ERG has several concerns regarding the mapping study presented in the CS. First, it is not clear why there was a preference for a mapping study through a survey and the SF-6D tool over and above performing a mapping exercise of QOLIE-31-P scores from the pivotal C017 study, or any other relevant study with QOLIE-31-P data, to EQ-5D using a published algorithm (67). The ERG considers that both the survey data and the QOLIE-31-P data in trial C017 present issues and that both mapping algorithms (by the company and by Wijnen et al (67)) are weak in the mapping of SF-6D and EQ-5D utilities, respectively.

Secondly, the mapping algorithm does not appropriately reflect the variability in observed SF-6D utility index scores, and, as pointed out by the company, it underestimates the range of predicted utilities. This indicates that the chosen OLS model, although offering the best fit from the list of models tested, it does not offer a good fit to the data. Finally, the variance adjustment implemented by the company as per the ERG's request, implied the doubling of the standard errors of the mapped utility estimates used to inform the model response states. This is down to the poor performance of the mapping algorithm. Therefore, the ERG considers that the mapped utility estimates used to populate the model are highly uncertain. For example, the adjusted utility estimate for the 'no response' (<50% reduction in seizures) health state has a mean of [redacted], but with a very wide 95% confidence interval spanning between [redacted] and [redacted].

Item 18: State-specific utilities in the cost-effectiveness model are highly uncertain.

4.2.10.5 Review of HRQoL and health states utility values used in the model

The company submission included the searches to identify studies on HRQoL or utilities relating to focal onset seizures. The company's methods for reviewing the HRQoL literature are outlined in Appendix H of the CS. The company indicates that it followed the guidance provided by the ISPOR Good Practices for Outcome Research Task Force.

The searches undertaken by the company identified 5 studies reporting average utility scores (Table 16 in Appendix H of the CS). A study from Thailand (68), using the EQ-5D-3L instrument to obtain utility values, categorised focal seizure patients into no improvement, a reduction in seizure frequency and seizure-freedom. Results indicated that patients observing a seizure reduction have a better HRQoL (0.79) than those who have no improvements (0.72), while those that are seizure-free (0.82) have a better HRQoL than those observing seizure reductions. The company implemented a scenario where the utility values in the model were sourced from Phumart et al (2018). This resulted in reduced incremental QALYs for cenobamate relative to the comparators.

The company uses the mapping algorithm to derive SF-6D utility estimates from patients at the end of the C017 study (last 28 days) according to their response rate. Predicted SF-6D results by response level are reported in Table 49, document B of the CS and are used to inform the utility values in the model. Due to small numbers in the ≥90% response rate category in the C017 study, health state utility values for ≥75% to <90% (high response) and for ≥90% and <100% (very high response) response levels are assumed equal and averaged across both health states.

Moreover, the company considers that none of the studies identified in the review can adequately characterise the HRQoL of patients in the subsequent ASM treatment health state or any of the following model health states. Utility values for subsequent ASM treatment, post-surgery and post-

VNS health states are assumed to be a weighted average of the response rate predicted utility values and patients' distribution among the different levels of response. The company also assumes that patients in the surgery and VNS health states have the same utility as patients with no response. Utility values used in the model are presented in Table 50 in document B of the CS.

The duration of and disutility associated with adverse events of treatment (cenobamate or any of the comparators) were collected from published literature to calculate the total QALY decrement for AEs. Disutilities associated with VNS and with surgery related events were sourced from a variety of studies published in the literature. The disutility of accidents due to seizure occurrence was also captured in the scenario analysis, where disutility duration for these acute events were assumed to be a month each.

4.2.10.6 Points for critique

The ERG considers the HRQoL systematic literature review to have been conducted in an appropriate manner. The search strategies presented in the submission were of a good standard and appropriate to identify HRQoL or utilities for focal onset seizures. However, the sources searched for published and unpublished studies were limited. Due to small numbers, higher response states are assumed to have equivalent (mapped) utility values. However, this again calls into question, the appropriateness of the company's choice of a more granular model structure for response states, when further assumptions need to be imposed to specify utility values for the higher response states.

The ERG is satisfied with the scenario implemented by the company which considers utilities according to those reported by Phumart et al. (2018). The ERG notes that no discussion was presented on the substantial differences between the mean (SE) utility estimates used by the company and the ones from Phumart et al. – e.g. no response/improvement: [redacted] (company) vs 0.72 (0.21) (Phumart et al). Putting aside the fact that these utility estimates are sourced from different countries, these differences show how uncertain the HRQoL estimates considered in the model are.

Moreover, the ERG does not understand why the company did not discuss or consider utilising the health utilities used in NICE CG137 (1). The NICE CG137 sourced their utility estimates from Selai et al (2005). The health state utilities used in the NICE CG137 model were 0.94 (mean, SE 0.024) for seizure freedom, 0.90 (mean, SE 0.020) for responders (between 50-99% reduction in seizures), and 0.84 (mean, SE 0.029) for no responders. Although recognising the limitations of this utility data, as described in NICE CG137, the ERG emphasises the limited availability of good quality utility data and the existing uncertainty surrounding the utility estimates used by the company.

4.2.10.7 Caregiver HRQoL

The company included a HRQoL disutility for caregivers. The company argues that this is in line with the NICE reference case and that successful treatment of epilepsy improves health for both patients and their caregivers. The carer utility values were obtained via a small caregiver survey ([redacted]) aimed at carers of patients with ≥3 FOS per week according to the duration of seizure-freedom, where EQ-5D-5L was used to assess their HRQoL. A summary of caregiver HRQoL, in terms of mean age- and sex-adjusted disutility values stratified by patient characteristics, is provided in Table 44 in document B of the CS. Carer disutilities used in the model are provided in Tables 51 and 52 in document B of the CS. In the model, each patient with epilepsy is assumed to need one carer.

4.2.10.8 Points for critique

The ERG considered the case presented by the company that direct health effects exist for both patients and caregivers. The ERG clinical advisors indicated that the HRQoL of carers is likely to be impacted by the role of caring for patients with epilepsy who have FOS and who require a carer. However, the clinical advisors emphasised that not all adult patients with FOS require a carer and many choose to live independent lives.

The ERG has concerns regarding the caregivers' survey, the estimation of disutilities from the survey results and the magnitude of the values estimated. The ERG considers that the CS was not clear if the survey collected evidence from carers of patients in study C017 or from carers from another setting. Moreover, the ERG questions the representativeness of this caregivers' (small) sample to the specific UK population seen in clinical practice. The CS provides no detail on how disutility values were derived. It is mentioned that estimates were obtained 'according to the duration of seizure-freedom' but the CS provides no detail on how seizure-freedom duration and response level disutilities were obtained from carers. The very high correlation implied in the health state-specific carer disutility values appears to contrast with the survey results presented in Table 44 in document B of the CS, where correlation between patients' number of seizures and carers' disutility [redacted]. Similarly, the correlation between seizure-free days and carers' disutility in Table 44 (document B in the CS) is poor and uncertain (for example, the mean disutility for 16-20 seizure-free days is [redacted], while it is only [redacted] for 21-27 seizure-free days), while carers' disutility is inversely correlated with occurrence of seizures of disabling nature.

Furthermore, the ERG questions the magnitude of the elicited disutilities and is concerned by the fact that uncertainty in these parameters are not considered in the model. For example, patients in the 'no response' health state have, on average, a utility value of [redacted], while their caregivers have an average disutility of 0.25, implying a total utility value of [redacted] ([redacted]) for this level of response, i.e.

considering carer disutility halved the utility used in the model. Given the major concerns with the disutility values used in the model for caregivers, the ERG excludes caregiver utility in its base case.

Item 19: The company estimate of carers' disutility is highly uncertain.

4.2.11 Resources and costs

The company conducted a systematic search to identify published cost and healthcare resource evidence for cenobamate and its comparators in partial onset seizures (see CS Appendix I). Only one UK study was identified, but not considered suitable for use in the economic model because the cost categories reported were not split out to describe what the costs comprised. Instead, the company used clinical expert surveys to inform: i) epilepsy event management resource; ii) routine monitoring resource use per response category; and iii) the prescribing pattern of background therapies in clinical practice.

In the company submission, the resource use and costs included: (i) drug acquisition, (ii) drug administration, (iii) routine monitoring, (iv) epilepsy event management, and (v) adverse drug reactions. Unit costs are informed by published sources (69-72) , published literature (73) (Chilcott et al 1999; Forbes et al 2003 reference details not provided by the company), HES data (74) and informed by previous NICE TA614 (75) . These were inflated to 2018/19 prices where appropriate and discounted at an annual rate of 3.5%.

4.2.11.1 Drug acquisition costs

In response health states (i.e. while patients are taking cenobamate or one of its comparators), drug acquisition costs were calculated per treatment period, split into titration and maintenance phases, and applied to patients who had not discontinued treatment. The drug acquisition costs included the cost of cenobamate and its comparators (the adjunctive therapies), and the cost of background therapy representing medications used concomitantly with the adjunctive therapies. Treatment compliance was considered but assumed equivalent across treatments (at [redacted]). The drug acquisition cost of cenobamate was obtained from the dose administered in study C021 for the titration phase (as titration is slower than in C017 and more representative of clinical practice), and the dose in trial C017 for the maintenance phase. The titration schedule and the mean dose for base case comparators are described in Table 60 and 61 in document B of the CS. The resulting drug acquisition cost, per model cycle is shown in Table 39.

Table 39. Drug acquisition cost per model cycle.

Drug	Drug acquisition cost per 28 days – titration phase	Drug acquisition cost per 28 days – maintenance phase
Cenobamate	[redacted]	[redacted]

Brivaracetam	£0	£129.64
Lacosamide	£97.95	£132.32
Eslicarbazepine acetate	£134.69	£157.98
Perampanel	£140.00	£140.00

In addition, it is assumed that all patients entering the model are also on background therapies defined as medications used concomitantly with adjunctive therapies. The ASMs included in background therapy and the proportion of patients receiving each ASM were sourced from the UK clinician survey. The total cost of background therapy per model cycle was £10.18. The ASMs included in background therapy, and their cost per 28 days is shown in Table 40.

Table 40 Distribution and cost of background therapy.

Drug	% prescribed	Drug cost per 28 days
Levetiracetam	[redacted]	£7.49
Lamotrigine	[redacted]	£4.68
Carbamazepine	[redacted]	£6.38
Sodium valproate	[redacted]	£19.12
Topiramate	[redacted]	£21.88
Clobazam	[redacted]	£6.98
Zonisamide	[redacted]	£4.72
Phenytoin	[redacted]	£11.32
Oxcarbazepine	[redacted]	£36.13
Pregabalin	[redacted]	£2.43
Phenobarbital	[redacted]	£12.27
Tiagabine	[redacted]	£87.43
Clonazepam	[redacted]	£38.55
Total		£10.18

In ‘subsequent ASM’ health state in the cost-effectiveness model, patients are assumed to receive cenobamate or one of the four comparators as an alternative to their adjunctive treatment. The distribution of patients amongst these treatments is based on the assumed market share of cenobamate once it is available. The distribution and the resulting cost of subsequent ASMs is shown in Table 41. In addition, all patients on subsequent ASMs are assumed to also receive background therapy described above (£10.18 per 28 days).

Table 41. Cost of subsequent ASMs.

Drug	% of subsequent ASMs	Drug cost per 28 days
Cenobamate	[redacted]	[redacted]
Brivaracetam	[redacted]	£129.64
Lacosamide	[redacted]	£132.44
Eslicarbazepine acetate	[redacted]	£157.92
Perampanel	[redacted]	£140.00
Total		£151.98

4.2.11.2 Drug administration costs

In 'response' health states – during treatment with cenobamate and its comparators – drug administration cost was calculated per treatment period, split into titration and maintenance phases, and applied to patients who had not discontinued treatment. Administration costs in the titration phase were based on the number of expected epilepsy outpatient (OP) visits (£177.00 per visit) and the need for electrocardiogram (ECG) monitoring (£481.00 per ECG). Administration costs in the maintenance phase were based on the cost of issuing repeat prescriptions (£29.50 per prescription) assuming four prescriptions are issues per year for each drug. The resulting administration costs are shown in Table 42.

Table 42. Drug administration cost.

Drug	Length of titration in days (model cycles)	Administration cost in titration phase, per model cycle	Administration cost in maintenance phase, per model cycle
Cenobamate	84 (3)	£177.00 -Three OP visits over 3 model cycles	£9.06 -Four prescriptions per year
Brivaracetam	0 (0)	£0.00 (no titration)	9.06 -Four prescriptions per year
Lacosamide	21 (1)	£835.00 -Two OP visits in one cycle -One ECG	9.06 -Four prescriptions per year
Eslicarbazepine acetate	21 (1)	£354.00 -Two OP visits in one cycle	9.06 -Four prescriptions per year
Perampanel	56 (2)	£265.50 -Three OP visits over 2 model cycles	9.06 -Four prescriptions per year

Subsequent ASMs, like cenobamate and its comparators, are assumed to require four prescriptions per year, costing £9.06 per cycle. Background therapy incurred no additional administration cost,

assuming prescriptions would be issued simultaneously with adjunctive treatment, both when used alongside third line therapy and subsequent ASMs.

4.2.11.3 Routine monitoring costs

The type of health resources associated with routine monitoring of treated patients were elicited in a survey from UK clinical experts. The number of hours of resource use per 28 days period in patients with drug-resistant FOS according to response to treatment were obtained. Total cost of routine monitoring by response is shown in Table 72 of the CS varying from [redacted] for no response to [redacted] for complete response.

4.2.11.4 Epilepsy event management costs

Epilepsy event management costs were estimated via UK clinical expert opinion elicited in the clinician survey. These were comprised by the management and the treatment of seizures, splitting these by seizure type. Total cost per seizure is presented in Table 79 of the CS. Costs associated with accidents due to seizure occurrence were included as a scenario analysis.

4.2.11.5 Adverse drug reaction costs

Adverse event costs were comprised of: i) treatment emergent adverse event (TEAE) costs; ii) adverse event costs associated with VNS; and iii) adverse event costs associated with surgery. The TEAEs during the titration and the maintenance phase were informed by the C021 open-label study and trial C017, respectively. The costs associated with TEAEs (Table 85 in document B of the CS) were sourced from NICE TA614. Adverse events associated with VNS and surgery (Table 86 and Table 87, respectively, in document B of the CS) were sources from relevant national data sources (70, 71).

4.2.11.6 Points for critique

The searches presented in the submission were generally appropriate, however, the sources searched for published and unpublished studies were fairly limited. The ERG believes that generally all relevant sources of resource use and costs have been considered and the methods used to estimate the cost of treatment with cenobamate and comparators are broadly appropriate. However, due to a lack of data, all resource use was based on clinical opinion. Therefore, the ERG highlights the substantial uncertainty in the resulting cost estimates.

The ERG highlights that the company estimates of healthcare costs, per level of response (28-day costs summarised in Table 43) are particularly high compared to previously published economic models where costs were £8.85 per 28 days (£115 per year) in patients who achieved seizure freedom, and £38.54 per 28 days (£501 per year) in those who were not seizure free (1). The healthcare costs in the CS are driven by the management of epileptic events and is one of the key drivers of costs in the model. The cost of management of epileptic events in Table 43 is calculated per seizure, and reflect the baseline number of seizures in the company base case, which is substantially higher than that in

the ERG base case. A lower number of seizures at baseline lower cost gradient across different levels of response, and consequently lowers the cost reduction associated with better response to treatment.

Table 43. Average healthcare cost per level of response, over 28-days.

	No response	Moderate response	High response	Very high response	Seizure freedom
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epileptic event management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The model assumes equivalent compliance. The ERG considers this to be a reasonable assumption given the assumed differences in adverse effects profiles across treatments and relative to cenobamate (Table 32 of document B in the CS).

The ERG does not consider assumptions regarding the cost of subsequent ASMs to be reasonable, where once a patient has failed one ASM and moves to subsequent ASMs, the drug acquisition cost (derived as the average cost of cenobamate and its comparators, weighted by their market share) includes the cost of the ASM that the patient has just failed. The ERG considers also that taking a distribution based on market share, which includes cenobamate that has not yet been approved and includes treatments that patients have previously failed on, is an over simplification. Using a distribution based on expected market share also doesn't align with using a 'general' odds ratio of no response with subsequent ASM relative to current ASM treatment (discussed in section 4.2.6.3).

The ERG notes also that resource use is largely based on evidence elicited from clinical experts. This approach brings added bias and uncertainty to the model.

Item 20: The cost of subsequent ASMs should not include cenobamate. Drug acquisition cost for ASMs may be overestimated due to inclusion of cenobamate.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The cost-effectiveness results of the company's base-case are shown in Table 44. The presented results were derived after correcting a typographical error in the model transition probabilities (corrected by the company in response to points for clarification). The ICER in the company base-case is dominant in both probabilistic and deterministic analyses.

Figure 51 and Figure 52 in the CS show the probabilistic scatter plot for the original base-case and the cost-effectiveness acceptability curve, respectively. The probability that cenobamate is cost-effective at a cost-effectiveness threshold of £30,000/QALY is [redacted] according to the original company's base-case. The results suggest that cenobamate is both less costly and more effective than its comparators. Higher response of cenobamate leads to higher total QALYs relative to comparators. The reduction in seizures achieved reduces also the cost of event management, which is the cost item that most contributes to total costs, implying lower total costs for cenobamate compared with alternatives.

Table 44. Company's base-case deterministic and probabilistic results.

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Cost-effectiveness results (deterministic)					
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness results (probabilistic)					
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NR, not reported; QALYs, quality-adjusted life years; SoC, standard of care;

Consequences of parameter uncertainty (probabilistic analysis) are concentrated around the additional health outcomes of cenobamate compared to its comparators. Differences may be explained by model non-linearities and the substantial uncertainty around the utility data informing it.

5.2 Company's sensitivity analyses

The company conducted several scenario analyses in CS (Table 93 in document B of the CS; pg 156-158), although justification for the choice of scenarios was not provided. The company conducted more scenarios in the reply to the clarification questions. In all scenarios presented cenobamate dominates relevant comparators exhibiting the lowest total cost and highest QALY gain.

The company also conducted deterministic one-way sensitivity analyses for all model parameters that were assigned distributions by setting these parameters to their upper and lower limits of their 95% confidence intervals. Where confidence intervals were not available, the company assumed that variance was 20% of the mean. Figure 54 (page 155 in document B of the CS) shows a tornado diagram of the 14 most influential parameters compared to lacosamide, the next cheapest comparator which is associated with the second most QALYs gained after cenobamate. The results indicate that effectiveness of lacosamide compared to cenobamate, and utility associated with no response are the most influential parameters.

5.3 Model validation and face validity check

The company describes the model validation process in Section B 3.11.1 of the CS. The ERG undertook further validation checks and identified three errors. A typographical error in transition probabilities was corrected by the company in the reply to clarification questions. An additional error in transition probabilities was identified in a scenario where the cycle length is extended but the probabilities of having VNS or surgery were not adjusted for the longer cycle length. Finally, one error identified and corrected by the ERG relates to how the response to subsequent treatment was derived and applied in the model. No other face validity issues were identified with the model.

The ERG prefers alternative assumptions to those employed in the company's base-case. These are described in Section 6.1.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

A summary of the main issues identified and critiqued in Section 4 along with the scenario where the ERG addresses each issue in its additional analyses is shown in Table 45.

Table 45. Summary of the main issues identified by the ERG.

Critique item and description The ERG considers that:		Dealt with in the ERGs base case	Dealt with in the ERG's Scenario analyses	Area of remaining uncertainty	Significant impact on ICER
Item 1	Model structure based on five levels of treatment response as opposed to three levels may not be appropriate because there is limited data to inform the effectiveness of the comparators relative to cenobamate for the more granular structure.	An.2		X	
Item 2	The approach to modelling subsequent ASMs following treatment discontinuation with cenobamate and its comparators does not reflect the range of treatment sequences seen in UK clinical practice.			X	
Item 3	The model cycle length may be too short to appropriately assess treatment response in clinical practice and capture a meaningful change in resource use and HRQoL from subsequent events.	An.3		X	
Item 4	The baseline number of seizures of [redacted] may represent an overestimate of the average number of seizures in UK patients eligible for cenobamate and its comparators.	An. 5	Sc. 3		
Item 5	All relevant comparators may not be appropriately included in the company submission for 3rd line adjunctive treatment of FOS because 2nd generation ASMs (namely, clobazam, zonisamide and topiramate) were excluded as relevant comparators.		Sc.2	X	
Item 6	Deriving transition probabilities directly from the observed data in trial C017 may overestimate response to treatment with cenobamate by failing to include all relevant evidence (specifically, trial C013), and to account for the placebo effect.			X	
Item 7	Transition probabilities may not reflect the slower cenobamate dose titration that will be used in UK clinical practice.			X	
Item 8	Response to treatment over time for cenobamate is highly uncertain.	An. 4 An. 13		X	
Item 9	There is considerable uncertainty in the estimate of the effectiveness of comparators relative to cenobamate derived from the NMA.		Sc1	X	X
Item 10	Exclusion of trial C013 from the NMA fails to take account of all relevant evidence on the effectiveness of cenobamate and comparators.	An. 6		X	
Item 11	The NMA model does not synthesise all outcomes required in the cost-effectiveness model.	An2		X	
Item 12	The NMA fails to take into consideration the correlation between the two outcomes, and potentially double counts patients with seizure freedom	An. 7			
Item 13	The NMA model does not adjust for the placebo effect, potentially biasing estimates of relative effect.	An. 8			

Item 14	Deriving the response to subsequent ASMs relative to cenobamate is likely to overestimate their effectiveness for subsequent ASMs.	An. 10		
Item 15	Applying the odds ratio of treatment resistance to the odds of no resistance likely to bias the response to rates for subsequent ASMs.	An. 9		
Item 16	The clinical effectiveness of subsequent ASMs is highly uncertain.		X	
Item 17	The method employed to estimate the probability of treatment discontinuation for the comparators relative to cenobamate is likely to overestimate discontinuation rates	An. 11 An. 12 An. 13	X	
Item 18	State-specific utilities in the cost-effectiveness model are highly uncertain		X	
Item 19	The company estimate of carers' disutility is highly uncertain	An.14	X	
Item 20	Drug acquisition cost for ASMs may be overestimated due to inclusion of cenobamate.	An. 15		

6.1 Exploratory and sensitivity analyses undertaken by the ERG

As shown in Table 45, the ERG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where the ERG considered that there was a more appropriate alternative approach, modifications were implemented in a cumulative manner and formed part of the ERG's preferred base case (analyses 1 – 15). Areas of remaining uncertainty were explored as sensitivity analyses to the ERG's base case (scenarios 1 and 2). Thorough descriptions of the analyses that form part of the ERG's base case and sensitivity analyses are presented in Section 6.1.1. and Section 6.1.2. respectively, and the impact on the ICER is detailed in Section 6.3.

6.1.1 Building the ERG base case

The analyses that contributed to the ERG's base-case are described below and summarised in Table 46. The ERG base-case comprises of 15 modifications cumulatively implemented.

Table 46. Building the ERG base-case. Description of analyses.

Analysis	Description
1. Corrected typographical errors in transition probabilities	Two errors were identified in transition probabilities described in section 5.3 and corrected.
2. Cost-effectiveness model structure based on three levels of response (no response with <50% seizure reduction; partial response with >50% and <100% response; and seizure freedom with 100% response).	The new model structure was used due to the lack of data needed to populate the company's more granular structure where five levels of treatment response were modelled (no response, moderate response, high response, very high response, and seizure freedom). The scenario was provided by the company.
3. Increasing the model cycle length to 84 days, starting in model cycle 6, with transition probabilities informed by study C017 OLE.	The scenario was used instead of the company's preferred 28-day cycle length and transition probabilities informed solely by trial C017. The scenario was provided by the company.
4. Extrapolation of treatment effect: assume all patients remain in the same state unless they discontinue treatment	Due to uncertainty in the treatment effect beyond the evidence end point, patients assumed to remain in the same response state unless they have treatment failure that results in movement to 'subsequent ASMs'

5. Baseline number of seizures informed by trial C013.	The trial was used to inform the baseline number of seizures due to concerns that the company's preferred estimate (based on clinical opinion) may overestimate the baseline number of seizures.
6. Inclusion of trial C013 in the NMAs.	The trial was added to the NMA as it was considered to be important evidence regarding the treatment effect of comparators, relative to cenobamate. The scenario was implemented by the company.
7. NMA model updated to account for correlation between outcomes.	The updated model was used to achieve the following limitations of the company's NMA model: - to prevent double counting of patients with seizure freedom; - to account for correlation between outcomes.
8. Placebo adjustment in the NMA	The company NMA model used to inform the effectiveness of comparator treatments was updated to account for variation in the placebo effect between trials in the NMA
9. Response to subsequent ASMs derived by applying the odds ratio of treatment resistance to the odds of no seizure freedom.	The method for deriving the treatment effect in subsequent ASMs was adjusted for consistency with the literature.
10. Effectiveness of ASMs calculated relative to the least effective comparator.	The relative risk of treatment resistance of ASMs was applied the probability of treatment resistance for the least effective comparator, rather than cenobamate, to ensure that subsequent ASMs are not more effective than 3rd line adjunctive treatment.
11. Time to treatment discontinuation for comparators informed by the NMA.	The NMA results were used instead of naïve hazard ratios derived from the literature. The scenario was provided by the company.
12. Starting in model cycle 6, assume treatment discontinuation for comparators identical to cenobamate.	Following initial 5 cycles of treatment, treatment discontinuation is assumed to be predominantly caused by a lack of response (rather than adverse events). Time-specific treatment failure beyond this time point is assumed to be identical to time to discontinuation of cenobamate.
13. Patients with no response after cycle 6 assumed to discontinue treatment	Patients were assumed to discontinue treatment after having no response for three months in model cycle 6. This is contrary to the company' base case where patients could stay in 'no response' indefinitely, and the probability of treatment discontinuation was independent of their level of response.
14. No carer disutility	Carer utilities were excluded from the model due to the substantial uncertainty in their value and the poor quality of the evidence used to inform them.
15. Cost of ASMs recalculated to exclude cenobamate.	When calculating the drug acquisition and administration cost for subsequent ASMs, the cost was averaged over 3rd generation adjunctive ASMs with cenobamate excluded (as it has not yet been recommended by NICE).

6.1.1.1 Analysis 1: Corrected typographical error in transition probabilities

Section 4.2.6.1 highlights the typographical error in the number of patients transitioning between states. The error was corrected by the company following points for clarification.

6.1.1.2 Analysis 2: Cost-effectiveness model structure based on three levels of response

As described in item 2 (section 4.2.2), the model structure based on five levels of treatment response (no response, moderate response, high response, very high response and seizure freedom) may not be appropriate because there is insufficient data to inform the relative effectiveness of the intervention and comparators on each level of response. Therefore, the ERG considers an aggregated response structure with health states of no response (<50% reduction in seizure frequency), response (≥50% to

99% reduction in seizure frequency) and seizure freedom (100% reduction in seizure frequency) to be adequate and incorporates it in the ERG's base case. The new model structure was provided by the company in response to points for clarifications (question B1).

6.1.1.3 Analysis 3: Increasing the model cycle length to 84 days, starting in model cycle 6, with transition probabilities informed by study C017 OLE.

Section 4.2.4 (item 3) suggests that the 28-day model cycles used in the company's base case may be too short to appropriately assess treatment response in clinical practice, and capture a meaningful change in resource use and HRQoL from subsequent events. The 28-day cycle length is also lower than cycle lengths in previous cost-effectiveness models for FOS identified in the company's review or in the NICE CG137. In the ERG base case, following the first five cycles the model cycle length increased to 84 days (approx. 3 months). In this scenario, transition probabilities for cenobamate in cycles 6 to 26 were informed from study C017 OLE. After cycle 26, the transition probabilities were extrapolated by averaging transition probabilities in cycles 6 to 26. The scenario was provided in the company's original submission, as an additional scenario.

6.1.1.4 Analysis 4: Extrapolation of treatment effect: assume all patients remain in the same state unless they discontinue treatment

In the company's model, transition probabilities observed in trial C017 (or C017 OLE) were extrapolated indefinitely, implying that patients continue to move between response states over time (section 4.2.6.1, item 8). The ERG implemented changes to the extrapolation of the treatment effect for all five treatment options, adopting methods used in NICE CG137. In the ERG base case, after cycle 5, patients were assumed to stay in the same response state until they discontinued treatment and moved to 'subsequent ASMs' state.

6.1.1.5 Analysis 5: Baseline number of seizures informed by trial C013

In the model, the baseline number of seizures was elicited from clinical experts and assumed to be [redacted]. This estimate is considerably lower than the baseline number of seizures in trials C013 and C017. The ERG considers the baseline number of seizures in trial C013 the least likely to result in an overestimate in the baseline number of seizures (see section 4.2.3 for details), and so used it in their base case. The resulting baseline number of seizures is [redacted] ([redacted] focal aware, [redacted] focal with impaired awareness, [redacted] focal to bilateral tonic-clonic), with the total number of seizures in each model cycle shown in Table 47. However, the ERG highlights that the baseline number of seizures is uncertain, and explores further scenarios in section 6.1.2.

Table 47. Baseline number of seizures in ERG base case.

Health state	Total number of seizures from study C013
Baseline	[redacted]

No response post-treatment (≥50% to <100%)	[redacted]
Aggregated response (≥50% to <100%)	[redacted]
Moderate response (≥50% to <75%)	[redacted]
High response (≥75% to <90%)	[redacted]
Very high response (≥90% to <100%)	[redacted]
Complete response (100%)	[redacted]
Subsequent ASM treatment	[redacted]
Post-surgery	[redacted]
Post-VNS	[redacted]

6.1.1.6 Analysis 6: Inclusion of trial C013 in the NMAs

The NMA used to estimate the treatment effect of comparators relative to cenobamate did not include trial C013. As discussed in section 4.2.6.2 (Item 10), Following points for clarification (question A3), the company provided a scenario where study C013 was included in the NMA. The ERG considers study C013 to be relevant evidence on the effectiveness of cenobamate that should be included in the network meta-analyses, and is part of the ERG's base case.

6.1.1.7 Analysis 7: NMA model updated to account for correlation between outcomes.

As discussed in section 4.2.6 (item 12), the treatment effect of comparators was derived from two independent network meta-analysis. The NMA did not report the odds ratio for each level of response modelled in the cost-effectiveness model. An adequate framework to synthesise these correlated outcomes is through the simultaneous modelling of all response rates, following the general principles outlined in the NICE DSU (47), section on ordered multinomial outcomes. As highlighted in Analysis 2 (section 6.1.1.2), the ERG advocates an aggregated model structure for the response health states. To comply with that model structure, a synthesis model simultaneously considering aggregated response levels of 50% and above and 100% was implemented by the ERG. The relative risks (and credible intervals) for these 2 response measures were used to directly inform the model, being this part of the ERG's base case.

6.1.1.8 Analysis 8: Placebo adjustment in the NMA

Placebo heterogeneity was detected among the trials informing the NMA – see section 3.4. The ERG extended the updated NMA model from Analysis 6 to explicitly adjust for placebo heterogeneity.

6.1.1.9 Analysis 9: Response to subsequent ASMs derived by applying the odds ratio of treatment resistance to the odds of no seizure freedom.

In the company model, the distribution of patients across different levels of response was derived by applying the odds ratio of treatment resistance (derived from the literature) to the odds of having no response (<50% seizure reduction) in trial C017. As discussed in section 4.2.6.3 (item 15), the study

that informed the odds ratio of treatment resistance defined treatment resistance as not achieving seizure freedom, rather than <50% seizure reduction. For consistency, when deriving the distribution of patients across different levels of response in the ERG' base case, the odds ratio is applied to the odds of seizure freedom, rather than no response. Distribution of patients across levels of response conditional on not achieving seizure freedom was assumed to be the same as in trial C017.

6.1.1.10 Analysis 10: Effectiveness of ASMs calculated relative to the least effective comparator.

In the company's model, patients who discontinue treatment with cenobamate or its comparators move to subsequent ASMs state. Effectiveness of subsequent ASMs was derived relative to cenobamate, assuming the odds of treatment resistance were 1.73 times higher in subsequent ASMs. As discussed in section 4.2.6.3 (item 14), this approach generates an unrealistic scenario where more patients achieve higher levels of response when subject to subsequent ASM treatments than when subject to any of the comparator treatments in 3rd line. Thus, the ERG considers as base case the effectiveness of subsequent ASM treatment relative to the least effective comparator as in Analysis 4, that is brivaracetam in the company base case.

6.1.1.11 Analysis 11: Time to treatment discontinuation for comparators informed by the NMA

In the company submission, time to treatment discontinuation for comparators was informed by naïve hazard ratios derived from published literature. All hazard ratios assumed implied that the risk of discontinuation in patients taking cenobamate was lower than that of comparators. As discussed in section 4.2.6.4 (item 17), the ERG has concerns regarding the approach taken and assumptions imposed, not appropriately reflecting the uncertainty surrounding these parameters. In the response to clarification questions, the results of an NMA for 'all-cause' discontinuation (not including study C013) was considered by the company as an alternative to the above. The ERG appreciates the concerns raised by the company that the results of this NMA underestimate the odds of discontinuing with comparators relative to cenobamate given the rapid titration verified in the C017 trial. Nonetheless, the ERG believes this is the best comparative evidence available for discontinuation. The ERG uses the company's scenario where 'all-cause' discontinuation relative to cenobamate is derived from the NMA, in its base case.

6.1.1.12 Analysis 12: Starting in model cycle 6, treatment discontinuation for comparators assumed to be comparable to cenobamate

In the company's model, transition probabilities observed in trial C017 (or C017 OLE) were extrapolated indefinitely, implying that patients continue to move between response states over time. Transition to 'subsequent ASMs' is informed by treatment-specific time to treatment discontinuation. The probability of discontinuation is applied to all response states, assuming the probability is the same for all patients, irrespective of their level of response. As discussed in section 4.2.6.1 (item 4), the ERG implemented changes to the extrapolation of the treatment effect for all five treatment

options, adopting methods used in the NICE CG137. In the ERG base case, after cycle 5, patients were assumed to stay in the same response state until they experienced treatment failure (assumed to be due to lack of treatment response) and moved to 'subsequent ASMs' state. From cycle 6 onwards, the probability of treatment failure (and discontinuation), was assumed to be the same for all comparators, informed by discontinuation observed in C017 OLE and C021.

6.1.1.13 Analysis 13: Patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state.

As discussed in section 4.2.6.4 (item 17), treatment discontinuation in the company's model was applied to all response states, where some patients could have no response but continue taking cenobamate indefinitely. In the ERG base case, patients who had no response for three months in cycle 6 were assumed to discontinue treatment and transition to the 'subsequent ASMs' health state.

6.1.1.14 Analysis 14: No carer disutility

The company quantitatively considered the health effects beyond that of the FOS patients, that is, the HRQoL of their carers. While the ERG praises the fact that these have been considered, when only a few TAs have done it in the past (47), the ERG questions the fact that all patients will require a carer, the quality of the evidence used to inform carers' disutility, and the magnitude of the estimated health effects (see section 4.2.10, item 19 for details). Therefore, the ERG, considers as base case not using the elicited caregiver disutilities.

6.1.1.15 Analysis 14: Cost of ASMs recalculated to exclude cenobamate

In company's model, patients who discontinue 3rd line treatment for FOS are assumed to move onto one of the remaining 3rd generation adjunctive treatments in subsequent lines of therapy. The drug acquisition and administration cost of subsequent ASMs was the average cost of treatment with cenobamate and its comparators, weighted by their expected market share once cenobamate becomes available. The company conservatively assumed that cenobamate would be a treatment option in the subsequent ASM treatment pathway given that patients who are treated with an alternative comparator initially would be eligible for its use if they do not derive a response to their allocated treatment. The ERG believes that the market share estimates in which this analysis is based upon are uncertain and unknown for cenobamate (item 20). Thus, the ERG considers as its base case the exclusion of cenobamate from the set of subsequent ASM therapies.

6.1.2 Scenario analyses to the ERG's base-case

Two scenario analyses to the ERG's base-case are described below.

6.1.2.1 Scenario 1: Assuming equal efficacy, equal discontinuation rates and ADRs between cenobamate and comparators

As discussed above in sections 3.2 and 4.2.4.2, the company used effectiveness evidence for cenobamate from study C017. This study while yielding accurate estimates of the effect of cenobamate in the trial participants (good 'internal validity'), it does not yield entirely relevant information about the effects of cenobamate in the target population (poor 'external validity'). Moreover, in the NMAs presented by the company, placebo heterogeneity was found across the included studies (discussed in detail in section 3.4), which may indicate the violation of basic NMA assumptions. Thus, the ERG considered a scenario where all ASM treatment being compared are expected to present equivalent efficacy, discontinuation rates and adverse reaction profiles. This scenario had the support of the ERG's clinical advisors.

6.1.2.2 Scenario 2: Varying the average baseline seizure frequency

This relates to Analysis 3 around the source for the baseline number of seizures to be used in the model. This has been found to be a key aspect in the model. The ERG thus explored the effect of varying the number of baseline seizures on the cost-effectiveness results.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

All results for the ERG base case and scenarios are based on a deterministic analysis because the time required to run the model probabilistically across all scenarios was not feasible within the time constraints of the STA. The results presented in Table 48 and Table 49 refer to the fully incremental cost-effectiveness analyses. When cenobamate is dominant to all other comparators, only the results of the next best treatment are shown. All analyses presented show that cenobamate brings lower costs at higher benefits relative to all its comparators in this evaluation.

However, the ERG notes that some analyses impact incremental costs and outcomes to a higher extent. Table 48 shows that analysis 5, where the baseline number of seizures was informed using data from trial C013 rather than clinical opinion, had the greatest impact on incremental costs relative to the company's base case. The reduced number of baseline seizures (compared to the company base case) substantially reduced the event management costs of comparators and, thus, reduced the incremental costs of the next best comparator relative to cenobamate. In analyses 6a and 6b, where trial C013 was included in the NMA used to estimate the effect of comparators relative to cenobamate, the decrease in the effect of cenobamate relative to its comparators resulted in a substantial decrease in cost savings and a decrease in QALYs gained with cenobamate relative to the comparators. This is because the inclusion of study C013 increased the effect of comparators on

seizure freedom, suggesting that brivaracetam was more effective than cenobamate. However, in analysis 7, when the NMA model was updated to account for correlation between the synthesised outcomes, the total cost of comparators increased and QALYs decreased relative to cenobamate. In the updated NMA implemented by the ERG, the effect of comparators on seizure freedom is lower and consistent with the company's base case.

In analysis 11, where the probability of treatment discontinuation is informed by the NMA rather than the naïve HRs provided by the company, there is a substantial increase in comparators' costs and a reduction in benefits relative to cenobamate. The change occurs because the NMA results imply that the discontinuation rate for comparators is lower than for cenobamate, unlike in the company's base case where all HRs were greater than 1, indicating that comparators would be discontinued quicker than cenobamate. With a lower discontinuation rate for comparators, patients stay in the no response health state for longer. The costs in 'no response' state are higher and HRQoL is lower than in 'subsequent ASMs' state, and as result, lower treatment discontinuation leads to higher costs and lower QALYs for comparators.

Table 48. Results of ERG's preferred assumptions.

Preferred assumption	Section in ERG report	Next best comparator	Incremental cost	Incremental QALYs	ICER £/QALY

CS base case		Lacosamide	[redacted]	-0.718	Dominant
1. Corrected typographical error in transition probabilities	4.2.6.1	Lacosamide	[redacted]	-0.715	Dominant
2. Analysis 1 + cost-effectiveness model structure based on three levels of response	4.2.2	Lacosamide	[redacted]	-0.660	Dominant
3. Analysis 1 + increased model cycle length to 84 days (starting in cycle 6) with transition probabilities informed by study C017 OLE	4.2.2	Lacosamide	[redacted]	-0.863	Dominant
4. Analysis 3 + extrapolation of treatment effect adjusted – patients remain in the same state unless they discontinue treatment	4.2.6.1	Lacosamide	[redacted]	-0.625	Dominant
5. Analysis 1 + baseline number of seizures informed by trial C013	4.2.3	Lacosamide	[redacted]	-0.715	Dominant
6a) Analysis 1 + inclusion of trial C013 in the NMAs	4.2.6.2	Brivaracetam	[redacted]	-0.247	Dominant
6b) Analysis 2 + inclusion of trial C013 in the NMAs	4.2.6.2	Brivaracetam	[redacted]	-0.176	Dominant
7. Analysis 6b + NMA model updated to account for correlation between outcomes	4.2.6.2	Lacosamide	[redacted]	-0.569	Dominant
8. Analysis 7 + placebo adjustment added to the NMA	4.2.6.2	Perampanel	[redacted]	-0.621	Dominant
9. Analysis 1 + response to subsequent ASMs derived by applying the odds ratio of treatment resistance to the odds of no seizure freedom	4.2.6.4	Lacosamide	[redacted]	-0.696	Dominant

10. Analysis 9 + effectiveness of ASMs calculated relative to the least effective comparator (eslicarbazepine)	4.2.6.4	Lacosamide	[redacted]	-0.727	Dominant
11. Analysis 10 + time to treatment discontinuation for comparators informed by the NMA	4.2.6.3	Lacosamide	[redacted]	-1.108	Dominant
12. Analysis 11 + time to treatment discontinuation for comparators in model cycles 6 onwards identical to C017	4.2.6.3	Lacosamide	[redacted]	-0.997	Dominant
13. Analysis 4 + patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state	4.2.6.3	Brivaracetam	[redacted]	-0.497	Dominant
14. Analysis 1 + no carer disutility	4.2.10	Lacosamide	[redacted]	-0.486	Dominant
15. Analysis 1 + cost of ASMs recalculated to exclude cenobamate	4.2.11	Lacosamide	[redacted]	-0.715	Dominant

In Table 49, Scenario 1 assumes equal efficacy, discontinuation rates and ADRs between cenobamate and comparators. It is, in effect, a cost comparison analysis between all alternative treatments and cenobamate where the only driver of results are the intervention and administration costs. Cenobamate [redacted], down to its [redacted], though providing equivalent benefits, it is dominated by lacosamide and remaining alternatives. [redacted].

In Scenario 2, when the average number of seizures at baseline is varied, the incremental QALY effect is unaffected as HRQoL for each level of response is assumed to remain the same as in the base case. However, the costs change, as shown in Figure 12. Decreasing the number of seizures decreases the reduction in the number of seizures in response to treatment. Consequently, the cost savings resulting from a reduction in the cost of seizure event management, also decreases. When average number of seizures at baseline is less than two, the cost reduction resulting from treatment with cenobamate becomes lower than the incremental cost of treatment with cenobamate, and cenobamate becomes costlier than the comparators. When the average number of seizures at baseline is 1,

lacosamide dominated all other treatment options. When the number of seizures was ≥2, cenobamate dominated all other treatment options.

Table 49. Results of ERG's scenario analyses.

Preferred assumption	Section in ERG report	Comparator	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
CS base case		Lacosamide	[redacted]	-0.718	Dominant
1. Analysis 1 + assuming equal efficacy, discontinuation rates and ADRs between cenobamate and comparators	4.2.6.2	Lacosamide	[redacted]	0.001*	Dominated
2. Analysis 1 + varying the average baseline seizure frequency	4.2.3	Lacosamide	See Figure 12	-0.718	£1,051 to dominant

* QALYs differ slightly between treatments because the length of titration phase (and the impact of titration-related ADRs on HRQoL) differs between drugs.

Figure 12. Cost savings for cenobamate (relative to lacosamide) when the baseline number of seizures is varied.

6.3 ERG's preferred assumptions

This section presents the results of the ERG's analyses that formed the ERG's base case in section 6.3.1. and the results of the ERG's sensitivity analyses, applied to the ERG's base case, in section 6.3.2. As in section 6.2, all presented results are based on a deterministic analysis.

6.3.1 Results of analyses building the ERG's base-case

Table 50 illustrates the results of the analyses that the ERG undertook as separate steps to form the ERG's base case. Across all analyses incremental costs remained high, suggesting that cenobamate has the potential to result in cost-savings compared to its comparators. This is because cenobamate is more effective than the comparators in terms of response to treatment from study C017, and the subsequent reduction in the number of seizures leads to higher QALYs and lower health care resource use [redacted].

As before, analysis 5, where baseline number of seizures (now informed by trial C013) was accumulated with Analysis 1 to 4, implied the biggest decrease in comparator's costs relative to cenobamate; however, cenobamate is still dominant. Moving patients with no response to the 'subsequent ASM treatment' state (analysis 13) also substantially reduces the cost difference to cenobamate. This is explained by the reduction of exposure time to therapy (drug costs, administration and monitoring), though still at lower benefits than cenobamate.

Table 50 ERG's preferred model assumptions

Preferred assumption	Comparator	Section in ERG report	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
CS base case	Lacosamide		[redacted]	-0.718	Dominant
1. Corrected typographical error in transition probabilities	Lacosamide	4.2.6.1	[redacted]	-0.715	Dominant
2. Analysis 1 + cost-effectiveness model structure based on three levels of response	Lacosamide	4.2.2	[redacted]	-0.660	Dominant
3. Analysis 2 + increased model cycle length to 84 days (starting in cycle 6) with transition probabilities informed by study C017 OLE	Lacosamide	4.2.2	[redacted]	-0.735	Dominant
4. Analysis 3 + extrapolation of treatment effect adjusted – patients remain in the same state unless they discontinue treatment	Lacosamide	4.2.6.1	[redacted]	-0.578	Dominant
5. Analysis 4 + baseline number of seizures informed by trial C013	Lacosamide	4.2.3	[redacted]	-0.578	Dominant

6. Analysis 5 + inclusion of trial C013 in the NMAs	Lacosamide	4.2.6.2		-0.338	Dominant
7. Analysis 6 + NMA model updated to account for correlation between outcomes	Lacosamide	4.2.6.2		-0.491	Dominant
8. Analysis 7 + placebo adjustment added to the NMA	Lacosamide	4.2.6.2		-0.541	Dominant
9. Analysis 8 + response to subsequent ASMs derived by applying the odds ratio of treatment resistance to the odds of no seizure freedom	Lacosamide	4.2.6.4		-0.524	Dominant
10. Analysis 9 + effectiveness of ASMs calculated relative to the least effective comparator	Lacosamide	4.2.6.4		-0.551	Dominant
11. Analysis 10 + time to treatment discontinuation for comparators informed by the NMA	Lacosamide	4.2.6.3		-0.845	Dominant
12. Analysis 11 + time to treatment discontinuation for comparators in model cycles 6 onwards identical to C017	Lacosamide	4.2.6.3		-0.761	Dominant

13. Analysis 12 + patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state	Lacosamide	4.2.6.3	[redacted]	-0.415	Dominant
14. Analysis 13 + no carer disutility	Lacosamide	4.2.10	[redacted]	-0.284	Dominant
15. Analysis 14 + cost of ASMs recalculated to exclude cenobamate **ERG's preferred assumptions (base case)**	Lacosamide	4.2.11	[redacted]	-0.284	Dominant

6.3.2 Results of the scenario analyses to the ERG's base-case

The ERG implemented variations to the ERG base case to test the robustness of the ERG model results to key clinically relevant assumptions, the results are shown in Table 51. Assuming equal efficacy, equal discontinuation rates and ADRs between cenobamate and comparators, cenobamate is shown to be more expensive than the comparators. The higher drug costs of cenobamate are driving this result. Cenobamate is dominated by comparator treatments, and if the comparison included even cheaper 1st and 2nd generation treatments, cenobamate would be even more likely dominated.

Table 51. ERG scenario analyses

Preferred assumption	Section in ERG report	Comparator	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
ERG base case		Lacosamide	[redacted]	-0.284	Dominant
1. Assuming equal efficacy, equal discontinuation rates and ADRs between cenobamate and comparators	4.2.6.2	Lacosamide	[redacted]	0.001	[redacted]
2. Varying the average baseline seizure frequency	4.2.3	Lacosamide	See Figure 13	-0.284	[redacted]

In Scenario 2, when the average number of seizures at baseline is varied, the incremental QALY effect is unaffected as HRQoL for each level of response is assumed to remain the same as in the base case. However, the costs change, as shown in Figure 13. As, discussed in section 6.2, decreasing the number of seizures decreases the cost saving with cenobamate. In the ERG base case, when the average number of seizures at baseline is less than three, the cost reduction resulting from treatment with cenobamate becomes lower than the incremental cost of treatment with cenobamate, and cenobamate becomes costlier than the comparators. The ICER is the lowest (£6375.91/QALY) when the number of seizures is 1.

Figure 13. Cost savings for cenobamate (relative to lacosamide) when the baseline number of seizures in ERG base case is varied.

6.4 Conclusions of the cost effectiveness section

The company submitted a cohort state-transition model that simulates the long-term, chronic nature of FOS. The company's economic evaluation positions cenobamate as a 3rd-line adjunctive therapy in accordance with NICE CG137, meaning that the model only evaluates cenobamate as adjunctive treatment in adult patients who have not been adequately controlled despite a history of treatment with at least two anti-epileptic products. The ERG, supported by its clinical advisors, considers that the set of relevant comparators to this evaluation should have included not only 3rd generation but also 2nd generation ASMs (namely, clobazam, zonisamide and topiramate). The *de novo* model structure submitted by the company is based on five levels of treatment response. The ERG considers that the model structure was not appropriately justified, largely being populated using estimates elicited from clinical opinion and single trial data. As this assessment contains several areas of uncertainty, the ERG recommends that cost-effectiveness results should be interpreted with caution.

In addition to the exclusion of relevant comparators and the appropriateness of the model structure, the company's model has several limitations and areas of remaining uncertainty. Firstly, the cycle length chosen is considered too short to appropriately assess treatment response in clinical practice and capture meaningful changes in resource use and HRQoL from subsequent events. Secondly, the elicited average number of baseline seizures is considered an overestimate of the true average number of seizures in UK patients eligible for cenobamate and its comparators. Sourcing transition probabilities solely from the C017 study is also seen as a limitation as it may be overestimating the effect of cenobamate, not accounting for the effect of placebo, not reflective of the up-titration period typically observed in UK clinical practice and not reflective of the medium/long-term treatment

response of cenobamate. Moreover, the approach taken by the company to estimate the effectiveness of comparators relative to cenobamate has a number of limitations, including exclusion of relevant evidence, independent modelling of subset of response outcomes and not controlling for between trial placebo heterogeneity. This, in addition to the absence of head-to-head studies comparing the evaluated treatments, brings added uncertainty to the derived relative effect estimates. Issues were also found in the approach taken to estimate the risk of discontinuation for comparators relative to cenobamate, with discontinuation rates likely to be overestimated. The approach to modelling subsequent ASM treatments does not reflect the range of treatment sequences seen in UK clinical practice, with the effectiveness of subsequent ASM treatments likely to be overestimated. Finally, mapped state specific utilities used in the model are considered highly uncertain.

To address these issues, the ERG made a number of changes to the company's base-case (see section 6.1). Firstly, the ERG considered the model structure based on three levels of response, rather than five. Second, starting in model cycle 6, it considered a model cycle length of 84 days, with transition probabilities informed by study C017 OLE, instead of study C017 only. It was also assumed patients to remain in the same response state unless they have treatment failure that results in movement to 'subsequent ASMs'. Thirdly, average number of baseline seizures were informed by trial C013, rather than clinical opinion. Study C013 was also considered relevant to derive relative treatment effectiveness and the NMA model was updated to reflect the continuous nature (and correlation) of the response outcomes, together with accounting for placebo heterogeneity. Moreover, and to be consistent with the literature, the ERG applied the effect of subsequent ASMs to the odds of no seizure freedom, with it being estimated relative to the least effective comparator (brivaracetam), instead of cenobamate. Furthermore, within the first 5 model cycles, time to treatment discontinuation for comparators was informed by the 'all-cause' discontinuation NMA, instead of naïve hazard ratios derived from the literature. Starting in model cycle 6, it was assumed that treatment discontinuation for comparators was identical to that of cenobamate, with patients remaining in the no response health state after cycle 6 assumed to discontinue treatment. The costs of ASM treatments were recalculated to exclude cenobamate, and finally, due to the uncertainty surrounding estimated carers disutilities, the ERG considered not to include these in its base case. The above are the ERG preferred assumptions that form the ERG base case. The ERG's base case estimates incremental costs of comparators relative to cenobamate to range from [redacted] to [redacted] per patient. This implies that cenobamate could offer considerable cost-savings to the NHS compared with all other treatment alternatives considered herein. The ERG's base case estimates incremental QALYs of comparators relative to cenobamate to range from -0.279 to -0.305 per patient. Thus, cenobamate offers cost-savings at higher benefits for patients, dominating all treatment alternatives. However, it must be noted that substantial structural and parameter uncertainty surround these economic model results and that these should be interpreted with caution.

Despite the ERG's attempt to address the key uncertainties, limitations in the evidence base mean that some of the uncertainties remain. The ERG considered two key variations to the ERG base case. The poor external validity of the pivotal trial C017, the substantial placebo heterogeneity in comparator trials, and the feedback obtained from the ERG clinical advisors on the effectiveness of cenobamate and of its comparators, supported the scenario of equal efficacy/equal discontinuation rates/ equal adverse reaction profiles between cenobamate and comparators, i.e. a cost comparison. Secondly, the ERG varied the average baseline seizure frequency to understand the impact on cost-effectiveness as this represented a key driver of the cost-effectiveness results. The results of the cost comparison scenario analysis [redacted]. Varying baseline seizures indicates that cenobamate is only cost saving when considering ≥3 seizures per month.

Overall, the ERG's preferred base case suggests that cenobamate is cost-effective and none of the ERG's additional analyses deviated from demonstrating that cenobamate dominates the comparators included in the company's submission. [redacted]

These conclusions are contingent on a number of key structural and parameter assumptions employed by the company as described above. With more evidence on the relative efficacy of cenobamate compared to comparator treatments, on treatment-specific discontinuation rates, and health-related quality of life utility values, the ERG highlights that once key structural and parameter uncertainties have been addressed, these may have a considerable influence on conclusions.

7 END OF LIFE

Due to the nature of the condition and treatment evaluated, the ERG believes that end of life criteria considerations do not apply to this appraisal.

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APPENDIX

$N_A = (O_A * N_A) / N_T$

Where N_A is the number of seizure type A (focal aware, focal impaired awareness or Focal to Bilateral Tonic Clonic) reported in a trial arm,

O_A is the number of seizure A observed in the trial arm

N_A is the number of patients in the trial arm who reported having at least one seizure A

N_T is the total number of patients in that trial arm.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Cenobamate for focal onset seizures in epilepsy [ID1553]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 1 April** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Company response to the draft ERG report

The Company would like to thank NICE and the ERG for the opportunity to review the draft ERG report. Issues identified by the Company are presented in this document. The key considerations are as follows:

- Factual inaccuracies that affect the base case scenario, presented in Issues 1-3, in particular:
    - The additional comparators proposed by the ERG are not relevant
    - Aspects of the base case specified by the ERG are implausible
    - It in inaccurate to state that the model structure submitted by the Company is unjustified
- Factual inaccuracies that require clarification, presented in Issues 4-8

In light of these comments, the Company request that the ERG revise their report and reconsider their base case model based on the evidence provided in this document.

Further supporting evidence to the factual inaccuracies are provided in Table 1.

Table 1: Number of seizures analysis - ERG analysis compared with analysis from the company

	Company base case (ERG Analysis)		Company base case (Company Analysis)	
Total number of seizures	**Incremental costs (£)**	**ICER**	**Incremental costs (£)**	**ICER**
1	[redacted]	Dominated by lacosamide	[redacted]	£1,050.75
2	[redacted]	Dominant	[redacted]	Dominant
3	[redacted]		[redacted]	
4	[redacted]		[redacted]	
5	[redacted]		[redacted]	
6	[redacted]		[redacted]	
7	[redacted]		[redacted]	
8	[redacted]		[redacted]	
9	[redacted]		[redacted]	
10	[redacted]		[redacted]	

11	[redacted]		[redacted]	
12	[redacted]		[redacted]	
13	[redacted]		[redacted]	
14	[redacted]		[redacted]	
15	[redacted]		[redacted]	

Issue 1 Proposed positioning of cenobamate in the treatment pathway (ERG's issue 1)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Eslicarbazepine is identified by the ERG as an irrelevant comparator to cenobamate in the following examples: **Section 1.3, Page 20:** "Clinical advice to the ERG considers that eslicarbazepine acetate is not a relevant comparator" **Section 2.2, Page 37:** "In addition, they noted that eslicarbazepine acetate was not a relevant comparator, as it is rarely used as adjunctive therapy." **Section, 2.3, Page 39, Table 3:** "they also found that eslicarbazepine acetate was not relevant to the decision problem as it is rarely used as adjunctive therapy."	**Section 1.3, Page 20:** "Clinical advice to the ERG considers that eslicarbazepine acetate is ~~not~~ a **less** relevant comparator **than brivaracetam, lacosamide and perampanel due to reduced use**" **Section 2.2, Page 37:** "In addition, they noted that eslicarbazepine acetate was ~~not~~ a **less** relevant comparator, as it is ~~rarely~~ used as adjunctive therapy **less frequently than brivaracetam, lacosamide and perampanel**." **Section, 2.3, Page 39, Table 3:** "they also found that eslicarbazepine acetate was ~~not~~ **less** relevant to the decision problem as it is ~~rarely~~ used as adjunctive therapy **less frequently than brivaracetam, lacosamide and perampanel**."	Based on Arvelle's market insights, [redacted] of patients with focal onset seizures treated adjunctively with 3rd generation ASMs are treated with eslicarbazepine acetate. Therefore, eslicarbazepine acetate is a relevant comparator to cenobamate, however it does have less frequent use than brivaracetam, lacosamide and perampanel.	These statements are accurate references to views of the ERG and its clinical advisers. As such they are not factual inaccuracies. The ERG notes that despite its rarer use in clinical practice, eslicarbazepine acetate was kept in the ERG base-case analyses.

Clobazam, topiramate and zonisamide are identified by the ERG as relevant comparators to cenobamate, in the following examples: **Section 1.3, Page 20:** "…clobazam, topiramate and zonisamide adjunctive therapies should have been included in the decision problem." **Section 2.4, Page 43:** "The ERG considers the 2nd generation ASMs clobazam, zonisamide and topiramate to be used as part of 3rd line adjunctive treatment of FOS in UK clinical practice, and therefore should have been considered as relevant comparators." **Section 4.2.4, Page 106:** "In their response to clarification questions (question A2), the company argued that clobazam, zonisamide and topiramate were not relevant comparators because they are 2nd generation ASMs."	The Company requests that the text is updated as follows: **Section 1.3, Page 20:** "…clobazam, topiramate and zonisamide adjunctive therapies ~~should~~ **may be relevant comparators that could** have been included in the decision problem." **Section 2.4, Page 43:** "The ERG considers the 2nd generation ASMs clobazam, zonisamide and topiramate **may** be used as part of 3rd line adjunctive treatment of FOS in UK clinical practice, and therefore **could** have been considered as relevant comparators. **Clinical advice to the Company, however, indicated that their use is primarily in earlier indications, and they should, therefore, not be considered relevant comparators."** **Section 4.2.4, Page 106:** "In their response to clarification questions (question A2), the company argued that clobazam, zonisamide and topiramate were not relevant comparators because they are 2nd generation ASMs **with use primarily in other indications, as validated by clinicians they engaged with**."	The Company would like to clarify that clobazam, zonisamide and topiramate were not only excluded because they are 2nd generation ASMs. The Company justified not considering these additional comparators based on the expert opinion of 14 neurology consultants and 2 clinical experts during model ratification. Reasons for their irrelevance to the decision problem include limited uptake in the third-line setting. As previously stated in the ERG Clarification Letter, clobazam is more commonly used as an acute treatment to end status epilepticus rather than as an ongoing adjunctive ASM. Additionally, since clobazam and topiramate are normally prescribed as a 2nd line adjunctive therapy, these therapies would not be considered as comparators to cenobamate, which is intended to be used as a 3rd line adjunctive treatment. Moreover, the likelihood of response to clobazam, topiramate and zonisamide in the anticipated patient population is low.[1]	The ERG's view that clobazam, topiramate and zonisamide should have been included in the decision problem was supported by the ERG clinical advisers. As such this is not a factual inaccuracy. The results of the survey conducted by the company suggest that, although 64% of patients may receive cenobamate if they "failed to respond to, are intolerant to, or are unsuitable for low cost therapies available in primary and secondary care," cenobamate may also be placed earlier in the treatment pathway for a significant minority of patients, where older generation treatments would still be considered suitable alternatives. The fact that clobazam and topiramate may be prescribed as 2nd line adjunctive therapy does not preclude the fact that they may also be considered relevant alternatives to cenobamate. This view was supported by the ERG clinical

		Therefore, they are less effective treatment options than the third-generation ASMs, which are used with preference in this indication due to their superior efficacy.	advisers. The ERG and its clinical advisers believe there is no evidence that third-generation ASMs have superior efficacy to older generation treatments in partial epilepsy. A large, recent NMA of ASMs for refractory partial-onset epilepsy concluded that newer ASMs were as efficacious as older treatments.(Hu et al. 2018) The evidence had a number of important limitations, notably a lack of head-to-head trials and no adjustments in the indirect treatment comparisons.
Section 1.4, Page 24: "The limited evidence and exclusion of several relevant comparators means that the relative efficacy and safety of cenobamate compared with other adjunctive ASMs is highly uncertain."	The Company requests that the text is updated as follows: "The **absence of direct treatment comparisons with** ~~limited evidence and exclusion of~~ ~~several~~ relevant comparators means that ~~the~~ **evidence of the** relative efficacy and safety of cenobamate compared with other adjunctive ASMs is ~~highly uncertain~~ **limited**."	The Company would like to clarify that the limited evidence started in the ERG report should be in reference to the lack of RCTs comparing cenobamate with other adjunctive ASMs directly. However, the ITC nevertheless demonstrated consistent trends favouring cenobamate relative to the comparator ASMs. Additionally, the Company would like to specify that the excluded comparators are second-line adjunctive treatments and therefore not relevant comparators as they do	Not a factual inaccuracy, but a matter of interpretation.

		not correspond to the anticipated license for cenobamate.	
Section 2.2.2, Page 37: "ERG clinical advisers also commented that levetiracetam may still be considered as a treatment option in combination with carbamazepine at this stage of the treatment pathway, and agreed that other 3rd line options (including phenobarbital, phenytoin, pregabalin and tiagabine) were less relevant due to their tolerability." **Section 2.3, Page 40:** "Although levetiracetam are commonly prescribed as first and second-line treatments, ERG clinical advisers stated they may also be used as an adjunct to carbamazepine in a third line setting and as such may be a relevant comparator."	The Company requests that the text is updated as follows: **Section 2.2.2, Page 37:** "ERG clinical advisers also commented that levetiracetam may still be considered as a treatment option in combination with carbamazepine at this stage of the treatment pathway, and agreed that other 3rd line options (including phenobarbital, phenytoin, pregabalin and tiagabine) were less relevant due to their tolerability. **Clinical advice to the Company, however, specified that as levetiracetam is prescribed in the first- and second-line setting, it is also not an appropriate comparator to cenobamate.**" **Section 2.3, Page 40:** "Although levetiracetam ~~are~~ **is** commonly prescribed as **a** first and second-line ~~treatments~~ **treatment**, ERG clinical advisers stated ~~they~~ **it** may also be used as an adjunct to carbamazepine in a third line setting and as such may be a relevant comparator. **Clinical advice to the Company, however, indicated that as levetiracetam is prescribed in the first- and second-line setting, it is not an appropriate comparator."**	As the intended use of cenobamate would be for a restricted population of patients as a 3rd line, second adjunctive therapy, levetiracetam in combination with carbamazepine would not be relevant comparators as they are more commonly prescribed in the 1st and 2nd line setting. The Company considered that the relevant comparators for the submission were those commonly used in the 3rd line, second adjunctive setting.	Not a factual inaccuracy. ERG clinical advisers' views are accurately presented.
Section 3.6, Page 93: "The company did not provide evidence for a number of older	The Company requests the text is updated as follows: "The company did not provide evidence for a	As stated above, clinical advisers to the Company have stated that topiramate, zonisamide and	As above, not a factual inaccuracy.

generation comparators deemed relevant by ERG clinical advisers (topiramate, zonisamide and clobazam), and only provided short-term evidence for all comparators, with treatment/follow-up periods ranging from seven to 19 weeks."	number of older generation comparators deemed relevant by ERG clinical advisers (topiramate, zonisamide and clobazam) **as clinical advisors to the Company did not deem these as relevant comparators to cenobamate. Although the ITC** provided only short-term evidence for all comparators, with treatment/follow-up periods ranging from seven to 19 weeks, **it demonstrated consistent trends favouring cenobamate with regards to efficacy."**	clobazam are not relevant comparators as they are poorly tolerated and less effective than the 3rd generation ASMs. The ITC was only able to demonstrate short-term comparative efficacy for cenobamate because studies demonstrating long-term efficacy, such as open-label extension studies, were excluded in the feasibility assessment as single-arm studies cannot be included in an NMA.	

Issue 2 The ERG's base case includes implausible assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Assuming that response to treatment cannot be elicited after cycle 6 is an implausible base case scenario. This is described in the following locations: **Section 1.6, Page 31:** "Analysis 3 + extrapolation of treatment effect adjusted – patients remain in the same state unless they discontinue treatment" **Section 4.2.6.1, Page 113:** "The ERG considers that the assumption in the company	The company requests that the ERG present this as a scenario analysis rather than it form their base case.	Assuming that response to treatment cannot be elicited after cycle 6 is not accurate. As reported in the CS, during the first year of the C017 OLE, [redacted] of all patients achieved a ≥50% reduction in seizures compared to baseline. However, when considering dosing during C017, [redacted] of those treated with 100 mg/day of cenobamate had a ≥50%	Not a factual inaccuracy. ERG's base case reflects assumptions made and validated in previous NICE guidance.

base case, i.e. that patients will continue to improve (respond to treatment) over time, is highly uncertain. For this reason, the ERG's base case adopts the approach taken in NICE CG137 (1). In model cycle 6, patients discontinue treatment if they have no response. The model cycle length is changed to 3 months to reflect that one month of no response would not lead to treatment discontinuation. Thereafter, patients stay in the same response health state Section unless they have treatment failure." **Section 6.1.1, Page 140, Table 41:** "Extrapolation of treatment effect: assume all patients remain in the same state unless they discontinue treatment" **Section 6.1.1.4, Page 142:** "In the ERG base case, after cycle 5, patients were assumed to stay in the same response state until they discontinued treatment and moved to 'subsequent ASMs' state." **Section 6.1.1.12, Page 145:** "In the ERG base case, after cycle 5, patients were assumed to stay in the same response state until they experienced treatment failure (assumed to be due to lack of treatment response) and moved to 'subsequent ASMs' state. From cycle 6 onwards, the probability of treatment failure (and discontinuation), was assumed to be the same for all comparators, informed by discontinuation observed in C017 OLE and C021." **Section 6.2, Page 148, Table 48:** "Analysis 3 + extrapolation of treatment effect adjusted – patients remain in the same state unless they discontinue		reduction in seizures compared to baseline during year 1 of the OLE, compared to 40.2% in the double-blind phase. Similarly, [redacted] of those treated with 200 mg/day had a ≥50% reduction in seizures compared to baseline during year 1 of the OLE, compared to 56.1% in the double-blind phase. This data is not at risk of attrition bias; 265 of the 266 cenobamate-treated patients in C017 entered the OLE. As such, increases in response to treatment are possible and have been observed. Moreover, in clinical practice if there is a lack of response, patients' dose would be adjusted in discussion with their clinician to ensure response is improved.	

treatment" **Section 6.4, Page 157:** "It was also assumed patients to remain in the same response state"			
Assuming that patients with no response in cycle 6 would automatically discontinue treatment is not appropriate. This is described in the following locations: **Section 1.6, Page 32:** "Analysis 12 + patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state" **Section 6.1.1, Page 141, Table 46:** "Patients were assumed to discontinue treatment after having no response for three months in model cycle 6. This is contrary to the company' base case where patients could stay in 'no response' indefinitely, and the probability of treatment discontinuation was independent of their level of response." **Section 6.1.1.13, Page 145:** "In the ERG base case, patients who had no response for three months in cycle 6 were assumed to discontinue treatment and transition to the 'subsequent ASMs' health state." **Section 6.2, Page 149, Table 48:** "Analysis 4 + patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' state"	The company requests that the ERG present this as a scenario analysis rather than it form their base case.	The movement of patients from 3rd generation ASMs to subsequent ASM therapy after 6 cycles of no response is accurate. Of the 266 patients completing the C017 study, 265/266 enrolled in the C017 regardless of treatment response. Furthermore, during the first year of the OLE, [redacted] of patients had ≥50% reduction in seizures compared to baseline. However, by the end of the first year of the OLE just [redacted] of patients had discontinued; this data demonstrates that patients do not discontinue treatment if they do not initially derive a response to treatment.	As above, this is not a factual inaccuracy. ERG's base case reflects assumptions made and validated in previous NICE guidance.

Issue 3 Assessment of the company's model structure (ERG's issue 5)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The Company's model structure was aligned with the C017 study endpoints and clinical opinion			
Section 1.1, Page 17: "Poorly justified model structure"	The Company requests that the text be amended to the following: ~~"Poorly justified~~ Model structure **aligned with the C017 primary and secondary endpoints"**	The current text is misleading and suggests little justification was given. The granular model was chosen as it aligns with the primary and secondary outcomes of the pivotal RCT for cenobamate (C017), where statistical significance was achieved, whilst building on the structure that has been adopted for cost-effectiveness analyses published for focal onset seizures. The model structure was validated as appropriate by clinicians.	Heading changed to "Inappropriate model structure given the current evidence".
Section 1.5, Page 100: "Considering the lack of evidence that patients receiving cenobamate are more likely to achieve ≥75% and ≥90% seizure reduction compared to the taking comparator treatments, and the uncertainty in resource use and HRQoL associated with different levels of response, the ERG believes that the more granular model structure is not appropriate because there is not sufficient evidence to populate the additional levels of response for the intervention and comparators"	The Company requests that the text be amended to the following: "Considering the ~~lack of~~ **limited direct** evidence ~~that patients receiving cenobamate are more likely to achieve~~ **for** ≥75% and ≥90% seizure reduction ~~compared to the taking~~ **with** comparator treatments, ~~and the uncertainty in resource use and HRQoL associated with different levels of response,~~ the ERG believes	Clinical data used to inform the additional levels of response for the intervention were derived from the primary and secondary outcomes of the pivotal RCT for cenobamate (C017), where significance was achieved and validated by clinicians. Resource use and utility data were generated by the Company via primary research for use directly in the model.	Text has been edited as follows. "Considering the lack of evidence that patients receiving cenobamate are more likely to achieve for ≥75% and ≥90% seizure reduction compared to the taking with comparator treatments, and the uncertainty in resource use and HRQoL associated with different levels of response, the ERG believes that the more granular model structure is not appropriate because there is not sufficient evidence to populate the additional

	that the more granular model structure is not appropriate because there is ~~not sufficient~~ **limited clinical** evidence to populate the additional levels of response for the ~~intervention and~~ comparators"		levels of response for the intervention and comparators." The ERG maintains that resource use and HRQoL evidence is extremely uncertain. This is discussed in detail in the ERG report.
Evidence for the effectiveness of comparators for ≥75% and ≥90% response rates			
Section 1.5, Page 25: "The ERG suggests an aggregated response structure with health states of no response (<50% reduction in seizure frequency), response (≥50% to 99% reduction in seizure frequency) and seizure freedom (100% reduction in seizure frequency), largely because there is insufficient evidence that cenobamate increases the probability of ≥75% and ≥90% reduction in seizure frequency compared to the comparators."	The Company requests that the text be amended to the following: "The ERG suggests an aggregated response structure with health states of no response (<50% reduction in seizure frequency), response (≥50% to 99% reduction in seizure frequency) and seizure freedom (100% reduction largely because there is ~~insufficient~~ **limited** evidence **supporting the** ~~that cenobamate increases the probability of ≥75% and ≥90% reduction in seizure frequency compared to the comparators.~~ **effectiveness of the comparators for the more granular structure"**	The ITC summarised in the CS showed that the odds of achieving a ≥50% response rate or seizure freedom during the maintenance period was higher with cenobamate compared to all third generation ASMs. Given the monotonicity of the function describing the proportion of patients achieving a reduction in seizure frequency with each treatment, this reasonably infers that seizure reduction is, on average, higher with cenobamate than the comparators. Therefore, greater proportions of patients treated with cenobamate will achieve the higher levels of response to treatment, i.e. ≥75% and ≥90% reduction in seizure frequency compared to baseline, than with the comparators. This further suggests that at higher levels of response, i.e. the ≥75% and ≥90% reduction in seizures frequency, the odds ratios would fall between the odds ratios of ≥50% reduction and seizure freedom.	Not a factual inaccuracy. In their response to points for clarification (Table 3, Appendix B), the company did not identify any evidence to inform the probability of ≥75% reduction in seizure frequency for two of the four comparators, and ≥90% reduction for any of the four comparators. Any estimate of the effect of comparators on ≥75% and ≥90% reduction in seizure frequency relative to cenobamate is based on assumptions.
Section 4.2.2.1, Page 100: "However, the company did not provide	The Company requests that the text be amended to the		Not a factual inaccuracy. The company did not provide any

evidence that cenobamate increases the proportion of patients who achieve ≥75% and ≥90% seizure reduction compared to the comparators"	following: "However, the company ~~did not provide~~ **provided limited** evidence that cenobamate increases the proportion of patients who achieve ≥75% and ≥90% seizure reduction compared to the comparators"	This assumption was validated with clinicians, who confirmed that the application of the odds ratios for the ≥50% responder rate to higher levels of response is conservative.	empirical evidence.
Section 6, Page 139, Table 45: "Model structure based on five levels of treatment response as opposed to three levels may not be appropriate because there is insufficient data to inform the relative effectiveness of the intervention and comparators for the more granular structure."	The Company requests that the text be amended to the following: "Model structure based on five levels of treatment response as opposed to three levels may not be appropriate because there is **limited** ~~insufficient~~ data to inform the relative effectiveness of the ~~intervention and~~ comparators for the more granular structure"		Edited as follows. Model structure based on five levels of treatment response as opposed to three levels may not be appropriate because there is limited data to inform the effectiveness of the comparators relative to cenobamate for the more granular structure.

Issue 4 Interpretation of efficacy data (ERG's issue's 2, 3 and 4)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Accuracy of reporting on the cenobamate studies			
Section 3.2.1.4, Page 52: "Patients initiated the titration phase with a cenobamate dose of	The company requests that the text be expanded to the following: "Patients initiated the titration phase with a	The current text is misleading and suggests that after a dose of 25 mg/day for two weeks, patients will have their dose increased by 50	Thank you. The sentence was edited as suggested.

12.5 mg/day for two weeks, followed by a dose of 25 mg/day for a further two weeks."	cenobamate dose of 12.5 mg/day for two weeks, followed by a dose of 25 mg/day for a further two weeks **and then increased to a dose of 50 mg/day for another two weeks**."	mg/day increments. The amended text is expanded to ensure that a titration dose of 50 mg/day was administered in weeks 5 and 6 before titration doses were increased every two weeks in increments of 50 mg/day.	
Section 3.2.3.1, Page 60: "This contrasts with the company's interpretation according to which a sustained decrease in median seizure frequency was observed at each additional four-week treatment interval.	The company requests that this text is removed.	The statement in the company submission does not refer to a constant rate of reduction in seizure frequency every four weeks. Rather, the initial reduction is sustained over the study.	The ERG referred to the statement from CS, Document B, p50, that following the first 4 weeks of the double-blind period, "sustained decreases in median seizure frequency were noted at each additional 4-week interval in the 200 mg and 400 mg cenobamate dose groups." The following additions were made to the sentence in Section 3.2.3.1 (see underlined): "This contrasts with the company's interpretation according to which, <u>following the first four weeks of the double-blind period</u>, a sustained decrease in median seizure frequency was observed at each additional four-week treatment interval <u>in the 200mg and 400mg</u>

			groups.”
Section 3.2.3.1, Page 60: “There was no statistically significant difference in efficacy between the 100 mg arm and placebo.” **Section 3.2.3.4, Page 62:** “There was no evidence that cenobamate administered at 100 mg doses was significantly more effective than placebo.”	The company requests that this text is removed as it in inaccurate.	There are instances where treatment with 100 mg of cenobamate was associated with a statistically significant improvement compared to baseline. This includes, but is not limited to, the primary endpoint of the C017 study – the proportion of patients achieving a ≥50% responder rate over the maintenance period of the study (p=0.036, Page 48 of the CS).	Thank you. The sentences were edited: “The figure also indicates a greater reduction in seizure frequency with higher doses of cenobamate; there was no statistically significant difference in efficacy between the 100 mg arm and placebo during the 9-13 weeks period and subsequently.” “There was no evidence that cenobamate administered at 100 mg doses was significantly more effective than placebo for 75%, 90% and 100% response outcomes.”
Section 3.2.4.4, Page 72: “In the group of patients receiving other Concomitant ASMs group, mean plasma levels of clobazam, lamotrigine, oxcarbazepine, and perampanel were lower at weeks 12 and 14 compared to baseline; the company concluded this indicated some induction of their metabolism by cenobamate.”	The Company requests that the text be amended to the following: “In the group of patients receiving other Concomitant ASMs group, mean plasma levels of clobazam, lamotrigine, oxcarbazepine, and perampanel were lower at weeks 12 and 14 compared to baseline; ~~the company concluded~~ this indicated some induction of their metabolism by cenobamate **as reported in the C021 CSR**.”	Text is misleading and assumes it was taken from the company submission. Text was sourced from the C021 CSR.	Edited for clarity.
Section 3.6, Page 93: “Trial C017 suggested that 100	To update the text as follows: “Trial C017 suggested that **the** 100 mg ~~doses~~	Justification as above.	Not factual inaccuracy, but a matter of interpretation (see

mg doses were not effective"	~~were~~ **dose was** not **as** effective **as higher doses**"		above). The sentence was edited to: "Trial C017 suggested that 100 mg doses may not be effective"
Generalisability of trial data			
Section 3.2.1.5, Page 53: "The design of the cenobamate studies presented in the CS was generally well-reported. However, the ERG is concerned that the design of trials C017 and C013 poorly reflect clinical practice."	The company requests that the text be expanded to the following: "The design of the cenobamate studies presented in the CS was generally well-reported. ~~However~~ **Whilst** ~~,~~ the ERG is concerned that the design of trials C017 and C013**, like studies for comparators, may** poorly reflect clinical practice, **evidence from the C021 study is more aligned with clinical practice and reports positive safety and persistence results**."	Though the company recognises that the duration of the C013 and C017 studies are relatively short, it is important to note that clinicians validated the observed clinical effectiveness of cenobamate despite this. Both efficacy and safety outcomes of cenobamate were validated by clinicians when compared to 3rd generation ASM treatments currently available in the UK. The company would also like it noted that titration in the C021 study reflects the anticipated titration schedule the will be used in clinical practice.	Not factual inaccuracy, but a matter of interpretation.
Section 3.2.2.1, Page 57: "ERG clinical advisers noted that the trial population was highly selected and did not reflect the population of patients with treatment-resistant FOS. In particular, they noted that the baseline seizure rates were higher than would be seen in clinical	The Company requests that the text be amended to the following: **Section 3.2.2.1, Page 57:** "ERG clinical advisers noted that the trial population was highly selected and did not reflect the population of patients with treatment-resistant FOS. In particular, they noted that the baseline seizure rates were higher than would	Though the company recognises that baseline seizure rates may be higher than expected for some patients in clinical practice for the C017 study, there are important considerations to note. There is broad variability in the range of seizures experience by patients with drug resistant	Not factual inaccuracy.

practice." **Section 3.6, Page 94:** "A number of issues regarding the generalisability of the trial populations were identified. Trial participants appeared to be highly selected, although selection criteria were only presented for cenobamate studies. In particular, the average baseline seizure rates of patients included in the ITC trials may be higher than would be seen in clinical practice."	be seen **for some patients** in clinical practice." **Section 3.6, Page 94:** "A number of issues regarding the generalisability of the trial populations were identified. Trial participants appeared to be ~~highly~~ **moderately** selected, although selection criteria were only presented for cenobamate studies. ~~In particular, the average baseline seizure rates of patients included in the ITC trials may be higher than would be seen in clinical practice.~~"	epilepsy. For patients with a lower frequency of seizures, it would have not been possible to detect meaningful outcomes; for example, in patients experiencing fewer than four seizures per 28 days, a 50% reduction in seizures would mean only a reduction in seizure frequency of 2 seizures per 28 days. In order to identify statistical significance, far more patients would need to be enrolled in the study. Therefore, the inclusion criteria of at least 8 partial seizures per 28 days ensures meaningful reduction in seizures and response rate can be observed. Moreover, clinical advisers to the Company reported that, on average, clinicians experience patients with drug resistant epilepsy who have more seizures than observed at baseline in the cenobamate studies. Furthermore, results presented on Page 53 of the CS demonstrate response to treatment regardless of number of seizures at baseline. Therefore, there are not generalisability issues with regards to seizure frequency at baseline.	
Section 3.3.1.1, Page 77:	The Company requests that the text be	The Company recognises that titration periods for included ITC	Not factual inaccuracy.

"Clinical advisers to the ERG added that titration periods are significantly shorter and more intense than would be seen in clinical practice. This limits the applicability of the trial evidence. In addition, the duration of titration, maintenance and treatment periods varied significantly across the trials, and four trials (all of brivaracetam) did not report a titration period. This limits the comparability of the trials and the validity of the ITC."	amended to the following: "Clinical advisers to the ERG added that titration periods are significantly shorter and more intense than would be seen in clinical practice. This limits the applicability of the trial evidence. In addition, the duration of titration, maintenance and treatment periods varied significantly across the trials, and four trials (all of brivaracetam) did not report a titration period. **Whilst** this limits the comparability of the trials and the validity of the ITC**, clinical advisers to the Company verified the outcomes of the ITC with comparators relative to cenobamate**."	studies are significantly shorter and more intense than would be seen in clinical practice. However, the open-label data from study C021 demonstrate tolerability over the anticipated use of cenobamate in clinician practice.	
Long-term efficacy of cenobamate and the comparators			
Section 3.3.3.1, Page 81: "ERG clinical advisers estimated that in clinical practice, one year follow-up is generally required to assess treatment failure. With a treatment period ranging from seven to 19 weeks, the trials may not have a sufficient follow-up to provide clinically meaningful efficacy results."	The Company requests that the text be amended to the following: "ERG clinical advisers estimated that in clinical practice, one year follow-up is generally required to assess treatment failure. With a treatment period ranging from seven to 19 weeks, the trials **included in the ITC** may not have a sufficient follow-up to provide clinically meaningful efficacy results. **However, results of the ITC were validated as aligned to clinical practice by clinical advisers to the Company. Moreover, long-term efficacy data from the C017 OLE demonstrate that response to treatment is sustained in those who remain on treatment**"	Though the Company recognises that there is variation in titration and maintenance periods between trials, clinical efficacy and safety derived from the ITC results were validated by clinicians as what they would observe in clinical practice.	Not factual inaccuracy, but a matter of interpretation.

Issue 5 Interpretation of discontinuation of comparators relative to cenobamate (ERG's issue 8)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.1, Page 17: "Data used to inform the rate of discontinuation for comparators implies that the risk of discontinuation in patients taking cenobamate is lower than that of comparators; however, these estimates are informed by non-comparative data and highly uncertain."	The Company requests the text is updated as follows: "Data used to inform the rate of discontinuation for comparators implies that the risk of discontinuation in patients taking cenobamate is lower than that of comparators **in line with data from open-label studies.**~~; however,~~ However, these estimates are informed by non-comparative data and, **therefore, rates of discontinuation relative to cenobamate are moderately** ~~and highly~~ uncertain."	Clinical experts to the Company advised that retention to treatment with cenobamate would be increased compared to other treatments due to increased seizure freedom. In the absence of relevant, indirectly compared data, hazard ratios for discontinuation with comparators relative to cenobamate were derived from published data on retention to treatment. These data included a large numbers of patients over long time periods for which the retention to treatment is reliable and reflects retention as expected from clinicians. The uncertainty in discontinuation with comparators arises only from the relative likelihood of discontinuation with cenobamate, as there are no direct comparisons of retention to cenobamate with alternative ASMs.	Not factual inaccuracy, but a matter of interpretation.
Section 1.5, Page 28: "All hazard ratios assumed implied that the risk of discontinuation in patients taking cenobamate was lower than that of comparators. Evidence from	The Company requests the text is updated as follows: **Section 1.5, Page 28:** "All hazard ratios assumed implied that the risk of discontinuation in patients taking cenobamate was lower than that of	As highlighted in the CS, TEAE-related discontinuation rates in the C017 study used in the NMA were substantially higher across the cenobamate 200 mg and 400 mg arms (13.6% and 19.8%, respectively) compared to the TEAE-	Section 1.5 This is not a factual inaccuracy. The text added by the company implies that the shorter titration period is the sole reason for the higher discontinuation rate with

the NMA implied the opposite effect." **Section 4.2.6.4, Page 123:** "The estimates from the NMA imply that discontinuation rate with cenobamate is higher than with comparators. This is consistent with the findings that cenobamate is more likely to leads to ADRs – the key reason for discontinuation when first starting treatment with a new ASM. However, the ERG recognises that the resulting estimates may underestimate the probability of treatment discontinuation, and so explore alternative scenarios where the discontinuation rate of cenobamate is the same as the discontinuation rate of the comparators."	comparators. **As forced titration in the C017 study led to elevated rates of treatment discontinuation during the double-blind treatment period, evidence** ~~Evidence~~ from the NMA implied the opposite effect**.**" **Section 4.2.6.4, Page 123:** "The estimates from the NMA imply that discontinuation rate with cenobamate is higher than with comparators **during the double-blind period of key trials**. This is consistent with the findings that**, during the double-blind period of key trials for the comparators,** cenobamate is more likely to leads to ADRs – **one of** the key ~~reason~~ **reasons** for discontinuation when first starting treatment with a new ASM. However, the ERG recognises that the resulting estimates ~~may~~ underestimate the probability of treatment discontinuation, and so explore alternative scenarios where the discontinuation rate of cenobamate is the same as the discontinuation rate of the comparators."	related discontinuation rates expected in clinical practice, likely due to a forced titration that is faster than expected in clinical practice.[2] Meanwhile, only [redacted] of patients discontinued in the C021 study where titration is aligned with the expected use of cenobamate in clinical practice.[3] Contrary to the available long-term evidence reported in the cited sources in the company submission, discontinuation rates of comparators are lower than cenobamate.[4–7] Therefore, it should be clarified that estimates of increased discontinuation with cenobamate relate only to the double-blind treatment period.	cenobamate than with comparators, observed in the NMA. There is no evidence to support that statement. Study C021 was fundamentally different to evidence included in the NMA, and so the length of titration may not be the sole reason for the differences in the discontinuation between the two studies. The limitations of naïve comparisons used to inform the discontinuation rate of comparators in the company base case are discussed in detail in the ERG report (section 4.2.6.4). Section 4.2.6.4 The section refers to generalising the NMA results to inform the discontinuation rate in the model. Reference to the double-blind period of the trial suggested by the company is thus not relevant. The ERG has corrected 'the key reason' to 'one of the key reasons'.

Issue 6 Interpretation of the quality-of-life evidence (ERG's issue 9)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.10.4, Page 128: "First, it is not clear why there was a preference for a mapping study through a survey and the SF-6D tool over and above performing a mapping exercise of QOLIE-31-P scores from the pivotal C017 study, or any other relevant study with QOLIE-31-P data, to EQ-5D using a published algorithm. The ERG…"	To update the text as follows: "~~First, it is not clear why there was a preference for a mapping study through a survey and the SF-6D tool over and above performing a mapping exercise of QOLIE-31-P scores from the pivotal C017 study, or any other relevant study with QOLIE-31-P data, to EQ-5D using a published algorithm.~~ The ERG…"	Reasons for the approach to quality of life have been justified. During the decision problem meeting, the inadequacy of EQ-5D for epilepsy were discussed. Moreover, limitations of QOLIE-31-P collected in the study were noted; as the questionnaire was only administered to English speaking patients, only a small share of the C017 patient population completed the questionnaire. Therefore, it was not possible to apply or derive a mapping from existing C017 data, as explained in question B29(c) of the clarification letter response to the ERG. Subsequently, the Company explained their preference for the SF-6D mapping tool in response to question B29c of the clarification letter response, which stated that: "there was a limited sample size in which QOLIE-31-P was collected in the C017 study; moreover, the duration of the C017 study was not sufficient to collect robust evidence for the long-term impacts to quality of life from treatment with cenobamate. Additionally, it has	Not factual inaccuracy, but a matter of interpretation.

		been acknowledged that the QOLIE-31-P does not map well to EQ-5D."	
Section 4.2.10.4, Page 128: "This indicates that the chosen OLS model, although offering the best fit from the list of models tested, it does not offer a good fit to the data."	The Company also requests that text on page 129 of the ERG report be expanded to include the input from clinical experts. "This indicates that the chosen OLS model, although offering the best fit from the list of models tested, it ~~does not offer a good fit to the data~~ **underestimates the incremental gains in quality of life associated with improved health states**."	Despite the underestimation of HSUV variation between response health states, clinical advisers to the Company noted that the only substantial disparity between the mean SF-6D utility values applied in the economic model and expected values clinical practice were for the seizure freedom health state. They advised that there would be a large increment in quality of life between patients who have achieved a very high response and those who have achieved seizure freedom. On average, there was no substantial deviation between the SF-6D values generated by the mapping study and what clinicians would expect in clinical practice for patients with 'no response', 'moderate', 'high' and 'very high' response rates.	Not factual inaccuracy. The mapping algorithm has a RMSE of approximately 0.1 for all models tested, which is considered high given the parameter space of SF-6D (going from 0.29 to 1). This plus the fact that the OLS mapping algorithm does not appropriately reflect the variability in observed SF-6D utility index scores, underestimating the range of predicted utilities, is indicative of a poor data fit.

Issue 7 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Incorrect reports			

Section 3.1.2, Page 46: "Cenobamate Trial C013(14)(Chung et al. 2020) was excluded from the ITC efficacy analyses (but included in the safety analyses), as the six-week maintenance period was deemed insufficient to demonstrate long-lasting efficacy(15)."	To update the text as follows: "Cenobamate Trial C013(14) was excluded from the ITC ~~efficacy~~ analyses ~~(but included in the safety analyses),~~ as the six-week maintenance period was deemed insufficient to demonstrate long-lasting efficacy (15)."	The base case ITC safety analysis did not include the Cenobamate Trial C013.	Thank you. The sentence was edited as suggested.
Section 3.2.4.1, Page 64: "During the double-blind period, 84 (76%) patients in the cenobamate 100 mg treatment group, 100 (90%) patients in the 200 mg treatment group and 70 (65%) patients in the 400 mg treatment group experienced at least 1 TEAE."	To update the text as follows: "During the double-blind period, **70 (65%)** ~~84 (76%)~~ patients in the cenobamate 100 mg treatment group, ~~100 (90%)~~ **84 (76%)** patients in the 200 mg treatment group and ~~70 (65%)~~ **100 (90%)** patients in the 400 mg treatment group experienced at least 1 TEAE."	Typographical error – incorrect figures for treatment arms	The sentence was edited as suggested.
Section 3.2.4.4, Page 70 "The overall modal daily dose of cenobamate was [redacted] (minimum dose: 50 mg, maximum dose: 400 mg) daily."	To update the text as follows: "The overall **mean** modal daily dose of cenobamate was [redacted] (minimum dose: 50 mg, maximum dose: 400 mg) daily."	Missing information	The sentence was edited as suggested.
Section 3.2.4.1, Page 67 "Four patients (4%) in the cenobamate 100 mg group, 8 (7%) patients in the 200 mg group, 10 (9%) patients in the 400 mg group and 6 (6%) patients in the placebo group experienced	To update the text as follows: "**Ten patients (9%)** ~~Four patients (4%)~~ in the cenobamate 100 mg group, **4 (4%)** ~~8 (7%)~~ patients in the cenobamate 200 mg group, **8 (7%)** ~~10 (9%)~~ patients in the 300 mg group, and 6 (6%) patients in the placebo group	Typographical error – incorrect figures for treatment arms	The sentence was edited as suggested.

SAEs."	experienced SAEs		
Section 3.2.4.4, Page 71 "Overall, [redacted] patients who received at least one dose of cenobamate reported a TEAE."	To update the text as follows: "Overall, [redacted] patients who received at least one dose of cenobamate reported a **treatment-related** TEAE."	Missing information	The sentence was edited as suggested.
Section 3.4, Page 85: [redacted]	To update the text as follows: [redacted]	Missing information	The sentence was edited as follows (additions in bold): [redacted]
Section 4.2, Page 97: "Upon starting treatment with cenobamate, or one of its four comparators, patients can have five different levels of treatment response, where higher levels of response are associated with lower mortality, higher Health Related Quality of Life (HRQoL) and lower healthcare resource use"	To update the text as follows: "Upon starting treatment with cenobamate, or one of its four comparators, patients can have five different levels of treatment response, where higher levels of response are associated with **fewer seizures,** lower mortality, higher Health Related Quality of Life (HRQoL), and lower healthcare resource use"	Missing information	Edited as suggested.
Section 4.2.2, Page 99: "Patients who discontinue treatment move to the 'subsequent ASM' state, representing subsequent pharmacotherapy with ASMs. Patients can then either stay in this state until death, or	To update the text as follows: Patients who discontinue treatment move to **either** the 'subsequent ASM' state, representing subsequent pharmacotherapy with ASMs~~. Patients can then either stay in this state until death~~, ~~or move onto~~ VNS or surgery. **VNS and surgery are both** one-off treatments	Misspecification – on discontinuation patients may immediately proceed to either ASM treatment, VNS or surgery.	Edited as follows. Patients who discontinue treatment move to the 'subsequent ASM' state, representing subsequent pharmacotherapy with ASMs, VNS or surgery. Patients can

move onto VNS or surgery – one-off treatments provided to a small proportion of patients with DRE"	provided to a small proportion of patients with DRE. **Patients stay in these states until death, whilst patients who move into the 'subsequent' ASM state may also move onto VNS or surgery.**		then either stay in this state until death, or move onto VNS or and surgery – are both one-off treatments provided to a small proportion of patients with DRE. VNS and surgery are modelled as tunnel states to ensure patients can only spend one cycle in each (due to the one-off nature of the treatments), followed by death from VNS or surgery, or 'post-surgery' and 'post-VNS' states where patients stay until they die. Patients in 'subsequent ASMs' state may also move onto VNS or surgery.
Section 4.2.2.1, Page 99: "The model structure is different to all models for FOS epilepsy identified in the company's review or in NICE CG137. "	To update the text as follows: The model structure ~~is different to all~~ **expands on the structure of the** models for FOS epilepsy identified in the company's review or in NICE CG137.	Missing information – model structure expands on existing structures identified.	The sentence is not factually inaccurate and the proposed edit changes the meaning of the sentence.
Section 4.2.4, Page 105: "The intervention is 3rd-line adjunctive treatment with cenobamate, as per the decision problem. Treatment with cenobamate involves a ≥10-week titration period, followed by maintenance treatment with 200mg or 400mg dose."	To update the text as follows: "The intervention is 3rd-line adjunctive treatment with cenobamate, as per the decision problem. Treatment with cenobamate involves a ~~≥10-week~~ **≥12-week** titration period, followed by maintenance treatment with 200mg or 400mg dose."	Typographical error - numerical	Edited.

Section 4.2.6.3, Page 118: "In the absence of an alternative source, the ERG's base case applied the odds ratio reported by Chen et al. (2018) to the probability of seizure freedom in trial C017 to derive response in subsequent ASMs..."	The Company requests that the text be updated as follows: "In the absence of an alternative source, the ERG's base case applied the odds ratio reported by Chen et al. (2018) to the probability of **not achieving** seizure freedom in trial C017 to derive response in subsequent ASMs…"	The odds ratio is applied to the probability of not being seizure free, rather than the probability of being seizure free.	Edited.
Section 4.2.6.4, Page 119: "The ERG considers this to be the preferred approach to model response to ASMs, and in their base case, the effectiveness of subsequent ASMs is derived relative to the least effective comparator – eslicarbazepine acetate."	To update the text as follows: "The ERG considers this to be the preferred approach to model response to ASMs, and in their base case, the effectiveness of subsequent ASMs is derived relative to the least effective comparator – ~~eslicarbazepine acetate~~ **brivaracetam"**	Typographical error – wrong comparator mentioned.	Edited.
Section 4.2.6, Page 119: "Item 15: Applying the odds ratio of treatment resistance to the odds of no resistance likely to bias the response rates for subsequent ASMs."	"Item 15: Applying the odds ratio of treatment resistance to the odds of no ~~resistance~~ **response** likely to bias the response rates for subsequent ASMs."	Typographical error	Edited.
Section 4.2.6.4, Page 120: "The alternative scenarios did not significantly impact the cost-effectiveness model results - the incremental costs for cenobamate relative to the comparators ranged between [redacted] and [redacted] with	To update the text as follows: "The alternative scenarios did not significantly impact the cost-effectiveness model results - the incremental costs for cenobamate relative to the comparators ranged between [redacted] and [redacted] [redacted] with C021 data only and between	Typographical error - numerical	Edited.

C021 data only and between [redacted] and [redacted] and with C017 OLE data only, while QALYs ranged between -0.752 and -1.011, and between -0.685 and -0.881, respectively."	[redacted] and [redacted] and with C017 OLE data only, while QALYs ranged between -0.752 and -1.011, and between ~~-0.685~~ **-0.684** and -0.881, respectively."		
Section 4.2.6.4, Page 123: However, the ERG recognises that the resulting estimates may underestimate the probability of treatment discontinuation, and so explore alternative scenarios where the discontinuation rate of cenobamate is the same as the discontinuation rate of the comparators.	The Company requests that the text be updated as follows: "However, the ERG recognises that the resulting estimates may underestimate the probability of treatment discontinuation **with comparators**, and so explore alternative scenarios where ~~the~~ **their** discontinuation rate ~~of cenobamate~~ is the same as ~~the discontinuation rate of the comparators~~ **cenobamate's after a fixed number of cycles**.	The text does not clearly describe the scenarios performed; please adjust the text as suggested to clarity.	Edited.
Section 4.2.7, Page 124: "A change in the number of seizures per level of response would not alter the ranking of cenobamate and its comparators, as QALYs are assumed to increase and resource use to decrease with the level of response. Thus, the higher the response to treatment, the higher the increase in QALYs will be and the higher the reduction in resource use will be observed."	"A change in the number of seizures per level of response would not alter the ranking of cenobamate and its comparators, ~~as QALYs are assumed to increase and~~ resource use ~~to decrease with the level of~~ **decreases whilst** response **increased; QALYs are unaffected by the number of seizures**. Thus, the higher the response to treatment, ~~the higher the increase in QALYs will be and~~ the higher the reduction in resource use will be observed."	Misrepresentation of model effects	Edited as follows. A change in the number of seizures per level of response would not alter the ranking of cenobamate and its comparators because, an increase in response decreases as QALYs are assumed to increase and resource use to decrease, while QALYs are unaffected by the number of seizures with the level of response. Thus, the higher the response to treatment, the higher the

			increase in QALYs will be and the higher the reduction in resource use will be observed.
Section 4.2.10.5, Page 130: "The disutility of accidents due to seizure occurrence was also captured in the model, where disutility duration for these acute events were assumed to be a month each."	To update the text as follows: "The disutility of accidents due to seizure occurrence was also captured in the model **as a scenario analysis**, where disutility duration for these acute events were assumed to be a month each."	Missing information	Edited as follows. The disutility of accidents due to seizure occurrence was also captured in the scenario analysis, where disutility duration for these acute events were assumed to be a month each.
Section 5.1, Page 137: "The presented results were derived after correcting a typographical error in the model transition probabilities (corrected by the company in response to points for clarification), and an error in the equation for deriving the incremental net monetary benefit for eslicarbazepine acetate (corrected by the ERG)"	The Company requests that the text be updated as follows: "The presented results were derived after correcting a typographical error in the model transition probabilities (corrected by the company in response to points for clarification)~~, and an error in the equation for deriving the incremental net monetary benefit for eslicarbazepine acetate (corrected by the ERG)~~."	The text should not be included as the formula in cell K14 on the results sheet, which describes the incremental net monetary benefit associated with the most costly comparator, has not been changed.	Text edited as suggested because incremental monetary benefit was not presented in the ERG report.
Section 6.2, Page 150, Table 2. Results of ERG's scenario analyses: "Dominated to dominant"	The Company requests that the text be updated as follows: "~~Dominated to dominant~~ "**Dominant to £1,051**"	Baseline seizure frequency does not affect the accumulation of QALYs in the model. Therefore, in the scenario where cenobamate is associated with more costs than lacosamide, it is also associated with more QALYs. Therefore, an	Edited to "£1,109 to dominant". The ICER of £1,109 was derived using the company base case after correcting the typographical error corrected in the points for clarification (analysis 1 in

		ICER should be reported.	the ERG report section 6). This has now been clarified in the report (Table 49, section 6.2)
Section 6.2, Page 150, Figure 12.	The Company requests that Figure 12 in the ERG report is updated using the data provided in Table 1.	The Company identified numerical errors for the incremental costs of lacosamide relative to cenobamate when the frequency of seizures at baseline are varied.	The incremental costs in Figure 12 were derived using the company base case after correcting the typographical error corrected in the points for clarification (analysis 1 in the ERG report section 6). This has now been clarified in the report (Table 49, section 6.2)
Section 6.3.1, Page 153: "20,5030"	To update the text as follows: **"20,030"**	Typographical error - numerical Analysis 10 + time to treatment discontinuation for comparators informed by the NMA. Error in incremental cost.	Edited.
Section 6.4, Page 157: "Moreover, and to be consistent with the literature, the ERG applied the effect of subsequent ASMs to the odds of no seizure freedom, with it being estimated relative to the least effective comparator (eslicarbazepine acetate), instead of cenobamate"	To update the text as follows: "Moreover, and to be consistent with the literature, the ERG applied the effect of subsequent ASMs to the odds of no seizure freedom, with it being estimated relative to the least effective comparator (~~eslicarbazepine acetate~~ **brivaracetam**), instead of cenobamate"	Typographical error – wrong comparator mentioned	Edited.

Spelling and grammar issues			
Section 1.4, Page 22: "In particular, the average baseline seizure rates of patients included the ITC trials may be higher than would be seen in clinical practice"	To update the text as follows: "In particular, the average baseline seizure rates of patients included **in** the ITC trials may be higher than would be seen in clinical practice"	Typographical error – grammar.	Edited.
Section 1.4, Page 24: "Due to the absence of head-to-head randomised controlled trials (RCTs) comparing cenobamate against relevant comparators, the company conducted an indirect treatment comparisons (ITC)"	To update the text as follows: "Due to the absence of head-to-head randomised controlled trials (RCTs) comparing cenobamate against relevant comparators, the company conducted ~~an~~ indirect treatment comparisons (ITC**s**)"	Typographical error – grammar.	Edited.
Section 2.1, Page 34: **"…** seizures (where patients experience-impaired awareness of their seizure)"	To update the text as follows: **"…** seizures (where patients **experience impaired**-awareness of their seizure)"	Typographical error – spelling	Edited.
Section 2.1.1, Page 34: "Approximately 60-70% of people with epilepsy seizure freedom"	To update the text as follows: "Approximately 60-70% of people with epilepsy **do not achieve** seizure freedom"	Typographical error – grammar	Edited.
Section 2.1.1, Page 35: "Most ASMs doses are titrated to a maintenance dose, then increased to a maximum tolerated dose"	To update the text as follows: "Most ASMs ~~doses~~ are titrated to a maintenance dose, then increased to a maximum tolerated dose"	Typographical error – grammar	Edited.
Section 2.3, Page 40: "Although levetiracetam are	To update the text as follows:	Typographical error – grammar.	Edited.

commonly prescribed as first and second-line treatments, ERG clinical advisers stated they may also be used as an adjunct to carbamazepine in a third line setting and as such may be a relevant comparator."	"Although levetiracetam ~~are~~ **is** commonly prescribed as **a** first and second-line treatment, ERG clinical advisers stated ~~they~~ it may also be used as an adjunct to carbamazepine in a third line setting and as such may be a relevant comparator."		
Section 2.3, Page 41: "Finally, the clinical studies for cenobamate demonstrate that carbamazepine and levetiracetam were the two of the most commonly used background therapies indicating that cenobamate is an adjunct to these rather than a comparator."	To update the text as follows: "Finally, the clinical studies for cenobamate demonstrate that carbamazepine and levetiracetam were ~~the~~ two of the most commonly used background therapies indicating that cenobamate is an adjunct to these rather than a comparator."	Typographical error – grammar.	Edited.
Section 2.3, Page 43: "Costs are considered form an NHS and Personal Social Services perspective."	To update the text as follows: "Costs are considered ~~form~~ **from** an NHS and Personal Social Services perspective."	Typographical error – spelling.	Edited.
Section 3.1.5, Page 48: "No further descriptions of models used were provided. Efficacy outcomes were the proportions of patients with ≥ 50, ≥ 75, ≥ 90, and 100% reduction in monthly seizure frequency during the maintenance treatment period compared with the pre-randomization baseline period"	To update the text as follows: "No further descriptions of models used were provided. Efficacy outcomes were the proportions of patients with ≥ 50**%**, ≥ 75**%**, ≥ 90**%**, and 100% reduction in seizure frequency per 28 days during the maintenance treatment period compared with the pre-randomization baseline period"	Missing information	Edited.
Section 3.2.1.1, Page 50, Table	To update the text as follows:	Typographical error – spelling.	

5: "All randomised subjects with at least one dose of cenobamate or placebo and any postbaseline seizure data"	"All randomised subjects with at least one dose of cenobamate or placebo and any **post-baseline** seizure data"		
Section 3.2.1.5, Page 53: "No evidence was provided to evaluate the impact of this protocol change on cenobamate's tolerability and efficacy, although this is likely to be relatively marginal as only 46 patients across all trial arms who initiated treatment prior to the protocol amendment."	To update the text as follows: "No evidence was provided to evaluate the impact of this protocol change on cenobamate's tolerability and efficacy, although this is likely to be relatively marginal as only 46 patients across all trial arms ~~who~~ initiated treatment prior to the protocol amendment."	Typographical error – grammar.	Edited.
Section 3.2.3.1, Page 60: "Similarly to Figure 4 above..."	To update the text as follows: ~~Similarly~~ "**Similar** to Figure 4 above..."	Typographical error – spelling.	Edited.
Section 3.2.4.1, Page 68: "During the double-blind treatment period, 11 (10.2%), 15 (13.6%) and 22 (19.8%) patients in the cenobamate 100 mg, 200 mg and 400 mg treatment groups discontinued due to AEs."	"During the double-blind treatment period, 11 (10.2%), 15 (13.6%) and 22 (19.8%) patients in the cenobamate 100 mg, 200 mg and 400 mg treatment groups discontinued due to AEs**, respectively**."	Grammar	Edited.
Section 3.2.4.5, Page 72: "The duration titration phase of trials C017 and C013 (6 weeks for both studies) was significantly shorter than that of study C021	To update the text as follows: "The duration **of the** titration phase of trials C017 and C013 (6 weeks for both studies) was significantly shorter than that of study C021 (12	Typographical error – grammar.	Edited.

(12 weeks), and is not reflective of clinical practice."	weeks) and is not reflective of clinical practice."		
Section 3.3.2, Page 77: "Where reported, most patients were receiving two-to-three concomitant ASM, although the proportion of patients receiving two or three ASMs varied between the trials arms."	To update the text as follows: "Where reported, most patients were receiving two-to-three concomitant ASM**s**, although the proportion of patients receiving two or three ASMs varied between the **trials'** arms."	Typographical error – grammar	Edited.
Section 3.3.3, Page 80: "The duration of the evaluation periods included in the ITC also varied across the trials, ranging from 7 to 14 weeks (CS Appendix D, table 13)."	To update the text as follows: "The duration of the evaluation periods included in the ITC also varied across the trials, ranging from 7 to 14 weeks (CS Appendix D~~, table 13~~ **table 11**)."	Typographical error – cross-referencing	The sentence refers to ITC inputs reported in Appendix table 13. No change required.
Section 3.4, Page 82: "Due to the absence of head-to-head comparisons between cenobamate and other adjunctive ASMs, the company conducted an indirect treatment comparison (ITC) to compare efficacy and safety outcomes of cenobamate with the following third generation ASMs: brivaracetam, perampanel, lacosamide, and esclicarbazepine acetate."	To update the text as follows: "Due to the absence of head-to-head comparisons between cenobamate and other adjunctive ASMs, the company conducted an ~~indirect treatment comparison~~ ~~(~~ITC~~)~~ to compare efficacy and safety outcomes of cenobamate with the following third generation ASMs: brivaracetam, perampanel, lacosamide, and ~~esclicarbazepine~~ **eslicarbazepine** acetate."	Typographical error – spelling. No need to define ITC again.	Corrected.
Section 3.5.3, Page 90:	To update the text as follows: **"**Joint synthesis ~~models~~ **model** results"	Typographical error – spelling.	Replaced with: "Joint synthesis models' results".

"Joint synthesis models results"			The table of headings was updated accordingly.
Section 3.5.3.2, Page 91: "Results for the joint synthesis models, adjusting for the placebo effect are presented in Table 22Table23."	To update the text as follows: "Results for the joint synthesis models, adjusting for the placebo effect**,** are presented in Table22~~Table23~~."	Typographical error – cross-referencing and grammar.	Replaced with: "Results for the joint synthesis models, adjusting for the placebo effect are presented in Table 22 and Table 23."
Section 4.1.1, Page 96: "The excluded publications were submissions to AWTTC that included model-based cost-effectiveness analyses of brivaracetam, perampranel and eslicarbazepine as adjuncts to therapy for FOS."	To update the text as follows: "The excluded publications were submissions to AWTTC that included model-based cost-effectiveness analyses of brivaracetam, ~~perampranel~~ **perampanel** and eslicarbazepine as adjuncts to therapy for FOS."	Typographical error – spelling	Corrected.
Section 4.2.2.1, Page 100: "The company argued that resource use and HRQoL in patients who achieved ≥75% or ≥90% reduction in seizures would differ to those who achieved only a 50 to 75% reduction, and therefore, using a less granular model structure, where only three levels of response are modelled, may underestimate the benefits of cenobamate, relative to its comparators."	To update the text as follows: "The company argued that resource use and HRQoL in patients who achieved ≥75% or ≥90% reduction in seizures would differ to those who achieved only a **50%** to 75% reduction, and therefore, using a less granular model structure, where only three levels of response are modelled, may underestimate the benefits of cenobamate, relative to its comparators."	Missing information.	Corrected.
Section 4.2.2.1, Page 100: "The ERG recognises that resource use and HRQoL in	To update the text as follows: "The ERG recognises that resource use and	Missing information.	Corrected

patients who achieve sustained ≥75% or ≥90% seizure reduction could differ to those who achieve only a 50 to 75% reduction."	HRQoL in patients who achieve sustained ≥75% or ≥90% seizure reduction could differ to those who achieve only a **50%** to 75% reduction."		
Section 4.2.2.1, Page 101: "According to ERG clinical advisors, patients with FOS epilepsy who discontinue third line adjunctive treatment can be prescribed any one of many ASMs available in the UK, and will likely cycle through many more lines of therapy."	To update the text as follows: "According to ERG clinical advisors, patients with FOS epilepsy who discontinue third line adjunctive treatment can be prescribed ~~any~~ one of many ASMs available in the UK, and will likely cycle through many more lines of therapy."	Typographical error – grammar.	Edited.
Section 4.2.2.1, Page 101: "Due to the lack of trial data, the relative effect of comparators on ≥75% and ≥90% seizure reduction was derived from their effect on ≥50% reduction estimated in the NMA, assuming that the relative effect (odds ratio) was the same in all three levels of response"	To update the text as follows: "Due to the lack of trial data, the relative effect of comparators on ≥75% and ≥90% seizure reduction was derived from their effect on ≥50% reduction estimated in the NMA, **conservatively** assuming that the relative effect (odds ratio) was the same in all three levels of response"	Missing information.	The original ERG statement is not factually incorrect.
Section 4.2.2.1, Page 102: "The company provided an additional scenario where, after the trial C017 end point, the cycle length was increases from 28 to 84 days (corresponding to cycle 5 in the model), and transition probabilities were informed by the C017 OLE trial instead of C017	To update the text as follows: "The company provided an additional scenario where, after the trial C017 end point, the cycle length was ~~increases~~ **increased** from 28 to 84 days (corresponding to cycle 5 in the model), and transition probabilities were informed by the C017 OLE trial instead of C017 trial alone."	Typographical error – spelling.	Corrected.

trial alone.”			
Page 4.2.6.1, Page 107: “..arms. proportion of patients with different levels of response in cenobamate and placebo arms at the end of the maintenance period in trial C017 is shown in Table 26.”	To update the text as follows: “**The** proportion of patients with different levels of response in **the** cenobamate and placebo arms at the end of the maintenance period **of** trial C017 is shown in Table 26.”	Typographical error – grammar.	Corrected.
Page 4.2.6.1, Page 109: “…47,182”	To update the text as follows: “**£**47,182”	Typographical error – numerical.	Edited as advised.
Page 4.2.6.1, Page 111: “…(30.18% in C017 compared to 46.04 to 64.2 in C021 and C017 OLE, respectively.”	To update the text as follows: “…(30.18% in C017 compared to 46.04% to 64.2% in C021 and C017 OLE, respectively.”	Missing information	Edited as advised.
Section: 4.2.6.2, Page 115: “The dose used in C013 is licensed, and so the ERG considers that, for consistency, C013 should not be excluded from the NMA on the basis of dose. Regarding validity of the results, the company argued that inclusion of trial C013 [redacted]	To update the text as follows: “The dose used in C013 is licensed, and so the ERG considers that, for consistency, C013 should not be excluded from the NMA on the basis of dose. Regarding validity of the results, the company argued that inclusion of trial C013 [redacted]	Typographical error – spelling.	Edited as advised.

Section 4.2.6.4, Page 120, Table 35: "Perampranel"	"~~Perampranel~~ **Perampanel**"	Typographical error - spelling	Edited as advised.
Section 4.2.6.4, Page 121: "The ERG believes that the searches may have excluded relevant studies, such as the study by (60), recommended by the clinical advisors to the ERG."	To update the text as follows: "The ERG believes that the searches may have excluded relevant studies, such as the study by **Novy et al.** (60), recommended by the clinical advisors to the ERG."	Missing information	Edited as advised.
Section 4.2.6.4, Page 124: "…..in patients who have 50% to <100% reduction in seizure frequency."	To update the text as follows: "…..in patients who have **≥50%** to <100% reduction in seizure frequency."	Typographical error – missing information	Edited as advised.
Section 4.2.8, Page 125: "The ERG is satisfied that epilepsy are likely to have higher risk of mortality than the general population"	To update the text as follows: "The ERG is satisfied that **patients with** epilepsy are likely to have higher risk of mortality than the general population"	Typographical error – grammar	Edited as advised.
Section 4.2.9.1, Page 125: "The ERG broadly agrees with the methods for accounting for adverse drug reactions in the cost-effectivenes model."	To update the text as follows: "The ERG broadly agrees with the methods for accounting for adverse drug reactions in the cost-~~effectivenes~~ **effectiveness** model."	Typographical error – spelling.	Edited as advised.
Section 4.2.10.2, Page 126: "However, the ERG wishes to highlightthat there is evidence in	To update the text as follows: "However, the ERG wishes to ~~highlightthat~~ **highlight that** there is evidence in the literature	Typographical error – spelling.	Edited as advised.

the literature to suggest that the QOLIE-31 tool is sensitive to measuring a seizure frequency reduction over 14 weeks' follow-up (64, 65)."	to suggest that the QOLIE-31 tool is sensitive to measuring a seizure frequency reduction over 14 weeks' follow-up (64, 65)."		
Section 4.2.11.3, Page 134: "Background therapy incurrs no additional administration cost, assuming prescriptions would be issued simultaneously with adjuvant treatment, both when used alongside third line therapy and subsequent ASMs."	To update the text as follows: "Background therapy ~~incurrs~~ **incurred** no additional administration cost, assuming prescriptions would be issued simultaneously with ~~adjuvant~~ **adjunctive** treatment, both when used alongside third line therapy and subsequent ASMs."	Typographical error – spelling.	Edited as advised.
Section 6.1.1.13, Page 145: "As discussed in section 4.2.6.1 (item 4), treatment discontinuation in the company's model …"	To update the text as follows: "As discussed in section ~~4.2.6.1~~ **4.2.6.4** (~~item 2~~ item **17),** treatment discontinuation in the company's model …"	Typographical error – wrong cross reference	Edited as advised.
Section 6.2, Page 146: "This is because the inclusion of study C013 increased the effect of comparators on seizure freedom, suggesting that brivaracetam was mode effective than cenobamate."	To update the text as follows: "This is because the inclusion of study C013 increased the effect of comparators on seizure freedom, suggesting that brivaracetam was ~~mode~~ **more** effective than cenobamate."	Typographical error – spelling.	Edited as advised.

Issue 8 Confidentiality markings

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response

Executive summary, Page 21: **“**Due to cenobamate higher drug costs, the ERG expects cenobamate to be dominated by remaining adjunctive therapies.”	Cenobamate drug costs have previously been marked as commercial in confidence in the company submission (Table 57, Page 126, Section B.3.5.1) and therefore should remain confidential.	Please amend the sentence to: “Due to cenobamate [redacted], the ERG expects cenobamate to be dominated by remaining adjunctive therapies.”	Edited as advised.

Section 2.2.2, Page 37: "In response to a request for clarification, the company specified the choice of comparators was in line with a consensus statement from a survey of 14 UK based neurology consultants, according to which cenobamate was "as an adjunctive therapy in adult patients with focal onset seizures with or without secondary generalisation who are not adequately controlled with at least two previously prescribed ASMs *and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies*" (ERG italics)."	The patient population has previously been marked as commercial in confidence in the company submission (Page 13, Section B.1.1) and therefore should remain confidential.	Please amend the sentence to: "In response to a request for clarification, the company specified the choice of comparators was in line with a consensus statement from a survey of 14 UK based neurology consultants, according to which cenobamate was "[redacted] *and who have failed to respond to, are intolerant to, or are unsuitable for first- or second-generation adjunctive therapies'* (ERG italics)."	Edited.
Section 3.2.3.1, Page 58: "The largest effects were generally observed in the maintenance phase population, and differences in absolute rates of response between the mITT and mITT-M population were most notable for seizure freedom in the 400 mg arm (6.3% in mITT population vs. 21.1% for mITT-M)" **Section 3.2.3.1, Table 7, Page 59-60:**	The results for the mITT population of the C017 study were not included in the CS, but should be marked as academic in confidence in the ERG report.	"The largest effects were generally observed in the maintenance phase population, and differences in absolute rates of response between the mITT and mITT-M population were most notable for seizure freedom in the 400 mg arm ([redacted] in mITT population vs. 21.1% for mITT-M)" The data within the columns under	Edited.

The data within the columns under the mITT heading are not marked up.		the mITT heading should be marked as academic in confidence.	
Section 4.2.2, Page 100: "The new model structure did not significantly impact the results: the incremental costs and QALYs change in favour of the comparators (e.g. incremental costs and QALYs for cenobamate relative to lacosamide reduced from £30,646 to £28,274 and from -0.715 to -0.660, respectively) but cenobamate remained dominant."	The results of the new model structure reported in the Company's response to the ERG's clarification questions (Question B4, Page 33; Question B29, Page 79) were marked as commercial in confidence and should be marked as such in the ERG report.	Please amend the sentence to: "The new model structure did not significantly impact the results: the incremental costs and QALYs change in favour of the comparators (e.g. incremental costs and QALYs for cenobamate relative to lacosamide reduced from [redacted] to [redacted] and from -0.715 to -0.660, respectively) but cenobamate remained dominant."	Edited.
Section 4.2.2, Page 102: "This scenario increased the incremental costs of cenobamate relative to the comparators from between £30,646 and £47,182 to between £49,140 and £64,728, and decreased the incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166…"	Any incremental costs for cenobamate should be marked as commercial in confidence in the ERG report.	Please amend the sentence to: "This scenario increased the incremental costs of cenobamate relative to the comparators from between [redacted] and [redacted] to between [redacted] and [redacted], and decreased the incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166…"	Edited.
Section 4.2.3, Page 102: "…whereas in the model, the average number of baseline seizures is assumed to be 13.38 (Table 10 in document B of the CS), based on clinical opinion." **Section 4.2.3, Page 103:**	As the results based on clinical opinion are academic in confidence, they should be marked as such in the ERG report.	Please amend the sentence to: "…whereas in the model, the average number of baseline seizures is assumed to be [redacted] (Table 10 in document B of the CS), based on clinical opinion." And	Edited.

"In the model, the average number of seizures is assumed to be 13.38 based on clinical opinion. The ERG considers this number to be an overestimate of the baseline number of seizures." **Section 4.2.3, Page 105:** "Item 4: The baseline number of seizures of 13.38 may represent an overestimate of the average number of seizures in UK patients eligible for cenobamate and its comparators."		"In the model, the average number of seizures is assumed to be [redacted] based on clinical opinion. The ERG considers this number to be an overestimate of the baseline number of seizures." And "Item 4: The baseline number of seizures of [redacted] may represent an overestimate of the average number of seizures in UK patients eligible for cenobamate and its comparators."	
Section 4.2.6.1, Page 107, Table 26: The contents of Table 26 are not marked.	Distribution of patients amongst health states is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	The contents of Table 26 should be marked academic in confidence.	Edited.
Section 4.2.6.1, Page 108, Table 27 The contents of Table 27 are not marked up.	Distribution of patients amongst health states is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	The contents of Table 27 should be marked academic in confidence.	Edited.
Section 4.2.6.1, Page 108, Table 28 The contents of Table 28 are not marked up.	Transition probabilities are not going to be published and should be marked commercial in confidence.	The contents of Table 28 should be marked commercial in confidence.	Edited.
Section 4.2.6.1, Page 108: "This scenario did not significantly impact the cost-effectiveness	Any incremental costs for cenobamate should be marked as commercial in confidence in the ERG report.	Please amend the sentence to: "This scenario did not significantly impact the cost-effectiveness results	Edited.

results – it changed incremental costs for cenobamate relative to the comparators from between £30,646 and £47,182 to between £49,140 and £64,728 and incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166."		– it changed incremental costs for cenobamate relative to the comparators from between [redacted] and [redacted] to between [redacted] and [redacted] and incremental QALYs from between -0.715 and -0.946 to between -0.955 and -1.166."	
Section 4.2.6.1, Page 109: "The error did not significantly impact the model results – incremental costs for cenobamate relative to the comparators decreased from between £30,814 and £47,342 to between £30,646 and 47,182, and incremental QALYs decreased from between -0.718 and -0.948 to between -0.715 and -0.946."	Any incremental costs for cenobamate should be marked as commercial in confidence in the ERG report.	Please amend the sentence to: "The error did not significantly impact the model results – incremental costs for cenobamate relative to the comparators decreased from between [redacted] and [redacted] to between [redacted] and [redacted], and incremental QALYs decreased from between -0.718 and -0.948 to between -0.715 and -0.946."	Edited.
Section 4.2.6.1, Page 111: "In C017 patients were more likely to receive a full 400mg dose (22.07% in C017 compared to 11.76% and 14.20% in C021 and C017 OLE, respectively), but less likely to receive more than 200mg (30.18% in C017 compared to 46.04 to 64.2 in C021 and C017 OLE, respectively)."	The percentage of patients on each dose should be marked as academic in confidence.	Please amend the sentence to: "In C017 patients were more likely to receive a full 400mg dose ([redacted] in C017 compared to [redacted] and [redacted] in C021 and C017 OLE, respectively), but less likely to receive more than 200mg ([redacted] in C017 compared to [redacted] to [redacted] in C021 and C017 OLE, respectively)."	Edited.
Section 4.2.6.2, Page 113, Table 32.	The distribution of patients across levels of response is marked as academic in	The data reported in Table 32 should be marked academic in confidence.	Edited.

Contents of Table 32 are not marked up.	confidence in the company submission and should be marked as such in the ERG report.		
Section 4.2.6.3, Page 118, Table 34. The contents of Table 34 are not marked up.	The distribution of patients across levels of response is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	Contents of the table should be marked academic in confidence.	Edited.
Section 4.2.6.4, Page 120, Table 35. The contents of Table 35 are not marked.	The probability of treatment retention is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	Contents of the table should be marked academic in confidence.	Edited.
Section 4.2.6.4, Page 121, Figure 11.	Retention to treatment is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	Figure 11 should be marked academic in confidence.	Edited.
Section 4.2.7, Page 123, Table 37	The number of seizures estimated in each health state is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	The contents of the table should be marked academic in confidence.	Edited.
Section 4.2.7, Page 123: "In the new model, the number of seizures was derived by assuming that patients with focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizures on average have a 81.58%, 79.85%, 79.66% seizure reduction on average, resulting in 2.62 seizures per 28 days, on average, in patients who have 50% to <100% reduction	Reduction in seizure frequency by health state and seizure type is marked as academic in confidence in the company submission and should be marked as such in the ERG report.	Please amend the sentence to: "In the new model, the number of seizures was derived by assuming that patients with focal aware, focal impaired awareness and focal to bilateral tonic-clonic seizures on average have a [redacted] seizure reduction on average, resulting in [redacted] seizures per 28 days, on average, in patients who have 50% to <100% reduction in	Edited.

in seizure frequency."		seizure frequency."	
Section 4.2.10.1, Page 126: "Improvements in terms of change from baseline were observed only in the placebo (mean(Δ)=3.76, SD(Δ)=11.4) and cenobamate 200 mg (mean(Δ)=0.62, SD(Δ)=12.0) arms, though the statistical significance of these gains was not tested. "	The QOLIE-31 scores as measured in the C017 study were marked as commercial in confidence in the company submission (Table 41, Page 111-112, Section B.3.4.1) and therefore should be marked as such in the ERG report.	Please amend the sentence to: "Improvements in terms of change from baseline were observed only in the placebo [redacted] and cenobamate 200 mg [redacted] arms, though the statistical significance of these gains was not tested."	Highlighted the relevant numbers.
Section 4.2.10.3, Page 127: "Socio-demographic characteristics of the 361 individuals (n=161 (44.6%) from the UK) with FOS included in the final analysis set can be found in Table 1 of Appendix H of the CS."	The socio-demographic characteristics are marked as academic in confidence in Appendix H of the company submission (Table 1, Page 11, Section H1.3.1) and therefore should be marked as such in the ERG report.	Please amend the sentence to: "Socio-demographic characteristics of the [redacted] individuals [redacted] from the UK) with FOS included in the final analysis set can be found in Table 1 of Appendix H of the CS."	Edited.
Section 4.2.10.3, Page 128: "…denoted by a narrower range (maximum - minimum) of values (0.61 vs 0.28, for observed and predicted, respectively)."	The SF-6D utility scores are marked as academic in confidence in the company submission (Table 43, Page 114, Section B.3.4.2) and therefore should be marked as such in the ERG report.	"…denoted by a narrower range (maximum - minimum) of values ([redacted], for observed and predicted, respectively)."	Edited.
Section 4.2.10.4, Page 129 "For example, the adjusted utility estimate for the 'no response' (<50% reduction in seizures) health state has a mean of 0.50, but with a very wide 95% confidence interval spanning between 0.0 and 1.0."	The utility values according to health state were marked as academic in confidence in the CS (Table 49, Page 120, Section B.3.4.5) and therefore should be marked as such in the report.	Please amend the sentence to: "For example, the adjusted utility estimate for the 'no response' (<50% reduction in seizures) health state has a mean of [redacted], but with a very wide 95% confidence interval spanning between [redacted]."	Edited.

Section 4.2.10.6, Page 130: "The ERG notes that no discussion was presented on the substantial differences between the mean (SE) utility estimates used by the company and the ones from Phumart et al. – e.g. no response/improvement: 0.50 (0.40) (company) vs 0.72 (0.21) (Phumart et al)."	The utility values for the cost-effectiveness analysis were marked as academic in confidence in the company submission (Table 53, Page 122, Section B.3.4.6) and therefore should be marked as such in the ERG report.	"The ERG notes that no discussion was presented on the substantial differences between the mean (SE) utility estimates used by the company and the ones from Phumart et al. – e.g. no response/improvement: [redacted] (company) vs 0.72 (0.21) (Phumart et al)."	Edited.
Section 4.2.10.7, Page 130: "The carer utility values were obtained via a small caregiver survey (n=86) aimed at carers of patients with ≥3 FOS per week according to the duration of seizure-freedom, where EQ-5D-5L was used to assess their HRQoL."	The caregiver quality of life patient characteristics are marked as academic in confidence in the company submission (Table 44, Page 116, Section B.3.4.3) and therefore should be marked as such in the ERG report.	Please amend the sentence to: "The carer utility values were obtained via a small caregiver survey [redacted] aimed at carers of patients with ≥3 FOS per week according to the duration of seizure-freedom, where EQ-5D-5L was used to assess their HRQoL."	Edited.
Section 4.2.10.7, Page 131: "For example, patients in the 'no response' health state have, on average, a utility value of 0.5, while their caregivers have an average disutility of 0.25, implying a total utility value of 0.25 (0.50-0.25) for this level of response, i.e. considering carer disutility halved the utility used in the model."	The caregiver quality of life patient characteristics are marked as academic in confidence in the company submission (Table 44, Page 116, Section B.3.4.3) and therefore should be marked as such in the ERG report.	Please amend the sentence to: "For example, patients in the 'no response' health state have, on average, a utility value of [redacted], while their caregivers have an average disutility of [redacted], implying a total utility value of [redacted] for this level of response, i.e. considering carer disutility halved the utility used in the model."	Edited.
Section 4.2.11.1, Page 133: "Treatment compliance was	The compliance rates for base case comparators were marked as academic in	Please amend the sentence to: "Treatment compliance was	Edited.

considered but assumed equivalent across treatments (at 96.6%)."	confidence in the company submission (Table 54, Page 125, Section B.3.5.1) and therefore should be marked as such in the ERG report.	considered but assumed equivalent across treatments (at [redacted])."	
Section 4.2.11.1, Page 132: "The total cost of background therapy per model cycle was [redacted]."	The total cost of background therapy is not marked as commercial in confidence in the CS (Page 132, Section B.3.5.1) and therefore should be marked as such in the ERG report.	Please amend the sentence to: "The total cost of background therapy per model cycle was £10.18."	Edited.
Section 4.2.11, Table 40, Page 133: The distribution and cost of background therapy is marked as academic in confidence.	In the company submission (Table 64, Page 134, Section B.3.5.1), % prescribed row is marked as academic in confidence and the cost per cycle is not marked up, but the % prescribed rows are marked as academic in confidence.	Please amend the mark-up of the "Drug cost per 28 days" column to not be marked up.	Edited.
Section 4.1.11, Table 41, Page 133: The "% of subsequent ASMs" and drug cost per 28 days columns are marked as academic in confidence.	In the company submission (Table 66, Page 137, Section B.3.5.1), the subsequent treatment distribution is marked as commercial in confidence.	Please amend the mark-up of the "% of subsequent ASMs" to commercial in confidence.	Edited.
Section 4.2.11.4, Page 134: "Total cost of routine monitoring by response is shown in Table 72 of the CS varying from £205.40 for no response to £17.88 for complete response."	The routine monitoring costs in the company submission (Table 72, Page 139, Section B.3.5.2) is marked as academic in confidence and therefore should be marked as such in the ERG report.	Please amend the sentence to: "Total cost of routine monitoring by response is shown in Table 72 of the CS varying from [redacted] for no response to [redacted] for complete response."	Edited.
Section 4.2.11.6, Page 135, Table 43 The contents of Table 43 are not marked up.	Healthcare costs for cenobamate are confidential and should therefore be marked as commercial in confidence.	The contents of the Table 43 should be marked as commercial in confidence.	Healthcare costs are identical for all comparators. In the report resource use is marked as AIC. The ERG has highlighted the table figures

			as AIC to match the company submission.
Section 6.1.1.5, Page 142: "In the model, the baseline number of seizures was elicited from clinical experts and assumed to be 13.38."	The baseline number of seizures should be marked as academic in confidence.	Please amend the sentence to: "In the model, the baseline number of seizures was elicited from clinical experts and assumed to be [redacted]."	Edited.
Section 6.1.1.5, Page 142: "The resulting baseline number of seizures is 6.95 (1.13 focal aware, 4.89 focal with impaired awareness, 0.93 focal to bilateral tonic-clonic), with the total number of seizures in each model cycle shown in Table 47."	The baseline number of seizures should be marked as academic in confidence.	Please amend the sentence to: "The resulting baseline number of seizures is [redacted] focal aware, [redacted] focal with impaired awareness, [redacted] focal to bilateral tonic-clonic), with the total number of seizures in each model cycle shown in Table 47."	Edited.
Section 6.1.1.5, Page 142-3, Table 47:	The baseline number of seizures should be marked as academic in confidence.	The contents of Table 47 should be marked academic in confidence.	Edited.
Section 6.2, Page 150, Table 49: The 'Incremental costs' column is not marked up.	The incremental costs are based on a price for cenobamate which has not yet been approved and therefore should be marked as commercial in confidence in the ERG report.	The 'Incremental costs' column should be marked commercial in confidence.	Edited.
Section 6.2, Page 151, Figure 12: The figure is not marked up.	The cost savings are based on a price for cenobamate which has not yet been approved and therefore should be marked as	Figure 12 should be marked commercial in confidence.	Edited.

	commercial in confidence in the ERG report.		
Section 6.3.2, Page 156, Figure 13: The figure is not marked up.	The cost savings are based on a price for cenobamate which has not yet been approved and therefore should be marked as commercial in confidence in the ERG report.	Figure 13 should be marked commercial in confidence.	Edited.
Section 6.4, Page 157: "The ERG's base case estimates incremental costs of comparators relative to cenobamate to range from £4,726 to £4,944 per patient."	The incremental costs are based on a price for cenobamate which has not yet been approved and therefore should be marked as commercial in confidence in the ERG report.	Please amend the sentence to: "The ERG's base case estimates incremental costs of comparators relative to cenobamate to range from [redacted] per patient."	Edited.

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1. Arvelle Therapeutics UK. Cenobamate clinician survey to understand approaches to tertiary prescribing: Final results.

2. Krauss GL, Klein P, Brandt C, *et al.* Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. *The Lancet Neurology* 2020. 19: 38–48.

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ERG response reference

Hu, Qingting, Fang Zhang, Wenhui Teng, Fangfang Hao, Jing Zhang, Mingxiao Yin, and Naidong Wang. 2018. 'Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis', *Journal of Neurology*, 265: 1-11.

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Technical engagement response form

Cenobamate for focal onset seizures in epilepsy [ID1553]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, Monday 17 May**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Samuel James**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Arvelle Therapeutics**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Positioning of cenobamate in the treatment pathway	**NO**	The ERG state that although positioning of cenobamate in the treatment pathway is clinically appropriate, it is more restrictive than the anticipated marketing authorisation, resulting in only a subset of suitable comparators being considered. The ERG suggest that topiramate, zonisamide and clobazam should be considered comparators and that the use of a cost-comparison model will enable comparisons of cenobamate with ASMs which have not been included in the network meta-analysis (NMA). Both these suggestions are inappropriate as these suggested comparators are not relevant and the use of a cost-comparison model would ignore the substantial improvements in clinical outcomes, and therefore in quality of life, that patients treated with cenobamate experience. Further details on the inappropriateness of these proposed approaches are detailed herein. Firstly, the additional comparators suggested by the ERG – topiramate, zonisamide and clobazam – are not relevant to the current UK clinical practice for the following reasons: - Around 20-30% of all patients with epilepsy will develop drug-resistant epilepsy (DRE).[1] The majority of patients with DRE will have suffered from epilepsy for many years including numerous years of unsuccessful treatment with various anti-seizure medicines (ASMs). Patients with DRE will have likely trialled several combinations of 1st and 2nd generation ASMs,

		including topiramate and zonisamide and therefore are unlikely to receive these therapies again. Patients who have previously trialled an ASM and not responded to treatment are unlikely to respond on a second attempt as the chance of seizure freedom declines with successive drug regimens.[2] The vast majority of DRE patients are, therefore, more likely to be treated with 3rd generation ASMs as they are newer therapies with fewer drug interactions, milder adverse events and have novel mechanisms of action compared to older generation ASMs[3] - Regarding the rate of adverse events, topiramate, zonisamide and clobazam have high-risk adverse event profiles. In particular, topiramate and zonisamide are associated with a significantly higher risk of cognitive side effects compared to other ASMs.[4] The cognitive side effects associated with topiramate and zonisamide are often severe and are common reasons why patients discontinue these treatments.[5,6] As patients with epilepsy are more likely to suffer from psychiatric comorbidities (having a 7-10-fold higher risk compared to the general population), clinicians are less likely to prescribe topiramate and zonisamide and more likely to prescribe 3rd generation ASMs given their adverse event profile.[7] - Moreover, as previously stated in the response to the ERG clarification questions, clobazam is most commonly used for short periods in patients with status epilepticus rather than as an ongoing adjunctive ASM according to clinical opinion.[8] Given this evidence, the Company therefore considers the ERG's suggestion of adding topiramate, zonisamide and clobazam as additional comparators to be inappropriate. Secondly, in order to facilitate comparisons with additional comparators that they deem relevant, the ERG suggest assuming equal efficacy, discontinuation rates

		and adverse reaction profiles across all treatments for a cost-comparison analysis. This is not appropriate as it does not reflect the following clinical evidence: 1) Cenobamate has demonstrated unprecedented clinical benefits compared to other ASMs. - The NMA, presented in the Company submission, demonstrates that cenobamate is associated with significantly improved outcomes in terms of responder rates and seizure freedom compared to the comparators included in the submission. - Recent reviews provide further confirmation of cenobamate's clinical benefit compared to other ASMs for the adjunctive treatment of focal seizures. The rate of seizure freedom was higher for the 200 mg and 400 mg doses of cenobamate (11.0-21.0%, respectively) during the 12-week maintenance treatment duration compared to eslicarbazepine acetate, ezogabine, lacosamide, levetiracetam, perampanel, topiramate, vigabatrin and zonisamide (where seizure freedom was reported in 2.0-8.7% of patients).[9] - The results of the open-label extension (OLE) of C017 have demonstrated that there are sustained long-term benefits of cenobamate in terms of seizure frequency reduction, seizure freedom, retention, and treatment-emergent adverse events. 2) Alternative ASMs are similar in terms of efficacy. - Published network meta-analyses, which synthesise evidence from thousands of patients enrolled in large randomised controlled trials (RCT) cohorts, provide support that alternative ASMs are similar in terms of efficacy, with brivaracetam being the most efficacious based on seizure freedom and dropout rates for patients with focal, DRE.[10,11]

		- In consideration of other possible comparators, with the evidence that alternative ASMs are similar in efficacy, it could be assumed that topiramate and zonisamide are as effective as brivaracetam. Although some evidence found that topiramate may offer additional clinical benefits in terms of reducing the incidence of long-term seizures compared to perampanel, oxcarbazepine, levetiracetam, pregabalin and zonisamide.[12] The superior efficacy in favour of topiramate, was however, only regarding the 50% responder rate and not the rate of seizure freedom. For the latter outcome, oxcarbazepine was found to be superior to topiramate in one review of patients with focal onset seizures.[13] Given the lack of evidence comparing topiramate and zonisamide and poor tolerability in comparison to 3rd generation comparators, the Company believe that the 3rd generation ASMs are the most relevant comparators. However, to consider the scenario where second generation ASMs are relevant comparators, a scenario analysis has been performed where zonisamide and topiramate are assumed to be equally as effective as brivaracetam, the most effective of the comparators assessed having the highest seizure freedom rate amongst 2nd and 3rd generation ASMs.[11] In these scenarios, the cost and length of titration of brivaracetam was replaced with either the costs and titration length of zonisamide and topiramate. Zonisamide has a titration of 4 weeks with a week each of 25 mg, 50 mg, 100 mg and 150 mg twice daily; the maintenance dose is 200 mg twice daily.[14] Topiramate has a titration of 6 weeks consisting of a week each of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg once daily; the maintenance dose is 300 mg once daily.[15] Costs of treatment were sourced from the British National Formulary (BNF) for the cheapest available pack size of each unit. The results, presented in Table 1 and Table 2 for zonisamide and topiramate, respectively, demonstrate that cenobamate continues to dominate against cheaper comparators.

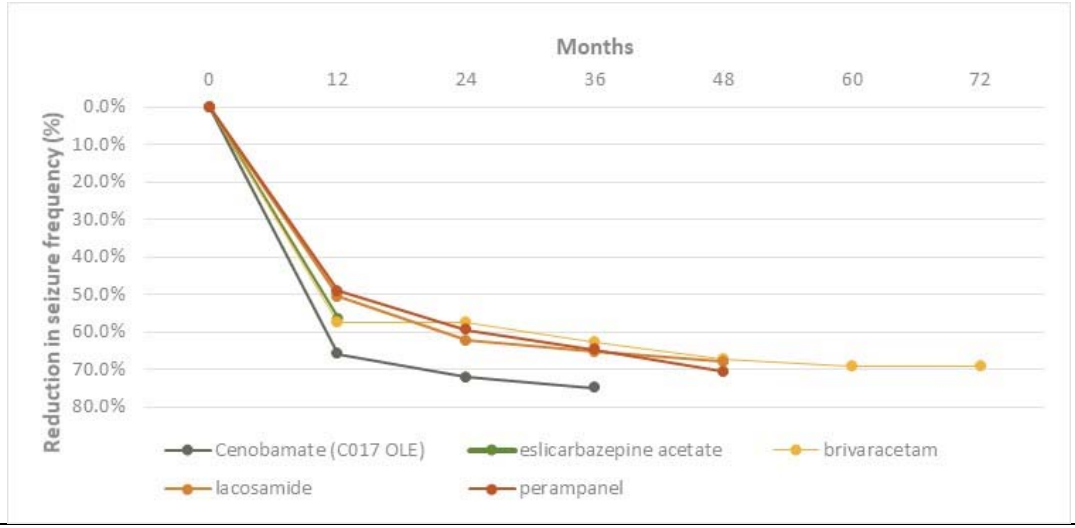
		Table 1. Cost-effectiveness results of cenobamate compared to zonisamide | | Total costs | Total QALYs | Incremental costs | Incremental QALYs | | Cenobamate | [redacted] | 6.955 | - | | | Zonisamide | 211,781 | 5.867 | [redacted] | -1.088 | Abbreviations: QALYs, quality-adjusted life-years. *Table 2. Cost-effectiveness results of cenobamate compared to topiramate* | | Total costs | Total QALYs | Incremental costs | Incremental QALYs | | Cenobamate | [redacted] | 6.955 | - | | | Topiramate | 213,860 | 5.867 | [redacted] | -1.088 | Abbreviations: QALYs, quality-adjusted life-years.
Key issue 2: Generalisability of cenobamate and comparator trials to clinical practice	**NO**	The ERG is concerned about the generalisability of studies, in particular that the baseline seizure frequency used in the economic model, obtained from expert clinical opinion, is higher than what is observed in clinical practice. However, the ERG's suggested approach of using C013 clinical data for the baseline seizure frequency to improve the generalisability of the trial population is not appropriate as the range of baseline seizure frequencies reported in the C013 study is not reflective of UK clinical practice. Moreover, clinical trials recruited participants according to eligibility criteria, including a minimum frequency of seizures and concomitant conditions which may be associated with greater frequency of seizures. Therefore, the range of seizures observed in patients enrolled in clinical trials is a censored observation of clinical practice, and as such data from alternative clinical trials would not be suitable. Real-world evidence generated from

		observational studies or clinical opinion would be more appropriate for deriving baseline seizure frequencies. Whilst the ERG has identified additional observational studies that may inform baseline seizure frequency in the economic model, the Company would like to clarify that the sources are not generalisable to UK clinical practice. - The data reported by Brodie et al. 2014 is not reflective of the general UK population for several reasons.[16] Firstly, as stated by the authors, the population in the study had less severe epilepsy than those recruited for the regulatory trial programs of the ASMs included in the study;[16] indeed the participants included in the study were not limited to those with DRE. This further calls into the question the generalisability of these results to UK clinical practice as patients with drug-resistant focal onset seizures often have more severe epilepsy, comorbidities, and a higher disease burden.[1] Additionally, the median number of previous antiepileptic drugs reported by trial participants was between 1-2 with a lower bound of 0 which, according to the NICE CG137, would make those enrolled eligible for first- and second-line treatments. This is not aligned with the anticipated use of cenobamate, in patients with DRE, defined as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules, where it is anticipated that patients will have trialled at least two or three previous ASMs.[17] Finally, there is a very large range of reported baseline seizure frequencies (between 1-480 seizures per month), which makes it difficult to interpret the median results reported,[16] especially with the omission of the interquartile range. Due to the skew in the reported seizure frequency at baseline, it is highly likely that the mean baseline frequency is far higher than the median. - The other observational studies cited by the ERG are also not reflective of the general UK population as they are small, single-centre studies reporting

		results from outside of the UK that do not represent a typical drug-resistant cohort.[18–21] In particular, Acar al. (2018) is not limited to patients with DRE and includes only patients from Turkey, Kurth et al. (2017) includes only patients from Germany, Liguori et al. (2018) includes only patients trialling a first adjunctive ASM in Italy, and Maschio et al. (2017) includes only patients with brain tumour trialling lacosamide as a first adjunctive in Italy.[18–21] - The data reported by the clinicians in the survey included in the Company submission is supported by a small quality of life study by Selai et al. (2015) of patients with uncontrolled epilepsy in the UK; it was reported that the majority of patients were experiencing >10 seizures per month.[22] However, this data is limited to 125 patients from a single UK site, and therefore the data reported by clinicians is more reliable. Baseline seizure frequency elicited by UK clinicians in a survey commissioned by the Company would be more relevant than alternative estimates proposed by the ERG. The 14 neurology consultants included in the survey, who were recruited from England and Scotland, saw a mean number of 55 adult epilepsy patients per month in their practice, which represents a large distribution of the UK patient population.[23] The Company believe the baseline seizure frequency reported by the clinicians, who see on average 770 patients per month, provides a more reliable estimate of this parameter than both the C013 study and the suggested additional evidence. Therefore, the Company believe that the baseline seizure frequency elicited from the UK clinician survey is the most reliable data in the absence of high-quality data reported across numerous sites in the UK for seizure frequency in drug-resistant patients. Regarding generalisability in other aspects of the cenobamate and comparator studies, the Company believe the trials are generalisable to clinical practice. In particular, although titration periods of varying durations were reported across

		studies included in the NMA, there were no major sources of heterogeneity identified in the feasibility assessment. Moreover, whilst some studies with shorter titration periods were included in the NMA, the C021 study was used to inform the safety and tolerability of cenobamate during titration in the economic model, aligning the model with outcomes observed in clinical practice. For comparators, the titration period as recommended in the summary of product characteristics (SmPC) was followed, with the NMA outcomes used to infer the relative likelihood of response during maintenance ensuring generalisability to clinical practice. Additional clinical data in the economic model was derived from the C017, the C017 OLE, and the C021 studies. The cenobamate trials are largely generalisable to clinical practice and any minor differences are not anticipated to result in a significant change in model outcomes.
Key issue 3: Long-term efficacy and safety of cenobamate and its comparators	**YES**	The ERG state that the long-term efficacy and safety of cenobamate compared to other relevant ASMs in highly uncertain and suggest synthesising effectiveness evidence on comparators by reflecting the continuous nature (and correlation) or the response outcomes, together with accounting for placebo heterogeneity. The ERG also recommend including the C013 study in the evidence synthesis. The Company argue that inclusion of the C013 study is inappropriate to inform long-term effectiveness given the short (6 weeks) titration period which is not long enough to determine long-term efficacy.[24] As shown in Appendix D of the Company submission, all but two studies of comparators included in the NMA had a maintenance periods of at least 12 weeks: two brivaracetam studies had a maintenance lasted seven and eight weeks. Though this would aid interpretation of the speed of response to treatment, inclusion of the C013 study in the NMA would skew the results over the long-term. In pursuit of reflecting the continuous nature of outcomes whilst accounting for placebo heterogeneity, the ERG modified the Company's NMA to compare 50% response rate and seizure freedom in a joint synthesis, placebo-adjusted model.

		The Company agree with the methodology pursued by the ERG to compare outcomes in the NMA. Assessing the clinical effectiveness of cenobamate and relevant comparators over the long-term is methodologically challenging due to the unavailability of longer duration RCTs, rendering the NMA of outcomes infeasible. Long-term data for cenobamate and comparators is available via OLE studies. These data would require more complex methodology (such as matched-adjusted indirect comparisons) for evidence synthesis which, considering the lack of heterogeneity identified in the RCTs for feasibility assessment, would be anticipated to produce results consistent with the NMA. However, data from the open-label studies for eslicarbazepine acetate (Halasz 2010), brivaracetam (O'Brien 2020), lacosamide (Rosenow 2016) and perampanel (Krauss 2018) supports that the differences seen in the short-term from the NMA are maintained in long-term use.[25–28] Clinical experts have also drawn attention to cenobamate's longer half-life compared with comparator anti-seizure medications. This implies that the clinical advantage of cenobamate would also be observed over a long-term period. Figure 1 below shows, amongst patients who remain on treatment, the long-term efficacy (i.e., median reduction in seizure frequency compared to baseline) of cenobamate compared with 3rd generation ASMs. When comparing outcomes in patients who remain on treatment, it is evident that the long-term differences between cenobamate and its second-line adjunctive ASM comparators are maintained, with the largest reduction in seizure frequency at each time point (relative reduction in seizure frequency over 1 year, 2 years and 3 years: 66.0%, 72.2%, and 74.9%, respectively). Therefore, the Company believe that extrapolating the outcomes from the ERG's joint synthesis, placebo-adjusted NMA over the long-term is appropriate.

		Figure 1: Reduction in seizure frequency of cenobamate compared with 3rd generation ASMs 
Key issue 4: Relative safety and efficacy of cenobamate against relevant comparators	**NO**	The ERG have suggested that effectiveness evidence on comparators should be synthesised by reflecting the continuous nature (and correlation) of the response outcomes, together with accounting for placebo heterogeneity. In pursuit of their recommended approach, the ERG revised the NMA methodology and updated the analysis; the Company agree with the methods used by the ERG to account for correlation between outcomes and alleviate the effect of placebo response heterogeneity. The results of the NMA demonstrate significantly improved response to treatment relative to the alternative comparators; reasons for the improved outcomes with cenobamate are clinically plausible as they originate from its unique, dual mechanism of action. Cenobamate is mechanistically distinct from other ASMs. As mentioned in Section B.1.2 of the Company submission, cenobamate is the only ASM which, at clinically relevant concentrations acts both as a positive allosteric modulator of $GABA_A$ receptors at non-benzodiazepine binding sites and

		preferentially blocks the persistent sodium current. A review of existing data by Guignet (2020) suggested that ASMs that target transient sodium current have a more selective pre-clinical anti-seizure profile compared to cenobamate.[29] Sodium channel blockage is the most common and best-characterized mechanism of currently available ASMs which allows for better understanding on how to treat patients with focal onset seizures (FOS).[30] Additionally, cenobamate's additional positive allosteric modulator mechanism of action provides a greater affinity between the $GABA_A$ receptor and cenobamate, resulting in a longer half-life. This gives cenobamate the potential to both prevent seizure initiation and limit seizure spread for longer periods of time. Unlike cenobamate, brivaracetam, eslicarbazepine acetate and perampanel have single mechanisms of action. The exact mechanism of action for brivaracetam is unclear but it attaches to the synaptic vesicle protein 2A, which helps to stabilise electrical activity in the brain and prevent seizures.[31] Eslicarbazepine acetate works by inhibiting voltage-gated sodium channels, especially in rapidly firing neurons; it shares the same molecular structure with carbamazepine and oxcarbazepine.[32] Perampanel binds to the AMPA receptor at a site on the extracellular domain of the channel protein. This induces a conformational change in AMPA receptor sub-units that limits their ability to translate agonist binding into channel opening. The net result limits seizure generation and seizure spread.[33] The single mechanisms of action of brivaracetam, eslicarbazepine acetate and perampanel result in a reduced likelihood of achieving ≥50% response rate or seizure freedom compared with cenobamate. Conversely, lacosamide has a hypothesised dual mechanism of action. Though its exact mechanism of action is considered unknown, it selectively enhances slow inactivation of voltage-gated sodium channels and interacts with collapsin response mediator protein-2, a protein mainly expressed in the central nervous system and involved in neuronal differentiation and axonal outgrowth.[34] The interaction however is not explicitly given.

		Therefore, based on the biochemical advantages that cenobamate's mechanism of action has, the superiority of cenobamate is demonstrated in its dual modes of action; that is, it predominately blocks persistent sodium currents and increases both phasic and GABA inhibition. As such, the NMA results are aligned with given the clinical advantage cenobamate demonstrates through its unique dual mechanisms of action.
Key issue 5: Poorly justified model structure	**NO**	The ERG suggest that a simplified three-state model, in line with previous assessments of adjunctive ASMs, such as for NICE CG137, should be adopted to assess the cost-effectiveness of cenobamate relative to alternative treatments for the adjunctive treatment due to insufficient data informing the relative effectiveness of cenobamate and comparators at the higher response levels, ≥75%-<90% and ≥90%-<100% reduction in seizure frequency.[8] As discussed in the Company submission, the five-state model structure adopted was selected to enable the assessment of higher levels of treatment response, which is associated with increased quality of life. This was validated by clinicians who agreed that achieving a ≥90% reduction in seizures is associated with greater quality of life (QoL) than those who achieve ≥75% reduction, similarly a ≥75% reduction is associated with greater QoL than a ≥50% reduction. Therefore, these higher levels of response to treatment are clinically important and their stratification is in line with the NICE reference case which stipulates that all direct health effects should be quantified in the economic model.[35] Due to a lack of comparator data, it is not possible to indirectly compare higher levels of response with cenobamate and the comparators. However, relative to comparators, more patients treated with cenobamate achieve a 50% response rate and seizure freedom; therefore, it is intuitive that this pattern is maintained at the higher levels of response due to the monotonic distribution of the proportions of patients achieving each level of response. Clinicians validated this and agreed that it is conservative to assume the odds ratios for higher levels of response were equal to the odds ratio of moderate response. Moreover, from the limited data,

		cenobamate is associated with greater proportions of patients achieving the 75% response rate compared to lacosamide and eslicarbazepine acetate; 30.6% and 46.3% of patients treated with cenobamate 200 mg and 400 mg, respectively, in C017 achieved a 75% response rate compared to a maximum of 24.6% and 16% reported for lacosamide and eslicabazepine acetate, respectively.[26,36,37] As QoL of patients is derived from patients enrolled in the C017 study, the less granular model structure biases the health state utility values in patients with a ≥50% and <100% response rate. This is because health state utility values will overestimate quality-adjusted life-years (QALY) gains for comparators due to larger proportion of patients within the cenobamate-treated sample achieving ≥75% and <100% response to treatment relative to the comparators. Moreover, simplification of the model structure, in keeping with the ERG preferred approach, overlooks key differences in costs and resource use that would occur in the higher response states as patients experience fewer seizures. For example, clinical expert opinion highlighted that routine monitoring resource use for patients with FOS would vary by response state, with the higher response states incurring fewer hours of resource use and subsequently fewer costs.[8] Additionally, savings observed in the management of seizures are overlooked with the simplified model. Compliant with the ERG's clarification questions, the Company presented the cost-effectiveness results when a simplified three-state model structure is used in response to Clarification Question B1. Results demonstrated that, whilst cenobamate still dominated all comparators considered in the economic model, cenobamate's total QALY decreased by 0.0381 whilst total QALY for all comparators increased by 0.0464-0.0693 compared to base case. However, in light of the evidence above, the Company believe that the more granular model structure better reflects total costs and QoL of patients who are treated with adjunctive ASM treatment. Therefore, the five-state model structure should be adopted in the base case.

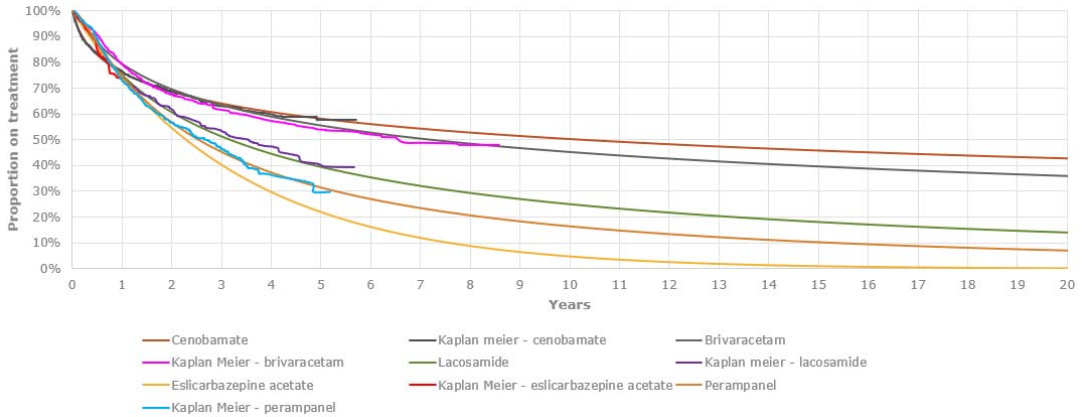
Key issue 6: Cost-effectiveness driven by cenobamate effectiveness	**NO**	The ERG suggest considering relevant evidence from study C013 for use in the economic model due to the ERG's understanding that omitting C013 excludes relevant evidence for cenobamate. However, the Company excluded C013 from the NMA because of the short maintenance duration which, as recognised by the European Medicines Agency (EMA), is not long enough to demonstrate long-term efficacy.[24] Moreover, inclusion of the C013 study skews the results of the NMA towards the level of initial response to treatment in the first six weeks, where a greater placebo response was observed. It was noted in the Company response to the ERG clarification question A3 that the inclusion of the C013 study increased the heterogeneity amongst the NMA results, further supporting that its inclusion in the NMA distorts the estimates of comparators effectiveness relative to cenobamate. As stated in response to issue 4, the Company agree with the methods used by the ERG to account for correlation between outcomes and alleviate the effect of placebo response heterogeneity. The consideration of correlation by the ERG has demonstrated further that cenobamate is associated with significantly improved outcomes compared to the alternative treatments. Additionally, the minimisation of placebo heterogeneity in the NMA has led to a decrease in placebo heterogeneity influencing the incremental differences between treatments; therefore, any placebo heterogeneity amongst the transition matrices defined by the C017 study clinical data is limited from influencing the model conclusions. When considering expected outcomes for patients treated with cenobamate, the probability of seizure response from the ERG placebo-adjusted NMA indicates what outcomes would be expected without placebo effects. The order of effectiveness of the comparators in the economic model at cycle 5 is consistent with the ranking from the joint synthesis models. Additionally, the probability of ≥50% seizure response from the placebo-adjusted NMA is aligned to the economic model results (54.6% vs 52.3%, respectively), demonstrating the minimal influence

		of placebo heterogeneity in the C017 clinical data. As such, the analyses performed by the ERG are appropriate. It should be noted that the ERG NMA considers seizure freedom over the maintenance period of the studies included, whereas the proportion of patients in the health state are those who are seizure-free over the last 28 days. This explains the differences in outcomes in the ERG NMA and economic model for seizure freedom at cycle 5 (8.1% vs 21.5%, respectively). The observed 21.5% of patients residing in the seizure-free health state aligns with the reported post-hoc analysis of the proportion seizure-free over time in the C017 study (Figure 11, Company Submission Document B), where it was reported that approximately 20% and 28% of patients treated with 200 mg and 400 mg of cenobamate were seizure-free during the last 4 weeks of maintenance treatment, respectively. This is compared to 21.0% and 11.0% of patients being seizure-free during maintenance treatment in the C017 study. The ERG also note that the extrapolation of cenobamate effect over time is highly uncertain as it assumed that patients would continue to improve over time. As described in the response to issue 3, a continued improvement over time was demonstrated in the C017 OLE due to retention of patients who respond to treatment. In the economic model discontinuation is applied equally to all on-treatment health states, regardless of response to treatment. As long-term discontinuation is most likely in those who do not respond to treatment, the proportion of patients who respond to treatment amongst those who are currently being treated will continue to increase inversely proportionally to the rate of discontinuation. Therefore, continually applying treatment effects of cenobamate and comparators over time is appropriate, reflecting the clinical effectiveness of treatments. Moreover, the ERG's suggestion of moving any patients in the no response health state to subsequent treatment after cycle 6 is inappropriate as there is no such stopping rule associated with ASM treatment, nor is there one specified for cenobamate in its SmPC or any of the clinical trial programs.

		Moreover, as specified in the protocol of the C017 OLE and C021 studies, dose adjustments are permitted which can incite response to treatment if this is not attained from the target dose; applying discontinuation in the economic model via the parametric curves accurately captures any discontinuation that may occur due to a lack of response. Whilst the Company disagree with the ERG's assumptions on the long-term effectiveness of cenobamate and comparators, the Company agree with the modifications made by the ERG to the NMA as the clinical effectiveness of cenobamate is closely aligned to the ERG's placebo-adjusted NMA outcomes, indicating minimal placebo heterogeneity in the transition matrices defining effectiveness for all treatments. Finally, the assumptions on long-term effectiveness of cenobamate, detailed here and more closely in the response to issue 3, highlight the response to treatment observed in clinical practice as the proportions of patients responding to treatment increasing amongst those who remain on treatment.
Key issue 7: Subsequent treatment	**NO**	The ERG suggest modelling of subsequent ASM lines of therapy instead of a single subsequent ASM treatment health state. Though the Company recognise that patients may move to further lines of subsequent ASM therapy, there is currently no guidance or recognised treatment pathway to inform the modelling of subsequent treatments. Moreover, with 18 adjunctive ASMs recommended by NICE, the number of subsequent ASM treatment combinations grows exponentially with the number of lines of subsequent ASMs considered. Therefore, the Company believe that one homogenous subsequent ASM health state is appropriate. In subsequent ASM treatment, patients have a diminishing likelihood of responding to successive lines of treatment.[38] Therefore, a conservative approach has been taken by the Company in utilising a homogenous health state and fixed associated cost in the economic model. The homogenous state reflects that subsequent lines

		of treatment are at most as effective as each other, which was supported by clinical opinion.[8] The ERG revised the parametrisation of the subsequent ASM health state by applying the odds ratio of no response to the risk of seizure freedom, as lack of response from the source was described as not obtaining seizure freedom. The ERG also applied the odds ratio to the best alternative comparator (brivaracetam), as applying the odds ratio to cenobamate (the most conservative approach) results in subsequent ASM treatment being more effective than the comparators. Finally, the ERG removed cenobamate from the basket of treatment to derive subsequent ASM therapy costs. With these changes suggested by the ERG, the Company believe that the effectiveness of subsequent ASM is appropriately parametrised.
Key issue 8: Uncertain rate of treatment discontinuation	**YES**	The ERG suggest using the 'all-cause' discontinuation results from the NMA as it considers this to be the best comparative evidence available for discontinuation but highlights uncertainty in these estimates due to the limitations of the evidence used to populate the NMA. Additionally, the ERG implemented equivalent discontinuation amongst all comparators from cycle 6, which is inappropriate given the different efficacy and safety profiles of treatments. Indeed, the Company do not believe the NMA is a suitable source for comparative evidence of discontinuation as results incorrectly imply that patients treated with cenobamate have higher odds of discontinuing treatment relative to the alternative comparators throughout the entire course of their treatment. This is inherited from the forced titration in the C017 study which caused increased discontinuation of cenobamate relative to what would be observed in clinical practice.[2] Given the time to discontinuation demonstrated in the C021 study, where titration was aligned with clinical practice, cenobamate is expected to have an increased retention to treatment in the first year compared to that observed in the C017 study. When comparing the retention to treatment with cenobamate in open-label studies (the C017 OLE and the C021 study), cenobamate was associated with greater

		proportions of patients on treatment after 12 months and beyond.[39] With increased response to treatment and seizure freedom compared to the alternative treatments, clinicians verified during ratification of the cost-effectiveness model that it would be expected that patients would remain on treatment with cenobamate for longer than the comparators. As such, informing the relative likelihood of discontinuation of comparators from the NMA and assuming equal discontinuation from cycle 6 does not adequately reflect discontinuation of cenobamate and the comparators observed in clinical practice. The Company acknowledge the uncertainty in the derivation of naïve hazard ratios chosen to better reflects retention to treatment of cenobamate and comparators in clinical practice. As such, the parametrisation of discontinuation with comparators has been revised in the economic model to accurately depict the long-term retention to treatment as demonstrated in the OLE studies of comparators (Table 38 of the Company submission).[28,40–42] Figure 2 shows the chosen parametric distributions and the Kaplan-Meier curves for cenobamate and each of the comparators. A more detailed description depicting the choice of curves is presented in the new evidence document. Contrary to results from the NMA, long-term retention to treatment for cenobamate is higher than all comparators except brivaracetam at Year 1 and beyond. Brivaracetam has higher retention at Year 1, but this drops off to levels below that of cenobamate. However, the Kaplan-Meier data for brivaracetam must be assessed with caution as retention is likely overestimated given that only discontinuation due to adverse events and lack of efficacy were considered in the publication from which the data was sourced. In fact, long-term retention to treatment from the original, preferred study cited in the Company submission also reported discontinuation due to other reasons such as patient's choice and lost to follow-up.[27] This study reported that 74.7% of patients remained on treatment after 1 year compared 79.8% in the Kaplan-Meier source.[27,43] Moreover, after 11 years just 2.4% of patients remained on treatment

		in the preferred source; this, therefore, highlights that the Kaplan-Meier data utilised for brivaracetam treatment retention is a conservative estimate. *Figure 2: Time to discontinuation based on long-term retention from published literature.*  In line with the Company's base case expectations of discontinuation rates and contrary to evidence from the NMA, data sourced from comparator open-label studies show the average time to discontinuation with cenobamate is longer than all comparators. Consequently, the Company believe it is inappropriate to assume that retention to treatment is identical amongst all comparators after cycle 6. Long-term retention rates sourced from open-label studies better reflect clinical practice and should be adopted in the base case rather than results from the NMA.
Key issue 9: Uncertain utility data	**NO**	The ERG suggest that utility data used in CG137 is adopted and that caregiver disutility is not considered. However, these methods both underestimate the health-related quality of life (HRQoL) benefits of treatment. Firstly, published data for health state utility values does not accurately identify HRQoL gains associated with seizure reduction. Utility data from Selai et al. (2005) is used in NICE CG137, however, this source is inappropriate because it is based on a limited sample of 125 patients.[44] Additionally, utility values according to

		response to treatment was based on few eligible responses with just 11 and 25 of the 125 patients reporting seizure freedom or ≥50% reduction in seizure frequency, respectively. With regards to alternative literature, the five studies reporting utility data identified by the Company via their SLR are not appropriate. Four of the five studies reported utility for health states not relevant to the economic model, with just one of the studies, Phumart et al. (2018), reporting utility according to response to treatment. However, these utility values were reported in a Thai population which is not relevant to UK decision making and utility values associated with ≥75% and ≥90% reduction in seizure frequency were not reported. Moreover, the utility increments between 'seizure-free', 'seizure reduction' and 'no improvement' did not reflect clinician expectations of a large utility increment between patients who show seizure reduction and those who achieve seizure freedom.[45] The mapping study performed by the Company is the most appropriate source for utility values. It is based on the responses to a survey of 361 patients with focal onset seizures. The mapping study from the survey identified that the frequency of seizures in the past 28 days, duration of seizure freedom and occurrence of focal to bilateral tonic-clonic seizures in the last 28 days are statistically significant explanatory variables for HRQoL (seizure frequency, $p<0.01$; duration of seizure freedom, $p<0.01$; occurrence of focal to bilateral tonic-clonic seizures, $p<0.05$). With frequency of seizures as an explanatory variable in the model, it is clear that relative reductions in seizure occurrence drive HRQoL such that the higher thresholds of response to treatment are important explanatory variables defining HRQoL. When the mapping is applied to the patients of the C017 study, differences were observed between patients with no response to treatment, 50% to <75% reduction in seizure frequency, 75% to <100% reduction in seizure frequency, and seizure freedom health states. It was not possible to detect differences between patients with 75% to <90% and 90% to <100% reductions in seizure frequency due to the very small number of patients (n=6) residing in the

		latter health state at the end of the study. Regardless, the findings of the mapping reflect the benefits in HRQoL of intermediate response rates (75%-<100% seizure reduction). The findings of the mapping study were discussed with clinicians, who indicated that the benefits in HRQoL associated with seizure freedom were underestimated. On average, clinicians estimated an incremental QALY gain of 0.11 between the seizure-free and ≥90%-<100 reduction in seizure frequency health states. This projected incremental gain from clinicians is far wider than an incremental gain of [redacted] between the same health states identified in the mapping study and 0.03 between seizure-free patients and those with a ≥50% reduction in seizure frequency as reported by Selai et al. (2005) and Phumart et al. (2018).[44,45] A scenario analysis using the average utility values based on clinical opinion showed higher total QALYs for all comparators in Section B.3.9 of the Company submission (cenobamate scenario analysis vs base case total QALYs: 0.981 vs 0.718). This further validates that the use of the mapping study is a conservative choice. Therefore, of the available data to parametrise patient utility values, the Company believe that the mapping study is the most appropriate. Secondly, the Company argue that the inclusion of caregivers will capture all direct health effects associated with focal onset seizures and is compliant with the NICE reference case. In the economic model, caregiver disutility was identified from a survey of carers of patients who experience ≥3 focal onset seizures per week, which is in line with the seizure frequency at baseline in the population of interest. Utility values of participants were collected from their responses to the EQ-5D-5L questionnaire and valued using the UK tariff; disutilities were calculated by taking the difference of individuals' utility from the expected age-adjusted utility in the general UK population generated as reported by Ara and Brazier 2010. As the values were not stratified by response, a first order linear regression was fitted to disutility values against average number of seizure-free days per 28 days. Caregiver disutility values stratified by health state were then calculated by identifying the average number of seizures free days per 28 days in each response

		category; it was assumed that seizures were distributed evenly throughout a 28-day cycle and patients had at most one seizure per day. The role of a carer is vital for patients with epilepsy, where caregivers: monitor medication adherence; offer support strategies for seizure management; and process and relay information about seizure symptoms to healthcare providers. Intense demand is placed on caregivers which can include coping with patient's psychological distress, dealing with frequent recurrence of seizures, and addressing concerns about potential injury and even death.[46] The role of a carer becomes particularly more important depending on seizure type and severity. Patients who experience generalised tonic-clonic seizures are at greater risk of injury than those who do not experience disabling seizures. Mahler (2018) identifies open wounds, fractures, dislocation, sprains and burns as some of the injuries that may arise from a seizure; therefore, those who are at risk of experiencing convulsive seizures require constant support in case of injury or accident.[47] Additionally, seizure occurrence may exacerbate concomitant conditions which increases the burden of epilepsy to caregivers. Carers of patients with epilepsy are typically those who live with the patient. In patients who have intellectual disabilities, which reportedly accounts for approximately 18-40% of patients with epilepsy, many still live in the family home where both parents are considered caregivers.[48–50] For patients with epilepsy who no longer live in the family home, their housemates, partners and children provide informal care. Therefore, the assumption that each patient has one caregiver is a conservative assumption; few patients with epilepsy are able to live alone due to the risks associated with accidents due to seizures. However, it was reported that 48 out of 80 patients with epilepsy presenting at a US hospital were accompanied by a caregiver.[51] As such, caregiver disutilities need to be taken into account in the analysis; assuming a single caregiver is a conservative assumption.

<table>
<tr>
<td>Key issue 10: Uncertain resource use data</td>
<td>YES</td>
<td>
The ERG suggest excluding the cost of cenobamate from subsequent ASMs, which the Company agree with.

The ERG, also suggest using the cost data from previously published literature, such as the one from the NICE CG137, to assess the impact of the cost values used in the Company's base case. However, this is not appropriate.

Firstly, the data used in CG137 is not appropriate for many reasons.[52] The data reported in NICE CG137 considers only hospital-based resource use over a 12-month period and does not consider the costs of diagnostic imaging or any community-based resource use. Referring to the source of the data, reported by Jacoby et al (1998),[53] hospital and community-based resource use amongst adults and children with epilepsy is stratified by seizure frequency (seizure-free, <1 seizure per month, and >1 seizure per month). Given that the baseline seizure frequency in the economic model is approximately 13 seizures per 28 days, stratification by <1 and >1 does not provide meaningful data to populate the economic model. Moreover, stratification of seizure frequency in this way does not relate to the health states assessed in NICE CG137 or in this economic model. NICE applied the same costs to all patients experiencing seizures, regardless of their frequency. In addition, NICE CG137 does not assess how resource use associated with seizure occurrence varies by type of seizure; focal to bilateral tonic-clonic are much more severe events and are associated with greater levels of resource use as identified from clinical experts' opinion. As such, the data published by Jacoby et al. (1998) does not accurately capture how resource use varies by seizure frequency. Nevertheless, the resource use reported by Jacoby is presented below to highlight the limitations related to taking into account hospital-based costs only.

Table 3 Summary of epilepsy-related costs and resource use as presented by Jacoby et al (1998)
<table>
<tr><th>Resource</th><th>Unit cost</th><th>Source</th><th>Frequency of use per 12 months</th></tr>
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				Seizure-free (n=350)	<1 seizure per month (n=174)	>1 seizure per month (n=168)
Hospital-based						
Inpatient admission	£1,397.93	NHS reference costs; weighted average of AA26C-AA26H inpatient attendances[54]		1	16	16
A&E	£168.00	NHS reference costs; service code 180[54]		2	23	27
Out-patient attendance	£177.00	NHS reference costs; service code 400[54]		18	42	49
EEG	£481.00	NHS reference costs; EY51Z[54]		4	21	22
CT/MRI	£105.00	NHS reference costs; average of direct access costs of RD01A and RD20A[54]		5	15	16
Blood test	£7.58	NHS reference costs; DAPS07[54]		22	43	52
Community-based						
Epilepsy-related GP consultations	£39.00	PSSRU; per surgery consultation lasting 9.22 minutes, with qualification costs, including direct care staff costs[55]		18	58	61

District/ practice nurse	£9.25	PSSRU; £37 per working hour, 15-minute duration assumed[55]	4	6	10
Health visitor	£72.00	NHS reference costs; N03G[54]	0	1	2
Social worker	£45.00	PSSRU; unit cost per hour of a social worker[55]	1	4	2
Psychologist/ psychiatrist	£155.00	NHS reference costs; MHSTOTHA[54]	2	2	8
Average cost per year of hospital-based care			£7,535.69	£45,666.79	£48,232.01
Average cost per year of community-based care			£1,094.00	£2,879.50	£3,945.50
Average total cost per year			£8,629.69	£48,546.29	£52,177.51
Average total cost per cycle			£663.82	£3,734.33	£4,013.65

Abbreviations: A&E, accident and emergency; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; GP, general practitioner; MRI, magnetic resonance imaging; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Costing the data reported by Jacoby et al. (1998) demonstrates a cost per 28 days of £663.82, £3,734.33, and £4,013.65 in patients who are seizure-free, experiencing <1 seizure per month, and experiencing >1 seizure per month, respectively. This is significantly higher than the costing obtained via clinical opinion on resource use, where patients with no response incur costs of £1,091.53 per 28 days. The costs per cycle obtained from clinician opinion of resource use is summarised below in Table 4 for comparison.

Table 4: Summary of resource use data used in the economic model based on clinician opinion of resource use

Costs per cycle	No response	≥50%-<75% reduction in seizures	≥75- <90% reduction in seizures	≥90%-<100% reduction in seizures	Seizure-free

Routine monitoring	£205.40	£117.99	£19.72	£19.72	£17.88
Epilepsy events	£886.13	£351.13	£150.43	£42.50	£0.00
Total	£1,091.53	£469.12	£170.15	£62.22	£17.88

The Company considered a scenario analysis incorporating the resource use from Jacoby et al. (1998), the preferred data source from the ERG where costs for routine monitoring and epilepsy event management were replaced with the costs derived from the published resource use estimates. In the scenario, patients who were seizure-free accrued a cost of £663.82 per cycle whereas patients experiencing seizures accrued a cost of £3,871.54 per cycle, the weighted average of costs in patients with <1 and >1 seizure per month. The results of the scenario analysis are presented in Table 5. The cost-effectiveness of cenobamate and alternative comparators using this data leads to far greater cost savings with cenobamate.

Table 5. Cost-effectiveness model results when resource use is based on Jacoby et al. (1998)

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER/QALY
Cenobamate	[redacted]	6.955			
Eslicarbazepine acetate	909,156	6.339	[redacted]	-0.616	Dominated
Perampanel	918,310	6.226	[redacted]	-0.729	Dominated
Lacosamide	925,733	6.147	[redacted]	-0.808	Dominated
Brivaracetam	946,614	5.868	[redacted]	-1.087	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

As use of resource use from Jacoby et al (1998) is associated with far greater incremental costs, the data presented by the Company is more conservative. In addition, the data reported by the Company is stratified by response to treatment, unlike the data obtained from Jacoby et al (1998), which is stratified by no seizures and <1 or >1 seizure per month. In summary, the Company believe that data

		obtained from clinical experts' opinion is more appropriate for use in the economic model.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

<table>
<tr><th>Key issue(s) in the ERG report that the change relates to</th><th>Company's base case before technical engagement</th><th>Change(s) made in response to technical engagement</th><th>Impact on the company's base case ICER</th></tr>
<tr><td colspan="3">Company's preferred base case following clarification questions</td><td>
<table>
<tr><td></td><td>Total costs (£)</td><td>Total QALYs</td><td>ICER/QALY</td></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.933</td><td></td></tr>
<tr><td>Lacosamide</td><td>214,146</td><td>6.218</td><td>Dominated</td></tr>
<tr><td>Perampanel</td><td>214,472</td><td>6.218</td><td>Dominated</td></tr>
<tr><td>Brivaracetam</td><td>216,696</td><td>6.170</td><td>Dominated</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>230,681</td><td>5.987</td><td>Dominated</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

Cenobamate dominates all comparators.
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<tr>
<td>Issue 3: Long-term efficacy and safety of cenobamate and its comparators</td>
<td>The Company used a 28-day cycle length, extrapolating the transition matrices observed in the C017 RCT over the maintenance period for the base case before technical engagement. Use of the 28-day cycle length and extrapolating the RCT data was used to ensure data was obtained from comparative, controlled study.</td>
<td>The Company has updated their base case to incorporate the C017 OLE data with 12-weekly cycles from completion of the available RCT data. This is implemented to demonstrate the response to treatment observed over greater treatment durations, which is identified as clinically relevant. This data demonstrates how response to treatment increases with time on treatment. This reflects the fact that, if response to treatment is not maintained, patients are more likely to discontinue treatment leaving the remaining population with a greater average response as non-responders are removed from the treatment cohort.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.984</td></tr>
<tr><td>Lacosamide</td><td>216,654</td><td>6.121</td></tr>
<tr><td>Perampanel</td><td>217,120</td><td>6.118</td></tr>
<tr><td>Brivaracetam</td><td>220,149</td><td>6.057</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>233,663</td><td>5.894</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
</table>

<table>
<tr>
<td>Issue 4: Relative safety and efficacy of cenobamate against relevant comparators</td>
<td>The Company had informed the relative efficacy and safety of cenobamate against relative comparators by independent modelling of ≥50% responder rates and seizure freedom in the NMA.</td>
<td>The updated NMA presented by the ERG have been used in the base case to inform the efficacy and safety of relevant comparators relative to cenobamate. Use of a joint synthesis, placebo-adjusted model ensures the most accurate incremental treatment differences are identified.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.984</td></tr>
<tr><td>Perampanel</td><td>215,763</td><td>6.135</td></tr>
<tr><td>Lacosamide</td><td>216,478</td><td>6.123</td></tr>
<tr><td>Brivaracetam</td><td>220,955</td><td>6.045</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>231,275</td><td>5.926</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
<tr>
<td>Issue 7: Subsequent treatment</td>
<td>Odds of no response to subsequent ASMs applied to the probability of not being seizure-free rather than the probability of no response.</td>
<td>The odds ratio of no response is applied to the odds of not achieving seizure freedom, in line with the reporting of the outcome in the Chen 2018 study.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>7.040</td></tr>
<tr><td>Perampanel</td><td>208,029</td><td>6.211</td></tr>
<tr><td>Lacosamide</td><td>208,913</td><td>6.198</td></tr>
<tr><td>Brivaracetam</td><td>213,784</td><td>6.116</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>225,301</td><td>5.985</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
</table>

<table>
<tr>
<td>Issue 7: Subsequent treatment</td>
<td>Odds of no response to subsequent ASMs was conservatively applied to cenobamate, which maximised the possible benefit from subsequent lines of treatment.</td>
<td>The odds ratio has been applied to brivaracetam to ensure that subsequent treatment is less effective than alternative comparators.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.955</td></tr>
<tr><td>Perampanel</td><td>212,349</td><td>6.096</td></tr>
<tr><td>Lacosamide</td><td>213,136</td><td>6.085</td></tr>
<tr><td>Brivaracetam</td><td>217,783</td><td>6.008</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>228,620</td><td>5.896</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
<tr>
<td>Issue 10: Uncertain resource use data</td>
<td>Cenobamate was conservatively included as a treatment option as part of the subsequent ASM treatments.</td>
<td>Cenobamate is no longer an option for subsequent ASM treatments.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.955</td></tr>
<tr><td>Perampanel</td><td>211,860</td><td>6.096</td></tr>
<tr><td>Lacosamide</td><td>212,657</td><td>6.085</td></tr>
<tr><td>Brivaracetam</td><td>217,330</td><td>6.008</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>228,242</td><td>5.896</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
</table>

<table>
<tr>
<td>Issue 8: Uncertain rate of treatment discontinuation</td>
<td>The Company had originally fit parametric curves to the cenobamate's Kaplan-Meier data, and identified naïve hazard ratios (HRs) that, when applied to cenobamate's parametric survival curves, would match the expected time to discontinuation of comparator treatments.</td>
<td>Parametric curves were fitted to publish Kaplan-Meier data for each of the comparators. The Kaplan-Meier's were obtained from figures published in key OLE studies and digitised to obtain retention to treatment over time. For each comparator, parametric curves were independently fit to accurately depict time to discontinuation.</td>
<td>Updated costs and QALYs are presented below:
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.955</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>194,998</td><td>6.339</td></tr>
<tr><td>Perampanel</td><td>202,728</td><td>6.226</td></tr>
<tr><td>Lacosamide</td><td>208,526</td><td>6.147</td></tr>
<tr><td>Brivaracetam</td><td>227,534</td><td>5.868</td></tr>
</table>
Abbreviations: QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
<tr>
<td colspan="3">Company's preferred base case following technical engagement</td>
<td>
<table>
<tr><th></th><th>Total costs (£)</th><th>Total QALYs</th><th>ICER/QALY</th></tr>
<tr><td>Cenobamate</td><td>[redacted]</td><td>6.955</td><td>-</td></tr>
<tr><td>Eslicarbazepine acetate</td><td>194,998</td><td>6.339</td><td>Dominated</td></tr>
<tr><td>Perampanel</td><td>202,728</td><td>6.226</td><td>Dominated</td></tr>
<tr><td>Lacosamide</td><td>208,526</td><td>6.147</td><td>Dominated</td></tr>
<tr><td>Brivaracetam</td><td>227,534</td><td>5.868</td><td>Dominated</td></tr>
</table>
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.
Cenobamate dominates all comparators.</td>
</tr>
<tr>
<td colspan="4">Numerous scenario analyses have been performed from the new Company preferred base case, including a scenario considering topiramate and zonisamide as comparators; in all scenario analyses cenobamate remains the dominant treatment.</td>
</tr>
</table>

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NICE National Institute for Health and Care Excellence

Technical engagement proposed new evidence form (company only)

Cenobamate for focal onset seizures in epilepsy [ID1553]

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **Friday 30 April**

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink.

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Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Is the new evidence expected to alter the company's base-case ICER?	Additional details about the proposed new evidence (if available)
Issue 8	**Alternative comparator parametric survival curves**	Given a lack of comparative data, the Company consider long-term retention data sourced from comparator open label studies as more appropriate estimates of treatment discontinuation for comparators as they	**YES**	Parametric survival models have been fit to each comparator using plots of long-term retention rates sourced from the open label studies presented in Table 38 of the Company submission. The O'Brien study evaluating long-term safety, efficacy and quality of life outcomes with adjunctive brivaracetam did not report retention to treatment plots.[1] As such, data from a study of brivaracetam by Toledo et al. was used to extract Kaplan Meier data.[2] Importantly this study only reported discontinuation due to adverse events and lack of efficacy which is likely to overestimate the rate of retention to treatment seen in clinical practice. Table 1 presents the studies used to extract data from the Kaplan Meier curves for each comparator. Data from the listed sources were digitised using GetData GraphDigitiser.[3] The data were then fitted to parametric distributions and curves were selected based on their statistical fit,

better reflect retention to treatment in clinical practice.

determined by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, and clinical plausibility.

Table 1: Published literature used to source retention to treatment plots.

Treatment	TTD source
Brivaracetam	Toledo (2016)[2]
Lacosamide	Rosenfeld (2014)[4]
Eslicarbazepine acetate	Hufnagel study (2013)[162]
Perampanel	Krauss (2018)[7]

Table 2 shows the resulting parametric distributions along with their respective AIC and BIC for brivaracetam. Whilst Gompertz was the best statistical fit to the data, it was not clinically plausible as it assumed discontinuation would cease. Therefore, the next best alternative was used, the generalised gamma (AIC: 6549.60, BIC: 6566.48).

Table 2: Brivaracetam AIC and BIC statistics from time-to-discontinuation using data from Toledo study.

Distribution	AIC	BIC
Exponential	7057.369942	7062.996025
Weibull	6724.369479	6735.621644
Gompertz	6520.356303	6531.608469
Log-logistic	6640.226053	6651.478218
Lognormal	6584.596793	6595.848959
Generalised Gamma	**6549.603272**	**6566.48152**

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 3 presents the AIC and BIC for Lacosamide. The lognormal was selected as the most appropriate curve for estimating treatment discontinuation since it had the lowest AIC and BIC values (AIC: 1210.82, BIC: 1218.68).

Table 3: Lacosamide AIC and BIC statistics from time-to-discontinuation using data from the Rosenfeld study.

Distribution	AIC	BIC
Exponential	1246.249277	1250.178866
Weibull	1230.922565	1238.781743
Gompertz	1215.601822	1223.461
Log-logistic	1217.535394	1225.394573
Lognormal	**1210.817793**	**1218.676972**
Generalised Gamma	1211.85414	1223.642907

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 4 presents the AIC and BIC for eslicarbazepine acetate. The exponential curve was selected as the most appropriate curve for estimating treatment discontinuation since it had the lowest AIC and BIC values (AIC: 362.00, BIC: 365.77).

Table 4: Eslicarbazepine acetate AIC and BIC statistics from time-to-discontinuation using data from the Hufnagel study.

Distribution	AIC	BIC
Exponential	**361.9887**	**365.7725**
Weibull	363.2105	370.7781
Gompertz	363.9805	371.5481
Log-logistic	362.2278	369.7955

Lognormal	362.6817	370.2493
Generalised Gamma	364.1178	375.4692

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 5 presents the AIC and BIC for perampanel. The lognormal was selected as the most appropriate curve for estimating treatment discontinuation since it had the lowest AIC and BIC values (AIC: 3321.60, BIC: 3331.81).

Table 5: Perampanel AIC and BIC statistics from time-to-discontinuation using data from the Krauss study.

Distribution	AIC	BIC
Exponential	3354.5648	3359.6698
Weibull	3356.5557	3366.7655
Gompertz	3348.7984	3359.0083
Log-logistic	3328.5051	3338.7150
Lognormal	**3321.6043**	**3331.8142**
Generalised Gamma	3322.7453	3338.0602

Bold text indicates statistical preference. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Error! Reference source not found. shows the chosen parametric distributions and the Kaplan Meier curves for cenobamate and the comparators. Long-term retention to treatment for cenobamate is higher than all comparators except Briviact which is likely to be lower as it does not consider patients who have discontinued due to other factors such as loss to follow up or withdrawal of consent.

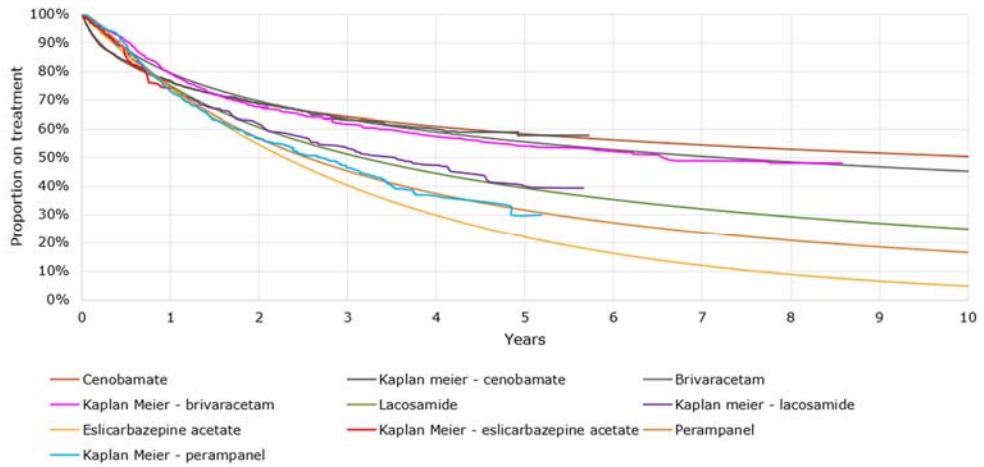
				Figure 1: Time to discontinuation based on long-term retention from published literature.  The aggregated results for the cost-effectiveness of cenobamate relative to the comparators is presented in Table 6. As in the ERGs base-case, cenobamate dominates all comparators. Over the lifetime time horizon, treatment with cenobamate was associated with 6.955 QALYs at a total cost of [redacted]

Table 6: Cost-effectiveness scenario results where discontinuation for comparators is based on parametric survival curves

	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cenobamate	[redacted]	6.955			-
Lacosamide	194,998	6.339	[redacted]	-0.616	Dominated
Perampanel	202,728	6.226	[redacted]	-0.729	Dominated
Brivaracetam	208,526	6.147	[redacted]	-0.808	Dominated
Eslicarbazepine acetate	227,534	5.868	[redacted]	-1.087	Dominated

References

1. O'Brien TJ, Borghs S, He QJ, *et al.* Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: An up to 11-year, open-label, follow-up trial. *Epilepsia* 2020. 61: 636–646.
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Clinical expert statement & technical engagement response form

Cenobamate for focal onset seizures in epilepsy [ID1553]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 17 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with focal onset seizures in epilepsy and current treatment options	
About you	
1. Your name	**Ley Sander iceberg**
2. Name of organisation	**1. UCL Queen Square Institute of Neurology** **2. National Hospital for Neurology & Neurosurgery** **3. Epilepsy Society**
3. Job title or position	**1. Professor of Neurology & Head of Department** **2. Consultant Neurologist** **3. Medical Director**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with focal epilepsy? ☐ a specialist in the clinical evidence base for focal epilepsy or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
The aim of treatment for focal onset seizures in epilepsy	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop seizures completely and therefore prevent the risk of premature death
9. What do you consider a clinically significant treatment	100% seizure reduction

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in focal epilepsy?	Up to 30% of patients with focal epilepsy have not benefited from drugs currently available. There is an urgent need to address these patients in terms of more effective and better-tolerated drugs.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Yes!
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines for the treatment of epilepsy in children and adults
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In general terms there is broad agreement on the care pathways for people with epilepsy

• What impact would the technology have on the current pathway of care?	Potentially a major impact
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, it would be an addition to the anti-seizure armamentarium
• How does healthcare resource use differ between the technology and current care?	Initial evidence suggests it is better in providing seizure freedom than some of the alternatives
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initially, in Specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
13. Do you expect the technology to provide clinically meaningful	Yes, as there is the expectation, it could benefit many patients in terms of seizure freedom

benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, active epilepsy with frequent seizure is a risk factor for premature mortality.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, if it lives up to the promise of an increased number of patients seizure free. Evidence strongly suggest that only seizure freedom has a lasting impact on quality of life
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	n/a
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	Similar to current drug alternatives. No extra needs

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not applicable
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, see 13
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	It is another drug but seems to have a higher odds of providing seizure freedom
• Does the use of the technology address any particular unmet need of the patient population?	Yes, improve seizure control
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Not much diferent from current alternatives
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	These are regulatory trials and do not reflect clinical practise or the real world.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	100% seizure reduction
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Unpredictable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How accurately does NICE clinical guideline CG137 represent NHS clinical practice for people with focal onset seizures in epilepsy? Are you aware of any new evidence or changes in	Yes, carbamazepine as a strong enzyme inducer has many chronic side effects and should not be a first-line option

current practice for the currently available comparator treatments since the publication of NICE clinical guideline CG137?	
23. How do data on real-world experience compare with the trial data?	Early indication from US colleagues is that result in real-world clinical use suggest even better results in terms of seizure freedom than the regulatory trials.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. Would cenobamate ever be used in people who have had	Probably

two previous monotherapies (i.e. no adjunctive therapy) in clinical practice?	
26. Are the following treatments relevant comparators for this population in the NHS: a. carbamazepine b. levetiracetam c. eslicarbazepine acetate d. clobazam e. topiramate f. zonisamide	Only levetiracetam and zonisamide but lacosamide and permpanel should also be in the list
27. What is your experience of dose titration of anti-seizure medications (ASMs) in clinical practice?	Start low and go slow !!!!!!!!!!!!!!!!!! a) Find the lowest effective dose

a. What is the aim of dose titration in focal onset seizures in epilepsy? b. Do different ASM's have different dose titration periods? How long is the average dose titration period? c. How frequently is the dose increased?	b) Yes, usually between 4 and 12 weeks c) About two weeks d) Every 2 weeks
28. Is percentage reduction in seizure frequency used in NHS clinical practice to assess disease severity and treatment response? a. If yes, what percent reduction is classed as a meaningful response?	a) 100% b) Three-time the previous gap between seizures. c) No seizues and no tolerability issues

b. What is the maximum duration of treatment appropriate to determine response? c. What other outcome measures are important to determine severity and treatment response for focal onset seizures in epilepsy?	
29. In the population of interest (drug resistant epilepsy with focal onset seizures requiring third-line treatment): a. how variable is seizure frequency? b. What is the average seizure frequency per	a) Large sprectrum of frequency from one seizure a year to several in one day. Average between 6 to 24 seizures in a year b) See above

month (in your clinical experience)?	
30. What treatments would be used following progression on third-line treatment? What factors influence this choice? Would you expect subsequent treatments: a. to differ for people who had cenobamate compared with current standard care? b. To be less or more effective depending on whether a patient had cenobamate at third-line?	Consideration of epilepsy surgery in a small number of patients
31. What are the psychological effects of living with focal onset seizures in epilepsy? How does	Terrible!!! Affects quality of life of the individual and extended family

this affect patient and caregiver's day-to-day quality of life?	

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Positioning of cenobamate in the treatment pathway	If effective in terms of providing seizure freedom will be used earlier than other alternatives
Key issue 2: Generalisability of cenobamate and comparator trials to clinical practice	Usually, results of regulatory trial under-represent outcomes in clinical practice

Key issue 3: Long-term efficacy and safety of cenobamate and its comparators	Not yet clear, but the benefits outweigh the risks.
Key issue 4: Relative safety and efficacy of cenobamate against relevant comparators	No major differences but early days!
Key issue 5: Poorly justified model structure	Seizure freedom should drive model
Key issue 6: Cost-effectiveness driven by cenobamate effectiveness	Possible
Key issue 7: Subsequent treatment	If of benefit reduction to monetheraphy should be attempted
Key issue 8: Uncertain rate of treatment discontinuation	Only clinical practice will determine

Key issue 9: Uncertain utility data	Reduction in mortality should be a major utility data point in any model
Key issue 10: Uncertain resource use data	
Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Seem to have the potential to make some now refractory patients seizure-free
- Long term and rare side effects not known and will need surveillance
- Evidence suggests that it is more effective option than some 3rd line drug for focal seizures
- Initial results in clinical practice in the USA very encouraging
- Seems devoid of tachyphylaxis

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

x☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Cenobamate for focal onset seizures in epilepsy [ID1553]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 17 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

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PART 1 – Treating a patient with focal onset seizures in epilepsy and current treatment options	
About you	
1. Your name	**Rhys Thomas**
2. Name of organisation	**Newcastle University, Newcastle-upon-Tyne Hospitals NHS Foundation Trust**
3. Job title or position	**Intermediate Clinical Lecturer, Honorary Consultant in Epilepsy**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with focal epilepsy? ☐ a specialist in the clinical evidence base for focal epilepsy or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

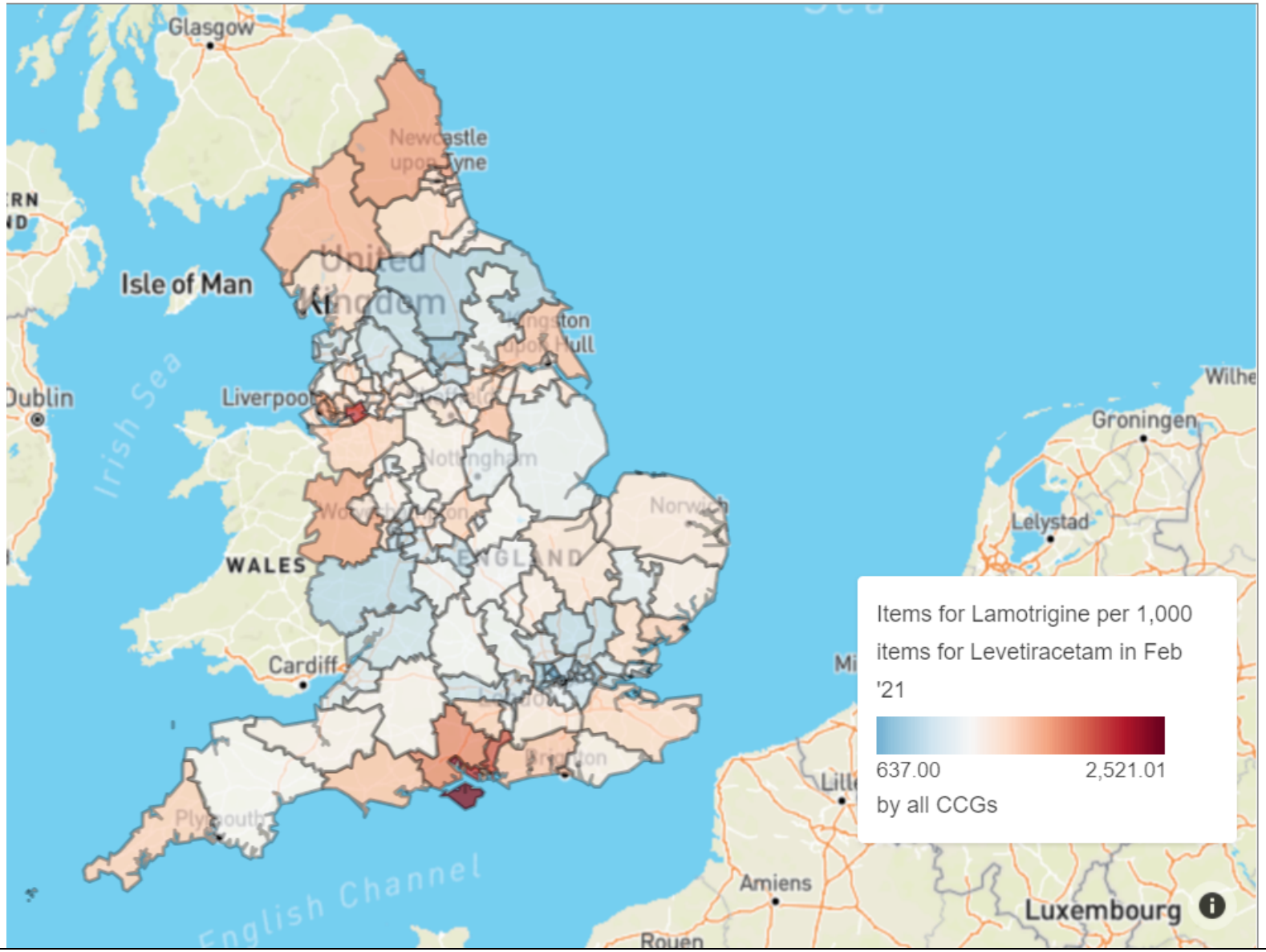
nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for focal onset seizures in epilepsy	

8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**The main aim is to retain or return independence.** The most efficient way of doing so is returning someone to a prolonged and reliable period of seizure freedom. This is most commonly achieved with taking anti-seizure medication daily. The optimum situation is no seizures, no side effects. Where this is not possible you may balance out some tolerable side effects to attain seizure freedom. This is important as driving privileges are only returned when seizure freedom is maintained. Alternatively you may choose to have 'near seizure freedom' - such as 75% or 90% of all seizures controlled. Or you may choose to control certain types of seizures – either the more disabling or distressing ones, or those which impact greatest on quality of life. Anti-seizure medications are the mainstay of treatment and are not thought to be directly disease modifying. However having fewer seizures and less life disruption will reduce common comorbidities such as mental health symptoms and reduce the risk of injury and premature death.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	This is not uniform and is based upon pragmatism. **Seizure freedom with minimal side effects would be considered to be a clinically significant response.** This however is not achievable with the currently available medication for 30% of patients. This would be while taking medication alone (monotherapy) or pairing medications up (adjunctive therapy). For some people *reducing* seizure frequency (without seizure cessation) would be an improvement – for example having none overnight will improve sleep quality and reduce anxiety, or for another person by preventing seizures that cause injury. For some people it is about reducing unscheduled hospitalisations. Returning to work, and returning to drive are significant responses but are only possible following prolonged seizure control. The industry standard for regulatory studies of 50% seizure reduction is not always clinically significant and would need to be validated by knowing what side effects have been produced to create this reduction, and knowledge of the individual's situation.

10. In your view, is there an unmet need for patients and healthcare professionals in focal epilepsy?	Undoubtedly – this is unequivocal. 30% of people with focal epilepsy never achieve seizure freedom despite multiple trials of medication. Epilepsy surgery is only an option for about 4% of adults, and not all of these achieve seizure freedom. There are multiple anti-seizure medications for focal epilepsy but they offer something different, because they are used either because of synergy i) they have a different mode of action and little drug-drug interactions; or ii) they have secondary benefits such as helping with weight loss or pain; or iii) we know that they are broadly safe in pregnancy; or iv) they are not more effective, but have a more benign side-effect profile. The benefits of an adjunctive anti-seizure medication with better efficacy than comparators – and specifically one that can produce seizure freedom in patients for whom we would have no optimism that seizure freedom is a realistic ambition – is possibly unique and definitely attractive.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The guidelines are only loosely adhered to because i) NICE is rewriting the current outdated guidance; ii) there are a paucity of head to head studies – SANAD excepted; iii) treatment is individualised. There is a *RIghtCare toolkit* for Epilepsy https://www.england.nhs.uk/rightcare/products/pathways/epilepsy-toolkit/ and NHS England have commissioned a pathway document (I am on that working group). There are also NICE pathways for epilepsy https://pathways.nice.org.uk/pathways/epilepsy Epilepsy is a brain state that reflects many scores of underlying diseases and as such there is no 'one size fits all'. Treatment of children is different from that of adults, and many would treat older adults differently too.

	Some patients are very sensitive to certain adverse effects such as cognitive, behavioural, balance or weight based and so not all adjunctive medicines are considered for everyone. It is not possible to correctly create a true list of first – second and third line medicines for these reasons and also because we prefer certain combinations of medicines. - Some medicines are too closely related to use together, such as levetiracetam and brivaracetam (they compete at the same biological targets). - Some medicines are so close in terms of mode of action – such as carbamazepine, oxcarbazepine, eslicarbazepine – that using two together would bring additive side effects without added efficacy. - Some medicines are used sparingly together because they have a similar mechanism – we prefer to pair drugs together with different modes of action, so called *rational polytherapy.* - Sometimes drugs are chosen because of their secondary effects, for example pain relief, mood stabilisation or weight loss. Patient choice matters and once daily medications are preferable to ones that need to be taken more frequently.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In addition to the above – patient and clinician enthusiasm for change matters. Conservative prescribers and non-specialists may accept poorer outcomes, greater side effects and are less likely to try new medication regimens. Some drugs are not universally available in the NHS and vary CCG to CCG such as access to brivaracetam. The map below shows the use of two common anti-seizure medications sued to control focal onset seizures in England; levetiracetam and lamotrigine. The darker the red colour favours levetiracetam use and blue favours lamotrigine. The data are current and come from openprescribing.net


Glasgow
Isle of Man
Dublin
Irish Sea
Liverpool
WALES
Cardiff
English Channel
Amiens
Rouen
Groningen
Lelystad
Luxembourg
Items for Lamotrigine per 1,000 items for Levetiracetam in Feb '21
637.00
2,521.01
by all CCGs

• What impact would the technology have on the current pathway of care?	It would be started primarily by neurologists with an interest in epilepsy for patients with a moderate to high seizure burden, for whom a significant seizure reduction would be beneficial. Patients would be those for whom at least two well-chosen prior anti-seizure medications have not worked (in combination or alone). These patients carry the greatest risk of all comorbidities including premature death. These patients would be willing to accept a mild-moderate side effect burden for the opportunity of a significant seizure reduction, or seizure freedom. Seizure freedom leads to improvement of all outcomes and reduced healthcare resource utilisation. Many of these adults will be working age and family members. These patients would be less likely to have multiple trials of less effective adjunctive and seizure medication. This may lead to fewer people having palliative vagus nerve stimulator surgery, and a small number of people not needing epilepsy surgical evaluation. Improved seizure control reduced unscheduled use of emergency services (aprox 3.5% of ambulance calls are for seizures) and reduce hospitalisations. Improved seizure control will permit more people to return to work, and family roles.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently in used outside of clinical trials. Yes, the technology would be used along-side or instead of existing anti-seizure medicines. The technology may reduce the number of people needing vagus nerve stimulator surgery or epilepsy surgery.
• How does healthcare resource use differ between the technology and current care?	

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The drug should be initiated by a specialist in epilepsy (such as a Neurology Consultant or a Paediatric Neurologist). These would typically be in secondary care and working in a neurology or neurosciences centre. Maintenance prescriptions can be written by any medical professional, but most notable the GP.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new facilities are required. There will be minimal training needed. Specifically this would be around the drug-drug interactions with cenobamate. This is not unusual for an anti-seizure medication. It would be helpful to have therapeutic drug monitoring of cenobamate levels available. Most anti-seizure medicines can be assayed at Chalfont https://epilepsysociety.org.uk/therapeutic-drug-monitoring
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. If the data from regulatory trials can be extrapolated in the way that we have successfully extrapolated data from prior similar trials then cenobamate will be 'remarkably effective; https://journals.sagepub.com/doi/full/10.1177/1535759720903032 Colleagues who have had access to cenobamate in the USA tell me that this is a much more efficacious anti-seizure medication that comparator drugs. I have been using cenobamate as part of an early access programme since November 2020. I have started 8 patients on this drug who have multi-drug refractory epilepsy and have never been seizure free. My experience is that this is a potent anti-seizure medication. I have patients who have never been seizure free that are either seizure free or near-seizure free.
• Do you expect the technology to increase length of life more than current care?	Probably. For there to be a demonstrable population wide change the drug would have to be used commonly. I suspect that this will remain a specialist only medicine for at least the medium term. At an individual level improved seizure care does lead to less risk, fewer injuries, less premature mortality and a reduced risk of sudden unexpected death in epilepsy (SUDEP). Public Health England (2018) report that there are 3,100 deaths each year associated with epilepsy, of which 49% are

	Premature. https://www.gov.uk/government/publications/deaths-associated-with-neurological-conditions
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Improved seizure control (either seizure freedom or near-seizure freedom) will be associated with less injury, fewer mental health symptoms, reduced healthcare utilisation, a reduction in premature mortality. All of these features improve quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes. We do not know how safe the medication is in pregnancy and so the drug will be used more commonly for people who are less likely to become pregnant. Typically, older adults are more sensitive to anti-seizure medication side effects and may not tolerate the drug as well. They are also more likely to be prescribed many concurrent medications and therefore will be at a higher risk of drug-drug interactions.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	The answer to question 14 pertains here too. This is a once daily medication. Adherence to medication is greatly improved when patients take once daily medications. Care must be taken when prescribing alongside other medications – for example it increases the serum levels of phenytoin and to a lesser extent reduces the levels of lamotrigine. Some clinicians may choose to order more frequent assays of anti-seizure medications.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These are not typically needed when starting anti-seizure medications. Clinical judgment and patient choice are used to individualise when to stop a medication that is not tolerable, or not effective.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No. This seems comprehensive to me.

quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the first anti-seizure medication of my lifetime that is demonstrably more potent than alternative choices. A more effective anti-seizure medicine has the potential to make a significant clinical impact on patient care, safety and quality of life.
• Is the technology a 'step-change' in the management of the condition?	Yes. If the seizure freedom and near seizure freedom rate from regulatory trials, reports from colleagues in the USA and my experience, is seen in the UK it would represent a step-change in management.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. 30% of patients do not achieve seizure control despite repeated trials with adequately-chosen anti-seizure medications.
19. How do any side effects or adverse effects	

of the technology affect the management of the condition and the patient's quality of life?	The adverse side effects here are broadly comparable with currently existing anti-seizure medications. The drug will be more tolerable when initiated slowly (which is the company's preference). The drug does not look as if it has a significantly more tolerable side effect profile than existing anti-seizure medications. In my opinion, the side effect profile from regulatory trials does not out-weigh the potency and efficacy reported.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No. These are regulatory trials. These are the standard trials that are needed to licence a medication. These regulatory trials are no more or less representative than other regulatory trials. Typically these studies exclude the very young and very old, people who may become pregnant, people with severe and enduring mental illness and substance abuse problems. The major short-coming of regulatory trials is the inability to gauge long-term clinical outcomes. The regulatory trials provided for cenobamate are unremarkable when compared with regulatory trials for other anti-seizure medications that are successful in UK clinical practice.
• If not, how could the results be extrapolated to the UK setting?	We can be reassured that although there will always be uncertainty when extrapolating regulatory trial results and trying to predict long-term seizure freedom, our experience of this process with other anti-seizure medications has been positive.
• What, in your view, are the most important outcomes, and were they	

measured in the trials?	**Seizure freedom, near-seizure freedom and long-term seizure freedom** and the most important outcomes. Regulatory trials dictate that the primary outcome focuses on the proportion of people who have a 50% seizure reduction. Despite this focus trial were able to report on short-term seizure freedom rates. This focus is not unusual, indeed it is mandated and is the norm. What is unusual is the proportion of people who attain seizure freedom in these studies.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes. Failure to respond to a medication in the short-term predicts failure to respond to a medication in the long-term. I am reassured that cenobamate is effective and a potent anti-seizure medication. Long-term it is tolerability that will determine retention, i.e. what proportion of people started on this drug will remain on this over time.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge, or my limited experience in prescribing this drug.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. All evidence I am aware of is in the public domain.

22. How accurately does NICE clinical guideline CG137 represent NHS clinical practice for people with focal onset seizures in epilepsy? Are you aware of any new evidence or changes in current practice for the currently available comparator treatments since the publication of NICE clinical guideline CG137?	The NICE guidance for the epilepsies is currently being re-written. It is no longer up to date with regards to medication, it was published in January 2012. There have been notable interim amendments most notably about anti-seizure medication safety in pregnancy. This is reflected – for example by *Appendix E: Pharmacological treatment* Which is no longer published "These tables were removed in February 2020 because they are no longer current"
23. How do data on real-world experience compare with the trial data?	There is a paucity of head-to-head studies. The best of these are SANAD (2007) and SANAD2 (2021). These report on long term tolerability and efficacy of commonly used anti-seizure medications as monotherapies. There are data on cenobamate up to eight years from starting on the drug https://pubmed.ncbi.nlm.nih.gov/33567400/ 76% of patients remained on the drug for between 3 and 8 years.

Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that are unique to the drug. There is a need for greater investment in epilepsy services, epilepsy Consultants and epilepsy specialist nurses.
24b. Consider whether these issues are different from issues with current care and why.	This does not differ from current care.
Topic-specific questions	
25. Would cenobamate ever be used in people who have had two previous monotherapies (i.e. no adjunctive therapy) in clinical practice?	Yes, in theory it may. It would be more likely to be used later in a treatment strategy.

26. Are the following treatments relevant comparators for this population in the NHS: a. carbamazepine b. levetiracetam c. eslicarbazepine acetate d. clobazam e. topiramate f. zonisamide	a. carbamazepine This is an older medication and is being used less as a first line adjunctive treatment because of concerns about long-term side effects such as osteoporosis, atherosclerosis. It is not a true comparator. b. levetiracetam This medication may be the first drug used as monotherapy. If it is not first monotherapy, it is the first adjunct. This is primarily because of rational polytherapy (it is not a sodium channel blocker) and the lack of relevant drug-drug side effects. Levetiracetam would be used higher up the decision tree than cenobamate. It is not a true comparator. c. eslicarbazepine acetate This is a newer anti-seizure medication used as an adjunct for focal onset seizures. As a once daily medication that is not a first line drug and is not a first adjunct, it is a reasonable comparator. d. clobazam This is an oft used anti-seizure strategy but is not considered a true anti-seizure drug. It is more commonly used as a short-term medication because tolerability to the drug leading to reduced long-term efficacy is a concern. It is not a true comparator. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004154.pub5/full?highlightAbstract=clobazam e. topiramate

	Topiramate may be chosen because it is one of the few anti-seizure medications that may promote weight loss. It is also a prophylactic medication for migraine. It is effective as an adjunctive medication. This may be a reasonable comparator. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001417.pub4/full?highlightAbstract=topiram%7Ctopiramat%7Ctopiramate f. zonisamide The recent SANAD2 publication may change how zonisiamde is prescribed in the UK. Prior SANAD papers were very influential. Zonisamide was neither more effective not more cost effective than lamotrigine, and there were more treatment failures. This does not make it an attractive adjunctive agent. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00247-6/fulltext
27. What is your experience of dose titration of anti-seizure medications (ASMs) in clinical practice? a. What is the aim of dose titration in focal onset seizures in epilepsy?	a. Dose titration in clinical practice is always slower and more conservative than in regulatory trials and often slower and more conservative than advised by the company. This is for a number of reasons 1. Drug options are limited and if a patient has intolerable side effects with a medication they will be less likely to remain on the medication and so a potentially useful option could be lost. Additionally patients will be less likely to return to this option years down the line. 2. Patients in the real world may be more risk adverse to side effects than patient s who volunteer for clinical trials.

b. Do different ASM's have different dose titration periods? How long is the average dose titration period? c. How frequently is the dose increased?	3. Patients in the real world may be more likely to be prescribed multiple drugs (particularly for conditions that exclude people from regulatory trials – such as mental health disorders). More medications lead to more side effects. The adage is to start low and go slow. b. Yes titration periods depend partly on 1) the half life of the drug and 2) the likelihood of that drug to cause unwanted side effects – such as lamotrigine and Stevens-Johnsons Syndrome. Other drugs can be started very promptly, such as levetiracetam. d. Typically drugs are increased weekly or fortnightly. Dose escalation regimens are personalised and can be much slower than this in some situations.
28. Is percentage reduction in seizure frequency used in NHS clinical practice to assess disease severity and treatment response? a. If yes, what percent reduction	a. No. There is no standardised way that seizure frequency reduction is measured. Patient report, backed up from diaries is a common way for clinicians to record seizure control. Typically letters will report what types of seizures are occurring and their frequency 'fortnightly' or 'clusters twice a year' etc. Percentage reduction in seizure frequency is a metric used in regulatory trials.

is classed as a meaningful response? b. What is the maximum duration of treatment appropriate to determine response? c. What other outcome measures are important to determine severity and treatment response for focal onset seizures in epilepsy?	However seizure freedom and near-seizure freedom and a form of percentage reduction in seizure frequency that are recorded and are clinically meaningful. b. Standard teaching is that a period of '**three times the typical inter-seizure interval'** is needed to know if a treatment is effective. For example if seizures are known to occur weekly, and have not now occurred for over three weeks, then seizures may have gone in to remission. c. As mentioned above. Seizure freedom rates. Long-term retention on the medication. Near seizure freedom rates. Return to driving, employment and family caring roles.
29. In the population of interest (drug resistant epilepsy with focal onset seizures	

requiring third-line treatment): a. how variable is seizure frequency? b. What is the average seizure frequency per month (in your clinical experience)?	a. This has not been adequately studied because there is no true biomarker for seizure frequency (there is no Hba1c for epilepsy). Studies using implantable or wearable devices conclude that diaries and patient report are inaccurate and predominantly under-report seizure frequency. Some studies report inter and intra individual patterns of seizure frequency. Epilepsy, or a tendency towards seizures, is a phenomenon shared by many biological processes and so the epilepsies are many diseases. They each will determine seizure frequency. b. An estimate here is guaranteed to be inaccurate and I don't want to be drawn on this. Estimates of people with treated and untreated epilepsy will vary greatly. A seizure once every 11 months may be seen to be 'infrequent'; but the individual still would be ineligible to drive.
30. What treatments would be used following progression on third-line treatment? What factors influence this choice?	The concept of anything after 'first line' treatments is not one that is easy to describe in epilepsy as treatment is so individualised. I suggest that – 1. The first drug may be levetiracetam (LEV) or lamotrigine (LTG) (carbamazepine in some centres) If LEV was not the first drug chosen it would be the first adjunct. 2. If LEV was chosen then carbamazepine, oxcarbazepine, topiramate or zonisamide may be used next.

Would you expect subsequent treatments: a. to differ for people who had cenobamate compared with current standard care? b. To be less or more effective depending on whether a patient had cenobamate at third-line?	If LTG was chosen then you may be less likely to use sodium channel blocker drugs and so topiramate or zonisamide or LTG may be used next. Not all of these drugs will eb used before a drug below is considered 3. If LEV was chosen eslicarbazepine, lacosamide, perampanel may be chosen next If LTG was chosen then lacosamide, perampanel or brivaracetam may be chosen next. In the schema above therefore eslicarbazepine, lacosamide, perampanel and brivaracetam can be considered as third line drugs. **What probably delineates these is that if they are ineffective they are completely withdrawn -last drug in, first drug out.** As stated before It is not possible to correctly create a true list of first – second and third line medicines for these reasons and also because we prefer certain combinations of medicines. - Some medicines are too closely related to use together, such as levetiracetam and brivaracetam (they compete at the same biological targets). - Some medicines are so close in terms of mode of action – such as carbamazepine, oxcarbazepine, eslicarbazepine – that using two together would bring additive side effects without added efficacy. - Some medicines are used sparingly together because they have a similar mechanism – we prefer to pair drugs together with different modes of action, so called *rational polytherapy.* - Sometimes drugs are chosen because of their secondary effects, for example pain relief, mood stabilisation or weight loss. a. I would suggest that if cenobamate, in keeping with third line drugs above, would be withdrawn if ineffective.

	b. If a patient needed further therapy following an ineffective trial of cenobamate this would not necessarily effect their chance of responding to another medication. However as a marker of success people who fail to respond to multiple medications are less likely to respond to the next – this is independent on the mechanism of each medication and is just a marker of disease severity.
31. What are the psychological effects of living with focal onset seizures in epilepsy? How does this affect patient and caregiver's day-to-day quality of life?	Not all people with epilepsy need a carer. This is more common for children with epilepsy or adults with intellectual disability and epilepsy. There is a large literature that demonstrates the psychological effects. These include – higher rates of depression and anxiety symptoms, higher rates of suicidality and completed suicide. There is a high degree of stigma associated with living with epilepsy. There is a lot of biographical disruption and people failing to attain their maximal potential. This is shown in Epilepsy Research UK's #ALifeInterrupted campaign https://epilepsyresearch.org.uk/alifeinterrupted/campaign-resources/

PART 2 – Technical engagement questions for clinical experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

Key issue 1: Positioning of cenobamate in the treatment pathway	It is not possible to correctly create a true list of first – second and third line medicines for these reasons and also because we prefer certain combinations of medicines. - Some medicines are too closely related to use together, such as levetiracetam and brivaracetam (they compete at the same biological targets). - Some medicines are so close in terms of mode of action – such as carbamazepine, oxcarbazepine, eslicarbazepine – that using two together would bring additive side effects without added efficacy. - Some medicines are used sparingly together because they have a similar mechanism – we prefer to pair drugs together with different modes of action, so called *rational polytherapy.* - Sometimes drugs are chosen because of their secondary effects, for example pain relief, mood stabilisation or weight loss. I suggest that – 4. The first drug may be levetiracetam (LEV) or lamotrigine (LTG) (carbamazepine in some centres) If LEV was not the first drug chosen it would be the first adjunct. 5. If LEV was chosen then carbamazepine, oxcarbazepine, topiramate or zonisamide may be used next. If LTG was chosen then you may be less likely to use sodium channel blocker drugs and so topiramate or zonisamide or LTG may be used next.

	Not all of these drugs will eb used before a drug below is considered 6. If LEV was chosen eslicarbazepine, lacosamide, perampanel may be chosen next If LTG was chosen then lacosamide, perampanel or brivaracetam may be chosen next. In the schema above therefore eslicarbazepine, lacosamide, perampanel and brivaracetam can be considered as third line drugs. **What probably delineates these is that if they are ineffective they are completely withdrawn -last drug in, first drug out.**
Key issue 2: Generalisability of cenobamate and comparator trials to clinical practice	Regulatory trials do not reflect clinical practice, predominantly because they are short and recruit a limited patient population. Thankfully these limitations have not hindered us previously where anti-seizure medications that are proven to reduce seizures in regulatory trials have also shown themselves to be effective in clinical practice. The high-seizure frequency seen in regulatory trials is a good thing. This allows investigators to reach outcomes sooner and reduces unnecessary drug exposure. Studying people with lower seizure frequencies would need much longer studies.
Key issue 3: Long-term efficacy and safety of cenobamate and its comparators	Cenobamate has shown remarkable efficacy in regulatory trials. In limited studies of patients treated for 3 to 8 eight years this effect is maintained. There is not a concerning safety concern with regards to this drug if prescribed by people with experience of prescribing anti-seizure medications. Side effects are dose related.

Key issue 4: Relative safety and efficacy of cenobamate against relevant comparators	C017 has been described as 'unique' in the high-seizure rate seen. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7160883/ Seizure freedom is very unusual in regulatory trials of adjunctive anti-seizure medications for people with focal onset seizures. A meta-analysis of the results of 62 pivotal placebo-controlled randomized trials of lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, zonisamide, pregabalin, lacosamide, and eslicarbazepine, and in pooled analyses of the 3 pivotal trials conducted both for perampanel and for brivaracetam, seizure-free rates ranged from 0% - 6.5%. In contrast the seizure-free rate was 21% in the cenobamate 400 mg group. Side effects and safety form regulatory trials are comparable to current anti-seizure medications.
Key issue 5: Poorly justified model structure	The attempt to model near seizure freedom is laudable. For some people seizure freedom is the ambition but it is not attainable without significant side effects. You might therefore attempt near seizure freedom with a drug, balancing seizure control v side effects vs quality of life.
Key issue 6: Cost-effectiveness driven by cenobamate effectiveness	The concern about C017 being poorly generalisable is based in C017 being a regulatory trial. All regulatory trials for anti-seizure medicines are poorly generalisable. Thankfully, experience dictates that medications that succeed in regulatory trials are also effective in clinical practice. The best evidence one can draw comes from comparing regulatory trials (key issue 4) and there has never been a drug that has a comparable rate of seizure freedom.

Key issue 7: Subsequent treatment	Agree. This is very difficult to model and practice varies across the UK. In part this is because we have drugs with similar efficacy – hence the need for more potent anti-seizure medications.
Key issue 8: Uncertain rate of treatment discontinuation	It is probable that when patients are making an individualised decision on whether to remain on a medication or not they are balancing efficacy with tolerability. A higher efficacy medication would be presumed to have greater medium and long term retention.
Key issue 9: Uncertain utility data	The longer that seizure freedom in maintained the more the improvements in quality of life. Regulatory trials are typically too short to see meaningful changes in QoL.
Key issue 10: Uncertain resource use data	Agree that when using cenobamate when seizure frequency is low affects cost gradient. However the chances of making someone seizure free or near seizure free would eb higher in someone with a lower seizure frequency. Seizure freedom is a very unusual treatment response from people who have a high seizure burden.
Are there any important issues that have been missed in ERG report?	No. Although I cannot agree with the statement on page 37 “In addition, they noted that eslicarbazepine acetate was not a relevant comparator, as it is rarely used as adjunctive therapy.” Openprescribing.net report 2300 items per month in England and table 41 shows it to be equivalent to brivaracetam.
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement:	

- There is an urgent unmet need for more potent anti-seizure medicines, particularly once daily medications that can lead to high levels of seizure freedom.
- How anti-seizure medications are chosen and combined is hard to model, because treatments are individualised.
- Regulatory trials differ from clinical trials and yet have been proven to be good predictors of the utility of anti seizure mediicnes in clinical practice.
- A percentage improvement in seizure freedom is not as clinically significant as seizure freedom which facilitates return to driving, employment and family caring roles.
- Seizure freedom has been shown to improve physical and mental health outcomes and reduce epilepsy associated risks such as premature death.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Cenobamate for focal onset seizures in epilepsy [ID1553]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Monday 17 May 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with focal onset seizures in epilepsy and current treatment options	
About you	
1.Your name	**Daniel Jennings**
2. Are you (please tick all that apply):	☐ a patient with focal onset seizures in epilepsy? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with focal onset seizures in epilepsy? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Epilepsy Action
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Speaking directly with clinicians and patients with focal onset seizures, and existing knowledge from input at previous stages of appraisal, including consultation and scoping workshop. Epilepsy Action also arranged a patient advisory group for people with focal epilepsy to attend and share experiences. ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with focal onset seizures in epilepsy? If you are a carer (for someone with focal onset seizures in epilepsy) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for focal onset seizures in epilepsy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Treatments for focal epilepsy include: • Pharmacological treatment • Psychological interventions • Ketogenic diet for children and young people • Vagus nerve stimulation (VNS) While there is increasingly a large choice of epilepsy medications, many cause side-effects, some of which can be severe and as debilitating as the seizures themselves. Only 52% of people with epilepsy are seizure free, either because their seizures are controlled by medication or due to surgery or other interventions. It is estimated that with the right treatment, the majority of people with epilepsy (70%) could be seizure free. Any new treatments that could address this gap would be welcome. Waiting times remain high in many areas, and have been exacerbated due to the ongoing pandemic. It is often difficult to access psychological interventions in many areas, a situation which again has been made worse by the current pandemic. For many people with epilepsy surgery is not a viable option. For those with a clearly identifiable area of the brain where seizures emanate surgery may be possible if damage to other parts of the brain can be avoided for some the risk of loss of function means surgery would be too high risk. Access to dietary therapies is limited as it requires close supervision by specifically trained HCPs

8. If there are disadvantages for patients of **current NHS treatments** for focal onset seizures in epilepsy (for example how cenobamate is given or taken, side effects of treatment etc) please describe these	
Advantages of this treatment	
9a. If there are advantages of cenobamate over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does cenobamate help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	

Disadvantages of this treatment	
10. If there are disadvantages of cenobamate over current treatments on the NHS please describe these? For example, are there any risks with cenobamate? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	Concerns about possible side effects. Many people with epilepsy already experience side effects from existing medication, and are worried about worsening side effects on new medication, and the potential for breakthrough seizures when switching medicines. Concerns about safety of use in pregnancy. People are increasingly aware of this issue due to sodium valproate. A recent CHM review highlighted that a number of epilepsy medications pose a risk of harm to the unborn baby if used in pregnancy. For many epilepsy medications there was not enough information about their safe use in pregnancy.
Patient population	
11. Are there any groups of patients who might benefit more from cenobamate or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	We believe that older people with late onset seizures are more likely to be focal and people with learning disabilities would benefit from cenobamate as a treatment option. Focal seizures can be difficult to diagnose in both these groups and including both these groups for consideration would provide a further treatment option that is not currently available.

Equality	
12. Are there any potential equality issues that should be taken into account when considering focal onset seizures in epilepsy and cenobamate? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-	

real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	We believe that people with both epilepsy and a learning disability should be given consideration as there is currently research proposed about ways of moving them from Carbamazepine to newer drugs. In addition, the STOMP campaign is about reducing additional drugs in that population

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. What is the impact of focal onset seizures in epilepsy on the quality of life of caregivers?	Caring for someone with epilepsy can be really demanding. Caring for someone with epilepsy can involve keeping them safe during a seizure, calling for medical help, or giving first aid or emergency medication and staying with them following a seizure. Among other things it can be hard to:

a. Is it common for a person with focal onset seizures to have multiple caregivers? b. What are the benefits of cenobamate for carers?	• Get the information you need about the person you're looking after • Get service providers to take your role seriously and involve you in information and decisions • Have enough time and energy to find places of possible support for you both • Stay healthy enough in mind and body to continue being the best carer you can be Depending on the on the severity of the person with epilepsy's condition, they may rely on carers to do a large number of everyday tasks, including cooking and helping them with travelling to and from hospital appointments etc. Some caregivers also report that their own employment opportunities are limited due to the demands of caring for someone with epilepsy. We are aware that people with focal onset seizures are likely to have one carer on an informal basis, who is usually a partner or family member. However, depending on the severity of their condition, and whether they also have a learning disability they may also have more formal support and an additional carer. The benefits of cenobamate would be controlling seizures, or reducing the number of seizures a person with epilepsy has, which would reduce the amount of support a carer would need to provide. Reducing the side effects of medication would also be beneficial as these can be as debilitating as seizures.
15. What are the psychological effects of living with focal onset seizures in epilepsy? How	Some people find that there are impacts on their daily life for example their ability to concentrate and the type of work they undertake or their confidence in travelling and under taking leisure activities. Receiving the initial diagnosis of epilepsy can be particularly overwhelming and distressing for people, given the impact it has on what you can and cannot do. Some people added that the diagnosis can affect how other

does this affect your day-to-day quality of life?	people see and treat you, leading to a loss of social connections, as well as the way they view themselves. Some people have also mentioned that the condition can make them feel like a burden, due to not being able to drive and other limitations which mean they rely on family and/or carers for support.
16. From a patient or caregiver perspective, what would you consider a successful outcome for an anti-seizure medication?	A successful outcome would be controlling seizures of the person with epilepsy. This would significantly reduce the amount of support that the individual would need. While even reducing the number of seizures a person experiences, completely controlling seizures has a much bigger impact on the indidvual's quality or life and mental health. In addition, reducing or eliminating the side effects that the individual experiences as a result of the medication would make a significant difference.
17. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?	As Cenobamate has potential as an adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two epilepsy medicines, patients, especially those with uncontrolled epilepsy would welcome an alternate treatment option. It is felt that the drug could be a very useful addition where none of the currently licensed drugs have been efficacious
15. Are there any important issues that have been missed in ERG report?	As mentioned above the potential for cenobamate as a treatment for people with both epilepsy and a learning disability and the campaign to move them from Carbamazepine to newer drugs is not mentioned in the ERG report.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- We welcome an additional treatment for people with focal onset epilepsy, specifically for people whose seizures have not been controlled by other medication
- It is important that concerns about safe use in pregnancy are addressed
- Possible side effects should be investigated and communicated to patients
- Consideration of people with both learning disabilities and epilepsy
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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  or
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-

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Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with focal onset seizures in epilepsy and current treatment options	
About you	
1.Your name	**Rebecca Longley**
2. Are you (please tick all that apply):	☒ a patient with focal onset seizures in epilepsy? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with focal onset seizures in epilepsy? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Epilepsy Action
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with focal onset seizures in epilepsy? If you are a carer (for someone with focal onset seizures in epilepsy) please share your experience of caring for them.	**Social impact –** legally not able to drive loss of confidence/self esteem lack of spontaneity as you have to plan ahead and then have to cancel at short notice unpredictability **Economic –** impact on work/ career and need to keep changing profession due to limits of the condition preclusion from certain professions too unwell to work at times or only part time extra costs of support

	reliance on benefits system prejudice from employers refusing to employ someone with epilepsy **Relationship/ friendship problems –** hard to make friends and keep them because of peoples' fear of the condition and responsibility it may impose on them. Confidence in telling a new partner long term partner impact on their life is huge. **Co-morbidity/side effect s of medication –** Living with uncontrolled epilepsy has meant I have developed a generalised anxiety disorder and have also had bouts of depression. I have had a number of occasions when I have felt suicidal. Lots of extra support from the NHS via GP, psychiatrist and psychological services. This is not unusual for someone with epilepsy with focal seizures. Memory problems due to neurological damage from continuing seizures and medication. This impacts further on employment, confidence etc. I have double vision due to a medication side effect – this has resulted in more hospital appointments and extra costs of specific prism lenses I have chronic skin problems as result of side effects of a medication, resulting in extra hospital visits. It is very common for people with epilepsy to develop other conditions as a result of medication side effects.

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for focal onset seizures in epilepsy on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	There are quite a number of medications (I have tried 5 adjunctive drugs) but there has not been any significant progress with controlling the c.3rd of people whose epilepsy remains uncontrolled, like mine. Patients often run out of drug options, or the side effects mean staying on a drug is not feasible, Other treatment options like surgery or a vagus nerve stimulator are not appropriate for most people. There is a lack of funding into epilepsy services and has been for a long time. In comparison to other neurological conditions, such as MS, epilepsy is receives far less of the funding and yet far more patients live with the condition. If funding into research were increased in line with the proportion that other less common neurological conditions receive, I believe we would save the NHS money in the long term. More people with controlled epilepsy = less demand on emergency services and other services like psychiatry. Most people with epilepsy have to play a balancing act between getting the best seizure control they can with the least/least damaging side efects of medication. From my involvement with Epilepsy Research UK and Epilepsy Action I would say my views are in line with other people who live with the condition or who are carers.
8. If there are disadvantages for patients of **current NHS treatments** for focal onset seizures in epilepsy	Side effects are many, but mainly the following:

(for example how cenobamate is given or taken, side effects of treatment etc) please describe these	cognitive slowing, giddiness, memory problems, headaches, loss of libido, mental health problems e.g. anxiety, excessive dry mouth leading to gum disease, early onset osteoporosis
Advantages of this treatment	
9a. If there are advantages of cenobamate over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does cenobamate help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.**	I have not been prescribed cenobamate but from what I have read and heard in the technical meeting it would seem that seizure control could be achieved even for people who have tried many other adjunctive treatments without success so far. If my epilepsy could be controlled it would have a hugely beneficial impact upon my life. I could drive again, regain my career, economically be better off, increase my independence and confidence and change my relationships with others who would view me differently. Less side effects could mean that cognitively I would function at a higher level, with improved word finding and regain my articulate old self. I would say that the ability to drive and general improved confidence and self esteem would have the biggest impact on my life.
Disadvantages of this treatment	
10. If there are disadvantages of cenobamate over current treatments on the NHS please describe these? For example, are there any risks with	Possible risk of a severe allergic reaction, but this is not exclusive to cenobamate, as other current epilepsy medications can cause this.

cenobamate? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	There would need to be discussions with women who are using the contraceptive pill, as cenobamate can interfere with this. Again this is relevant to a few other anticonvulsants. For patients who have a history of suicidal ideation, and serious mental health problems it would possibly not be suitable. As a much newer drug there is uncertainty about side effects, especially cumulatively and in conjunction with other anticonvulsants.
Patient population	
11. Are there any groups of patients who might benefit more from cenobamate or any who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	For people who have uncontrolled epilepsy and have tried more than one adjunctive medication it may bring some benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering focal onset	Sadly there is still a high degree of both public ignorance and stigma with regards to epilepsy. As stated earlier there is also an inequity with regards to access to NHS funds for the condition in terms of

seizures in epilepsy and cenobamate? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	research into the condition currently. A large percentage of people with uncontrolled epilepsy experience mental health and memory problems, both due to the chemical changes the seizures cause, as side effects of some medications, and also due to the psychological impact of living with a life changing condition with huge ramifications upon the individuals quality of life. Knowledge of focal seizures in the general public, and even with some medical practitioners, is poor. This means that experiencing these types of seizures in public, places of education etc, can often be misinterpreted, overlooked or inaccurately assessed. People with learning difficulties are particularly vulnerable to receiving inequitable access to support and suitable medication. Greater numbers of people are developing epilepsy, particularly elderly people as a result of co-morbidity, and again accessing appropriate medication could be limited.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14. What is the impact of focal onset seizures in epilepsy on the quality of life of caregivers? a. Is it common for a person with focal onset	Not everyone with epilepsy has a carer. Many people try to lead as independent a life as possible, but for some and all, there are times when support /care is necessary. It may be that some with focal epilepsty have more than one care giver, e.g. both parents. Impacts on the carers life are - Physical time – they have to put their needs second if the person with epilepsy needs physical support, driving, emotional support etc. Financial – the extra costs that epilepsy can bring will affect the household budget

seizures to have multiple caregivers? b. What are the benefits of cenobamate for carers?	Emotional – the worry living with/ caring for someone with an unpredictable and dangerous condition can bring. This can have a huge impact on the carer. Their individual life choices may well be affected. Such as taking early retirement, not going away alone etc. If cenobamate can bring seizures under control this would revolutionise a carers life in some instances.
15. What are the psychological effects of living with focal onset seizures in epilepsy? How does this affect your day-to-day quality of life?	The unpredictability of seizures means that life is uncertain and not without risk. This can create an underlying lack of confidence, anxiety and self-esteem. The impact of pre and post seizure aspects such as memory loss exacerbate these psychological effects. Additionally, tiredness as a direct result of seizure activity and medication side effect creates a sense of inadequacy Practical consequences, such as inability to drive and barriers to employment, emphasise the impact on self-actualisation.
16. From a patient or caregiver perspective, what would you consider a successful outcome for an anti-seizure medication?	A truly successful outcome would be that someone's epilepsy is controlled, with minimal medication side effects. The poor relation of this would be a substantial lessening of the number of seizures experienced.
17. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any	The possibility that for those whose epilepsy has remained stubbornly uncontrolled, that it could become controlled. It is the weighing up always of the impact of possible side effects against possible full seizure control, or reduction in seizures.

benefits of this treatment that have not been captured?	
15. Are there any important issues that have been missed in ERG report?	

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- living with focal epilepsy has a huge impact upon the individual's life.
- there is a need to extend the life chances of someone with refractory epilepsy by offering new treatment options
- weighing up drug side effects against seizure control is the biggest issue
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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Technical engagement response form

Cenobamate for focal onset seizures in epilepsy [ID1553]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **5:00pm, Monday 17 May**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Eisai Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Positioning of cenobamate in the treatment pathway	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 2: Generalisability of cenobamate and comparator trials to clinical practice	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 3: Long-term efficacy and safety of cenobamate and its comparators	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 4: Relative safety and efficacy of cenobamate against relevant comparators	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 5: Poorly justified model structure	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 6: Cost-effectiveness driven by cenobamate effectiveness	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 7: Subsequent treatment	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**

Key issue 8: Uncertain rate of treatment discontinuation	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 9: Uncertain utility data	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**
Key issue 10: Uncertain resource use data	**NO**	**Agree with the issue raised and have no further comments, new evidence, data or analyses to add.**

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: None	**N/A**	**NO**	**No further comments, new evidence, data or analyses to add.**

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	**Briefly describe the company's original preferred assumption or analysis**	**Briefly describe the change(s) made in response to the ERG report**	**Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER**
..	..	..	**[INSERT / DELETE ROWS AS REQUIRED]**
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Evidence Review Group's Critique of the Company's Response to the Technical Engagement Process

Cenobamate for focal onset seizures in epilepsy [ID1553]

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Date completed	28/05/2021

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

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1 Overview of the Company's response to the issues raised at technical engagement

A number of key issues were raised by the ERG in its appraisal report, which were discussed at technical engagement. These relate to:

Issue 1: Positioning of cenobamate in the treatment pathway

Issue 2: Generalisability of cenobamate and comparator trials to clinical practice

Issue 3: Long-term efficacy and safety of cenobamate and its comparators

Issue 4: Relative safety and efficacy of cenobamate against relevant comparators

Issue 5: Poorly justified model structure

Issue 6: Cost-effectiveness driven by cenobamate effectiveness

Issue 7: Subsequent treatment

Issue 8: Uncertain rate of treatment discontinuation

Issue 9: Uncertain utility data

Issue 10: Uncertain resource use data

The company provides commentary on each of these issues in their response document to technical engagement, with additional data in response to Issues 3 and 8. To inform Issue 3, the company presented additional longer-term evidence on reduction in seizure frequency from open-label studies of 3rd generation ASMs included in their model. For Issue 8, the company updated their method for obtaining discontinuation rates through the fitting of parametric distributions to data extracted from open-label observational studies. The ERG provides a critical evaluation of the company response below.

2 Critique of the company's response to the issues raised at technical engagement

2.1 Issue 1: Positioning of cenobamate in the treatment pathway

The company reiterated that topiramate, zonisamide and clobazam should not be considered in the decision problem. They argued that 'the vast majority of DRE patients' are 'more likely to be treated with 3rd generation ASMs as they are newer therapies with fewer drug interactions, milder adverse events and have novel mechanisms of action compared to older generation ASMs.'

The ERG raises two issues with these statements. First, there appears to be no consensus in UK practice on the most appropriate 3rd line adjunctive ASMs; secondly, there is no conclusive evidence that 3rd generation ASMs are significantly more effective, safer or more tolerable than older generation ASMs.

a. No consensus that cenobamate should only be placed against 3rd generation ASMs.

The ERG believes there is no clear consensus among clinical experts on a definitive list of adjunctive therapies to which cenobamate should be compared against. Whilst ERG clinical advisers noted zonisamide, topiramate and clobazam should be added to the company's decision problem (ERG report Sections 2.2 and 2.3), one NICE clinical expert (Ley Sander) noted that only levetiracetam, zonisamide, lacosamide and perampanel should be considered,(1) whilst another (Rhys Thomas) noted that topiramate and eslicarbazepine acetate were appropriate options, whilst carbamazepine, clobazam and levetiracetam were not true comparators, and zonisamide was not an attractive option due to its limited efficacy.(2) Despite differences in views among these clinical experts, none of them recommended that only 3rd generation ASMs should be considered in the decision problem.

The results of the survey of 14 UK clinical experts conducted by the company suggested that, although 64% of patients may receive cenobamate if they failed to respond to, are intolerant to, or are unsuitable for low cost therapies available in primary and secondary care (i.e. 1st and 2nd generation ASMs), cenobamate may also be placed earlier in the treatment pathway for a significant proportion of patients (36%), where older generation treatments would still be considered suitable alternatives. (3) NICE Clinical Expert Ley Sander noted that, if cenobamate is effective at providing seizure freedom, it will be used earlier than other alternative ASMs.(1)

b. No conclusive evidence that 3rd generation ASMs are more effective, safer or more tolerable.

The ERG believes there is no conclusive evidence that 3rd generation ASMs have superior efficacy, safety and tolerability to older generation treatments in focal onset epilepsy. A large NMA of ASMs

for refractory partial-onset epilepsy concluded that newer ASMs were as efficacious as older treatments, and did not show that 3rd generation therapies had a more favourable safety and tolerability profile.(4) Another NMA of 2nd and 3rd generation ASMs concluded that, although topiramate had the highest surface under the cumulative ranking curve (SUCRA) for 50% response, levetiracetam had a better balance of efficacy and tolerability compared with 3rd generation ASMs.(5) As noted previously, existing NMAs have a number of limitations including lack of head-to-head evidence and lack of adjustments in the indirect comparisons.(6)

Overall, due to the lack of consensus on choice of comparators, lower cost of older generation ASMs and lack of conclusive evidence that 3rd generation treatments are significantly more effective, safer or better tolerated than relevant older generation ASMs, the ERG believes that restricting the decision problem comparators to 3rd line, 3rd generation adjunctive ASMs is not clinically appropriate and likely to overestimate the cost-effectiveness of cenobamate.

The company argues that the scenario presented by the ERG of a cost-comparison model (see sections 6.1.2.1 and 6.2 of the ERG report) would ignore clinical improvements that patients treated with cenobamate experience. This scenario assumed that all treatments (cenobamate and comparators) had the same safety/tolerability and effectiveness profiles and the only difference between the treatments were intervention and administration costs. The ERG notes that this scenario was undertaken in face of the multiple uncertainties identified in the company's base-case analysis and detailed across the ERG report, including uncertainties about the efficacy and safety of cenobamate relative to the comparators (for example, the limitations identified in the company's NMA used to derive effectiveness estimates for cenobamate and comparators). The ERG's clinical advisers were supportive of this scenario with the view that the majority of the ASMs, including cenobamate, are expected to have similar effectiveness in practice.

As described in Section 6.2 of the ERG report, this scenario analysis resulted in cenobamate being [redacted], due to its [redacted], and [redacted]. Given the potential exclusion, by the company, of several relevant comparators, this scenario analysis concludes that [redacted].

To consider the scenario where 2nd generation ASMs are relevant comparators, the company's technical engagement response presents the results of a scenario analysis where zonisamide and topiramate are assumed to be equally as effective as brivaracetam. Results of this scenario show that cenobamate dominate both zonisamide and topiramate, as it did for brivaracetam. The ERG considers that this analysis, although partially mitigating the ERG and clinical advisers' concerns about

exclusion of relevant comparators, does not adequately address the remaining limitations identified by the ERG regarding the effectiveness of cenobamate relative to its comparators.

2.2 Issue 2: Generalisability of cenobamate and comparator trials to clinical practice

The company stated that the cenobamate trials are largely generalisable to clinical practice and any minor differences are not anticipated to result in a significant change in model outcomes. The ERG disagrees that cenobamate trials are representative of clinical practice, but accepts that assuming a range of plausible baseline severity values is unlikely to significantly affect the cost-effectiveness of cenobamate against 3rd generation, 3rd line adjunctive therapies, as shown on Fig. 13 in section 6.3.2 of the ERG report.

ERG clinical advisers and NICE clinical experts (CE TE response) noted that, as regulatory trials, the cenobamate trials do not reflect clinical practice. As discussed in the ERG report (Section 3.2) cenobamate trials were conducted in narrower populations (e.g. exclusions of patients with progressive disease and/or disabilities), with significantly faster titration periods compared with clinical practice, and with limited follow-up; similar limitations apply to the comparator trial evidence. The extent to which the comparator trial evidence populations compare with the cenobamate trial participants is not clear (ERG report Section 3.3). Both ERG clinical advisers thought that patients in the C017 trial (and to a lesser extent, the C013 trial) had higher average seizure frequency at baseline than usually observed in UK clinical practice. We anticipate that the accuracy of this opinion can be confirmed or rejected by specialist committee members.

The ERG agrees with the company that there is a large spectrum in seizure frequency among DRE patients, and that the published evidence on 'true' baseline seizure frequency is limited (see ERG Section 3.2.2). In the absence of published evidence, and given apparent differences of opinion between ERG clinical advisers and clinicians surveyed by the company, rather than advocating for a precise estimate of baseline severity, the ERG preferred to evaluate the impact of assuming a range of seizure frequency estimates on the model outputs (ERG Report Section 6.3.2).

2.3 Issue 3: Long-term efficacy and safety of cenobamate and its comparators

The ERG agrees with the company that the lack of longer-term RCT evidence makes a standard NMA for longer-term seizure outcomes unfeasible.

The company presented additional longer-term evidence on reduction in seizure frequency from four open-label studies of 3rd generation ASMs included in their model.(7-10) This showed 3 years follow-up data for cenobamate, 1 year for eslicarbazepine acetate, 4 years for perampanel and lacosamide and 6 years for brivaracetam (Figure 1, Arvelle TE response, p.12). Overall, the evidence presented suggests that cenobamate patients experienced a higher reduction in seizure frequency from baseline compared with other 3rd generation treatments. This evidence was not included in the company's updated model.

The ERG checked the additional evidence in Figure 1 of the company's response to TE against the publications provided by the company, and have a number of concerns about its validity. The company did not report the methods used to identify and extract this evidence, and how missing data and attrition bias were accounted for (the high risk of attrition bias for cenobamate's long-term evidence is discussed in ERG report Section 3.2.3.2). Given the limited long-term evidence, all comparisons across ASMs are naïve and unadjusted, and at high risk of confounding. The company did not present longer-term data on seizure freedom, safety or tolerability.

Overall, the limited additional evidence presented by the company does not affect the ERG's conclusions that the long-term efficacy and safety of cenobamate compared to other relevant ASMs is highly uncertain.

The company disputed the appropriateness of including C013 in the ERG base-case. The ERG believes that, in view of the evidence presented, the exclusion of C013 from the model is not justified and therefore it is appropriate to include. This is fully discussed in the ERG report (Section 3.4.1, 4.2.3 and 4.2.6).

2.4 Issue 4: Relative safety and efficacy of cenobamate against relevant comparators

The ERG recognises that cenobamate uses a distinct mechanisms of action. Although the efficacy results of the cenobamate trial evidence are promising, there is currently insufficient evidence to

determine whether, and to what extent, cenobamate's mode of action translates into improved effectiveness outcomes or different tolerability compared with other relevant ASMs.

As discussed in ERG report Section 3.4, the company's ITC analyses [redacted] The company's ITC analyses were also limited by differences in populations and designs across the trials included in the ITC (ERG Report Section 3.4), and some unexplained heterogeneity remained following the ERG's adjusted ITC analyses (ERG Report Section 3.5). The lack of head-to-head comparative evidence, limitations of the ITC and exclusion of several relevant comparators (as discussed under Issue 1) means that the relative efficacy and safety of cenobamate compared with other adjunctive ASMs is uncertain.

Other concerns raised in the ERG report include differences in mean seizure frequency at baseline between C017 arms (Section 3.2.2), and unexplained differences in efficacy outcomes between trials C017 and C013 (Section 3.2.5); the clinical plausibility of efficacy results of trial C017 was also questioned by ERG clinical advisers. Due to limited evidence, the long-term tolerability and safety of cenobamate is uncertain compared with more established adjunctive ASMs, and long-term drug monitoring is needed.

2.5 Issue 5: Poorly justified model structure

In their response to technical engagement, the company reiterated that the model structure used in the company's base case analysis is more appropriate than that implemented in the ERG's base case analysis. The company's model included five different levels of response to the third line ASMs: no response (0 to <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 seizure freedom (100% reduction). This is more granular than the ERG's preferred model structure with three levels of response: 0 to <50%, 50 to <100%, and 100% seizure reduction. The company reiterated its initial arguments that the more granular structure is more appropriate because health and cost outcomes in patients with ≥75% or ≥90% seizure reduction are likely to be different to those with 50 to <75% seizure reduction. The company argues that patients in the cenobamate arm are more likely to have these higher levels of response and that, subsequently, the less granular model structure would underestimate the benefits of cenobamate.

The ERG acknowledges resource use and HRQoL in patients who achieve sustained ≥75% or ≥90% seizure reduction could differ to those who achieve only a 50% to 75% reduction, but notes that the company did not provide evidence that cenobamate increases the probability of ≥75% and ≥90% reduction in seizure frequency compared to the comparators. The ERG provided an additional scenario in their report, where all five levels of response were synthesised in the NMA. However, even with this additional NMA, the effectiveness evidence for comparators at 75 and 90% is scant; only the C017 study provided evidence for the 90% response and a further four studies provided evidence for the 75% response (3 for lacosamide, 1 for eslicarbazepine acetate and none for the other comparators). Therefore, the NMA substantially borrowed from the complete evidence for all cuts from a single cenobamate study.

Furthermore, the company did not provide evidence of important differences in costs and health-related quality of life between different levels of treatment response. The uncertainty in these differences is further reflected in clinical expert statements at technical engagement. Specifically, one clinician (Lay Sander on question 13) highlighted that "evidence strongly suggest that only seizure freedom has a lasting impact on quality of life". In contrast, Rhys Thomas (question 9) implied that seizure reduction can improve patients' HRQoL, for example, if patients stop having seizures at night.

Therefore, the ERG maintains that the less granular structure is more appropriate to inform a comparison of cenobamate with its relevant comparators.

2.6 Issue 6: Cost-effectiveness driven by cenobamate effectiveness

The company assumed that the proportion of patients who remain on treatment would continue to improve, i.e. the proportion of patients with high and very high response among patients still on cenobamate would continue to increase over time. Their justification was that non-responders were more likely to discontinue treatment than responders, and so over time, a greater proportion of patients still on treatment would be responders. The company also assumed that the probability of patients who discontinue treatment was the same for to all levels of response.

As discussed in further detail under Issue 8, the ERG considers equal treatment discontinuation across all levels of response to be implausible. Thus, the ERG assumed that after 32 weeks of treatment (first 6 model cycles), patients who have no response (<50% reduction in seizures) for three months (model cycle 6) would discontinue treatment. Since the discontinuation rate in the ERG base case depends on response, the proportion of patients with moderate response (50 to <75% reduction), high response (75 to <90% reduction), and very high response (90 to <100% reduction) who remain on treatment were assumed to stay in the same response state.

Therefore, the ERG maintains the appropriateness of the assumption that patients who have not responded to treatment for 3 months after approximately 6 months from treatment initiation, discontinue treatment and move to subsequent treatment (subsequent ASM health state).

2.7 Issue 7: Subsequent treatment

The ERG implemented several changes to the company's model to estimate costs and outcomes in patients who move on to subsequent ASMs. These are listed in the company's response to Issue 7, at technical engagement. The company has since accepted all changes recommended by the ERG.

The ERG emphasises that the cost-effectiveness model is a simplification of the treatment of FOS epilepsy in practice, as it does not reflect that subsequent ASMs could include numerous additional lines of treatment and the potential effect of treatment sequencing (please see Section 4.2.2.1 of the ERG report).

2.8 Issue 8: Uncertain rate of treatment discontinuation

The ERG suggested using 'all-cause' discontinuation results from the NMA to inform the discontinuation rate for cenobamate and its comparators in the first 6 model cycles (32 weeks of treatment) (ERG Report Section 4.2.6.4). The differential discontinuation rate is used to reflect differences in adverse event profiles of different comparators. Thereafter, treatment discontinuation is assumed to occur when patients have no response to treatment for three months (model cycles 6+) or due to treatment failure in patients who had previously responded. Discontinuation due to treatment intolerance is assumed to only occur in the first 6 model cycles. The ERG assumed that the discontinuation rate in responders is assumed to be equivalent for all comparators due to a lack of evidence that treatment failure in responders is different between comparators. As stated in the ERG report, this approach is consistent with previous appraisals of ASMs in the UK (11-14). The ERG highlighted the limitations of the evidence included in the NMA but preferred it to the rates provided by the company. The company used naïve comparisons informed by observational studies identified in a non-structured review. The estimates of discontinuation rate used in the company model provided a very poor fit to the data reported in the selected studies (ERG Report Section 4.2.6.4).

In their response to technical engagement, the company disagreed with using the NMA results to inform the short term discontinuation rate and with using the same discontinuation rate for all comparators after cycle 6.

Using the NMA results to inform the short-term discontinuation rate

In their response to technical engagement, the company objected to using the NMA results to inform the discontinuation rate. The company expressed concern that the NMA results overestimate the discontinuation rate of cenobamate relative to the comparators, because the studies included in the NMA (C013 and C017) had a steeper dose titration than expected in clinical practice (phenomena also seen in comparator trials, expect for brivaracetam), and therefore could have led to a higher discontinuation rate due to adverse events. Instead, the company prefers to inform the discontinuation rate using naïve comparisons.

The company updated their method for obtaining discontinuation rates; the updated methods and the resulting discontinuation rates are detailed in Figure 2 of the technical response and the 'new evidence' document. The company used three of the studies used in the original submission (15-17), and one additional study (18) to inform the discontinuation rate; all four studies were open-label observational studies. The updated method for informing discontinuation in the economics model involved digitising the time to discontinuation curves from each of the studies, independently fitting a range of single parametric distributions to each of these curves, and selecting the parametric distribution that best fitted each digitised curve. The time to discontinuation rates estimated across time by the selected parametric distributions were directly applied in the economic model.

Although the methodology now used is seen as an improvement compared to the 'goal seek' method (function in Excel) previously used in the CS to derive the hazard ratio (relative to cenobamate), the ERG believes that this additional analysis still does not address the limitations of using naïve comparisons as highlighted in the ERG report. The naïve comparisons have no common comparator between studies, and so fail to take account of heterogeneity between studies that can confound outcomes (e.g. number and type of concomitant therapies), potentially biasing the estimates of relative effect (in this case, time to discontinuation of comparators relative to cenobamate).

The ERG recognises that the discontinuation rate in studies C013 and C017 (used in the NMA) may overestimate discontinuation with cenobamate because dose titration was steeper in these studies than it is in practice. However, the ERG highlights that the same is likely to be the case with the studies used to inform the discontinuation rate of comparators in the NMA. Therefore, the ERG recognises that there is considerable uncertainty in the relative discontinuation rate between the comparators, but maintains that the NMA is a more appropriate source for informing the discontinuation rate in the economics model than the naïve comparisons suggested by the company, due to the challenges highlighted above.

Assuming equal long-term discontinuation rate for all comparators

The company used the probability of discontinuation derived from naïve comparisons in all model cycles, stating that equal discontinuation is inappropriate as retention is expected to be higher for more effective treatments. The ERG agrees that treatment discontinuation due to lack of efficacy could be higher for less effective treatments. The ERG reflected this in their model by discontinuing treatment in non-responders; as result, treatments that are less effective will lead to a higher proportion of non-responders who then discontinue treatment. For example, in the ERG base case, 5 years after starting treatment (in model cycle 26), 35.5% of patients in the cenobamate arm continue to receive treatment, compared to 13.0%, 15.0%, 15.1%, 15.9%, taking brivaracetam, perampranel, lacosamide and esclicarbazepine, respectively.

2.9 Issue 9: Uncertain utility data

Health states utility values used in the model

Due to the absence of studies with adequate utility data to inform the economic model, a mapping study was performed by the company. The mapping algorithm developed by the company was considered poor in its performance by the ERG and, as pointed out by the company itself, does not appropriately reflect the variability in observed SF-6D utility index scores, underestimating the range of predicted utilities. Thus, the ERG considered the mapped utility estimates used to populate the model to be highly uncertain (see Section 4.2.10 of the ERG report).

The ERG report also highlighted that the company submission did not discuss or consider utilising the health utilities used in NICE CG137 (sourced from Selai (2005)(19)). In the company's response to technical engagement, the company indicates that the utility data from Selai (2005) (19) is an inappropriate source as it is based on a limited sample size of 125 patients. The ERG recognised the limitations of these utility data, as these limitations were clearly described in the NICE CG137 (see section 4.2.10.6 of the ERG report) and, thus, chose to consider the company's utility data in the ERG base case. However, the ERG continues to emphasise the limited availability of good quality utility data to inform the model and the uncertainty surrounding the mapped utility estimates derived and used by the company.

Caregiver utility values used in the model

The company included in their model a HRQoL disutility for caregivers. Caregiver disutilities were sourced from a small, poorly reported caregiver survey (n=86) of questionable representativeness to UK population seen in clinical practice. The ERG raised concerns about how state-specific disutilities

were derived from this survey as no detail was provided (Section 4.2.10.8 of the ERG report). In the company's response to technical engagement, the company briefly indicates that a first order linear regression model was used to obtain stratified disutility values by health state by identifying the average number of seizure-free days per 28 days in each response category. That is, the company made an unadjusted link between the average number of seizure-free days and carers' disutility values derived from the survey data. These data are shown in Table 44 in document B of the CS – and is here shown in Table 1 below for completeness. It is not clear to the ERG how this information was used to estimate disutilities for each level of response in the economic model (shown in Table 51 in document B of the CS and also transcribed below in Table 2). Since little information is provided on how these response-level disutilities were derived, the ERG remains unable to evaluate the robustness of the methodology used or the validity of the estimates obtained. In particular, the ERG highlights that in Table 1, disutility is inversely proportional with seizure freedom except for the four patients who were seizure free for 21-27 days, that is, overall, the increase in seizure free days implies an increase in the mean disutility. This contradicts the relationship between seizure-freedom and carers' disutility reported in Table 2.

Table 1. Caregivers' disutilities by seizure-free period (reported in Table 44 in document B).

Variable	N	Percentage	Mean disutility (SD)
Seizure-free period (days)			
0 to 5			
6 to 15			
16 to 20			
21 to 27			
Not sure			

Table 2. Carers' disutility by response health state

	Carer disutility
No response (<50% reduction)	
Moderate Response (Responder Rate ≥50% and <75%)	
High Response (Responder Rate ≥75% and <90%)	
Very High Response (Responder Rate ≥90% and <100%)	
Seizure-freedom (100% reduction in seizure frequency)	

Thus, the ERG remains concerned with the magnitude of the elicited disutilities for caregivers and with the fact that uncertainty in these parameters were not considered in the model. And, as previously highlighted in the ERG report (see Section 4.2.10.8), the ERG still considers the company estimate of carers' disutility to be highly uncertain.

The company argued that the inclusion of HRQoL disutility for caregivers was in line with the NICE reference case and that successful treatment of epilepsy improves health for both patients and their caregivers. The ERG clinical advisers indicated that the HRQoL of carers is likely to be impacted by the role of caring for patients with epilepsy who have FOS and who require a carer. Thus, the ERG does not dispute the fact that HRQoL disutility of caregivers is in line with the NICE Reference case. However, the ERG disputes the use of the highly uncertain carergiver disutilities derived by the company and used in the model. The ERG also disputes that carergiver disutilities should be applied to all FOS epilepsy patients, as not all FOS epilepsy patients require a carer. This latter point was highlighted by the ERG's clinical advisers and confirmed by NICE patient (Rebecca Longley) and clinical (Rhys Thomas) advisers in their response to technical engagement.

2.10 Issue 10: Uncertain resource use data

In the company's model, resource use was informed by clinical opinion. The ERG base case used the same resource use estimates as the company, but the ERG report highlighted the uncertainty in the resulting cost estimates, as resource use was based on clinical opinion, rather than evidence-based data. To explore the impact of this uncertainty, the ERG suggested using resource use data from previously published literature, such as NICE CG137 (see Section 1.5 of the ERG report). In their response to technical engagement, the company provided an additional scenario where resource use was informed using estimates from Jacoby (1998),(20) as used in NICE CG137. However, the results (reported in Tables 3, 4 and 5 of the company's technical engagement response) were incorrect - the company used the percentage of patients who utilise healthcare resource use reported in Jacoby (1998)(20) as if these represented the frequency of use of healthcare resources, thus inflating the state-specific cost of healthcare by 100. The corrected estimates are provided in Tables 3-5 below.

Table 3. Summary of resource use data used in the company's base case, ERG base case and the company's scenario analysis

Scenario	Costs per cycle	No response	≥50%-<75% reduction in seizures	≥75- <90% reduction in seizures	≥90%- <100% reduction in seizures	≥50%-<100% reduction in seizures	Seizure-free
Company and ERG base case (informed by expert opinion)	Routine monitoring	£205.40	£117.99	£19.72	£19.72	£52.48	£17.88
	Epilepsy events	£886.13	£351.13	£150.43	£42.50	£181.36	£0.00
	Total	£1,091.53	£469.12	£170.15	£62.22	£233.84	£17.88
Jacoby (1998)(20)	Total	£38.72	£38.72	£38.72	£38.72	£38.72	£6.64

Table 4. Cost-effectiveness model results when resource use is based on Jacoby (1998): company's base case.

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER/QALY
Cenobamate	[redacted]	6.955			
Eslicarbazepine acetate	43,428	6.339	[redacted]	-0.616	[redacted]
Perampanel	43,609	6.226	[redacted]	-0.729	Dominated
Lacosamide	43,872	6.147	[redacted]	-0.808	Dominated
Brivaracetam	43,824	5.868	[redacted]	-1.087	Dominated

Table 5. Cost-effectiveness model results when resource use is based on Jacoby (1998): ERG's base case.

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER/QALY
Cenobamate	[redacted]	11.151			
Eslicarbazepine acetate	42,879	10.873	[redacted]	-0.278	[redacted]
Perampanel	42,281	10.860	[redacted]	-0.013	101,500
Lacosamide	42,270	10.867	[redacted]	0.007	Dominated
Brivaracetam	41,276	10.846	[redacted]	-0.021	47,333

The resource use in Jacoby (1998)(20) indicates a substantially lower difference in costs between different levels of response, which consequently increases the incremental cost of cenobamate. In this scenario, cenobamate no longer dominates the comparators both under the company's and ERG's preferred model assumptions.

In their response to technical engagement, the company highlighted the limitations of using estimates from Jacoby (1998)(20) to inform resource use in the model. The ERG welcomes this critique and agrees that generalisability of the estimates in CG137 is uncertain. However, the ERG maintains that there is substantial uncertainty in the resource use estimates used in the company and ERG base cases (informed by clinical opinion), and emphasises that, as shown in Tables 3 to 5 above, any overestimation of the differences in resource use between different levels of response will overestimate the cost savings associated with treatment with cenobamate relative to its comparators.

3 Critique of the company's preferred base-case following technical engagement

The company submitted a revised base-case following technical engagement. This base-case accepts the following ERG's preferred assumptions:

1. (relates to issue 3) Incorporating the C017 OLE data with 12-weekly cycles from completion of the available RCT data;
2. (relates to issue 4) Use of the updated NMA presented by the ERG on the efficacy and safety of relevant comparators relative to cenobamate. The NMA performs a joint synthesis of all relevant levels or response and by adjusting for placebo heterogeneity across included studies;
3. (relates to issue 7) The odds ratio of no response is applied to the odds of not achieving seizure freedom, in line with reporting of the outcome in the Chen 2018 study.
4. (relates to issue 7) The odds ratio has been applied to brivaracetam to ensure that subsequent treatment is less effective than alternative comparators.
5. (relates to issue 10) Cenobamate is no longer an option for subsequent ASM treatments.

The company did not agree with the ERG's proposal of:

1. A model structure based on three levels of response (issue 5);
2. The inclusion of study C013 in the NMA (issue 2);
3. The use of the results from the 'all-cause' discontinuation NMA to inform time to discontinuation and the assumption of the same time to discontinuation from cycle 6 onwards (issue 8);
4. Adjustment over the extrapolation of treatment effect, that is, patients remain in the same state unless they discontinue treatment (issue 3);
5. Time to treatment discontinuation for comparators in model cycles 6 onwards is assumed to be the same as that for cenobamate in C017 (issue 8);
6. Patients with no response after cycle 6 assumed to move to the 'subsequent ASMs' health state (issue 8);
7. Baseline number of seizures informed by trial C013 (issue 2);
8. Not including carer disutility (issue 9)

The cost-effectiveness results of the company's original and revised base-case analysis, as well as the ERG's base-case results indicate that cenobamate remains dominant over the set of alternative treatments compared.

The company also presented cost-effectiveness results for the following additional scenarios:

1. That topiramate and zonisamide are as effective as brivaracetam (relating to issue 1)
   Under this scenario, cenobamate continues to dominate against cheaper comparators, as depicted from Table 1 and Table 2 of the company's technical engagement response, for zonisamide and topiramate, respectively.
2. The use of Jacoby (1998)(20) resource use, instead of clinical opinion (relating to issue 10)
   This was discussed in section 2.10 above, where corrections to the estimates offered by the company's technical engagement response are also presented.

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