NICE National Institute for Health and Care Excellence

Part 1 | **All confidential information redacted**

Slides for PUBLIC

Cenobamate for focal onset seizures in epilepsy [ID1553]

Lead team presentation

1st committee meeting

Chair: Peter Jackson

Lead team: Stuart Davies, Richard Nicholas, Nigel Westwood

ERG: Centre for Reviews and Dissemination and Centre for Health Economics – University of York

Technical team: Sharlene Ting, Adam Brooke, Nicole Elliott

Company: Arvelle Therapeutics

5th August 2021

History of appraisal

1 December 2020	**Company submission**
28th January 2021	**CHMP positive opinion**: "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 2 anti-epileptic medicinal products"
14th May to 14th June 2021	**Technical engagement**
14th June 2021	**Stakeholder feedback to technical engagement** • Company: new evidence and analyses (issues 3, 8 and 10) • 2 clinical experts nominated by company • 2 patient experts nominated by Epilepsy Action • Comparator company (eslicarbazepine, perampanel) – Eisai Limited

Key issues – clinical effectiveness

Positioning of cenobamate

- Where in the treatment pathway would cenobamate be used in the NHS? As a 2nd line adjunctive treatment (not in specialist setting)?
- What are the appropriate comparator treatments?

Cenobamate clinical evidence

- Are the groups comparable at baseline?
- Do the populations reflect the type of patient who might be offered cenobamate in the NHS? If no, how is this likely to be an 'effect modifier'?
- Is the response seen in the placebo group in C013 typical? If not, what are the likely reasons for the high placebo response observed?
- Company accepts the ERG's placebo-adjusted, joint synthesis NMA using mITT data but disagrees with including C013. Should data from C013 be included to inform short term clinical effectiveness of cenobamate?
- Is cenobamate clinically effective?

Key issues – cost effectiveness

Model structure

- Which model structure is preferred? Company's 5-state or ERG's 3-state model?
- How should transition probabilities be modelled?
- How should stopping treatment be modelled? Company's naïve comparison using OLE studies or ERG's approach using NMA for first 6 cycles and then assuming equal stopping rates for all comparators?

Health-related quality of life for patients and carers

- Are the patient utility values plausible?
- Are the carer disutility values plausible? How should they be applied in the model?

Resource use and costs

- Are the resource use for drug administration plausible? Is the cost of £481 for 1 ECG plausible?
- Are the resource use for routine monitoring plausible? Would patients whose condition show no response to treatment see a neurologist, GP, Outpatient nurse and GP nurse every 28 days?
- Are the estimates of resource use, particularly for patients having focal aware seizures plausible?
- Are the cost estimates for treating seizures (separate and in addition to the cost of 'acute management') plausible?

Epilepsy – disease background

Definition: neurological disorder characterised by recurrent spontaneous seizures (focal or generalised) due to abnormal balance of excitation and inhibition in brain

Epidemiology: ~362,000 to 415,000 people in England have epilepsy

- Infants and older age groups at greatest risk
- ~50% of adults with active epilepsy have comorbidities (e.g. depression, anxiety, dementia, migraine, heart disease, peptic ulcers, arthritis, learning disabilities)

Causes

- Stroke: ~50% new-onset epilepsy cases in adults (1 in 4 over 65 years old)
- Other: infection, brain injury, brain tumours and neurodegenerative disorders

Drug-resistant epilepsy (refractory to treatment or uncontrolled)

- Up to 30% do not become and stay seizure free with 2 appropriate and tolerated anti-seizure medicines (ASMs) either as monotherapies or in combination
- Chances of having a year of seizure freedom decreases with each ASM trialled

Impact: behavioural changes, psychological and physical symptoms negatively affect day-to-day and quality of life, and increase risk of death

- Informal care from family (financial impact): patients may often need support in daily activities (e.g. cooking, transport), with treatment and epilepsy management (routine and during seizures)

Epilepsy – current management

NICE Clinical Guideline

- CG137 (currently being updated, expected publication March 2022) – NICE clinical experts consider it does not represent clinical practice (loosely followed)

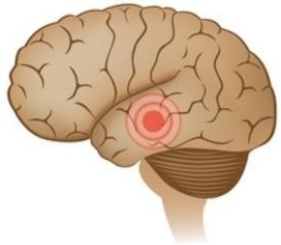
Aims of treatment

- Main aim: retain or regain independence via prolonged and reliable period of seizure freedom or 'near seizure freedom' (high % of all seizures controlled vs. control of certain types of seizures e.g. more disabling or distressing ones)
- Highly individualised approach with consideration of cognitive, behavioural, balance and weight-based secondary effects of treatment
- Patient preference for once daily medicines → greater adherence

Management: trial and error approach

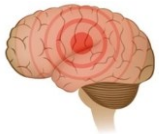
- >30 ASMs, 18 recommended by NICE
- Usually 2 or 3 ASMs at a time; consideration of combinations (e.g. biological targets, mechanism of action – rational polytherapy)
- Titrated to maximum tolerated doses to minimise adverse events and improve tolerability (start low, go slow)
- May take 1 year to confirm treatment failure before prescribing other ASM
- Variation in ASM choice and treatment sequencing due to paucity of data and clinician/individual preferences

Focal onset seizures

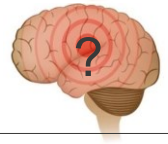


Starts in 1 side of brain
Affects >60% of patients with epilepsy

Other seizure types (not in TA):



Generalised onset
Starts in both sides of brain



Unknown onset

Increasing severity

Focal aware
- Awareness during seizure retained
- Brief seizures, lasting <2 minutes

Focal impaired awareness
- Reduced awareness during seizure
- Patients unable to respond and will have no memory of seizure

Motor onset
- jerking (clonic)
- stiffness (tonic)
- loss of muscle tone (atonic)
- automatisms (repeated or automatic movements)

Non-motor onset
- automatic (e.g. heart rate, breathing)
- behavioural arrest
- cognitive
- emotional
- sensory

May progress to **focal to bilateral tonic-clonic seizures**
- Starts in 1 side of brain and spreads to both. Most severe: high morbidity, mortality
- Tonic phase: lose consciousness, generalised muscle stiffening
- Clonic phase: rhythmical jerking of arms/legs (may lose control of bladder/bowel, bite tongue/cheek or have difficulty breathing)
- Active part lasts 1 to 3 minutes (medical emergency if > 5 minutes)

Patient perspective: Epilepsy Action

Impact of focal seizures

- Diagnosis may be overwhelming and distressing; loss of ability to perform some activities, independence and social connections; may affect how people view and treat person
- Physical effects variable but can be debilitating, affecting ability to concentrate and work
- Psychological stress, anxiety and fear of having seizures in public can affect confidence in undertaking even simple daily tasks
- Impact of (multiple, daily) focal impaired awareness seizures may be demanding on carers: provide first aid, prevent further injury, and administer emergency medicine

Unmet need

- Only 52% of people with epilepsy are seizure free (controlled by ASMs or other treatments)
- Many ASMs cause side-effects that can be as severe and as debilitating as seizures
- High waiting times in many areas (worsened due to COVID-19); difficulty accessing psychological and dietary treatments
- Surgery carries high risk and may not be suitable for many
- Relevant comparators: brivaracetam, eslicarbazepine, lacosamide and perampanel

Concerns about new medicines

- Worsening side effects and breakthrough seizures when switching medicines
- Safe use in pregnancy and suitability for people with learning disabilities

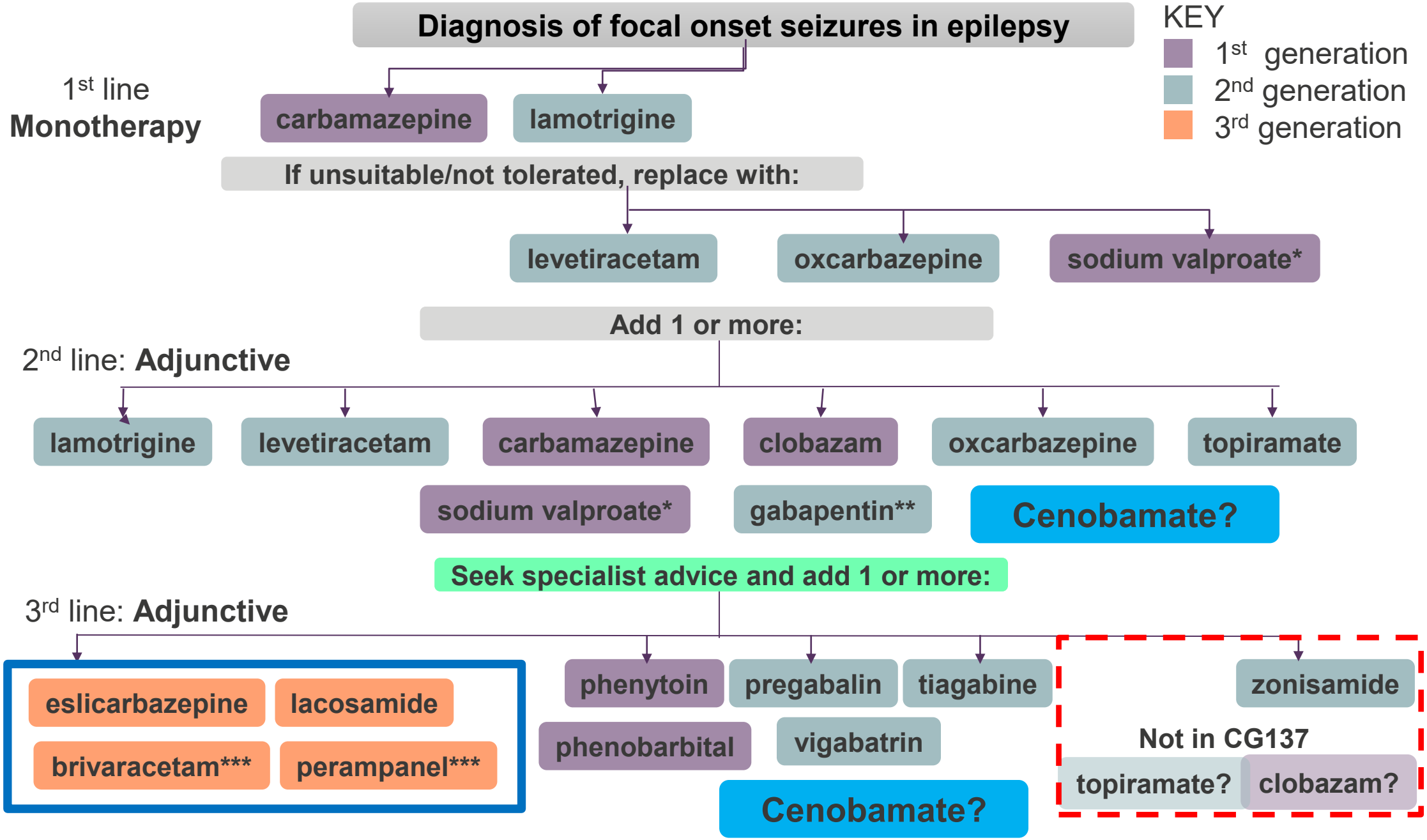
Cenobamate (Ontozry)

Marketing authorisation	**Adjunctive treatment** of focal onset seizures with or without secondary generalisation in adults with epilepsy whose condition has not been adequately controlled despite a **history of treatment with at least 2 anti-epileptic medicines**
Dual mechanism of action	Novel tetrazole alkyl carbamate derivative that prevents seizures from starting and limits seizure spread by: • reducing repetitive neuronal firing by inhibiting voltage-gated sodium currents • modulating $GABA_A$ ion channels to increase release of inhibitory neurotransmitters that reduce neuronal activity
Administration	Oral
Dosage	Initial dosage of 12.5mg once daily, titrated over ≥12 weeks to recommended maintenance dosage of 200mg once daily. Maximum dosage is 400mg once daily
List price	• Titration packs of 14 in doses ranging from 12.5mg to 200mg: XXXXX to XXX per pack • Maintenance packs of 28 in doses ranging from 50mg to 200mg: XXX to XXX per pack • Titration phase: XXX per patient • Maintenance phase: XXXXX per patient per year (XXX per day)

Decision problem

	NICE scope	Company
Population	Adults with uncontrolled focal onset seizures with or without secondary generalisation in epilepsy in whom adjunctive therapy is needed	Narrower in line with MA: **condition has not been adequately controlled despite a history of treatment with at least 2 anti-epileptic medicines**
Comparators	Established adjunctive clinical management, including *but not limited* to: • **brivaracetam acetate** • carbamazepine • **eslicarbazepine acetate** • **lacosamide** • levetiracetam • **perampanel**	**Excludes** carbamazepine and levetiracetam from NMA because: • CG137: 1st or 2nd line monotherapy or adjunctive ASM • UK clinical experts: 1st or 2nd line; inappropriate comparators • Cenobamate studies: commonly used as background therapies Also excludes 1st and 2nd generation ASMs
Outcomes	• Change in seizure frequency • Seizure free rate • Time to first seizure • Response rate • Seizure severity • Mortality • Adverse effects of treatment	As scope **Seizure severity** categorised by seizure type: • focal aware • focal impaired awareness • focal to bilateral tonic-clonic

NICE CG137 treatment pathway and cenobamate positioning



*Sodium valproate should not be used by women and girls of childbearing potential. **Gabapentin is a Class C controlled substance since 1 April 2019. ***Based on NICE evidence summaries

Issue 1: Positioning of cenobamate

Company

- Indicated when condition has been inadequately controlled on 2 ASMs, making cenobamate a 3rd line adjunctive therapy (CG137; **specialist setting**)
- Positioning is more restrictive than MA: placed against 3rd generation 3rd line adjunctive therapies only
  - Most patients with DRE likely to be treated with 3rd generation ASMs because of fewer drug interactions, milder adverse events and novel mechanisms of action
  - Other ASMs not relevant to UK clinical practice

ERG

- No consensus cenobamate should be placed against only 3rd generation ASMs
  - Company and ERG clinical experts all had differing opinions on appropriate comparators; none agreed with 3rd generation ASMs only
  - If cenobamate is more effective in terms of seizure freedom, it will likely be used earlier than other ASMs
- No conclusive evidence 3rd generation ASMs are more effective, safer or more tolerable than other ASMs
  - Large NMA of ASMs for refractory focal-onset epilepsy concluded that newer ASMs were as efficacious as older ones (Hu et al. 2018)
  - Another NMA suggested topiramate may have higher accuracy, and levetiracetam had better balance of efficacy/tolerability than 3rd generation ASMs (Zhuo et al. 2017)
- Suggest including 3 other ASMs – topiramate, zonisamide and clobazam

Issue 1: Positioning of cenobamate

Clinical experts (ERG and NICE)

levetiracetam carbamazepine	ERG clinical experts suggest when used together, these ASMs are still relevant at 3rd line adjunctive
eslicarbazepine	ERG clinical experts suggest eslicarbazepine is rarely used as an adjunctive therapy. NICE clinical experts disagree noting 2300 items used per month in England (from openprescribing.net)
zonisamide	NICE clinical experts note recent publication (SANAD2; 2021) may change how zonisamide is prescribed in UK – not more clinically or cost effective than lamotrigine; more treatment failures
topiramate	NICE clinical experts: 1 of few ASMs that may promote weight loss and is a prophylactic medicine for migraine. An effective adjunctive medicine
clobazam	NICE clinical experts: often used but not a true ASM – used short term because of low tolerability and reduced long-term efficacy

ERG: provides cost-comparison scenario (assumes equal effectiveness, discontinuation and adverse events of all treatments) to demonstrate decision problem uncertainty

Company: provides scenario analysis that assumes zonisamide and topiramate have equal efficacy to brivaracetam

Company and ERG comparators at 3rd line

	In CG137 at 3rd line	Not in CG137 at 3rd line
Company base case	eslicarbazepine* lacosamide	brivaracetam perampanel
Additional comparators in scenario analyses	zonisamide	topiramate clobazam
Excluded by Company and ERG	tiagabine pregabalin vigabatrin phenytoin phenobarbital	

KEY
- 1st generation
- 2nd generation
- 3rd generation

*eslicarbazepine excluded from ERG base case

◉ *Where in the treatment pathway would cenobamate be used in the NHS? As a 2nd line adjunctive treatment (not in specialist setting)?*
◉ *What are the appropriate comparator treatments?*

Clinical evidence

- 2 RCTs (C017 and C013): regulatory studies
- 2 open-label extension/safety studies (C017 OLE and C021)

Used in economic model:

- C017 and C017 OLE: clinical effectiveness and safety of cenobamate
- C021: safety and tolerability of cenobamate (slower titration as anticipated in clinical practice)

Cenobamate studies

Adults (18-70 years) with drug-resistant focal seizures despite ≥1 ASM in last 1 or 2 years and 1-3 concomitant ASMs at baseline (continued)

Included in NMA or economic model

CO17 (phase 2 RCT)

- Multinational (17), multicentre (107), double-blind, dose-response
- **N=437; 17.6% (n=77) stopped treatment**
- 3 doses (100 or 200 or 400mg/day) *vs* placebo
- Baseline: 8 weeks (≥8 FOS; no seizure-free interval >25 days at baseline evaluation period)
- Titration: 6 weeks; start 50mg
- Maintenance: 12 weeks
- Primary endpoint: ≥50% reduction in seizures from baseline during maintenance

CO17 OLE (ongoing)

- Single-arm, open-label extension for patients completing C017
- **N=355; 39.7% (n=141) stopped treatment**
- 300mg/day
- Baseline: 2 week blinded conversion to 300mg

CO21 (ongoing)

- Phase 3, single-arm, open-label, multinational (17), multicentre (137) safety / pharmacokinetic
- **N=1347; 20% (n=269) stopped treatment**
- 200 to 400mg/day
- Titration: 12 weeks; start 12.5mg
- Maintenance: 40 weeks
- Primary outcome: frequency and severity of adverse events

Outcomes used in economic model:

- change in seizure frequency
- response rates (≥50%, ≥75%, ≥90%, 100%)
- seizure rate over time
- adverse effects

Excluded from Company NMA

CO13 (phase 2 RCT)

- Multinational (US, Poland, India, South Korea), multicentre, double-blind
- **N=222; 9.4% (n=21) stopped treatment**
- 200mg/day (**no 400mg dose***) *vs* placebo
- Baseline: 8 weeks (≥3 seizures over 28 days; no 21-day seizure-free intervals)
- Titration: 6 weeks; start 50mg
- **Maintenance: 6 weeks (*reasons for exclusion)**
- Primary endpoint: % change from baseline in seizure frequency per 28 days in treatment period
- Other outcomes: ≥ 50% responder rate (% of patients who had 50% reduction in seizure frequency during treatment period)

NB: C013 OLE (ongoing)

Baseline characteristics

Characteristic	CO17 RCT				C017 OLE	C021	C013 RCT	
	100mg	200mg	400mg	Placebo	300mg	200-400mg	Placebo	200mg
N	108	110	111	108	355	1339	109	113
Mean (SD) age in years	39 (12)	41 (12)	40 (10)	40 (12)	40 (12)	40 (13)	38 (11)	36 (11)
% female	47	51	53	46	48	50	53	49
Mean (SD) and median^ (IQR) baseline number of seizures per 28 days	21†† (31) 10 (6-20)^	32†† (64) **11** (6-26)^	26†† (68) 9 (6-22)^	25†† (73) **8** (6-19)^	NR	NR	**15** (29)	**16** (25)
Mean (SD) or median* (max, min) years since diagnosis	26 (13)	23 (13)	24 (14)	23 (14)	NR	23 (14)‡	21* (2, 61)	20* (2, 53)
Seizure types by history, %								
Focal impaired awareness	82	76	79	78	NR	77	84	73
Focal to bilateral tonic-clonic	64	55	65	56	NR	59	62	64
Background/concomitant ASMs, %								
Lacosamide	NR	NR	NR	NR	NR	24	19	24
Topiramate	NR	NR	NR	NR	NR	13	19	22
Clobazam	16	11	15	5	NR	13	16	20
Levetiracetam	44	44	45	38	NR	39	49	45
Carbamazepine	27	25	23	36	NR	28	39	34
Lamotrigine	41	25	45	28	NR	33	31	36
Oxcarbazepine	14	16	17	12	NR	13	24	21
Valproate sodium	21	26	25	28	NR	31	18	15
Valproic acid					NR		11	13

††mITT-M population for Europe, Australia, New Zealand and South Africa; ‡n=1336

- *Are the groups comparable at baseline?*
- *Do the populations reflect the type of patient who might be offered cenobamate in the NHS?*
- *If no, how is this likely to be an 'effect modifier'?*

Issue 2: Generalisability of cenobamate trials – baseline seizure frequency

ERG

- ERG clinical experts: most patients with FOS who would be eligible for cenobamate in clinical practice would not meet selection criteria of C017 and C013
  - Baseline seizure frequency requirements higher and more stringent for C017 (≥8 FOS over 8-week pre-randomisation) **[mean 21-32; median 8-11 seizures]** than C013 (≥3 seizures over 28 days) **[mean 15-16; median NR seizures]**
  - Data from Scottish centre (Brodie et al. 2014) for 5 prospective audits of ASMs (n=707 total) reported **median 4 seizures** for 4 cohorts (median of 12 for 1 cohort)
  - Reported mean/median monthly seizure frequency from 4 smaller single centred non-UK studies (n=11 to 70) is more variable (**2.4 to 22.2**)
  - Median baseline seizure frequency for trials in company network meta-analysis ranged from **6.7 to 15**

NICE clinical experts: high-seizure frequency in regulatory trials is useful: reaches outcomes sooner and reduces unnecessary drug exposure. Studying disease with lower seizure frequencies would need much longer studies

ERG: potential issue of regression to the mean for high baseline seizure frequency. Used C013 baseline seizure frequency in base case. Provided sensitivity analysis using a range of baseline seizure frequencies to show impact on results (preferred)

Issue 2: Generalisability of cenobamate trials – other issues

ERG

- **Exclusion criteria**: excluding patients with progressive CNS disease or "psychiatric illness, psychological, or behavioural problems" limits generalisability to clinical practice
- **Titration periods** (6 weeks): faster than in clinical practice. Impacts on uncertainty of efficacy and safety of cenobamate compared to clinical practice
- **Seizure frequency outcome**: % reduction in seizure frequency is a regulatory outcome, not commonly used in clinical practice to inform treatments decisions. Clinical relevance highly variable depending on individual preferences/treatment goals and absolute baseline seizure frequency (for example, reduction of 100 to 50 vs 10 to 5)

NICE clinical experts

- Cenobamate regulatory trials are no more or less generalisable than other ASM regulatory trials that are successful in UK clinical practice
- Results of regulatory trials usually under-represent outcomes in clinical practice. Major limitation is inability to gauge long-term clinical outcomes. However, ASMs shown to reduce seizures in regulatory trials have also shown themselves to be effective in clinical practice

Clinical trial results

Cenobamate vs placebo

- C017 and C013: seizure reduction results
- C017 OLE: longer term seizure freedom
- C021: safety and stopping cenobamate in clinical setting

Cenobamate vs 3rd generation ASMs (brivaracetam, eslicarbazepine, lacosamide, perampanel)

- Network meta-analyses + ERG adjustments

C017: Reduction in seizure frequency

% response: seizure reduction	C017 RCT								C017 OLE 4-5 year follow up
	mITT – treatment period (titration plus maintenance)[a]				mITT – maintenance phase only[b]				
	Placebo (N=106)	100mg (N=108)	200mg (N=109)	400mg (N=111)	Placebo (N=102)	100mg (N=102)	200mg (N=98)	400mg (N=95)	300mg
≥ 50%	**22%**	41%*	58%*	60%*	**25.5%**	40.2%*	56.1%*	64.2%*	81.1%
≥ 75%	8.5%	16.7%	21.1%*	35.1%*	9.8%	16.7%	30.6%*	46.3%*	54.9%
≥ 90%	0.9%	4.6%	11.9%*	20.7%*	2.9%	8.8%	17.3%*	28.4%*	42.2%
100% (seizure free)	0%	1.9%	7.3%*	6.3%*	1.0%	3.9%	11.2%*	21.1%*	24.8%

*statistically significant vs placebo p<0.05

[a]used in ERG NMA (in line with all comparators)

[b]used in company original NMA

ERG: Large placebo effect; reasons unclear. ERG clinical experts consider potential for regression to the mean associated with high baseline seizure frequency (see Issue 2)

ERG: No evidence cenobamate 100mg is significantly more effective than placebo for 75%, 90% and 100% response outcomes

ERG: Promising evidence that cenobamate (200mg and 400mg doses) is effective at reducing seizure frequency in the short term compared to placebo

C013: Reduction in seizure frequency

% response: seizure reduction	C013 RCT		C017 RCT (for comparison)	
	ITT – treatment period (titration plus maintenance [6 weeks only])		mITT – treatment period (titration plus 12 week maintenance)	
	Placebo (N=113)	200mg (N=108)	Placebo (N=106)	200mg (N=109)
≥ 50%	22.2%	50.4%*	**22%**	58%*
Post-hoc analysis				
	(N=106)	(N=102)		
≥ 75%	20.6%	38.7%*	8.5%	21.1%*
≥ 90%	8.8%	34.0%*	0.9%	11.9%*
100% (seizure free)	8.8%	28.3%*	0%	7.3%*

High placebo response

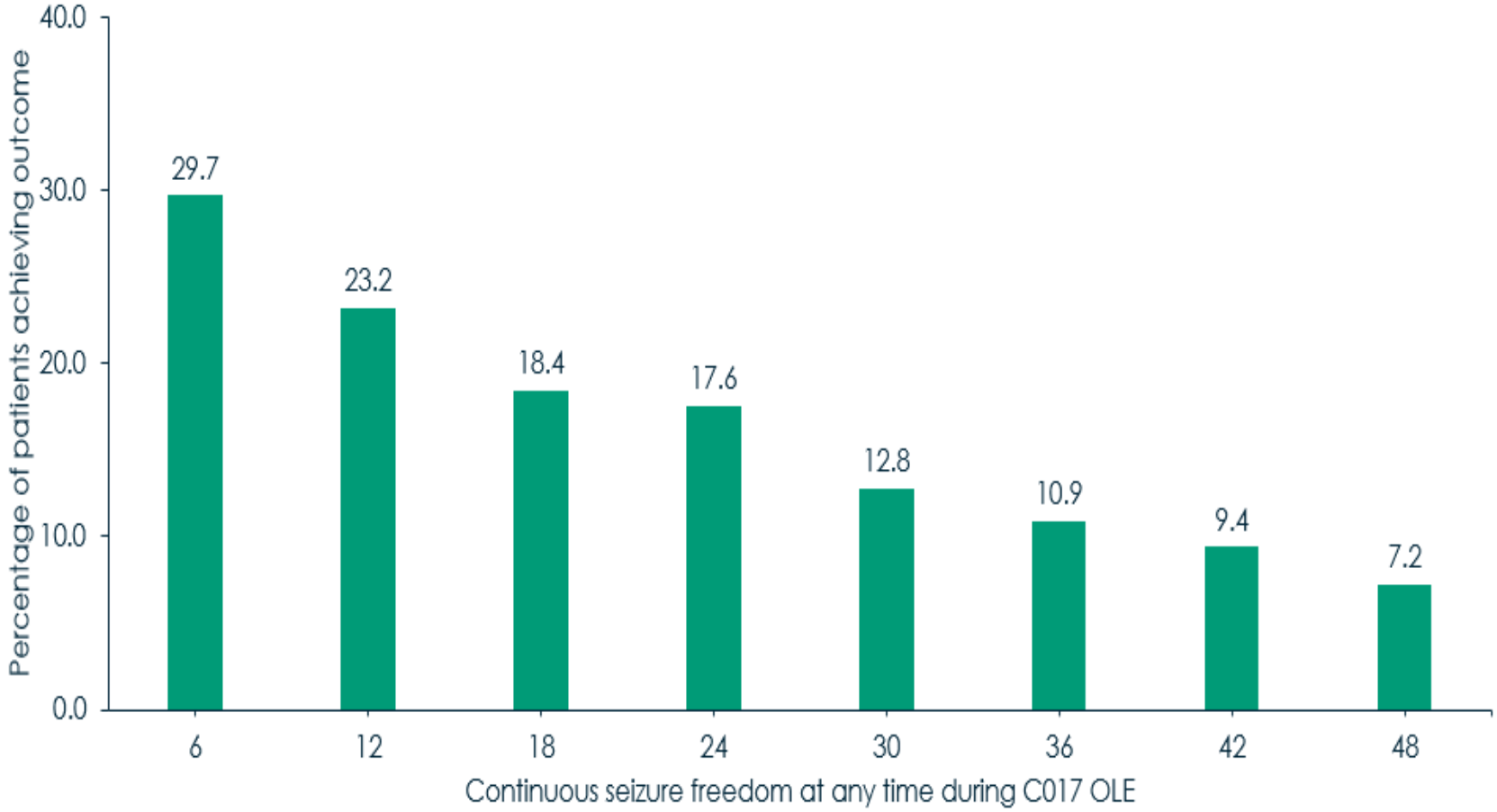
*statistically significant vs placebo p<0.05

Company

- Considers C013 (registrational trial) should be excluded from NMA and economic model because maintenance period too short (6 weeks) and did not have arm with 400mg dose

◉ *Is the response seen in the placebo group in C013 typical? If not, what are the likely reasons for the high placebo response observed?*

C017 OLE: Longer term seizure freedom (4 years)

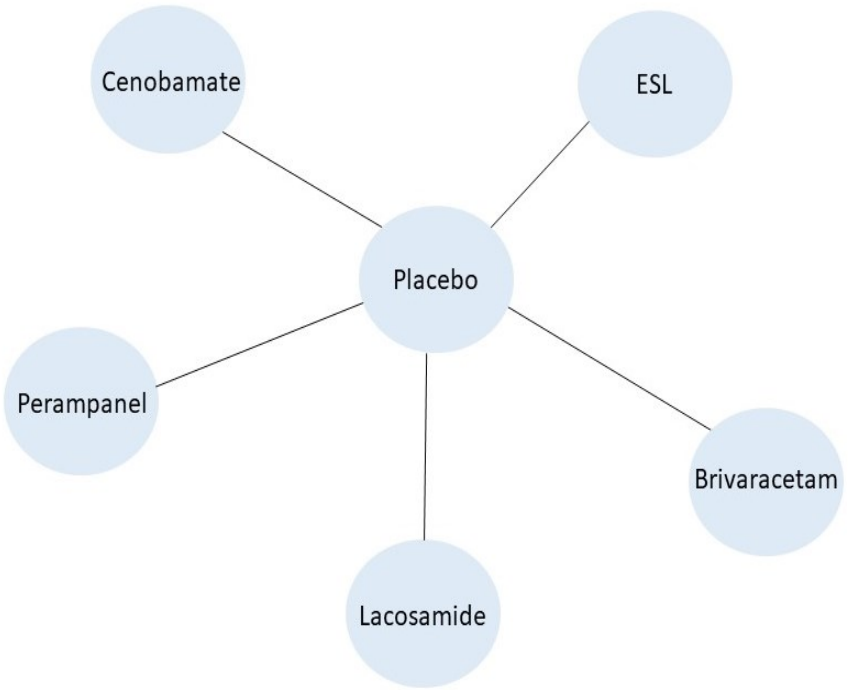


ERG

- Some evidence of longer term effectiveness but high risk of attrition bias due to high rate of treatment stopping (40%) at latest cut-off (July 2019)
- Evidence only for cenobamate. No evidence relative to placebo or other ASMs because of lack of comparators – highly uncertain

Company's network meta-analysis

ASMs	Number of trials	Total N	Study period (year)	Range of study duration (weeks)			
				Baseline	Titration	Maintenance	Treatment
Cenobamate	1 (**C017**)	437	2013-2015	8	6	12	18
Disagrees with including	C013	222	2011-2013	8	6	**6**	12
Brivaracetam	6	2414	2004-2013	4-8	0-8	**0-8**	7-16
Eslicarbazepine	4	1700	2004-2012	8	2	12	14-18
Lacosamide	4	1856	2002-2014	8	4-6	12	16-18
Perampanel	4	2192	2008-2014	6	6	13	19



Comparator	Outcomes and number of studies			
	≥50 response	Seizure freedom	Any TEAEs	Stopping (TEAEs)
Cenobamate	1	1	1	1
Brivaracetam	6	6	4	5
Eslicarbazepine	4	4	4	4
Lacosamide	4	4	2	3
Perampanel	4	4	4	4

- Conducted within Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling
- All outcomes were dichotomous, assumed data followed binomial likelihood distribution
- Random effects models used
- Evaluation periods varied across trials (7 to 14 weeks)

ERG adjustments to company network meta-analysis

- **Joint synthesis model:** company model synthesised ≥50% response and seizure freedom (100% response) as independent outcomes in separate NMAs
  - ERG Model 1 synthesises ≥50% response and 100% response simultaneously
  - ERG Model 2 synthesises all 4 response levels (≥50%, ≥75%, ≥90% and 100%) simultaneously; can include limited response level data from other comparators
- **Placebo-adjustment:** to account for variation in placebo response across trials, ERG fit meta-regression models → strong assumption that placebo effect is same across all ASMs
- **C013 data:** company excluded C013 because maintenance phase was only 6 weeks and did not include 400mg dose. ERG considered justification inconsistent with other trials in NMA that had similar maintenance periods; noted only 14% of patients in CO21 had 400mg dose (see Issue 6)
- **Efficacy evidence from treatment period (m-ITT) for all treatments:** company used mITT for **treatment period** (definitions not provided for each trial) for **all comparators only**, but used **mITT-M** (maintenance phase only; ignores any seizures during treatment phase) for **cenobamate only**. ERG considers company has not justified this discrepancy. For consistency with all comparators, the **ERG used mITT data for C017 and C013**
- **Correction:** ERG corrected error in implementing values with 0 cells

At technical engagement, company accepts ERG's joint synthesis and placebo-adjusted models using mITT (treatment period) data including C013 and C017 in its revised base case, but continues to disagree with the inclusion of C013 data

ERG NMA results: absolute effects

Treatment	Model 1			Model 2				
	Probability of response (%)		Rank	Probability of response (%)				Rank
	≥50%	100%		≥50%	≥75%	≥90%	100%	
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company

- Used relative risk from NMA to estimate transition probabilities for **comparators only** in its economic model (for cenobamate, it used absolute mITT-M data from C017 only)
- Provided scenario analysis in economic model that topiramate and zonisamide (ASMs not included in NMA) have equal efficacy to **brivaracetam** (most effective comparator in company's NMA; least effective in ERG's NMA)

ERG: limitations of network meta-analysis

- **Evidence network:** linked only by placebo; no head-to-head comparisons so consistency could not be checked (assumption of equal placebo efficacy may not be justifiable)
- **Baseline characteristics**: baseline severity, distribution of concomitant therapies are not reported consistently. ERG considers evidence is insufficient to support assumption that trial populations are homogenous
- **Titration and maintenance periods**: titration periods are more intense than in clinical practice for most comparators, some trials did not report titration periods. Treatment response is extracted over different time periods
- **Follow up**: all RCTs in network had insufficient duration to assess effectiveness. ERG clinical experts note that it may take 1 year to confirm treatment failure before switching to other ASM

◉ *Company accepts the ERG's placebo-adjusted, joint synthesis NMA using mITT data but disagrees with including C013. Should data from C013 be included to inform short term relative clinical effectiveness of cenobamate?*
◉ *Is cenobamate clinically effective?*

Summary of adverse events

	Number of patients (%)							
	CO13		CO17				C017 OLE	C021
	Placebo	200mg	Placebo	100mg	200mg	400mg	300mg	200-400mg
N	109	113	108	108	111	108	355	1340
≥1 TEAE	69 (63)	86 (76)	76 (70)	70 (65)	84 (76)	100 (90)	313 (88)	1185 (88)
Treatment-related TEAEs	50 (46)	67 (59)	46 (43)	62 (57)	72 (65)	92 (83)	262 (74)	1000 (75)
Died due to TEAE	NR	NR	NR	NR	NR	NR	NR	4 (0.3)
Stopped treatment due to TEAE	3 (3)	5 (4)	5 (5)	11 (10)	15 (14)	22 (20)	33 (9)	175 (13)
Serious AEs	4 (4)	2 (2)	6 (6)	10 (9)	4 (4)	8 (7)	72 (20)	137 (10)

TEAE, treatment-emergent adverse event

Treatment emergent adverse events (TEAEs)

Study	Comments
C013 (200mg)	Most common TEAEs: somnolence (22.1%), dizziness (22.1%), headache (12.4%)
C017 (variable dose; 300mg in OLE)	Most common TEAEs: somnolence, dizziness, fatigue (generally higher during titration phase) Evidence of dose-response relationship for safety and tolerability
C021 (225.4mg mean dose) – June 2020 data cut	Most common TEAEs: somnolence (n=405, 30%), dizziness (n=359, 27%), fatigue (n=252, 19%) and headache (n=208, 16%). Potential evidence of interaction with background ASMs phenytoin and phenobarbital

- **ERG**: NMA suggests potential trend for higher occurrence of TEAEs for cenobamate vs brivaracetam and lacosamide, and higher rate of stopping treatment because of TEAEs

Company NMA results: adverse events

	C017 only		C013 and C017	
Comparator	Any TEAEs	Stopping due to TEAEs	Any TEAEs	Stopping due to TEAEs
Odds Ratios relative to cenobamate (95% CrI)				
Brivaracetam	0.62 [redacted]	0.39 [redacted]	[redacted]	[redacted]
Eslicarbazepine	1.04 [redacted]	0.75 [redacted]	[redacted]	[redacted]
Lacosamide	0.63 [redacted]	0.49 [redacted]	[redacted]	[redacted]
Perampanel	0.91 [redacted]	0.56 [redacted]	[redacted]	[redacted]
Placebo	0.47 [redacted]	0.23 [redacted]	[redacted]	[redacted]
Model Outputs				
Between-study SD	[redacted]	[redacted]	[redacted]	[redacted]
DIC	[redacted]	[redacted]	[redacted]	[redacted]
Mean total RD	[redacted]	[redacted]	[redacted]	[redacted]

Issues 3+4: Long-term and relative efficacy and safety

Company

- ERG joint synthesis placebo-adjusted NMA show significantly improved response to cenobamate relative to comparators
  - Due to cenobamate dual mechanism of action vs single mechanism of action of brivaracetam, eslicarbazepine and perampanel
- Long-term data for cenobamate and comparators is available via OLE studies; short-term effects are often maintained in long-term use
- Company clinical experts: cenobamate longer half-life vs comparators suggests clinical advantage of cenobamate likely be observed over long term

NICE clinical expert

- C017 'unique' in high seizure-free rate (21% in 400mg arm; mITT-M)
- Seizure freedom is unusual in regulatory trials of adjunctive ASMs for people with FOS
  - Meta-analysis of 62 pivotal placebo-controlled RCTs 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 brivaracetam: seizure-free rates ranged from 0% - 6.5%
- Side effects and safety from regulatory trials are comparable to current ASMs

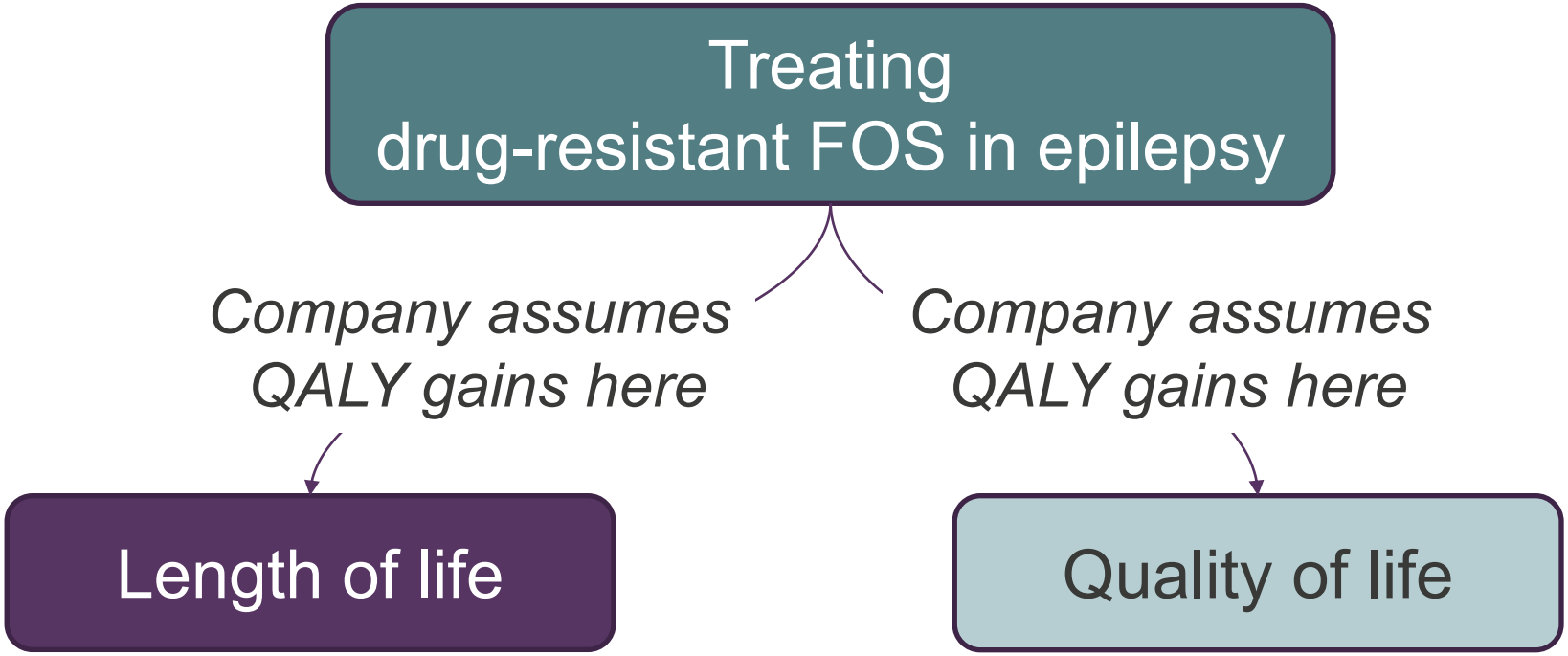
Issues 3+4: Long-term and relative efficacy and safety

- **NMA results:** consistent trends favouring cenobamate for seizure frequency and freedom, but also higher rates of adverse events and treatment stopping
- **Uncertainty in company NMAs:** precision of NMA estimates limited; wide credible intervals; all comparisons between active treatments crossed line of no significance. Lack of head-to-head trials and significantly limited by differences in trial populations and designs
- **Plausibility of evidence:** unexplained differences in efficacy outcomes between C017 and C013; plausibility of efficacy results of C017
- **Mechanism of action**: acknowledges cenobamate has distinct mechanisms of action but considers there is currently insufficient evidence to determine how cenobamate's mode of action translates into improved effectiveness outcomes or different tolerability
- **Exclusion of comparators**: not all relevant comparators included in network (Issue 1)
- **Length of follow up:** up to 1 year is needed to assess treatment failure. All included trials may not have sufficient follow up to provide clinically meaningful efficacy results. Consider long-term drug monitoring is needed. Any interpretation beyond 18-weeks of treatment is highly uncertain

Cost effectiveness

- Model structure: 3-state of treatment response vs 5-state
- Transition probabilities: used NMA to model transitions between health states (for comparators only); C017 direct trial data for cenobamate
- Patient and carer quality-of-life evidence
- Resource use by health state

Where do QALY gains come from in company's model?



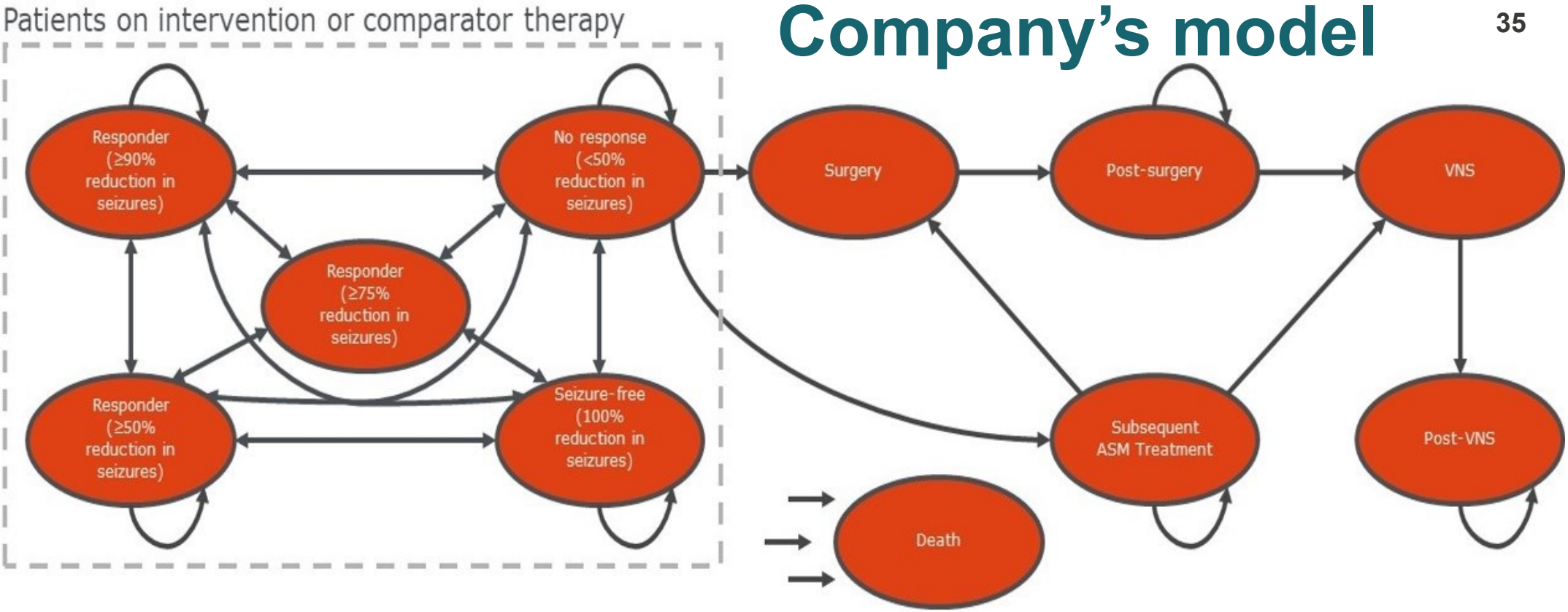
Increase in QALYs comes from improving quality of life and increasing length of life as a result of:

- *fewer seizures and fewer people stopping treatment, that are associated with an increase in utility and lower mortality*
- *greater the response, for example, becoming seizure free, the greater the QALYs accrued*

NICE

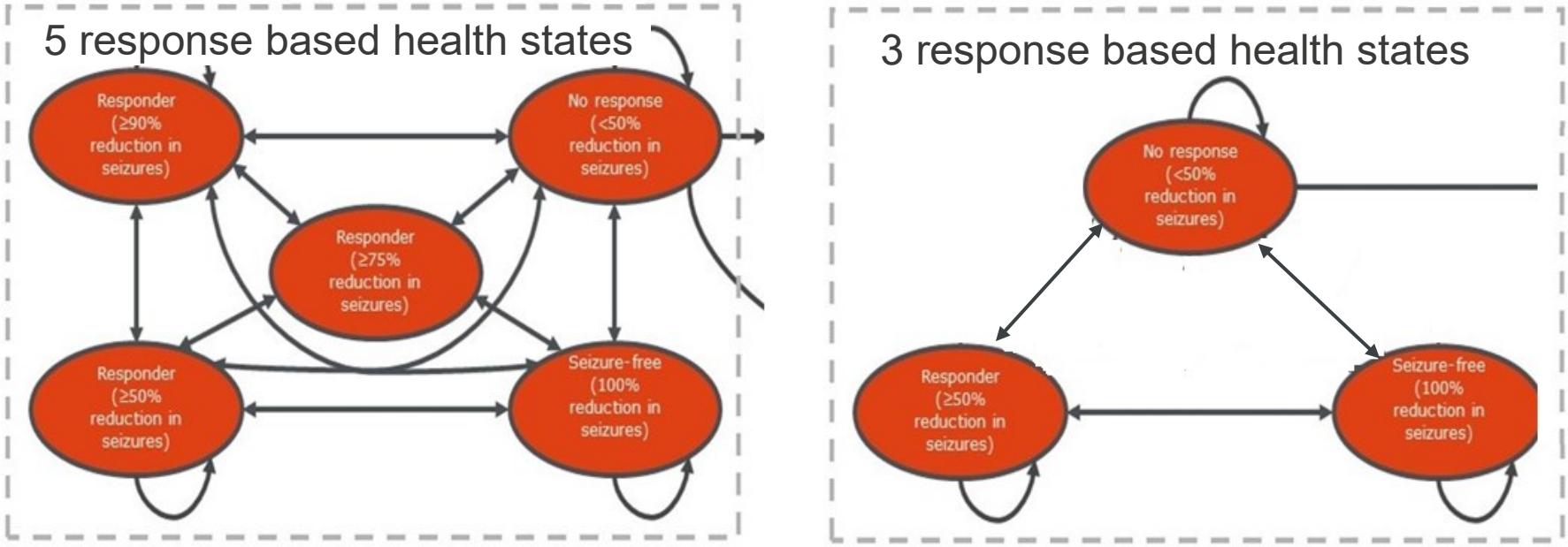
QALY, quality-adjusted life year

Company's model



- de novo Markov model with 5 treatment response health states (higher levels of response associated with higher HRQoL and lower healthcare resource use)
- Lifetime horizon (60 years), **12 weekly cycle (originally 28 days)**, NHS/PSS, 3.5% discount rate
- Cenobamate vs brivaracetam, eslicarbazepine, lacosamide or perampanel (outcomes assumed to be independent of any prior treatment)
- Population: 40 years, 51% male
- Patients start in 'no response' state, move between 5 states until they stop treatment (move to 'subsequent ASM' state – independent of previous treatment and constant over time) or die
- Mortality risk in 5 states assumed to be higher than general population (100% response: HR=1.6; <100% response: HR=2.4)
  Adverse drug reactions and carer disutility modelled

Issue 5: Model structure



Company

- Consider 5-state model captures health states closer to full seizure control (≥75% and ≥90% seizure reduction) which more patients on cenobamate achieve
- Simplified 3-state model (used in CG137) overlooks key differences in costs and resource use that would occur in higher response states as patients experience fewer seizures

NICE clinical experts

- Seizure freedom should drive model as it is the aim of treatment but may not be attainable without significant side effects

Issue 5: ERG comments on model structure

- All models for FOS epilepsy in company's review and CG137 use 3 response levels: none (<50% reduction), partial (50% to <100% reduction) and seizure freedom (100% reduction)
- No data for NMAs on ≥75% and ≥90% seizure reduction
  - Company assumed same effectiveness estimates as for ≥50% reduction NMA for comparators
  - Some evidence for 75% response (3 for lacosamide, 1 for eslicarbazepine) → NMA substantially borrowed complete response level evidence from a 1 cenobamate trial
- Acknowledge resource use and HRQoL in patients who achieve sustained ≥75% or ≥90% seizure reduction could differ to patients who achieve 50% to 75% reduction **but**
  - Company provides no evidence that cenobamate increases probability of ≥75% and ≥90% response vs comparators
  - Company provides no evidence of important differences in costs and HRQoL between different levels of treatment response
- 5-state model inappropriate; model inputs largely based on clinical opinion and 1 trial; cannot use published evidence (e.g. for utility values) for this level of disaggregation
- In response to clarification, company provided 3-state model by aggregating moderate, high and very high response states
  - **ERG's preferred structure (base case)**: 3-state model is more appropriate to inform a comparison of cenobamate with other ASMs

◉ *Which model structure is preferred? Company's 5-state or ERG's 3-state model?*

Treatment effectiveness – transition probabilities (C017)

% response: seizure reduction	C017 RCT							
	mITT – treatment period (titration plus maintenance)				mITT – maintenance phase only			
	Placebo (N=106)	100mg (N=108)	200mg (N=109)	400mg (N=111)	Placebo (N=102)	100mg (N=102)	200mg (N=98)	400mg (N=95)
≥ 50%	[redacted]	[redacted]	[redacted]	[redacted]	25.5%	40.2%*	56.1%*	64.2%*
≥ 75%	[redacted]	[redacted]	[redacted]	[redacted]	9.8%	16.7%	30.6%*	46.3%*
≥ 90%	[redacted]	[redacted]	[redacted]	[redacted]	2.9%	8.8%	17.3%*	28.4%*
100% (seizure free)	[redacted]	[redacted]	[redacted]	[redacted]	1.0%	3.9%	11.2%*	21.1%*

*statistically significant vs placebo p<0.05

Distribution at end of cycle 5

Treatment	No response (<50% reduction)	≥50% reduction	≥75% reduction	≥90% reduction	Seizure-freedom (100% reduction)
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
200mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG

- Should include C013 data. Company uses cenobamate miTT-maintenance only trial data directly
- Cenobamate transition matrices provided by company, not changed by ERG. Transition probabilities for comparators conditional on cenobamate transitions and ERG NMA results (also relative to cenobamate)

Issue 6: Transition probabilities

ERG concerns with transition probability method and calculations

- **Numerical error:** deriving transition probabilities **corrected in ERG base case**
- **Evidence informing transition probabilities:** results from C017 only (particularly mITT-M) may overestimate treatment response of cenobamate and QALY gain, and underestimate resource use. **C013 data included in ERG base case (company accepted in base case)**
- **Placebo effect:** may be caused by various factors other than background therapy such as regression to the mean (see Issue 2). Failing to account for placebo effect may overestimate cenobamate response and underestimate resource use
- **Duration of cenobamate titration phase:** company modelled 8-week titration period shorter than in clinical practice. C021 titration may have been 10-12 weeks or longer. Possibility that higher doses lead to better outcomes. Overestimates QALY gain and underestimates resource use
- **Dose of cenobamate:** company assumes 50% of patients take each dose (200mg and 400mg):

Dose	Modelled % taking dose	C017 OLE % taking dose	C021 % taking dose (mean dose XXXX)
200mg	~50%	20%	37%
400mg	~50%	14%	12%

Issue 6: Transition probability extrapolation

ERG concerns with transition probability extrapolation

Company

- **Revised base case**: transition probabilities in cycles 6 to 26 informed using C017 OLE data (duration of follow up) and in cycles 27 to 462 using average transition probabilities from cycles 6 to 26 – this leads to continual improvement over time

ERG

- Considers company's base-case assumption that patients will continue to improve over time is highly uncertain
- **ERG base case (as in CG137)**:
  - Probability of >50% or 100% response derived from NMA and applied in first 20 weeks; cycle length is 3 months to reflect that 1 month of no response would not stop treatment
  - In cycle 6, patients stay in same response health state unless they have treatment failure, informed by time to stopping treatment in C017 OLE and C021 (see Issue 8)
  - Patients stop treatment if no response and move to 'subsequent ASMs' health state
  - Response in subsequent cycles independent of treatment received; based on probabilities from published study of cost-effectiveness of ASMs. Probabilities of seizure freedom applied to all subsequent cycles

Issue 6: Transition probabilities for comparators

ERG concerns with transition probabilities for comparator treatments

Company

- NMA results used to derive relative risks of response vs cenobamate for comparator ASMs
- Also used ERG's placebo-adjusted joint synthesis NMA in its revised base case but
  - Continues to disagree with the inclusion of C013 (inappropriate due to short 6-week titration period and did not include 400mg dose)

ERG

- **C013 data:** NMA includes all licensed doses of comparators. Cenobamate dose (200mg) used in C013 is licensed. ERG considers that C013 should be included in NMA – **included in ERG base case**
- **Efficacy assumptions for higher response levels in 5-state model:** Company NMAs on ≥50% and 100% response only. Company assumed moderate (≥50 and <75%), high (≥75% and <90%) and very high (≥90% and <100%) response identical to ≥50% response. Plausibility of this assumption is unclear
- **Weakness of NMA:** reiterates limitations of NMA (see slide 26)

Issue 6: Distribution of patients at end of cycle 5

Distribution (%) of living patients across levels of response, for different treatment options at end of cycle 5					
Level of response	**<50%**	**50 to <75%**	**75 to <90%**	**90% to <100%**	**100%**
Cenobamate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampranel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[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]

Distribution for subsequent ASMs, VNS and surgery assumed to be constant over time

◉ *How should transition probabilities be modelled?*

Issue 7: Subsequent treatment

Company

- After stopping treatment, company modelled 3 subsequent options (effectiveness independent of previous line of treatment): ASMs (first), VNS (vagus nerve stimulation) and surgery
  - Subsequent ASMs: applied odds ratio (OR) of no response with each line of ASM (1.73, Chen et al 2018) to OR of no response in C017
  - VNS and surgery: 2.7% and 2% per year (0.21% and 0.15% per model cycle) respectively based on clinical opinion (effectiveness based on non-comparative studies)
    - Assumed to have small mortality risk (0.86% per model cycle for VNS and 0.97% for surgery) based on literature
- **Single homogenous subsequent ASM health state:** recognise that patients may move to further lines of subsequent ASM therapy, but currently, no recognised treatment pathway to inform modelling of subsequent treatments
  - Conservative to assume homogenous health state with fixed associated cost. Homogenous state reflects that subsequent lines of treatment are at most as effective as each other, supported by clinical opinion

Issue 7: Subsequent treatments

ERG proposed changes to the model accepted by company

ERG

Subsequent ASM health state: ERG changes (all accepted by company)

- Revised parameterisation of subsequent ASM health state: applied 1.73 to probability of not achieving 100% response in C017 (estimate highly uncertain due to differences in follow up between Chen et al. and C017)
- Effectiveness of subsequent ASMs (≥4th line) greater in model than effectiveness of comparators → implausible: effectiveness of subsequent ASMs derived relative to brivaracetam, rather than cenobamate
- Removed cenobamate from basket of treatment to derive subsequent ASM therapy costs

VNS and surgery health states: ERG comments

- Company model assumes VNS and surgery not offered before 4th line ASMs
  - Some patients in C017 had VNS before cenobamate
    - Few patients undergo VNS and surgery before 3rd line → unlikely to impact model results
- Frequency and outcomes of VNS and surgery are uncertain but direction of effect is generally plausible → unlikely to have substantial effect on model results

Clinical experts

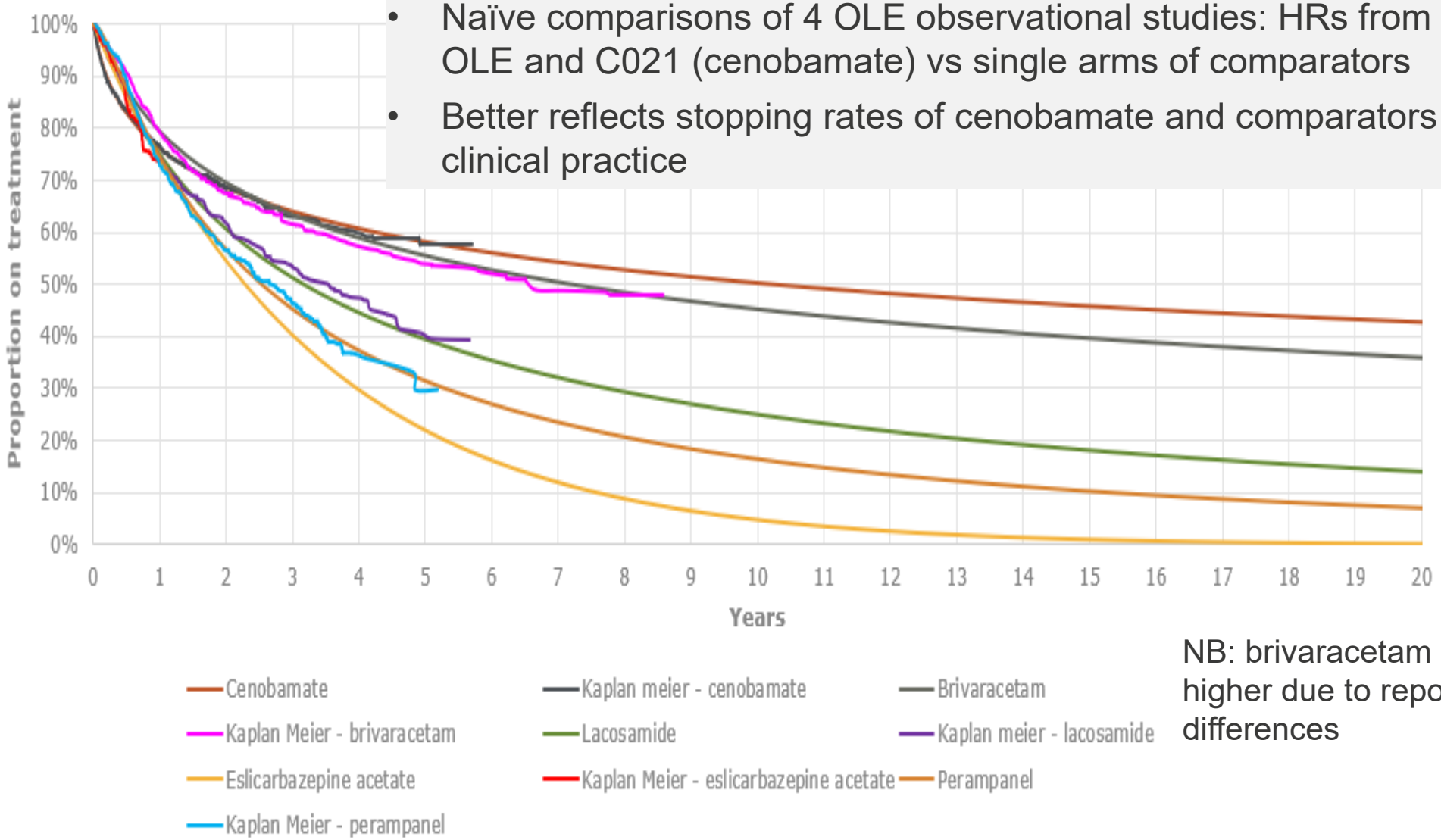
- Subsequent treatment is very difficult to model and practice varies across UK, partly because drugs have similar efficacy
- Need for more potent ASMs

Issue 8: Stopping treatment

Company uses unadjusted hazard ratios from OLE studies

Company updated approach after technical engagement

- Naïve comparisons of 4 OLE observational studies: HRs from C017 OLE and C021 (cenobamate) vs single arms of comparators
- Better reflects stopping rates of cenobamate and comparators in clinical practice



NB: brivaracetam may be higher due to reporting differences

Issue 8: Stopping treatment

ERG uses NMA estimates to model short term discontinuation (first 32 weeks)

ERG comments on company's approach

- **Combining C017 OLE and C021:** unclear whether studies should be combined (hazards of stopping treatment do not converge; populations may be different) → little impact on results
- **Targeted searches for comparator studies:** company may have missed relevant studies
- **Naïve comparison:** does not take into account heterogeneity between studies and potential confounding

ERG base case

- **ORs from NMA for 'all-cause discontinuation'** to inform probability of stopping treatment in short term (first 6 cycles) → provides best comparative evidence
  - Recognises C013 and C017 may overestimate stopping rates for cenobamate as dose titration was steeper than in clinical practice. Likely same issue for comparator studies (except brivaracetam)
- For patients continuing treatment, **same stopping rates** for all comparators from **cycle 6**
  - No evidence treatment failure in responders is different between comparators. Consistent with previous appraisals of ASMs in UK
- **Scenario analyses** where stopping rates of comparators are same as cenobamate

Issue 8: Stopping treatment

Probability of stopping treatment in model cycles 1 to 5

Model cycle	Cenobamate	Brivaracetam	Eslicarbazepine	Lacosamide	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]

ERG's 'all-cause' discontinuation odd ratios relative to cenobamate

vs cenobamate	Odds ratios, median (95% credible interval)
Placebo	[redacted]
Brivaracetam	[redacted]
Eslicarbazepine	[redacted]
Lacosamide	[redacted]
Perampanel	[redacted]

Issue 8: Stopping treatment

Company considers NMA an inappropriate source of short-term evidence

Company

- NMA inappropriate source for short-term comparative evidence of stopping treatment (up to cycle 6)
  - overestimates stopping rate of cenobamate relative to comparators because C013 and C017 had a steeper dose titration than expected in clinical practice
  - C021 titration aligned with clinical practice showed lower stopping rates in 1st year compared to C017
- Inappropriate to assume that stopping rates are identical for all comparators after cycle 6

Company cinical experts

- When patients make individualised decisions on stopping treatment, balance between efficacy and tolerability
- Higher efficacy medicine likely to have lower medium and long term stopping rates

◉ *How should stopping treatment be modelled? Company's naïve comparison using OLE studies or ERG's approach using NMA for first 6 cycles and then assuming equal stopping rates for all comparators?*

Issue 9: Patient health-related quality of life

Company

- Measured HRQoL in C017 using Quality of Life in Epilepsy (QOLIE-31-P) instrument. No significant differences between arms → suggest follow up period too short to show meaningful benefit in HRQoL (not used in economic model)
- Used mapping algorithm from a survey of SF-36 and QOLIE-31-P questionnaires (n=361 patients with FOS epilepsy)

ERG

- Company's mapping algorithm does not reflect variability in observed SF-6D utility index scores; underestimates range of predicted utilities. Unclear rationale for approach used
- Published evidence suggests QOLIE-31 is sensitive to measuring seizure frequency reduction over 14 weeks of follow up
- Sensitivity analysis using data from CG137 (Selai 2005, n=125) → minimal impact on ICER
- Need for better quality utility data – highly uncertain utility values, overlapping between states. In PSA, random samples of utilities in higher response states often lower than in lower response states, so company manually changed them to prevent illogical values

Level of response	Mean utility (SD) from mapping study	Mean utility from CG137 reference
None (<50% reduction)	XXXX	0.83
Moderate (≥50% and <75% response)	XXXX	0.88 – 0.93 (dependent on seizure frequency per month)
High (≥75% and <90% response)	XXXX	
Very high (≥90% and <100% response)	XXXX	
Seizure-freedom (100% response)	XXXX	0.94

◉ *Are the patient utility values plausible?*

Issue 9: Carer quality of life

Company includes carer disutility. ERG excludes as company's approach uncertain

ERG

- **HRQoL disutility for caregivers**: company sourced caregiver disutility from a small, poorly reported caregiver survey (n=86); unclear representative of UK population
- **Lack of detail:** concerns about how state-specific disutilities were derived from survey (company provided little detail). Unable to evaluate survey's methodology or validity of estimates. Notes inconsistencies between carer disutilities and survey results
- **Magnitude of benefit:** magnitude of elicited disutilities are high (similar magnitude of benefit for seizure freedom for patient's HRQoL)
- **Number of patients that require care:** ERG clinical advisers suggest that **not everyone will need a carer** and disutility should not apply to all patients
- **NICE reference case:** agrees that HRQoL disutility is in line with NICE reference case but disagrees with how it is applied

ERG base case: removed carer disutility

Health state: level of response	Carer disutility
None (<50% reduction)	XXXX
Moderate (≥50% and <75% response)	XXXX
High (≥75% and <90% response)	XXXX
Very high (≥90% and <100% response)	XXXX
Seizure-freedom (100% response)	XXXX

◉ *Are the carer disutility values plausible? How should they be applied in the model?*

Issue 10: Resource use – treatment cost overview

Cost of background ASMs

ASM	% prescribed	Drug cost per 28 days
Levetiracetam	35%	£7.49
Lamotrigine	29%	£4.68
Carbamazepine	16%	£6.38
Sodium valproate	12%	£19.12
Topiramate	4%	£21.88
Clobazam	3%	£6.98
Zonisamide	3%	£4.72
Oxcarbazepine	2%	£36.13
Phenytoin	2%	£11.32
Pregabalin	1%	£2.43
Clonazepam	0.4%	£38.55
Phenobarbital	0.4%	£12.27
Tiagabine	0.4%	£87.43

Cost of subsequent ASMs

ASM	% of subsequent ASMs	Drug cost per 28 days
Cenobamate	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]

*removed after technical engagement

Cost of subsequent invasive treatments

Treatment	Cost per procedure (£)
Surgery	23,125
Vagus nerve stimulation	10,222

Issue 10: Resource use – drug administration

ASM	Titration in days (model cycles)	Drug administration costs per 28 days	
		Titration	Maintenance
Cenobamate	84 (3)	£177 - 3 OP visits	£9.06 - 4 prescriptions per year
Brivaracetam	0	no titration	
Eslicarbazepine	21 (1)	£354 - 2 OP visits	
Lacosamide	21 (1)	**£835** **- 2 OP visits** **- 1 ECG (£481)**	
Perampanel	56 (2)	£265.50 - 3 OP visits	

Cost per epilepsy outpatient (OP) visit and ECG monitoring: NHS reference costs
Cost of 15-minute GP telephone appointment: PSSRU 2018 and inflated using NHSCII inflation indices

◉ *Is the resource use for drug administration plausible? Is the cost of £481 for 1 ECG plausible?*

Issue 10: Resource use – routine monitoring

Setting of care: appointments (based on clinical opinion)	Routine monitoring: hours of resource use per 28 days				
	No response	Moderate response	High response	Very high response	Complete response
GP	1	0.54	0.08	0.08	0.08
GP nurse	0.29	0.14	0.07	0.07	0.07
Neurologist outpatient	0.86	0.5	0.07	0.07	0.07
Outpatient nurse	1	0.62	0.31	0.31	0.15
Total costs	**£205.40**	**£117.99**	**£19.72**	**£19.72**	**£17.88**

◉ *Is the resource use for routine monitoring plausible? Would patients whose condition show no response to treatment see a neurologist, GP, Outpatient nurse and GP nurse every 28 days?*

Issue 10: Resource use – epilepsy management

Company: management of seizures **over 28-day period** estimated via UK clinical expert opinion, comprise of **acute management** and **acute treatment**. Assumes that

- GPs refer patients to A&E (focal aware) **or** neurologist (focal to bilateral tonic-clonic)
- Patients presenting to primary care nurse are **all** referred to neurologist

	Focal aware		Focal impaired awareness		Focal to bilateral tonic-clonic	
% of seizures needing medical attention	**2.9**		**8.6**		**30.8**	
Costs by initial presentation to health care services	**% patients presenting**	**% needing treatment**	**% patients presenting**	**% needing treatment**	**% patients presenting**	**% needing treatment**
A&E attendance*	26.8	9.3	44.3	19.8	62.1	37.5
GP appointment*	45.1	8.9	26	8.5	16.5	3.9
Primary care nurse appointment*	7.7	0.8	6.4	1.1	5.5	1
Other	20.1	8.5	23.4	8.5	16	5.1
% hospitalised		22.9		21.4		36.3
Average duration in hospital		1.7		2		2.3
% referred to other services	28.6		18		21	

*in patients needing medical attention

◉ *Are the estimates of resource use, particularly for patients having **focal aware** seizures plausible?*

Issue 10: Resource use – epilepsy management

Company assumes:

- Hospitalised patients all use resources related to epilepsy event management regardless of if they respond to treatment or not

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	22.4%
Conventional EEG, EMG or Nerve Conduction Studies, 19 years and over	68.6%
Routine tests for underlying infection	100%

Acute treatment of seizures

Treatment setting	Focal aware	Focal impaired awareness	Focal to bilateral tonic-clonic
A&E	£0.80	£11.61	£11.61
GP appointment	£168.79	£1.25	£177
Primary care nurse appointment	£0	£177	£177
Cost of services and treatment received during hospital admission (£)	£235.08	£235.08	£235.08
Total acute treatment cost per seizure (£)	£2	£4.70	£30.28

◉ Are the cost estimates for treating seizures (separate and in addition to the cost of 'acute management') plausible?

Issue 10: Resource use – cost per seizure

Total cost per seizure			
Cost category	**Focal aware**	**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

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

Level of response	Focal aware	Focal impaired awareness	Focal to bilateral tonic-clonic	Total
None	50.07	181.21	610.60	841.87
Moderate	21.25	100.22	197.95	319.42
High	9.15	38.96	102.42	150.53
Very high	4.84	16.79	52.00	73.63
Complete	0	0	0	0
Subsequent ASMs				525.31
VNS				841.87
Post-VNS				425.70
Surgery				841.87
Post-surgery				228.75

Issue 10: Resource use

Scenario	Costs per 28 days	No response	≥50%-<75% response	≥75- <90% response	≥90%- <100% response	≥50%-<100% response	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) – CG137	Total	£38.72	£38.72	£38.72	£38.72	£38.72	£6.64

ERG

- **Company estimates of 28-day healthcare costs are high** compared to published models: £8.85 for seizure freedom and £38.54 for not seizure free
  - Management of epileptic events key driver of costs: lower baseline seizures lower cost gradient across different levels of response
- Company provided additional scenario using resource estimates from Jacoby (1998) as used in CG137 (ERG corrected error in reporting of 100 fold difference)
  - Resource use in Jacoby (1998) indicates substantially lower difference in costs between different levels of response → increases incremental cost of cenobamate
  - Key limitation in Jacoby is they report resource use in patients who have >1, <1 or 0 seizures per month. **In scenario using Jacoby**, company assumes that patients with **90% response rate have same resource use as those with no response**
- Generalisability of estimates from CG137 is uncertain
- Overestimating differences in resource use between different response levels will overestimate cost savings with cenobamate relative to its comparators

Cost-effectiveness results

- Company revised base case
- ERG base case assumptions and model changes
- ERG scenarios:
  - Cost comparison and alternative comparator estimation
  - Baseline seizure frequency range

Company revised base case

1. Includes C017 OLE data with 12-weekly cycles from completion of C017
2. Uses ERG placebo-adjusted joint synthesis NMA
3. Applies odds ratio of no response to odds of not achieving seizure freedom, in line with reporting of outcome in Chen 2018
4. Applies odds ratio to brivaracetam to ensure that subsequent treatment is less effective than alternative comparators
5. Excludes cenobamate in subsequent ASM treatments

	Total costs (£)	Total QALYs	ICER/QALY
Cenobamate	XXX	6.955	-
Eslicarbazepine	194,998	6.339	Dominated
Perampanel	202,728	6.226	Dominated
Lacosamide	208,526	6.147	Dominated
Brivaracetam	227,534	5.868	Dominated

ERG base case construction

Assumption	Analysis
Error correction	Corrected typographical errors in transition probabilities
Model structure	3 state levels of response
	Increased cycle length to 84 days, starting in cycle 6, with transition probabilities informed by C017 OLE
	Extrapolation of treatment effect: all patients remain in same state unless they stop treatment
Key baseline input	Baseline number of seizures informed by C013
NMA adjustment	Include C013
	Updated to account for correlation between outcomes and prevent double counting (joint synthesis)
	Placebo adjustment
Subsequent ASMs	Response to subsequent ASMs derived by applying odds ratio of treatment resistance to the odds of no seizure freedom
	Effectiveness of subsequent ASMs calculated relative to least effective comparator
	Cost of subsequent ASMs recalculated to exclude cenobamate
Stopping treatment	Time to stopping treatment for comparators informed by NMA
	Starting in model cycle 6, assume stopping treatment for comparators identical to cenobamate
	Patients with no response after cycle 6 assumed to discontinue treatment
HRQoL	No carer disutility

ERG base case results

	Next best comparator	Incremental cost	Incremental QALYs	ICER £/QALY
CS base case	Lacosamide	XXX	XXX	Dominant
ERG base case	Lacosamide	XXX	XXX	Dominant

Disaggregated costs – ERG base case

Cost of items (£)	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine	Perampanel
Treatment cost	XXXXX	**4,622**	**5,332**	**6,544**	**5,587**
Subsequent ASMs	XXXXX	**26,222**	**25,687**	**25,514**	**25,729**
Administration	XXXXX	**1,414**	**2,244**	**1,778**	**1,930**
Routine monitoring	XXXXX	**26,157**	**25,821**	**25,703**	**25,866**
Epilepsy event management	XXXXX	**50,408**	**49,647**	**49,379**	**49,750**
Adverse event	XXXXX	**429**	**432**	**464**	**458**
Total cost	XXXXX	**109,251**	**109,163**	**109,381**	**109,320**

ERG exploratory analysis 1 – cost-comparison

	Next best comparator	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
ERG base case	Lacosamide	XXXX	-0.284	Dominant
Assuming equal efficacy, equal stopping rates and adverse drug reactions for cenobamate and comparators	Lacosamide	XXXX	0.001	XXXX

ERG exploratory analysis 2 – baseline seizure

ERG

- As baseline seizure varies, incremental QALY effect is unaffected. HRQoL for each level of response is assumed to remain same as in base case, but costs change
- ERG base case: if seizures <2, cost reduction from treatment with cenobamate becomes lower than incremental cost of cenobamate, and cenobamate becomes costlier than comparators

	Next best comparator	Incremental cost	Incremental QALYs	Cumulative ICER £/QALY
ERG base case	Lacosamide	XXXX	-0.284	Dominant
Varying average baseline seizure frequency	Lacosamide	see figure	-0.284	XXXX

ERG sensitivity analysis – alternative resource use data

ERG base case + resource use data from Jacoby (1998)

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER/QALY
Cenobamate	XXXX	11.151	-	-	-
Eslicarbazepine	42,879	10.873	XXXX	XXXX	XXXX
Perampanel	42,281	10.860	XXXX	-0.013	101,500
Lacosamide	42,270	10.867	XXXX	0.007	Dominated
Brivaracetam	41,276	10.846	XXXX	-0.021	47,333

Other issues

Innovation

- MHRA designated cenobamate Promising Innovative Medicine status: potential to fulfil an unmet need in drug-resistant patients with focal-onset seizures

Equalities

- No equalities issues identified

End of Part 1