Appendix

Table Appendix 1 - Cenobamate transition probabilities including cycle 6+ exptrapolation [1]

	No response	Moderate response	High response	Very high response	Complete response
Baseline -> Cycle 1					
No response	74.32%	11.82%	6.36%	1.82%	5.68%
Cycle 1 -> Cycle 2					1
No response	65.44%	15.90%	8.56%	2.45%	7.65%
Moderate response	0.00%	100.00%	0.00%	0.00%	0.00%
High response	0.00%	0.00%	100.00%	0.00%	0.00%
Very high response	0.00%	0.00%	0.00%	100.00%	0.00%
Complete response	0.00%	0.00%	0.00%	0.00%	100.00%
Cycle 2 -> Cycle 3					1
No response	54.84%	17.20%	18.28%	1.08%	8.60%
Moderate response	26.09%	34.78%	15.22%	2.17%	21.74%
High response	7.41%	29.63%	25.93%	3.70%	33.33%
Very high response	12.50%	12.50%	25.00%	25.00%	25.00%
Complete response	9.09%	4.55%	18.18%	4.55%	63.64%
Cycle 3 -> cycle 4		1	1		1
No response	81.67%	13.33%	3.33%	0.00%	1.67%
Moderate response	28.21%	51.28%	10.26%	0.00%	10.26%

High response	18.92%	21.62%	29.73%	5.41%	24.32%
Very high response	0.00%	50.00%	16.67%	0.00%	33.33%
Complete response	8.11%	2.70%	5.41%	2.70%	81.08%
Cycle 4 -> Cycle 5	· · · · · · · · · · · · · · · · · · ·	<u>'</u>	<u>'</u>		
No response	71.21%	19.70%	3.03%	0.00%	6.06%
Moderate response	25.64%	41.03%	20.51%	5.13%	7.69%
High response	26.32%	26.32%	36.84%	10.53%	0.00%
Very high response	33.33%	0.00%	0.00%	33.33%	33.33%
Complete response	4.44%	2.22%	8.89%	11.11%	73.33%
Cycle 6+ (average of C	<i>Cycle 2 -> 3, C</i>	$Cycle 3 \rightarrow 4 a$	nd Cycle 4 ->	5)	·
No response	69.24%	16.74%	8.21%	0.36%	5.44%
Moderate response	26.64%	42.36%	15.33%	2.43%	13.23%
High response	17.55%	25.86%	30.83%	6.55%	19.22%
Very high response	15.28%	20.83%	13.89%	19.44%	30.56%
Complete response	7.21%	3.16%	10.83%	6.12%	72.68%
			1		

Table Appendix 2 - Cenobamate transition probabilities when C017 data is included (including cycle 27+ extrapolation) [1], [2]

	No response	Moderate response	High response	Very high response	Complete response		
Baseline -> Cycle 1							
No response	74.32%	11.82%	6.36%	1.82%	5.68%		
Cycle 1 -> Cycle 2	1	1	1	1			

No response	65.44%	15.90%	8.56%	2.45%	7.65%
Moderate response	0.00%	100.00%	0.00%	0.00%	0.00%
High response	0.00%	0.00%	100.00%	0.00%	0.00%
Very high response	0.00%	0.00%	0.00%	100.00%	0.00%
Complete response	0.00%	0.00%	0.00%	0.00%	100.00%
Cycle 2 -> Cycle 3					
No response	54.84%	17.20%	18.28%	1.08%	8.60%
Moderate response	26.09%	34.78%	15.22%	2.17%	21.74%
High response	7.41%	29.63%	25.93%	3.70%	33.33%
Very high response	12.50%	12.50%	25.00%	25.00%	25.00%
Complete response	9.09%	4.55%	18.18%	4.55%	63.64%
Cycle 3 -> cycle 4					
No response	81.67%	13.33%	3.33%	0.00%	1.67%
Moderate response	28.21%	51.28%	10.26%	0.00%	10.26%
High response	18.92%	21.62%	29.73%	5.41%	24.32%
Very high response	0.00%	50.00%	16.67%	0.00%	33.33%
Complete response	8.11%	2.70%	5.41%	2.70%	81.08%
Cycle 4 -> Cycle 5	1	1	1		1
No response	71.21%	19.70%	3.03%	0.00%	6.06%
Moderate response	25.64%	41.03%	20.51%	5.13%	7.69%
High response	26.32%	26.32%	36.84%	10.53%	0.00%
Very high response	33.33%	0.00%	0.00%	33.33%	33.33%

Complete response	4.44%	2.22%	8.89%	11.11%	73.33%
Cycle 5 -> Cycle 6					
No response	79.63%	12.96%	4.63%	0.93%	1.85%
Moderate response	30.14%	43.84%	15.07%	6.85%	4.11%
High response	9.84%	32.79%	29.51%	18.03%	9.84%
Very high response	0.00%	16.33%	28.57%	30.61%	24.49%
Complete response	4.88%	7.32%	2.44%	17.07%	68.29%
Cycle 6 -> Cycle 7					
No response	75.25%	17.82%	3.96%	0.99%	1.98%
Moderate response	30.26%	47.37%	14.47%	6.58%	1.32%
High response	4.08%	20.41%	26.53%	40.82%	8.16%
Very high response	5.13%	12.82%	30.77%	33.33%	17.95%
Complete response	0.00%	2.13%	4.26%	10.64%	82.98%
Cycle 7 -> Cycle 8					
No response	74.19%	21.51%	4.30%	0.00%	0.00%
Moderate response	17.14%	54.29%	20.00%	5.71%	2.86%
High response	5.00%	22.50%	47.50%	25.00%	0.00%
Very high response	0.00%	4.55%	34.09%	45.45%	15.91%
Complete response	2.00%	2.00%	8.00%	22.00%	66.00%
Cycle 8 -> Cycle 9					
No response	88.00%	8.00%	4.00%	0.00%	0.00%
Moderate response	26.15%	49.23%	16.92%	4.62%	3.08%
<u>-</u>					

High response	12.73%	23.64%	43.64%	12.73%	7.27%
Very high response	0.00%	6.67%	24.44%	51.11%	17.78%
Complete response	0.00%	4.76%	2.38%	14.29%	78.57%
Cycle 9 -> Cycle 10					
No response	75.95%	21.52%	1.27%	0.00%	1.27%
Moderate response	22.22%	51.85%	14.81%	7.41%	3.70%
High response	2.04%	20.41%	46.94%	18.37%	12.24%
Very high response	0.00%	7.89%	23.68%	55.26%	13.16%
Complete response	0.00%	2.22%	2.22%	15.56%	80.00%
Cycle 10 -> Cycle 11		1		1	1
No response	72.06%	26.47%	1.47%	0.00%	0.00%
Moderate response	25.86%	46.55%	20.69%	3.45%	3.45%
High response	4.76%	28.57%	35.71%	19.05%	11.90%
Very high response	0.00%	7.32%	26.83%	48.78%	17.07%
Complete response	0.00%	0.00%	2.08%	10.42%	87.50%
Cycle 11 -> Cycle 12					
No response	77.97%	18.64%	3.39%	0.00%	0.00%
Moderate response	25.86%	50.00%	20.69%	1.72%	1.72%
High response	7.50%	35.00%	35.00%	17.50%	5.00%
Very high response	2.86%	14.29%	22.86%	48.57%	11.43%
Complete response	0.00%	3.77%	3.77%	9.43%	83.02%
<i>Cycle 12 -> Cycle 13</i>		1	1	1	1

No response	80.33%	14.75%	3.28%	0.00%	1.64%
Moderate response	21.67%	60.00%	16.67%	1.67%	0.00%
High response	15.79%	21.05%	39.47%	18.42%	5.26%
Very high response	0.00%	6.67%	16.67%	60.00%	16.67%
Complete response	0.00%	0.00%	3.92%	13.73%	82.35%
<i>Cycle 13 -> Cycle 14</i>					
No response	68.66%	26.87%	4.48%	0.00%	0.00%
Moderate response	15.09%	58.49%	22.64%	3.77%	0.00%
High response	5.88%	11.76%	52.94%	23.53%	5.88%
Very high response	0.00%	3.03%	21.21%	42.42%	33.33%
Complete response	2.04%	0.00%	6.12%	4.08%	87.76%
Cycle 14 -> Cycle 15					
No response	83.64%	12.73%	3.64%	0.00%	0.00%
Moderate response	13.21%	73.58%	9.43%	1.89%	1.89%
High response	2.38%	28.57%	42.86%	19.05%	7.14%
Very high response	0.00%	0.00%	26.92%	42.31%	30.77%
Complete response	0.00%	0.00%	9.09%	16.36%	74.55%
Cycle 15 -> Cycle 16					
No response	80.00%	12.00%	8.00%	0.00%	0.00%
Moderate response	24.56%	49.12%	17.54%	7.02%	1.75%
High response	8.33%	22.22%	47.22%	16.67%	5.56%
Very high response	0.00%	6.90%	13.79%	48.28%	31.03%
	1	1	1	1	1

Complete response	0.00%	0.00%	0.00%	9.43%	90.57%
<i>Cycle 16 -> Cycle 17</i>					
No response	85.71%	8.93%	1.79%	1.79%	1.79%
Moderate response	15.91%	59.09%	15.91%	4.55%	4.55%
High response	2.94%	29.41%	41.18%	23.53%	2.94%
Very high response	0.00%	10.34%	13.79%	55.17%	20.69%
Complete response	0.00%	0.00%	3.39%	13.56%	83.05%
<i>Cycle 17 -> Cycle 18</i>					
No response	78.18%	18.18%	3.64%	0.00%	0.00%
Moderate response	13.64%	63.64%	15.91%	4.55%	2.27%
High response	3.57%	21.43%	42.86%	25.00%	7.14%
Very high response	0.00%	5.88%	11.76%	52.94%	29.41%
Complete response	1.69%	3.39%	11.86%	18.64%	64.41%
<i>Cycle 18 -> Cycle 19</i>					
No response	85.71%	10.20%	2.04%	0.00%	2.04%
Moderate response	20.83%	56.25%	14.58%	2.08%	6.25%
High response	6.25%	34.38%	40.63%	15.63%	3.13%
Very high response	2.63%	5.26%	18.42%	50.00%	23.68%
Complete response	0.00%	0.00%	2.00%	14.00%	84.00%
<i>Cycle 19 -> Cycle 20</i>					
No response	75.47%	18.87%	5.66%	0.00%	0.00%
Moderate response	15.56%	64.44%	15.56%	4.44%	0.00%

High response	0.00%	31.03%	41.38%	10.34%	17.24%
Very high response	3.13%	3.13%	18.75%	37.50%	37.50%
Complete response	0.00%	0.00%	5.56%	12.96%	81.48%
<i>Cycle 20 -> Cycle 21</i>					
No response	72.34%	21.28%	4.26%	2.13%	0.00%
Moderate response	18.37%	61.22%	14.29%	6.12%	0.00%
High response	9.68%	29.03%	22.58%	32.26%	6.45%
Very high response	0.00%	4.17%	16.67%	50.00%	29.17%
Complete response	0.00%	3.28%	1.64%	13.11%	81.97%
Cycle 21 -> Cycle 22	!	1	I		I
No response	69.57%	30.43%	0.00%	0.00%	0.00%
Moderate response	20.00%	54.00%	20.00%	2.00%	4.00%
High response	5.00%	25.00%	55.00%	10.00%	5.00%
Very high response	0.00%	8.82%	38.24%	50.00%	2.94%
Complete response	0.00%	0.00%	0.00%	6.78%	93.22%
<i>Cycle 22 -> Cycle 23</i>			I		
No response	78.57%	16.67%	4.76%	0.00%	0.00%
Moderate response	16.28%	55.81%	20.93%	0.00%	6.98%
High response	5.88%	32.35%	35.29%	11.76%	14.71%
Very high response	0.00%	4.35%	8.70%	47.83%	39.13%
Complete response	1.75%	0.00%	1.75%	14.04%	82.46%
<i>Cycle 23 -> Cycle 24</i>	I	1			I

No response	65.22%	26.09%	8.70%	0.00%	0.00%
Moderate response	18.52%	51.85%	18.52%	3.70%	7.41%
High response	5.56%	33.33%	33.33%	22.22%	5.56%
Very high response	0.00%	7.69%	15.38%	46.15%	30.77%
Complete response	0.00%	0.00%	2.70%	8.11%	89.19%
Cycle 24 -> Cycle 25					
No response	87.50%	12.50%	0.00%	0.00%	0.00%
Moderate response	14.29%	42.86%	42.86%	0.00%	0.00%
High response	0.00%	12.50%	62.50%	25.00%	0.00%
Very high response	0.00%	25.00%	25.00%	50.00%	0.00%
Complete response	6.67%	0.00%	0.00%	0.00%	93.33%
Cycle 25 -> Cycle 26					
No response	100.00%	0.00%	0.00%	0.00%	0.00%
Moderate response	0.00%	66.67%	0.00%	0.00%	33.33%
High response	0.00%	66.67%	0.00%	33.33%	0.00%
Very high response	0.00%	0.00%	50.00%	50.00%	0.00%
Complete response	0.00%	0.00%	0.00%	25.00%	75.00%
Cycle 27+ Extrapolatio	on				
No response	78.76%	16.97%	3.49%	0.28%	0.50%
Moderate response	19.31%	55.25%	17.50%	3.72%	4.22%
High response	5.58%	27.72%	39.15%	20.87%	6.69%
Very high response	0.65%	7.67%	23.17%	47.42%	21.09%
	1	1	1	1	1

Table Appendix 3 – Relative Risks of response to treatment relative to cenobamate (base case comparators) [3]

Treatment	Perampanel	Lacosamide	Eslicarbazepine acetato	Brivaracetam
>50% response rate	0.59	0.66	0.65	0.63
Seizure freedom	0.29	0.38	0.36	0.34

Table Appendix 4 - Background therapy cost per cycle [4], [5]

Drug	DDD (mg)	Units per package	Dosage (mg)	Ex-factory price per package	Cost per DDD	Cost per cycle	Percentage of patients
Levetiracetam	1500	60	500	€ 20.08	€ 1.00	€ 28.11	32.30%
Lamotrigine	300	56	100	€ 15.98	€ 0.86	€ 23.97	16.40%
Carbamazepine	1000	30	200	€ 1.64	€ 0.27	€ 7.65	8.00%
Sodium valproate	1500	40	200	€ 2.79	€ 0.52	€ 14.65	16.30%
Topiramate	300	60	100	€ 21.34	€ 1.07	€ 29.88	9.00%
Clobazam	20	30	10	€ 10.20	€ 0.68	€ .19.04	10.00%
Zonisamide	200	56	100	€ 19.05	€ 0.68	€.19.05	4.80%
Phenytoin	300	30	100	€ 1.13	€ 0.11	€ 3.16	3.10%
Oxcarbazepine	1000	50	600	€ 11.44	€ 0.38	€ 10.68	12.20%
Phenobarbital	100	20	100	€ 0.91	€ 0.05	€ 1.27	5.60%

 Table Appendix 5 - Seizures management costs

		Focal aware seizure		Focal impaired awareness seizure		Focal to Bilateral Tonic- Clonic Seizure	
Seizures Requiring Medical Assistance (%)		2.90%		8.60%		30.80%	
Treatment Setting	Unit cost	Proportion of PcE Accessing Services	Proportion of PcE Requiring Treatment	Proportion of PcE Accessing Services	Proportion of PcE Requiring Treatment	Proportion of PcE Accessing Services	Proportion of PcE Requiring Treatment
Emergency Department Access for Patients Requiring Medical Care (%)	€465.29 (average cost between yellow and red codes [6]; inflation- adjusted to 2023 [7])	57.08%	19.74%	65.45%	29.20%	79.51%	47.99%
Other Access for Patients Requiring Medical Care	€ 22,00 (Code 89.13 [8])	42.92%	10.03%	34.55%	12.52%	20.49%	6.49%
Hospitalization costs							
Proportion of Patients Requiring Hospitalization (%)	€2241.00 (average of DRG 562 and DRG 563 [9])	3.30%		3.10%		5.30%	
Average Length of Stay (Da	ys)	1.6	7	2.00		2	.33
Proportion of Patients Referred to Other Services (%)	€ 22,00 (Code 89.13 [8])	75.00% 70.00%		00%	30.00%		

 Table Appendix 6 - Incidence rates of adverse events by treatment

Cenobamate	Brivaraceta m	Lacosamide	Eslicarbazepine acetate	Perampanel	Source

Odds ratio of adverse events vs cenobamate	-	0.66	0.66	1.11	0.97	[10]	
	Titra	Titration phase: probability of patients experiencing adverse event					
Adverse event	Cenobamate	Brivaraceta m	Lacosamide	Eslicarbazepine acetate	Perampanel		
Somnolence	7.91%	5.60%	5.60%	8.59%	7.72%	[11]	
Dizziness	6.51%	4.61%	4.61%	7.07%	6.35%		
Fatigue	4.43%	3.14%	3.14%	4.81%	4.32%		
Headache	2.97%	2.10%	2.10%	3.22%	2.90%		
Viral upper respiratory tract infection	1.88%	1.33%	1.33%	2.04%	1.84%		
Upper respiratory tract infection	1.57%	1.11%	1.11%	1.70%	1.53%		
Nausea	1.53%	1.08%	1.08%	1.66%	1.49%		
Diplopia	1.49%	1.05%	1.05%	1.62%	1.45%		
Balance disorder	1.41%	1.00%	1.00%	1.53%	1.38%		
	Maintenance phase: probability of patients experiencing adverse event					Source	
Adverse event	Cenobamate	Brivaraceta m	Lacosamide	Eslicarbazepine acetate	Perampanel		

Somnolence	5.70%	4.03%	4.03%	6.19%	5.56%	[1]
Dizziness	5.43%	3.84%	3.84%	5.89%	5.29%	
Headache	2.85%	2.02%	2.02%	3.09%	2.78%	
Balance disorder	0.46%	0.32%	0.32%	0.50%	0.45%	
Nystagmus	0.92%	0.65%	0.65%	1.00%	0.90%	
Ataxia	0.92%	0.65%	0.65%	1.00%	0.90%	
Dysarthria	0.69%	0.49%	0.49%	0.75%	0.67%	
Fatigue	4.63%	3.28%	3.28%	5.03%	4.52%	
Gait disturbance	1.39%	0.99%	0.99%	1.51%	1.36%	
Diplopia	2.60%	1.84%	1.84%	2.82%	2.54%	
Constipation	0.69%	0.49%	0.49%	0.75%	0.67%	
Nausea	0.23%	0.16%	0.16%	0.25%	0.22%	
Vomiting	0.69%	0.49%	0.49%	0.75%	0.67%	
Fall	0.92%	0.65%	0.65%	1.00%	0.90%	
Upper respiratory tract infection	0.92%	0.65%	0.65%	1.00%	0.90%	
Backpain	0.23%	0.16%	0.16%	0.25%	0.22%	
Vertigo	0.69%	0.49%	0.49%	0.75%	0.67%	

Decreased appetite	0.23%	0.16%	0.16%	0.25%	0.22%			
Adverse event		Subsequent as	sm treatment: pro	bability adverse even	ıt	Source		
Somnolence		2.50%						
Dizziness		2.04%						
Fatigue		1.38%						
Headache		0.92%						
Viral upper respiratory tract infection		0.58%						
Upper respiratory tract infection		0.48%						
Nausea		0.47%						
Diplopia		0.46%						
Balance disorder		0.43%						
Adverse event		Vagus nerve s	timulation: proba	bility of adverse even	ıt	Source		
Voice alteration hoarseness			54.50%			[12]		
Cough		•						
Dyspnoea								
Pain		24.10%						
Parathesis			13.40%					

Infection	5.00%	
Adverse event	Surgery: probability of adverse event	Source
Neurological complications	8.80%	[13]
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%	

Table Appendix 7 - Cost-Eeffectiveness ana	lysis results including C017 OLE trial data

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Cenobamate	145,054.73€	7.59			
Lacosamide	177,960.17€	6.66	-32,905.44 €	0.93	Dominante
Perampanel	184,327.97€	6.62	-39,273.24 €	0.98	Dominante
Brivaracetam	187,414.42€	6.59	-42,359.69€	1.01	Dominante
Eslicarbazepine	194,057.06€	6.36	-49,002.34 €	1.24	Dominante
acetate					

Cost item	Cenobamate	Brivaracetam	Lacosamide	Eslicarbazepine acetate	Perampanel
Treatment cost	23,831.29€	13,210.03 €	6,602.86 €	14,994.84€	11,409.60€
Cost of subsequent ASM treatments	9,145.17€	13,134.59€	13,821.07€	11,028.14€	14,114.10€
Monitoring cost associated with administration	5,114.94€	5,344.55€	5,280.08 €	5,597.92€	5,226.37€
Follow-up cost	1,982.54 €	2,762.34 €	2,707.92 €	2,864.93 €	2,724.59€
Seizure management cost	103,893.37€	152,222.71 €	148,839.49€	158,412.42€	150,004.77€
Adverse event management costs	1,087.43€	740.21 €	708.74 €	1,158.82€	848.54 €
Total	145,054.73 €	187,414.42 €	177,960.17€	194,057.06 €	184,327.97€

Table Appendix 8 - Results by cost category including C017 OLE trial data

References

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