Redacted

NICE National Institute for Health and Care Excellence

Cannabidiol for Dravet Syndrome

Lead Team Presentation

1st appraisal committee B meeting

Chair: Amanda Adler

Lead team: Mark Chapman, Megan John, Tony Wootton

Technical team: Alan Lamb, Ross Dent, Nicole Elliott

Company: GW Pharma

ERG: Kleijnen Systematic Reviews

30 July 2019

Disease background – Dravet Syndrome

- Severely debilitating, lifelong and treatment-resistant form of epilepsy
- Very rare: prevalence 0.4 in 10,000 people
- Symptoms include prolonged convulsive seizures leading to emergency hospital visits
- High risk of sudden unexpected death in epilepsy
- Can cause cognitive and functional impairment
  - Autism, attention deficit hyperactivity disorder, sleep disorders and absent language skills common
- Mortality estimated around 20%
  - Most deaths occur before 10 years of age
  - Better seizure control may reduce mortality
- Big impact on patients and caregivers

Patient and carer perspectives

High unmet need for new treatments

- ‘Seizure control very poor in most people living with the condition’
- Freedom from convulsive seizures would be valuable

Co-morbidities are important

- ‘Dravet Syndrome is not just seizures – co-morbidities can often be more problematic to manage than the seizures’
- ‘Side effects from treatments can increase some of the symptoms of the co-morbidities’

Substantial impact on carers

- Patients often require round the clock care “which is difficult to resource and relentless”
- ‘[sudden unexpected death in epilepsy] is never far from our thoughts’
- Impact on health, finances, employment and relationships

Anticipated marketing authorisation

Population different from decision problem

- Population in decision problem “People with seizures inadequately controlled by established clinical management”
- Committee for Medicinal Products for Human Use (CHMP) of European Medicines Agency (EMA) adopted ‘positive opinion’ on 26th July 2019
  - Indicated for “use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), **in conjunction with clobazam**, for patients 2 years of age and older.”
- Company submitted new evidence following CHMP opinion on 26th July:
  - Not validated by Evidence Review Group (ERG)

[redacted]

Cannabidiol (Epidyolex, GW Pharma)

Marketing authorisation	Use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.

Mechanism	• Anticonvulsant mechanisms unknown. Thought to:
	  • Reduce neuronal hyper-excitability and inflammation via intracellular calcium
	  • Inhibit cellular uptake of adenosine and modulate adenosine-mediated signalling

Administration	Oral as 100 mg/ml cannabidiol (CBD) solution in sesame oil + anhydrous ethanol + sucralose + strawberry flavouring. Does not contain tetrahydrocannabinol (THC) Weight-based dosing. Starting dose 2.5 mg/kg twice daily for 1 week Recommended maintenance dose 5 mg/kg twice daily (CBD 10) Maximum recommended dose 10 mg/kg twice daily (CBD 20)
Acquisition cost	List price is **** per 100 ml (100 mg/ml) bottle proposes a ‘patient access scheme’ = simple discount to list price

NICE Clinical Guideline in development

- NICE is developing a Clinical Guideline on cannabis-based products for medicinal use
- Final scope includes severe treatment-resistant epilepsy
- Not specifically looking at Dravet or Lennox-Gastaut syndromes
  - may cross refer to Technology Appraisal guidance if compatible with timelines
- Consultation on draft guideline August 2019

[redacted]

Company original decision problem

	NICE scope	Company
Population	Seizures inadequately controlled by established clinical management	• seizures inadequately controlled by established clinical management, or • where clinical management unsuitable or not tolerated
Comparator	Established clinical management without cannabidiol: which may combine: • sodium valproate • topiramate • clobazam • stiripentol • ketogenic diet • vagus nerve stimulation	
Outcomes	• seizure frequency • response rate • seizure severity • incidence of status epilepticus • mortality • adverse effects of treatment • health-related quality of life	• convulsive + overall seizure frequency • % of people free of convulsive seizures • no. with episodes of status epilepticus • mortality • adverse effects of treatment • health-related quality of life • Caregiver Global Impression of Change/Change in Seizure Duration

[redacted]

Company submitted new evidence following CHMP opinion

- Top-line clinical data for clobazam subgroup
  - Primary outcomes, key secondary outcomes
  - Clinical data did not include:
    - baseline characteristics (including baseline seizure frequency)
    - all relevant secondary outcomes
- Economic analysis for clobazam subgroup
  - New base case cost-effectiveness results and scenario analyses
  - Economic analysis did not include:
    - detailed description of changes to model inputs (transition probabilities, costs etc.)
    - full set of scenario analyses provided in original base case

[redacted]

Clinical effectiveness

Treatment pathway and positioning of CBD

NICE clinical guideline 137

Pharmacological therapy

1st line therapy

sodium valproate, topiramate

Adjunctive therapy

clobazam, stiripentol

Other adjunctive therapies used in practice

Levetiracetam

Non-pharmacological therapy After non-response to appropriate anti epileptic drugs

Ketogenic diet

Resective surgery

Vagus nerve stimulation (when resective surgery is not suitable)

Company's positioning

CBD
In conjunction with clobazam
After 2 appropriate anti epileptic drugs have failed to achieve seizure freedom

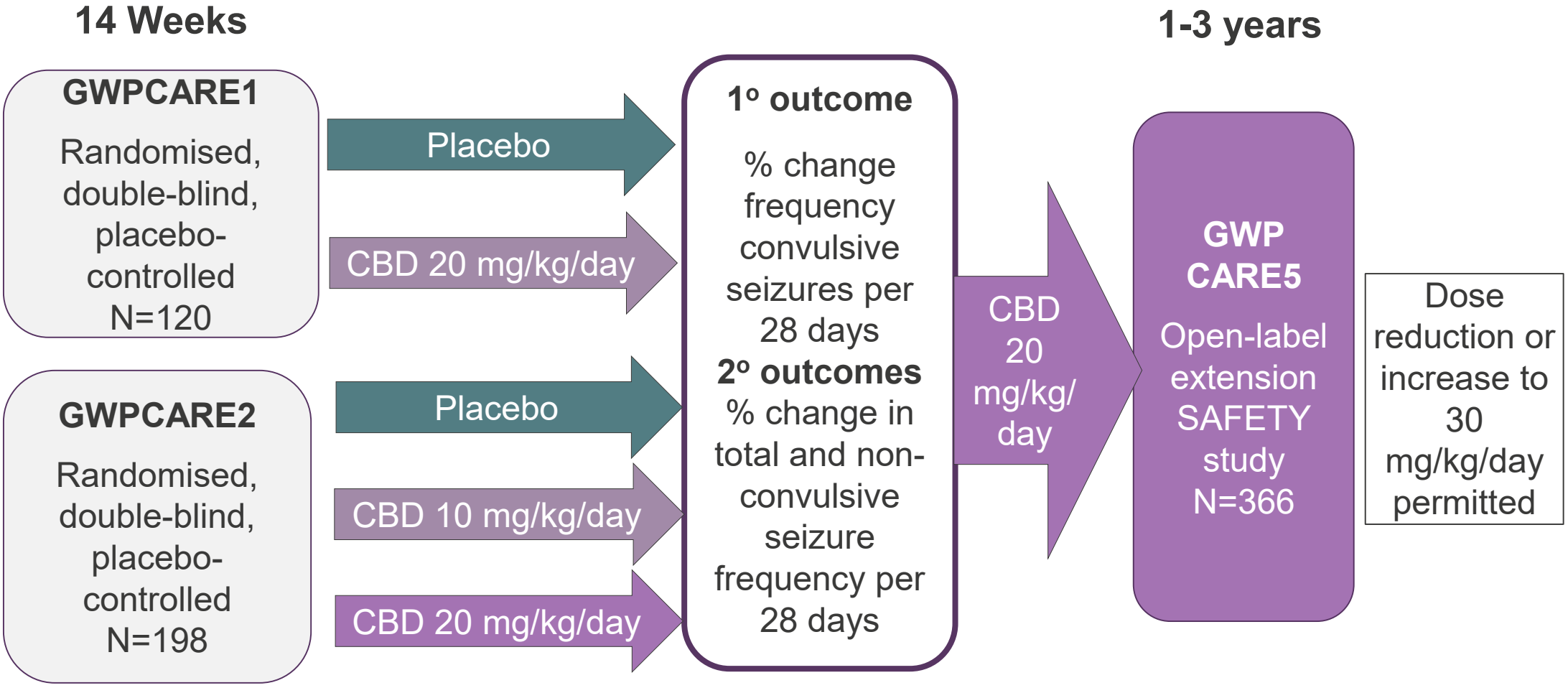
◉ *Technical team concluded the company's positioning of cannabidiol is appropriate – does the committee agree?*

Studies and relation to company's model

	GWPCARE1 Controlled trial	GWPCARE2 Controlled trial	GWPCARE5 Uncontrolled follow-up	Used in model?
Population	Aged 2 to18 not completely controlled with anti-epileptic drugs, with <4 convulsive seizures in 28 days	Aged 2 to18 not completely controlled with anti-epileptic drugs, with ≥4 convulsive seizures in 28 days	All patients in either Dravet Syndrome or Lennox Gastaut trials	Yes
Intervention	CBD 10 + usual care, CBD 20 + usual care			Partly. CBD 10
Comparison	Placebo + usual care		No control group	Yes. Usual care
1º outcome	% reduction convulsive seizures /28 days		Adverse events	Yes
Other outcomes	% reduction in total seizures % reduction in non-convulsive seizures		% reduction in seizure frequency (all sub types)	No
Quality of life	Quality of Childhood Epilepsy		No	No, company did a vignette study
EQ-5D?	No	No	No	-
Mortality	No	No	No	Values from lit.
Costs	No	No	No	Values from lit. and experts

2 trials + 1 follow-on: GWPCARE1, 2 and 5

Age 2 to 18 years, Dravet, not controlled by anti-epileptic drugs



Company used data from **GWPCARE1 (placebo). GWPCARE2 (placebo and 10 mg/kg/day)** and **GWPCARE5** in its economic model.

◉ Appropriate to combine placebo data?

Abbreviations: CBD, cannabidiol

Baseline characteristics – full population

2 trials recruited patients whose seizures inadequately controlled with a mean of **4 to 5** AEDS and who had tried a mean of **3** AEDs in the past

	GWPCARE1		GWPCARE2		
	CBD 20	Placebo	CBD 10	CBD 20	Placebo
n	76	76	[redacted]	[redacted]	[redacted]
Mean age, SD Range	16.0 (10.8) 2.6 to 48	15.3 (9.3) 2.6 to 43.4	[redacted]	[redacted]	[redacted]
Gender: % male	45	44	[redacted]	[redacted]	[redacted]
Ethnicity: % white	73	69	[redacted]	[redacted]	[redacted]
Baseline frequency/ 28 days: median (range)					
Total seizures	41 ([redacted])	24 ([redacted])	[redacted]	[redacted]	[redacted]
Convulsive seizures	15 ([redacted])	12 ([redacted])	[redacted]	[redacted]	[redacted]
Number of prior Anti-epileptic drugs (AEDs)					
Mean (SD)	4.6 (4.3)	4.6 (3.3)	[redacted]	[redacted]	[redacted]
Concurrent AEDs					
Mean (SD)	3.0 (1.0)	2.9 (1.0)	[redacted]	[redacted]	[redacted]

Results of clinical trials – full population

convulsive seizures reduced with cannabidiol; control group also improved

	GWPCARE1		GWPCARE2		
	CBD 20	Placebo	CBD 10	CBD 20	Placebo
n	61	59	[redacted]	[redacted]	[redacted]
1º outcome: Frequency convulsive seizures per 28 days					
Baseline, median	12.4	14.9	[redacted]	[redacted]	[redacted]
Treatment period, median	5.9	14.1	[redacted]	[redacted]	[redacted]
% change + IQR (trial 1 or 95% CI trial 2)	-38.9 -69.5 to -4.8	-13.3 -52.5 to -20.2	[redacted]	[redacted]	[redacted]
Comparison to placebo, 95% CI	Difference: -22.8 -41.1 to -5.4		Rate ratio: [redacted]	Rate ratio: [redacted]	N/A
2º outcome: 100% reduction in convulsive seizures					
n, %	3 (4.9%)	0 (0%)	[redacted]	[redacted]	[redacted]

Results include people not taking clobazam; **not** indicated for treatment with CBD

Abbreviations: CBD, cannabidiol; CI, confidence interval; IQR interquartile range

Results of clinical trials

subgroup also taking clobazam

Data in red box used to derive transition probabilities in model

		Overall	N	Subgroup with clobazam	N
CONVULSIVE SEIZURES PER 28 DAYS Percentage Reduction from Baseline[a]					
GWPCARE2	Placebo	26.9%	65		
	10 mg/kg/day	48.7%	66		
	20 mg/kg/day	45.7%	67		
GWPCARE1	Placebo	13.3%	59		
	20 mg/kg/day	38.9%	61		
Difference or Percent Reduction Compared with Placebo (95% CI)					
GWPCARE2	10 mg/kg/day	29.8% (8.4%, 46.2%) p=0.0095			
	20 mg/kg/day	25.7% (2.9%, 43.2%) p=0.0299			
GWPCARE1	20 mg/kg/day	22.8% (5.4%, 41.1%) p=0.0123			

Company

- used different statistical methods to calculate % reduction and p-value for overall population/ subgroup with clobazam
- did not provide baseline seizure frequency for clobazam subgroup
- did not indicate whether any patients taking clobazam achieved seizure freedom

◉ Does the treatment appear effective for this subgroup? Was this subgroup pre-specified? Did the company adjust for multiple comparisons?

Abbreviations: CBD, cannabidiol; CI, confidence interval;

Transitioning treatment with CBD to adults

- Trials did not include adults → efficacy uncertain

Clinical experts

- Age alone should not exclude treatment
- No reason to expect efficacy to differ for adults + children

⊙ ***Is it appropriate to assume adults benefit from CBD?***

[redacted] Abbreviations: CBD, cannabidiol

Adverse effects

Company states:

- Cannabidiol generally ‘well-tolerated’
- Common adverse events: vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion, lethargy, somnolence and diarrhoea
- Raised liver aminotransferases more common at higher dose
- Ongoing single arm follow-on study GWPCARE5 will define safety

◉ Is CBD well tolerated?
◉ Are there adverse effects that should be in the model?

[redacted]

Criteria for ‘stopping’ treatment for insufficient effect (rather than ‘discontinuing’ for intolerance)

Background	Clinical experts	Technical team
Company • Did not use stopping rule in the clinical trials • used stopping criteria proposed by NHS England in updated base-case: – Stop if frequency of target seizure types (convulsive seizures) do NOT reduce by **30%**	• Reasonable to determine this outcome at a minimum of **3 months** on a stable dose, then at 6 months, 1 year and each subsequent follow-up, as with current treatments • Treatment would usually stop were CBD ineffective, unless better tolerated	• NHS England criteria appropriate • Frequency per clinical expert views

- *What is the committee view on stopping rule – does it account for regression to mean?*
- *Given ‘regression to the mean’, would the rule by more likely to keep people on treatment that didn’t work, than stop treatment in people in whom it would work?*

Company did not model non-convulsive seizures

- Non-convulsive seizures and total seizures were 2º outcomes in trials (**see next slide)**
- Company did not model them, but they may impact quality of life
- Company provided **scenario analyses** to demonstrate uncaptured benefits

ERG:

- Unclear how company conducted scenario analysis or how analysis shows the effect of quality of life of non-convulsive seizures

Technical team:

- Benefits of fewer non-convulsive seizures difficult to capture in model
- Model may exclude benefits

[redacted]

Non-convulsive seizures not in model

		Overall	N	Subgroup With Clobazam	N
TOTAL SEIZURES PER 28 DAYS					
Percentage Reduction from Baseline[a]					
GWPCARE2	Placebo	29.7%	65		
	10 mg/kg/day	56.4%	66		
	20 mg/kg/day	47.3%	67		
GWPCARE1	Placebo	9.0%	59		
	20 mg/kg/day	28.6%	61		
Difference or Percent Reduction Compared with Placebo, p-value[b]					
GWPCARE2	10 mg/kg/day	38.0%			
		P=0.0003			
	20 mg/kg/day	25.1%			
		P=0.0255			
GWPCARE1	20 mg/kg/day	19.20			
		P=0.0335			

Company did not provide data for the % reduction in non-convulsive seizures for the clobazam subgroup

- *Are there important quality of life benefits not captured in the QALY calculation relating to reduced non-convulsive seizures?*

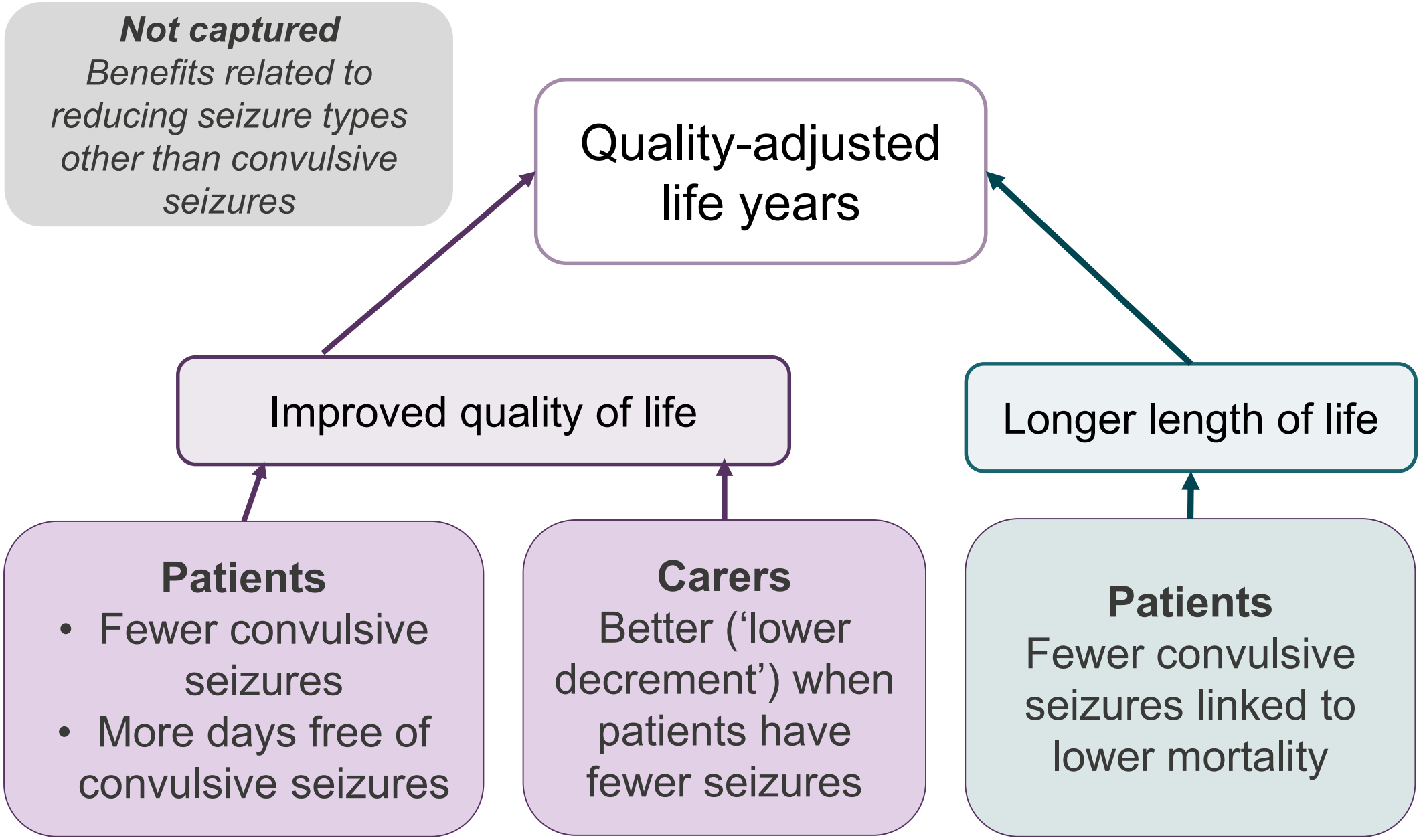
Doses higher in open label extension study than in license and company's model

Background	ERG and experts	Technical team
• Company used data from GWPCARE5 for months 3 to 27 in the model • Average dose in GWPCARE5 ↑ maintenance dose company models (CBD 10) **Company justifies this:** • Subgroup analysis shows no 'significant difference' in the 1º and 2º endpoints between low dose (≥[redacted] to <[redacted] mg/kg), high dose (≥[redacted] to <[redacted] mg/kg) and full population → no dose response and results generalisable	**ERG** Subgroup analysis based on small numbers and does not include the highest dose (>21 mg/kg) group → does not prove or disprove a dose response relationship Might overestimate treatment effect of CBD **Scenario analyses**: • Models cost of the higher dose • efficacy based on GWPCARE1/2 **Clinical experts** Could not state definitively whether high dose comparable to lower doses	• No robust evidence there is no dose response → using GWPCARE5 data in model introduces uncertainty • Acceptable to use GWPCARE5 data in model in absence of alternative data

⊙ *Is study likely to be big enough to find a difference?*
⊙ *Inappropriate to compare subgroups to whole group?*

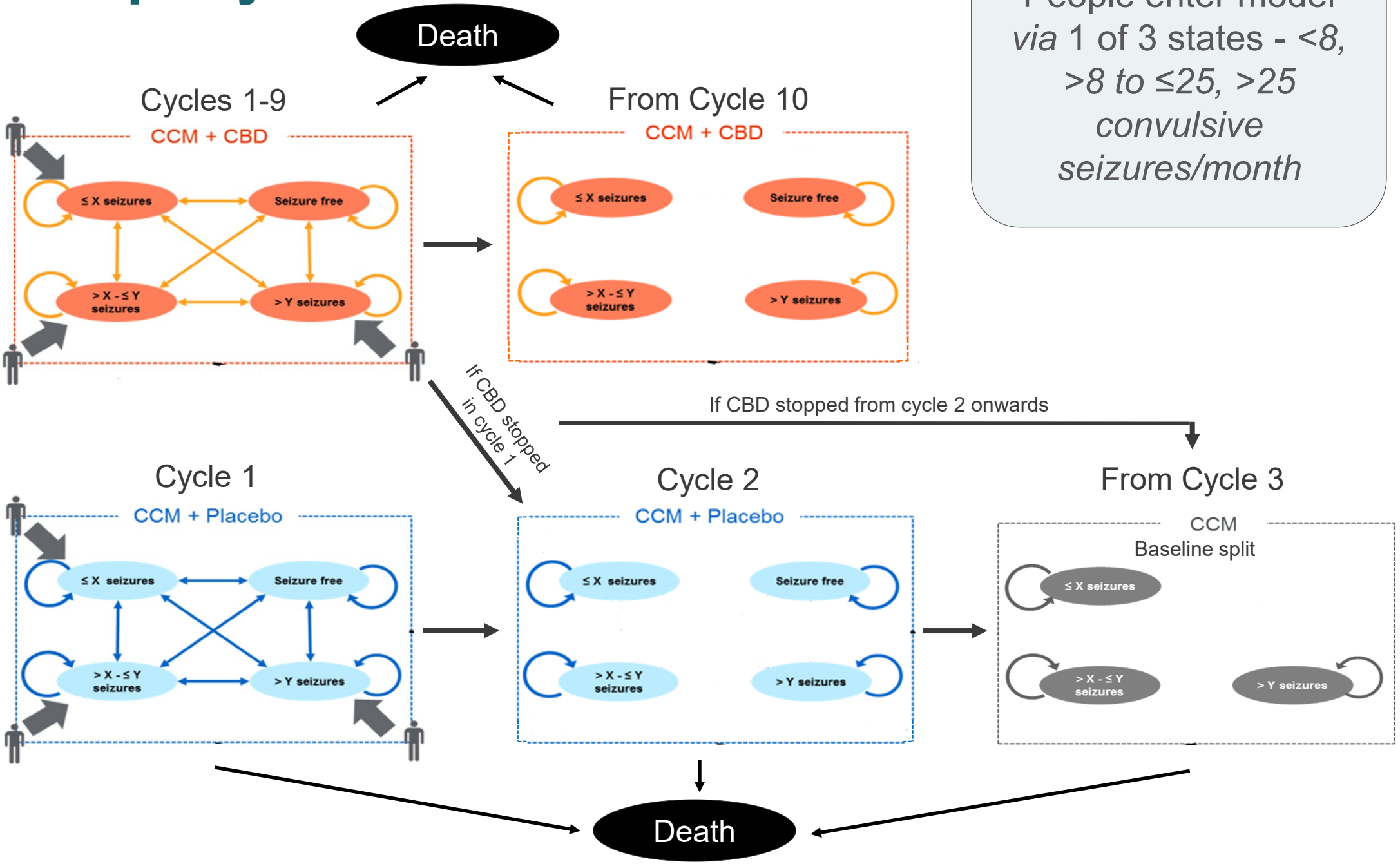
Cost effectiveness

Overview: how quality-adjusted life years accrue



Company's model structure

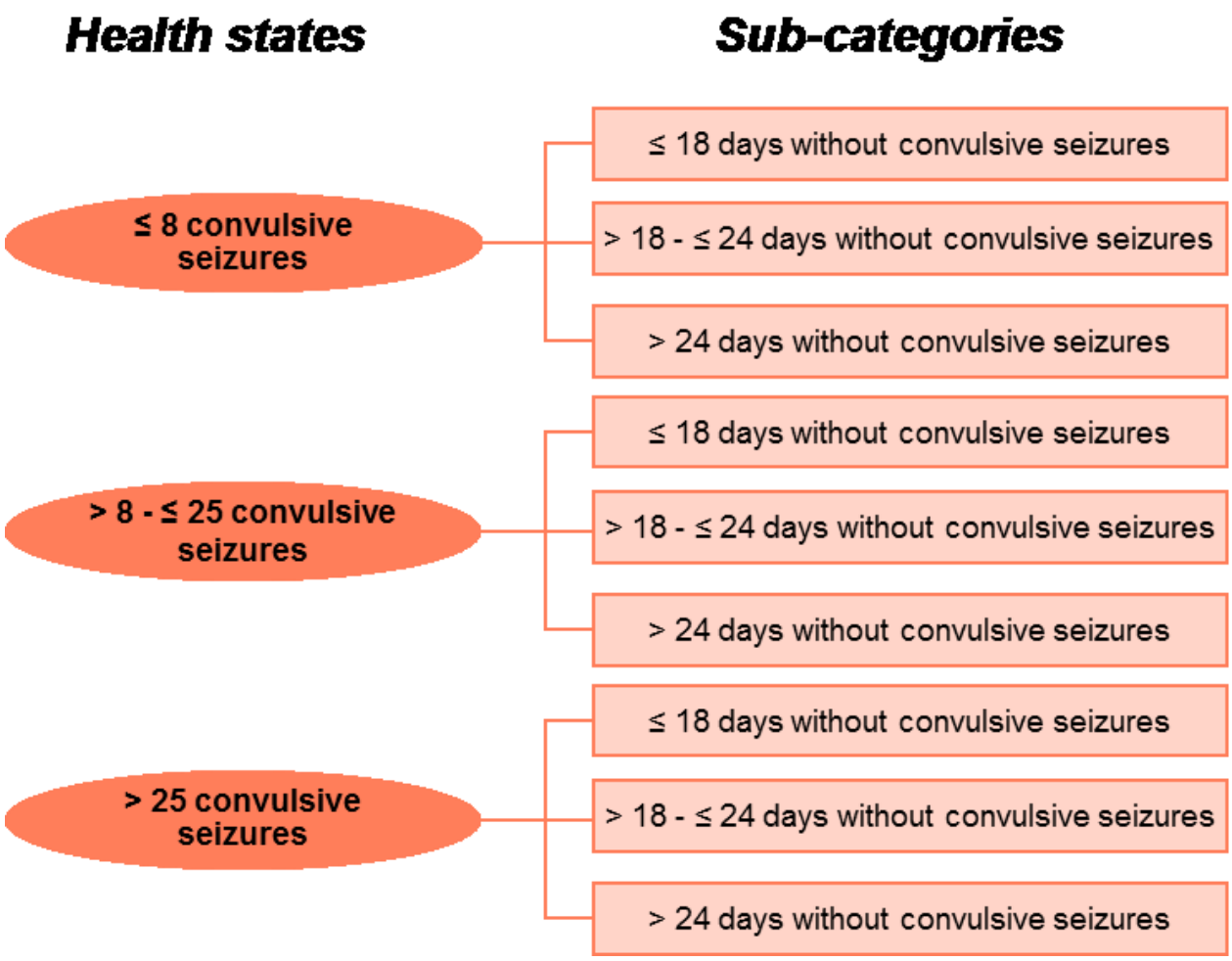
People enter model *via* 1 of 3 states - *<8, >8 to ≤25, >25 convulsive seizures/month*



Abbreviations: CBD, cannabidiol; CCM, current clinical management

Company's model structure

4 health states defined by convulsive seizure frequency; 3 sub-categories in each defined by days without convulsive seizures



Model features

- Time horizon: 50 years
- Cycle length: 3 months
- Only accounts for convulsive seizures (primary endpoint in trials)
- Treatment effect removed after cycle 2 for CCM and discontinuing CBD patients

All patients in the convulsive seizure-free health state are in the category with the most seizure-free days

⊙ *Is the model structure appropriate?*

How company models clinical evidence

Clinical trials

GWPCARE 1 and 2

Randomised, double-blind, placebo-controlled trials - 14 weeks

GWPCARE 5

Open-label extension study - 2 years

Parameters in model

- Baseline health states
- Efficacy: transitions between health states, proportion of patients in health state sub-categories (i.e. number of seizure free days) for CBD and usual care
- Discontinuation rates
- Adverse event probabilities

Company Survey

Vignette Study

Survey of people with Dravet syndrome + carers

Parameters in model

- Patient utility values for **all** health states and sub-states
- Carer utility decrements for two highest seizure frequency health states **only**

Literature

Cohort studies and survey of parents of children with Dravet syndrome

Parameters in model

- Disease specific mortality rates (for SUDEP and non-SUDEP related deaths)

Abbreviations: CBD, cannabidiol; SUDEP, sudden unexpected death in epilepsy

Modelling days without convulsive seizures

Background	ERG and experts	Technical team
Company assumes CBD improves quality of life by: 1. Reducing number of convulsive seizures **and** 2. Increasing number of days free of convulsive seizures In model: patients on CBD are allocated to sub-states with more convulsive seizure-free days than comparator	• **ERG:** company's assumption overestimates CBD's benefit because patients who take CBD revert to better health state with more seizure free days after discontinuing or stopping CBD • **Clinical experts:** quality of life will depend on the patients and their existing pattern of convulsive seizures	• Not appropriate to assume that the number of days without convulsive seizures will depend on treatment allocation → number of convulsive seizure-free days should be equal for CBD and comparator • Notes this has a small effect on cost effectiveness

- *Is it appropriate to assume and model cannabidiol increasing the number of days free of convulsive seizures?*
- *Does this 'double count' benefits from lowering the frequency of seizures?*

Abbreviations: CBD, cannabidiol; CCM, current clinical management

Relative treatment effect

Company does not consistently model relative treatment effect

Background	ERG and experts	Technical team
• Large placebo response in the trials • Company excludes 'placebo effect' in comparator arm after 2 cycles (6 months) in its updated base case (**see next slide**) **Company** justifies this noting: • Placebo effect higher than other trials in Dravet Syndrome • Consistent reduction in seizures of 40-50% across trials • **Scenario analysis:** Based on ERG scenario: GWPCARE1 and 2 outcomes used for first 9 cycles (27 months)	**Clinical experts** Both placebo and drug effects may vary over time → regression to the mean **ERG** Same mechanism causing high placebo effect would lead to improved treatment effect for CBD, this is the basis for using RCT evidence	• **Relative efficacy** of CBD vs comparator should be constant over the model time horizon

- *Is it appropriate to only capture placebo response for 2 cycles of the model?*
- *Are there alternative approaches to modelling the relative treatment effect?*

Relative treatment effect

GWPCARE 1 and 2
Randomised, double-blind, placebo-controlled trials 14 week duration

GWPCARE 5
Open-label all participants get CBD extension study
2 year duration

Cycle = 3 months

Updated base case

	Cycles 1-2	Cycles 3-9	Cycles 10+
CBD	GWPCARE 1 and 2	GWPCARE 5	Cycle 9 states (until discontinuation or death)
CCM	GWPCARE 1 and 2	Back to baseline	

Scenario analysis based on ERG scenario

	Cycles 1-9	Cycles 10+
CBD	GWPCARE 1 and 2	Cycle 9 states (until discontinuation or death)
CCM	GWPCARE 1 and 2	Back to baseline

[redacted]

Extrapolating effect of CBD beyond trials

Background	ERG and experts	Technical team
Company assumes that: • After 27 months patients remain in same health state until they stop CBD or die • Discontinuation rates capture waning of treatment effect • In base case, continuation is: • **[redacted]% of patients on treatment at 3 years, and [redacted]% at 5 years** • **Scenario analysis:** long-term discontinuation rate increases from [redacted]% to [redacted]% to account for underestimating waning	**ERG** No evidence to support this assumption, company could capture waning separately **Clinical experts** • Return to baseline frequency of seizures should be apparent within a year • If CBD effect wanes, then clinicians will increase dose of other treatments	• No evidence that CBD is effective CBD after 2 years → long-term efficacy is key source of uncertainty in the model • Company's scenario analysis does not fully address the uncertainty

- *What is the best way to capture waning of treatment effect?*
- *Are the company's assumed discontinuation rates plausible?*

Would clinicians increase the dose of CBD?

Background	Others' responses	Technical team
Company • Base case: all patients take CBD 10 and increasing dose NOT considered • Rationale: only people with potential to reduce seizures further and/or be free of seizures will increase dose to CBD20 • **Scenario analysis:** Weighted average dose is [redacted] based on [redacted]% of people in trials with >75% in response in receiving CBD 20	**Clinical experts** • Unlikely clinicians would offer higher dose if CBD 10 had no effect • Dose increase if: – effect appeared to decrease over time – partial response • Clinicians should assess at: 3, 6, 12 months after starting CBD and at each follow-up • Expect to offer 20% of patients a higher dose	Company's base case may not capture costs Company's scenario analysis may underestimate costs of CBD Would prefer scenario where 20% increase to 20 mg/kg/day after cycle 1

⊙ *Would people increase dose, if so what proportion?*
⊙ *Has the company accounted appropriately for the costs and benefits?*

*rounded

How to model health-related quality of life?

Company did not use trials' measure of quality of life, instead did a 'vignette' study

Background	Others' responses	Technical team
Company: • GWPCARE2 included Quality of Life in Childhood Epilepsy • Company did not use citing: – low response rates – No mapping algorithm to EQ-5D • Company considers that literature offers limited EQ-5D values not aligned with health states in model → vignette study of people with Dravet Syndrome and carers **(next slide)**	**ERG** • Company overestimates utility values for health state reflecting freedom from convulsive-seizures • Using a vignette study worse than valuing public preferences with validated scales measuring utility	• Company's approach may be justified, but has limitations. • Company provided **scenario analysis** using utility values from Verdian et al (study in Lennox-Gastaut syndrome) → showing similar ICER to the company's updated base case • But, company did not provide details of how it adjusted these values

- *Is a low response and no mapping algorithm sufficient to exclude trial-based data?*
- *Are the company's methods for its vignette study robust?*

Company's estimates of quality of life

Model (Vignette study

Health state number convulsive seizures	Sub-state number of days free of seizures	Mean quality of life scores
No seizures	No seizures	****
≤ 8 seizures	≤18 seizure-free days	****
	>18-≤24 seizure-free days	****
	>24 seizure-free days	****
>8 - ≤ 25 seizures	≤18 seizure-free days	****
	>18-≤24 seizure-free days	****
	>24 seizure-free days	****
> 25 seizures	≤18 seizure-free days	****
	>18-≤24 seizure-free days	****
	>24 seizure-free days	****

Literature
Dravet syndrome

Source	DISCUSS survey	
	Europe N=584	UK N=72
Mean quality of life scores	0.42	0.38 range -0.17 to 0.88

Lennox-Gastaut syndrome

Source	Verdian
Mean quality of life scores	21-28 drop seizures per week: 0.02 <-50%: 0.10 -50% to -75%: 0.5 >-75%: 0.596

⊙ *Are these quality of life values plausible?*

How to capture carers' quality of life?

Comments: Company and clinical experts

Company

- Includes carer quality of life
  - Values from vignette study
- **Validated**: using values from **Campbell, 2018**
  - US study
  - estimated Dravet Sydrome carer' utility by using the EQ-5D Index score: estimated utility **0.78 (±0.17)**
- Original base case included 1 carer, updated to 1.8 from literature

Company's modelled values for quality of life values

Seizures	Mean utility decrement
None	-
≤8	-
>8 to ≤25	****
>25	****

Clinical experts:

- Child with Dravet may have 2 to 4 carers (parents + grandparents)
- 2 carers accompany adult patients in clinics

[redacted]

How to capture carers' quality of life?

Comments: ERG and Technical Team

ERG

- Company's method vignette study unsuitable because:
  - Vignettes were condition-specific→ did not include dimensions e.g. mobility, self care
  - Used people with the condition, rather than general public
  - Respondents asked only to evaluate 3 vignettes → data not sufficiently detailed
  - Excluded non-convulsive seizures in descriptions → may incorrectly estimate carer QoL
- Issues with company's scenario analysis:
  - Company calculated decrements by subtracting Campbell utility score (0.78) from 1 (utility score of perfect health) → overestimate QoL decrement compared with subtracting from the utility score for the general population (**see example below**)

- *Using company's approach subtracting from full health value of 1*

  Overall carer disutility = 1- 0.78 = 0.22
- *Subtracting from US general population values:*

  Overall carer disutility = 0.825- 0.78= 0.045

Technical team:

- Potentially appropriate to include more than 1 carer
- Company's vignette study may overestimate carer QoL (not validated by Campbell)

⊙ *Should the model include carer quality of life? If so, how many carers?*

⊙ *Would this differ for children and adults? Are the company's values appropriate?*

Whether to model median or mean body weight

CBD dosing and cost depend on body weight

Background	ERG and Stakeholders	Technical team
Company used median rather than mean body weight in the model **Company** justifies this: • to account for the asymmetric weight distribution because of outliers	**ERG:** • Median weight underestimates the mean • Not reasonable to use median • Mean dosage must depend on mean weights and outliers are part of this	• Not appropriate to use median weight

⊙ *Is the company's use of median weight appropriate?*

[redacted]

Is company's model outcome credible?

ERG

- When setting company's model to same input values for both treatment with and treatment without CBD, model output favours CBD
- 'Lack of symmetry'
  - Company should identify what causes this asymmetry and justify or remove reason
  - May be "unexplained" features of model code

Company

- Notes it provided settings where QALY gain equal for both arm
  - **ERG:** these apply only to specific settings and should apply in base case

⊙ *Are the model outputs credible?*
⊙ *Is the model 'fit for purpose'?*

Company assumes that CBD lengthens life

- CBD not associated with longer life in trials, but company proposing that CBD lengthens life
- Company assumes that:
  - People with seizures have a higher death rate than general population
  - People without convulsive seizures have same death rate as people without any type of seizure (from Cooper et al)

- *Is there evidence that preventing seizures in epilepsy prolongs life?*
- *Is it reasonable to assume that seizure frequency is associated with an increased risk of death?*

[redacted]

Other issues considered during technical engagement

Issue	Updated base case?
Current clinical management should be based on trials rather than company survey/clinician advice	Yes
Company assumed everybody who stays on CBD would be on 10mg/kg/day dose for duration of model but average dose in open label study higher than that	No
Company used 15 years time horizon in base case but lifetime more appropriate as mortality benefit expected	Partially – 50 years
Company adjusted literature values to estimate the mortality in each seizure state in the model; there is no evidence for this	Yes
Health effects of adverse events should be captured in model, but impact on cost-effectiveness results is likely to be small	No
Discontinuation rates used by the company after cycle 1 not informed by evidence and lacked face validity – prefer ERG approach	Yes
Cost of ketogenic diet and vagus nerve stimulation not in model – unlikely to have large impact on cost effectiveness estimates	No
Resource use, for the “seizure-free” health state may be underestimated as it is not completely seizure-free and dose not include monitoring cost – not expected to have a large effect on cost effectiveness estimates	No

Innovation and Equality

Innovation

- **The company** considers the drug to be innovative.
- **Clinical experts** advise that it will be an addition to the currently available anti-epileptic drugs and unlikely to represent a step change in treatment since no patient in any of the included trials achieved complete freedom from seizures.

Equality

- Comments from stakeholders during scoping noted that there was often difficulty in accessing treatment as an adult, particularly where drugs were not licensed for adults – despite there being no difference in the condition

⊙ *Is cannabidiol innovative*
⊙ *Any equality issues?*

Cost effectiveness results

- The company have provided updated results from subgroup taking clobazam
  - not validated by ERG
- Company's patient access scheme has not yet been approved
- Results illustrate the potential effect of changes to assumptions used in the model

[redacted]

Company's updated base case

Included some but not all of technical team's preferred assumptions

Technical team preferred assumptions	Included?
Mix of anti-epileptic drugs in comparator arm based on that in the GWPCARE trials	Y
Same mortality rate in all health states except seizure-free state	Y
Dose of concomitant anti-epileptic drugs is stable	Y
Stopping rule aligned with that proposed by NHS England	Y
Include impact of adverse events on quality of life in model	N
Mean rather than median body weight	N
Relative efficacy estimates constant over model time horizon	N
Equal number of days without convulsive seizures	N
Include waning of treatment effect	N
Using the average dose from the trials	N
Lifetime time horizon	N

[redacted]

Company's base case cost effectiveness estimates

clobazam subgroup with proposed discount

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental cost effectiveness ratio £/QALY
Usual care alone	£356,822	3.25	-	-	-
Cannabidiol + usual care	£395,585	4.68	£38,763	1.43	**£27,181**

[redacted]

Company's scenarios (1) – with proposed discount

Scenario	Rationale	Incremental costs	Incremental QALYs	ICER
Company's updated Base Case	-	£38,763	1.43	**£27,181**
Outcomes from GWPCARE1/2 applied for cycles 1-8 (ERG scenario) for both arms	Taking account of placebo effect	£35,100	1.20	£29,277
Long-term discontinuation rates increased from 5% to 10%	Capturing treatment effect waning	£29,633	1.26	£23,551
Include costs for dose increases	Dose escalation	£54,007	1.37	£39,305
Utilities from Verdian (LGS)	Alternative utilities	£38,763	1.15	£33,774

⊙ *Which scenarios are relevant?*

Abbreviations: LGS, Lennox-Gastaut syndrome

Company's scenario analyses (2)

Potential impact of uncaptured benefits of fewer non-convulsive seizures

Increase in QALY-gain	QoL reduction per person*	Incremental costs	Incremental QALYs	ICER
0% (base case)		£38,763	1.43	**£27,181**
5%	0.030	£38,763	1.50	£25,893
10%	0.065	£38,763	1.57	£24,709
20%	0.013	£38,763	1.71	£22,649

As the uncaptured QALY gain increases, the ICER decreases

⊙ *Is the impact of this uncaptured benefit on cost effectiveness meaningful?*

[redacted]

ERG base case

ERG presented 2 base cases:

1. Assuming a constant treatment effect after 27 months (as company)
2. Assuming no treatment effect after 27 months (as no evidence after this)

Other ERG preferred assumptions have since been incorporated by the company into their updated base case except:

- ERG used mean rather than median weight (increases ICER)
- ERG did not include carer quality of life impact (large effect on ICER)
- ERG assumed number of days without seizures in each health state did not depend on treatment (small effect on ICER)

[redacted]

Technical team's preferred assumptions

- Many of the technical team's preferred assumptions could not be implemented in the model
- Assumptions which are expected to substantially increase the cost-effectiveness estimates are in **bold**
  - Mean rather than median body weight
  - Lifetime time horizon
  - Equal number of days without convulsive seizures
  - **Relative treatment effect maintained for whole time horizon**
  - **Decrease in treatment effect over time**
  - **Costs included for dose increases – proportion of people increasing aligned with clinical opinion**

[redacted]

Summary of key issues

- Indicated for people taking clobazam only
- Is the stopping rule modelled by the company appropriate?
- Are there important quality of life benefits not captured relating to reduced ‘non-convulsive’ seizures?
- Does the model correctly capture the relative treatment effect of cannabidiol compared with usual care?
- Do the results of GWPCARE5 reflect the maintenance dose?
- Do rates of discontinuing treatment ‘capture’ waning of treatment effect through discontinuation rates?
- Are the quality of life values plausible?
- Should the effect on carer’s quality of life be captured in the model?
- Does the company’s model generate reliable results?
- Any equality issues?