NICE National Institute for Health and Care Excellence

Confidential information redacted

Cannabidiol for Lennox-Gastaut Syndrome

Lead Team Presentation

1st appraisal committee B meeting

Chair: Amanda Adler

Lead team: Mark Chapman, Megan John, Tony Wootton

Technical team: Dalia Dawoud, Ross Dent, Nicole Elliott

Company: GW Pharma

ERG: Kleijnen Systematic Reviews

30 July 2019

Background – Lennox Gastaut Syndrome

- Severely debilitating, lifelong and treatment-resistant form of epilepsy
- Triad of seizures (multiple types), characteristic waves on electroencephalogram (EEG) and cognitive impairment
- Rare: prevalence 2 in 10,000 children from two years of age
- Symptoms include sudden drop seizures which cause injuries; patients may wear helmets
- Status epilepticus can occur
- Seizures increase cognitive impairment which can be associated with behavioural problems.
- High risk of sudden unexpected death in epilepsy
- A US study estimates all-cause mortality to be 14 times that of the general population

[redacted]

Patient and carer perspectives

- **High unmet need**
  - Limited treatment options. Anti-epileptic drugs are largely the same
  - LGS severely impact quality of life of patients and caregivers
  - The ideal is freedom from seizures, but this is rarely achieved with current treatments.
- **Co-morbidities are important**
  - “Severe learning difficulties” and “complex health needs”
  - Wider effect of seizures lead to other health problems
- **Substantial impact on carers**
  - “the impact on our mental health and wellbeing has been significant”
  - Parent carer reported “recent bought of serious ill health attributable in part to a weakened immune system” they link to the exhaustion of caring for their child

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) adopted positive opinion on 26 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)

Trials offered higher dosages than license permits

Marketing authorisation	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.
Mechanism of action	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 of CBD is [redacted] per 100 ml (100 mg/ml) bottle. Company 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 expected August 2019

[redacted]

Company original decision problem

	NICE scope	Company
Population	Seizures inadequately controlled by established clinical management	• seizures inadequately controlled by current or prior established clinical management, or • where current clinical management is unsuitable or not tolerated • Essentially, failure of adequate trial of 2 tolerated and appropriately chosen drugs as monotherapies or in combination
Comparator	Established clinical management without cannabidiol, which may combine • sodium valproate • rufinamide • felbamate • levetiracetam • lamotrigine • lamotrigine • topiramate • clobazam • 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	• drop/overall seizure frequency • proportion of people drop seizure-free • no. with episodes of status epilepticus • mortality • adverse effects of treatment • health-related quality of life • Caregiver Global Impression of Change and Change in Seizure Duration

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 (table of transition probabilities 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

First line therapy
Sodium valproate

Adjunctive therapy
Lamotrigine

Subsequent adjunctive therapy
Rufinamide

Other adjunctive therapies
Topiramate, Clobazam, Felbamate

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

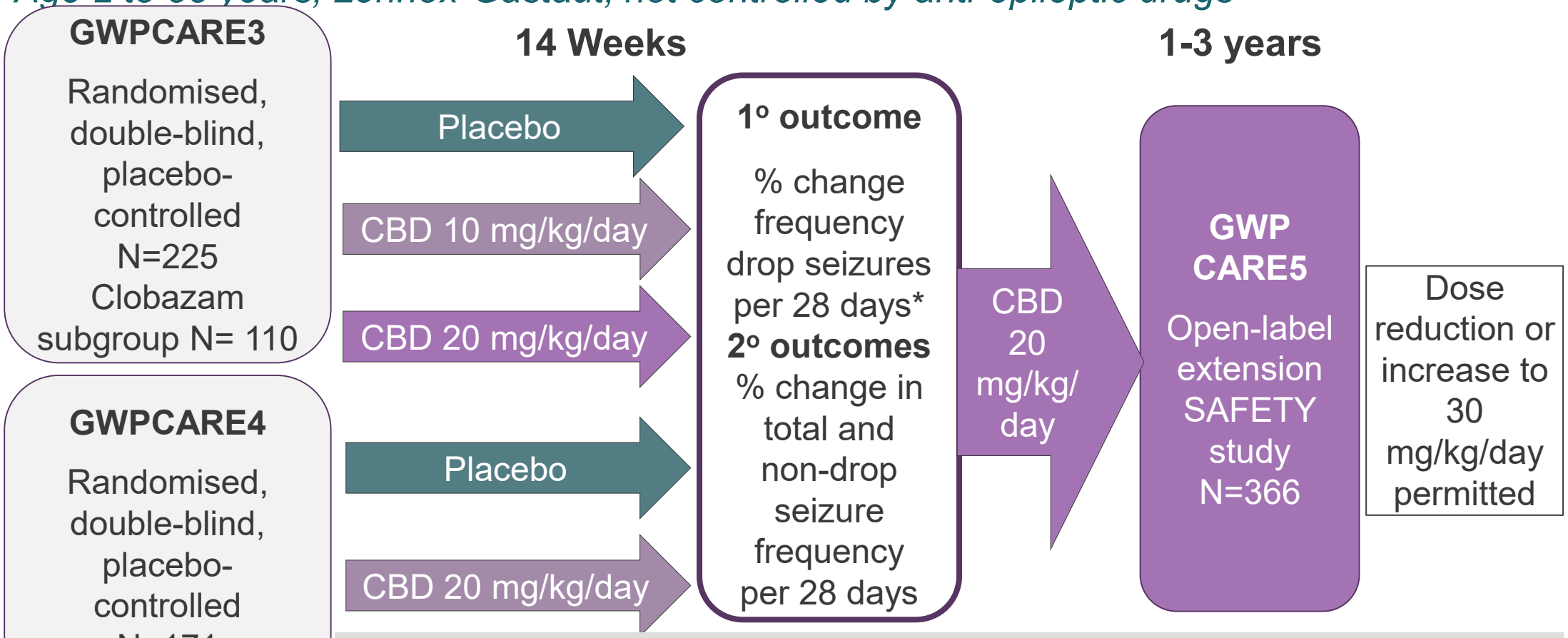
◉ Technical team concluded the company's positioning of cannabidiol is appropriate – does the committee agree?

Studies and relation to company's model

	GWPCARE3 Controlled trial	GWPCARE4 Controlled trial	GWPCARE5 Uncontrolled follow-up	Used in model?
Population	Aged 2 to 55 incompletely controlled on 1 or more drugs, with ≥2 drop seizures/week	Aged 2 to 55 not responded to treatment with ≥2 drugs with ≥2 drop seizures/week	All patients in either Dravet Syndrome or Lennox Gastaut trials	Yes. Total population and subgroup on clobazam
Intervention	CBD10 + usual care, CBD20+ usual care			Partly. CBD 10
Comparison	Placebo + usual care		No control group	Yes. Usual care
1º outcome	% reduction drop seizures /28 days		Adverse events	Yes
Other outcomes	% reduction in total seizure non-drop seizure		% 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	-
Costs	No	No	No	Values from lit. and experts

2 trials + 1 follow-on: GWPCARE3, 4 and 5

Age 2 to 55 years, Lennox-Gastaut, not controlled by anti-epileptic drugs



**Drop seizure definition:*
GWPCARE3 'atonic, tonic or myoclonic or absence seizures that would lead to a fall if not supported. GWPCARE4 'attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.'

Abbreviations: CBD, cannabidiol

◉ ***Are drop seizures defined similarly in each trial? Appropriate to combine placebo data?***

Baseline characteristics- full population

2 trials recruited patients whose seizures inadequately controlled with a median of **3** AEDS and who had tried a median of **6** AEDs in the past

	GWPCARE3			GWPCARE4	
	CBD 10	CBD 20	Placebo	CBD 20	Placebo
n	73	76	76	86	85
Mean age, SD Range	15.4 (9.5) 2.6 to 42.6	16.0 (10.8) 2.6 to 48	15.3 (9.3) 2.6 to 43.4	15.5 (8.7) 2.7 to 39	15.3 (9.8) 2.8 to 45.1
Gender: % male	40	45	44	45	43
Ethnicity: % white	56	73	69	75	79
Baseline frequency/ 28 days: median (Interquartile range)					
Total seizures Drop seizures Non-drop seizures	165 (81 to 359) 87 (41 to 190) 96 (14 to 280)	174 (83 to 392) 86 (38 to 162) 94 (22 to 278)	181 (90 to 431) 80 (48 to 148) 78 (22 to 216)	145 (72 to 386) 71 (27 to 156) 94 (20 to 311)	177 (69 to 360) 71 (47 to 144) 85 (21 to 220)
Number of prior Anti-epileptic drugs (AEDs)					
Median Range	6 0 to 21	6 1 to 18	6 1 to 22	6 1 to 18	6 0 to 28
Concurrent AEDs					
Median Range	3 1 to 5	3 0 to 5	3 1 to 5	3 1 to 5	3 1 to 4

Results of key clinical trials- Full population

Drop seizures reduced with cannabidiol; control group also improved

	GWPCARE3			GWPCARE4	
	CBD 10 + CCM	CBD 20 + CCM	Placebo + CCM	CBD 20 + CCM	Placebo + CCM
n	73	76	76	86	85
1º outcome- drop seizure frequency per 28 days					
Baseline, median	86.9	85.5	80.3	71.4	74.7
Treatment period, median	50.0	44.9	72.3	31.4	56.3
% change + IQR	-37.2 -63.8 to -5.6	-41.9 -72.4 to -1.3	-17.2 -37.1 to 0.9	-43.9 -69.6 to -1.9	-21.8 -45.7 to 1.7
Difference compared to placebo, 95% CI	-19.2 % -31.2 to -7.7	-21.6% -34.8 to -6.7	N/A	-17.2% -30.3 to -4.1	

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

Abbreviations: CBD, cannabidiol; CCM, current clinical management; CI, confidence interval

Results of key clinical trials- subgroup on clobazam

Data in red box used to derive transition probabilities in model

Drop seizures reduced with cannabidiol; Trials show no decrease in mortality or increase in quality of life

		Subgroup With Clobazam	N
Outcome: DROP SEIZURES PER 28 DAYS			
Measure: % Reduction from Baseline			
GWPCARE3	**Placebo**	[redacted]	[redacted]
	CBD 10	[redacted]	[redacted]
	CBD 20	[redacted]	[redacted]
GWPCARE4	**Placebo**	[redacted]	[redacted]
	CBD 20	[redacted]	[redacted]
Difference or % Reduction Compared with Placebo (95% CI*), p-value			
GWPCARE3	**CBD 10**	[redacted]	
	CBD 20	[redacted]	
GWPCARE4	**CBD 20**	[redacted]	

Abbreviations: CBD, cannabidiol; CCM, current clinical management; CI, confidence interval *Rounded

Results of key clinical trials

subgroup on clobazam

- **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

◉ Is cannabidiol effective for this subgroup?
◉ Is the subgroup analysis sufficiently powered?

Abbreviations: CBD, cannabidiol; CI, confidence interval;

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	Stakeholders	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 the frequency of target seizure types (i.e. drop 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-drop seizures

- Non-drop seizures and total seizures 2^{o} outcomes in trials
- 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-drop seizures

Technical team:

- Benefits of fewer non-drop seizures difficult to capture in model
- Model may exclude benefit

Non-drop seizures not in model

2º Outcome		Subgroup With Clobazam	N
Outcome: TOTAL SEIZURES PER 28 DAYS			
Measure: % Reduction from Baseline			
GWPCARE3	Placebo	[redacted]	[redacted]
	CBD 10	[redacted]	[redacted]
	CBD 20	[redacted]	[redacted]
GWPCARE4	Placebo	[redacted]	[redacted]
	CBD 20	[redacted]	[redacted]
Difference or % Reduction Compared with Placebo (95% CI), p-value*			
GWPCARE3	CBD 10	[redacted]	
	CBD 20	[redacted]	
GWPCARE4	CBD 20	[redacted]	

Abbreviations: CBD, cannabidiol; CI, confidence interval, *Data for the with clobazam subgroup are estimated from a negative binomial regression analysis.

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

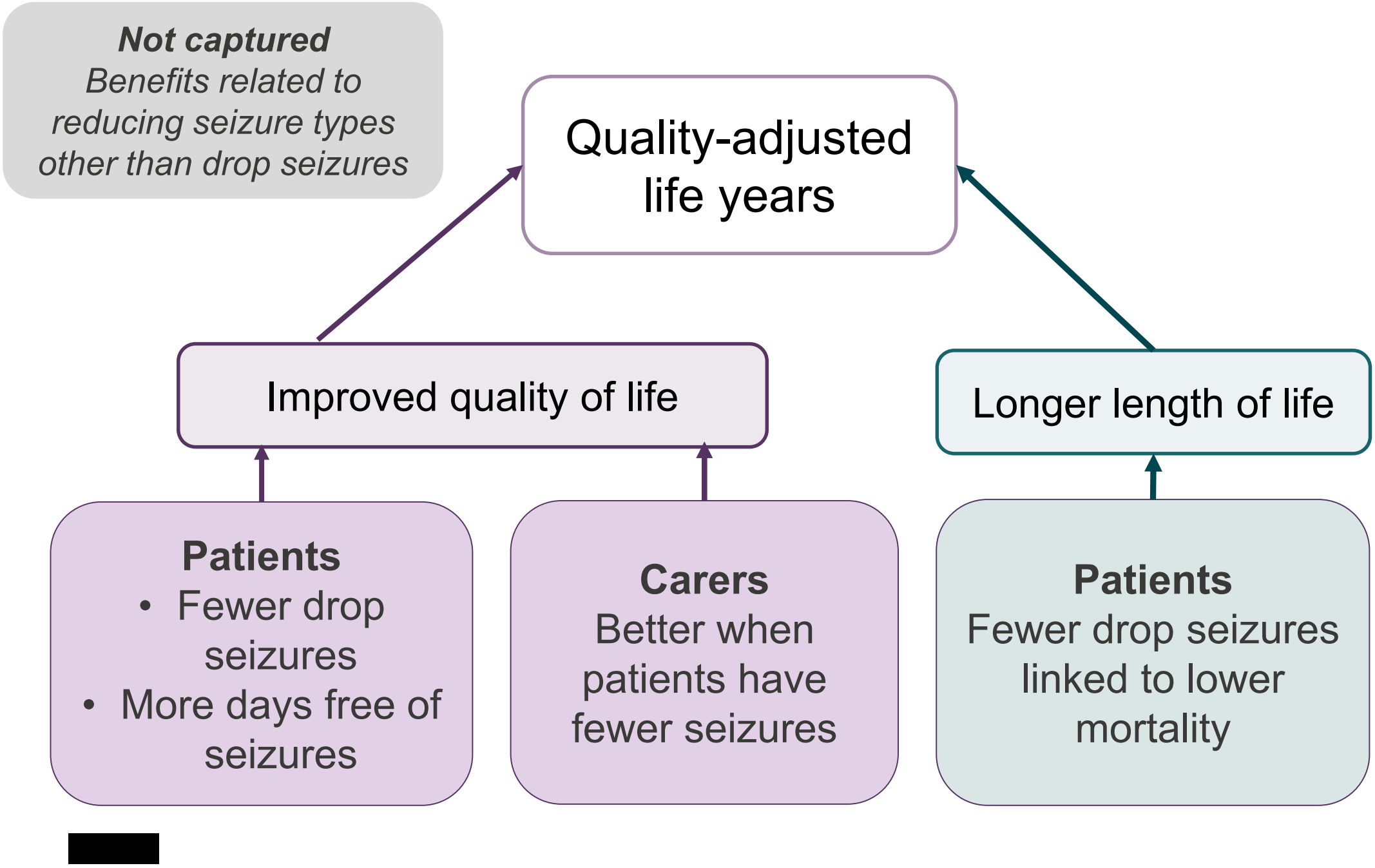
Doses higher in open label extension study than in license and company's model

Background	ERG and Stakeholders	Technical team
• Company used data from GWPCARE5 for months 6 to 27 in the model • Average dose in GWPCARE5 > maintenance dose company models (CBD 10) **Company justifies this:** • Subgroup analysis in full population shows no "significant difference" in the 1º and 2º endpoints between low dose (≥[redacted] to[redacted] mg/kg/day), high dose (≥[redacted]to <[redacted]mg/kg/day) 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/day) → does not prove or disprove a dose response relationship Might overestimate CBD treatment effect **Scenario analyses:** • Models cost of the higher dose • Efficacy based on GWPCARE3 **Clinical experts** Could not state definitively whether high dose comparable to lower doses	• Likely to be no dose response on average • GWPCARE5 likely to be the best source of data to use in model

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

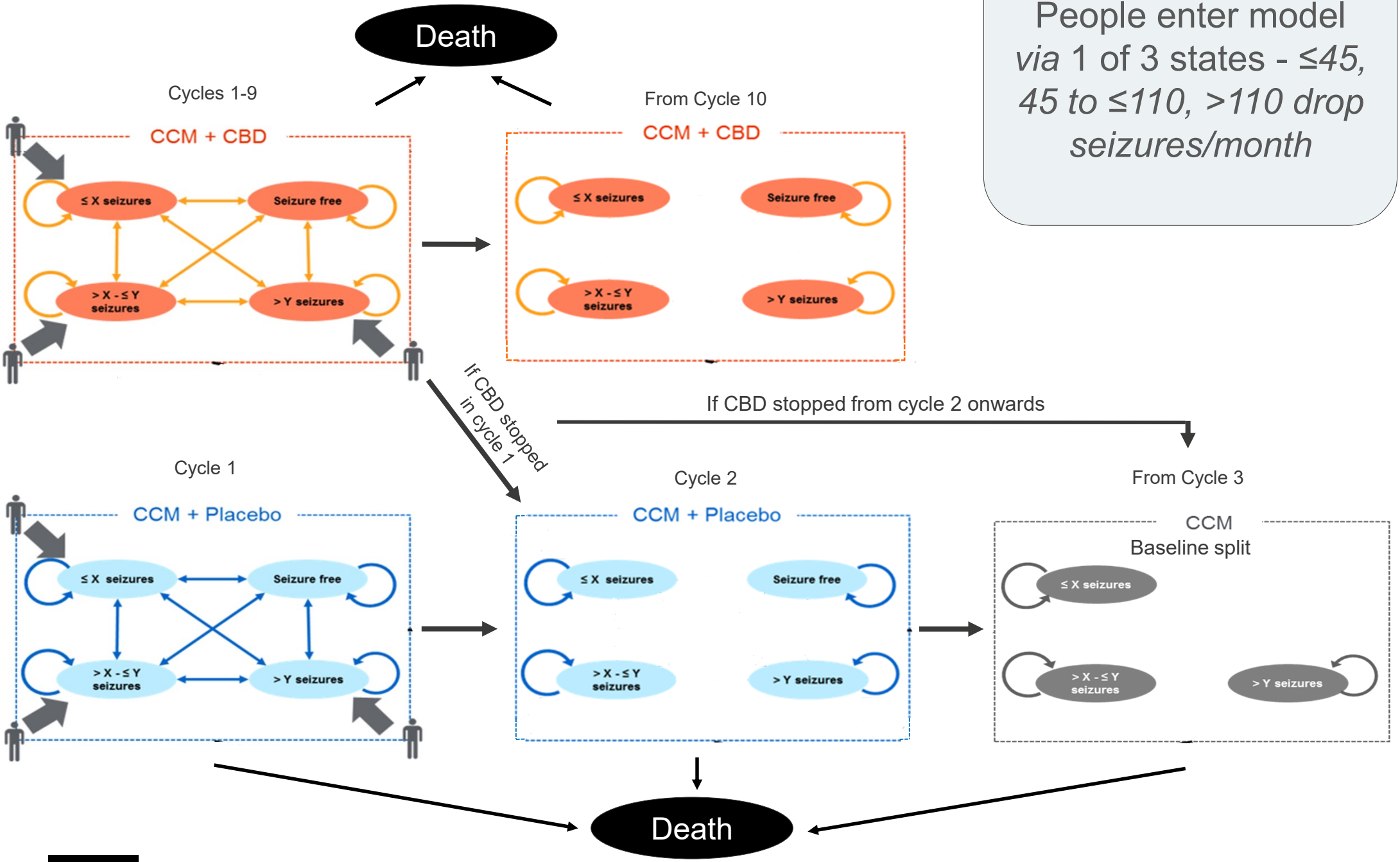
Cost effectiveness

Overview: how quality-adjusted life years accrue



Company's model structure

People enter model *via* 1 of 3 states - ≤45, 45 to ≤110, >110 drop seizures/month

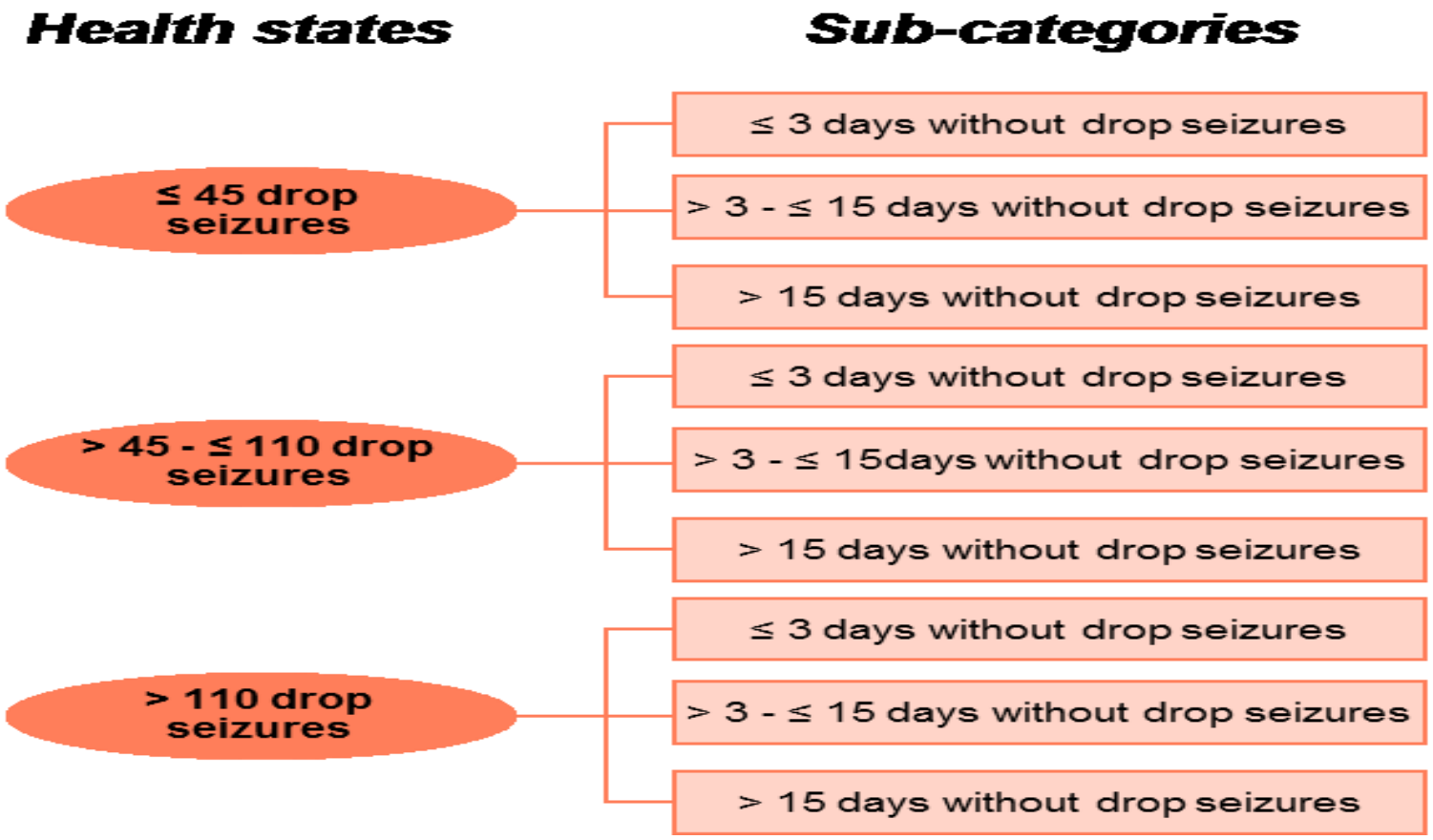


[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management

Company's model structure

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



All patients in the drop 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 3 and 4

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 CCM
- Discontinuation rates
- Adverse event probabilities

Company Survey

Vignette Study

Survey of people with Lennox-Gastaut + 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 Lennox-Gastaut Syndrome

Parameters in model

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

[redacted]

Abbreviations: CBD, cannabidiol; CCM, current clinical management; SUDEP, sudden unexpected death in epilepsy

Modelling days without drop seizures

Background	ERG and Stakeholders	Technical team
Company assumes CBD improves quality of life by: 1. Reducing number of drop seizures **and** 2. Increasing number of days free of drop seizure In model: patients on CBD are allocated to sub-states with more drop 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 drop seizures	• Not appropriate to assume that the number of days without drop seizures will depend on treatment allocation → number of drop 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 drop seizures?*
- *Does this 'double count' benefits from lowering the frequency of seizures?*

Abbreviations: CBD, cannabidiol; CCM, current clinical management

Relative treatment effect

Company did not consistently model relative treatment effect

Background	ERG and Stakeholders	Technical team
• Large placebo response in the trials • Company excludes 'placebo effect' in comparator arm after 2 cycles (6 months) in its latest base case (**see next slide**) **Company** justifies this noting: • Placebo effect higher than other trials in LGS • Consistent reduction in seizures of 40-50% across trials • **Scenario analysis:** GWPCARE 3 and 4 outcomes used for 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 • Scenario analysis does not maintain relative treatment effect of CBD over time, so may disfavour CBD

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

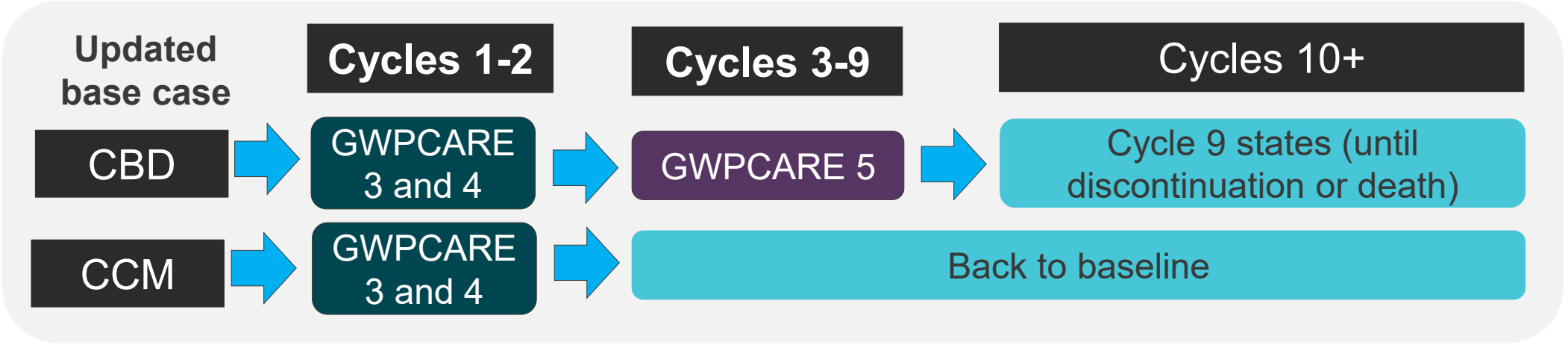
Abbreviations: CBD, cannabidiol; ICER, incremental cost-effectiveness ratio

Relative treatment effect

GWPCARE 3 and 4
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



[redacted]

Extrapolating effect of CBD beyond end of studies

Background	ERG and Stakeholders	Technical team consideration
Company assumes that: • After 27 months patients remain in same health state until they stop CBD or die • Discontinuation rates captures waning of treatment effect • In base case, continuation is: • **■% of patients on treatment at 3 years, and ■% at 5 years** • **Scenario analysis**: long-term discontinuation rate increases from ■% to ■% 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 after 2 years → long-term efficacy is key source of uncertainty in the model • Company's scenario analysis is 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 CBD 20 • **Scenario analysis:** Model dose of [redacted] weighted 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	ERG and/or stakeholders	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 Lennox Gastaut Syndrome and carers **(next slide)**	**ERG** • Company overestimates utility values for health state reflecting freedom from drop-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 did visual analogue scale not time trade off • Company provided **scenario analysis** using utility values from Verdian et al → 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

Company's base case utility values

Number of drop seizures	Number of seizure free days	Mean quality of life scores
No seizures	No seizures	[redacted]
≤ 45 seizures	≤ 3 drop seizure-free days	[redacted]
	>3 to ≤15 drop seizure-free days	[redacted]
	> 15 drop seizure free days	[redacted]
>45 to ≤ 110 seizures	≤ 3 drop seizure-free days	[redacted]
	>3 to ≤15 drop seizure-free days	[redacted]
	> 15 drop seizure free days	[redacted]
> 110 seizures	≤ 3 drop seizure-free days	[redacted]
	>3 to ≤15 drop seizure-free days	[redacted]
	> 15 drop seizure free days	[redacted]

⊙ *Are these quality of life values plausible?*

Company's scenario

Verdian et al 2018 Quality of life values

TTO	**21-28 seizures /wk (anchor)**: 0.393 **<50% reduction**: 0.461 **≥50% and <75% reduction**: 0.605 **≥75% reduction**: 0.699
EQ-5D VAS	**21-28 seizures /wk**: 0.02 **<50% reduction**: 0.414 **≥50% and <75% reduction**: 0.556 **≥75% reduction**: 0.677
EQ-5D Index	**21-28 seizures/wk**: 0.02 **<50% reduction**: 0.100 **≥50% and <75% reduction**: 0.500 **≥75% reduction**: 0.596

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	-
≤45	-
>45 to ≤110	[redacted]
>110	[redacted]

Clinical experts:

- Child with LGS 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 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-drop seizures in descriptions → may incorrectly estimate carer decrements
- 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 decrements (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 with seizures and LGS have same death rate as people with seizures and Dravet syndrome (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 and company has not provided analysis at list price
- 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 drop seizures	N
Include waning of treatment effect	N
Using the average dose from the trials	N
Lifetime time horizon	N

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	£188,438	-1.35	-	-	-
Cannabidiol + usual care	£240,956	0.45	**£52,519**	**1.79**	**£29,280**

*Note: the QALY change in patients on usual care without CBD is spread across the patient and an average of 1.8 caregivers over 50 years.
It does not represent a worse-than-death outcome for any individual

[redacted]

Company's scenarios (1) – with proposed discount

Scenario	Rationale	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company's base Case	-	**£52,519**	**1.79**	**£29,280**
Outcomes from GWPCARE3/4 applied for cycles 1-9 for both arms	Alternative approach to account for placebo effect	£44,404	1.19	£37,224
Long-term discontinuation rates increased from 5% to 10% per cycle for all health states other than drop-seizure free	Capturing treatment effect waning	£41,665	1.57	£26,475
Include costs for dose increases	Capture dose escalation	£61,497	1.80	£34,228
Utilities from Verdian 2018	Published utility values for LGS	£52,519	1.48	£35,552
Caregiver disutilities from Campbell 2018	Published carer utilities	£52,519	1.77	£29,704

⊙ *Which scenarios are relevant?*

[redacted]

Company's scenario analyses (2)

Potential impact of uncaptured benefits of fewer non-drop seizures

Increase in QALY-gain	Equivalent QoL reduction per person	Incremental costs	Incremental QALYs	ICER
0% (base case)		**£52,519**	**1.79**	**£29,280**
5%	1.88	£52,519	2.45	£27,885
10%	1.97	£52,519	2.57	£26,617
20%	2.15	£52,519	2.80	£24,406

As the uncaptured QALY gain increases, the ICER decreases

- *What is the likely impact on cost effectiveness of having excluded non-drop seizures?*

[redacted]

ERG base case

ERG presented 2 base cases for the overall population (**not the licensed indication population**):

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 drop 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-drop’ 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 valid results?
- Any equality issues?

[redacted]