Cannabidiol for treating seizures caused by tuberous sclerosis complex

For public, **no** academic or commercial in confidence information

Technology appraisal committee B [15th September 2022]

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Company: GW Research

NICE National Institute for Health and Care Excellence

Background, tuberous sclerosis complex

Multifaceted disease with no cure; seizures most common neurological symptom

Definition: rare genetic disorder characterized by growth of numerous noncancerous tumours (tubers) in many parts of body

- Most commonly affects:


Brain

Eyes

Kidneys

Heart

Lungs

Skin

Caused by: Mutations in TSC1 / TSC2 gene involved in cell growth regulation

Symptoms: Condition present from birth but symptoms may not immediately appear.

- Heterogeneity in presentation dependant on organ affected
- Tumour formation in brain can disrupt neurological connections leading to seizures
  - Epilepsy most common neurological symptom – up to 84% of people with TSC †
  - People with refractory epilepsy at high risk of TSC-associated neuropsychiatric disorders (TAND):
    - umbrella term for range of cognitive, behavioural, and psychiatric manifestations with significant QoL impact

Aim of treatment: No cure for TSC-associated epilepsy: treatments aim to manage symptoms but some limit tumour growth

Mortality: Data limited, but reduced life expectancy linked to TSC-associated epilepsy due to status epilepticus (prolonged seizure or many in quick succession) or Sudden Unexpected Death in Epilepsy (SUDEP).

- Complications in kidneys, lung and brain can also be life threatening if untreated.

Prevalence: TSC estimated 1 in 18,861*; estimated 1555 people have refractory TSC-associated epilepsy in England†

Source: *company submission, average of publicly available prevalence figures; † Chu-Shore et al. (2010)

Seizures in TSC-associated epilepsy

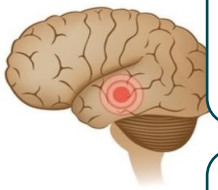
High variability of seizure type and burden depending on tuber location

- 80% of people with TSC-associated seizures diagnosed within their first 2 years: small proportion of people have seizure onset in adulthood

Increasing burden and clinical challenge

Focal onset seizures: starts in 1 side of brain

>68% of patients with TSC-associated epilepsy at initial presentation



Focal aware

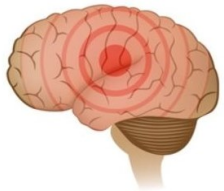
- Awareness during seizure retained
- Brief seizures, lasting <2 minutes

Focal impaired awareness*

- Reduced awareness during seizure
- Unable to respond, no memory of seizure

May progress to generalised seizures: affects both sides of brain*

Usually results in loss of consciousness, includes



- Tonic: generalised muscle stiffening
- Clonic: rhythmical jerking of arms/legs
- Atonic: loss of muscle tone (usually leading to falls)
- Tonic-clonic (2-phase seizures)
- Focal onset seizures evolving to bilateral tonic-clonic

Most severe: high morbidity, mortality

Infantile spasms:

occur in ~40% of patients with TSC-associated epilepsy within 1st 3-8 months

- Later transform into other seizure types

Clinical experts

- High variability in seizure type, severity and frequency in TSC
- Almost any type of seizure possible: depends on tuber location in brain

*seizure types considered in the company's decision problem

Patient perspectives: Tuberous Sclerosis Association

High quality of life impact for patients and families; unmet need for effective treatments

Impacts the whole family *"both mentally and physically"*

- Seizures can be traumatic and dangerous for patients
- 30% have severe intellectual disability requiring life-long "*round-the-clock care*" (carer or residential facility)
  - Challenging to manage TAND related symptoms: "*anger and mood swings*"; "*no concept of danger*"
  - Brain damage can cause mobility issues that limit daily activity
  - Financial implications for carers: many cannot work as some patients are "*not able to live independently*"
- Traumatic for siblings to observe seizures; normal family activities affected by behavioural issues

Unmet need for treatments to control seizures and behaviour problems

- Current options inadequate:
  - Not uncommon to try up to 20 drugs: short duration of seizure control
  - Often cause intolerable side effects (involuntary movements, aggression, drowsiness)
- TSC-associated epilepsy generally hard to control due to learning disabilities

Cannabidiol a welcome treatment option

- Reduced seizure severity and frequency (alone or with clobazam) can '*transform*' patient QoL: improve mood & sleep
- Improved mental health of whole family: seizure freedom allows normal activities
- Non-toxic, temporary side effects: AEs can be controlled with dose reduction
- Tolerable to take orally

AE, adverse effect; ASM, anti-seizure medication; TAND, TSC-Associated Neuropsychiatric Disorders

Clinical perspectives: Association of British Neurologists

Pathway poorly defined; complex to define response to treatment

Multifactorial disease with significant QoL impact

- TAND complications (cognitive impairment, behavioural difficulties) can be hard to manage
- Risk of injury from seizures and falls, increased risk of SUDEP
- Refractory TSC epilepsy should initially be managed at a tertiary centre by a MDT including renal and epilepsy input (potential follow up in secondary care)

Defining treatment response is complex

- Seizure freedom key outcome: rarely achieved in people with TSC
    - Defining response as 30% reduction in disabling seizures after 6 months at stable dose acceptable (as TA614 and TA615)
    - Reduction of tonic-clonic seizures can reduce SUDEP

Cannabidiol would provide an additional ASM to use adjunctively

- May need additional monitoring at initiation:
    - can increase exposure to current ASMs (requiring dose adjustment)
- Side effects: most commonly diarrhoea, vomiting, fatigue, pyrexia, somnolence, and abnormal liver-function tests
- Cannabidiol not tested against other individual ASMs in clinical trials

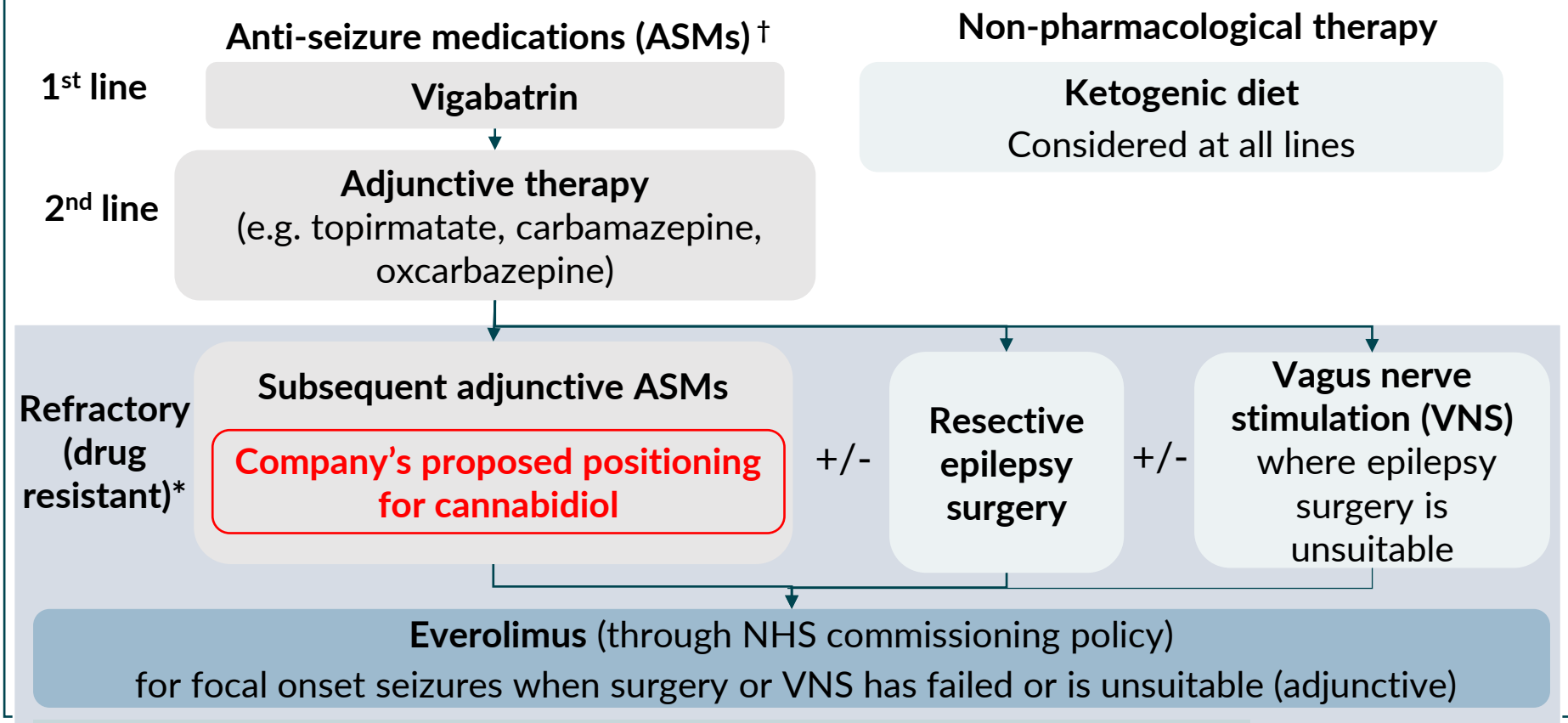
ASM, anti-seizure medication; QoL, quality of life; SUDEP, Sudden unexpected death in epilepsy; TA, technology appraisal; TAND, TSC-Associated Neuropsychiatric Disorders

Treatment pathway

Main refractory epilepsy treatment is combinations of ASMs +/- surgery and vagus nerve stimulation

- NICE Guideline 217 (epilepsy in children, young people and adults) has no specific recommendations for TSC-associated seizures. Clinical guidelines from the European Consensus Meeting recommend:

Figure 1 Treatment pathway for TSC



Clinical experts

- Pathway not well defined:
- No specific guidelines for TSC-related seizures:
  - Clinicians try combinations of several common ASMs
- May use cannabidiol in people assessed for surgery; except in people with multifocal seizures
- Use with clobazam not mandated in licence but likely added if poor response to cannabidiol in clinical practice

How would you define refractory TSC-associated epilepsy?
Would cannabidiol ever be used in non-refractory epilepsy?
Would cannabidiol be used before surgery and VNS?
Where does everolimus sit in the pathway?

**Defined by International League Against Epilepsy as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".* † Previous appraisals refer to anti-epileptic drugs (AEDs): ASMs used to align with terminology in updated clinical guideline. Source: adapted from company submission, Figure 3

Recent NICE appraisals for cannabidiol

Recommended with clobazam for treating seizures caused by Dravet and Lennox-Gastaut syndrome

No published NICE technology appraisals for TSC-related seizures, but cannabidiol recommended in 2 related indications

Table 1 Recent NICE appraisals

Technology appraisal	Intervention	Indication	Recommendation	Positioning
TA614 (published December 2019)	Cannabidiol with clobazam	Seizures associated with Dravet syndrome in people aged 2 years and older	Recommended as an option only if: • the frequency of convulsive seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment	After 2 ASMs to align with clobazam use in UK clinical practice
TA615 (published December 2019)	Cannabidiol with clobazam	Seizures associated with Lennox–Gastaut syndrome		

NICE

ASMs, anti-seizure medications

Cannabidiol (Epidyolex, GW Research Ltd)

Twice daily dosing including dose titration to maximum dose based on response

Table 2 Technology details

Marketing authorisation	MHRA approval received 5th August 2021 *"for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older"* • Also licenced with clobazam as adjunctive therapy for seizures associated with Lennox-Gastaut or Dravet syndrome

Mechanism of action	• Exact mechanism unknown: may reduce seizure frequency by controlling excitability of nerve cells through modulation of:
	  • intracellular calcium via GPR55 and TRPV-1 channels
	  • adenosine-mediated signalling via the ENT-1 transporter.

Administration	Oral solution, twice daily administration
Price	• List price: £850.29 per 100 ml (100 mg/ml) bottle • List price for 12 months of treatment (weighted by age): Year 1 £23,662, Year 2 £24,007* • A confidential patient access scheme is in place for this technology.

	Week 1	Week 2+	Increase in dose for inadequate response (week 2 onwards)
Dose, mg/kg/day*	5	10	Weekly increments of 5mg/kg/day to max 25mg/kg/day
*cumulative dose from twice daily administration			

How would cannabidiol dosing work in clinical practice? How would the maintenance dose be determined based on response?

*Source: company budget impact test. ENT, equilibrative nucleoside transporter; GPR, G protein-coupled receptor; TRPV, transient receptor potential vanilloid

Decision problem

Company excludes scoped comparator and includes additional population and outcomes

Table 3 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	ERG comments
Population	People with tuberous sclerosis complex (TSC) whose seizures are inadequately controlled by established clinical management.	Includes people with TSC **where usual-care is unsuitable or not tolerated** to align with the ILAE definition of 'refractory' epilepsy*	Company's updated wording differs from scope but unlikely to bias modelling
Comparators	Established clinical management without cannabidiol, such as: • Anti-seizure medications (ASMs) • Everolimus • Vagus nerve stimulation • Ketogenic diet • Surgical resection	Everolimus included as later line treatment but not comparator: in line with NHS England Clinical Commissioning Policy	Potential everolimus would form part of usual care in people where ASMs not tolerated
Outcomes	• Change in frequency of seizures • Response to treatment • Adverse effects of treatment • Health-related quality of life	Includes seizure-free days as outcome: • Important to patients • Modelled for cannabidiol appraisals in Dravet and Lennox–Gastaut syndrome	Cannot assume same outcomes relevant for different appraisals

*defined by the International League Against Epilepsy (ILAE) as *"failure of adequate trials of two **tolerated** and appropriately chosen and used anti-epileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom."*

Key issue: Population and comparators

Company's population includes 'people with TSC where usual care is unsuitable or not tolerated': not in scope

Company: Population same as scope: updated wording aligns with ILAE definition of refractory: *failure of adequate trials of two **tolerated** and appropriately chosen and used AED schedules….*

- May 'fail' drug due to side effects: No standard care if disease refractory

ERG comments

- Company misinterpreted ILAE definition: should be 'both tolerated *and* ineffective', not '*not* tolerated or ineffective'
- Usual care where ASMs not tolerated may differ from where ineffective: everolimus usual care in this population?

RECAP: population in

- ***Scope:*** *"People with tuberous sclerosis complex (TSC) whose seizures are inadequately controlled by established clinical management"*
- ***Licence:*** *"adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older"*

Clinical expert:

- Rare but may stop ASM due to side effects
- In clinical practice may try 5 or 6 different treatments before class refractory

Everolimus:

- only used in small number: not responded to ASMs & not eligible for surgery
- likely used after cannabidiol: more side effects and monitoring
- can shrink tubers: treats other aspects of TSC (kidney tumours, facial rash, SEGA): people with these symptoms have everolimus instead of cannabidiol

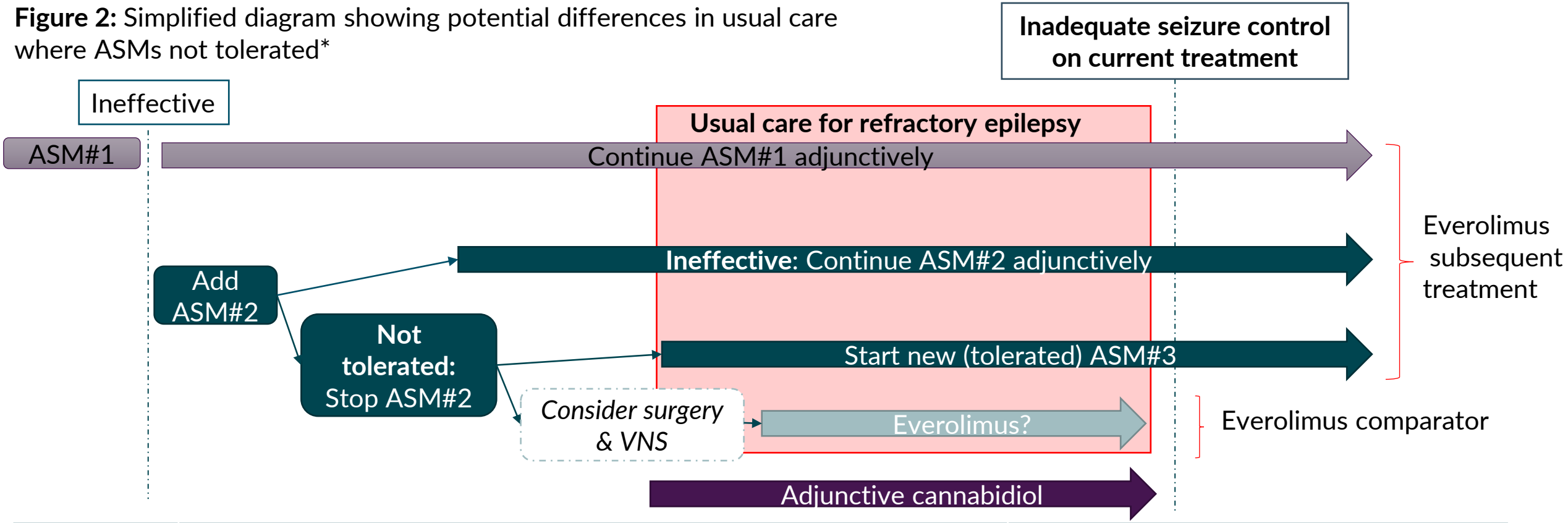
Is the distinction between not tolerated and not effective made in NHS clinical practice? If yes, how?
Are there defined therapeutic doses for ASMs?

AED, anti-epileptic drug; ASM, anti-seizure medication; ILAE, International League Against Epilepsy; SEGA, subependymal giant cell astrocytoma

Key issue: Population and comparators

Different ASMs in usual care at same point in pathway if earlier ASM not tolerated: different comparators?

Figure 2: Simplified diagram showing potential differences in usual care where ASMs not tolerated*



Stopping rules	Everolimus	Cannabidiol
	• IF frequency or severity of seizures not reduced by ≥50% at 28 weeks • OR unacceptable toxicity	• IF seizure frequency not ≥30% less than baseline (assessed every 6 months)

What is usual care in people who stop ASMs due to intolerance?

ASM, anti-seizure medication. *people likely on >2 ASMs in clinical practice.

Key issues: clinical effectiveness

Including population and comparators in UK clinical practice and generalisability of company's pivotal trial

Table 4 Key issues (1)

Key issue	Resolved?	ICER impact
Decision problem		
Population and relevant comparators	Partially – for discussion	Unknown impact
Quality-of-life instrument	Yes	-
GWPCARE6 trial		
Generalisability to NHS practice (usual care treatments, small UK population)	No – for discussion	Unknown impact
Between arm variations in usual care treatments	No – for discussion	Unknown impact
Systemic literature review		
Missing evidence from the SLR	Yes	-
Methodological uncertainties	Yes	-

Key: Discussion;

SLR, systematic literature review; UK, United Kingdom

Key issues: cost effectiveness

Uncertainty in many modelling inputs but many have limited effect on ICER; cannabidiol dose is model driver

Table 5 Key issues (2)

Key issue	Resolved?	ICER impact
Modelling cost effectiveness		
Variation in patient characteristics between age categories and impact on treatment costs	No – for discussion	Small
Average dose of cannabidiol	No – for discussion	Large
Modelling of seizure–free days	No – for discussion	Medium
Modelling TSC-associated neuropsychiatric disorders (TAND)	No – for discussion	Small
Utilities		
Comparability of patient utilities with other cannabidiol appraisals	No – for discussion	Unknown
Seizure-free health state utility value for caregivers	Partially – for discussion	Small
Application of caregiver disutilities	No – for discussion	Small
Health care resource use		
Comparability of resource use with literature and other cannabidiol appraisals	No – for discussion	Medium

Key: Model driver: >£10,000 per QALYS gain change from base case; Medium impact: £5,000- £10,000 per QALYS gain change from base case; Small impact: <£5,000 per QALY gained change from base case
Discussion

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials

Evidence for cannabidiol comes from RCT supported by ongoing observational data

Table 6 Clinical trial designs and outcomes

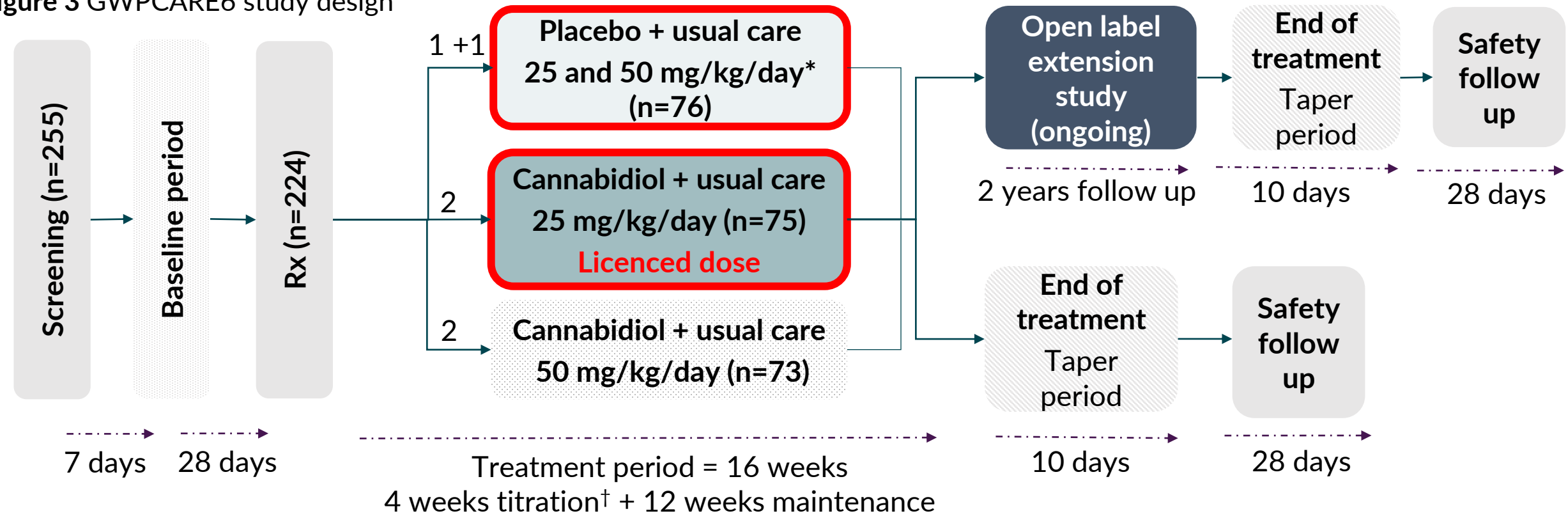
	GWPCARE6	GWPCARE6 OLE (ongoing)	EAP (ongoing)
Design	Phase 3 double-blind, randomised controlled trial	Open label extension of GWPCARE6	Open label expanded access programme
Population	1 to 65 years*; history of uncontrolled TSC-associated epilepsy with ASMs.	Completed GWPCARE6	US patients taking CBD for treatment-resistant epilepsy
Cannabidiol	25 mg/kg/day (n=75) and 50 mg/kg/day (n=73) with usual care	25mg/kg/day starting dose (n=199) with usual care	Individually optimised dose (max 25-50 mg/kg/day‡, n=34) with usual care
Comparator	Placebo with usual care (n=76)	None	None
Treatment	16 weeks	2 year follow up	Up to 4.5 years
1° outcome	% change in number of TSC-associated seizures during the treatment period	Incidence of adverse events	Unknown
Key 2° outcomes	• % 'responders'† • Δ in TSC-associated seizure-free days • % with AEs, any / treatment related SAE • Δ in S/CGIC score (QoL)	• Δ in seizure frequency (total and number per 28 days) • % 'responders'† • Δ in Overall condition and QoL	• Δ in seizure frequency • AEs and SAEs
In model?	**Yes –25mg/kg/day and pooled placebo data**	No	No

*Approved indication for Epidyolex is in patients aged ≥ 2 years. †Defined as ≥50% reduction in TSC-associated seizure frequency; ‡ max dose dependant on study site. AE, adverse event; CBD, cannabidiol; EAP, expanded access program; N, number; OLE, open label extension; QoL, quality of life; SAE, serious adverse event; S/CGIC, subject/ caregiver global impression of change; US, United States.

GWPCARE6 study design

16 week RCT comparing 2 doses of cannabidiol with placebo; only 25mg/kg/day data used in model

Figure 3 GWPCARE6 study design



Key inclusion criteria

- Stable on ≥1 ASM & other interventions (e.g. ketogenic diet and VNS) for 4 weeks
- ≥8 TSC-associated seizures in baseline period, with ≥1 seizure in ≥3 of 4 weeks
- No history of pseudo-seizures / illness in last 4 weeks that may affect seizure frequency
- No epilepsy surgery in prior 6 months / not being considered for surgery

Red = used in company's model.
*placebo doses pooled for analysis
† Incremental increase from starting dose 5mg/kg/day every 2 days by:

- 5 mg (up to 25 mg/kg/day)
- 2.5 mg (up to 50 mg/kg/day)

ASM, anti-seizure medication; Rx, randomisation. Source: adapted from company submission, Figure 5

GWPCARE6 baseline characteristics

ERG: several key issues with GWPCARE6 population affecting generalisability to UK clinical practice

Table 7 GWPCARE6 baseline characteristics

Characteristic	Placebo + usual care	CBD 25mg/kg/day + usual care
n	76	75
UK patients	3	2
Median age, year (minimum, maximum)	11 (1, 56)	12 (1, 57)
Number of ASMs, median (minimum, maximum)		
Previous	4 (0, 15)	4 (0, 13)
Current	3 (1, 5)	3 (0, 4)
Current AEDs (>20%), n (%)		
Valproic acid	35 (46)	29 (39)
Vigabatrin	17 (22)	28 (37)
Levetiracetam	24 (32)	19 (25)
Clobazam	25 (33)	17 (23)
Concomitant non-pharmacological therapies, n (%)		
Vagus nerve stimulation	8 (11)	10 (13)
Ketogenic diet	2 (3)	0 (0)
TSC-associated seizures per 28 days, median (Q1, Q3)	54 (26, 102)	56 (21, 101)

Based on company submission, Table 6

Key issue: Small number of UK patients

Key issue: Wide range of baseline ASMs

Key issue: Variation in vigabatrin use between arms

Potential issue: Variation in clobazam use between arms?

ASM, anti-seizure medications; CBD, cannabidiol

GWPCARE6 baseline characteristics

Patient characteristics and range of baseline ASMs in the study may not reflect UK clinical practice

Key issue: Small number of UK patients
Company: • HTA advisory board: generalisable to UK setting • TSC orphan disease: recruitment challenges • Baseline characteristics similar across locations • Inappropriate to compare UK trial patients to expected UK population /whole trial cohort: small sample size
ERG: UK baseline characteristics = only 3.3% total trial cohort Accept limitations of small population but: • Company didn't support generalizability of UK patients with published data • Baseline characteristics outside pre-defined diagnostic criteria may differ from UK clinical practice

Key issue: Wide range of baseline ASMs
Company: No standard care once patient refractory: cycle through many different ASMs • Usual care at clinician discretion in trial • Company experts: 'Basket' of usual care in GWPCARE6 aligned with clinical practice • Huge number of potential combinations: inappropriate to adjust for differences in usual care from NHS setting
ERG: • Relative treatment effect for cannabidiol may differ if background therapies in trial better/worse than clinical practice • More info on ASMs in trial useful
Clinical experts: • Usual to cycle through ASMs: individualised regimes of several drugs to achieve seizure control

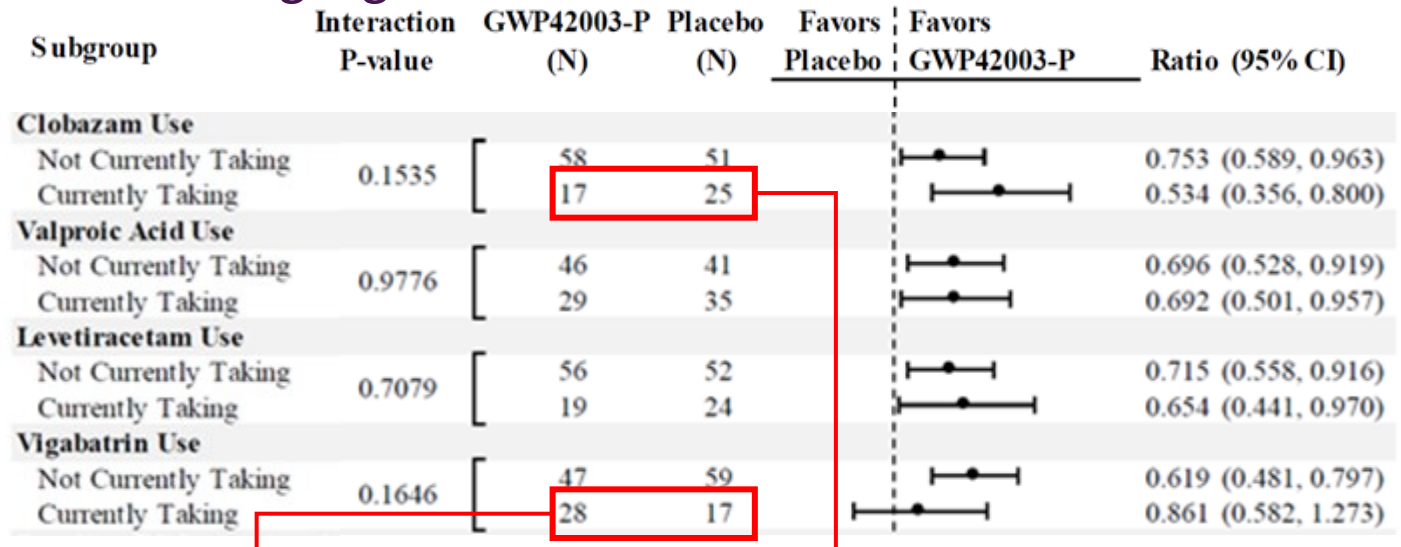
How does the trial population compare to the UK population with TSC?
How comparable are the treatments forming usual care between GWPCARE6 and NHS clinical practice?

ASM, anti-seizure medications; CBD, cannabidiol

Differences in usual care treatments between arms

Between arm variability in the number of people taking vigabatrin and clobazam in GWPCARE6

Figure 4 GWPCARE6 subgroup analyses



Subgroup	Interaction P-value	GWP42003-P (N)	Placebo (N)	Favors Placebo / Favors GWP42003-P	Ratio (95% CI)
Clobazam Use					
Not Currently Taking	0.1535	58	51		0.753 (0.589, 0.963)
Currently Taking		17	25		0.534 (0.356, 0.800)
Valproic Acid Use					
Not Currently Taking	0.9776	46	41		0.696 (0.528, 0.919)
Currently Taking		29	35		0.692 (0.501, 0.957)
Levetiracetam Use					
Not Currently Taking	0.7079	56	52		0.715 (0.558, 0.916)
Currently Taking		19	24		0.654 (0.441, 0.970)
Vigabatrin Use					
Not Currently Taking	0.1646	47	59		0.619 (0.481, 0.797)
Currently Taking		28	17		0.861 (0.582, 1.273)

Key issue: 1.7 x vigabatrin use in cannabidiol vs placebo arm

- *Function of disease severity at diagnosis (more advanced disease already stopped vigabatrin)?*
- *More likely to respond to cannabidiol without vigabitrin*

Company: >75% of GWPCARE6 prior vigabatrin (43% stopped before study)
No statistically significant difference in treatment effect with/without vigabatrin

ERG comments: difference in baseline characteristics unlikely occurred by chance (vigabatrin = <1 in 40): flawed randomisation?

- Vigabatrin: may influence outcomes but direction of effect unclear
- Clobazam: may overestimates treatment effect if not used in UK practice

More people had clobazam in placebo vs cannabidiol arm

- *Drug – drug interaction increases clobazam and cannabidiol metabolite levels -> may increase pharmacological effects*
- *Cannabidiol for Lennox-Gastaut and Dravet Syndrome: MA includes clobazam*

Clinical experts: literature suggests difference in effect for cannabidiol with clobazam.

- Clobazam associated with side effects: risk benefit management

Patient experts: some patients report seizure control with clobazam + cannabidiol but lack of response to cannabidiol alone

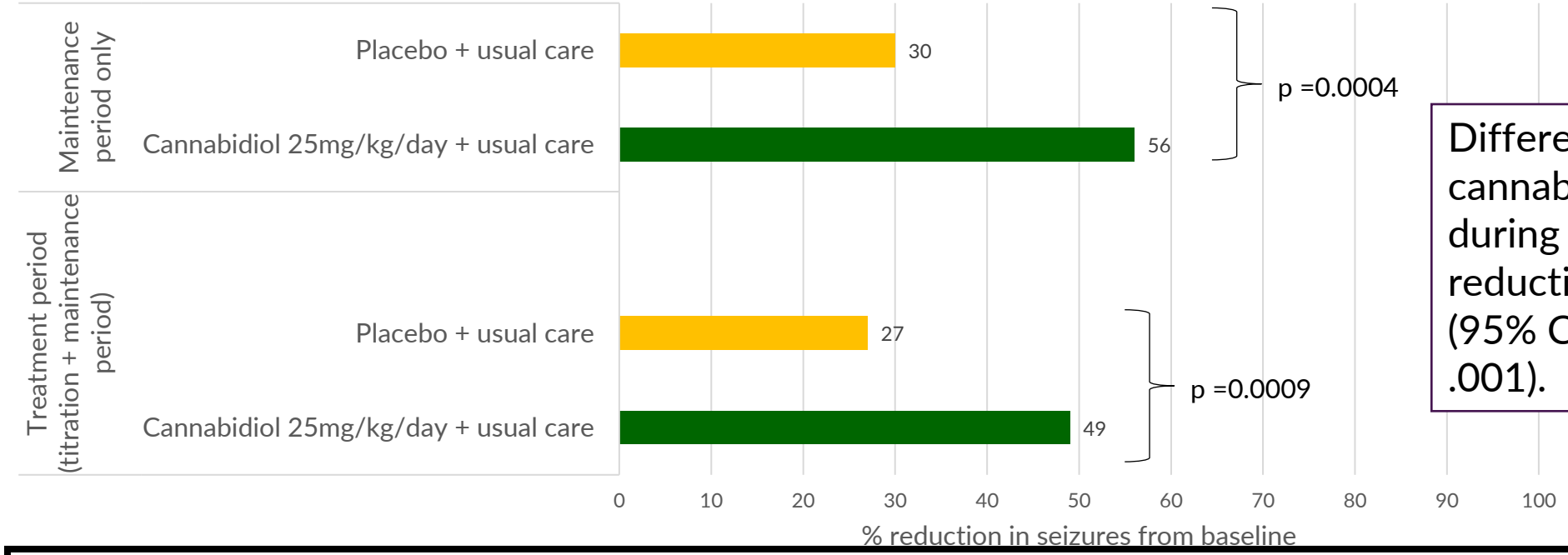
How are clobazam or vigabatrin likely interact with cannabidiol treatment? Is this likely to affect the generalisability of the GWPCARE6 results? How much is clobazam used in clinical practice?

CI, confidence interval; N, number

GWPCARE6 results: Primary outcome

Results suggest reduction in seizure frequency with cannabidiol vs. placebo throughout the study

Figure 5 Change in TSC-associated seizures during the treatment period compared to baseline in GWPCARE6 (ITT analysis set)



Difference between cannabidiol and placebo groups during treatment period (% reduction from placebo): 30% (95% CI, 14% to 43%; P=< .001).

ERG comments: *Primary outcome appropriate*

- 94% of seizures in GWPCARE6 classed as TSC-associated (excluded absence, myoclonic, focal sensory seizures and infantile/ epileptic spasms)
- Definition of primary outcome approved by regulatory bodies
- Baseline seizure frequency measurement (number of seizures in 28 day baseline period) appropriate

NICE

CI, confidence interval; ITT, intention to treat

GWPCARE6 results: secondary outcomes

Higher proportion achieve seizure reduction/seizure free days with cannabidiol vs. placebo

Figure 6 Proportion achieving key seizure reduction outcomes compared with baseline in GWPCARE6 (ITT analysis set)

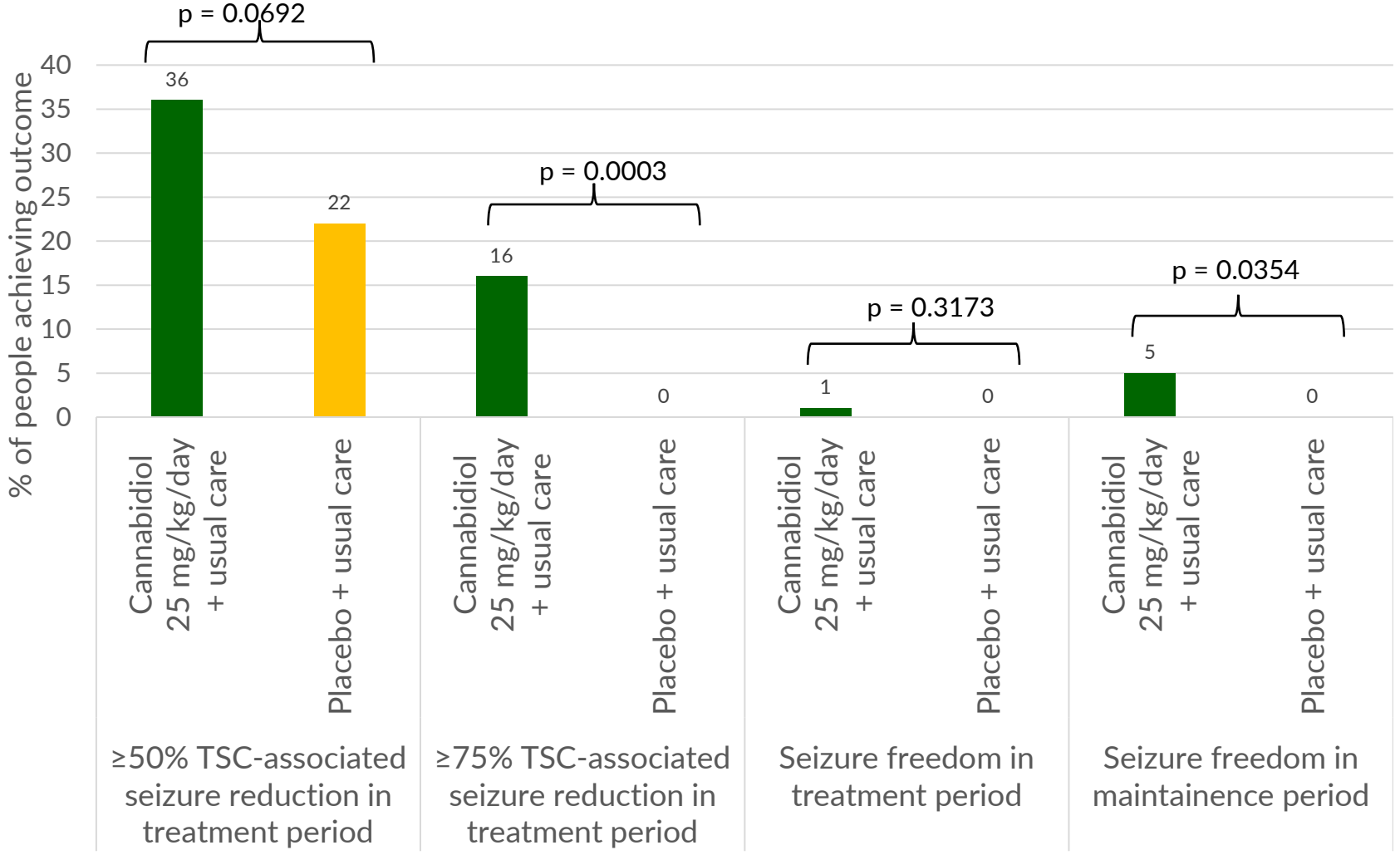
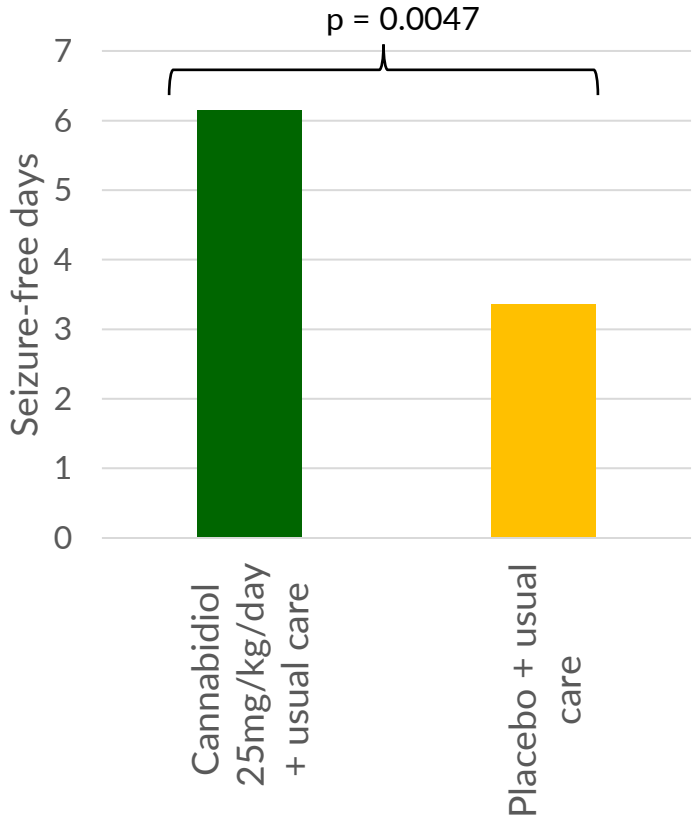


Figure 7 Mean change in seizure free days compared with baseline during treatment period of GWPCARE6 (ITT analysis set)



What are the committee's views on the clinical effectiveness results for cannabidiol + usual care compared with placebo + usual care?

ITT, intention to treat

GWPCARE6 results: Quality of life

Company states issues with trial QoL measure; results vary depending on instrument used

Table 8 Quality of life measures and results in GWPCARE6

Questionnaire collected in GWPCARE6	Measures	Change from baseline, cannabidiol 25 mg/kg/day versus placebo
Quality of Life in Childhood Epilepsy [QOLCE]	0 (worst) to 100 (best) scale covering physical and cognitive function, emotional well-being, social function, behaviour, energy/fatigue, seizure worry	Overall QoL: mean treatment difference 1.5 (95% CI -3.3, 6.3, p= 0.5316)
Quality of Life in Epilepsy [QOLIE]-31-P		Overall QoL: mean treatment difference -4.2 (95% CI -25.1, 16.8 p= 0.6868)
Subject/Caregiver Global Impression of Change (S/CGIC)	7-point scale: 1 (very much improved) to 7 (very much worse)	+69% cannabidiol arm, +39% placebo arm (odds ratio 2.25 (95% CI, 1.24-4.07, p=0.0074))

*Positive odds ratios favours cannabidiol. Source: company submission figure 8 and appendices, Figure 8 and 9

Company: discount QOLCE/QOLIE-31-P results because:

- No validated disease specific instruments or robust mapping algorithms to EQ-5D
- inappropriate for severe epilepsy (e.g. questions re school/work in people with physical/learning disabilities): high chance of missing data

S/CGIC better represents QoL change: captures impact on overall condition based on entire seizure and comorbidity burden

- Not preference based so can't be used to derive utilities.

ERG comments: QOLCE/QOLIE-31-P results not statistically significant but:

- validated for measuring seizures in children
- In pre-hoc study plan: company decided inappropriate post-hoc
- Not reported in main company submission: outcome reporting bias?

How does cannabidiol impact quality of life for people with TSC-related seizures? Are the QOLCE/QOLIE-31-P acceptable measures for TSC?

Abbreviations: CI, confidence interval; QoL, quality of life; SD, standard deviation

NICE

Adverse events

GWPCARE6 AEs mostly mild to moderate but potential for drug-drug interactions

Table 9 Adverse events in the GWPCARE6 trial

Event	Cannabidiol 25 mg/kg/day (n=75) N (%)	Placebo (n=76) N (%)
All-causality TEAEs	70 (93)	72 (95)
Treatment related TEAEs	52 (69)	40 (53)
Treatment-related TEAEs leading to discontinuation	8 (11)	2 (3)*
Treatment related serious TEAEs	8 (11)	0
AEs recorded by ≥10% of participants		
Diarrhoea	23 (31)	19 (25)
Decreased appetite	15 (20)	9 (12)
Somnolence	10 (13)	7 (9)
Vomiting	13 (17)	7 (9)
Pyrexia	14 (19)	6 (8)
Alanine aminotransferase increased	9 (12)	0
Upper respiratory tract infection	7 (9)	10 (13)
Aspartate aminotransferase increased	8 (11)	0
Gamma-glutamyl transferase increased	12 (16)	0
SAEs of special interest		
Status epilepticus	2 (3)	1 (1)

*IMP discontinued in the open-label extension. Source: adapted from company submission, tables 7 and 8

ERG comments

- Most AEs mild to moderate, within 1st 2-4 weeks and resolved by end of trial.
- Cannabis-based medicines may lead to drug-drug interactions (not proven in cannabidiol)
  - Effects likely avoided in trial by exclusion and dose modification of concurrent ASMs: less well managed in clinical practice?

Other considerations: Reported AEs based on 25 mg/kg/day dose: higher than expected in clinical practice

Have all the relevant safety issues been captured and taken into consideration? What adverse events are being avoided by using 12mg/kg/day instead of 25 mg/kg/day?

AE, adverse event; N, number; SAE, serious adverse event; TEAE, treatment emergent adverse event

Key issue: Indirect treatment comparison

ERG: systematic literature review did not present all relevant comparator evidence

Background

Company did not conduct an indirect treatment comparison with scoped comparators

ERG comments:

- Insufficient detail to prove SLR limited bias and error: may not provide full picture of current evidence
  - No pre-published protocol
  - Data extraction methods unclear
  - Multiple RCTs with potential comparator evidence excluded:
    - Metformin: excluded for mode of action but could have been used in ITC
    - Everolimus: used at later line
- Concerned that no efficacy/safety studies on common ASMs identified so re-ran SLR with updated search terms
  - 41 new studies identified
- But, of identified trials, only GWPCARE6 reported correct combination of interventions, comparators and population: only study of relevance.

Company:

- Full SLR conducted for anti-epileptics in TSC (N=79):
  - focused on studies relevant to decision problem (comparator = usual care with ASMs)
- ERG's SLR identified only 1 study of relevance published at time of initial search that met inclusion criteria:
  - for vagus nerve stimulation: not considered a comparator
- ITC not relevant to decision problem

Have all the relevant data for comparators been identified and taken into consideration? Is metformin a comparator for cannabidiol?

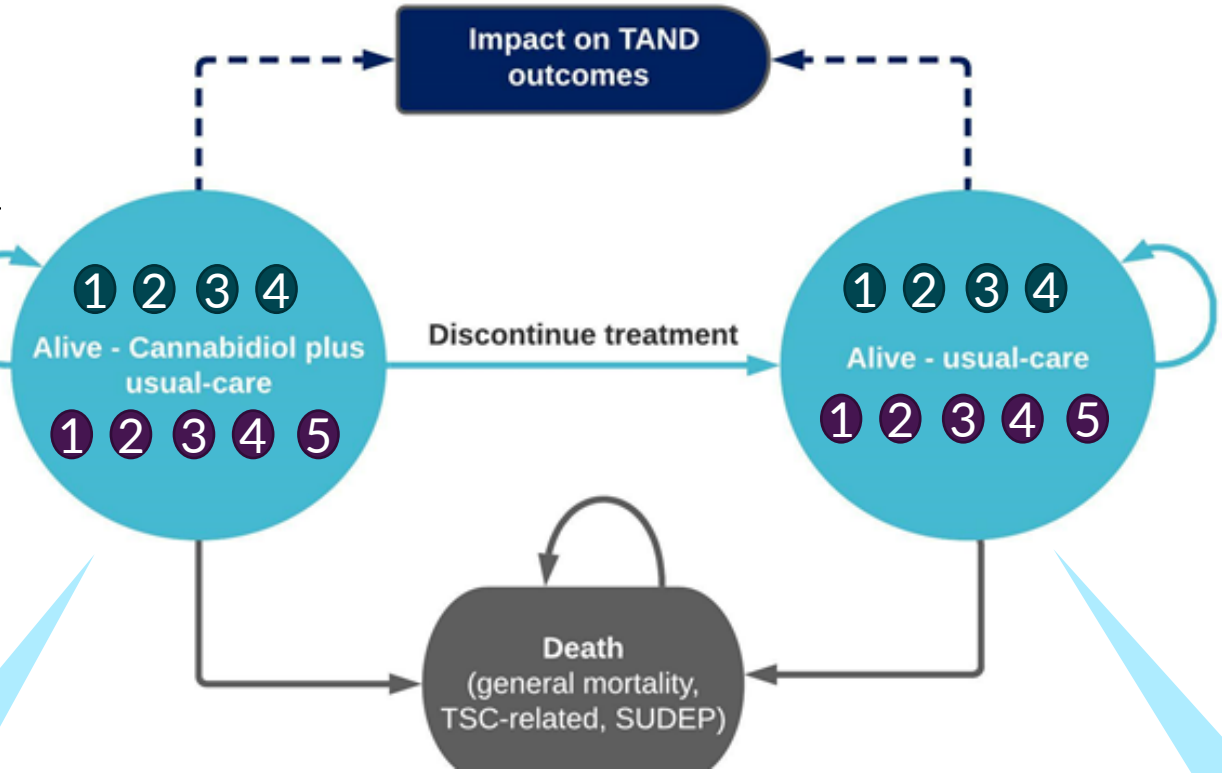
ASM, anti-seizure medications; ITC, indirect treatment comparison; RCT, randomised controlled trial; SLR, systematic literature review

Cost effectiveness

Company's model overview

3 state cohort-based model considering seizure frequency and seizure-free days

Figure 8 Model structure



Specific costs for:
- Adverse events
- Managing TAND
- Subsequent treatments

HRQoL for:
- SAEs (disutility)
- Delaying TAND (cannabidiol, ages 2 to 6 only)
- Carers (disutility)

'Alive' sub health states with HCRU and HRQoL based on:

Number of seizures per week (HCRU):	Seizure free	≤2	2-7	≥7	
Number of seizures per day (HRQoL):	Seizure free	≤ 1	>1 - ≤2	>2 - ≤4	≥4

Source: Based on Figure 12 of the company submission SUDEP = sudden unexpected death in epilepsy; TSC = tuberous sclerosis complex; TAND = tuberous sclerosis complex-associated neuropsychiatric disorders

Assumptions of the company's model

No mortality benefit for cannabidiol; efficacy determined by improvement in seizure frequency & seizure-free days

Table 10 Assumptions in the company's model

Input	Assumption
Population	People with TSC-associated epilepsy ≥2 years with inadequately controlled seizures on established clinical management
Clinical efficacy	• Δ in TSC-associated seizure frequency and seizure-free days • Only generalised and focal with impaired awareness seizures considered • Effect on seizures maintained whilst on cannabidiol
Utilities	Estimated for every sub-health state based on seizure frequency and type
Resource use	• People transition from children to adults at age 17 • 31% require support (e.g. assisted living or live-in residential units) and transition to these services at 27 years
Mortality	• No mortality benefit for cannabidiol but increased risk of SUDEP vs. general population for both arms

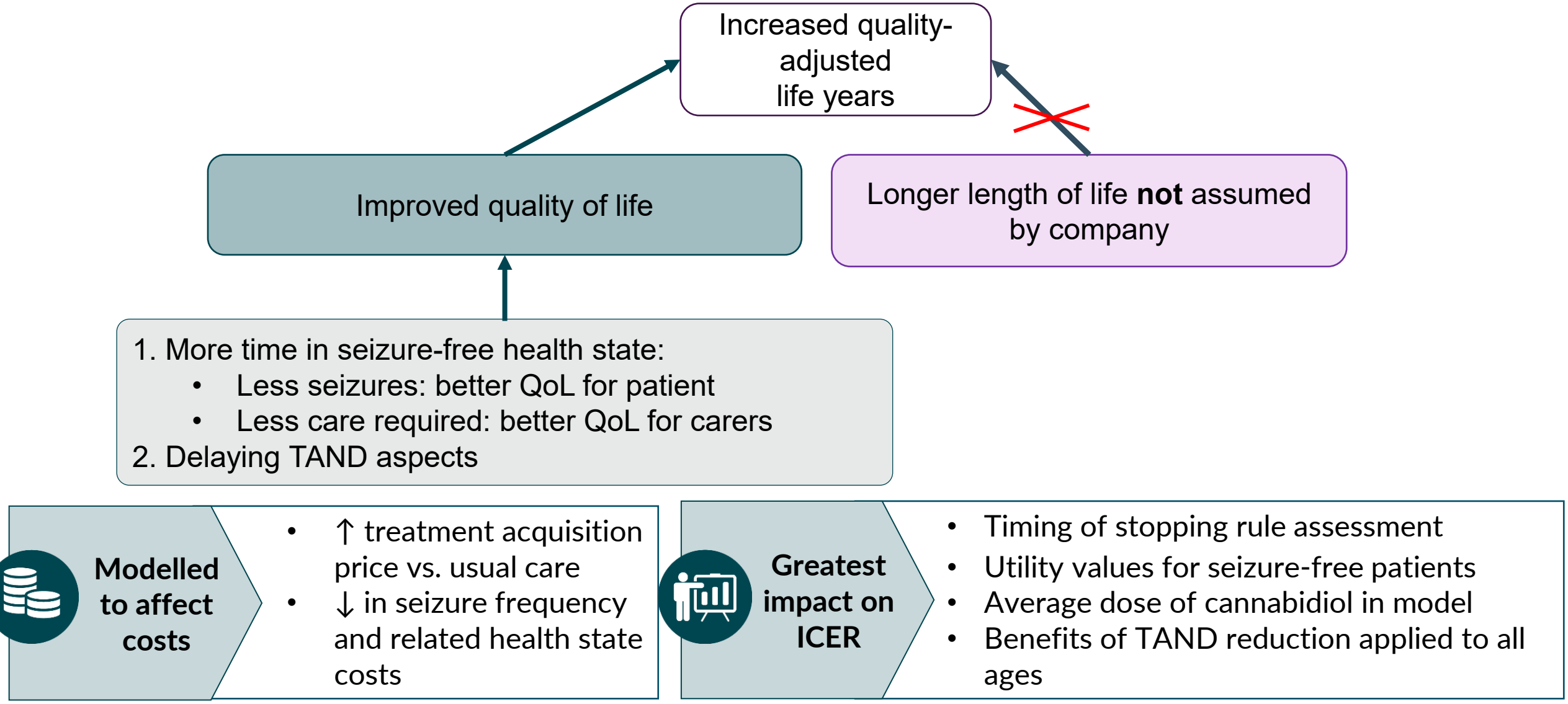
TAND	• Applies only to 2 -6 year olds as:
	  • 'Non-responders'* and usual care: cost for managing TAND aspects
	  • 'Responders'* to cannabidiol: reduced cost + utility benefit for delaying TAND aspects

*'responders' to treatment = people with ≥50% seizure frequency reduction over 6 months

How quality-adjusted life years accrue in company's model

Improved quality of life from reduced seizures and delaying TAND; no mortality benefit assumed for cannabidiol

Figure 9 How quality-adjusted life years accrue in company's model



How the company incorporated evidence into model

Table 11 Input and evidence sources

Input	Assumption and evidence source
Population	GWPCARE6 baseline data, split into 4 age categories
Baseline seizures	• Seizure frequency: GWPCARE6 baseline period • % seizure type (generalised, focal with impairment, combined): week 16 GWPCARE6 data assumed constant over time
Intervention	Cannabidiol + usual care
Comparator	Usual care alone
Efficacy estimates (both arms)	• GWPCARE6, week 16 data used in regression models to predict change in seizure free days and seizure frequency. Assumed maintained over time.
Mortality	• Age-adjusted background TSC mortality: Zöllner et al. (2020) . Risk of SUDEP: Amin et al. (2017)
Adverse events	GWPCARE6, week 16 data for severe TEAEs
TAND	• Prevalence of TAND aspects: Vries et al. (2015) (TOSCA registry) • % aged 2 -6 with reduction in TAND (≥50% seizure frequency reduction): GWPCARE6 ITT cohort
Stopping treatment rates	*Discontinuation rate:* ≥week 16: GWPCARE6; Week 17- 88: OLE; Long term: TA615 (LGS) *Stopping rule if seizure frequency not ≥30% less than baseline*: 6 & 12 months: OLE data; 18 & 24 months: 12 month OLE rate
Subsequent treatment	7.7% start everolimus at 2 years (usual care) or on discontinuation of cannabidiol: TOSCA registry
Utilities	• Seizures (patient & carer): company vignette weighted by seizure type in GWPCARE6, week 16 • Seizure free days (patient): Lo et al., (2021) • Disutility for SAEs: Kinderen et al. (2016).; Increments for delaying TAND: Vries et al. (2015)

Health care resource use and costs into model

Table 12 Input and evidence sources HCRU and costs

Input	Assumption and evidence source	ERG comments
Resource use	Delphi panel consensus validated by Shepherd et al	All HCRU data from Delphi panel (not real world evidence). HCRU in Shephard et al and Dephi panel not comparable. *Scenarios*: a) use TA614 and TA615 hospital costs; b) ↓ hospital admissions by 50%
Costs	ASMs and everolimus: MIMS and EMIT Monitoring costs: assumed LFT tests 4 x in 1st year only, NHS Reference costs 2019 to 2020 TAND: Gustavsson et al. 2011	

Table 13: Health care resource use costs by seizure frequency category in the company's model

HCRU per week (per cycle)	Generalized seizures (£)		Focal with impairment seizures (£)	
	Paediatric	Adult	Paediatric	Adult
Seizure-free	53	541	40	533
≤ 2 seizures	143	594	99	569
> 2 – ≤ 7 seizures	289	716	195	631
> 7 seizures	700	994	428	768

Source: company submission, table 26. HCRU, health care resource use

Table 14: Comparison with Shepherd et al & other cannabidiol TAs for 1st 3 years (GP visits, hospitalisation, other drugs, outpatient visits)

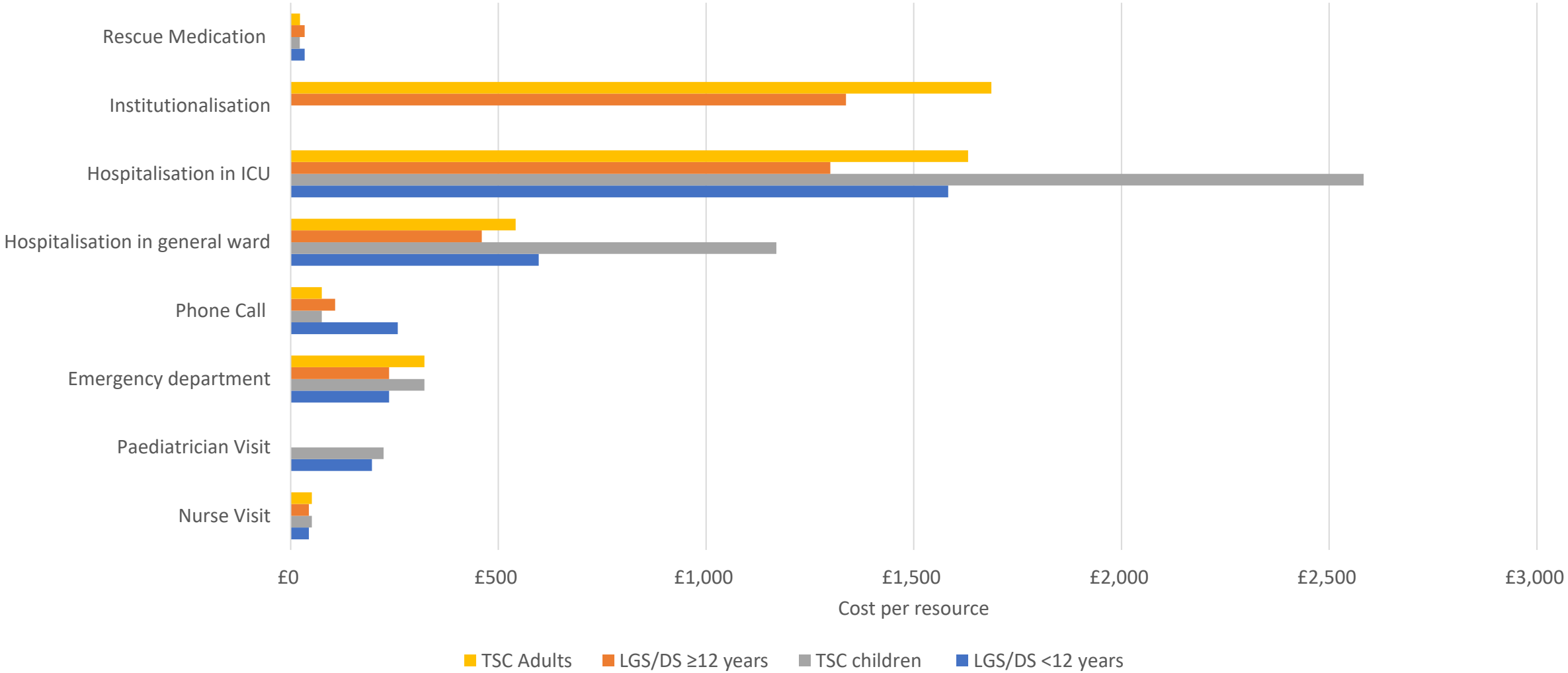
	Company submission, ID1416	Shepherd et al	TA614 (Dravet)	TA615 (Lennox-Gastaut)
Absolute costs, usual care	£55,578	£44,259	£43,867	£14,875
Δ in costs with cannabidiol	-£13,638	-	-£7,520	-£3,401
% change	25%	-	17%	23%

Source: company submissions for cannabidiol in TSC, Dravet Syndrome and Lennox-Gastaut syndrome, Shepherd et al.

What are the committee's views on the cost and resource use in the model? How comparable are the HCRU estimates from the company's model and Shepherd et al?

Comparison of health care resource use and costs across TAs

Figure 10: Comparison of cost per resource across cannabidiol indications



How would resource use differ between TSC, Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS) in clinical practice? Are company's estimates plausible?

Key issues: Population in the model

Data from1 year olds used in model (excluded from licence); varying % of females across age groups

Key issue: Population includes 1 year olds

Modelled efficacy outputs, response rates, discontinuation rates & baseline characteristics informed by GWPCARE6 ITT population

- *Includes N=9 >1 year old (cannabidiol N=3, placebo N=6): not in licence*

Company: All >2 years old at end of trial: Inappropriate to exclude <1 year olds due to small trial population (orphan disease)

- Conservative: Results excluding 1 year olds similar to ITT population (slightly less favourable to cannabidiol)
- Drug costs excluded 1 year olds

ERG: ITT not reflective of clinical practice: likely conservative but hard to predict impact on ICER

Table 15: Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline & Treatment Periods (ITT Analysis Set)

	N (CBD/ placebo)	% reduction from baseline (CBD / placebo)	Treatment ratio	
			% reduction	95% CI
ITT	75 / 76	47% / 27%	0.699 [30%]	0.567, 0.861
2+ years	72 / 70	50% /28%	0.695 [31%]	0.560, 0.862

Note: Treatment period is defined as Day 1 to Day 113. Source: company response to TE, Table B

Key issue: % female in GWPCARE6 varies across age categories : impacts weight and BSA used for drug costs

- *Modelled weight & BSA maintained >18 years old*

Company: Discrepancy is non-significant (p =0.453)

- Varied characteristics expected in orphan disease
- % female has minimal impact on ICER
- At 10 years in model <[redacted]% on cannabidiol (average age 24 years): general population weight & BSA for 24 year olds (average 73kg, BSA 1.85) comparable to GWPCARE6

ERG: may overestimate mean weight & BSA used for drug costs: impact uncertain but unlikely model driver

- Weight & BSA may not be maintained in adults

Table 16: Baseline characteristics in the company model

	Age, years			
	2 – 6	7 – 11	12 – 17	≥18
% female (SD)	38 (7)	42 (7)	53 (9)	35 (6)
Mean body weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean BSA, m^2 (SD)	0.77 (0.17)	1.09 (0.18)	1.51 (0.24)	1.84 (0.31)

ERG report, table 4.3

BSA, body surface area; ITT, intention to treat; m, meter; N, number; SD, standard deviation

What impact does including 1 year olds have on the cannabidiol's effect? Should they be excluded from the company's model?

Key issue: Modelled dose of cannabidiol (1)

Company models lower dose than licenced, states better reflects clinical practice

Background: Fixed average dose of 12 mg/kg/day in model

- Patients in GWPCARE6 titrated to 25 mg/kg/day: mean dose in trial cohort at end of treatment = 23 mg/kg/day (SD 4 mg/kg/day)

Summary for product characteristics: cannabinol for TSC

1. Titrate to 10 mg/kg/day in week 1 and asses response

2. Further weekly increments +5 mg/kg/day to max 25 mg/kg/day based on response (individual benefit & risk)

Company

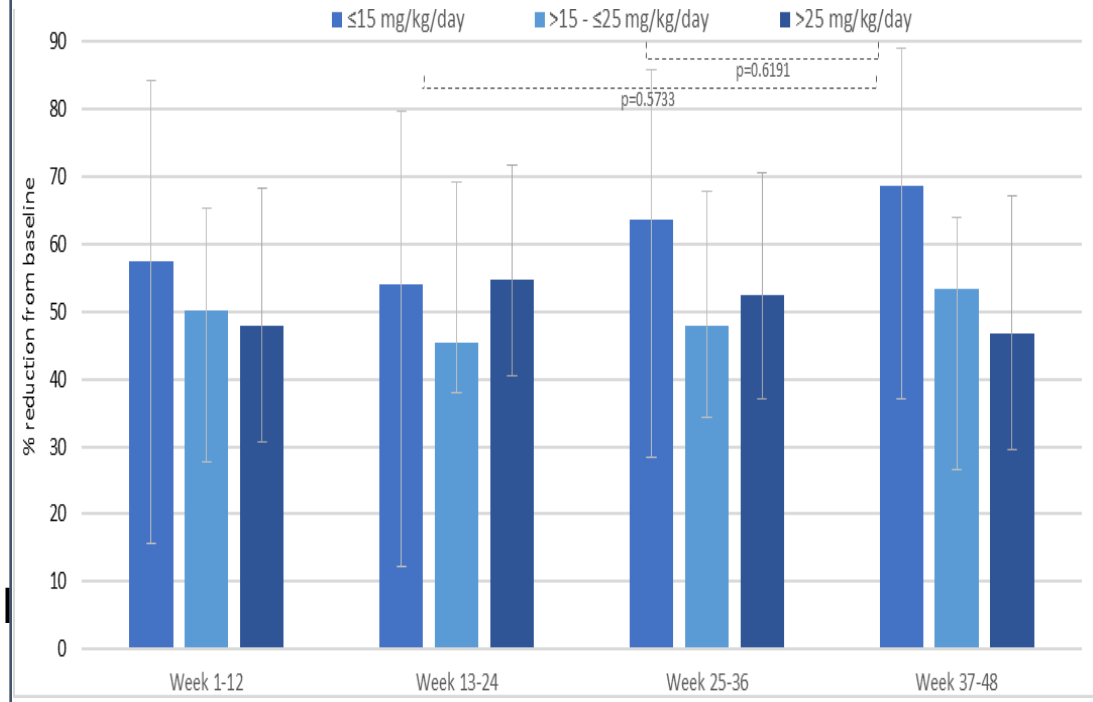
25 mg/kg/day is max *not* target dose:

- average dose in clinical practice likely lower: 12 mg/kg/day accounts for range of expected doses

Modelled dose supported by:

- German dispensing data in N= 118 TSC patients:
  - median dose 12.2 mg/kg/day (IQR 6.7) in children and 7.8 mg/kg/day (IQR: 5.7) in adults
- Company's clinical experts: expected dose in clinical practice max ~12 mg/kg/day
- OLE results: spectrum of maintenance doses -> similar response across dose levels
- Lennox-Gastaut and Dravet syndrome: no numerical/ statistical efficacy difference for 10 and 20mg/kg/day cannabidiol (EMA approved 10mg/kg/day maintenance dose)

Figure 12: Seizure reduction from baseline by modal dose in the GWPCARE6 OLE study



Source: company response to technical engagement, Figure 1

EMA, European Medicines Agency; IQR, interquartile range; N, number; OLE, open label extension; SD, standard deviation

Key issue: Modelled dose of cannabidiol (2)

ERG: little data supports company's modelled dose; model driver

ERG comments: *unclear if modelled dose reflects UK clinical practice*

- Plausible that average dose ~12 mg/kg/day but company did not provide data on individual doses in the trial to verify: may be higher in clinical practice
- Limited evidence to support 12 mg/kg/day average dose:
  1. OLE data not convincing as:
     - Does not specify patients numbers in each category
     - Absence of dose response on average doesn't mean that some patients will not need a higher dose to obtain response
  2. German data may not be representative of UK population
- Unclear why maintenance dose not 10mg/kg/day: mandated by EMA for Dravet and Lennox-Gasteut
- ERG scenarios exploring alternative dosing (10, 15 and 25mg/kg/day) significantly impact ICER

Clinician expert comments

- Dosing used in clinical trials somewhat arbitrary
- Dose response not linear: limited further benefits after a certain dose
  - Many patients will need lower dose than the licenced 25mg/kg/day

Previous assumptions: *12 mg/kg/day preferred by committee for Dravet and Lennox-Gasteut syndrome*

- Experts: increase above maintenance dose if large drop in seizure frequency to aim for seizure freedom
- 20% modelled to have max dose (20 mg/kg/day) = average 12 mg/kg/day

What are the committee's views on the company's modelling of the dose of cannabidiol? What dose of cannabidiol is most plausible in clinical practice?

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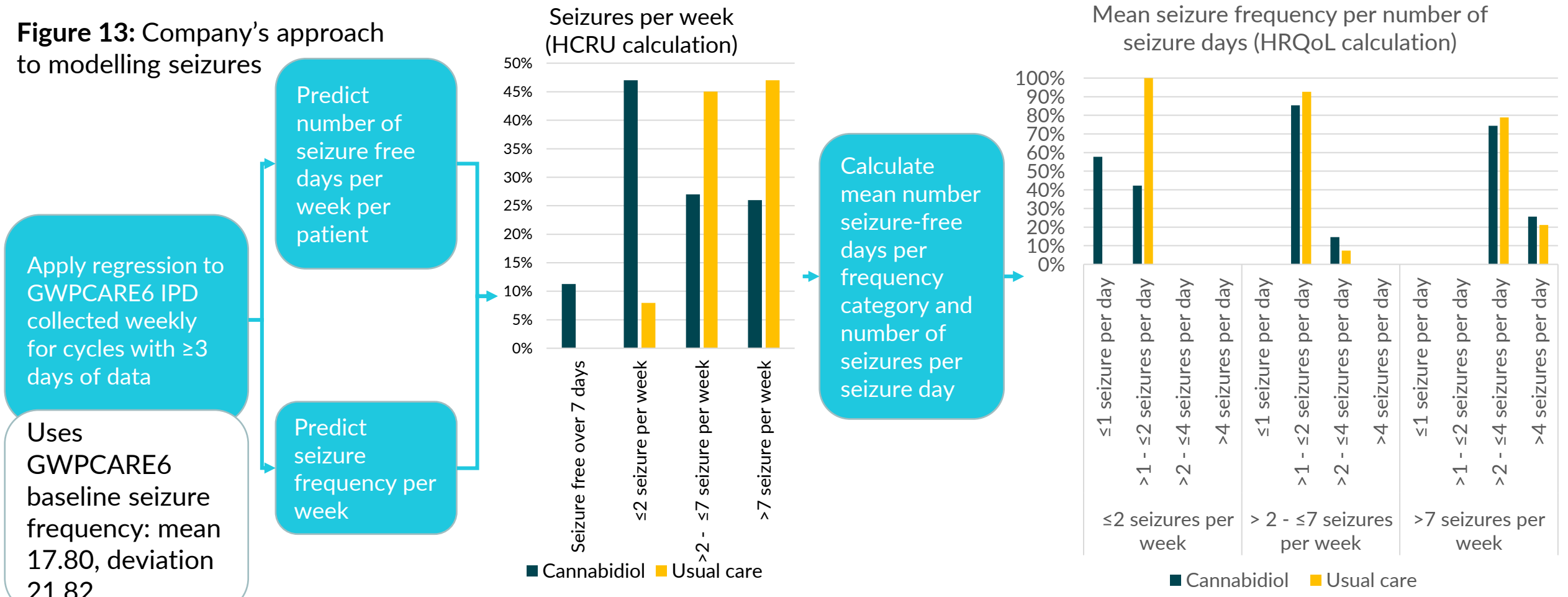
Background: Company's modelling of seizures

GWPCARE6 data used to predict seizure free days and seizure frequency

Figure 13: Company's approach to modelling seizures



Adjusted for distribution of generalised, focal impaired awareness and combined seizures in GWPCARE6 at week 16. **Company assumes relative effectiveness at 16 weeks maintained for modelled time horizon.**

How plausible are the companies modelled seizure frequency calculations for people with TSC?

HCRU, health care resource use; HRQoL, health related quality of life

Background: Company's linear regression model results

Non-significant trend for ↑ seizure frequency and ↓ odds of seizure free days with placebo vs. cannabidiol

Company

- Non-significance of relative effect due to low power from dual model approach and using weeks instead of full trial period (16 weeks)
  - Single negative binomial model for seizure frequency on all days (sensitivity analyses) showed statistically significant effect v placebo

ERG comments

- Baseline seizure rate important predictor of seizure severity: not a treatment modifier in subgroup analyses
- Justification for treatment*time weak and not supported by expert opinion
- Limitations to analyses, but may predict seizure-free days and seizure frequency sufficiently accurately
- OLE seizure frequency data aligns with estimated values but no OLE data on seizure-free days

OLE, open label extension

Table 17: Results of the linear regression model

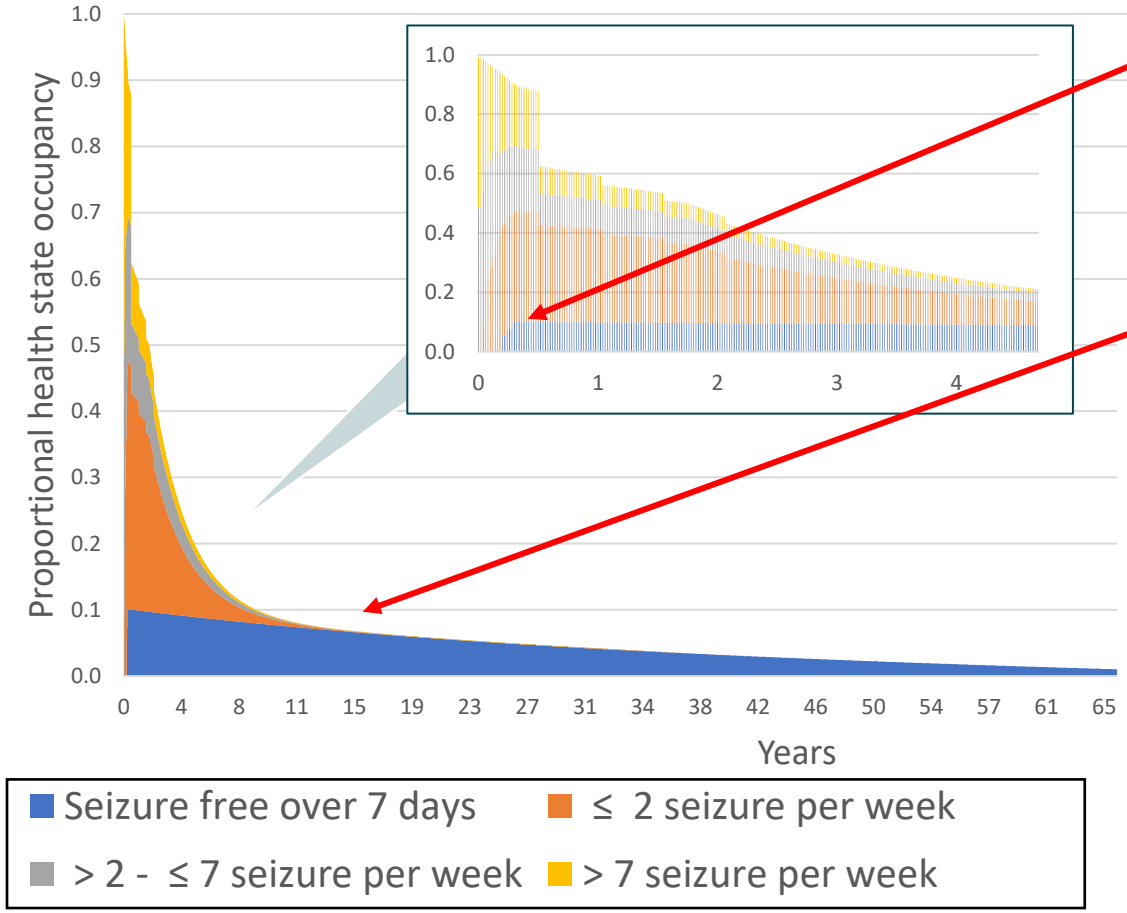
	Seizure-free days (SE)	Seizure frequency (SE)
	+ve = favourable outcome	*-ve = favourable outcome*
Log (cycle) *Effect of cannabidiol over time*	0.536* (0.116, p=<0.001)	-0.062 (0.025, p=0.012)
Baseline seizure rate (scaled) *Effect of high baseline seizure rate on outcome*	-2.803* (0.248, p= <0.001)	0.494*(0.029, p=<0.001)
Placebo vs. cannabidiol	*-ve favours cannabidiol*	*+ve favours cannabidiol*
Treatment = Placebo (Ref = Cannabidiol 25 mg/kg/day) *Relative effect over 1 cycle*	-0.518 (0.328, p= 0.114)	-0.011 (0.069, p=0.877)
Treatment (Placebo) * log (cycle) *Relative effect over time*	-0.241 (0.161, p=0.135)	0.052 (0.032, p=0.107)

Source: Table 13 of company submission; SE = standard error; Ref = reference treatment; Orange* = statistically significant result

What are the committee's views on the company's regression analyses?

Background: Seizure health state occupancy in the model

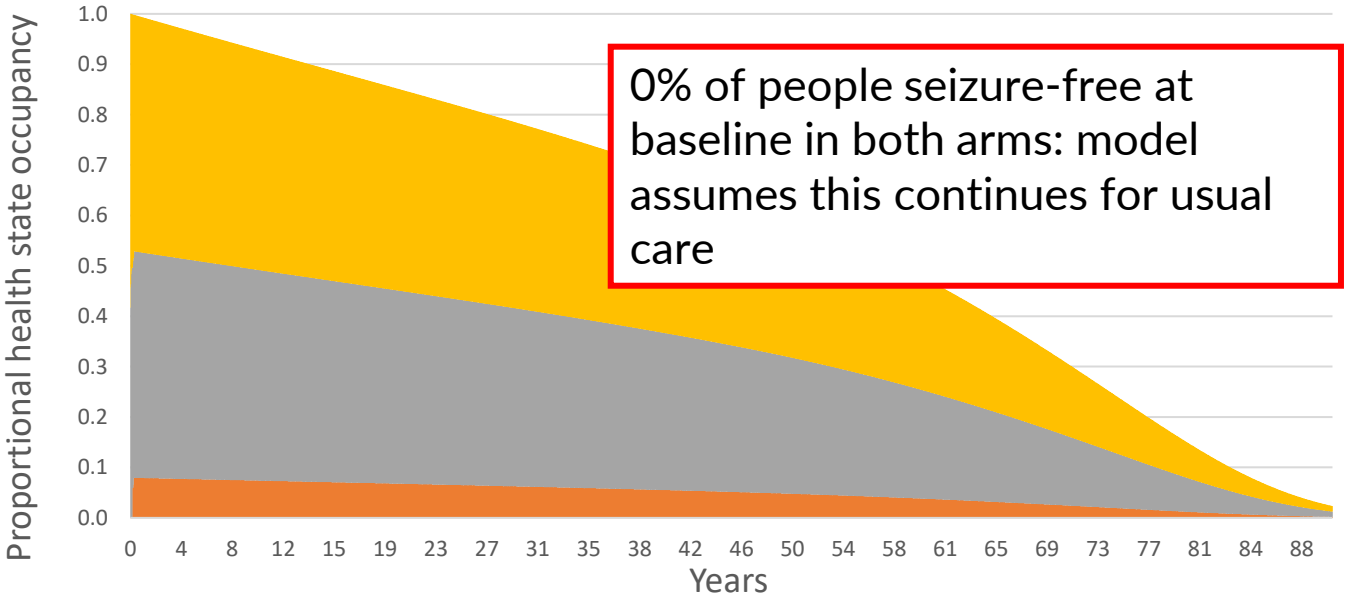
Figure 14: Health state occupancy for people having **cannabidiol (pre-progression)** in the company's model



From 10 weeks, 11% cannabidiol patients are 'seizure-free over 7 days' (company modelled using a cut off of **6.5 days**)

Most people who remain on treatment long-term modelled to be seizure-free: stopping rule if seizure frequency not ≥30% less than baseline

Figure 15: Health state occupancy for people having **usual care (pre-progression)** in the company's model



0% of people seizure-free at baseline in both arms: model assumes this continues for usual care

Key issue: Application of seizure free days in the model

ERG: company's application of seizure freedom may overestimate cannabidiol's treatment effect

ERG comments: 6.5 day cut-off for 'seizure-free over 7 days' overestimates % seizure-free in cannabidiol arm

- *Scenario:* cut-off of 7 days: no patients in either arm are seizure-free:
  - Predicted seizure-free days per week with binomial regression model = 6.62 cannabidiol, 5.89 placebo
  - Impacts HCRU and discontinuation rates: large impact as 16 week effect maintained for full time-horizon
- Some having usual care may be seizure-free over 7 days in clinical practice:
  - median 4 ASMs in GWPCARE6 -> some had less: benefit from further options?
- Company assumes patients refractory over lifetime: unlikely as would try subsequent treatments

Company

- Binomial logistic regression cant predict 0 or 7 days:
  - 6.5 days closest rounding cut-off point
- Experts: unlikely seizure-free with usual care
- ERG's scenario doesn't reflect OLE: 19% seizure free at 72 weeks with cannabidiol
- *Scenario*: cut-off of 6.61 days for 'seizure-free for 7 days'

Clinical expert: Seizure freedom key outcome:

- Rarely achieved in people with TSC
- Partial seizure reduction may not reduce risk and improve QoL

Table 18: Potential cut-offs for modelling 'seizure free over 7 days'

Cut-off for 'seizure free for 7 days'	Company/ERG
6.5 days	Company & ERG base case
6.61 days	Company scenario
7 days	ERG scenario

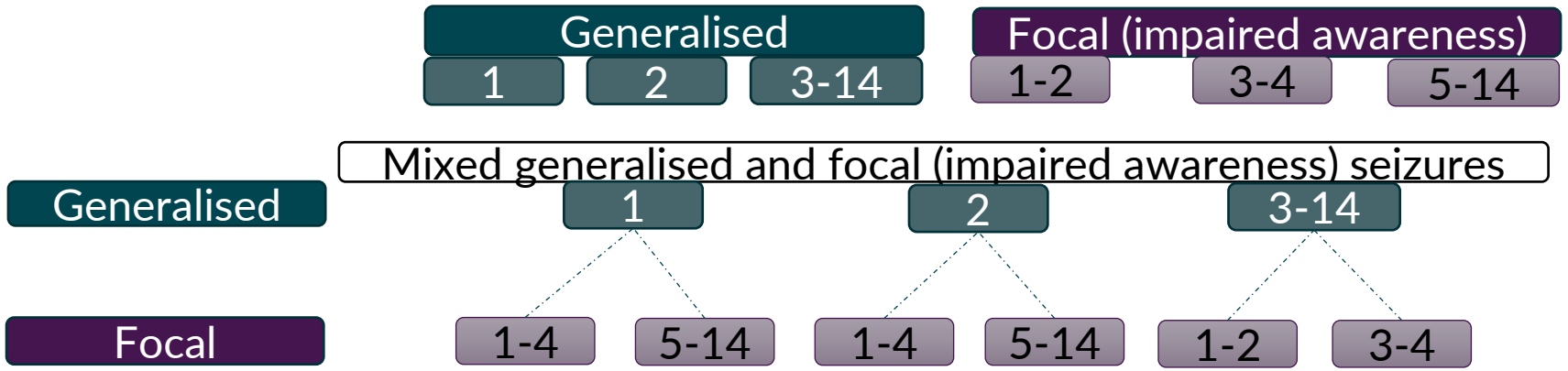
How should seizure freedom be modelled?
Which cut-off for 'seizure-free for 7 days' best reflects clinical practice?
Would cannabidiol's effect on seizures be maintained?

ASM, anti-seizure medication; HCRU, health care resource use; OLE, open label extension, QoL, quality of life

Background: Modelling utilities

Time trade off values for seizure type and frequency weighted by prevalence in the GWPCARE6 trial

Figure 16: Company's approach to deriving health state utilities (seizure frequency per day)



- Time trade off values collected in vignette for each combination of seizure type and frequency for both patients and carers
- Utilities in the model: weighted by % seizure type and seizure frequency combinations in week 16 of GWPCARE6

Table 18: Health state utilities applied in the company's model (capture impact of seizures only)

Health state, seizures per day	Patient utility	Carer disutility*	Reference
Seizure-free	[redacted]	[redacted]	Lo et al., (2021)
≤1	[redacted]	[redacted]	Company vignette, adjusted to account for seizure type distribution
>1 - ≤2	[redacted]	[redacted]	
>2 - ≤4	[redacted]	[redacted]	
>4	[redacted]	[redacted]	

Source: table 4,12, ERG report. *calculated using baseline utility of 0.881: average adult aged 45 years (ONS data: average age of a mother of a 13-year-old child).

NB: utility values taken from the company's model: seizures per day differ from those reported in the company submission

ERG comments: *seizure-free utility value for carers uncertain*

Company:

1) Assumes all caregivers mothers
2) Doesn't capture other TSC-related symptoms requiring care
3) Didn't correct for caregiver aging

Scenarios: vary utility value for seizure-free health

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Utilities across health states

Variation in patient and carer utility values across cannabidiol indications

Background

- Published data available for Lennox-Gastaut and Dravet Syndrome from vignettes in general public (conducted after publication of TA614 and 615 based on committee feedback)

Table 19: Comparison of patient and carer utility values across cannabidiol indications

Company submission ID1416, TSC			Lo et al. 2021, LGS				Lo et al. 2021, DS			
Seizures per day (any type)	Patient utility	Carer utility†	Drop seizures per day	Seizure free days	Patient utility*	Carer utility*	Convulsive seizures per day	Seizure free days	Patient utility*	Carer utility*
Seizure-free	[redacted]	[redacted]	Seizure-free	>15	0.722	0.790	Seizure-free	>24	0.781	0.874
≤1	[redacted]	[redacted]	≤45	>3 - ≤15	0.282	0.506	≤8	>18- ≤24	0.652	0.762
>1 - ≤2	[redacted]	[redacted]	>45 - ≤110	>15	0.152	0.364	>8 - ≤25	>24	0.620	0.752
>2 -≤4	[redacted]	[redacted]	>45 - ≤110	≤3	−0.065	0.120	>8 - ≤25	≤18	0.407	0.564
>4	[redacted]	[redacted]	>110	>15	−0.055	0.209	>25	>18- ≤24	0.380	0.613
-	-	-	>110	≤3	−0.282	−0.098	>25	≤18	0.168	0.465

Source: table 4,12, ERG report, Lo et al, supplemental table IV and V. † caregiver utility calculated by applying disutility to baseline utility of 0.881: average adult aged 45 years (ONS data: average age of a mother of a 13-year-old child)

* based on UK mean from vignettes in general public, not utilities accepted in the LGS and DS appraisals

Are the company's modelled utility values plausible? How does the severity and burden of care for TSC differ from LGS and DS?

DS, Dravet Syndrome; LGS, Lennox-Gastaut Syndrome; TA, technology appraisal

Key issue: Number of carers

ERG: company's modelling of 2 carers additively does not account for 'sharing' of care burden

Company: ***Applies vignette carer disutilities additively for 2 x carers.***
Justified by:

- Risk of injury/death from seizures, multiple co-morbidities; may need lifelong 24hr care
- Approach conservative:
  - captures cumulative QoL impact of many carers
- Updated paper by Lagae et al (2019) (DISCUSS study for Dravet syndrome, N=584) suggests total 2.06 carers
  - 84% of total care by 1° carer
  - 122% by partners, family members, friends etc
- Vignette adjusted for carer being 1 of 2
- Carer disutility applied additively in HST3

Previous assumptions: committee agreed additive approach may not capture 'sharing' of care burden for Dravet (DS, TA614) & Lennox-Gasteut (LGS, TA615) syndrome

- Preferred scenario: 1.8 x carers informed by Lagae et al 2017

ERG comments: Unlikely both carers provide equal care: disutilities may differ (not specified in vignette)

- Vyas et al: total TSC seizure specific hours spent caring = 11; 7 hrs were 1° carer
- N° carers over time & effect on other family members uncertain

***ERG base case*:** 1.8 x carers as per TA614, TA615 and TA808 (fenfluramine)

Clinical expert

- Heterogeneity in seizure severity and frequency in refractory TSC-associated epilepsy: spectrum of care burden
- Additional disorders (including TAND) also affect care needs
- Differences between TSC and DS/LGS may affect comparability across diseases:
  - *Seizure type:* DS mostly myoclonic seizures, TSC and LGS multiple
  - *Severity*: LGS generally refractory but DS hugely variable
  - *Associated learning disabilities*: characteristic of DS but not for TSC

How plausible are the company and ERG's assumptions on the number of carers for a TSC patient? How does the care burden for people with TSC compare to those with Dravet Syndrome?

hr, hour; N, number; TA, technology appraisal; HST3: Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

Key issue: Modelling care for institutionalised patients

ERG base case includes reduced carer disutility for patients who are institutionalised

Background:

- Delphi panel consensus: 31% TSC patients institutionalised at average age of 27 years
  - Company assumes no reduction in burden of care when patients institutionalised (still 2 carers in model)
- Same proportion of patients institutionalised regardless of seizure frequency

ERG comments:

1. Institutionalisation costs in company's base case: utility values not adjusted for care reduction
   - **Base case:** assumes 50% reduction in carer disutility for 31% of adults
2. Potential that seizure-freedom linked to reduced institutionalisation
   - *Scenario*: a) 0% institutionalisation in seizure-free health state; b) as above + 10% ↓ institutionalisation for other health states

Company: ERG's approach inappropriate:

- Although carers QoL may improve with patient being institutionalised, still have:
  - Concerns: risk of injury from seizures or worsening of seizures and TAND aspects in new environment
  - Every day life centred around visiting patient and accompanying them to healthcare visits
  - Guilt about separating patient from family
- *Scenarios*: 50% ↑ in caregiver utility for 31% adults

Clinical expert: Carers remain involved when patients institutionalised:

- attend hospital appointments for ongoing surveillance, visit regularly

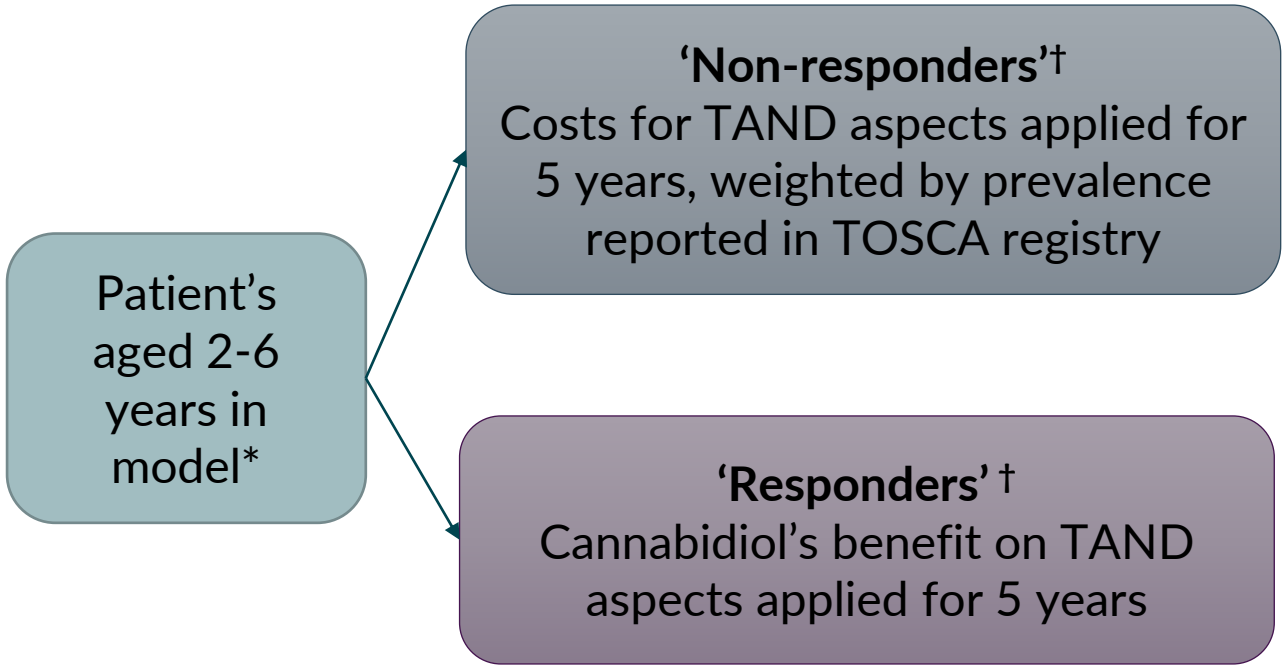
How would carers quality of life be affected by patient institutionalisation? What is the most plausible approach to modelling this?

QoL, quality of life; TAND, TSC associated neuropsychiatric disorders

Background: Company's modelling of TAND

Impact on TAND applied as reduced costs and utility benefit for 'responders' to cannabidiol

Figure 17: Company's approach to modelling TAND aspects



*Delphi panel suggested treatment with cannabidiol most beneficial at an early age.

† Responders = 50% seizure frequency reduction over 6 months (Delphi panel 'near consensus' that 47.5% seizure frequency reduction would reduce progression of TAND aspects)

ADHD, attention deficit hyperactivity disorder; TAND, TSC-related neuropsychiatric disorders; TE, technical engagement

Key aspects of TAND identified by Delphi panel.

Table 20: Prevalence data for 2-6 year olds (Vries et al)

Age bands used by de Vries et al	≤2 & >2 to ≤5
N	584
Prevalence of TAND aspects from Vries et al	
Delayed development	8.4%
Behavioural issues	54.8%
Intellectual disability	5.5%
Autism Spectrum Disorder	11.5%
ADHD	10.4%
Anxiety disorders	1.5%

Source: ERG report, Table 4.6

Table 21: Costs and utilities associated with TAND in 2–6 year olds in company's model (after TE)

	'Non-responders' and usual care arm	'Responders'
Weighted average cost of TAND per cycle	£50.47	£25.24
Utility benefit for delaying TAND	-	0.09

Source: adapted from company submission, Table 24 and 29

Key issue: TAND

ERG: Many uncertain assumptions inform modelling of TAND

Company: TAND important to include: large impact on the lives of patients and caregivers

- Updated modelling of TAND at TE to include more conservative assumptions
- Scenario: TAND benefit applied to all age groups.

ERG comments: ***uncertainty in modelling of TAND:***

- Potential double counting of treatment effect on TAND: may also be captured in seizure frequency vignettes
- Uncertainties include:
  - No data on TAND from clinical trials in model: resource use based on external data
  - Near (not full) consensus of the Delphi panel as to % seizure reduction for benefit in TAND aspects
  - All ages included in responder calculations, but only applied to 2 to 6 year olds
  - ***ERG base case:*** excludes TAND aspects

Patient expert

- Behavioural issues related to TAND extremely challenging for patients and their families: large QoL impact
- Some carers report improvements in sleep and behaviour with cannabidiol

Clinical expert

- TAND complications (cognitive impairment, behavioural difficulties) may improve with reduced seizure frequency
- Spectrum of severity with TAND: ranges from fairly independent to requiring care with all aspects of daily living
- Early seizure control key to improving TAND aspects

QoL, quality of life; TAND, TSC-related neuropsychiatric disorders; TE, technical engagement

How frequent is TAND in people with TSC? What is the impact on patients and carers? To what extent is TAND preventable by controlling seizures? How should TAND aspects, and cannabinol's effect on them, be modelled?

Summary of company and ERG base case assumptions

Assumptions on TAND and carer disutility differ between base cases

Table 22: Assumptions in company and ERG base case

Assumption	Company base case	ERG base case
Effect of TAND	Conservative TAND mitigation benefit applied to patients aged (2-6 years) with a 50% response rate at 6 months: • for 5 years only • Using lowest reported utility (0.09)	Removal of TAND aspects from the base case
Application of carers disutility	2 carers applied additively	1.8 caregivers applied additively
Adjustment of carer utility for institutionalisation	No adjustment	0.5 caregivers assumed for 31% of patients aged ≥ 18 years
Assumptions updated at TE (in both the ERG and company base case)		
Carer utility for seizure free health state (used to calculate disutility for non-seizure free states) from general utility for a 43 year old woman (0.897)		
Inclusion of age related utility cap for patients		
Correction of general population mortality from age 97		

NICE

QoL, quality of life; TAND, TSC-related neuropsychiatric disorders; TE, technical engagement

Summary of key company and ERG scenarios

Key scenarios vary the population, dose of cannabidiol and application of carer utility in the model

Table 23: Key scenarios provided by the company and ERG

Uncertainty	Company scenarios	ERG scenarios
Population	Varying baseline % female (applies to all ages): • 42% (average in GWPCARE6) • 35% (min in GWPCARE6 age categories) • 53% (max in GWPCARE6 age categories)	Varying weight and BSA in model: • Increase of 5% • Decrease of 5%
Average dose cannabidiol	-	• 15 mg/kg/day • 20 mg/kg/day
Average dose everolimus	-	• Based on TOSCA registry (Reduced 9% for 2-6 year olds and 34% for >6 year olds)
Cut-off 'seizure-free at 7 days'	6.61 days (regression model predicted max threshold of seizure-free days = 6.62)	7 days
Health care resource use	-	• Hospitalisation costs and admissions from TA614 & 615 • 0% institutionalisation for seizure-free health state • 0% institutionalisation for seizure-free health state, 10% for other health states
Carer utility seizure-free health state	-	• 0.85 • 0.80 • 0.75
Carers disutility	• 1.8 x carers • 50% increase in carer utility for 31% of patients to reflect institutionalised patients	-

BSA, body surface area;

Comparison of assumptions: NICE appraisals for cannabidiol

Company considered committee preferences for previous appraisals in the modelling

Table 24 Assumptions in the cannabidiol appraisals for Dravet syndrome (TA614) & Lennox–Gastaut syndrome

Assumption	Dravet syndrome (TA614) & Lennox–Gastaut syndrome (TA615)		TSC (ID1416) Company assumptions
	Company assumptions	Committee preferred	
Long-term relative efficacy	Maintained over time (while on treatment)	Likely to diminish over time	Maintained over time (while on treatment): supported by OLE and EAPs data
Maintenance dose of cannabidiol	10 mg/kg/day	12 mg/kg/day	12 mg/kg/day
Stopping rule	Stopping rule if seizure frequency not ≥30% less than baseline assessed every 6 months	Appropriate	• Stopping rule per TA614 and TA615 • Additional discontinuation rate based on GWPCARE6, OLE and TA615
Mortality benefit for cannabidiol	Included	Insufficient evidence to prove benefit	Excluded
Source of health state utilities	Vignette in patients and caregivers	Vignettes in general population as per NICE reference case	Vignette in general population
Number of caregivers assumed	2	1.8	2

NICE EAP, expanded access program; OLE, open label extension; TA, technology appraisal

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

ICER, incremental cost effectiveness analysis, PAS, patient access scheme

Other considerations: Equality and Innovation

Equalities considerations identified; cannabidiol offers more tolerated treatment option

Equality considerations

Patient organisation

- Half of people with TSC have learning disabilities (e.g. intellectual impairment, memory/attention issues).

Committee should also note that cannabidiol is indicated for use in children (2 years and over) and adults

Innovation

Company: Step change in TSC-associated epilepsy treatment because:

- Orphan disease with high unmet need: life-long treatment resistant form of epilepsy
- Inadequate control with current range of ASMs
- High patient and carer burden
- Favourable safety profile

Professional organisation:

- Reduces seizure burden and associated risk but not a step change in treatment as other ASMs available to manage the condition

Are there any equalities issues that should be considered for cannabidiol?
Does cannabidiol represent a step change in treatment for TSC-associated epilepsy?

NICE

ASM, anti-seizure medications

Other considerations: Uncaptured benefits

Company and clinical experts: some benefits of cannabidiol may not be captured in modelling

Uncaptured benefits

Company:

- Benefit on mortality risk from SUDEP
- Improving the quality of life of the wider family, including siblings
- Increasing carer productivity and associated societal benefits of carers being able to work
- Reducing duration/severity of seizures
- Long-term impact of improved seizure control on comorbidities and injuries

Clinical experts: Safety concern if cannabidiol is not recommended as people may obtain cannabidiol commercially: lack of regulation

Are there any uncaptured benefits that should be considered for cannabidiol?

SUDEP, sudden unexpected death in epilepsy

Key issues: unresolved after technical engagement

Table 25 Key issues

	Key issue	Resolved?	ICER impact
Decision problem	Population and relevant comparators	Partially	Unknown
GWPCARE6 trial	Generalisability to NHS practice (usual care treatments, small UK population)	No	Unknown
	Between arm variations in usual care treatments	No	Unknown
Modelling cost effectiveness	Variation in patient characteristics between age categories: impacts treatment costs	No	Small
	Average dose of cannabidiol	No	Large
	Modelling of seizure–free days	No	Medium
	Modelling TSC-associated neuropsychiatric disorders (TAND)	No	Small
Utilities	Comparability of patient utilities with other cannabidiol appraisals	No	Unknown
	Seizure-free health state utility value for caregivers	Partially	Small
	Application of caregiver disutilities	No	Small
Resource use	Comparability with literature and other cannabidiol appraisals	No	Medium

Key: Discussion; Model driver: >£10,000 per QALYS gain change from base case; Medium impact: £5,000 - £10,000 per QALYS gain change from base case; Small impact: <£5,000 per QALY gained change from base case

NICE National Institute for Health and Care Excellence

Thank you.