NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Appraisal Committee Meeting – 15 September 2022
1st Committee meeting

The **final scope** and **final stakeholder list** are available on the NICE website.

Pre-technical engagement documents

1. **Company submission summary** from GW Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Tuberous Sclerosis Association
   b. Association of British Neurologists

4. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

5. **Technical engagement response from company**

6. **Technical engagement responses and statements from experts:**
   a. Dr Pooja Takhar – clinical expert, nominated by Tuberous Sclerosis Association
   b. Lisa Suchet – patient expert, Tuberous Sclerosis Association

7. **Appraisal Committee Meeting presentation slides**

Please note that the full submission, appendices to the company's submission and company model will be available as a separate file on NICE Docs for information only.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Document A

Company evidence submission summary for committee

GW Research Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

June 2022

File name	Version	Contains confidential information	Date
ID1416_CBD in TSC_Document A_AICCIC_07Jun2022	**V1**	**Yes**	**07 June 2022**

Instructions for companies

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This submission summary must not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted. Please submit a draft summary with your main evidence submission. The NICE technical team may request changes later.

When cross referring to evidence in the main submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Abbreviations

Abbreviation	Definition
AED	Anti-epileptic drug
DS	Dravet syndrome
HCRU	Healthcare resource use
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
LGS	Lennox–Gastaut syndrome
NHS	National Health Service
OLE	Open-label extension
PAS	Patient access scheme
QALY	Quality-adjusted life year
STA	Single technology appraisal
SUDEP	Sudden unexpected death in epilepsy
TAND	TSC-associated neuropsychiatric disorders
TSC	Tuberous sclerosis complex
TTO	Time trade-off

Submission summary

A.1. Health condition

Tuberous sclerosis complex (TSC) is a rare (orphan; prevalence 1 in 18,861), autosomal dominant, multisystemic disorder characterized by the formation of benign tumours (known as hamartomas) in multiple organ systems, most notably the brain, skin, kidneys, lungs and heart. TSC leads to severe, often debilitating neurological disorders, including epilepsy, which is experienced by around 80% of patients.

TSC-associated epilepsy is a devastating and life-threatening form of epilepsy that presents early in childhood and is associated with refractory seizures and poor outcomes. In addition to the high seizure burden, there are cognitive and behavioural difficulties collectively known as TAND (TSC-associated neuropsychiatric disorders) that prevent children from achieving independence in adult life. This has a profound impact on the quality of life experienced not only by the patients but also by their families and carers. Mortality rates are higher than in the general population. Uncontrolled epilepsy is among the most common causes of death in TSC as a result of status epilepticus or sudden unexpected death in epilepsy (SUDEP).

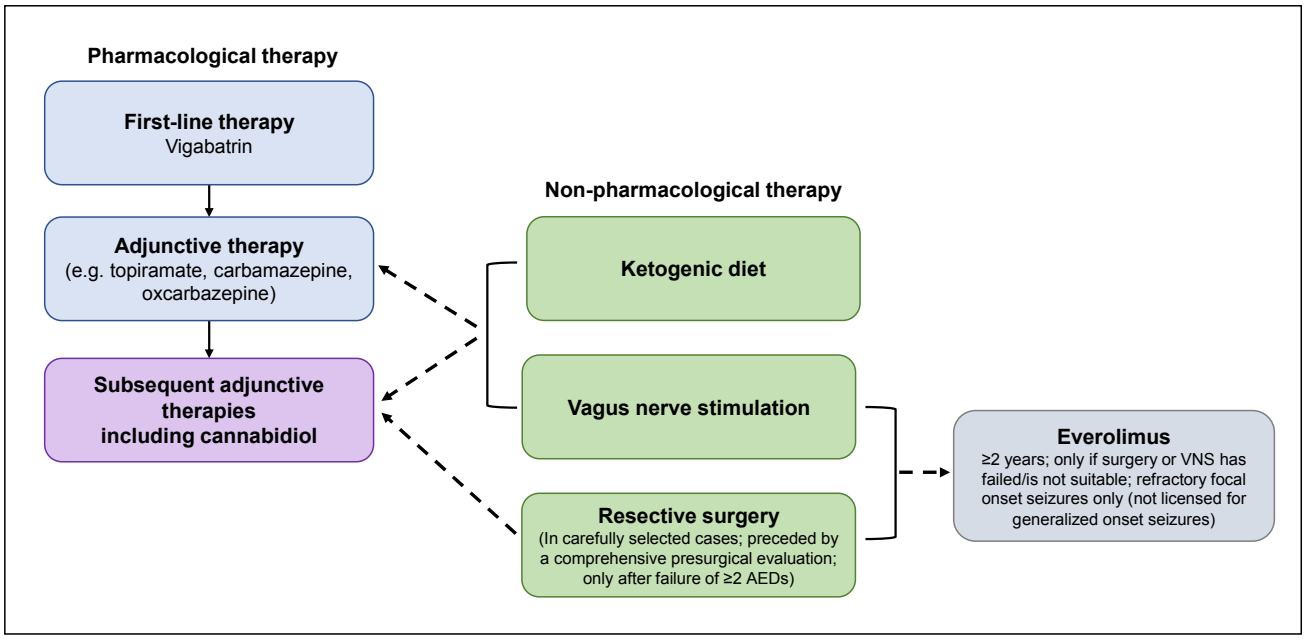
Despite the availability of a broad range of anti-epileptic drugs (AEDs), non-pharmacological interventions and invasive resective surgery (see Figure 1), up to two-thirds of patients with TSC-associated epilepsy currently do not achieve seizure control and continue to be at risk of hospitalization and death. Patients entering the Epidyolex® GWPCARE6 trial had already tried and discontinued up to 15 AEDs (median: four), with some taking up to five AEDs concurrently (median: three).

There remains a substantial unmet need for a well-tolerated treatment to provide early and effective seizure control and improve the overall condition of patients with TSC-associated epilepsy without markedly increasing adverse events.

A.2. Clinical pathway of care

For patients with TSC-associated seizures considered for treatment with cannabidiol, it will be an add-on treatment for refractory seizures in people aged 2 years and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom (Figure 1). This is in line with the International League Against Epilepsy's (ILAE) definition of a refractory patient.

Figure 1: Clinical pathway for TSC-associated seizures including cannabidiol



Key: AED, anti-epileptic drug; TSC, tuberous sclerosis complex; VNS, vagus nerve stimulation.

A.3. Equality considerations

The use of cannabidiol is unlikely to raise any equality issues. Patient age is defined in the indication: Epidyolex is indicated for use as adjunctive therapy for seizures associated with TSC in patients 2 years of age and older.

A.4. The technology

Table 1: Technology being appraised – B.1.2 (page 11)

UK approved name and brand name	Cannabidiol/Epidyolex®
Mechanism of action	Cannabidiol has a novel, multi-modal mechanism of action. The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown. Cannabidiol reduces neuronal hyper-excitability and inflammation through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).
Marketing authorisation/CE mark status	The European Commission approved the marketing authorization for Epidyolex (cannabidiol) in LGS and DS on 19 September 2019. A submission for a Type II variation application was made to the EMA on 13 March 2020. The submission sought to expand the use of cannabidiol for the treatment of seizures associated with TSC. The European Commission approved the marketing authorization for Epidyolex (cannabidiol) in seizures associated with TSC on 16 April 2021. The MHRA approved the Type II variation application for Epidyolex (cannabidiol) as an adjunctive treatment of seizures associated with TSC for patients 2 years of age and older on 5 August 2021.
Indications and any restriction(s) as described in the summary of product characteristics	Epidyolex is indicated for use as adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older. Epidyolex is indicated for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.
Method of administration and dosage	Oral administration. For LGS and DS, the recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/ day) for 1 week. After 1 week, the dose should be increased to a maintenance dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 10 mg/kg twice daily (20 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 20 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule. For TSC, the recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/ day) for 1 week. After 1 week, the dose should be increased to a dose of 5 mg/kg twice daily (10 mg/kg/day) and the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of

	12.5 mg/kg twice daily (25 mg/kg/day). Any dose increases above 10 mg/kg/day, up to the maximum recommended dose of 25 mg/kg/day, should be made considering individual benefit and risk and with adherence to the full monitoring schedule.
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	The list price of cannabidiol is £850.29 per 100 ml (100 mg/ml) bottle.
Patient access scheme (if applicable)	A simple PAS is in place with the Department of Health for Epidyolex in DS and LGS. The company proposes that the PAS should be extended to the TSC-associated epilepsy indication. The PAS price is [redacted] per 100 ml (100 mg/ml) bottle.
Key: CE, cost-effectiveness; DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, patient access scheme; TSC, tuberous sclerosis complex.	

A.5. Decision problem and NICE reference case

The submission covers the technology's full marketing authorization for this indication.

The company submission differs from the final NICE scope and the NICE reference case (see Table 2).

Table 2: The decision problem – B.1.1 (page 9)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with TSC whose seizures are inadequately controlled by established clinical management	People with TSC whose seizures are inadequately controlled by current or prior established clinical management. People with TSC where usual-care is unsuitable or not tolerated.	This is in line with recommendations in NICE Clinical Guideline 137 (CG137).
Intervention	Cannabidiol in addition to current clinical management	Cannabidiol in addition to current clinical management ('usual-care')	Not applicable
Comparator(s)	Established clinical management without cannabidiol, such as: • ASMs • Everolimus • Vagus nerve stimulation • Ketogenic diet • Surgical resection	Established clinical management without cannabidiol, such as: • AEDs (also known as ASMs) • Vagus nerve stimulation • Ketogenic diet • Surgical resection Everolimus is included in the submission as a later line treatment.	In line with the NHS England Clinical Commissioning Policy (Everolimus for refractory focal onset seizures associated with TSC [ages 2 years and above], 2018), and the drug's safety/tolerability profile, everolimus is included in this submission as a later line treatment. Everolimus is not specifically an AED, but it may be considered as a last-line treatment option for people aged 2 years and older with refractory focal onset seizures associated with TSC (everolimus is not licensed

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			for generalized onset seizures) who have not adequately responded to treatment with at least two different AEDs given at therapeutic doses, and where epilepsy surgery has failed or is unsuitable and where vagus nerve stimulation has failed or is not considered appropriate by the patient, or their carer, in discussion with the treating clinician. Since everolimus is an immunosuppressant agent initially developed to prevent transplant rejection and for oncology indications, it is associated with a safety and tolerability burden, including non-infectious pneumonitis, increased infection risk, hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, myelosuppression and metabolic disorders. It should be noted that everolimus has a separate indication/dosing schedule in TSC that is not specifically related to seizures: for the treatment of subependymal giant cell astrocytoma, a benign tumour of the brain, where it is used in adults and children whose brain tumour cannot be surgically removed. For this indication and dosage, it may be considered in TSC earlier in the pathway, but not specifically for the treatment of seizures.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Change in frequency of seizures • Response to treatment • Adverse effects of treatment • Health-related quality of life	The outcome measures to be considered include: • Change in frequency of seizures • Response to treatment • Adverse effects of treatment • Health-related quality of life • Seizure-free days	Both seizure-free days and seizure frequency are important outcomes for patients with TSC-associated epilepsy. Previous submissions to NICE for cannabidiol in DS and LGS explicitly modelled seizure-free days and seizure frequency.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. A lifetime time horizon for estimating clinical and cost-effectiveness will be used. Costs will be considered from an NHS and Personal Social Services perspective.	Not applicable
Perspective for outcomes	All direct health effects, whether for patients or, when relevant, carers	All direct health effects, for patients and carers	Not applicable
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D	Health effects expressed in QALYs.	Trial data were unsuitable for use. A systematic and targeted literature review did not report any relevant

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	is the preferred measure of health-related quality of life in adults.	Health states: utilities sourced from vignettes in a general population sample valued using a TTO measure.	studies. EQ-5D is not sensitive in patients with severe epilepsy and fails to capture the impact of changes in seizure frequency. No suitable measure was identified to use to collect data directly from patients via a survey. ERG commentary (in the cannabidiol in DS and LGS NICE submissions) stated that the valuation of health-related quality of life should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method. This has been done for this appraisal. The vignette TTO data collection is in line with guidance in the NICE reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Vignettes in a general population sample valued using a TTO measure.	As above
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Representative sample of the UK population	Not applicable

Key: AED, anti-epileptic drug; ASM, anti-seizure medication; DS, Dravet syndrome; EMA, European Medicines Agency; LGS, Lennox–Gastaut syndrome; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; TSC, tuberous sclerosis complex; TTO, time trade-off.

A.6. Clinical effectiveness evidence

Table 3: Clinical effectiveness evidence

Study title	**GWPCARE6/GWEP1521/NCT02544763** (Thiele 2020)[1]	**GWPCARE6 open-label extension (NCT02544750)** (Thiele 2021)[2]
Study design	Phase III double-blind, randomized, placebo-controlled, multi-centre, multinational study	Phase III open-label extension study
Population	Children and adults aged 1 to 65 years* with a clinical diagnosis of TSC and a well-documented clinical history of epilepsy not completely controlled by their current AEDs. Taking one or more AEDs at a dose that had been stable for at least 1 month. At least eight TSC-associated seizures in the initial 28-day baseline period, with at least one seizure in at least 3 of the 4 weeks. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation, which were not counted as AEDs) stable for 4 weeks prior to screening.	Patients with TSC-associated refractory epilepsy aged 1-65 years* who had completed the GWPCARE6 randomized controlled trial
Intervention(s)	Cannabidiol 25 mg/kg/day in addition to usual-care	All participants received cannabidiol in addition to usual-care. Investigators could decrease or increase the participant's dose until the optimal dose was found.
Comparator(s)	Placebo in addition to usual-care	Not applicable
Outcomes specified in the decision problem **Note:** the decision problem specified that the outcome measures to be considered include:	• **Percent change in the number of TSC-associated seizures during the treatment period (16 weeks, comprising 4 weeks dose titration and 12 weeks dose maintenance) compared with baseline** • Number of patients considered treatment responders during the treatment period, defined as those with a ≥ 50% reduction in TSC-associated seizure frequency • **Change in number of TSC-associated seizure-free days**	• The primary endpoint of the study is safety and tolerability (measured via adverse events) • Key secondary endpoints include: – Percentage reduction in TSC-associated seizures – Responder rates – Quality of life (measured using the Subject/ Caregiver Global Impression of Change (S/CGIC) scale).

• Change in frequency of seizures • Response to treatment • Adverse effects of treatment • Health-related quality of life	• Number of participants with TRAEs • **Serious TEAEs classified as severe and considered to be treatment-related** • Change from baseline in Subject/Caregiver Global Impression of Change (S/CGIC) score at the participant's last visit • Changes in QOLCE or QOLIE-31-P score	
Reference to section in submission	B.2.2	B.2.11
Key: AED, anti-epileptic drug; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event, TSC, tuberous sclerosis complex. **Note:** *, The approved indication for Epidyolex is in patients aged ≥ 2 years.		

A.7. Key results of the clinical effectiveness evidence

A.7.1. Primary endpoint: change in number of TSC-associated seizures

In the GWPCARE6 randomised controlled trial, the 'treatment period' lasted 16 weeks: a 4-week 'titration period' followed by a 12-week 'maintenance period'. The primary endpoint was the change in number of TSC-associated seizures during the treatment period compared to the baseline period (intention-to-treat analysis set).

As noted in Document B, Section B.2.6.1, the GWPCARE6 trial met its primary endpoint, demonstrating that cannabidiol had a statistically significant and clinically meaningful effect compared with placebo (in addition to usual-care) in the median percentage reduction from baseline in TSC-associated seizure frequency. The reduction in seizure frequency compared with baseline for the cannabidiol 25 mg/kg/day plus usual-care group was 49% vs 27% for placebo plus usual-care (p = 0.0009).

During the maintenance period only of GWPCARE6 (i.e. the 12-week stable dosing period after titration), cannabidiol 25 mg/kg/day plus usual-care demonstrated a 56% reduction in TSC-associated seizures vs 30% with placebo plus usual-care (p = 0.0004).

A.7.2. Key secondary endpoints

All key secondary endpoints in GWPCARE6 were supportive of the primary endpoint:

- ***Treatment responders (≥ 50% TSC-associated seizure reduction)***
  - 36% of patients taking cannabidiol (25 mg/kg/day) plus usual-care had ≥ 50% seizure reduction vs 22% with placebo plus usual-care (p = 0.0692)
- ***Treatment responders (≥ 75% TSC-associated seizure reduction)***
  - 16% of patients taking cannabidiol (25 mg/kg/day) plus usual-care had ≥ 75% seizure reduction vs 0% with placebo plus usual-care (p = 0.0003)

- ***TSC-associated seizure-free days***
  - Patients taking cannabidiol (25 mg/kg/day) plus usual-care demonstrated a nominally statistically significant percentage of improvement in TSC-associated seizure-free days. Patients taking cannabidiol experienced an additional 2.8 seizure-free days per month vs the placebo group (p = 0.0047)
- ***TSC-associated seizure-freedom and total seizure-freedom***
  - The patients in the GWPCARE6 trial were particularly treatment-resistant, having tried and failed a median of four AEDs prior to entering the trial and continuing to take a median of three AEDs throughout the trial. Given the highly refractory nature of the trial population, achieving seizure-freedom is a key result
  - Despite the refractory nature of their epilepsy, in the maintenance period of the trial (the 12-week period when patients had completed titration and were on a stable dose), TSC-associated seizure-freedom was achieved in four of the 75 patients (5.4%) taking cannabidiol (25 mg/kg/day) plus usual-care compared with none of the 76 patients in the placebo plus usual-care group (p = 0.0354)
  - In the treatment period (the 16-week period including a 4-week titration followed by 12 weeks on a stable dose), one patient in the cannabidiol (25 mg/kg/day) plus usual-care arm achieved TSC-associated seizure-freedom vs none in the placebo plus usual-care arm (p = 0.3173)
  - Overall, one patient in the cannabidiol (25 mg/kg/day) plus usual-care group, experienced *total* seizure-freedom (i.e. no seizures of any type) during the treatment period, an important result in this highly refractory population

A.7.3. Quality of life - Subject/Caregiver Global Impression of Change score

The Subject/Caregiver Global Impression of Change (S/CGIC) is a patient-reported outcome (PRO) assessment completed by patients and caregivers. S/CGIC has been included in other Phase III studies for severe epilepsies and is an accepted measure of the patient's overall condition as a proxy for quality of life.

Scores are not reported at baseline as S/CGIC is a measure of change. Prior to randomization, the patient or caregiver is asked to write a brief description of the patient's overall condition as a memory aid. At the end of the treatment period, the patient/caregiver assesses the status of the patient's overall condition (compared with before treatment) on a seven-point scale: 'Very Much Improved'; 'Much Improved'; 'Slightly Improved'; 'No Change'; 'Slightly Worse'; 'Much Worse'; and 'Very Much Worse'.

S/CGIC represents a meaningful measure of health-related quality of life (HRQL) as it captures an estimate of the effect of treatment on the patient's overall condition based on his/her entire seizure and co-morbidity burden, thereby providing valuable information on the clinical meaningfulness of the therapy.

Using this measure, patients and caregivers reported an improvement in patients' overall condition in 69% of those receiving cannabidiol (25 mg/kg/day) plus usual-care vs 39% receiving placebo plus usual-care (Odds ratio [OR]: 2.25; nominal p = 0.0074).

A.8. Evidence synthesis

No meta-analyses, indirect treatment comparisons or mixed treatment comparisons were conducted.

Refractory epilepsy (also known as drug-resistant epilepsy) has been defined by the ILAE as failure of adequate trials of two tolerated and appropriately chosen and used AED regimens (as monotherapies or in combination) to achieve sustained freedom from seizures. A high proportion of patients with TSC-associated seizures are refractory despite taking a variety of AEDs, reflecting the complexity of the condition and the fact that patients are resistant to or are unable to tolerate current AEDs.

In the Phase III clinical trial of cannabidiol in TSC-associated epilepsy, the intervention was cannabidiol in addition to usual-care and the comparator was usual-care without cannabidiol (i.e. usual-care plus placebo). For patients considered for treatment with Epidyolex, it will be an add-on treatment for refractory seizures in people aged 2 years and older once two other appropriate AEDs, trialled to a maximally tolerated dose, have failed to achieve seizure freedom.

Therefore, the only viable comparator is established clinical management (usual-care).

A.9. Key clinical issues

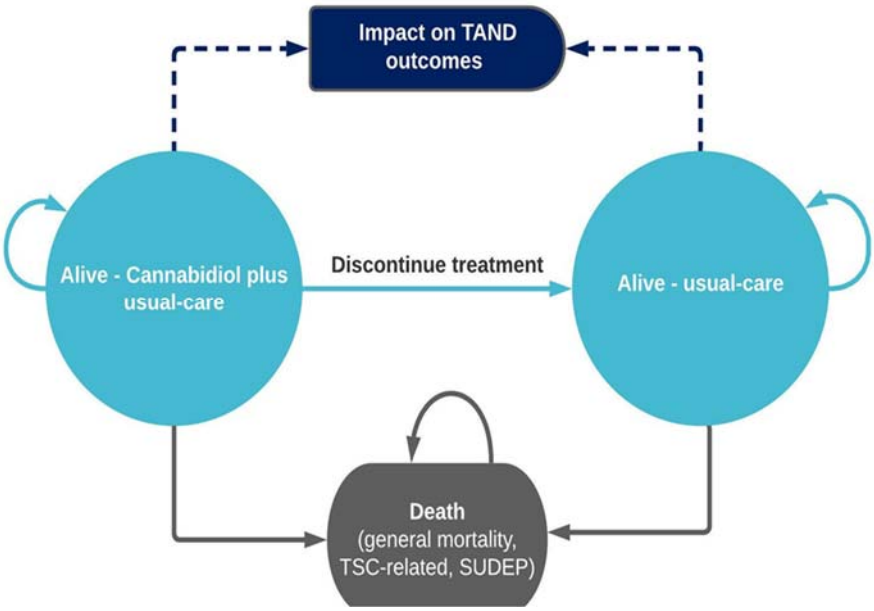
Not applicable.

A.10. Overview of the economic analysis

In line with the Epidyolex licence for TSC-associated epilepsy, the economic analysis estimates the cost-effectiveness of cannabidiol (Epidyolex®) plus usual-care as an adjunctive therapy for seizures associated with TSC in patients aged ≥ 2 years versus usual-care.

An overview of the modelling approach is provided in Table 4, with full details provided in Document B, Section B.3.2.2 (pages 70–80). A model process diagram is presented in Figure 2.

Table 4: Overview of the model approach

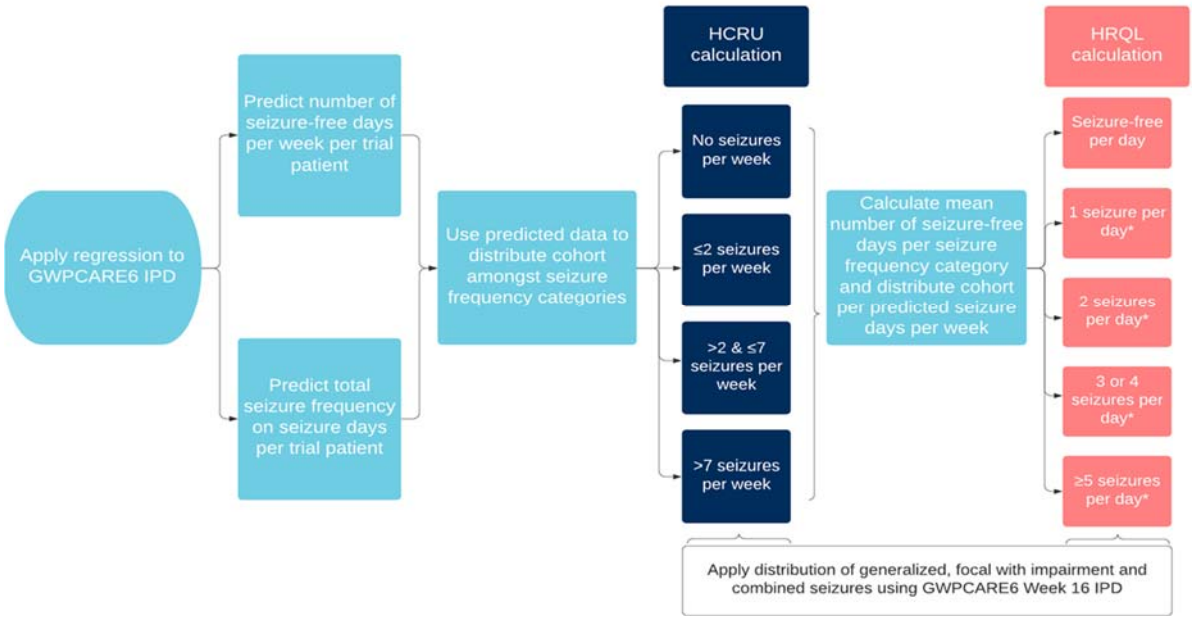
Model approach	A de novo cohort-level model predicting the expected probability of seizure-free days and associated seizure frequency was developed to evaluate the cost-effectiveness of cannabidiol in TSC-associated epilepsy.
Model structure	 **Key:** SUDEP, sudden unexpected death in epilepsy; TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex.
Seizure types	The model considers the impact of treatment on focal seizures with impairment of consciousness or awareness and generalized seizures.[a]
Treatment efficacy	Two independent regression models were applied sequentially to the GWPCARE6 (treatment period, NCT02544763) individual patient-level data to produce coefficients that were used to predict seizure-free days and seizure frequency.
Model outcomes	Health effects were measured in terms of life years and QALYs.

Time horizon	Given the chronic nature of the disease and a model-starting population age of 2 years, a lifetime time horizon (maximum of 100 years) was adopted in the model.
Cycle length	In line with the GWPCARE6 clinical trial weekly data collection, a 7-day cycle length was applied in the model.
Mortality	Probabilities for background mortality were estimated from age-specific general population mortality rates based on UK national life tables 2016–2018.[3] Background excess TSC mortality and background SUDEP mortality was included at the same rate in both arms.
HRQL	Vignettes using TTO methods valued by the general population were used to elicit utilities for patients and caregivers. In the model analysis, caregiver utilities are applied as decrements.
Long term relative efficacy	The base case analysis assumes a constant relative treatment effect following the 16-week blinded phase of GWPCARE6 maintained over the model time horizon, whilst patients are on cannabidiol plus usual-care treatment.
Stopping rules	A stopping rule is applied every 6 months for 2 years. The base case analysis assumes that cannabidiol treatment is stopped if seizure frequency has not fallen by at least 30% from baseline. This is in line with the stopping rule requested by NICE/NHS England in the DS/LGS appraisals.
Discontinuation	In addition to the stopping rule, the model includes discontinuation rates to reflect patients discontinuing treatment during the 16-week GWPCARE6 blinded trial period and the follow up OLE study (period of 72 weeks). A long-term discontinuation rate based on expectations across refractory epilepsies is applied post the OLE period for the model time horizon. This rate is in line with the long-term discontinuation rate requested by NICE in the DS/LGS appraisals. Patients who discontinue no longer receive the treatment effect observed with cannabidiol.
TAND	The impact of treatment on TAND (intellectual disability, delayed development, behavioural issues, autism spectrum disorder, ADHD, anxiety disorders) via an impact on seizure frequency change is included in the analysis.
Subsequent treatment	Patients who discontinue treatment with cannabidiol are expected to receive subsequent treatment (usual-care) with combinations of AEDs, everolimus and/or non-pharmacological treatments. The usual-care basket of AEDs is informed by the GWPCARE6 trial. The proportion receiving everolimus (7.7%; for the treatment of patients with focal-onset seizures) is informed by a retrospective analysis of the TOSCA registry.[4]

Key: ADHD, attention deficit hyperactivity disorder; DS, Dravet syndrome; HRQL, health-related quality of life; LGS Lennox-Gastaut syndrome; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; QALY, quality-adjusted life year; SUDEP, sudden unexpected death in epilepsy; TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex; TTO, time trade-off.

Note: [a], Generalized seizures are categorized as tonic-clonic, tonic, clonic or atonic seizures and focal seizures evolving to bilateral tonic-clonic seizures.

Figure 2: Model process diagram – B.3.2.2 (page 73)



Key: HCRU, healthcare resource use; HRQL, health-related quality of life; IPD, individual patient-level data.
Note: *, Seizure frequency per day categories are aligned to HRQL data collected by seizure type.

Model seizure frequency categories for HCRU and HRQL

Previous health technology assessment (HTA) submissions evaluating cannabidiol in Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) defined model health states based on low, medium and high seizure frequency and associated seizure-free days.[5, 6] The categorization of seizure frequency and seizure-free days allows for differential healthcare resource use (HCRU) and HRQL values to be calculated based on levels of seizure frequency and seizure-free days.

To model the HRQL and HCRU associated with differential seizure frequency and seizure-free days, the ‘alive health state’ is divided into sub-health states representing different seizure frequency categories. Different seizure frequency categories were defined for HRQL and HCRU to appropriately capture the patient, caregiver and clinician experience and impact on costs to the NHS and Personal Social Services.

In line with feedback from NICE during the DS/LGS appraisals, HRQL data were collected using vignettes in a general population valued using time trade-off (TTO)

methodology. Taking on board the previous ERG and NICE feedback, the vignette descriptions were designed to accurately capture the HRQL profile of people with TSC-associated epilepsy and their caregivers. The vignette health states varied in terms of seizure frequency and severity on seizure days.

HCRU in the model was informed by the results of a two-round Delphi panel study involving 10 clinical experts. The resource utilization questions in the Delphi panel study were framed using weekly seizure frequency rather than daily seizure frequency. The weekly time period and categories used were defined based on clinician feedback on the most easily understood units of measurement when thinking about average patients and corresponding annual HCRU.

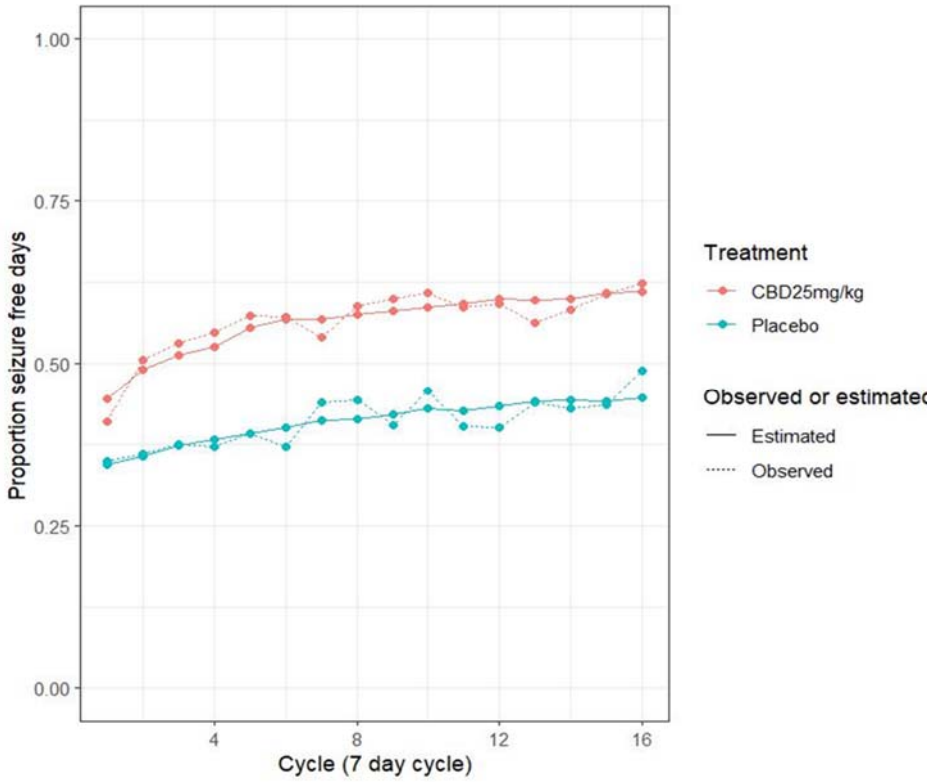
A.11. Incorporating clinical evidence into the model

Data for cannabidiol plus usual-care and placebo plus usual-care from the treatment period of the blinded GWPCARE6 clinical trial (Weeks 1–16) and data for cannabidiol from the 72 weeks of the open-label extension (OLE) Period (Weeks 17–88) were used to inform model inputs and validate model assumptions.

Efficacy data for cannabidiol plus usual-care and placebo plus usual-care were sourced from the treatment period of the GWPCARE6 trial.

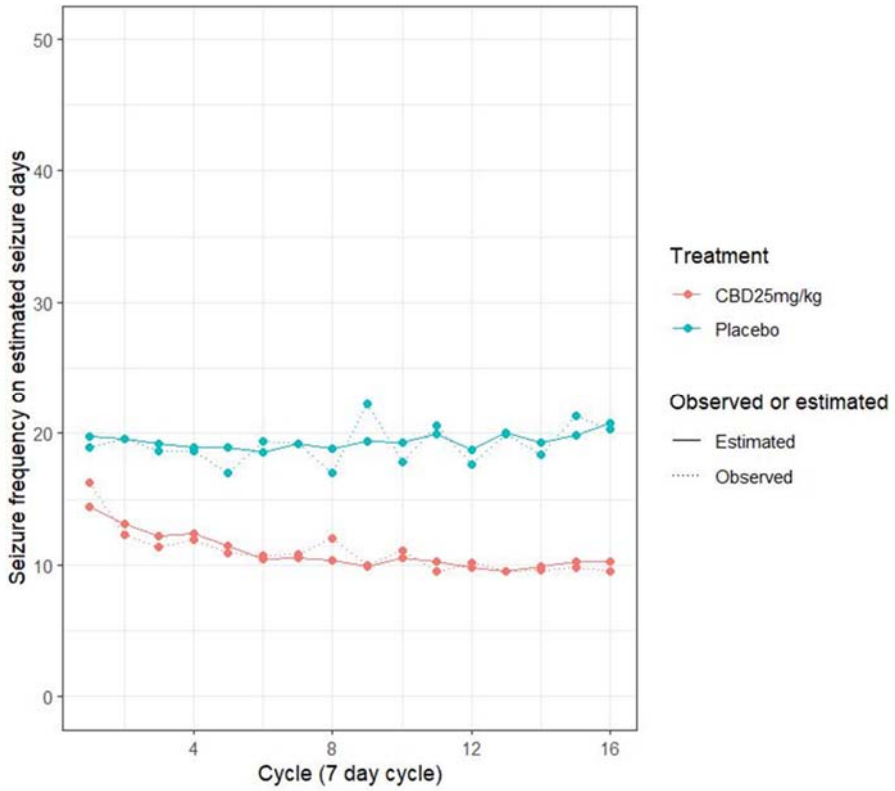
First, a binomial regression model was used to predict the proportion of seizure-free days per 7-day cycle; then, a negative binomial model was used to predict the total seizure frequency on the non-seizure-free days per 7-day cycle. The regression coefficients were applied to each patient's baseline seizure frequency from the GWPCARE6 trial at each 7-day model cycle to predict seizure-free-day and seizure frequency distributions. These individual calculations were used to distribute the cohort amongst sub-health-states representing different seizure frequency categories. Figure 3 and Figure 4 present the fitted values from the regression compared with the observed values from the GWPCARE6 (treatment period) and show that the model provides a good fit for the data.

Figure 3: Seizure-free days proportions for all observed cycles – B.3.3.2 (page 91)



Key: CBD, cannabidiol.

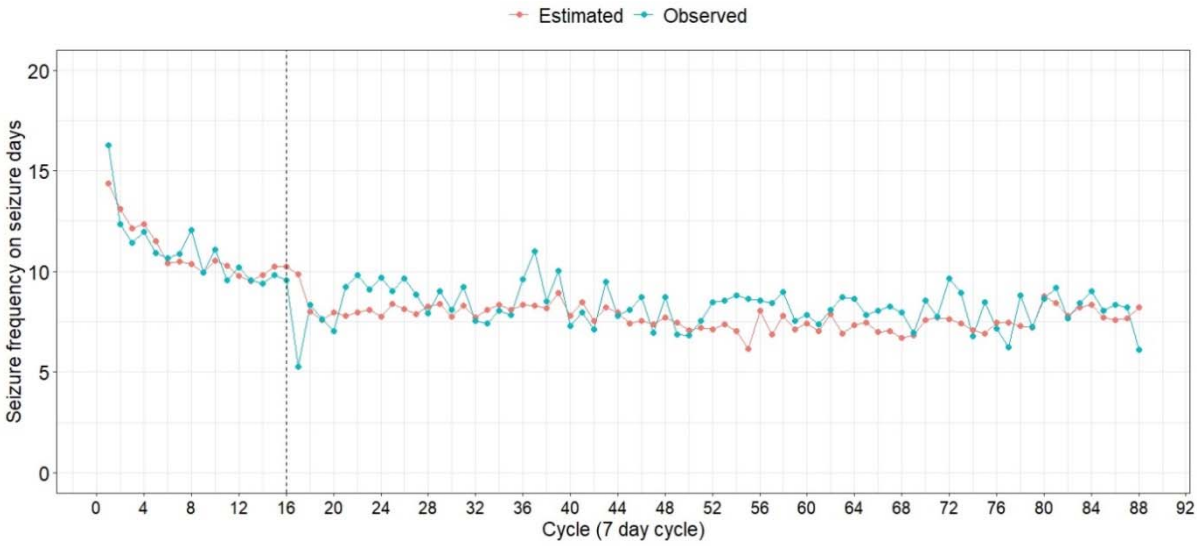
Figure 4: Seizure frequency on seizure days for all observed cycles – B.3.3.2 (page 91)



Key: CBD, cannabidiol.

The GWPCARE6 OLE data were used as validation of the predicted seizure frequency data. The OLE data were not used in the regression model as data were collected on a weekly basis rather than a daily basis, the number of seizure-free days was not recorded during the OLE and the number of missing days was not recorded. Figure 5 presents the extrapolated seizure frequency data from the fitted seizure frequency model compared with the observed OLE data. Overall, the regression model provides reasonable predictions for seizure frequency throughout the blinded trial and the OLE period.

Figure 5: Observed and estimated seizure frequency on observed and estimated seizure days during the OLE – B.3.3.2 (page 93)



Notes: Dashed line indicates the start of the OLE. Data are presented for the cannabidiol 25 mg/kg/day arm from the core trial.

The OLE data were also used to inform other model parameters such as stopping rule rates, discontinuation rates and TAND response rates.

Health-related quality of life data

The utility data collected in GWPCARE6 using the Quality of Life in Childhood Epilepsy (QOLCE) and Quality of Life in Epilepsy (QOLIE-31-P) questionnaires was deemed to be unsuitable for use in the economic model due to the following: the low response rates to the QOLIE-31-P (n = 11 in the cannabidiol arm and n = 10 in the placebo arm); lack of a published mapping algorithm for the QOLCE for the

paediatric population (described in Document B, Section B.3.4.2 and Section B.3.4.3); and the authors of the only mapping algorithm for QOLIE-31-P considering it to have only weak-to-moderate correlation with the EQ-5D.[7, 8]

A systematic literature review and two targeted literature reviews identified no suitable published utility data to inform patient or caregiver utilities for the analysis (Document B, Section B.3.4.4). Alternative options to collect HRQL data were therefore explored in line with NICE guidance[9], including patient and caregiver surveys and vignettes.

Patient and caregiver surveys were ruled out as an option due to the lack of a valid preference-based measure to use in a population with TSC-associated epilepsy. The validity of the EQ-5D has been questioned in this patient population.[7, 8, 10] A study which investigated mapping the QOLIE-31-P to the EQ-5D-3L found that it was unable to capture small changes in seizure frequency over time and could not measure epilepsy-specific concepts such as seizure anxiety.[8] In addition, a comparison of the instruments used in the GWPCARE6 trial to collect HRQL data with the EQ-5D found there was a limited overlap between the instruments and the EQ-5D, indicating that the EQ-5D is not suitable in this population to capture HRQL (see Document B, Section B.3.4.4 for more detail).

Vignettes were explored as an option as they can be constructed to suit the model health states and designed to reflect the patient condition and caregiver burden. Vignettes have been used in previous submissions for cannabidiol in DS and LGS.[5, 6, 11] Given the unsuitability of the trial HRQL data, lack of published utility data and a suitable preference-based measure, vignettes were selected as the best approach to collect HRQL for patients and caregivers.

To address issues associated with the methodology used for the collection of HRQL noted by NICE in the submissions for DS and LGS[12, 13], the health state vignettes were valued by a representative sample of the UK general population using TTO methods. The vignette descriptions included other aspects of TSC and TSC-associated epilepsy and were developed with input from healthcare professionals and caregivers (Document B, Appendix R).

A.12. Key model assumptions and inputs

The key assumptions of the economic analysis are described in Table 5. TSC-associated epilepsy is a rare (orphan) condition predominantly impacting children, limiting the data available for this small population. While the modelling approach made the best use of the clinical data available, in the absence of data, use of published literature and elicitation of data from experts was necessary. As acknowledged by NICE in their updated manual, there are certain conditions, such as rare diseases, for which evidence generation is particularly difficult. Therefore, in this circumstance, acceptance of a higher degree of uncertainty may be considered by the Committee.[9]

Table 5 presents the range of assumptions embedded in the economic analysis and how they have been made to minimize potential bias.

Table 5: Key model assumptions and inputs

Model input and cross reference	Source/assumption	Justification
Time horizon (Section B.3.2.2, page 78)	Lifetime	A lifetime horizon was used to capture all differences in costs and outcomes for all patients
Cannabidiol treatment dose in model analysis (Section B.3.2.3, page 81)	The model base case analysis uses an average cannabidiol dose of 12 mg/kg/day	Given the body of evidence supporting the efficacy of cannabidiol at a dose of 10 mg/kg/day[4-7], the lack of a dose response above 10-12 mg/kg/day, the worsening adverse event profile observed at higher doses, and the cautious 'low and slow' approach taken by UK physicians when increasing the dose of AEDs, it is likely that many UK patients with TSC-associated epilepsy will be treated at doses well below the maximum SmPC dose of 25 mg/kg/day.[14] Therefore, the 'average' dose used in the cost-effectiveness analysis base case reflects that *across a cohort of patients in clinical practice* there will be a spectrum of doses ranging from ≤ 10 mg/kg/day to the maximum of 25 mg/kg/day.
Long-term relative treatment effect (Section B.3.3.3, page 96-98)	The base case analysis assumes the relative treatment effect is consistent and maintained for the model time horizon while patients are on treatment with cannabidiol plus usual-care	The assumption of maintained benefit for cannabidiol in the longer term is supported by evidence of a consistent and durable treatment effect in patients treated with cannabidiol observed in OLE studies for TSC-associated epilepsy[15], DS and LGS[16, 17] and an expanded access programme in the US.[18] Assuming the relative treatment effect is consistent over the model time horizon is in line with NICE's preferred assumptions from the LGS[13] and DS[19] submissions.
Stopping rule assessment rate (Section B.3.3.5, page 107-108)	A 30% response stopping rule is applied at 6 months; patients whose seizure frequency has not reduced by 30% relative to baseline stop treatment.	This response rate aligns with the NICE recommended assessment rate for cannabidiol in LGS and DS.[5, 6] This assumption was validated with clinical experts at a health technology assessment advisory board.[20]

Model input and cross reference	Source/assumption	Justification
Discontinuation (Section B.3.3.5, page 102-103)	Discontinuation due to adverse events over the GWPCARE6 treatment period (cycles 1 - 16) is applied equally across seizure frequency health states. Once patients have discontinued treatment, they cannot the active treatment again	The analysis includes a discontinuation rate to reflect patients withdrawing from treatment due to adverse events based on data from the GWPCARE6 treatment period. It is reasonable to assume this, as patients continue to receive usual-care, with a proportion of patients receiving subsequent treatment with everolimus.
	Discontinuation rates for any reason during the OLE period (cycles 17 - 88) are applied to each seizure frequency health state and are applied to the cannabidiol plus usual-care arm only	The discontinuation rates during the OLE period are applied to the cannabidiol plus usual-care arm only, as only cannabidiol treatment was assessed during the OLE period. The rates were calculated per each seizure frequency sub-health state to reflect the varying levels of discontinuation evidenced in the OLE.
	The long-term discontinuation rate applied in the NICE appraisal for LGS is used in the base case analysis from model cycle 89	In the absence of longer-term discontinuation data beyond the 72-week OLE period, the long-term discontinuation rate used in the NICE appraisal for LGS was applied to the cannabidiol plus usual-care arm; discontinuation rates are expected to follow a similar trajectory because LGS is a similar severe epilepsy syndrome.[13]
Mortality (Section B.3.3.6, page 103-105)	Excess TSC-related mortality is applied equally to both treatment arms.	Patients with TSC have significant morbidity and mortality, both related to seizures (SUDEP) and unrelated. As data on mortality could not be collected within the timeframe of the GWPCARE6 trial, to be conservative, cannabidiol is assumed to have no impact on any of the aspects of TSC mortality.
	SUDEP mortality risk is applied equally across health states	To be conservative, cannabidiol is assumed to have no impact on SUDEP-related mortality despite information from the Ryvlin study[21] indicating that patients on efficacious treatments have a lower risk of SUDEP. This presents a source of potential benefit that has not been included in the cost-effectiveness analysis

Model input and cross reference	Source/assumption	Justification
TAND (Section B.3.3.8, page 107-111)	A utility increment and a 50% reduction in management costs is applied for a lifetime to patients (aged 2–6) who, after 6 months of treatment, have at least a 50% reduction in seizure frequency compared to baseline.	This assumption is based on clinical feedback that a reduction in seizure frequency is likely to lead to a reduction in TAND.[20] The relevant aspects of TAND, the age from which it is better to start treatment, and the required reduction in seizure frequency were informed by a two-round Delphi panel study involving 10 clinical experts.
HRQL (Section B.3.4.4, page 121-123)	Daily patient and caregiver utility values collected via a vignette study in the general population valued using time trade-off methodology.	The trial data were not suitable for mapping and the SLR and TLR did not report any relevant studies to inform the model. No appropriate preference-based measures were identified for use to directly elicit values in this population. The TTO study conducted was designed to address NICE feedback on the vignette studies used in the LGS/DS submissions which were valued in a live epilepsy population using VAS.[13, 19]
Number of caregivers (Section B.3.4, page 113-115)	Number of caregivers is assumed to be two per patient	The number of caregivers is based on the 2019 publication by Lagae[22], which states that, on average, patients with DS need more than two caregivers, approximately 2.06 caregivers. DS is a similar severe form of epilepsy and TSC-associated epilepsy patients are expected to require a similar level of care.
Healthcare resource use (Section B.3.5.2, page 136)	Resource use data collected using a two-round Delphi panel study involving 10 clinical experts	No UK resource use sources were identified from the SLR which could be used to directly inform the economic model. The resource use from the Delphi study was validated using a 2017 study by Shepherd et al.[23] which collected resource use in patients with TSC.

Key: DS, Dravet syndrome; EAP, expanded access programme; HRQL, health-related quality of life; LGS, Lennox–Gastaut syndrome; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; SmPC, summary of product characteristics; SUDEP, sudden unexpected death in epilepsy; TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex; TTO, time trade-off; VAS, visual analogue scale.

A.13. Base case ICER (deterministic)

Table 6 displays the base case cost-effectiveness results for cannabidiol plus usual-care compared with placebo plus usual-care. All results are presented including the current patient access scheme (PAS) in place for cannabidiol in DS/LGS, with a list price of £850.29 and a PAS price of [redacted] per 100 ml bottle (100 mg/ml).

Cannabidiol is estimated to provide additional discounted quality-adjusted life years (QALYs) of [redacted] (when including caregiver QALYs) at an additional discounted cost of [redacted]. The estimated incremental cost-effectiveness ratio (ICER) for cannabidiol is £12,876. As discussed in Section A.17 below, under the latest NICE methods, cannabidiol would meet the criteria for the application of a disease severity QALY modifier of 1.2. The results with consideration of the disease severity modifier, as detailed in Document B, Section B.3.3.9 and Section A.17 below, are presented in Table 7 with the ICER reducing to £10,730. The results demonstrate that cannabidiol is a cost-effective use of NHS resources when considering the severity of TSC-associated epilepsy.

As outlined in Section A.1, TSC-associated epilepsy is a rare condition (with n = 1,215 patients expected in England) impacting predominantly children. As acknowledged by NICE in their updated manual, cost-effectiveness estimates are inherently uncertain for small populations such as these; therefore, these analyses should be considered within that context, with a higher degree of uncertainty acceptable.[9] Nevertheless, the conservative nature of the cost-effectiveness approaches outlined in Table 5 means that even the results presented in Table 6 in isolation strongly suggest that cannabidiol is a valuable option in England for NHS patients with TSC-associated epilepsy and their families.

Table 6: Base case results (deterministic) – B.3.8 (Table 31, page 152)

Technologies	Total costs	Total QALYs		Incremental costs	Incremental QALYs	ICER (£/QALY)
Placebo plus usual-care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			
Cannabidiol plus usual-care	[redacted]	Patient QALY	[redacted]	[redacted]	[redacted]	£12,876
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 7: Results (deterministic), including disease severity modifier – B.3.8 (Table 32, page 152)

Technologies	Total costs	Total QALYs		Incremental costs	Incremental QALYs	ICER (£/QALY)
Placebo plus usual-care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			
Cannabidiol plus usual-care	[redacted]	Patient QALY	[redacted]	[redacted]	[redacted]	£10,730
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

A.14. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted where all inputs were varied simultaneously over 1,000 iterations. Distributional assumptions were driven by data wherever possible, and, in the absence of data, loose distributional assumptions were employed to ensure robust parameter uncertainty analysis (Document B, Section B.3.6). There is a [redacted] and [redacted] likelihood that cannabidiol is cost-effective at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 8: Base case results (probabilistic) – B.3.9 (Table 36, page 156)

Technology	Mean total costs	Mean total QALYs	Incremental		ICER (£/QALY)
			Mean costs	Mean QALYs	
Placebo plus usual-care	[redacted]	[redacted]			
Cannabidiol plus usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£14,074
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Figure 6: Scatterplot of probabilistic results – B.3.9 (Figure 20, page 156)

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

A.15. Key sensitivity and scenario analyses

Figure 7 shows a tornado diagram depicting the 10 parameters that have the greatest influence on the ICER versus placebo plus usual-care in one-way sensitivity analyses.

These results demonstrate that the ICER is most sensitive to the stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven seizures per week (the highest seizure frequency category), the patient utility value applied to seizure-free patients, and response rates used to estimate the proportion of patients who benefit from a reduction in TAND symptoms.

Figure 7: Tornado diagram – B.3.9 (Figure 22, page 158)

Key: CBD, cannabidiol; HS, health state; ICER, incremental cost-effectiveness ratio; pw, per week; TAND, TSC-related neuropsychiatric disorders; UC, usual-care.

Results of the top seven most influential scenario analyses are shown in Table 9. Further scenario analyses exploring parameter, methodological and structural uncertainties around the base case results are reported in Document B, Section B.3.9.3.

The results were relatively insensitive for most analyses, with cannabidiol remaining cost-effective in all scenarios at a WTP threshold of £20,000 per QALY gained.

The most influential scenario, which resulted in a dominant ICER, and has the largest impact resulting in cost-savings for the cannabidiol arm, is associated with the inclusion of wider social costs: social and educational care resource use, which was elicited via the two-round Delphi panel study.

Table 9: Key scenario analyses – B.3.9 (Table 37, page 160)

Scenario	Scenario detail	Brief rationale	Impact on base-case ICER
Base case ICER			£12,876
Age group to which TAND benefit applies	Applied to all patients	Exploration of the impact on cost-effectiveness of a key TAND assumption	£4,674
TAND benefit applied for how long [years]	5 years	Examine shorter impact of treatment on TAND aspects	£14,203
Patient HRQL source	Tritton 2019 (EQ-5D)[24]	Examine impact of different patient HRQL sources	£12,535
	Vergeer 2019 (HUI-3)[25]		£13,346
Number of caregivers	Three caregivers	To reflect impact on wider family, increase in number from two to three	£10,101
Resource use (inclusion of social care and educational costs)	Inclusion of resource costs related to social care and education support	To investigate the impact of including the wider cost of patient care	Dominant
Subsequent treatment with everolimus (applied to a proportion of patients in both arms)	Everolimus is not included as subsequent treatment	To examine impact of excluding everolimus as a later-line treatment option	£13,550
Cannabidiol dose	10 mg/kg/day	To reflect dose used in DS and LGS submissions	£7,326

Key: ICER, incremental cost-effectiveness ratio; HRQL, health-related quality of life; HUI-3, health utilities index three; NICE, National Institute for Health and Care Excellence; TAND, TSC-associated neuropsychiatric disorders.

A.16. Innovation

Up to two-thirds of patients with TSC-associated epilepsy are refractory to currently available treatments, many of which were developed more than 20 years ago, and some more than 50 years ago.

Epidyolex is an innovative therapy for patients with TSC-associated seizures. It is the first cannabinoid in its class, with a novel, multi-modal mechanism of action, different to that of other AEDs. In clinical trials involving patients with TSC-associated epilepsy (who had tried numerous other treatments without achieving seizure control), cannabidiol has demonstrated clinically and statistically significant reductions in seizure frequency and has a consistent, well-defined and manageable safety and tolerability profile.

Additional benefits of cannabidiol that are not captured in the QALY calculation include the value of:

- A beneficial impact on the mortality risk related to sudden unexpected death in epilepsy (SUDEP)
- Improving the quality of life of the wider family, including siblings
- Increasing caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not needing to give up work to care for a patient with TSC-associated epilepsy
- Reducing the duration/severity of seizures (the model only captures seizure frequency)
- The long-term impact of improved seizure control on co-morbidities and injuries

Cannabidiol represents a step-change in the treatment of TSC-associated epilepsy, offering patients who live with the constant threat of seizures and who otherwise have extremely limited treatment options the opportunity of a well-tolerated, long-term treatment with sustained efficacy. It reduces seizure frequency and gives patients the potential for seizure-freedom or additional seizure-free time, as well as the possibility of reducing TAND, limiting neurological decline and improving developmental outcomes.

For further information see the section on Innovation in the main submission: Document B, Section B.2.12 (page 58).

A.17. Disease severity modifier criteria

The updated 2022 NICE methods guidance introduced new criteria to reflect in exceptional circumstances the severity of disease within decision making.[9] The company is aware that this submission is being assessed under the old methods guidance. However, given that the guidance was recently updated in order to support patients with severe diseases, we considered it appropriate to provide an indication of the severity of TSC-associated epilepsy and the impact of this on the economic analysis.

As described in Section A.1, patients with TSC-associated epilepsy have reduced life expectancy and significant lifetime morbidity. Patients with TSC-associated epilepsy are expected to experience an absolute shortfall of between 12 and 18 QALYs over a lifetime horizon. As summarized in Table 10, cannabidiol as a treatment within the population defined in this decision problem satisfies the criteria for the application of a QALY weight of 1.2.

Table 10: Decision modifier – severity criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment meets an absolute QALY shortfall that is the future health, including quality and length of life, that is lost by people living with a condition, compared with the expected future health without the condition over the remaining lifetime of the patients.	The calculated lifetime (discounted) QALYs for patients with TSC-associated epilepsy treated with placebo plus usual-care consistent with the patient population of GWPCARE6: [redacted]	Section B.3.3.9 Page 111–112
	The calculated lifetime (discounted) QALYs patients without TSC-associated epilepsy consistent with the patient population characteristics of GWPCARE6: [redacted]	
	Model calculated an absolute shortfall of [redacted] QALYs for patients with TSC-associated epilepsy versus patients without	

A.18. Budget impact

Aligned with the outcomes of the cost-effectiveness analyses, when the PAS is applied, the net budget impact of cannabidiol remains under the £20 million threshold throughout the 5-year time horizon, as summarized in Table 11.

Table 11: Budget impact – company BIA document

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Total population of England (2 - 65 years) in 2022	45,848,224				
TSC prevalence rate (0.0053%)	2,431				
Proportion of patients with TSC-associated epilepsy (80.0%)	1,945				
Refractory to anti-epileptic drugs (62.5%)	1,215				
Eligible prevalent population[a]	**1,215**	**1,215**	**1,236**	**1,256**	**1,276**
Total number of live births in England		593,297	596,022	598,760	601,511
TSC incidence rate (0.0099%)		59	59	59	59
Proportion of patients with TSC-associated epilepsy (80.0%)		47	47	47	47
Refractory to anti-epileptic drugs (62.5%)		29	29	30	30
Incident population[b]		**29**	**29**	**30**	**30**
Patient died (in previous year: by year end)[c]		-9	-9	-9	-10
Total population (adjusted for prevalence, incidence and mortality)[d]	**1,215**	**1,236**	**1,256**	**1,276**	**1,296**
Total discontinuation (in previous year by year end)		[redacted]	[redacted]	[redacted]	[redacted]
Total stopping (in previous year: by year end)		[redacted]	[redacted]	[redacted]	[redacted]
Total discontinuation and stopping (cumulative)		[redacted]	[redacted]	[redacted]	[redacted]
Eligible for treatment[e]	1,215	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1 2022	Year 2 2023	Year 3 2024	Year 4 2025	Year 5 2026
Treatment Uptake (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated with cannabidiol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average treatment cost per person	Cannabidiol annual cost (including first-year titration) by age group: Age 2–6 years: [redacted] Age 7–11 years: [redacted] Age 12–17 years: [redacted] Age ≥ 18 years: [redacted] Cannabidiol long-term annual cost (not including first year of treatment) by age group: Age 2–6 years: [redacted] Age 7–11 years: [redacted] Age 12–17 years: [redacted] Age ≥ 18 years: [redacted]				
Estimated annual drug cost offsets[f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated annual management and adverse event cost offsets[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated annual budget impact on the NHS in England	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: NHS, National Health Service.
Note: a: Prevalent population from Year 2+, is calculated as a function of prevalence, incidence and mortality from the previous year
b: Incident population is calculated from birth incidence from 2 years previous
c: Patient mortality is calculated at year-end and applied to the following year calculations
d: Total population is adjusted for prevalence (at year end), mortality (at year end) and incidence
e: Eligible population in Year 2+ is calculated as a function of total population less cumulative discontinuation/stopping. All prevalent patients are assumed to be immediately eligible for treatment. As discontinuation/stopping rules apply from Year 1, the population who are eligible for treatment decreases over time as it is assumed there is no retreatment with cannabidiol
f: Annual drug costs offsets include a 10% reduction in AED costs to reflect the reduced use of concomitant AEDs in patients receiving cannabidiol and a reduction in the time spent using everolimus as a later line treatment due to the increased effectiveness of cannabidiol versus usual-care AEDs
g: Management and adverse event cost offsets includes the reduced management (outpatient and hospitalization) costs for patients treated with cannabidiol due to reduced seizure frequency

A.19. Interpretation and conclusions of the evidence

TSC-associated epilepsy is a debilitating, lifelong and treatment-resistant form of epilepsy, with an increased risk of death as a result of SUDEP or status epilepticus. Up to two-thirds of patients are refractory to current treatments.

Cannabidiol has been robustly evaluated in patients with refractory TSC-associated epilepsy in a global randomized controlled trial (GWPCARE6) and its associated ongoing OLE study.

- The blinded study met its primary endpoint: patients taking cannabidiol experienced a median 49% reduction in TSC-associated seizures versus 27% on usual-care ($p = 0.0009$), a clinically meaningful result. Cannabidiol also increased the chance of achieving TSC-associated seizure-freedom and/or additional seizure-free days
- Cannabidiol has a well-defined safety and tolerability profile. Most adverse events were mild to moderate, transient and resolved by the end of the trial
- The ongoing OLE study demonstrates that the efficacy of cannabidiol in reducing seizures is sustained in the longer term. Interim data up to 72 weeks demonstrating durability of outcomes have been reported

As outlined in section A.16 (Innovation) above, additional benefits of cannabidiol that are not captured in the economic analysis include: a beneficial impact on the SUDEP mortality risk; improving the quality of life of the wider family, including siblings; increasing caregiver productivity; reducing the duration/severity of seizures; the long-term impact of improved seizure control on co-morbidities and injuries.

Cannabidiol offers patients with refractory TSC-associated seizures the opportunity of a well-tolerated, long-term treatment with sustained efficacy. It reduces seizures and gives patients the potential for seizure-freedom or additional seizure-free time, as well as the possibility of reducing TAND, limiting neurological decline and improving developmental outcomes.

Over a lifetime time horizon, the ICER for cannabidiol in addition to usual-care versus usual-care alone is £12,876 per QALY gained. Thus, cannabidiol is cost-effective in patients who have extremely limited other treatment options.

The number of refractory patients with TSC-associated epilepsy eligible for treatment with Epidyolex is estimated to be 1,215. Cannabidiol will have a limited budget impact due to the orphan nature of TSC-associated epilepsy, as well as cost offsets associated with disease management.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Clarification questions

May 2022

File name	Version	Contains confidential information	Date
ID1416 Cannabidiol ERG Clarification Letter v1.1 - company responses 06May2022	1.0	Yes	06 May 2022

Section A: Clarification on effectiveness data

Searches

A1. The ERG noted that the Medline search appears to contain Emtree subject headings rather than MeSH terms. It also states that the search was conducted via Embase. Please can you confirm that by this you mean a search of the Embase database conducted on the understanding that it now contains all records from Medline or was this a separate search of both resources using the same strategy?

We confirm that we searched Medline via the Embase database, on the understanding that it now contains all records from Medline.

A2. Whilst reference checking is mentioned in Appendix H for the targeted literature review, there is no mention of it in Appendix D for the main searches. Please confirm whether this took place for the main systematic literature review (SLR).

Yes, reference checking of existing systematic literature reviews was conducted for the main SLR, to identify additional relevant publications.

Decision problem

A3. Priority: Whereas the final NICE scope does not include people with Tuberous sclerosis complex (TSC) where usual care is unsuitable or not tolerated by current or prior established clinical management, the company does. The company claims that this modified population is justified because it is "*in line with recommendations in NICE Clinical guideline 137 (CG137).*"

a. Please specify where in NICE Clinical Guideline 137 it explicitly makes recommendations for people with TSC where usual care is unsuitable or not tolerated.

Nice Clinical Guideline 137 does not *explicitly* make recommendations for people with TSC-associated epilepsy.

However, more generally for all patients with epilepsy, NICE CG137 makes the following recommendation: "Treatment should be reviewed at regular intervals to ensure that children, young people and adults with epilepsy are not maintained for

long periods on treatment that is ineffective or *poorly tolerated".* This applies to patients with TSC-associated epilepsy.

Furthermore, it is well known that certain AEDs are not suitable for all patients. For example, sodium valproate is associated with a risk of teratogenicity, therefore it is often deemed to be *unsuitable* for women of childbearing age. NICE CG137 states "Do not offer sodium valproate to women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years) unless other options are unsuitable, ineffective or not tolerated and the pregnancy prevention programme is in place".

b. Please specify what constitutes usual care.

In TSC-associated epilepsy, because there is no standard of care once a patient is refractory, various terms have been used (interchangeably) to describe the variety of treatments used in an attempt to gain seizure control. These terms include, for example, 'current clinical management', 'established clinical management', 'usual-care'.

In the GWPCARE6 trial of cannabidiol, patients entering the trial were permitted to be taking any AEDs/other treatments (except those listed as exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/ combinations of treatments are what are referred to as 'usual-care' in our submission. Cannabidiol was an add-on to usual-care.

Please see question A9 below for further detail.

c. Is there a difference between the treatments termed as usual care and established clinical management? If yes, please specify.

No, the terms are used interchangeably.

d. Please specify the main reasons that account for the unsuitability or intolerability of usual care.

Reasons for unsuitability include: teratogenicity risk (e.g. sodium valproate for females of childbearing age); contraindications/cautions (e.g. carbamazepine is contra-indicated for patients with a history of bone marrow depression; topiramate

should be used with caution in patients with acute porphyrias, metabolic acidosis and/or glaucoma); patient/caregiver preference (for example, some parents choose not to allow their child to have certain drugs due to their side-effect profile/perceived risk).

Reasons for intolerability: this is usually related to side-effects. Examples include: vigabatrin is associated with visual defects; benzodiazepines are associated with drowsiness. Patients/caregivers may choose to discontinue a treatment as a result of these side-effects.

e. Please specify the criteria used to judge whether usual care is classified as unsuitable.

This is a decision taken for each individual patient by the clinician, in conjunction with the patient, the patient's caregivers and/or the multidisciplinary team responsible for the patient's care.

f. Please specify the criteria used to judge whether usual care is classified as not tolerated.

This is a decision taken for each individual patient by the clinician, in conjunction with the patient, the patient's caregivers and/or the multidisciplinary team responsible for the patient's care.

g. Please provide a comparison of effectiveness, safety and cost-effectiveness for cannabidiol versus all relevant comparators for patients who do and do not receive usual care.

As outlined above, *all* patients receive usual-care. Cannabidiol is an add-on to usual-care.

A4. Priority: Whereas the final NICE scope lists everolimus as a comparator, in their submission (Document B), the company lists it as a later line of therapy. The company justifies this based on:

a. NHS England Clinical Commissioning Policy (Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above) 2018)[1]. Please elaborate on how this document supports using

everolimus as a later line therapeutic option as opposed to its indication specified in the final NICE scope?

The comparator in the final NICE scope is “Established clinical management without cannabidiol”.

In the NHS England Clinical Commissioning Policy, everolimus is positioned as a later line treatment. For a patient to be eligible for treatment with everolimus, there is a need not only for inadequate response to two or more AEDs, but also for failure/ruling out of both epilepsy surgery and vagus nerve stimulation (VNS) by a multidisciplinary team including, but not limited to, a radiologist, and a neurology specialist with experience in TSC management. There is also a stated requirement to have local availability of services to support therapeutic drug monitoring.

It should be noted that everolimus is only licensed for a *subset* of TSC-associated seizures. It is indicated as adjunctive treatment of patients aged 2 years and older whose refractory *partial onset seizures*, with or without secondary generalisation, are associated with TSC. Unlike cannabidiol, everolimus is *not* licensed for generalised onset TSC-associated seizures.

In the NHS England Clinical Commissioning Policy, the ‘Criteria for Starting treatment’ are as follows:

Patients aged 2 years and older with a confirmed diagnosis of TSC related seizures whose *refractory partial-onset seizures* (focal onset seizures) are associated with TSC, AND

- whose TSC-related seizures have not adequately responded (meaning 2 or more partial onset seizures per month OR recurrent status epilepticus to treatment with at least 2 different AEDs titrated to a therapeutic dose; AND
- who have previously been considered for surgical resection as assessed by a designated Children’s Epilepsy Surgery Service (CESS) or adult specialised epilepsy surgery service. Specifically, the CESS / specialised adult service will have previously decided that:
    - there is no brain abnormality which can be identified as causing seizures that can be removed surgically without unacceptable risks; OR

    - there are multiple or infiltrative brain abnormalities which may be causing seizures which cannot be removed surgically; OR
    - surgery has been performed and the seizures have not adequately reduced in frequency or severity; AND
- who have been considered for VNS and:
    - VNS was not considered appropriate as the next treatment option by the patient, or their carer in discussion with the treating clinician; OR
    - VNS has been performed and seizures have not adequately reduced in frequency or severity; AND
- for whom, in the opinion of a properly constituted multi-disciplinary team (MDT) (as defined in the governance arrangements), everolimus is considered more appropriate than a trial of an alternative AED (in line with NICE CG137 which states that treatment strategies should be individualised).

b. "*The drug's [everolimus'] safety/tolerability profile*" (stated in company submission, Document B). Please provide evidence contrasting the safety/tolerability of cannabidiol with that of everolimus?

Everolimus is an mTOR inhibitor. The mTOR inhibitors are anti-tumour agents with immunosuppressive properties. In addition to TSC-associated seizures, everolimus is indicated for treatment of advanced or progressive malignancies (breast cancer, neuroendocrine tumours, and renal cell carcinoma), as well as non-cancerous tumours in patients with TSC. Adverse reactions to everolimus include non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing, metabolic disorders, and myelosuppression.

The safety and tolerability profile of cannabidiol is consistent, well-defined and manageable, as demonstrated across five randomised controlled Phase III trials in severe refractory epilepsies, including TSC-associated epilepsy, DS and LGS. In GWPCARE6, most adverse events were mild to moderate, transient and resolved by the end of the trial. The most common adverse events were diarrhoea (31% of patients treated with 25 mg/kg/day cannabidiol vs 25% of patients in the placebo group), decreased appetite (20% and 12%, respectively), vomiting (17% and 9%, respectively) and somnolence (13% and 9%, respectively).

c. That everolimus is not specifically an anti-seizure medication (ASM). Can the company please state why not being specifically an ASM is relevant to whether it is included in the final NICE scope and should be used as a comparator by the company?

In the draft scope prior to the decision problem meeting, everolimus was included as follows: “Anti-epileptic drugs, which may include everolimus”.

The company was simply pointing out that everolimus is *not* an AED/ASM. It is an mTOR inhibitor with prior indications in immunosuppression and cancer.

d. Everolimus’ “*safety and tolerability burden*” (stated in company submission Document B). Given that all the comparators (as well as the intervention) also have potential adverse effects, please justify excluding everolimus as a direct comparator on this basis.

The comparator in the NICE final scope is “Established clinical management without cannabidiol”. Therefore everolimus alone is not a direct comparator, regardless of its safety and tolerability burden.

e. In the company submission (Document B), the company states that everolimus “*may be considered in TSC earlier in the pathway, but not specifically for the treatment of seizures.*” Can the company please provide additional rationale for this assertion?

Everolimus has a separate indication/dosing schedule in TSC that is not specifically related to seizures: for the treatment of subependymal giant cell astrocytoma (SEGA), a benign tumour of the brain, where it is used in adults and children whose brain tumour cannot be surgically removed. For this indication and dosage, it may be considered in TSC earlier in the pathway, but it is licensed to treat SEGA and not specifically for the treatment of TSC-associated seizures.

A5. Regarding the addition of seizure-free days as an outcome, please provide evidence regarding the extent to which seizure-free days are correlated with seizures.

Seizure-free days is not an addition to the outcomes. Change in seizure-free days was a pre-planned secondary endpoint in the GWPCARE6 clinical trial and has been

included as an outcome in prior submissions for refractory epilepsies: TA614 and TA615 and ID1109.[2-4] It is a clinically important outcome for patients and caregivers and a crucial element when considering the impact and efficacy of cannabidiol in patients with TSC-associated epilepsy. In the GWPCARE6 trial, patients taking cannabidiol (25 mg/kg/day) experienced an additional 2.8 seizure-free days per month vs the placebo group (p=0.0047).[5]

The previous models accepted by NICE for cannabidiol in DS and LGS included seizure-free days as an important aspect of quality of life. Auvin et al. reinforce the importance of seizure-free days as a specific outcome, concluding that, whilst fewer seizures and additional seizure-free days both improved quality of life in caregivers and patients, seizure-free days had the greatest impact on patient quality of life.[6]

As detailed in Document B, improvements in quality of life and patient wellbeing are linked to both the number of seizures experienced, as well as how these seizures are distributed over time. A period of seizure-free time (whether several hours in a day, or seizure-free days) has the potential to improve quality of life for patients and their families.

Additionally, feedback from clinicians and patient organisations also highlights the importance of seizure-free days:

- Clinical experts at an advisory board meeting highlighted that seizure-free days matter more in terms of quality of life than a change in seizure frequency.[7]
- “Whilst reductions in convulsive seizures and drop seizures are of most medical benefit, other changes in seizure activity, including altering patterns of seizures leading to increased seizure-free days, should be viewed as clinically/statistically significant.” - Epilepsy Action, comment on HTA for cannabidiol in DS and LGS.[8, 9]

Therefore, it is clinically important to include seizure-free days as an outcome in the analysis.

We would expect to see a moderate negative correlation between seizure frequency and seizure-free days, i.e. a reduction in seizure frequency might lead to an increase in seizure-free days. However, although seizure frequency and seizure-free days

may be moderately correlated, it is possible to experience a reduction in seizure frequency without a corresponding increase in seizure-free days and vice versa.

The NICE committee conclusion from the ACD for TA614 and TA615 considered it appropriate to capture the benefits of having more seizure-free days. However, the committee also considered that the approach used (categorisation into number of seizures, and then subdivision of these into number of seizure-free days) may have resulted in 'double-counting' the benefits of reducing the frequency of seizures.

To address this, the modelling approach used in the current submission allows for the separate modelling of seizure-free days and seizure frequency, whilst also accounting for the correlation between both. Firstly, a binomial regression model was used to predict the proportion of seizure-free days per cycle. Secondly, a fitted negative binomial model was used to predict the total seizure frequency on the non-seizure-free days per cycle. The correlation between both outcomes is therefore captured, as seizure frequency is only estimated for the days in each cycle when patients are expected to have seizures.

GWPCARE6 trial and data analysis

Population

A6. Priority: Table 4 in the company submission lists the UK as one of the GWPCARE6 study locations. Please provide the number of UK patients randomised and provide the baseline characteristics of these patients by study arm.

Eleven patients from the UK were screened, and 7 of the 11 were randomised. Two of the seven were randomised to the 50 mg/kg/day dose and are not included here. The baseline characteristics of the other 5 patients from the UK are shown in Table 1 below.

Table 1: UK patients - baseline characteristics

Patient	UK 1	UK 2	UK 3	UK 4	UK 5
Study arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	UK 1	UK 2	UK 3	UK 4	UK 5
Previous AEDs (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current AEDs (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking clobazam?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking valproic acid?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking vigabatrin?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking levetiracetam?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: F, female; M, male; W/C, White/Caucasian

A7. Priority: Please discuss the generalisability of the study baseline characteristics to the general UK population (with supporting documents).

The company considers that the GWPCARE6 study baseline characteristics are generalisable to the general UK population:

- UK specialist clinicians agree that the participants with TSC-associated epilepsy in the GWPCARE6 trial broadly reflect the characteristics of people seen in their clinical practice in the UK National Health Service (NHS). This was noted in an HTA advisory board meeting[7] and also confirmed in recent discussions (conducted to inform our responses to the ERG) with two UK clinical experts - consultant neurologists Professor Finbar O'Callaghan and Dr Sam Amin.
- The GWPCARE6 trial included UK patients (see Table 1 in question A6 above)
- The diagnostic criteria for TSC-associated epilepsy in the trial were based on international guidelines, which are applicable to UK patients.

Comparator

A8. Priority: Please provide evidence that the comparator treatments in the GWPCARE6 trial are representative of UK clinical management. In particular, please compare and contrast the comparator in the trial with established clinical management or usual care as would be the case in NHS clinical practice.

A9. Cannabidiol appears to have been given to patients who remain on the clinical management (usual care) that they were on before the start of the trial.

a. Please clarify if the usual care interventions permitted during the trial were protocol-specified.

b. Please list all permitted usual care interventions, and provide data about the patients who received these, divided according to treatment group.

c. Please list any other permitted concomitant medications (non-usual care) and provide data about how many patients in each arm received these.

A9. a, b and c. We confirm that cannabidiol was an add-on to usual-care. The usual-care interventions were not protocol-specified. Patients entering the GWPCARE6 trial were permitted to be taking any AEDs/other treatments (except those in the exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/combinations of treatments are what are referred to as 'usual-care' throughout our submission.

Refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control. As a result, ‘usual-care’ comprises many different AEDs/combinations of AEDs - demonstrating that there is no standard of care once a patient is refractory.

Table 2 and Table 3 below show the range of different drugs available, and thus the huge number of potential combinations.

Table 2: GWPCARE6 – prior and concomitant AEDs

	Median number of prior medications	**Median number of concomitant AEDs**	**Concomitant AEDs (5 most common)**
Placebo (n=76)	4 (up to 15)	3 (up to 5)	45% valproate 33% vigabatrin 29% levetiracetam 27% clobazam 22% lamotrigine
Cannabidiol 25 mg/kg/day (n=75)	4 (up to 13)	3 (up to 4)	

Table 3: Concomitant AEDs

Table 8.2-6 Concomitant Antiepileptic Medications (Excluding Rescue Medications) (Safety Analysis Set)				
Therapeutic Class Preferred Term	**25 mg/kg/day GWP42003-P (N=75) n (%)**	**50 mg/kg/day GWP42003-P (N=73) n (%)**	**Pooled Placebo (N=76) n (%)**	**Total (N=224) n (%)**
Patients taking any concomitant medications	**74 (98.7)[a]**	**73 (100)**	**76 (100)**	**223 (99.6)**
Barbiturates and derivatives	**3 (4.0)**	**3 (4.1)**	**2 (2.6)**	**8 (3.6)**
Phenobarbital	2 (2.7)	3 (4.1)	1 (1.3)	6 (2.7)
Primidone	1 (1.3)	0	1 (1.3)	2 (0.9)
Benzodiazepine derivatives	**25 (33.3)**	**30 (41.1)**	**32 (42.1)**	**87 (38.8)**
Clobazam	17 (22.7)	19 (26.0)	25 (32.9)	61 (27.2)
Clonazepam	6 (8.0)	9 (12.3)	4 (5.3)	19 (8.5)
Lorazepam	2 (2.7)	1 (1.4)	2 (2.6)	5 (2.2)
Midazolam	1 (1.3%)	0	1 (1.3%)	2 (0.9)
Clorazepate dipotassium	0	1 (1.4)	0	1 (0.4)
Nitrazepam	0	1 (1.4)	0	1 (0.4)
Carboxamide derivatives	**30 (40.0)**	**22 (30.1)**	**24 (31.6)**	**76 (33.9)**
Oxcarbazepine	13 (17.3)	12 (16.4)	10 (13.2)	35 (15.6)
Carbamazepine	11 (14.7)	9 (12.3)	6 (7.9)	26 (11.6)
Rufinamide	7 (9.3)	1 (1.4)	8 (10.5)	16 (7.1)
Eslicarbazepine acetate	2 (2.7)	0	1 (1.3)	3 (1.3)
Fatty acid derivatives	**42 (56.0)**	**50 (68.5)**	**46 (60.5)**	**138 (61.6)**
Valproic acid	29 (38.7)	36 (49.3)	35 (46.1)	100 (44.6)
Vigabatrin	28 (37.3)	29 (39.7)	17 (22.4)	74 (33.0)
Tiagabine hydrochloride	0	0	1 (1.3)	1 (0.4)
Hydantoin derivatives	**0**	**0**	**3 (3.9)**	**3 (1.3)**
Phenytoin	0	0	3 (3.9)	3 (1.3)
Other antiepileptics	**56 (74.7)**	**55 (75.3)**	**58 (76.3)**	**169 (75.4)**
Levetiracetam	19 (25.3)	22 (30.1)	24 (31.6)	65 (29.0)
Lamotrigine	17 (22.7)	15 (20.5)	18 (23.7)	50 (22.3)
Lacosamide	16 (21.3)	15 (20.5)	12 (15.8)	43 (19.2)
Topiramate	7 (9.3)	14 (19.2)	12 (15.8)	33 (14.7)
Zonisamide	9 (12.0)	2 (2.7)	7 (9.2)	18 (8.0)
Felbamate	6 (8.0)	3 (4.1)	4 (5.3)	13 (5.8)
Perampanel	4 (5.3)	5 (6.8)	1 (1.3)	10 (4.5)
Gabapentin	1 (1.3)	2 (2.7)	1 (1.3)	4 (1.8)
Pregabalin	0	2 (2.7)	1 (1.3)	3 (1.3)
Brivaracetam	0	1 (1.4)	1 (1.3)	2 (0.9)
Selective immunosuppressants	**1 (1.3)**	**0**	**1 (1.3)**	**2 (0.9)**
Everolimus[b]	1 (1.3)	0	0	1 (0.4)
Sirolimus[c]	0	0	1 (1.3)	1 (0.4)
Succinimide derivatives	**1 (1.3)**	**0**	**0**	**1 (0.4)**
Ethosuximide	1 (1.3)	0	0	1 (0.4)

A10. Please provide more detail on the decision-making process underlying choice of the ‘usual care’ treatments. Were these decisions made freely on the basis of clinical need at the discretion of the attending clinician, or were they taken from a list of pre-hoc agreed ‘usual care’ treatments (if so please specify them)?

The patient's 'usual-care' was at the discretion of the clinician (for the reasons outlined in question A9 above).

A11. There was a large discrepancy between groups at baseline for use of vigabatrin, with 37% of the cannabidiol group using it compared to 22% of the placebo group. This was offset by slightly larger uses of valproic acid, levetiracetam and clobazam in the placebo group. Given that vigabatrin is considered the first line drug (company submission, Figure 4, Document B), this discrepancy may have important influences on outcome. Please explain how this potential threat to internal validity has been accounted for in the analysis.

The company does not consider that there is a threat to internal validity.

As stated in our submission, vigabatrin is recommended as first-line monotherapy for TSC-associated *infantile spasms* and/or focal seizures in children <1 year old. Vigabatrin is associated with irreversible visual field defects, including blindness in severe cases, and is therefore not suitable for all patients.

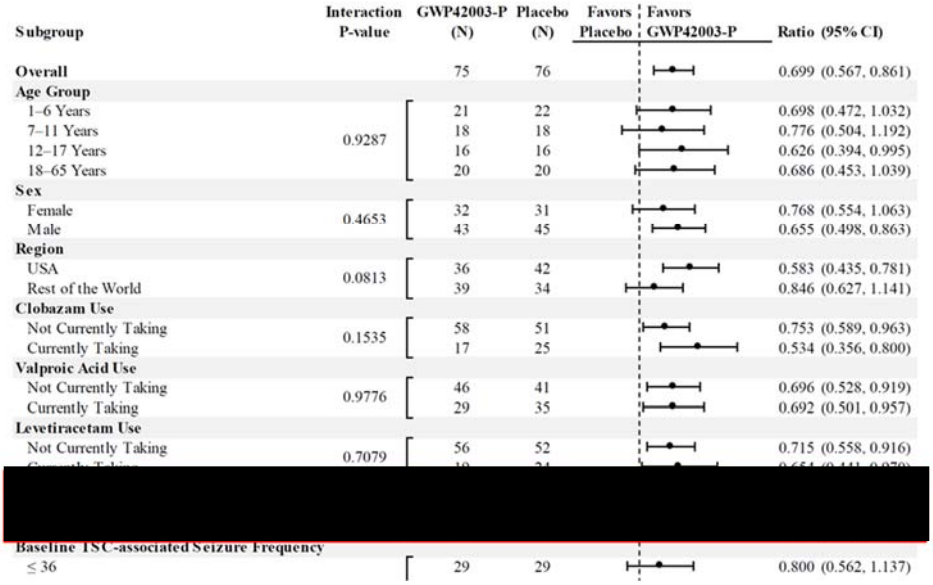
As explained in question A9, refractory patients with TSC-associated epilepsy may cycle through many AEDs in an attempt to achieve seizure control.

The majority of patients with refractory TSC-associated epilepsy in the GWPCARE6 trial had already *tried and failed* vigabatrin i.e., the drug did not lead to seizure control. The GWPCARE6 trial population had failed to achieve seizure control with a median of 4 AEDs prior to entering the study. Vigabatrin was among the most common of these AEDs, having already been tried and stopped by 43% of patients prior to entering the study. In addition, a further 33% of patients were taking vigabatrin on entering the study, meaning that, by definition, it was not working as they were not achieving adequate seizure control. Therefore, in total, >75% of the GWPCARE6 trial population had already failed to achieve seizure control with vigabatrin.

The results of a pre-specified subgroup analysis show no effect on the primary endpoint whether the patient was taking or not taking vigabatrin (see Figure 1 below).

Figure 1: Subgroup analysis of the primary endpoint

Figure 8.4.1.3.1-1 Subgroup Analysis of the Primary Endpoint (25 mg/kg/day GWP42003-P vs. Placebo): Negative Binomial Regression Effect Modification Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)



Outcomes

A12. Priority: Section 5.5.2.5 of the clinical study report (CSR) states, "*Effects on quality of life were therefore measured using the QOLCE/QOLIE-31-P questionnaires which have good construct validity, internal consistency, test-retest reliability, and sensitivity to epilepsy severity*."[10] Section 10.1 of the CSR states: "*these patients had a poor quality of life based on the low mean overall QOLCE and QOLIE-31-P scores of approximately 44–50 at baseline*."[10] Yet, the company did not present detailed data for this outcome in their submission.

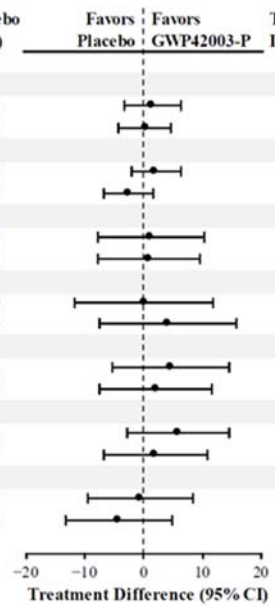
a. **Please provide all outcome data that reports results of the QOLCE/QOLIE-31-P questionnaires.**

Please see Figure 2 below for QOLCE and Table 4 below for QOLIE-31-P.

Figure 2: Change from Baseline to End of Treatment in QOLCE

Figure 8.4.1.2.2.5-1 ANCOVA of Change from Baseline to End of Treatment in Quality of Life in Childhood Epilepsy Score (2–18 Years by Subscale (ITT Analysis Set)

Subscale Comparison vs. Placebo	GWP42003-P (N)	Placebo (N)	Treatment Difference (95% CI)	Nominal P-value
Overall Quality of Life[a]				
25 mg/kg/day GWP42003-P	37	45	1.5 (−3.3, 6.3)	0.5316
50 mg/kg/day GWP42003-P	47	45	0.3 (−4.2, 4.7)	0.9023
Behavior				
25 mg/kg/day GWP42003-P	44	49	2.0 (−2.2, 6.3)	0.3443
50 mg/kg/day GWP42003-P	49	49	-2.5 (−6.7, 1.6)	0.2282
Attention/Concentration				
25 mg/kg/day GWP42003-P	38	43	1.2 (−7.9, 10.4)	0.7889
50 mg/kg/day GWP42003-P	46	43	0.9 (−7.8, 9.6)	0.8349
Social Interactions				
25 mg/kg/day GWP42003-P	37	40	0.1 (−11.7, 11.8)	0.9904
50 mg/kg/day GWP42003-P	38	40	4.1 (−7.5, 15.8)	0.4827
Other Cognitive				
25 mg/kg/day GWP42003-P	35	35	4.6 (−5.4, 14.5)	0.3634
50 mg/kg/day GWP42003-P	41	35	2.1 (−7.5, 11.6)	0.6686
Language				
25 mg/kg/day GWP42003-P	31	29	5.9 (−2.8, 14.6)	0.1789
50 mg/kg/day GWP42003-P	30	29	2.0 (−6.8, 10.8)	0.6480
Memory				
25 mg/kg/day GWP42003-P	24	22	-0.6 (−9.5, 8.3)	0.8953
50 mg/kg/day GWP42003-P	23	22	-4.3 (−13.3, 4.8)	0.3521



[a] The overall quality of life score is calculated by taking the mean of the subscale scores.

Note: The placebo arms were pooled for the analysis of efficacy.

Note: The change from baseline is analyzed using an ANCOVA model with baseline and age group (1–6, 7–11, 12–17 years) as covariates and treatment group as a fixed factor.

Table 4: Change from Baseline to End of Treatment in QOLIE-31-P

Table 8.4.1.2.2.6-1	Change from Baseline to End of Treatment in Quality of Life in Epilepsy, Version 2 Score (19 Years and Above) by Subscale (ITT Analysis Set)		
Subscale Statistics	25 mg/kg/day GWP42003-P (N=75)	50 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Overall Quality of Life[a]			
n	11	8	10
Mean (SD)	−8.4 (32.33)	−10.9 (11.78)	−0.1 (27.14)
Energy			
n	11	8	10
Mean (SD)	−3.2 (23.70)	−2.8 (21.85)	−0.7 (23.54)
Mood			
n	12	8	10
Mean (SD)	−17.3 (32.77)	−4.8 (15.93)	11.2 (22.10)
Daily Activities			
n	11	8	10
Mean (SD)	−5.0 (26.15)	−14.3 (30.87)	9.8 (28.73)
Cognition			
n	10	8	10
Mean (SD)	−8.7 (35.31)	0.6 (50.57)	14.9 (33.02)
Medication Effects			
n	11	8	10
Mean (SD)	−7.3 (46.36)	−26.9 (27.25)	9.5 (23.34)
Seizure Worry			
n	10	8	10
Mean (SD)	7.4 (34.58)	−18.5 (33.13)	0.6 (3.50)
Total Score			
n	10	8	10
Mean (SD)	−3.3 (19.50)	−7.6 (12.41)	3.1 (8.09)

[a] The overall quality of life score is calculated by taking the mean of the subscale scores.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Each score can range from 0 to 100, where 0 represents the lowest or poorest category and 100 represents the highest level of functioning.
Note: Positive changes from baseline represent an improvement in condition.

b. Please state how the QOLCE/QOLIE-31-P questionnaire results were accounted for in the efficacy conclusions.

GWPCARE6 attempted to capture HRQL using the general epilepsy quality of life instruments QOLCE and QOLIE-31-P. However, as outlined in the company's submission, there are significant challenges in collecting HRQL data in clinical trials involving patients with *severe and refractory* epilepsies such as TSC-associated epilepsy:

- There are no validated disease-specific instruments
- These types of general epilepsy QoL instruments do not work well for severe epilepsy (for example, asking questions about social interactions for a patient with TSC-associated epilepsy who has physical/learning disabilities that mean they do not attend school, go to work, or have any social interactions)

- Since many of the questions in general QoL instruments are unsuitable, there are missing data, making it difficult to draw meaningful conclusions

Over the GWPCARE6 trial period, most differences in the QOLIE-31-P and QOLCE were in favour of cannabidiol, but none were statistically significant. However, missing or non-applicable items were an issue for both instruments.

Neither the QOLIE-31-P or QOLCE are validated measures of HRQL for TSC-associated epilepsy. Although they are used in clinical trials of patients with general epilepsy, they are not appropriate for the very severe end of the epilepsy spectrum, where patients have an exceptionally high frequency/burden of seizures and substantial levels of learning difficulties, making many of the questions unsuitable. This is a likely reason for the high levels of missing data evidenced for both measures used in the GWPCARE6 study. The extent of the missing data for both instruments used in the clinical trials limited their ability to draw conclusions from the data.

A more meaningful measure of HRQL from the GWPCARE6 clinical trial is the Subject/Caregiver Global Impression of Change (S/CGIC), which captures an estimate of the effect of treatment on the patient's overall condition based on his/her entire seizure and comorbidity burden, thereby providing valuable information on the clinical meaningfulness of the therapy. Using S/CGIC, patients and caregivers reported an improvement in patients' overall condition in 69% of those receiving cannabidiol (25 mg/kg/day) plus usual-care versus 39% receiving placebo plus usual-care. However, the S/CGIC measure is not preference-based and therefore could not be used to derive utilities.

A13. Many of the outcomes were measured by changes from baseline. The ERG would like to know more about how baseline measurements compared with measurements taken during the trial period. Specifically, in the trial period, seizure frequency and seizure free days were assessed on each day from the baseline to the completion of dosing using an IVRS diary

a. Please state how baseline seizure free days were measured.

b. Please state how baseline seizure frequency was measured.

c. Please highlight all differences between how seizure frequency and seizure free days were measured at baseline and for the trial period.

The measurements were the same during the baseline period baseline and the trial period.

Eligible patients entered the trial at the screening visit (Day −35) and began a 7-day screening period. Patients who successfully completed this then began a 28-day baseline period on Day −28. Patients who satisfied all eligibility criteria were then randomized on Day 1.

An interactive voice response (IVRS) system was used daily to record information on seizures. During the baseline period and the double-blind participation in the trial, the caregiver made daily calls into an interactive voice response system (IVRS) to log the seizures experienced by the subject within the previous 24 hours.

Adverse events and drug-drug interactions

A14. Appendix F and Section B.2.10 of the company submission refer to adverse reactions from the GWPCARE6 trial.

a. Please provide the follow-up period and tool used for adverse events reporting.

A paper diary was used daily to record information on adverse events (AEs).

All AEs (including serious AEs) observed by the investigator or reported by the patient/caregiver during the trial were recorded on the patient's Case Report Form at all trial visits, questioning the patient/caregiver further if necessary.

An AE was defined as any new unfavourable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which occurred following screening (Visit 1) and at any point up to the post-treatment safety follow-up visit (Visit 12, for patients who did not enter the OLE), which may or may not be considered related to the IMP. Any event that was the result of a trial procedure was to be recorded as an AE.

Unless entering the OLE trial (in which case patients would have been monitored for AEs for the duration of the OLE) the trial required that patients be actively monitored for AEs up to 28 (+3) days after the last dose of IMP, until Visit 12.

b. Please provide the metric used to classify the severity of adverse events in Table 3 of Appendix F and Table 8 in the company submission.

For all AEs and serious AEs, the clinical trial investigators were required to assign severity and document this on the Case Report Form.

The method is described in the trial protocol as follows:

"When describing the severity of an AE, the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious."

An AE was considered serious if it: (1) was fatal; (2) was life-threatening; (3) required inpatient hospitalization or prolonged existing hospitalization; (4) was persistently or significantly disabling or incapacitating; (5) was a congenital anomaly/birth defect; or (6) was a medically significant event that, based upon appropriate medical judgment, may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

c. Please clarify if the published SAEs in Table 3 of Appendix F were reported in all participants or in ≥10% of participants.

All participants.

A15. It is well known that cannabis-based medications through interference with CYP3A4 enzymes, have the potential to initiate drug-drug interactions that may lead to serious drug toxicities and side effects in real world practice.

The company is somewhat concerned that no supporting evidence/references have been provided to support the speculation (about 'cannabis-based medications' and not specifically Epidyolex) that "*It is well known that* cannabis-based medications through interference with CYP3A4 enzymes, have the potential to initiate drug-drug interactions that may lead to *serious drug toxicities and side effects* in real world practice".

We respectfully request that this is removed before the document is in the public domain so that questions a, b and c are standalone without this introduction.

a. As the GWPCARE6 CSR states that, "*Care was to be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates…*"[10] please clarify if certain medications were disallowed during the trial to prevent these potentially toxic drug-drug interactions from occurring.

As above, we respectfully request that the words 'potentially toxic' are removed from this question.

The GWPCARE6 study protocol stated that *"Care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethylclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7."* However, these medications were not disallowed during the study.

As per the GWPCARE6 trial exclusion criteria, the following medications were prohibited for the duration of the trial:

- Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage
- Recreational or medicinal cannabis or synthetic cannabinoid-based medications (including Sativex) within 3 months prior to or during the trial

- Any other IMP taken as part of a clinical trial
- Felbamate if taken for less than 1 year prior to screening
- Oral mTOR inhibitor

b. Please clarify if the dosage of concomitant ASMs that patients were stable on for 1 month prior to screening, would have been modified by the investigator during the trial considering potential drug-drug interactions.

Throughout the duration of the trial, doses of concomitant AEDs and any non-pharmacological regimens for epilepsy were to remain stable. However, due to potential pharmacological interactions between cannabidiol and other concurrently administered drugs, the doses of concomitant AEDs could be adjusted following discussion with the GW medical monitor(s) if there were any clinical symptoms indicative of a safety concern. If, during the blinded phase, plasma concentrations of concomitant AEDs were found to be altered following administration of IMP, or if there were side effects suspected of being related to an elevation in the concomitant AED concentration, the investigator was to contact the GW medical monitor to discuss best management. Decisions were to be based on clinical symptoms and not plasma levels of AEDs.

c. With an emphasis on adverse events, please discuss the external validity of the trial to real world practice considering this issue.

In this orphan population of refractory patients with severe TSC-associated epilepsy, polypharmacy is common in an attempt to achieve seizure control. Because of this, patients in the GWPCARE6 trial were taking up to 5 concomitant AEDs/numerous different combinations of AEDs, so any interpretation of potential drug-drug interactions is limited.

The Epidyolex® Summary of Product Characteristics includes comprehensive information for prescribing clinicians on *“Interaction with other medicinal products and other forms of interaction”*. As is mandatory for licensed drugs, the SmPC describes potential interactions with a number of drug classes, not just CYP3A4.

As stated clearly in the SmPC, it will be the decision of the prescribing clinician as to whether dose adjustments to other medicinal products used in combination with cannabidiol should be made in real world practice:

"A physician experienced in treating patients who are on concomitant antiepileptic drugs (AEDs) should evaluate the need for dose adjustments of cannabidiol or of the concomitant medicinal product(s) to manage potential drug interactions".

A16. The GWPCARE6 CSR states that, *"The use of rescue medication was allowed when necessary… Overall, 78 patients (34.8%) were recorded as taking rescue medications."*[10]

a. Please discuss which rescue medications were used during the trial.

The most common class of rescue medication was benzodiazepine derivatives. These included diazepam, clonazepam, midazolam, midazolam hydrochloride, lorazepam, clobazam and clorazepate dipotassium (see Table 5).

The most common rescue medication was diazepam.

b. Please provide the frequency of use of rescue medications (by common class) per arm.

Similar proportions of patients across the treatment groups were recorded as taking rescue medications: 25 patients [33.3%] in the 25 mg/kg/day cannabidiol group, and 26 patients [34.2%] in the placebo group.

Table 5 below provides a summary of the use of rescue medications in the GWPCARE6 trial.

Table 5: Summary of rescue medications

Data analyses

A17. Priority: Please provide subgroup analyses for:

a. **the efficacy and safety of cannabidiol as an add-on to usual care based on GWPCARE6 patients' prior and concomitant seizure interventions; and**

As outlined in questions A3.b and A9 above, in the GWPCARE6 trial of cannabidiol, patients entering the trial were permitted to be taking any AEDs/other treatments (except those listed as exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/combinations of treatments are what are referred to as 'usual-care' in our submission. Cannabidiol was an add-on to usual-care.

Refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control. As a result, 'usual-care' comprises many different AEDs/combinations of AEDs - there is no standard of care once a patient is refractory.

This was seen in the GWPCARE6 trial population. Patients entering the GWPCARE6 trial had already failed to achieve seizure control with a median of 4 (and up to 15) AEDs prior to entering the study, and were currently taking a median of 3 (and up to 5) AEDs.

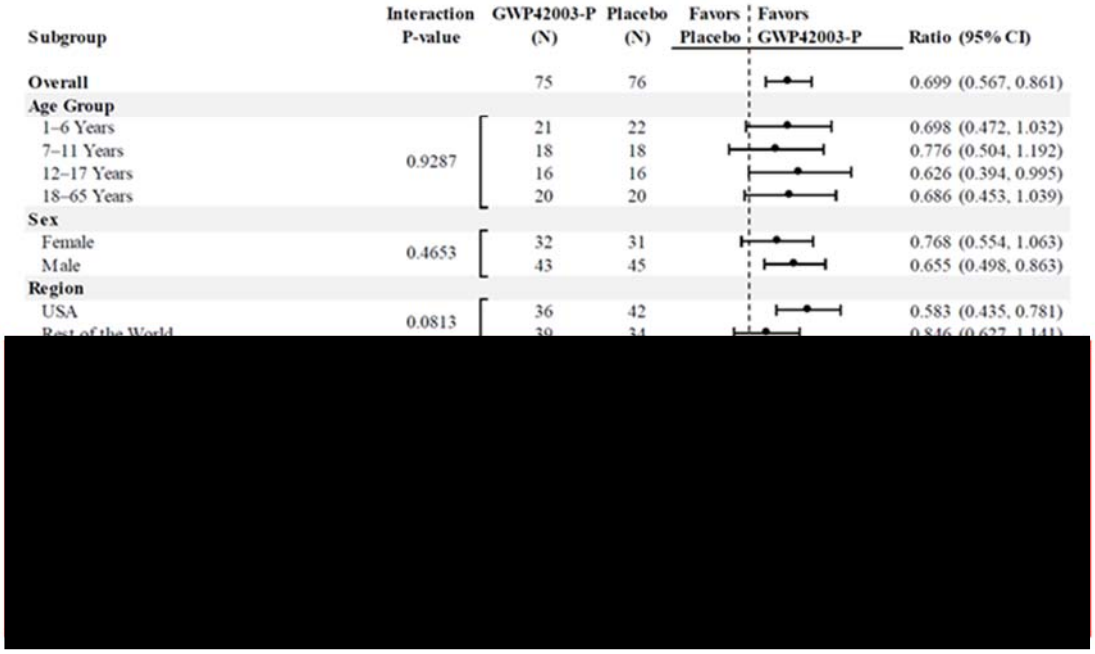
As discussed during the ERG clarification meeting, and as shown in Table 2 and Table 3 above, the range of different drugs being taken, and thus the number of potential combinations, is huge.

The pre-specified subgroup analysis (see Figure 3 below) provided here demonstrates that the main concomitant AEDs in the GWPCARE6 study (clobazam, valproic acid, levetiracetam and vigabatrin) have no impact on the efficacy of cannabidiol.

This was similar for LGS and DS, and is why NICE decided for LGS and DS that the only relevant comparator was 'current clinical management' or 'usual-care'.

Figure 3: Subgroup analysis of the primary endpoint

Figure 8.4.1.3.1-1 Subgroup Analysis of the Primary Endpoint (25 mg/kg/day GWP42003-P vs. Placebo): Negative Binomial Regression Effect Modification Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)



The safety and tolerability profile of cannabidiol is consistent, well-defined and manageable, as demonstrated across five randomised controlled Phase III trials in severe refractory epilepsies, (including TSC-associated epilepsy, Dravet syndrome and Lennox-Gastaut syndrome), where patients had tried and failed various AEDs, or were taking numerous combinations of concomitant AEDs.

In GWPCARE6, most adverse events were mild to moderate, transient and resolved by the end of the trial. The safety profile of cannabidiol observed in the GWPCARE6 study was consistent with findings from previous studies, with no new safety risks identified.

b. by the presence and absence of drug-resistant TSC-associated epilepsy.

All patients entering the trial had TSC-associated epilepsy that was not responding to their prior or current AEDs. One of the GWPCARE6 trial inclusion criteria was as follows: “Experienced at least eight seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks”.

A18. Please specify whether the trial was powered to show the superiority of cannabidiol to usual care as an add-on.

We confirm that the trial was powered to show the superiority of cannabidiol to usual care as an add-on.

A19. The CSR states that a patient’s treatment assignment could be unblinded if unblinding was “*essential to make a decision on the medical management of the patient*.”[10] Please specify how many patients were unblinded in each group?

One site unblinded a patient after they experienced an adverse event of rash with eosinophilia. Sponsor medical approval was not in place prior to unblinding. The patient was withdrawn.

A20. It is stated in the statistical analysis section that secondary endpoints are analysed using a per protocol analysis.

a. Please clarify if this means that an intention to treat (ITT) analysis has *not* been used for these outcomes.
b. If so, please provide an ITT analysis for these outcomes.

We apologise if this caused confusion. In the Statistical Analysis section of Document B, the sentence reads “Primary analyses used the ITT analysis set. Only the primary and key secondary endpoints were analysed using the per protocol analysis set.” The ITT analysis set was the primary analysis set for all efficacy endpoints.

Systematic review

A21. Priority: The ERG notes that despite the broadness of the eligibility criteria, no efficacy/ safety studies on common ASMs such as valproate, lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, etc, appear to have been identified in the SLR. The ERG reran the conditions facets (lines #1 to #3) from the Embase strategy reported in Appendix D Table 1 of the company submission. The strategy was run as closely as possible to the company's strategy using Ovid syntax and the same limits. A facet for anti-epileptics including the named drugs Valproate (or Valproic acid), Vigabatrin, and Lamotrigine was added and finally a randomised controlled trial (RCT) study design limit was applied. From the resulting 167 hits, 51 were deemed to be includes at title and abstract screening (please see Appendix 1). Of those 51, 2 were duplicate references and 3 were published in 2022 after the company submission searches were undertaken. Of the remaining studies, 2 appeared in the company submission list of included studies and 3 were listed as excludes. For the remaining 41 studies, please confirm:

a. If the papers in Appendix 1 were retrieved by your searches?

A general note about the SLR: we conducted a full SLR to identify all relevant studies on the efficacy and safety of pharmacological interventions for TSC-associated seizures. However, our submission to NICE focused on those studies that were most relevant to the decision problem of the use of cannabidiol as add-on therapy to usual-care. The studies of standard anti-epileptic drugs were considered to be describing the efficacy and safety of usual-care interventions and so were not reported in the submission. We have included the details of these additional studies in a supplementary document for completeness (see separate document entitled "Supplement_SLR_Additional_Studies_Apr2022").

The table has been updated with the detailed answers to this question. In brief, only 2 of the citations identified by the ERG were not identified by our search for the full SLR, and these were both earlier conference abstracts of papers that had been included ([13] Franz et al 2017, [22] French et al. 2016).

b. If so, explain why they were excluded. Please introduce a column to the table in Appendix 1 with the reason for exclusion.

The table has been updated with this information (see separate document entitled "NICE_ERG_QueryReferences_CompleteTable_Apr2022"). Most of these studies were included in the full SLR but not in the submission as they were secondary publications of included studies, were listed in the table of secondary publications but not cited in the reference list, or were not considered relevant to the decision problem. Data from these studies has been summarised in the supplementary report that accompanies this response (see separate document entitled "Supplement_SLR_Additional_Studies_Apr2022").

A22. Pertaining to question A21:.

a. Please confirm if restrictions were placed on outcomes of interest during title & abstract, and full paper screening stages.

Abstracts and full texts were excluded if they did not report outcomes relating to seizure rates, severity or frequency or other epilepsy-related outcomes or did not relate to a general population with TSC who may or may not have seizures. Studies were excluded if they only assessed non-seizure-related manifestations of TSC. No other restrictions were placed during abstract screening.

Old conference abstracts with no poster or additional data available were generally excluded for not reporting enough data to be useful, but those with useful data were included unless a corresponding full-text publication was available that reported the same outcome data as the abstract.

b. Please provide a table clearly outlining the PICOS (inclusion/ exclusion criteria) used during title and abstract, and full text screening in the SLR.

Inclusion/exclusion criteria used in the full SLR are shown in the table below:

Criterion	Inclusion criteria	Exclusion criteria
Population	Efficacy and safety: Seizures associated with TSC Economic and quality of life studies: General population with TSC with or without seizures	All topics: exclude studies where the only outcomes of interest relate to non-epilepsy manifestations of TSC
Intervention	Any drug intervention or none	
Comparators	Any or none	

Criterion	Inclusion criteria	Exclusion criteria
Outcomes	Any clinically relevant topics relating to TSC-related seizures, including: Epidemiology: incidence/prevalence, risk factors, biomarkers, diagnosis, mortality/survival; Efficacy and safety of interventions for seizures; Guidelines and treatment pathways; Quality of life, utilities, social impact; Economic evaluations; Cost and resource use; Impact on work and productivity, education and learning	Pharmacokinetic/ pharmacodynamic studies with no clinical outcomes
Study methodology	Randomised controlled trials Single-arm clinical trials Retrospective or prospective observational studies including database/registry studies, case-control, cross-sectional studies Systematic literature reviews of relevant studies to identify additional relevant publications Narrative reviews on the epidemiology and burden of illness of TSC-associated epilepsy Study protocols for relevant RCTs	Conference abstracts with a corresponding full-text publication and no additional data were excluded unless they related to efficacy RCTs.
Study size	RCTs: any Other studies: >5 participants	
Language	Epidemiology: English full texts only Other topics: Any	
Publication date	Any	

A23. Please specify which risk of bias (RoB) tool was used for conducting the quality assessment of the GWPCARE6 trial. In addition, provide brief justifications for domain decisions.

The quality assessment of the GWPCARE6 trial and other RCTs was completed using the Cochrane Risk of Bias (ROB2) tool.[11] This was summarised in the submission and the full evaluation reported below, with further justifications for domain decisions for GWPCARE6 added.

	Franz 2013	French 2016	GWPCARE6 (Thiele 2020)	Kotulska 2020	Amin 2021
1. Randomisation process					
1.1 Was the allocation sequence random?	Yes	Yes	Yes (stratified by age, sequence generated by independent statistician)	PY	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes	PY (details not reported)	PY	Yes

	Franz 2013	French 2016	GWPCARE6 (Thiele 2020)	Kotulska 2020	Amin 2021
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	PN	No	PN	No
Risk of bias judgement	Low	Low	Low	SOME	Low
2. Deviations from intended interventions					
2.1 Were participants aware of their assigned intervention during the trial?	No	No	No (placebo-controlled using identical vials)	Yes	No
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	No	No (placebo-controlled using identical vials)	PY	No
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	NA	NA	N	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA	NA	NA	NA
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes (negative binomial regression analysis stratified by age for number of seizures, Cochran-Mantel-Haenszel test for proportion with ≥25%, ≥50%, ≥75%, and 100% reduction in the number of primary end point seizures)	Yes	Yes
Risk of bias judgement	Low	**Low**	**Low**	SOME	Low
3. Missing outcome data					
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes	PY	Yes (primary outcome used ITT analysis, other outcomes reported for all randomised patients)	Yes	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA
Risk of bias judgement	Low	Low	Low	Low	Low
4. Measurement of the outcome					
4.1 Was the method of measuring the outcome inappropriate?	No	No	No (patient/caregiver reported seizure rates, analysed	No	No

	Franz 2013	French 2016	GWPCARE6 (Thiele 2020)	Kotulska 2020	Amin 2021
			by hierarchical sequence procedure)		
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	PN	No	PN	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No	NA	PY	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA	NA	PY	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA	PY	NA
Risk of bias judgement	Low	Low	Low	SOME	Low
5. Selection of the reported result					
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes	Yes	Yes	Yes
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	No	No	No	No
5.3 2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No	No	No	No	No
Risk of bias judgement	Low	Low	Low	Low	Low
Overall bias	Low	Low	Low	SOME	Low

A24. Please provide more information on the study selection, data extraction, and quality assessment process. Specifically, please state how many reviewers were involved at each stage, if these processes were conducted independently, how consensus was carried out, and if a third reviewer was involved in resolving disagreements.

Studies were selected for inclusion in the SLR if they met the inclusion criteria detailed in our previous response.

Two researchers independently screened each abstract and any discrepancies were agreed in discussion with the project leader.

One researcher and the project leader independently screened each full text publication to confirm that it met the inclusion criteria, with any disagreements resolved by discussion.

One researcher extracted data from included papers into an Excel template and a second researcher validated the data extraction. Any areas of uncertainty were checked by the project leader during the report synthesis and sign-off process.

Two researchers independently evaluated the risk of bias of each included study and the assessment was signed off by the project leader.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Priority: The proportions for seizure type (generalized, focal with impairment, or combined) were based on week 16 data from the GWPCARE6 trial.

a. Please justify why the proportions were based on week 16 data and not on the average proportions from the trial (company submission, Appendix L).

As detailed in Document B, Section B.3.2.2, and as shown in Figure 4 below, the proportions change minimally over the 16-week trial period. Therefore, the base case analysis uses the Week 16 data from the GWPCARE6 trial as this was the point of completion of the Core Trial Period and is expected to reflect the distribution of seizure types following treatment over a longer time horizon more accurately.

b. Please explore the effect of using the average proportions in a scenario analysis.

The results for the scenario analysis based on the average proportions data reported are provided in Table 6. Note that the scenario is inclusive of the change in the base case requested as per question B13.a.

The scenario shows minor sensitivity to the change, with cannabidiol demonstrating a marginally higher incremental QALY and a slightly lower ICER.

Table 6: Scenario analysis results (PAS price)

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£12,229

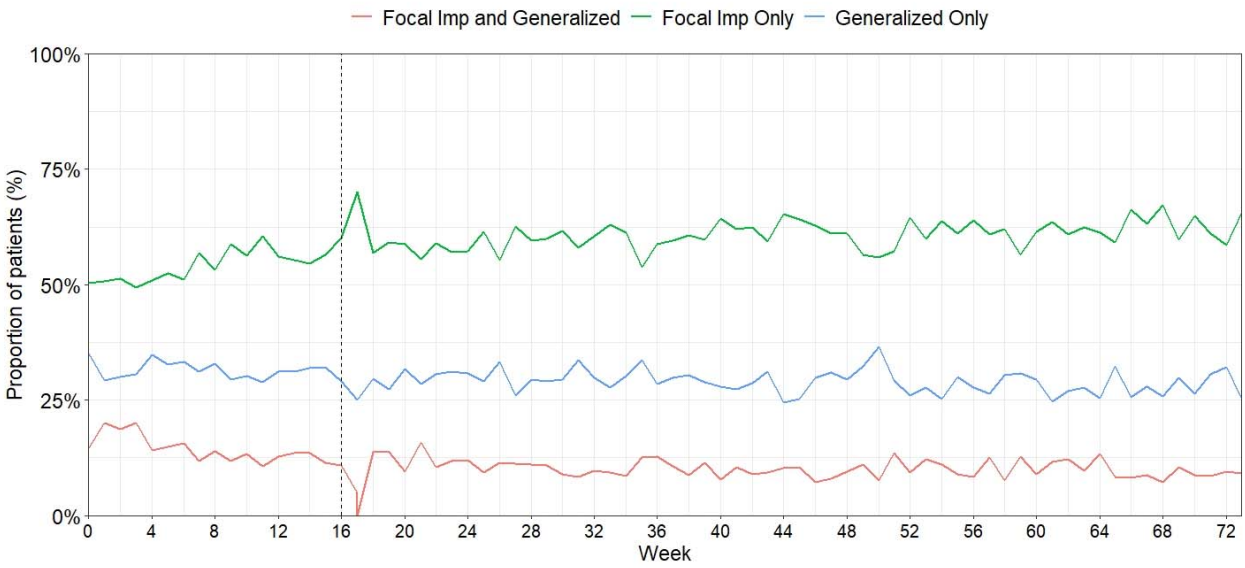
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: *Discounting is applied to QALYs and cost.

c. Please comment on comparability of seizure type proportions as observed in the blinded trial period of GWPCARE6 versus proportions observed in the open label extension (OLE) study. Are these values assumed to remain stable, or would non-response and discontinuation affect the relative proportions? Please provide clinical expert opinion or other evidence of clinical plausibility to support your answer.

The observed data in Figure 4 demonstrate that seizure type proportions are consistent over time. The data show that there is minimal change over the open-label extension. Therefore, it is reasonable to assume that the Week 16 data from the GWPCARE6 trial is reflective of the OLE period and of the extrapolated Week 16 data over time. The Week 16 proportions are modelled to remain constant over time in both treatment arms; this assumes that discontinuation and stopping due to non-response does not affect the relative proportions.

This is supported by UK clinical expert opinion. In recent discussions conducted to inform our responses to the ERG, Professor Finbar O'Callaghan and Dr Sam Amin confirmed that the seizure type proportions are generally stable over time.

Figure 4: Observed proportion of patients by seizure type: Core Trial Period and OLE



Key: Focal Imp - Focal with impairment of awareness seizures
Note: Patients in the cannabidiol 25 mg/kg and placebo arms are pooled to calculate the average observed seizure frequency by seizure type

Population

B2. Although the modelled population is said to be patients ≥2 years old, the GWPCARE6 ITT population that was used to inform the model included also children aged 1 year-old.

a. Please comment on the impact of including the 1-year-olds for estimating efficacy inputs, discontinuation rates, TSC-associated neuropsychiatric disorders (TAND) responses and patient baseline characteristics.

The population enrolled in the GWPCARE6 trial included nine children aged <2 years old at the date of screening (three in the cannabidiol 25 mg/kg/day arm and six in the placebo arm) who were included in the GWPCARE6 ITT analysis.

The GWPCARE6 ITT analysis, including data for the children aged <2 years old at screening, was used to inform model inputs including efficacy inputs, discontinuation rates and TAND response rates and patient baseline characteristics in the cost-effectiveness analysis as detailed below:

- Patient level data from the GWPCARE6 blinded trial period are utilized within the regression analysis to predict the expected probability of seizure-free days and associated seizure frequency
- Data on patients discontinuing treatment from the GWPCARE6 blinded trial period and open-label extension are used to calculate the proportion of patients expected to discontinue treatment during the trial period and OLE period
- Patient level data on treatment response (≥ 30% reduction in seizure frequency) from the GWPCARE6 blinded trial period and the open-label extension are used to calculate stopping rates
- Data on patients who experienced a ≥50% response (reduction in seizure frequency) from the GWPCARE6 blinded trial period and open-label extension are used to calculate TAND response rates, which are then used to calculate the proportion of patients who may benefit from TAND mitigation.
- Patient baseline characteristics are used to calculate drug costs and mortality. Note: patient characteristics used to calculate drug costs exclude patients aged 1 year-old.

As shown in Appendix L, Figure 7, the subgroup analysis demonstrates that age is not a treatment effect modifier.

In addition, as shown in Table 7 below, all but two of the patients who were <2 years old at the screening visit had reached age 2 by the end of the trial. Therefore, it is reasonable to assume that the outcomes in the <2 year olds would be similar to the overall trial outcomes. Excluding these patients would unnecessarily reduce patient numbers in an already small trial population (due to the nature of the orphan disease), break trial randomisation and increase model uncertainty by reducing sample size.

b. Please provide these data separately for the 1-years olds in the GWPCARE6 ITT population or perform a scenario excluding the 1-year-olds from the ITT population in estimating model inputs.

Table 7 shows the baseline characteristics of the patients from the cannabidiol 25 mg/kg/day and placebo arms who were <2 years old at the *date of screening* for the GWPCARE6 study.

These baseline characteristics are similar to the baseline characteristics of the overall population.

Due to the very small number of patients aged <2 years and considering that all except two patients had reached age 2 by the end of the trial, it is not expected that stopping rule rates, discontinuation rates or TAND response rates would be significantly different for these patients compared to the overall outcomes.

Therefore, separate outcome data for these patients are not provided.

Table 7: Patients <2 year of age at screening - baseline characteristics

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study arm	25 mg	25 mg	25mg	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Age >2 years at end of trial	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous AEDs (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current AEDs (n)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking clobazam?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking valproic acid?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking vigabatrin?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taking levetiracetam?	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Note**: patient's actual age was [redacted] years

Key: F, female; M, male; W/C, White/Caucasian

B3. In Table 12 of the company submission which displays the baseline characteristics of the model population, the % female varies quite drastically between age categories. Please check this is correct and highlight whether and where in the model the % female has an effective impact.

We confirm that the data are correct. Please note the % female input by age group is not used in the cost effectiveness analysis. It is provided to allow for a measure of comparability across age groups, as mean age, mean weight and mean BSA all change with age (as shown in Table 8). The observed range reflects the demographics of a rare orphan disease population. It is reasonable to observe variation across patient groups where there are small patient numbers.

Please note that we do not consider the variation to be 'drastic' (p-value: 0.453); the largest variation relative to the other age categories is observed in the patient group with the smallest patient numbers (aged 12-17 years [Table 8]).

Table 8: GWPCARE6 population baseline characteristics by age group

Age banding	2–6 years	7–11 years	12–17 years	≥ 18 years
N	34	36	32	40
Mean age, years (SD)	4.47 (1.36)	9.37 (1.51)	14.9 (1.66)	28.1 (9.65)
% female (SD)	38.20% (6.56%)	41.70% (6.94%)	53.10% (9.39%)	35.00% (5.53%)
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)
Key: BSA, body surface area; SD, standard deviation.				

Intervention, technology and comparators

B4. Priority: The final scope mentions the following treatments as comparators: anti-seizure medications (ASMs), everolimus, vagus nerve stimulation, ketogenic diet, and surgical resection. In the company submission the comparator reflects the control arm of the GWPCARE6 trial, in which patients were treated with ASMs, and on ketogenic diet, vagus nerve

stimulation, and who underwent surgery more than 6 months before screening.

a. **In Section 3.2.3.2. it is stated that the comparator in the cost-effectiveness analysis is usual care, consisting of a combination of ASMs. Please provide a justification for not including the ketogenic diet, vagus nerve stimulation, and surgery, as comparators in the economic model.**

The comparator in the final NICE scope is “Established clinical management without cannabidiol”.

Ketogenic diet, vagus nerve stimulation (VNS) and resective surgery are part of the treatment pathway for TSC-associated epilepsy (see Figures 3 and 4 in Document B of the company’s submission), and therefore part of the ‘established clinical management’ (or ‘usual-care’) mix that cannabidiol would be added to.

Use of a ketogenic diet, VNS and/or prior surgery was not an exclusion criterion in the GWPCARE6 clinical trial. Any non-pharmacological interventions for epilepsy (e.g. ketogenic diet and VNS) had to have been stable for 1 month prior to screening and throughout the duration of the trial. Patients who had undergone prior surgery for epilepsy were also not excluded, provided that the surgery was not within the 6 months prior to screening. Approximately 1.3% and 11.2% of patients in GWPCARE6 were on a ketogenic diet and VNS, respectively, at baseline, spread fairly evenly across the treatment arms.

There is no evidence to suggest that levels of use of ketogenic diet, VNS and/or resective surgery would differ greatly between patients receiving usual-care only or receiving usual-care plus cannabidiol. Therefore, any effects of these treatments would apply equally to both arms of the model. Similarly, costs of the ketogenic diet, VNS and/or surgery, and disutilities associated with adverse events/complications, would apply equally to both arms.

Based on the above, ketogenic diet, VNS and resective surgery are already included in the comparator by virtue of their contribution to both arms of the model as part of the ‘usual-care’ mix.

b. **Please provide scenario analyses with usual care including a combination of ASMs, ketogenic diet, vagus nerve stimulation, and surgery, as comparator in the economic model.**

Please see the response to question B4.a above.

Given that ketogenic diet, VNS and/or resective surgery are part of 'usual-care' and can reasonably be considered to contribute equally to the treatment effect with and without cannabidiol, none of these interventions in isolation is considered an appropriate comparator to cannabidiol.

c. **Everolimus was not included in the company submission as a comparator but as later line treatment (see question A4). Please provide a scenario with everolimus as a comparator.**

The comparator in the final NICE scope is "Established clinical management without cannabidiol".

For the reasons outlined in Document B of the company's submission and in the answers to question A4. above, the company does not consider everolimus in isolation to be a relevant comparator. However, as noted here, we have included it in the model as a later line treatment.

Please also refer to the answers to question B6. below.

B5. The efficacy (and safety) data of cannabidiol 25 mg/kg/day from the GWPCARE6 trial was used to populate the cannabidiol arm in the cost-effectiveness model. The average dose of cannabidiol used in the cost-effectiveness model to calculate the drug costs is 12 mg/kg/day based on the early onset of effect observed in the GWPCARE6 trial and similar results found in a real-world study.

a. Please explain the choice for an average dose of 12 mg/kg/day in the base-case analysis and how this would reflect 'a spectrum of doses ranging from ≤10 mg/kg/day to the maximum of 25 mg/kg/day'.

Since the objective of the cost-effectiveness modelling is to represent a cohort in UK clinical practice, a dose that represents this cohort has been used in the model,

rather than considering the dosing of individuals. For this reason, the dose used in the model to calculate ICERs is an *average* dose.

According to the Epidyolex Summary of Product Characteristics, for TSC-associated seizures, the dose should be increased to 10 mg/kg/day and then the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can then be further increased *only if needed*.

Thus, an *average* dose of 25 mg/kg/day would imply that some patients are above the maximum licensed Epidyolex dose in TSC of 25 mg/kg/day (i.e. off-label use) or that *all* patients are treated with the maximum daily dose of 25 mg/kg/day, which is not plausible.

By using an *average* dose of 12 mg/kg/day case in the model, we can account for the range of doses seen in clinical practice across a *cohort* of UK patients with TSC-associated epilepsy, as clinicians aim to optimize the dose for individual patients. As stated in our original submission, in real-world clinical practice, there will be a spectrum of doses ranging from ≤10 mg/kg/day to the maximum of 25 mg/kg/day.

Feedback from clinical experts and real-world data support this assumption of using an *average* dose of 12 mg/kg/day in the model:

- Since the NICE submission, the company has obtained data from a German dispensing database (INSIGHTS) on real-life dosing. The daily dose was estimated from a group of patients with Epidyolex prescriptions in 2021. The indication for the prescription was not available in the database, therefore a TSC diagnosis was inferred from a record of any use of vigabatrin or everolimus in the preceding 3 years. Body weight of patients was estimated from age and gender average weight in the German general population. From a total of 118 patients, the observed median dose was 12.21 mg/kg/day in children (inter-quartile range 6.67) and 7.77 mg/kg/day (IQR: 5.68) in adults
- Discussions across Europe with expert clinicians who have experience of using Epidyolex in clinical practice suggests that the average dose in real-world clinical practice will be around or below 12 mg/kg/day

b. Please add options for 15, 20 and 25 mg/kg/day to the cannabidiol dose scenario in the model (instead of now only 10 and 12 mg/kg/day) to explore effects on costs and ICER.

This option has now been included in the model.

However, for the reasons outlined in question B5.a above and B5.c below, we strongly disagree that *average* doses of 15, 20 and 25 mg/kg/day would be representative of the likely dosing of cannabidiol in real-word practice in TSC-associated epilepsy.

c. Please justify the assumption that a dose of 12 mg/kg/day has the same efficacy and safety as 25 mg/kg/day. The lack of a dose response relation in Lennox-Gastaut syndrome and Dravet syndrome may not be generalizable to TSC; please also provide evidence on lack of a dose response relation (between the 25 and 50 mg/kg/day doses) from GWPCARE6.

The company considers that the efficacy outcomes from the GWPCARE6 study in TSC-associated epilepsy will be reflective of patients receiving lower average doses in clinical practice.

The totality of the evidence in the cannabidiol clinical trial programme in refractory epilepsies to date does not support a clear dose response above 10 mg/kg/day. This was also concluded by the EMA in setting the maintenance dose of 10 mg/kg/day for DS and LGS.

According to the Epidyolex Summary of Product Characteristics, for TSC-associated seizures, the dose should be increased to 10 mg/kg/day and then the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can then be further increased *only if needed*.

As outlined in Document B of the company's submission, the early onset of efficacy at lower doses observed during titration in GWPCARE6 (TSC-associated epilepsy) is consistent with the demonstrated efficacy of cannabidiol at 10 mg/kg/day from the Phase 3 studies GWPCARE3 (in LGS) and GWPCARE2 (in DS).

Together with the lack of dose response observed between 10 mg/kg/day and 20 mg/kg/day in the DS and LGS studies, the available clinical data across five pivotal

Phase 3 trials support the potential for cannabidiol efficacy to become clinically apparent at doses much lower than 25 mg/kg/day.

Furthermore, the company considers that the evidence from the other severe epilepsy syndromes, LGS and DS, is applicable to TSC-associated epilepsy for the following reason:

- Seizures are not a disease in themselves: they are a manifestation of different disorders that can lead to abnormal neuronal activity in the brain. The term epilepsy refers to the disease, disorder or syndrome involving recurrent seizures. Terms to describe and classify types of seizure have been developed by the International League Against Epilepsy (ILAE) broadly based on how and where the seizure begins in the brain (focal or generalised) and the person's level of awareness during a seizure (aware or impaired awareness). This ILAE operational classification of seizure types can be used to classify seizures across different aetiologies, that is, it is specifically designed to be applied to seizures where the underlying disease/syndrome is different. Thus, although a patient may be diagnosed with a particular epilepsy/epilepsy syndrome based on specific clinical/diagnostic features, each individual seizure type experienced within those epilepsy syndromes/disorders will be the same, according to the ILAE classification.

- Therefore, although the type(s) of seizures that predominate may vary between severe epilepsies/syndromes such as those caused by TSC, DS and/or LGS, the individual seizures are the same. For example, a generalised tonic-clonic seizure resulting from TSC-associated epilepsy would be similar to a generalised tonic-clonic seizure as a result of Dravet syndrome, or an atonic seizure resulting from TSC-associated epilepsy would be similar to an atonic seizure as a result of Lennox-Gastaut syndrome.

- Since cannabidiol is specifically treating the *seizures* caused by TSC (and DS/LGS) and not the underlying disease or syndrome itself, it will work in the same way to reduce seizures whether they are caused by TSC, DS or LGS.

- Based on the above, we consider that the evidence for cannabidiol in DS and LGS is generalizable to TSC-associated epilepsy.

B6. Everolimus was considered as a subsequent treatment in the model for 7.7% of the cohort. Patients in the cannabidiol arm receive everolimus after discontinuation of cannabidiol, patients in the placebo arm are assumed to receive everolimus at 2 years after the trial period.

a. Please justify the 2yr + 16-week year time point at which patients in the placebo arm would receive everolimus and provide supporting evidence.

There is limited information regarding the positioning or timing of everolimus as a later line treatment in TSC-associated epilepsy.

In the NHS England Clinical Commissioning Policy (see question A4.a above), everolimus is positioned as a later line treatment due to the need not only for inadequate response to two or more AEDs, but also for failure/ruling out of both epilepsy surgery and vagus nerve stimulation (VNS) by a multidisciplinary team.

The TOSCA registry indicates that everolimus is used in only a small proportion (7.7%) of patients.[12] There may be various reasons for this, including, for example:

- Clinicians may have concerns regarding the use of mTOR inhibitors in children, specifically regarding their effect on growth and gonadal function over the long-term[13]
- Standard recommendations advise against concomitant use of everolimus with ketogenic diets in children with epilepsy, due to additive toxicity with hyperlipidaemia[13]
- Patients/caregivers may prefer to try other AEDs with titration/monitoring/side-effect profiles perceived as being more manageable before moving to everolimus, due to concerns about using a drug that has a toxicity profile associated with its original indications in oncology/immunosuppression.

For the purposes of the model, it was assumed that, at 2 years post the trial, placebo plus usual-care patients will have tried other AEDs, and a proportion of these patients would then receive treatment with everolimus as an option later in the treatment pathway.

Two scenarios are provided to address the uncertainty in this assumption, assuming a 1-year delay and 3-year delay post the trial for patients to cycle through other AEDs before considering everolimus as a treatment option. Note that the scenario is inclusive of the change in the base case as per question B13.a.

The results for the scenario analysis based on varying the start date for a proportion of usual-care patients receiving everolimus, are provided in Table 9 (1-year delay) and Table 10 (3-year delay).

The scenarios shows low sensitivity to the change, with cannabidiol demonstrating a marginal change in incremental costs (lower for a 1-year delay, higher for a 3-year delay) and ICER (lower for a 1-year delay, higher for a 3-year delay).

Table 9: Scenario analysis results (PAS price) – usual-care proportion of patients start everolimus delay – 1 year

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£12,654

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost.

Table 10: Scenario analysis results (PAS price) – usual-care proportion of patients start everolimus delay – 3 years

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£12,775

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost.

b. The proportion of 7.7% was based on the TOSCA registry.[12] Please comment on how representative the population in the TOSCA registry is when considering UK clinical practice for the population in this appraisal.

TOSCA is a multicentre, international disease study designed to collect data, retrospectively and prospectively, on patients with TSC from countries worldwide.

Recognising that TSC-associated epilepsy is an orphan disease, we consider that the TOSCA registry provides the most comprehensive and representative data source currently available. Almost 60% of the patients in the TOSCA registry were from European countries, with 32 patients from the UK.[12]

c. Please justify that the proportion of 7.7% may be considered to apply to both the cannabidiol and usual care (placebo) arm and provide supporting evidence.

In the model, we have assumed that 7.7% of patients discontinuing cannabidiol or continuing on usual-care would receive treatment with everolimus later in the TSC-associated epilepsy treatment pathway. This proportion was based on data from the TOSCA registry, which represents the best currently available data for patients taking everolimus for TSC-associated epilepsy.

Given that refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control and that there is no standard of care once a patient is refractory, we do not consider it unreasonable to assume that a similar proportion of patients in both arms will eventually receive everolimus.

d. Only drug costs for everolimus were considered in the model. Please justify why effects were not considered.

The effect of everolimus is not incorporated into the model for several reasons:

- A similar proportion (7.7%) of cannabidiol patients who discontinue treatment and patients in the placebo plus usual-care arm receive everolimus as a subsequent treatment, therefore the impact on effects would be expected to be similar across arms

- There are no data to support the effect of everolimus post treatment with cannabidiol
- The licence for everolimus is restricted to partial-onset seizures only: this does not fully reflect the modelled population

Therefore, in the absence of any relevant clinical data, the efficacy impact could not be included in the analysis. We have adopted a pragmatic approach and examined everolimus as a later line treatment by applying the cost impact (applied as a one-off cost) to a proportion of patients in both model arms.

e. Please provide a scenario taking into account an effect of everolimus on seizure frequency.

As per our response to question B6.d above, it is not possible to provide a scenario taking into account the effect of everolimus on seizure frequency when given as a later line treatment.

f. Please provide a scenario where everolimus is excluded as a subsequent treatment.

A scenario excluding everolimus as a subsequent treatment is provided below in Table 11. Additionally, it is provided in Appendix 2, alongside the updated sensitivity analysis that was included in the original submission. Note that the scenario is inclusive of the change in the base case as per question B13.a. The scenario shows low sensitivity to the exclusion of everolimus, with a marginal change in incremental costs.

Table 11: Scenario analysis results (PAS price)

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£13,389

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost.

Clinical parameters and variables

B7. Priority: Regression models were used to estimate the effectiveness of cannabidiol compared with usual care.

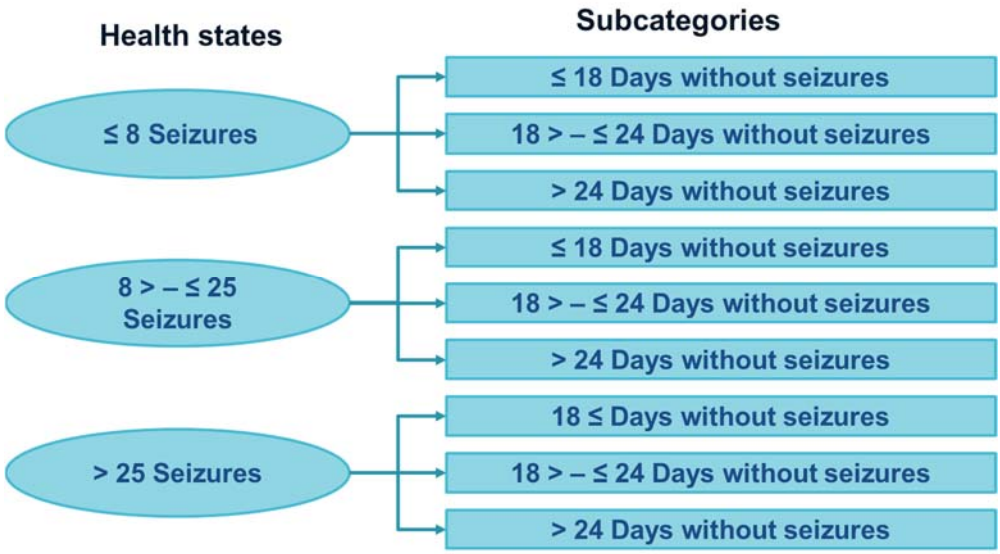
a. **Please provide any predefined statistical plan that was made for the regression modelling and justify the appropriateness of the analyses if no predefined statistical plan was used.**

Text from the analysis plan designed to support the economic analysis is provided below.

The previous NICE model for cannabidiol developed for TA614 and TA615 used transition matrices to capture the efficacy for each treatment in terms of seizure frequency and seizure-free days, as shown in Figure 5 (for DS; the LGS model structure is similar but with different seizure numbers/seizure-free days). Given the incorporation of both seizure frequency and seizure-free days in this structure, a total of nine separate transitions were required to be populated.

The transition matrices provided a simple model structure but led to criticism due to the perceived arbitrary choice of bands and wide range of seizure frequency.[14, 15] In addition, given the low sample size in the DS and LGS on-clobazam data (86 patients and 74 patients, respectively), using the health states to further divide the patient population led to very small sample sizes in some transitions. As both of these structural issues are still relevant for the analysis of the GWPCARE6 trial data, alternative methods were considered.

Figure 5: DS model structure (28-day cycle)



Key: DS, Dravet syndrome.

Regression methods

Regression approaches were considered beneficial in terms of their ability to estimate the proportion of seizure-free days and not just seizure frequency without further subdividing the data into additional heath states to accurately capture the impact on quality of life in patients and caregivers. Based on clinical feedback, the need to capture the benefit of seizure-free days specifically is important given the substantial quality of life benefit for patients and caregivers associated with seizure-free days.

The daily data from the core randomised controlled trial aspect of GWPCARE6 were used for the regression analyses. It was not feasible to incorporate the OLE data into the regression analysis to predict seizure frequency and seizure-free days as the OLE data were collected on an approximately weekly basis and the number of seizure-free days per week were not recorded. The OLE data were instead used for validation (see Document B, Figure 16 in the company submission).

Three model structures were considered to model the seizure frequency and seizure-free days of patients in GWPCARE6:

- Generalized estimating equations (GEEs) for generalized linear models – this approach estimates population-averaged model parameters and their standard

errors. In the presence of missing data, GEE requires the strong assumption of missing completely at random; however, it is unclear whether this assumption holds for the GWPCARE6 data.[16] In addition, GEE models may yield biased results when the sample size is small, as such this method was not considered further.[17]

- Hurdle models – a two-part model that specifies one process for zero counts (seizure-free days) and another process for positive counts (seizure days)
- Generalized linear mixed models (GLMMs) – independent mixed effects regression modelling of the proportion of seizure-free days and seizure frequency was considered over more simplistic regression models to estimate count data (such as standard Poisson and single negative binomial models) as it allowed for more explicit estimation of the proportion of seizure-free days (which may be underestimated using more simplistic methods)

The independent modelling of seizure-free days and seizure frequency using GLMMs was favoured over hurdle models due to the ease of interpretation and increased flexibility in the modelling. As such, results for the independent modelling of seizure-free days and seizure frequency were preferred and were included within the company's submission.

Independent modelling of the proportion of seizure-free days and seizure frequency

This approach analysed weekly data utilizing a two-step regression approach (described below) to predict seizure-free days and seizure frequency on seizure days; regression models were fitted using the lme4 R package.[18, 19]

1. The proportion of seizure-free days per cycle (7 days) was modelled using binomial regression. Binomial regression was used as the data on seizure-free days are dichotomous with two possible outcomes: a seizure-free day or a non-seizure-free day. Therefore, the proportion of seizure-free days per week can be estimated
    a. It is acknowledged that, by analysing these data as a proportion, the probability of each seizure-free days in the cycle per week should be

independent and constant; however, independence is not satisfied as multiple records per week are used to calculate this proportion per patient (as the data are recorded daily). Given the variability in seizure frequency day to day and the expectation that, within a cycle of one week, the chance of a seizure-free day is anticipated to be similar, it was assumed that seizure-free days are independent of each other within the analysis

   b. There are a limited number of cycles where data are not collected each day in the cycle. The estimated proportions become more variable for cycles where the data collected are very limited. As such, the proportion of seizure-free days is only estimated for cycles where 3 or more days of data are available

2. Subsequently, a negative binomial regression model was fitted to the subset of seizure frequency data for days on which patients experienced at least one seizure. Negative binomial regression was used as the seizure frequency data are count data. A negative binomial model was chosen over Poisson regression as the assumption that the variance is equal to the mean is relaxed. This regression type been described as a good choice to estimate transition probabilities in the presence of small sample sizes and where data is over-dispersed[20]

   a. Specifically, the subset of seizure frequency data for days on which patients experienced at least one seizure is generated, and the total seizures in the cycle are calculated along with the number of records for which data are available. For example, for a patient who has three seizure-free days in a cycle, the total number of seizures in the remaining 4 days would be calculated (and the number of records would be four)

   b. An offset to account for the differing ‘exposure’ is included in the model. This accounts for any missing days. For the example above, it is important to recognize that the number of seizures that the patient experienced was over 4 days rather than the possible seven.

   c. The fitted negative binomial model estimates the seizure frequency per day, conditional on patients experiencing at least one seizure (i.e. seizure

frequency on non-seizure-free days), as the number of records with seizures per week is included as an offset within the analysis. Seizure frequency for the appropriate number of seizure days can be estimated by including the offset when using the model to predict seizure frequency.

b. The regression models have both a random intercept and random slopes. Please justify adopting random slopes (instead of only using a random intercept).

Random effects were incorporated into the regression analyses as the analysis datasets include repeated measures for each patient for which there is an inherent correlation between observations of the same patient. Two levels of random effect were applied in the model:

- Random intercept – the intercept value is assumed to follow a distribution and each patient may have a different intercept value
- Random slope – the change in outcomes over time will follow a distribution and the rate of change will vary by each patient (i.e. some patients may improve faster than others, while others may decline over time). Without the inclusion of the random slope, the analysis assumes that the change in outcomes is the same for all patients, which is a strong assumption to make

To assess further the inclusion of the random slope, the regression model was fit with and without the random slope and the goodness of fit statistics were compared. Table 12 displays the goodness of fit statistics for each of the regression models with and without the inclusion of the random slope.

Typically, if the difference in the AIC and BIC score between two models is <5, the models are deemed to fit equally as well. When random slopes are included within the regression models, both the AIC and BIC scores (presented in Table 12) improve in both models. The goodness of fit statistics improve by over 280 for the seizure-free days regression model, and by over 160 for the seizure frequency (on seizure days) regression model.

This improvement therefore suggests that the inclusion of the random slope drastically improves the goodness of fit for both regression models. In turn, this supports the assumption that all patients do not have the same response over time.

Table 12: Goodness of fit statistics – regression models with and without a random slope

Model	Fixed effects	Random effects	AIC	BIC
Seizure-free days	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	Intercept, slope	5,863.1	5,909.0
Seizure-free days	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	Intercept	6,154.6	6,189.1
Seizure-frequency on seizure days	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	Intercept, slope	10,188.8	10,238.8
Seizure-frequency on seizure days	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	Intercept	10,373.2	10,406.6
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.				

c. Please provide an option in the model to allow the regression models to have only random effects in the intercept (and not in the slopes).

An option has been included in the cost-effectiveness model to exclude the random slope from the regression. The results of this analysis is presented in Table 15 and demonstrates that removing the random slope coefficient has a limited impact on the ICER. Table 13 and Table 14 present the coefficients for the seizure-free days and seizure frequency (on seizure days) regression models respectively.

As per the response to question B7.b above, the inclusion of the random slope improves the goodness of fit for both models and it is clinically implausible for all patients to have the same response over time. As such, we maintain that the base case analyses including this random effect are the most appropriate.

Therefore, the scenario result excluding the random slope (Table 15) should be interpreted with caution.

Table 13: Binomial seizure-free day model without random slope – coefficients

Covariate	Estimate	SE	p-value
Intercept	-0.773	0.258	0.003
Treatment = placebo Ref = cannabidiol 25 mg/kg/day	-0.521	0.361	0.149
Log (cycle)	0.451	0.043	<0.001
Baseline seizure rate (scaled)	-2.307	0.238	<0.001
Treatment (placebo) * log (cycle)	-0.181	0.058	0.002
Key: SE, standard error.			

Table 14: Negative binomial seizure frequency (on seizure days) model without random slope – coefficients

Covariate	Estimate	SE	p-value
Intercept	0.876	0.058	<0.001
Treatment = placebo Ref = cannabidiol 25 mg/kg/day	-0.037	0.079	0.643
Log (cycle)	-0.066	0.018	<0.001
Baseline seizure rate (scaled)	0.473	0.032	<0.001
Treatment (placebo) * log (cycle)	0.068	0.024	0.004
Key: SE, standard error.			

Table 15: Scenario analysis results (PAS price) – using regression model without a random slope

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£16,992
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years. **Note:** *Discounting is applied to QALYs and cost.					

d. Please elaborate on the procedures to select covariates for the regression models. What candidate covariates and interaction terms were considered and why? What were the criteria to in- or exclude covariates and interaction terms?

Covariate adjustment was generally considered within the regression analyses for both prognostic factors and treatment effect modifiers to estimate outcomes at a cohort level. However, adjustment for prognostic factors was not considered necessary within this analysis as patients in the GWPCARE6 trial were randomized and patient characteristics are observed to be well balanced.

To determine whether adjustment for treatment effect modifiers was required, the subgroup analysis results for the primary endpoint from GWPCARE6 were explored. This showed that age group, sex, region, clobazam use, valproic acid use, levetiracetam use, vigabatrin use, baseline TSC-associated seizure frequency, number of concurrent AEDs, number of prior AEDs and composite of number of prior AEDs and concurrent AEDs were not observed as statistically significant treatment effect modifiers (see Figure 7, in Appendix L, Document B in the company submission). Therefore, covariate adjustment for treatment effect modifiers was also not deemed necessary. If a characteristic had been observed to be a treatment effect modifier, then an interaction term with treatment would have been considered.

Although additional adjustment is not required, to accurately capture changes over time, the following covariates were included within the regression analyses:

- Treatment (cannabidiol 25 mg/kg/day or placebo)
- Cycle (log transformed; continuous covariate) – by including treatment cycle as a continuous covariate, extrapolating the covariate would assume that a patient's outcomes would continue to improve indefinitely with time. A log transformation was therefore also considered, which slows the improvement of outcomes over time. Note, this is discussed further in the response to question B7.e.
- Treatment by cycle interaction – it is anticipated that the change in seizure frequency and seizure-free days over time will differ by treatment. As such, an interaction term was considered
- Baseline seizure frequency per week (continuous covariate) – the impact of treatment is anticipated to differ depending on the level of seizure frequency the patient is experiencing prior to treatment. As such, a covariate for baseline seizure frequency was estimated to accurately capture the variation in the patient population. To provide one overall estimate of baseline seizure rate to include in

both the regression models, the baseline seizure frequency covariate includes days where patients had no seizures in the estimate. Note that the baseline seizure frequency covariate was centred to prevent issues with convergence

- Offset for number of records. The offset term is used to account for the different 'exposure' for patients, as some patients may have less than 7 days of data recorded in a week. The offset term assumes there is a linear relationship between the number of seizures and the number of records. To incorporate an offset term into a negative binomial analysis, an additional covariate is added to the regression equation; however, the coefficient for the offset covariate is fixed to a value of one and the log of this value is taken to match the link function
- Random intercept – the intercept value is assumed to follow a distribution and each patient may have a different intercept value
- Random slope – the change in outcomes over time will follow a distribution and the rate of change will vary by each patient (i.e., some patients may improve faster than others while others may decline over time). Note: this is discussed further in the response to question B7.b.

e. A log-transformation was performed to reduce the improvement that was associated with increasing cycles (over time). Please justify why a log-transformation is preferred for this purpose.

Cycle was considered as a proxy for time within the regression analysis. However, it was determined that the inclusion of cycle as a continuous covariate without transformation would not be appropriate for inclusion within the regression model, as this would assume that patients would continuously improve over time, which is unlikely to hold for the full-time horizon.

The log transformation is a common transformation for positive, right skewed data which in this case allows for the improvement in patients to reduce over time. As such, this was utilized within the regression analysis.[21] Use of a categorical covariate for cycle was also considered. However, this would rely on arbitrarily selecting a number of categories and the cut-off times for each of the categories.

f. Please provide details/results of any other transformations considered and/or tested.

Table 16 presents the goodness of fit statistics for the regression models using no transformation, square root transformation and the log transformation on cycle. The square root transformation was not included in the response to question B7.e but is included here as it is considered as an alternative to the log-transformation for right skewed data.[21] Similar to the log-transformation, the square root transformation also reduces the improvement of patients over time, but the rate of change may be slower.

For each of the regression models, the results in Table 16 indicate that the log-transformation on cycle provides the best fitting model, whereas the models without any transformation provide the worst fitting models based on both AIC and BIC. For the seizure frequency on seizure days regression model, both the AIC and BIC for the model using the square root transformation are within 5 points of the scores for the log-transformation model, suggesting the goodness of fit for these models are comparable.

Using the square root transformation on cycle has very little impact on the ICER (see Table 17). This option has been included in the model.

Table 16: Goodness of fit statistics – regression models using different transformations on cycle

Model	Transformation on cycle	Covariates	AIC	BIC
Seizure-free days	No transformation	Treatment + cycle + treatment * cycle + baseline seizure frequency	5914.6	5960.6
Seizure-free days	Square root	Treatment + sqrt (cycle) + treatment * sqrt (cycle) + baseline seizure frequency	5876.4	5922.4
Seizure-free days	log	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	5863.1	5909.0
Seizure-frequency on seizure days	No transformation	Treatment + cycle + treatment * cycle + baseline seizure frequency	10197.7	10247.7
Seizure-frequency on seizure days	Square root	Treatment + sqrt (cycle) + treatment * sqrt (cycle) + baseline seizure frequency	10191.2	10241.2

Seizure-frequency on seizure days	log	Treatment + log (cycle) + treatment * log (cycle) + baseline seizure frequency	10188.8	10238.8

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion.
Note: All regression models presented include a random intercept and slope

Table 17: Scenario analysis results (PAS price) – using square root transformation on cycle.

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£12,419

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost.

g. Please provide diagnostics of the regression models, including multicollinearity.

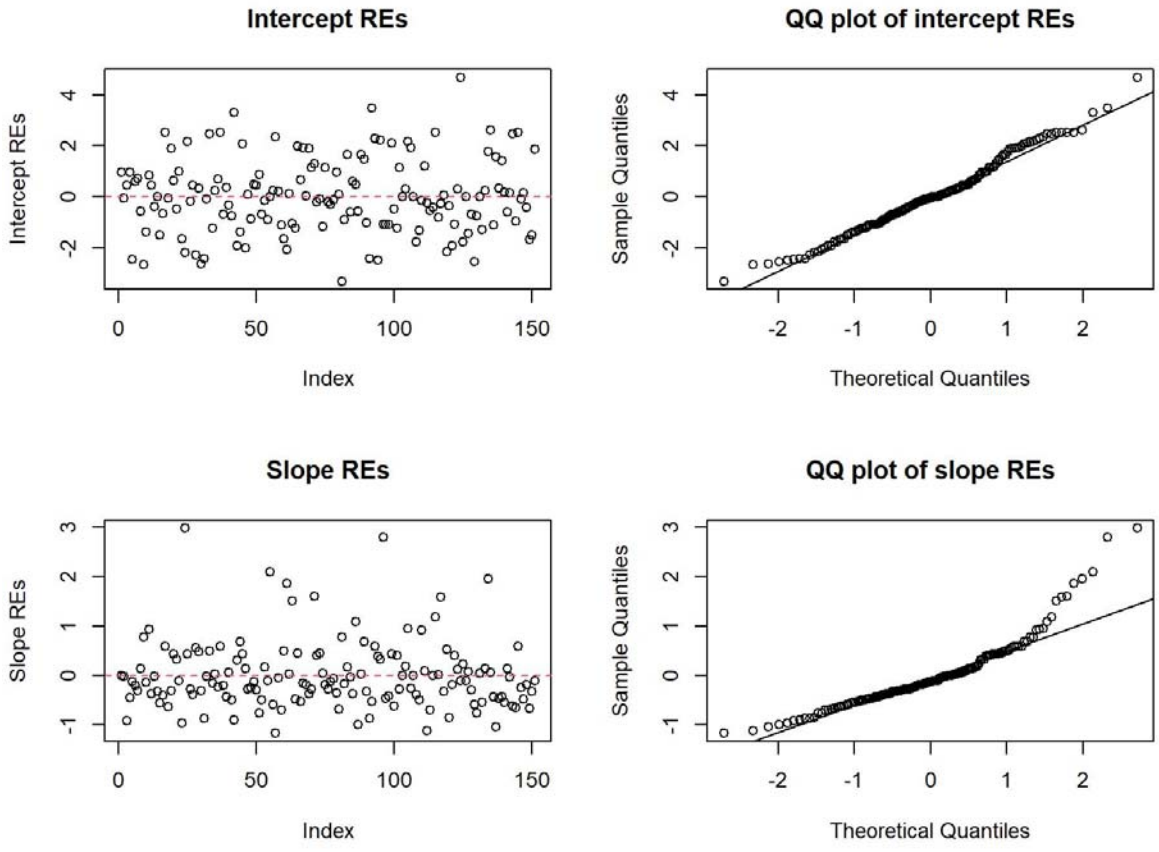
Diagnostic plots to assess the suitability of the fitted binomial seizure-free days model are presented in Figure 6 and Figure 7. There are no clear issues with the model fit (with the exception of one outlying value for the Pearson residuals; see Figure 7). The assumption of normality of the random effects is also demonstrated to be an approximately appropriate assumption (see Figure 6). The slight bow in the slope random effect quantile-quantile plot should be considered as a potential limitation of the model. However, the need to include a random effect for slope is clear based on the goodness of fit statistics (see response to B7.b).

Diagnostic plots to assess the suitability of the fitted negative binomial model for seizure frequency are presented in Figure 8 and Figure 9. The assumption of normality of the random effects is demonstrated to be a reasonable assumption (see Figure 8). The slight bow observed in both the intercept and slope random effect quantile-quantile plot should be considered as a potential limitation of the model. However, the need to include both random effect terms is clear based on the goodness of fit statistics (see response to B7b). The residual plots in Figure 9 show some outlying observations for the lower fitted values (i.e. fewer seizures); however,

this may be expected given the data are highly concentrated. In addition, the associated histograms suggest the residuals are approximately normally distributed suggesting there are no major issues with the model fit.

The Spearman's rank correlation coefficient has been used to assess the correlation between the predictors included in the model (treatment, baseline seizure frequency (scaled) and log[cycle]). Results for the seizure-free days and seizure frequency model are presented in Table 18 and Table 19, respectively. Results suggest that there is minimal correlation between variables (values < 0.1).

Figure 6: Diagnostic plots for the random effects terms – binomial seizure-free days model



Key: QQ, quantile-quantile; REs, random effects.

Figure 7: Diagnostic plots for the residuals – binomial seizure-free days model

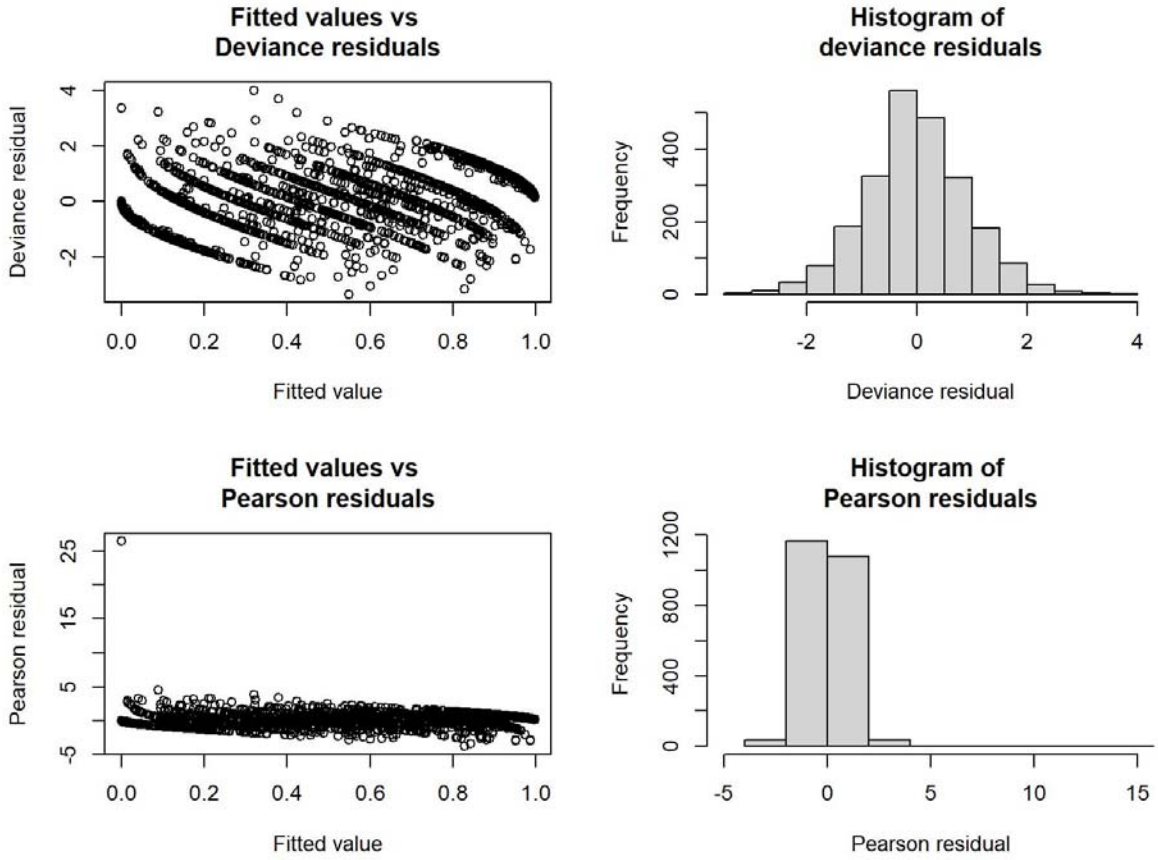
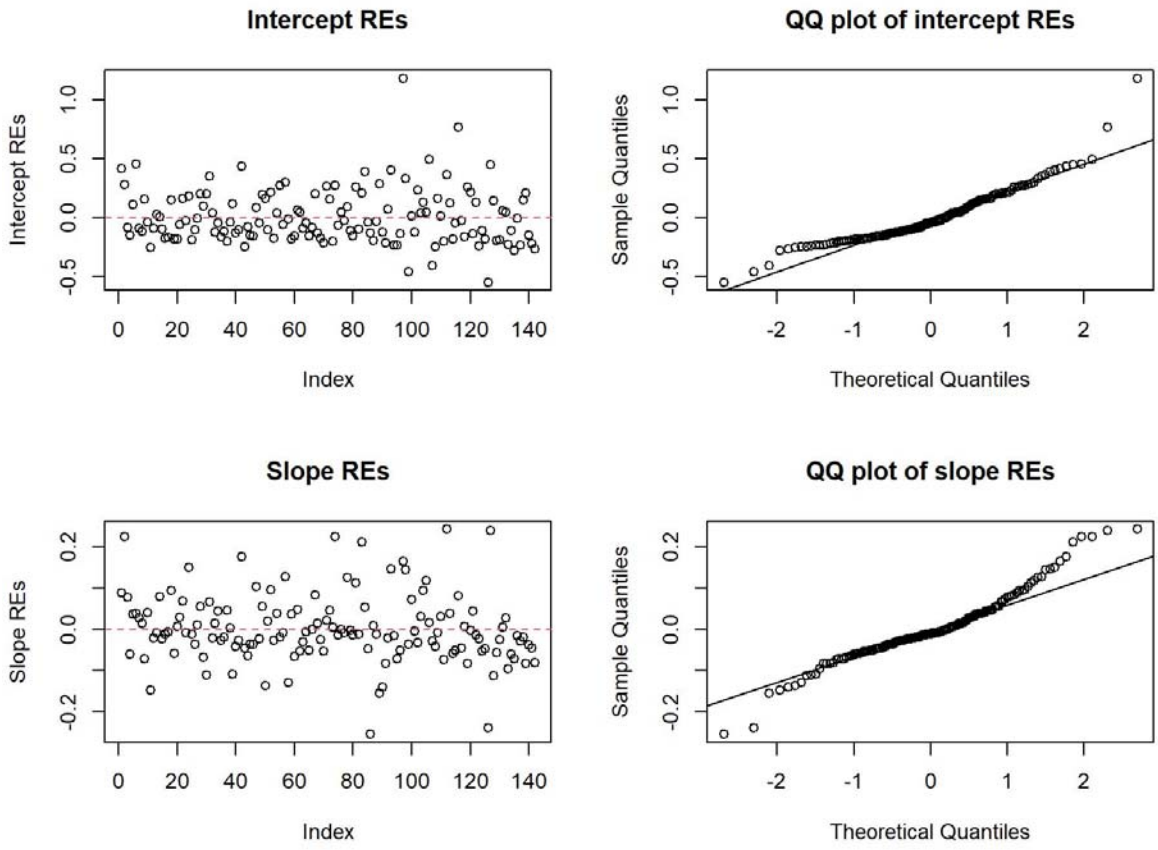


Figure 8: Diagnostic plots for the random effects terms – negative binomial seizure frequency model



Key: QQ, quantile-quantile; REs, random effects.

Figure 9: Diagnostic plots for the residuals – negative binomial seizure frequency model

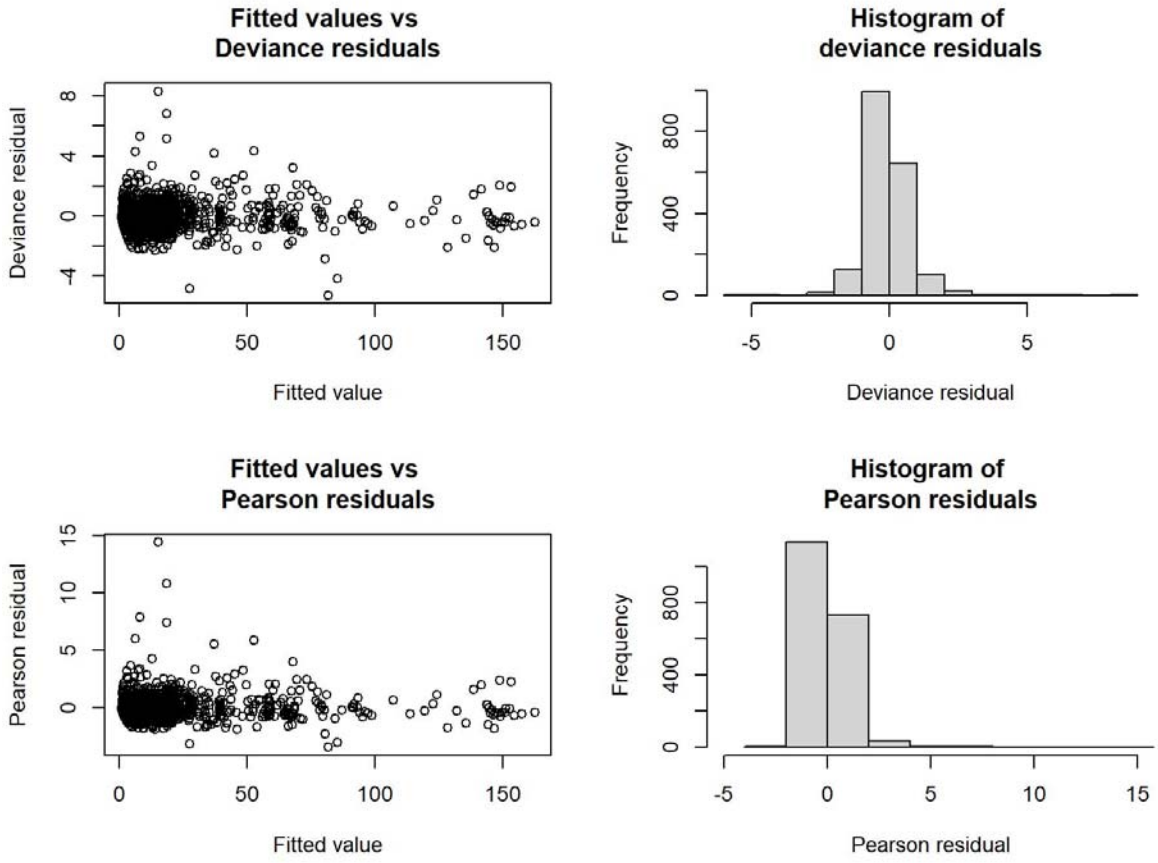


Table 18: Spearman's rank correlation coefficient – binomial seizure-free days model

	Treatment	Log(cycle)	Baseline seizure frequency (scaled)
Treatment	1.000	0.027	0.067
Log(cycle)	0.027	1.000	0.001
Baseline seizure frequency (scaled)	0.067	0.001	1.000

Table 19: Spearman's rank correlation coefficient – negative binomial seizure frequency model

	Treatment	Log(cycle)	Baseline seizure frequency (scaled)
Treatment	1.000	0.038	0.019
Log(cycle)	0.038	1.000	0.012
Baseline seizure frequency (scaled)	0.019	0.012	1.000

h. Please clarify and justify how missing data were handled for the estimation of the regression models.

Within the core trial period, data were reported on 15,339 out of 16,180 possible days (~95%). Therefore, the amount of missing data during the core trial period is low, suggesting that the impact of the missing data may be negligible and that imputation approaches are not required.[22]

However, as detailed in response to B.7a, additional considerations were made within the regression analysis:

- For the seizure-free days regression analysis, the proportion of seizure-free days per week is estimated rather than the absolute number of seizure-free days per week. Given that the estimated proportions become more variable where data are limited, the proportions are estimated for cycles where at least 3 days of data were available; note, the seizure days in these cycles were still included within the seizure frequency analysis

- For the seizure frequency on seizure days regression analysis, an offset term was included to account for the different 'exposure' for patients, as some patients may have less than 7 days of data recorded in a week. For example, if data are only available for 5 days in week, then the proportion of seizure days and the seizure frequency on seizure days may be applied to a 7-day period.

B8. Priority: Long-term extrapolation is based on 16 weeks data. The company submission states that '*The base case analysis assumes that the relative treatment effect is consistent and maintained over the model time horizon, whilst patients are on cannabidiol plus usual-care treatment*.'

a. **Please confirm that this is implemented by keeping all proportions fixed after 16 weeks, which implies that all patients maintain week 16 seizure frequency and seizure free days and can only move (worsen) when they discontinue cannabidiol or die.**

We confirm that all patients on treatment with cannabidiol plus usual-care maintain week 16 seizure frequency and seizure-free days, and move when they discontinue cannabidiol or die.

b. **Please comment on the clinical plausibility of the model result that none of the patients in the usual care arm are seizure-free during the entire time horizon, given that natural variation is seen in TSC-related epilepsy. Please provide clinical expert opinion as well as supporting empirical evidence to accompany the response.**

As described in Document B of the company's submission, TSC-associated epilepsy presents a significant clinical challenge as up to two-thirds of patients are refractory to currently available treatments and do not achieve seizure control.

In the GWPCARE6 Phase 3 clinical trial, patients had tried and discontinued up to 15 AEDs (median 4) in order to try to achieve seizure control, with some taking up to 5 AEDs concurrently (median 3) and still not gaining control of their seizures.

Therefore, it is highly unlikely that a patient who is already refractory would become seizure-free just by continuing on their existing usual-care treatment.

The clinical plausibility of this was supported by feedback from recent discussions with two UK clinical experts, Professor Finbar O'Callaghan and Dr Sam Amin.

c. Please comment on the clinical plausibility of the assumption that the relative treatment effect of cannabidiol is maintained over a patient's lifetime, whilst on treatment.

There is currently no clinical evidence to suggest that the Epidyolex treatment effect falls over time. Epidyolex has shown sustained durability of effect over the OLE period of GWPCARE6 (TSC-associated epilepsy) and in the GWPCARE5 OLE study (DS/LGS). In addition, a stable and durable long-term effect with Epidyolex has also been evidenced in a US Expanded Access Programme.

A reduction in treatment effect is already 'built in' to the economic model via conservative assumptions on long-term discontinuation rates and the use of stopping rules. This reflects clinical practice, and is evidence-based.

The use of these conservative and evidence-based discontinuation assumptions and stopping rules throughout the model means that patients stay in the model in the longer term only as long as they remain on treatment and *are receiving a sufficient treatment effect*. For many patients, this is a relatively short time in comparison to the time horizon of the model.

Table 20 below shows that, at 10 years, around 9% of patients remain on treatment. By 20 years, this has fallen to less than 6% of patients.

Table 20: Proportion of patients remaining on treatment (cannabidiol) over time

Year	1	5	10	20
Percentage of patients	55.3%	18.1%	8.9%	5.8%

Note: the proportion of patients on treatment is inclusive of the change in the base case as per question B13.a.

d. Please provide a scenario where the effect of cannabidiol whilst on treatment decreases over time, to explore the impact of the above assumption on the costs, QALYs, and the ICER.

Feedback from recent discussions (conducted to inform our responses to the ERG) with two UK clinical experts (Professor Finbar O'Callaghan and Dr Sam Amin) indicates that, in real-world clinical practice, a patient with TSC-associated epilepsy who was not receiving benefit from an AED would be taken off that treatment quickly. This is a particularly common practice in severe epilepsy, where patients cycle through a large number of AEDs over their lifetime. In line with responsible prescribing practices, clinicians, patients and caregivers would not want a patient to remain on a treatment that was no longer adding value.

This means that a situation in which a patient was on a treatment for a period of time and then remained on that treatment long term if it reduced in effectiveness is not a plausible scenario.

However, in response to this request from the ERG, efforts to model the consequences of a reduction in treatment effect have been made within the confines of the economic model structure.

We have provided a scenario where patients who would otherwise discontinue cannabidiol treatment continue for an extra 16 cycles and incur the extra cost of cannabidiol but with no treatment benefits. (Note that the scenario is inclusive of the change in the base case as per question B13.a).

This is applied assuming a lag between a loss of treatment effect and discontinuing cannabidiol by modelling that a proportion of patients (range: 10-100%) who discontinue incur all the cannabidiol treatment cost but receive no treatment benefit for an extra 16 weeks.

This delay of 16 weeks is likely to be a conservative assumption. The two UK clinical experts confirmed that, if a patient with TSC-associated epilepsy under their care were to stop having a satisfactory response to their anti-seizure medication (ASM), the ASM would be stopped almost immediately and certainly within 'a couple of months'.

The results in Table 21 demonstrate that there is a minor impact on the ICER when assuming that the maximum number (100%) of discontinuing cannabidiol patients incur the extra cost of cannabidiol but receive no treatment benefit.

Table 21: Scenario analysis results (PAS price)

	Scenario	ICER
Updated base case as per question B13.a.	-	£12,712
Percentage of discontinuing cannabidiol patients treated for an extra 16 cycles incurring all treatment costs but no treatment benefits	10%	£12,946
	15%	£13,062
	20%	£13,179
	25%	£13,296
	50%	£13,879
	75%	£14,462
	100%	£15,045

B9. Priority: The effect on TAND was included in the model (as a reduction in resource use and an increase in health-related quality of life (HRQoL)) when the seizure frequency was reduced by at least 50%.

a. **Please justify the use of seizure frequency based on a relative scale (50% reduction). Please consider in your answer company submission section B.3.1.2 which discusses how a method based on a percentage reduction in seizure frequency may not accurately capture costs and quality of life outcomes.**

As outlined in Document B of the company's submission, the cognitive and behavioural difficulties known as TSC-associated neuropsychiatric disorders (TAND) that prevent children from achieving independence in adult life can have a profound impact on the quality of life experienced not only by the patients but also by their families and carers.

We acknowledge that the approach taken to modelling the devastating impact of TAND is not ideal. However, we have made our best efforts with the limited available evidence. In this case, the evidence available was seizure frequency based on a relative scale (% reduction).

This pragmatic approach was an attempt to broadly quantify the impact on costs and quality of life outcomes of this important aspect of TSC-associated epilepsy.

b. Please clarify whether the 50% reduction threshold was defined as a reduction in seizure frequency, in seizure free days, or a combination of both, and how this definition aligns with the definition of 'seizure frequency' the experts in the Delphi panel used.

The 50% reduction threshold was defined as a reduction in seizure frequency.

The Delphi panel returned a near consensus that the reduction in seizure frequency required to reduce the progression of TAND aspects would be 47.5%. To be conservative, we used a 50% reduction in the model.

This was implemented in the model by applying the benefit of reducing the progression of TAND to the proportion of patients who experienced a reduction of seizure frequency of at least 50% following treatment initiation with cannabidiol plus usual-care or placebo plus usual-care.

c. Please provide a scenario where the threshold for reduction of seizure frequency to include an effect on TAND is 75%.

The results for the scenario analysis based on the threshold for reduction of seizure frequency to include an effect on TAND of 75%, are provided in Table 22. Note that the scenario is inclusive of the change in the base case as per question B13.a.

The scenario shows minor sensitivity to the change, with cannabidiol demonstrating a marginally lower incremental cost, higher incremental QALY and a slightly lower ICER.

Table 22: Scenario analysis results (PAS price)

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£11,994

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost.

d. Please provide a scenario analysis excluding TAND.

The results for the scenario analysis based on the exclusion of any TAND mitigation, are provided in Table 23. Note that the scenario is inclusive of the change in the base case as per question B13.a.

The scenario shows minor sensitivity to the change, with cannabidiol demonstrating a marginally higher incremental cost, lower incremental QALY and a slightly higher ICER.

Table 23: Scenario analysis results (PAS price)

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£14,391

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: *Discounting is applied to QALYs and cost.

e. Seizure frequency has an impact on resource use and HRQoL, but also on TAND which in turn has again impact on resource use and HRQoL. Although the TAND aspects have a distinct impact on resource use and HRQoL, there may also be overlap with aspects already captured in the vignettes for instance. Please comment on the possible impact of this duplicating effect (i.e., double counting) and explain how it could be corrected.

We acknowledge that there may be some overlap. However, as explained in question B9.a above, we took a pragmatic approach in an attempt to model the devastating impact of TAND on patients and their carers/families.

Whilst not ideal, we made our best efforts with the limited data available. As can be seen in question B9.d above, there is minor sensitivity in the model to TAND.

f. **The company submission states on p110 that the proportion of patients who experienced a reduction of seizure frequency of at least 50% following treatment initiation was informed by an analysis of GWPCARE6 data, and that the reduction in progression of TAND was applied for that proportion. From the model it would seem however that the proportion is informed by the modelled percentages per seizure frequency category. Please provide from the GWPCARE6 data the proportions of patients experiencing at least 50% reduction in seizure frequency at 6 months, by age category (and separately for the 1-year-olds).**

To clarify, the proportion of patients who achieved at least a 50% response (reduction) in seizure frequency compared to baseline was calculated based on the same method used to calculate the stopping rule rates, as detailed in Appendix O. The same method was used to maintain consistency across model inputs.

The proportion of patients who achieved at least a 50% response (reduction) in seizure frequency compared to baseline for patients aged 2-6 years is provided in Table 24**.** The data is provided for patients aged 2-6 years, which aligns with the population for whom TAND mitigation benefits are applied in the base case analysis, and for all patients. Other age groups (including patients aged 1 year old) are not provided as these are not used in the model analysis.

A total of 11 patients (cannabidiol arm) and 14 patients (usual-care arm) were available to inform the TAND response rates for patients aged 2-6 years. Given this limited sample size, using only data for the 2-6 year old age category produces unrealistic outcomes, with responses for all but one health state based on 4 patients or less. Therefore, in both the model base case, where benefits are only applied for patients aged 2-6 years, and in the scenario which applies benefits to all patients, the data on TAND response rates were taken from the full population.

Table 24: Proportion of patients who are TAND responders per seizure frequency category (≥ 50% rates) – aged 2-6 and all patients

	Cannabidiol treatment arm			Usual-care treatment arm		
≥ 50% response rate - aged 2-6						
	N	**Responders**		**N**	**Responders**	
≤ 2 seizures per week	4	4	100.00%	2	2	100.00%
> 2 – ≤ 7 seizure per week	4	1	25.00%	4	1	25.00%
≥ 7 seizures per week	3	0	0.00%	8	1	12.5%
≥ 50% response rate – all patients						
≤ 2 seizures per week	18	14	77.78%	12	8	66.67%
> 2 – ≤ 7 seizure per week	16	7	43.75%	22	10	45.45%
≥ 7 seizures per week	17	4	23.53%	37	4	10.81%

***Note**: It is assumed that patients who are seizure-free are responding fully. Patient seizure frequency per day information is unavailable from the GWPCARE6 OLE period to calculate seizure-free per day rate.

In the GWPCARE6 open-label extension, usual-care treatment arm patients switched to receive cannabidiol. Therefore, usual-care response rates at Week 16 are used and assumed to be the same as the response rates for patients on cannabidiol in the open-label extension at Week 26 (i.e. 6 months).

B10. The following questions relate to validation regression estimates versus OLE data:

a. Please confirm that the data presented for the OLE in Figure 16 of the company submission do not contain patients who were on placebo during the blinded phase.

We confirm that the data presented for the OLE in Figure 16 in Document B of the company submission is based on patients who received cannabidiol 25 mg/kg in the blinded phase.

b. In the OLE, there was no data on seizure free days, only on seizure frequency. Please clarify what is meant in Figure 16 on the y-axis with:

'seizure frequency on seizure days'. How is this defined and how does this compare to what was estimated in the regression model?

During the blinded phase, data for seizure frequency were collected daily for each patient. In the OLE, patients/caregivers were instructed to complete a weekly seizure reporting diary meaning that seizure frequency data were collected approximately every 7 days. Due to the different nature of seizure collection in the OLE, the following assumptions were necessary when summarising the data per week:

- The number of days between collections was the number of days seizures occurred over. However, a cut-off of 7 days was used where there were more than 7 days between records as in some cases this value was high
- Seizures collected over periods of 12 weeks occurred evenly over each week – seizures were grouped into 12-week blocks (Week 1 to 12, Week 13 to 24, etc.) which were then used to derive the average number of seizures per 7 days. This was done to adjust for multiple collections in some weeks
- Seizures occurred on every day of the collection period – this assumption was required as it was not possible to extract the number of seizure-free days from the data

Therefore, the observed data in Figure 16 of the company submission represents the average 7-day seizure frequency based on all assumed days of the collection period.

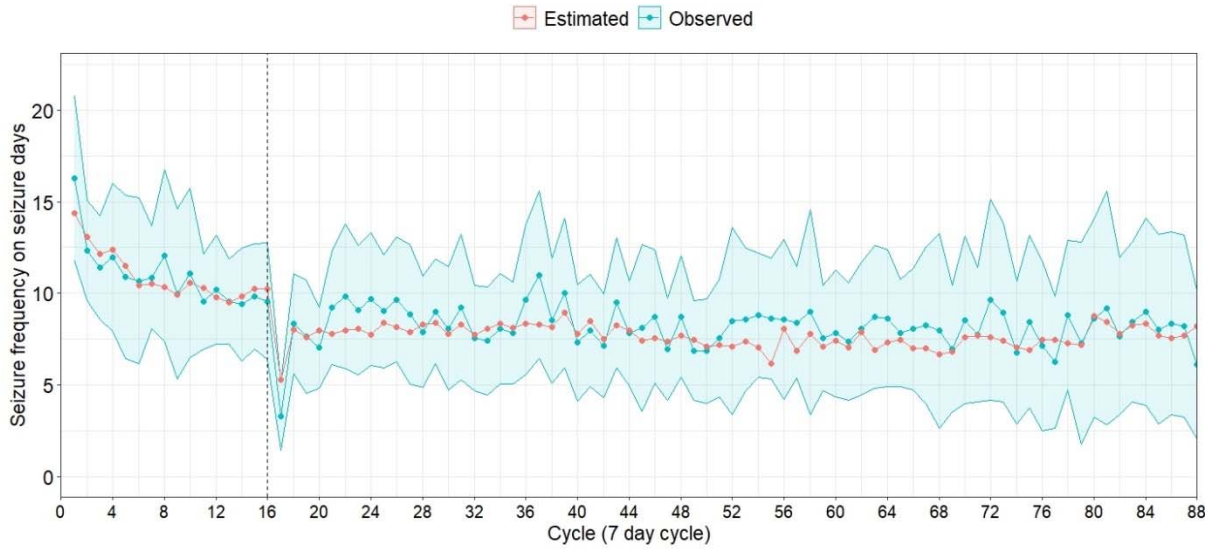
c. Please comment on the fact that in Figure 16, on average there seems to be underprediction of the seizures. Please provide in a table the numerical data behind the figure with percentual deviation from observed seizure frequency per cycle.

Figure 10 presents the observed and estimated (using both the fixed and random effect) seizure frequencies with 95% confidence intervals for the observed data. Note that all point estimates are identical to those shown in Figure 16 of the company submission, except at Week 17, where data were re-estimated to include only patients with observed values. The predicted values (shown in red) fall well within the 95% confidence interval of the observed data (shown in blue). In addition, the area under the curve (AUC) for the observed data is less than 5% different from the

predicted curve [755 (95% confidence interval: 430, 1080), compared with 715]. Again, the AUC for the predicted data falls well within the 95% confidence interval for the observed curve. Although we note that the AUC for the predicted curve is marginally lower than the AUC for the observed curve, there is variability in the observed OLE data, which is likely due to the nature of the data collection and derivation (described in response to B10.b).

Although it is possible that the number of seizure days per week of the OLE are underestimated in the observed data due to the assumption that seizures occur on all collection days (bullet 3 above), this may be counteracted with the number of collection days assumption (bullet 1 above). Although we acknowledge there are limitations with the data collection in the OLE, the estimates suggest that the model provides reasonable predictions for seizure frequency throughout the OLE period.

Figure 10: Observed and estimated seizure frequency



Notes: Dashed line indicates the start of the open-label extension. Data are presented for the cannabidiol 25 mg/kg/day arm from the core trial. 95% confidence intervals are presented for the observed data.

Table 25: Observed and estimated seizure frequency data

Cycle	Observed (95% confidence interval)	Estimated	Percentage deviation
1	16.3 (11.8, 20.8)	14.4	11.70%
2	12.3 (9.6, 15.1)	13.1	-6.10%
3	11.4 (8.6, 14.2)	12.2	-6.60%
4	12.0 (7.9, 16.0)	12.4	-3.30%
5	10.9 (6.4, 15.4)	11.5	-5.60%
6	10.7 (6.2, 15.2)	10.4	2.60%
7	10.9 (8.1, 13.7)	10.5	3.30%
8	12.0 (7.4, 16.7)	10.4	14.00%
9	10.0 (5.3, 14.6)	9.9	0.20%
10	11.1 (6.5, 15.7)	10.6	4.80%
11	9.6 (7.0, 12.2)	10.3	-7.50%
12	10.2 (7.2, 13.2)	9.8	3.80%
13	9.6 (7.2, 11.9)	9.5	0.30%
14	9.4 (6.3, 12.5)	9.8	-4.70%
15	9.8 (7.0, 12.7)	10.3	-4.30%
16	9.6 (6.4, 12.7)	10.3	-7.20%
17	3.3 (1.4, 5.1)	5.3	-60.30%
18	8.4 (5.6, 11.1)	8	4.30%
19	7.6 (4.5, 10.7)	7.6	0.70%
20	7.0 (4.8, 9.2)	8	-13.40%
21	9.2 (6.1, 12.3)	7.8	15.50%
22	9.8 (5.9, 13.8)	8	18.90%
23	9.1 (5.6, 12.6)	8.1	11.20%
24	9.7 (6.1, 13.3)	7.7	20.00%
25	9.0 (5.9, 12.1)	8.4	7.20%
26	9.7 (6.3, 13.1)	8.2	15.60%
27	8.8 (5.0, 12.6)	7.9	11.00%
28	7.9 (4.9, 10.9)	8.3	-4.80%
29	9.0 (6.2, 11.8)	8.4	6.90%
30	8.1 (4.7, 11.4)	7.8	3.90%
31	9.2 (5.3, 13.2)	8.3	10.10%
32	7.6 (4.7, 10.4)	7.7	-2.30%
33	7.4 (4.4, 10.4)	8.1	-9.30%
34	8.1 (5.0, 11.1)	8.4	-3.80%
35	7.8 (5.1, 10.6)	8.1	-3.20%
36	9.6 (5.5, 13.7)	8.4	13.10%
37	11.0 (6.4, 15.6)	8.3	24.40%
38	8.5 (5.1, 11.9)	8.2	3.90%

Cycle	Observed (95% confidence interval)	Estimated	Percentage deviation
39	10.0 (5.9, 14.1)	9	10.80%
40	7.3 (4.1, 10.5)	7.8	-6.60%
41	8.0 (4.9, 11.0)	8.5	-6.30%
42	7.1 (4.3, 9.9)	7.5	-5.50%
43	9.5 (5.9, 13.0)	8.2	13.20%
44	7.8 (5.0, 10.7)	8	-1.80%
45	8.1 (3.6, 12.7)	7.4	8.60%
46	8.7 (5.1, 12.4)	7.6	13.50%
47	7.0 (4.2, 9.7)	7.4	-6.10%
48	8.7 (5.4, 12.0)	7.7	11.50%
49	6.9 (4.2, 9.6)	7.5	-8.50%
50	6.8 (4.0, 9.7)	7.1	-3.50%
51	7.5 (4.4, 10.7)	7.2	4.60%
52	8.5 (3.4, 13.6)	7.1	16.10%
53	8.6 (4.7, 12.5)	7.4	13.80%
54	8.8 (5.4, 12.2)	7	20.20%
55	8.6 (5.3, 11.9)	6.2	28.60%
56	8.6 (4.2, 12.9)	8.1	5.90%
57	8.4 (5.4, 11.4)	6.9	18.50%
58	9.0 (3.4, 14.6)	7.8	13.30%
59	7.6 (4.7, 10.5)	7.1	5.90%
60	7.8 (4.4, 11.3)	7.4	4.90%
61	7.4 (4.2, 10.6)	7.1	4.50%
62	8.1 (4.5, 11.7)	7.9	2.20%
63	8.7 (4.8, 12.6)	6.9	20.60%
64	8.6 (4.9, 12.4)	7.3	15.10%
65	7.8 (4.9, 10.8)	7.5	4.60%
66	8.0 (4.7, 11.4)	7	13.20%
67	8.2 (4.0, 12.5)	7	14.90%
68	8.0 (2.6, 13.3)	6.7	15.90%
69	7.0 (3.5, 10.4)	6.8	1.80%
70	8.6 (4.0, 13.1)	7.6	11.10%
71	7.8 (4.1, 11.4)	7.7	0.50%
72	9.7 (4.2, 15.1)	7.6	21.10%
73	9.0 (4.1, 13.9)	7.4	17.30%
74	6.8 (2.9, 10.7)	7.1	-4.40%
75	8.5 (3.8, 13.2)	6.9	18.30%
76	7.1 (2.5, 11.8)	7.5	-4.60%
77	6.2 (2.6, 9.8)	7.5	-19.50%
78	8.8 (4.7, 12.9)	7.3	17.60%

Cycle	Observed (95% confidence interval)	Estimated	Percentage deviation
79	7.3 (1.7, 12.8)	7.2	1.00%
80	8.6 (3.2, 14.0)	8.8	-1.50%
81	9.2 (2.8, 15.6)	8.4	8.20%
82	7.7 (3.4, 11.9)	7.8	-1.60%
83	8.4 (4.1, 12.8)	8.2	2.40%
84	9.0 (3.9, 14.1)	8.4	7.10%
85	8.0 (2.9, 13.2)	7.7	3.90%
86	8.4 (3.4, 13.3)	7.6	9.40%
87	8.2 (3.3, 13.2)	7.7	6.40%
88	6.1 (2.1, 10.2)	8.2	-34.50%

B11. At baseline (cycle 0) the proportion of seizure-free patients is 7% in both arms.

a. Please explain why the proportion of seizure-free patients in both arms drops to 0% in the first week (cycle 1).

b. Please justify, providing clinical expert opinion, the clinical plausibility of this sudden change.

c. Please provide a scenario where proportion of seizure-free patients is 0% at baseline.

Please note that, while relooking at these data in response to this question, we noticed that erroneous baseline (cycle 0) data in the model was included. Data was left over from the exploratory phase of the model development and has therefore been removed. As the data was not used, there is no impact on the modelled ICERs. We apologise for the error.

B12. Table 16 of the company submission presents the discontinuation rate per cycle per seizure frequency category. Please explain:

a. How were the discontinuation rates in Table 16 calculated, were the 3-month rates divided by 13 to get from a 3-month to a 1-week rate? Also please clarify

whether the original rates from technology appraisal (TA) 615[23] were actually rates or probabilities.

The discontinuation rates in Document B, Table 16, for long term discontinuation, were 3-month rates sourced from NICE TA615. To calculate a weekly rate suitable for use in the economic model, these were divided by 91 days (equivalent to 13 weeks) and multiplied by 7 days (1 week) to get from a 3-month to a 1-week rate**.**

To clarify, the discontinuation rates used in technology appraisal TA615 were presented as rates per cycle (3-month cycle).

b. How the rates compare to other cannabidiol trials or TAs, such as TA614[24]

Table 26 presents the rates used in TA614, TA615 and ID1416. For comparative purposes, the rates used in TA614 and TA615 have been converted from a 3-month to a 1-week rate, using the calculation outlined in response to B12.a. The 3-month rates from TA614 and TA615 are presented in Appendix 3. The rates calculated from the GWPCARE6 trial and open-label extension data for ID1416 are broadly comparable to the rates used in TA614 and TA615.[8, 9]

Table 26: Discontinuation rates from TA614, TA615 and ID1416 (per week)

	<12 years			**≥12 years**		
Time period for application of rate	**Cycle 1[a]**	**Subsequent cycles (cycles 2-9)**	**Long term cycles[b] (cycle 10-)**	**Cycle 1**	**Subsequent cycles**	**Long term cycles**
Lennox-Gastaut Syndrome						
Seizure free	0.43%	0.04%	0.04%	0.43%	0.04%	0.04%
≤ 8 seizures	0.43%	0.04%	0.77%	0.43%	0.11%	0.77%
>8 - ≤ 25 seizures	0.43%	0.59%	0.77%	0.43%	0.46%	0.77%
> 25 seizures	0.43%	0.59%	0.77%	0.43%	0.46%	0.77%
Dravet syndrome						
Seizure free	0.45%	0.04%	0.04%	0.45%	0.04%	0.04%
≤ 8 seizures	0.45%	0.18%	0.77%	0.45%	0.21%	0.77%
>8 - ≤ 25 seizures	0.45%	0.38%	0.77%	0.45%	0.30%	0.77%
> 25 seizures	0.45%	0.38%	0.77%	0.45%	0.30%	0.77%

TSC-associated epilepsy (population aged ≥ 2 years)				
Time period for application of rate	**Weeks 1-16[c]**	**Subsequent cycles (weeks 17-88)**	**Long term cycles (week 89-)**	
Seizure-free	0.67%	0.04%	0.04%	
≤ 2 seizures	0.67%	0.14%	0.77%	
>2 - ≤ 7 seizures	0.67%	0.29%	0.77%	
>7 seizures	0.67%	0.44%	0.77%	
Key: a: Cycle length of 3 months used in TA614 and TA615. **b**: The long term rate presented is as per the final NICE committee agreed rate for TA614 and TA615 (10%). **c**: Timeframe reflects clinical trial period for GWPCARE6				

B13. Table 17 of the company submission shows the proportion of patients discontinuing treatment based on the stopping rule.

a. The proportion of patients with > 2 and ≤ 7 seizure per week stopping at 12, 18, and 24 months was 0% because of small patient numbers in the OLE study. Please correct this inconsistency by using the average of the proportion with ≤ 2 seizures per week and ≥7 seizures per week in the base case.

As discussed on the ERG clarification call (28th April 2022), the base case analysis has been updated, to include the scenario where an average of the ≤ 2 seizures per week and ≥7 seizures per week is applied to the >2 –≤7 seizures per week health state.

The updated base case results of the comparison between cannabidiol plus usual-care and placebo plus usual-care are presented in Table 27. The results demonstrate that cannabidiol is a cost-effective use of NHS resources to treat seizures in patients aged ≥ 2 years with TSC-associated epilepsy at a WTP threshold of £20,000 per QALY gained.

The base case results with consideration of the disease severity modifier, as detailed in Document B, Section B.3.3.9, are presented in Table 28. These results also demonstrate that cannabidiol is a cost-effective use of NHS resources when considering the severity of TSC-associated epilepsy.

Updated sensitivity analysis is provided in Appendix 2.

Table 27: Updated base case results

Technologies	Total costs (£)*	Total QALYs*		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			
Cannabidiol + usual-care	[redacted]	Patient QALY	[redacted]	[redacted]	[redacted]	£12,712
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: *Discounting is applied to QALYs and cost.

Table 28: Updated base case results (including disease severity multiplier)

Technologies	Total costs (£)*	Total QALYs*		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			
Cannabidiol + usual-care	[redacted]	Patient QALY	[redacted]	[redacted]	[redacted]	£10,594
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: *Discounting is applied to QALYs and cost.

b. Please justify why the stopping rule was not applied after 24 months.

Patient level data on treatment response (≥ 30% reduction in seizure frequency) from the GWPCARE6 blinded trial period and the open-label extension are used to calculate stopping rates.

There are currently no data beyond this to enable us to apply an evidence-based stopping rule. For this reason, a long-term discontinuation rate is also applied post the OLE period to reflect patients discontinuing therapy due to non-response and other factors over the long-term.

To note: applying the stopping rule up to 24 months is in line with the stopping rule frequency requested by NICE/NHS England in the technology appraisals for cannabidiol in LGS and DS.

c. Provide scenarios with the stopping rule also applied after 24 months.

There are currently no data available to do this, so any scenario provided would be arbitrary.

However, it would be expected that if an arbitrary extrapolated stopping rule were applied after 24 months, this would result in a lower ICER.

B14. Please provide the formula for calculating the TSC-related mortality and sudden unexpected death in epilepsy (SUDEP) per 11.08 and 8 years, respectively, to annual mortality risks (page 105 of company submission).

The TSC-related mortality rate calculation is detailed in Appendix P. Briefly the calculation is as follows:

$$\frac{273\ deaths}{3376\ patients} \Big/ 11.08\ years = 0.736\%\ \text{per year} \times \frac{7}{365.25} = 0.014\%\ \text{per cycle}$$

The SUDEP mortality rate calculation is detailed in Appendix P. Briefly the calculation is as follows:

$$\frac{4\ deaths}{284\ patients} \Big/ 8\ years = 0.176\%\ \text{per year} \times \frac{7}{365.25} = 0.003\%\ \text{per cycle}$$

Adverse events (AEs)

B15. Section 3.3.4 of the company submission describes the inclusion of adverse events in the cost-effectiveness model. Please explain:

a. The difference in definition of serious and severe events.

Serious adverse event: In the GWPCARE6 trial, an AE was considered serious if it: (1) was fatal; (2) was life-threatening; (3) required inpatient hospitalization or prolonged existing hospitalization; (4) was persistently or significantly disabling or incapacitating; (5) was a congenital anomaly/birth defect; or (6) was a medically significant event that, based upon appropriate medical judgment, may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above.

Severe adverse event: For all AEs and serious AEs, the clinical trial investigators were required to assign severity and document this on the Case Report Form. The method is described in the trial protocol as follows:

"When describing the severity of an AE, the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE.

If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity.

A severe AE is not the same as a SAE. For example, a patient may have severe vomiting but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious."

b. How exactly the event rates in Table 15 of the company submission can be derived from, or are related to, Table 3 of Appendix F.

The event rates in Table 15 of the company submission are *Serious* treatment-emergent adverse events (TEAEs), that were *classified as severe* by the investigator and were considered to be *treatment-related*.

These are the adverse events that would drive the most costs associated with the drug and are therefore the most appropriate to use in the model.

Table 3 of Appendix F is simply a list of treatment-emergent adverse events (serious and non-serious).

c. Why AE rates were based on the first 16 weeks, and not the adverse events from the extended trial period as the serious AE incidence in the OLE study was still 15%. Please validate 16-week AE data with the OLE study data.

The company considered this to be a conservative approach. The inclusion of serious AEs from the randomized clinical trial period is likely to be an overestimate of costs.

For example, the rate of serious adverse events in the cannabidiol 25 mg/kg/day arm in the randomized trial period was 21.3%. As noted by the ERG above, this decreased to 15% in the OLE.

Based on real-world evidence, it is likely that this rate might be even lower in real-world clinical practice. For example, a real-world study of cannabidiol use in patients demonstrated that slower titration of the cannabidiol dose delivered better tolerability with comparable efficacy to previous trials.[25]

Health related quality of life

B16. Priority: A vignette study was used to estimate the HRQoL for the different health states.

a. According to the health-related quality of life task and finish group report (2020),[26] the DSU recommends that EQ-5D data collected for each vignette should be valued using a relevant value set. Please explain which EQ-5D value set was used.

The company did not use the EQ-5D value set, as the accepted preference elicitation TTO method was used to value the vignettes directly. This method was used as it is a standardised interview method for valuing health states, in line with methods used to value the EQ-5D-3L. According to the DSU report, vignettes can be

valued using a range of different techniques: clinical experts (or general population or patients) proxy-completing EQ-5D for the vignette health state; valuation with members of the general public or patients using preference elicitation techniques such as time trade-off (TTO); or eliciting values from clinical experts (for example using a Delphi method).

Standard measures such as the EQ-5D questionnaire fail to capture many aspects of the severity and complexity of severe and refractory epilepsies such as TSC-associated epilepsy. A feasibility assessment was conducted to determine the strength of evidence for the suitability of the EQ-5D and other generic or condition specific preference-based measures in refractory epilepsies (see Appendix R). Two studies evaluating the use of the EQ-5D found only weak correlations between the EQ-5D and condition specific measures. Mukuria et al concluded that, given the lack of correlation and joint responsiveness between the measures, using the EQ-5D for a cost-effectiveness analysis, including for mapping, is not recommended.[27] No other preference-based measures with confirmed psychometric validity in the population of interest were identified. On this basis, given that we were unable to find a suitable measure that could be used directly in patients, the only alternative option was to generate vignettes that accurately reflected the TSC-associated epilepsy population and value these in the general population to generate utilities.

b. Please clarify the exact methods used to calculate time trade-off (TTO) weights for the combined seizure health states (Table 21 of the company submission).

As detailed in Lo et al, 2021, in order to keep the length of the TTO valuation interviews manageable, only one vignette with a combination of both seizure types was developed.[28] For the other possible health states with a combination of seizure types, utility weights were estimated through linear interpolation of the differences between the TTO-values states. The methods used to calculate the TTO weights are detailed in Document B, Section B.3.4.4.1, and are consistent with the method outlined in Lo et al, 2021 (see Table 29 below).

The estimates were made assuming that disutility increases in a linear fashion with increasing seizure frequency. Values for the states with the lowest and highest number of seizures (valued using the TTO vignette method) were used as anchoring

points to allow values of other states with seizure frequencies falling within this range to be estimated.

Table 29: Estimation of utility values using TTO-valued heath states

		No. of focal seizures with impairment awareness per day			
		0	**1-2**	**3-4**	**5-14**
No. of generalized seizures per day	**0**	HS1	HS2	HS3	HS4
	1	HS5	*HS5-(Diff (HS7, HS8/2)*		*HS5 –(Diff (HS7, HS8)*
	2	HS6	*HS5-(Diff (HS7, HS8/2)*		*HS6 –(Diff (HS7, HS8)*
	3-14	HS7	*Mean (HS7, HS8)*		HS8
Key: Diff, difference between health states; HS, health states; TTO, time trade off **Note**: Italic text indicates estimation of utility values for states not valued in the time-trade off study					

c. Please provide a comparison of the utility values by seizure frequency and seizure type in Tables 20-24 of the company submission with those from TA614[24] and TA615.[23]

The VAS was used to elicit QoL data in TA614 and TA615. Since the VAS scores were not considered to be the most appropriate estimates to elicit utility values, we followed feedback from NICE and adopted the more rigorous preference-based TTO method for this submission.

For comparison, utility values from TA614 and TA615 are provided below.

TA614

Summary of mean VAS scores for cost-effectiveness analysis

Health state	State	VAS scores Mean (SE)	Justification (average of HS in utility study)
No seizures*	No seizures	0.753 (0.049)	'No seizure'
≤ 8 seizures	≤ 18 seizure-free days†	0.00	NA
	> 18 - ≤ 24 seizure-free days	0.572 (0.041)	DS_8_24. DS_6_24
	> 24 seizure-free days	0.611 (0.046)	DS_8_28. DS_6_28. DS_4_28
>8 - ≤ 25 seizures	≤ 18 seizure-free days	0.361 (0.033)	(DS_25_8. DS_25_12. DS_25_18). DS_16_18
	> 18 - ≤ 24 seizure-free days	0.443 (0.039)	(DS_25_21. DS_25_24). (DS_16_21. DS_16_24)
	> 24 seizure-free days	0.466 (0.052)	DS_25_28. DS_16_28
> 25 seizures	≤ 18 seizure-free days	0.235 (0.024)	DS_32_4. DS_32_8. DS_32_12
	> 18 - ≤ 24 seizure-free days	0.374 (0.033)	DS_32_18. DS_32_21
	> 24 seizure-free days	0.445 (0.048)	DS_32_24. DS_32_28

*All seizures refer to convulsive seizures
†This health state is included for completeness; no values were obtained as this is not a possible state
Abbreviations: DS, Dravet syndrome; HS, health state; NA, not applicable; SE, standard error

Summary of mean caregiver VAS score utility decrements

Health state		Mean decrements (standard error)
No seizures	No seizures	-
≤8 seizures	≤18 seizure-free days	-
	>18 - ≤24 seizure-free days	-
	>24 seizure-free days	-
>8 - ≤25 seizures	≤18 seizure-free days	-0.201 (0.052)
	>18 - ≤24 seizure-free days	-0.201 (0.052)
	>24 seizure-free days	-0.201 (0.052)
>25 seizures	≤18 seizure-free days	-0.244 (0.054)
	>18 - ≤24 seizure-free days	-0.244 (0.054)
	>24 seizure-free days	-0.244 (0.054)

TA615

Summary of mean VAS scores for cost-effectiveness analysis

Health state	Health states in the questionnaire	Utility value: mean (standard error)	Justification (average of HS in utility study)
No seizures	No seizures	0.833 (0.026)	'No seizures'
≤45 seizures	≤ 3 seizure-free days	0.331 (0.046)	LGS_45_3, LGS_45_1
	>3-≤15 seizure-free days	0.453 (0.038)	LGS_45_9, LGS_45_15, LGS_45_6, LGS_45_12, LGS_20_12, LGS_20_15
	> 15 seizure free days	0.559 (0.039)	LGS_45_18, LGS_20_18
>45 - ≤110 seizures	≤ 3 seizure-free days	0.289 (0.044)	LGS_80_3, LGS_80_1, LGS_ 60_1, LGS_ 60_3, LGS_110_3, LGS_110_1
	>3-≤15 seizure-free days	0.402 (0.039)	LGS_110_6, LGS_110_9, LGS_110_15, LGS_110_12, LGS_80_6, LGS_80_9, LGS_80_12, LGS_80_15, LGS_60_6, LGS_60_9, LGS_60_15, LGS_60_12
	> 15 seizure free days	0.471 (0.040)	LGS_110_18, LGS_80_18, LGS_60_18
>110 seizures	≤ 3 seizure-free days	0.235 (0.044)	LGS_130_1, LGS_130_3
	>3-≤15 seizure-free days	0.385 (0.041)	LGS_130_6, LGS_130_9, LGS_130_12, LGS_130_15
	> 15 seizure free days	0.458 (0.054)	LGS_130_18

*All seizures refer to drop seizures
Abbreviations: LGS, Lennox Gastaut; HS, health state

Summary of mean caregiver VAS score utility decrements

Health state		Mean decrements (standard error)
No seizures	No seizures	-
≤45 seizures	≤3 seizure-free days	-
	>3-≤15 seizure-free days	-
	>15 seizure free days	-
>45 - ≤110 seizures	≤3 seizure-free days	-0.268 (0.065)
	>3-≤15 seizure-free days	-0.268 (0.065)
	>15 seizure free days	-0.268 (0.065)
>110 seizures	≤3 seizure-free days	-0.403 (0.088)
	>3-≤15 seizure-free days	-0.403 (0.088)
	>15 seizure free days	-0.403 (0.088)

d. Justify the relatively large utility decrements associated with the seizure frequencies health states (for patients and caregivers), using expert opinion, empirical evidence and reference values from other diseases as benchmarks.

In recent discussions (conducted as part of providing answers to the ERG clarification questions), two UK clinical experts (Professor Finbar O'Callaghan and Dr

Sam Amin) confirmed that TSC-associated epilepsy and its associated consequences would have a ‘high negative impact’ on the quality of life of both patients and caregivers.

The relatively low utility values for the seizure health states are not unexpected given the number of seizures, TAND aspects and comorbidities, and the consequent impacts on the patient and his/her caregivers, as described by the vignettes in the TTO study. The detailed vignette descriptions outline the devastating situation in which patients or caregivers may find themselves. The vignettes were drafted with input from caregivers who highlighted the considerable impact that caring for a patient with TSC-associated epilepsy has on their wellbeing and quality of life.

We would like to reiterate the severe impact of TSC-associated epilepsy on the quality of life not only of patients but also on that of their families and caregivers. The burden of care and the effects of TSC-associated seizures on the patient can necessitate changes in virtually all aspects of the lives of caregivers and family members. The various aspects of TAND are an additional burden for caregivers already trying to cope with seizures.

Caring for a child or loved one with TSC-associated epilepsy is a 24-hour responsibility. Patients often have complex needs, severe impairment of daily functioning and a history of epilepsy-related events, such as injuries and hospitalisations related to seizures. Caring for them dictates work schedules, family time and leisure activities. Caregivers suffer significant anxiety and depression, social isolation, poor sleep quality, emotional distress, and a considerable impact on their ability to work, often resulting in financial difficulties.

Whilst ‘general epilepsy’ undoubtably has an impact on the quality of life of patients and caregivers, TSC-associated epilepsy (in common with other forms of epilepsy that are at the extremely severe, refractory and life-threatening end of the disease spectrum, such as DS and LGS) takes this impact to another level.

Thus, in the context of the severe impact on both patients and caregivers outlined above, the relatively large utility decrements associated with the seizure frequencies health states (for patients and caregivers) are not unexpected.

e. Please provide external validation (with data if available or else with expert opinion) for the health state utilities from the vignette study.

Scenario analyses have been run applying alternative utilities from the studies by Tritton 2019[29] and Vergeer 2019[30] previously described in Document B of the company's submission.

Using these alternative utility values has a minor impact on the ICER (see Table 35 below).

f. Please explain the calculations used to transform the vignette health states into the health state utilities for the model.

An explanation of the calculation, including a worked example to calculate the utility for the health state 'one seizure' per day is provided in Appendix R, Section R4. The utility calculations for two seizures per day, three or four seizures per day and five or more seizures per day are calculated using the same method as outlined in the worked example. Utility values for caregivers are calculated using the same method.

B17. Priority: The utilities in the model were not corrected for age. Particularly in the seizure-free state this results in unrealistically high QALYs at older age. Please provide an updated cost-effectiveness model including an age-related decrement for the health state utilities or apply a cap to ensure that utilities do not go above those of the general population for the corresponding age.

As requested, a general population utility value cap on the patient utility values, ensuring that utilities do not exceed the age- and gender-matched population norms, has been added into the model. The seizure-fee health state is the only health state that exceeds population norms over a lifetime horizon. A cap on this utility has been added to the model and is applied when the seizure free utility of 0.725 exceeds population norms which first occurs at age 86 (0.723). The gender-matched population norms reported by Alava et al, 2017 were used to inform the cap, in line with NICE DSU guidance.[31, 32]

The results for the scenario analysis based on the addition of a patient utility cap, are provided in Table 30. The scenario shows very little sensitivity to the addition of a patient utility cap, with a minimal change to the ICER.

Table 30: Scenario analysis results (PAS price)

Technologies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£12,713

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
Note: *Discounting is applied to QALYs and cost.

B18. Caregiver disutilities were assumed to apply additively to two caregivers. However, it is unlikely that both caregivers provide equal care to the patient. For example, Vyas et al.[33] showed that all household members together spent a total of 11 seizure-specific hours per week, of which 7 hours were spent by the primary caregiver. This indicates that disutilities might also differ between caregivers. Also, in TA614[24] and TA615,[23] the committee concluded linearly extrapolating to 2 caregivers was not preferable.

a. Please justify that caregiver utility decrements included in the cost-effectiveness model are on an additive scale, assuming both caregivers would have the same disutility.

The vignette study specifically assessed caregiver quality of life in the context of the respondent being one of two primary caregivers. Therefore, it is reasonable to assume that the caregiver utility estimates are representative of an individual's quality of life decrement where another carer was present.

In previous NICE submissions with a carer disutility included for more than one carer (e.g. ataluren for DMD (HST3); disutility applied for 2 and 3 carers), there is a precedent where each carer was allocated the same disutility.

In a broader context, including utilities for two caregivers also reflects the impact of TSC-associated epilepsy on the quality of life of the wider family. Whilst we acknowledge that not every patient will have two primary caregivers (although many will need more than two), the company is aware that there are often many other people contributing to the care of the patient (for example, siblings, grandparents, aunts, uncles, family friends). The cumulative impact on the quality of life of all these

other caregivers more than compensates for any additive effect in the two main caregivers.

In TA614 and T615, NICE particularly recognised the negative impact of severe epilepsies on a patient's siblings.

b. Please provide a scenario where disutilities for only 1 caregiver are included.

The improvement in quality of life for both patients and caregivers is an extremely important part of the value of cannabidiol in TSC-associated epilepsy. This was recognised by NICE in the appraisals of cannabidiol in other severe epilepsies (DS and LGS).

For the following reasons, we do not consider that a scenario where disutilities for only 1 caregiver are included is reasonable:

- In a severe and life-threatening disease such as TSC-associated epilepsy, patients are at a significant ongoing risk of injury and death from their seizures, have multiple co-morbidities and often require lifelong round-the-clock care from multiple caregivers
- The DISCUSS study reported by Lagae et al[41] (discussed in Document B of the company's submission) indicated that the *minimum* number of caregivers required for a patient with refractory severe epilepsy is at least two
- Two UK clinical experts consulted as part of this response to the ERG clarification questions indicated that having at least two caregivers was usual for patients with TSC-associated epilepsy
- Including disutilities for 2 caregivers reflects the quality of life impact of round-the clock care of a patient with TSC-associated epilepsy, but does not account for the impacts on the wider family, such as siblings. Each family carer has the burden, worry and psychological distress of caring for a patient at risk of injury and even death from their seizures. It would be expected that incorporating the full effect of TSC-associated epilepsy on the lives of all family members would result in a further reduction of the ICER.

For these reasons, the company considers that only including the impact on 2 caregivers in the base case is conservative.

B19. The following questions relate to caregiver utility values:

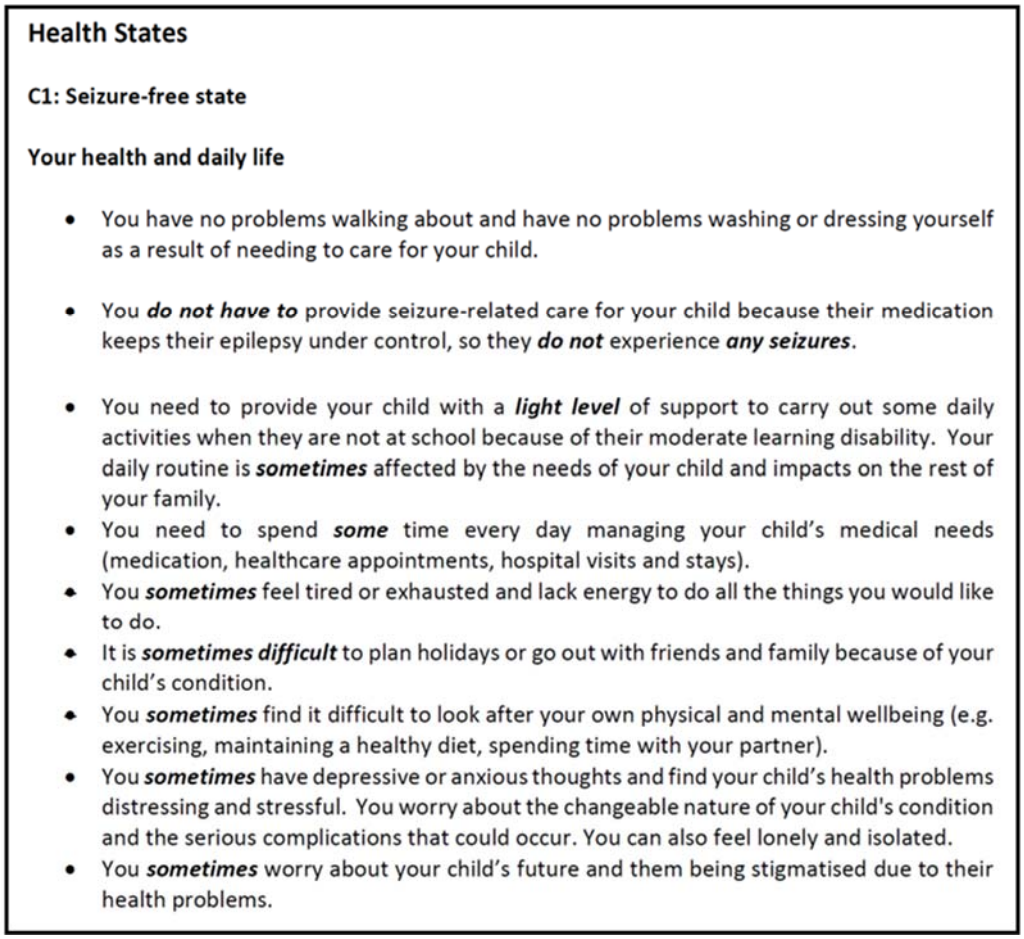
a. Please comment on the fact that the seizure-free health state value estimated in the vignette study is 0.905 for caregivers, which is used as a base for calculating the disutilities in the non-seizure free health states. The study by Vyas et al.[33] shows that overall time spent caring for patients with TSC is 128 hours per week, of which 11 hours per week seizure specific. This implies that when a patient is seizure-free, the caregiver may still have many worries, so a utility score of 0.905 may overestimate carer HRQoL for this health state.

The vignette study estimated a caregiver utility of 0.905 for the seizure-free health state value. The vignette health state description is shown below (see Figure 11). Participants (as caregivers) were asked to consider some worry for the care of their child. Additionally, participants were asked to adopt the perspective of one of two primary caregivers/parents of a 13-year-old child.

Assuming the caregiver is a parent of the child (mother), based on ONS data, the average age of mothers at childbirth in 2019 was 30.7 years.[34] For a 13-year old child, this implies an average parent age of 43 years. The utility for an adult (female) aged 43 is 0.897, which is very similar to the utility estimated for the seizure-free health state value (potentially over-estimated by 0.008). Therefore, the utility value for the seizure-free health state elicited by the vignettes is reflective of a carer population in real-world practice.

It should also be noted that the vignette study included all background information relating to ‘worries’ equally in the vignettes for the seizure-free state and all the seizure states. As a result, even if the seizure-free utility value was a slight over-estimate, it would be expected that the utility values for the seizure states would also be slightly over-estimated. Therefore, the calculated decrements would be unchanged and the same as those used in the model.

Figure 11: Caregiver vignette – seizure-free health state



Health States

C1: Seizure-free state

Your health and daily life

- You have no problems walking about and have no problems washing or dressing yourself as a result of needing to care for your child.
- You ***do not have to*** provide seizure-related care for your child because their medication keeps their epilepsy under control, so they ***do not*** experience ***any seizures***.
- You need to provide your child with a ***light level*** of support to carry out some daily activities when they are not at school because of their moderate learning disability. Your daily routine is ***sometimes*** affected by the needs of your child and impacts on the rest of your family.
- You need to spend ***some*** time every day managing your child's medical needs (medication, healthcare appointments, hospital visits and stays).
- You ***sometimes*** feel tired or exhausted and lack energy to do all the things you would like to do.
- It is ***sometimes difficult*** to plan holidays or go out with friends and family because of your child's condition.
- You ***sometimes*** find it difficult to look after your own physical and mental wellbeing (e.g. exercising, maintaining a healthy diet, spending time with your partner).
- You ***sometimes*** have depressive or anxious thoughts and find your child's health problems distressing and stressful. You worry about the changeable nature of your child's condition and the serious complications that could occur. You can also feel lonely and isolated.
- You ***sometimes*** worry about your child's future and them being stigmatised due to their health problems.

b. Please also comment on the possibility of applying an age-related decrement or general population cap on the utility value for the caregivers and the impact on the ICER.

We would not expect that applying an age-related decrement or general population cap on the utility value for the caregivers would impact the ICER.

The impact of caring for a patient with TSC-associated epilepsy would reasonably be expected to be higher as the caregiver gets older. Therefore, as the age-related utility goes down, it would do so for all health states such that the absolute difference in the utility value between the seizure-free state and the seizure states would stay the same.

Cost and healthcare resource use

B20. Please provide a scenario analysis where resource use was informed by the health care resource use reported by Shepherd et al.[35] instead of the Delphi panel values.

Shepherd et al, 2017 was reviewed as a potential source of data to inform the economic model during the development phase. However, the study was not considered suitable to inform healthcare resource use for several reasons. These include:

- The Shepherd study did not collect data based on any TSC-associated epilepsy outcomes such as seizure frequency. As healthcare resource use is anticipated to be higher with increasing seizure frequency, using the data collected by Shepherd in the model will overestimate the healthcare resource use burden associated with the lowest seizure frequency health states and underestimate resource use associated with the higher seizure frequency health states and fail to capture the benefit of cannabidiol in reducing seizure frequency and therefore healthcare resource use burden, which was included in previous submissions in rare epilepsies.[4, 8, 9]

- The study population in Shepherd et al. does not fully align with the modelled population. Only 60% of the study population were defined as having refractory epilepsy, based on a definition of being prescribed ≥ 2 concomitant antiepileptic drugs during their entire recorded history (data collected based on CPRD and HES records between 1997-2012); with the remainder receiving no AEDs (12%) or only one AED (28.2%). As patients with refractory epilepsies are associated with higher healthcare burden[36, 37], the data presented by Shepherd is likely to underestimate the healthcare resource use burden associated with TSC-associated epilepsy.

- Using the collected data recorded between 1997 to 2012, Shepherd et al. calculated mean healthcare resource use based on the most recent 3-year period of continuous data for each person. As part of the validation of the Delphi panel, the elicited resource use estimates were compared to the Shepherd data. The clinician who assisted in this, Dr Kingswood, noted that treatment practice has

changed since the Shepherd study was conducted, with new guidance issued in 2018, changing the treatment paradigm.[38] Treatment practice has moved more care from general practice to specialist centres, leading to a possible over-reporting of GP visits and under-reporting of outpatient visits in the Shepherd et al. study.

Given these limitations, the Shepherd data is not considered suitable for use as a scenario for healthcare resource use.

Company's base-case results and sensitivity analyses

B21. The following questions relate to the probabilistic sensitivity analysis (PSA)

a. Please explain what could be causing the outliers to the northeast in the incremental cost-effectiveness plane (Figure 20 in the company submission)

The probabilistic analysis (PSA) results are presented in Document B, Section B.3.9.1. The PSA results are broadly comparable to the deterministic analysis results; however, the PSA contains several outlier results, as shown in in Document B, Section B.3.9.1, Figure 20. The following tests were undertaken during model development to test the PSA analysis.

Firstly, all probabilistic distributions were checked to ensure the correct distributions were being used. Next, the most important sets of parameters were tested, by individually switching these parameters to a deterministic setting for each PSA run including utilities, costs, stopping and discontinuation rates and the output of the regression analysis, the coefficients which are used to predict seizure frequency and seizure-free days. The skewed costs effectiveness plane and outlier results are driven by the regression analysis, specifically the non-linearity of the regression coefficients combined with the non-linear probabilistic analysis. In this circumstance, it is reasonable to expect a non-uniform cost-effective plane. Additionally, as acknowledged in the updated NICE methods guidance, cost-effectiveness estimates are inherently uncertain for small populations such as those associated with orphan diseases. Therefore, these analyses should be considered within that context, with a higher degree of uncertainty considered acceptable.[39]

b. Please run a PSA with 5,000 simulations

The model has been updated to allow a maximum of 5,000 PSA iterations. As requested, a PSA was conducted in which all inputs were varied simultaneously over 5,000 iterations, based on their distributional information. Note that the updated PSA was run inclusive of the change to the base case requested for B13.a.

The results are summarized in Table 31 and are also presented on a cost-effectiveness plane in Figure 12 and cost-effectiveness acceptability curve in

Figure **13**. The PSA results are broadly comparable with the deterministic analysis, and the PSA results presented in Document B, Section 3.9.1.

Table 31: Mean probabilistic sensitivity analysis results

Technology	Mean total costs (£)	Mean total QALYs	Incremental		ICER (£/QALY)
			Mean costs (£)	Mean QALYs	
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£14,196
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Figure 12: Probabilistic sensitivity analysis cost-effectiveness plane (5,000) simulations

Figure 13: Probabilistic sensitivity analysis cost-effectiveness acceptability curve (5,000 iterations)

The cost-effectiveness acceptability curve suggests that there is a [redacted] and [redacted] likelihood that cannabidiol is cost-effective at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively.

c. Please add a worksheet to the model recording the disaggregated outcomes per simulation of the PSA – to enable diagnosing the cause of outliers

The model has been updated to include an additional sheet providing disaggregated outcomes per simulation of the PSA (see the "PSA_data" sheet).

Validation and transparency

B22. The results of the validity assessments or detailed validation exercises (i.e., specific black-box tests) are not described in company submission section B.3.11.

a. Please provide a detailed description of the validity assessment performed as well as the results.

b. Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

A technical review of the cost effectiveness model was independently undertaken by Swansea Centre for Health Economics (SCHE).

The SCHE technical review followed internationally recognised ISPOR principles of model validation. The overall integrity of the data was checked. SCHE also conducted internal validation to ensure that the model engine works in the manner which it was designed, and the coding of the model was quality checked to detect any errors.

The validity of the model base case analysis and sensitivity analyses was explored This included extreme values testing to ensure that varying parameter input values had a viable and expected impact on outputs.

The process followed the methods outlined in the TECH-VER checklist.

The SCHE report is provided in the reference pack.[40]

B23. Please provide cross validations, i.e., comparisons with other relevant NICE TAs focussed on similar, potentially relevant, diseases (e.g., related NICE recommendations and NICE Pathways listed in the final scope) and elaborate on the identified differences regarding:

a. Model structure and assumptions

b. Input parameters related to:

    i. Clinical effectiveness
    ii. Health state utility values
    iii. Resource use and costs
    iv. Estimated (disaggregated) outcomes per comparator/ intervention
    v. Life years
    vi. QALYs
    vii. Costs

Please refer to Appendix G of the company's original submission.

Section C: Textual clarification and additional points

C1. When describing the population in Table 3 of the company submission, the following sentence does not seem to make sense: “All medications or interventions for epilepsy (including a ketogenic diet and vagus nerve stimulation, which were not counted as ASMs) stable for 4 weeks before screening.” Please clarify.

As for the rest of the ‘Population’ row in Table 3, Document B, the wording is abbreviated as appropriate for a table. As a complete sentence, it would read “All medications or interventions for epilepsy (including a ketogenic diet and vagus nerve stimulation, which were not counted as AEDs) had to be stable for 4 weeks before screening”.

Appendix 1

Reference	In company submission?
[1] Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. Journal of Child Neurology 1991;6(2_suppl):2S52-2S59.	No
[2] Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. Journal of child neurology 1991;Suppl 2:S52-59.	Duplicate
[3] Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. Journal of Child Neurology 1991;6(SUPPL. 2):2S52-2S59.	Duplicate
[4] Chiron C, Dumas C, Jambaque I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Research 1997;26(2):389-395.	No
[5] Cock H, Wu JY, Devinsky O, Joshi C, Miller I, Roberts C, et al. Time to onset of Cannabidiol (CBD) treatment effect and resolution of adverse events in the tuberous sclerosis complex Phase 3 randomised controlled trial (GWPCARE6). Developmental Medicine and Child Neurology 2021;Conference: Annual Meeting of the British Paediatric Neurology Association. Virtual. 63(SUPPL 1):77.	No
[6] Collins JJ, Tudor C, Leonard JM, Chuck G, Franz DN. Levetiracetam as adjunctive antiepileptic therapy for patients with tuberous sclerosis complex: A retrospective open-label trial. Journal of Child Neurology 2006;21(1):53-57.	No
[7] Curatolo P, Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. The Lancet Child and Adolescent Health 2018;2(7):495-504.	No
[8] Cusmai R, Moavero R, Bombardieri R, Vigevano F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy and Behavior 2011;22(4):735-739.	No
[9] De Vries PJ, Franz DN, Lawson JA, Yapici Z, Polster T, Nabbout R, et al. Adjunctive everolimus therapy for the treatment of refractory seizures in people with tuberous sclerosis complex. Journal of Intellectual Disability Research 2016;Conference: 19th International Research Symposium of the Society for the Study of Behavioural Phenotypes, SSBP. Siena Italy. 60(9):839.	No
[10] Ding Y, Wang J, Zhou Y, Yu L, Zhang L, Zhou S, et al. Quality of life in children with tuberous sclerosis complex: A pediatric cohort study. CNS Neuroscience and Therapeutics 2021;27(3):280-288.	Excluded: no results reported

	ERG: Agrees
[11] Franz D, Lawson J, Nabbout R, Curatolo P, De Vries P, Berkowitz N, et al. Adjunctive everolimus therapy for the treatment of refractory seizures associated with tuberous sclerosis complex: Results from a randomized, placebo-controlled, phase 3 trial. Annals of Neurology 2016;Conference: 45th Annual Meeting of the Child Neurology Society. Vancouver, BC Canada. 80(Supplement 20):S317.	No
[12] Franz D, Lawson J, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Efficacy and safety of everolimus based on prior and concomitant antiepileptic drugs in patients with tuberous sclerosis complex (TSC)-associated treatment-refractory seizures: A subanalysis of the phase 3 EXIST-3 study. Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN 2018;90(15 Supplement 1).	No
[13] Franz D, Lawson J, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Sustained seizure reduction with adjunctive everolimus for treatment-refractory seizures associated with tuberous sclerosis complex (TSC): Long-term results from the phase 3 EXIST-3 study. Annals of Neurology 2017;Conference: 46th Annual Meeting of the Child Neurology Society. Kansas City, MO United States. 82(Supplement 21):S281-S282.	No
[14] Franz D, Lawson J, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Sustained seizure reduction with adjunctive everolimus for treatment-refractory seizures associated with tuberous sclerosis complex (TSC): Long-term results from the phase 3 EXIST-3 study. Neurology 2017;Conference: 69th American Academy of Neurology Annual Meeting, AAN 2017. Boston, MA United States. 89(8):e100.	No
[15] Franz D, Lawson J, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Efficacy and safety of everolimus based on prior and concomitant antiepileptic drugs in patients with tuberous sclerosis complex (TSC)-associated treatment refractory seizures: Subanalysis of the phase 3 exist-3 study. Annals of Neurology 2018;Conference: 47th National Meeting of the Child Neurology Society, CNS 2018. Chicago, IL United States. 84(Supplement 22):S337.	No
[16] Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, et al. Sustained seizure reduction with adjunctive everolimus for treatment-refractory seizures associated with tuberous sclerosis complex (TSC): Long-term results from the phase 3 exist-3 study. Annals of Neurology 2017;Conference: 142nd Annual Meeting of the American Neurological Association, ANA 2017. San Diego, CA United States. 82(Supplement 21):S65-S66.	No
[17] Franz DN, Tillema JM, Care MM, Holland-Bouley K, Agricola K, Tudor C, et al. Everolimus reduces seizure activity in patients with tuberous sclerosis complex (TSC). European Journal of Neurology 2011;Conference: 15th Congress of the EFNS. Budapest Hungary. Conference Publication:(var.pagings). 18(SUPPL. 2):568.	No
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Appendix 2: Updated base case analyses (as per Question B13.a.)

Updated base case incremental cost-effectiveness analysis results disaggregated outcomes

Table 32 summarizes the patient QALY gain by component. The QALY gain associated with seizure-free days is the biggest driver of the incremental QALY associated with cannabidiol plus usual-care, compared with placebo plus usual-care, equating to [redacted] of the incremental QALYs. The placebo plus usual-care arm had greater QALYs associated with the higher seizure frequency health states, reflecting the greater distribution of placebo plus usual-care patients within these states compared with cannabidiol plus usual-care.

Table 32: Summary of patient QALY gain by component

Component		**QALY Cannabidiol + usual-care**	**QALY Placebo + usual-care)**	**Increment**	**Absolute increment**	**% absolute increment**
Health state	Seizure-free per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 1 seizure per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 1–≤ 2 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 2–≤ 4 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 4 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event disutility		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAND delay increment		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	**Total absolute increment**	**100%**
Key: QALY, quality-adjusted life year; TAND, TSC-associated neuropsychiatric disorders.						

Table 33 summarizes the caregiver QALY decrements by health state. The base case analysis uses the seizure-free health state as the reference health state to calculate caregiver decrements. Therefore, there are no QALY decrements in this health state. The incremental QALY difference is driven by the difference between the model arms in the higher seizure frequency health states, reflecting the higher proportion of placebo plus usual-care patients who are distributed within the higher seizure frequency health states.

Table 33: Summary of caregiver QALY gain by component

Component		QALY Cannabidiol + usual-care	QALY Placebo + usual-care)	Increment	Absolute increment	% absolute increment
Health state	Seizure-free per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 1 seizure per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 1 - ≤ 2 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 2 - ≤ 4 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 4 seizures per day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	**Total absolute increment**	**100%**
Key: QALY, quality-adjusted life year; TAND, TSC-associated neuropsychiatric disorders.						

A breakdown of cost by resource use type is presented in Table 34. Costs are presented by seizure frequency health state per week. The total lifetime discounted cost per patient for cannabidiol plus usual-care is [redacted]; for placebo plus usual-care patients the total lifetime discounted cost per patient is [redacted]

The treatment cost associated with cannabidiol is one of the main drivers of the incremental cost of treatment compared to usual-care; however, this is offset by the

increased health state costs in the higher seizure frequency heath state (> 7 seizures per week) in the usual-care arm. Cost drivers for both arms include TAND management and health state costs.

Use of cannabidiol plus usual-care results in lower costs in the higher seizure frequency health states (> 2–≤ 7 seizures per week, and > 7 seizures per week) compared to placebo plus usual-care.

Table 34: Summary of costs by component

Component		Cost Cannabidiol + usual-care	Cost Placebo + usual-care	Increment	Absolute increment	% absolute increment
Treatment costs						
Drug acquisition costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Usual-care costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAND related cost		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state costs	Seizure-free over 7 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	≤ 2 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 2 - ≤ 7 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	> 7 seizures	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	**Total absolute increment**	**100%**
Key: TAND, TSC-associated neuropsychiatric disorders.						

Probabilistic sensitivity analysis

A PSA was conducted in which all inputs were varied simultaneously over 5,000 iterations, based on their distributional information. These results are provided in response to question B21 above.

Deterministic sensitivity analysis

The top 10 influential parameters on the ICER are presented as a tornado diagram. Each value was varied based on its uncertainty parameters.

Figure 14 presents the updated OWSA for cannabidiol plus usual-care compared with placebo plus usual-care with parameters shown in descending order of ICER sensitivity.

These results demonstrate that the ICER is most sensitive to the stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven seizures per week (highest seizure frequency category), the patient utility values applied to seizure-free patients, and response rates used to estimate the proportion of patients who benefit from a reduction in TAND symptoms.

Figure 14: Results of one-way sensitivity analysis

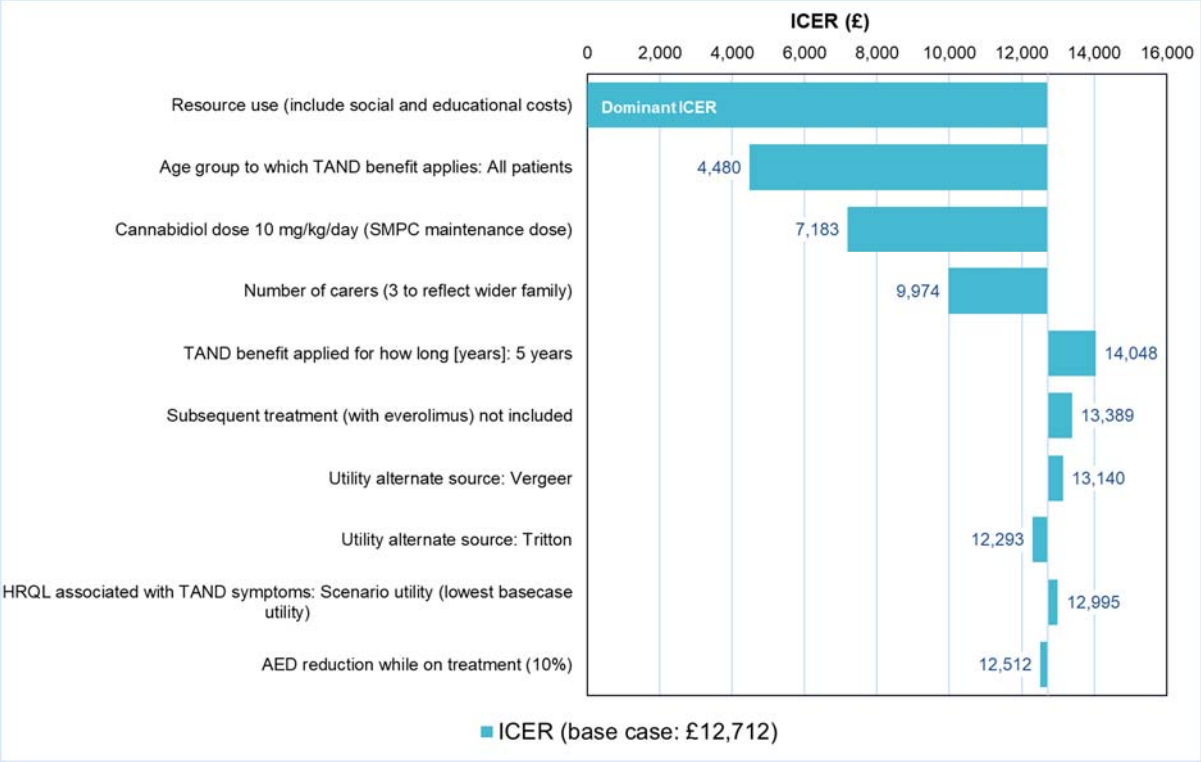
Key: CBD, cannabidiol; ICER, incremental cost-effectiveness ratio; HS, health state; pw, per week; TAND, TSC-associated neuropsychiatric disorders; UC, usual-care.

Scenario analysis

The scenarios (updated) explored in the model are presented in Table 35. The top 10 most influential scenarios on the ICER are presented below in Figure 15. The results were relatively insensitive for most analyses, with cannabidiol remaining cost-effective in all scenarios at a WTP threshold of £20,000 to £30,000 per QALY gained.

The most influential scenario, which resulted in a dominant ICER, and has the largest impact resulting in cost savings for the cannabidiol arm, is associated with the inclusion of wider social costs: social and educational care resource use, which was elicited via the two-round Delphi panel study.

Figure 15: Top 10 most influential scenarios on the ICER (deterministic) (PAS price)



Key: AED, anti-epileptic drug; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; SmPC, Summary of Product Characteristics; SUDEP, sudden unexpected death in epilepsy; TAND, TSC-associated neuropsychiatric disorders; UC, usual-care.

Table 35: Scenario analysis results

Scenario name	Base case	Scenario	ICER (£)
Base case			£12,712
Discount rate	3.5%	0.0%	£12,810
Discount rate	3.5%	6.0%	£12,670
AED reduction (while on treatment with cannabidiol)	None	10% reduction in AED costs	£12,512
Stopping rule assessment rate	At least 30% reduction in seizure frequency required to continue treatment* (see question B13.)	At least 30% reduction in seizure frequency required to continue treatment using observed trial data	£12,876
Age group to which TAND benefit applies	Age 2–6 years	All patients	£4,480
TAND benefit applied for how long [years]	Lifetime	5 years	£14,048
HRQL associated with TAND symptoms	Base case utilities	Scenario utilities	£12,995
Subsequent treatment with everolimus (applied to a proportion of patients in both arms)	Everolimus is included as a subsequent treatment	Everolimus is not included as subsequent treatment	£13,389
Patient HRQL source	TSC Vignette study[28]	Tritton 2019 (EQ-5D)[29]	£12,293
		Vergeer 2019 (HUI-3)[30]	£13,140
Number of caregivers	2 caregivers	3 caregivers (to reflect impact on wider family)	£9,974
Resource use (inclusion of social care and educational costs)	Not included	Included	Dominant
Cannabidiol dose	12 mg/kg/day	10 mg/kg/day	£7,183

Key: DS, Dravet syndrome; ICER, incremental cost-effectiveness ratio, HRQL, health-related quality of life; HUI-3, health utilities index three; LGS, Lennox-Gastaut Syndrome; NICE, National Institute for Health and Care Excellence; SUDEP, Sudden unexpected death in epilepsy; TA, Technology appraisal; TAND, tuberous sclerosis complex-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex.
Note: * Reduction in focal with impairment of awareness seizures and generalized seizures.

Appendix 3: Dravet syndrome and Lennox-Gastaut syndrome 3-month rates

Table 36: Discontinuation rates from TA614, TA615 (per cycle)

	<12 years			≥12 years		
Time period for application of rate	**Cycle 1[a]**	**Subsequent cycles (cycles 2-9)**	**Long term cycles[b] (cycle 10-)**	**Cycle 1**	**Subsequent cycles**	**Long term cycles**
Lennox-Gastaut Syndrome						
Seizure free	[redacted]	[redacted]	0.50%	[redacted]	[redacted]	0.50%
≤ 8 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	10.00%
>8 - ≤ 25 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	10.00%
> 25 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	10.00%
Dravet syndrome						
Seizure free	[redacted]	[redacted]	0.50%	[redacted]	[redacted]	0.50%
≤ 8 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	5.00%
>8 - ≤ 25 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	5.00%
> 25 seizures	[redacted]	[redacted]	10.00%	[redacted]	[redacted]	5.00%

Key: a: Cycle length of 3 months used in TA614 and TA615. **b**: The long term rate presented is as per the final NICE committee agreed rate for TA614 and TA615 (10%).

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	Dr Pooja Takhar

2. Name of organisation	Tuberous Sclerosis Association
3. Job title or position	Head of Research and Policy
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Tuberous Sclerosis Association (TSA) is the only UK charity focused on improving the lives of people affected by rare genetic disorder Tuberous Sclerosis Complex (TSC). We provide help for today and hope for tomorrow by: • Providing direction or a listening ear through our support and information services for the TSC community, including through our UK-wide TSA Support Line. • Organising events and opportunities across the UK and virtually for those affected by TSC, allowing the TSC community to come together and feel less alone. • Funding internationally-significant research into the causes, diagnosis, management and treatment of TSC that has the greatest impact on those affected by the condition. • Campaigning on behalf of the TSC community to ensure that the TSC community has consistent and meaningful access to social support and healthcare provision. You can find more about our charity at www.tuberous-sclerosis.org. The TSA does not have members, but we support over 4,000 people across the UK who are in contact with the charity including individuals living with TSC, their family, carers and friends.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	The TSA has a policy on working with the medicines industry which you can find here: https://tuberous-sclerosis.org/working-with-the-medicines-industry/ The TSA has received the following funding from GW Pharma Ltd in the last 12 months: • £20,000 in sponsorship for the International TSC Research Conference held in June 2021 • £577 involvement fee for TSA Chief Executive to take part in a Europe-wide Patient Advisory Group on Epidyolex • £1,260 for developing caregiver interview guide, and encouraging completion of an online QoL survey about impact of TSC on carers • £600 payment for TSA Chief Executive and TSA Head of Research to give an overview of the charity's work to GW Pharma staff and to take part in a panel Q&A about TSC.

<table>
<tr><td>If so, please state the name of manufacturer, amount, and purpose of funding.</td><td>The TSA has also received the following funding from comparator company Novartis in the last 12 months:
£2,500 in exhibition fees for a virtual stand at the International TSC Research Conference held June 2021.</td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No.</td></tr>
<tr><td>5. How did you gather information about the experiences of patients and carers to include in your submission?</td><td>The TSA used our monthly e-newsletter, website and social media channels to raise awareness that we would like to speak to anyone living with TSC who has tried Epidyolex® to inform our submissions on this medicine. We stated that: “The TSA needs to speak to as many people as possible who have tried this new medicine to understand its benefits and risks.” We asked those with experience of the medicine to contact our research team and arrange a time for a telephone interview about their experience.

We carried out interviews with seven people in the UK who care for someone living with TSC to inform our submission. Four out of seven patients received Epidyolex® due to a co-diagnosis of Lennox-Gastaut syndrome. Three out of seven patients received Epidyolex® as part of the recent clinical trial. All seven patients had refractory epilepsy with only a partial response to treatment with anti-epileptic drugs.

Details of the families we spoke to are (as of September 2021):
<table>
<tr><th></th><th>Age of patient (as of Sept 2021)</th><th>Sex of patient</th><th>Co-diagnosis of Lennox-Gastaut Syndrome</th><th>Currently on Epidyolex®</th><th>Participated in clinical trial</th></tr>
<tr><td>Family A</td><td>16 years</td><td>Male</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Family B</td><td>13 years</td><td>Female</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Family C</td><td>37 Years</td><td>Female</td><td>Yes</td><td>No</td><td></td></tr>
<tr><td>Family D</td><td>19 years</td><td>Female</td><td>No</td><td>No</td><td>Yes</td></tr>
<tr><td>Family E</td><td>12 years</td><td>Male</td><td>No</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Family F</td><td>7 years</td><td>Male</td><td>Yes</td><td>No</td><td></td></tr>
<tr><td>Family G</td><td>15 Years</td><td>Male</td><td>Yes</td><td>Yes</td><td></td></tr>
</table></td></tr>
</table>

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Tuberous Sclerosis Complex (TSC) is a rare genetic condition. Every month around 10 babies are born with TSC in the UK. TSC causes growths to develop in different organs around the body, such as the brain, lungs, kidneys, eyes, heart and skin. These growths are sometimes referred to as benign (non-cancerous) tumours. When they cause problems, it is mainly because of their size and where they are growing in the body. Eight out of ten people with TSC have epilepsy that typically starts in infancy and is difficult to control using epilepsy medication. Five out of every ten people with TSC have learning disabilities. Around three in ten people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Nine out of ten people with TSC develop TSC-associated neuro-psychiatric disorders (TAND) which can include autism spectrum disorders, attention deficit hyperactivity disorders, aggression, depression, anxiety and sleep disorders which have a serious impact on family life. When a TSC diagnosis is made, the whole family is affected both physically and mentally. TSC has a great impact on families' quality of life and on their ability to cope with the disease and support the child's ability to reach an acceptable level of well-being. Families and carers have reported the experience of losing control and feelings of despair and helplessness. They have shared their day-to-day struggles with their children's behaviour including what it's like to manage the rage, anger and mood swings. It not only affects their relationship with their child who has TSC but also their relationship with each other and the wider family circle including siblings who feel left-out and neglected as the parents focus on the needs of their child with TSC. In many instances, parents have had to give up work to become full time carers. There are additional costs for home improvements associated with TSC: the TSA Support Line receives regular calls from parents wishing to access our small family grants to purchase fridges to store medication or batches of ketogenic food, replace washing machines, tumble dryers, beds and bedding urgently needed to cope with the impact of urinary and faecal incontinence, and invest in improvements to make back gardens secure and safe for children with no sense of danger to play in. One family with a young child told us (family F): "Our lives changed completely when our son who is now seven years old was diagnosed with TSC as it impacts on every member of the family. We are never in a stable situation. Our son is unable to speak, he is unbalanced physically, he has brain damage to the left side, which impacts the right side of body, he has a buggy and can't do long walks. He can't eat, he can't drink out of a straw. He has subclinical seizures and shows signs when they are coming on. He has tired moments and attends a special needs classroom in a mainstream school. He has one to one care and can't be left alone – he must be with an adult at all times. He is a lovely boy, with strong emotional intelligence, and the intellectual intelligence of a 3 to 4 year-old.

	I gave up my job as a CEO to look after my son. He had 21 seizures a day at birth. He needs one-to-one care. My family can't go to social events as we normally would as our son has autistic traits. We are unable to attend events such as weddings, and organising day care for him is hard work. We have lots of support from aunts, uncles and grandparents. Our son disrupts social events, screaming to go home after a few minutes. This affects my and my husband's time with his younger sister. We are always looking for an easy escape route at social events and when out and about. His behaviour can upset his sister. He is spoon fed and eats blended foods." A mother shared the impact of TSC on her 16 years-old son (family A): "He was diagnosed at 12 months old and seemed to be developing normally until about 5-years old. He has behaviour issues. He gets cross and throws things across the room, he has anger issues and can be aggressive. Our son goes to respite, he is very full on and challenging for me. He shouts a lot, so we avoid outings. When younger cousins come to stay over, he has to be watched at all times – he sometimes throws things across the room, and if he wants to run across the room he does so. He has no concept of danger. He is very vulnerable. I can't remember the last time I slept through the night or had more than eight hours of sleep. I can't take him out on my own - he is too big to control when a seizure hits. He relies on his family for thinking as he doesn't understand danger." A mother of a 12 years-old who has TSC shared how TSC impacts her son's and their family life (family E): "He is the youngest of four children, and his siblings do not have TSC. I had to give up work to care for my youngest son full time. It is hard for the family to go out – he sometimes screams when he has seizures, and this usually frightens children and other people out and about and everyone looks. It's easier to just stay at home. Me and his Dad take turns to stay at home with our son and look after him." One mother with an adult daughter living with TSC (37 years old) told us (family C): "She has to have two people with her 24 hours a day because of seizures and behaviour. She has no idea of danger, so she could just walk into the road and be hit by a car and she wouldn't know what to do. You have to keep everything out of her way as she will drink whatever is in the cupboard, she would pick up and eat whatever is lying around so she has to be monitored. She has had problems with breathing as she doesn't chew properly so it becomes a choking hazard. She has to be fed to make sure she has swallowed properly otherwise she'll continue eating even whilst choking. You cannot leave her with food, she would choke, she would die. Food has to be cut up or mashed."

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	All of the families we interviewed told us that patients had tried five or more epilepsy medicines in the past. Three individuals had tried between 15 and 20 drugs. Most of them stated that there tends to be a “honeymoon period” where the prescribed drug works for a short duration, then it stops working and they move to next medication. Two out of seven patients had tried the ketogenic diet. The ketogenic diet is a high fat, low carbohydrate, controlled protein diet that has been used since the 1920s for the treatment of epilepsy. You can find out more from the NHS, for example: https://www.evelinalondon.nhs.uk/resources/patient-information/Ketogenic-diet-information-for-families.pdf. The diet is a medical treatment and is usually only considered when at least two suitable medications have been tried and not worked. Family B told us that the diet did work initially and was the best therapy so far for seizure control, but sadly it only worked for the first few months. The family persisted with this as it was worth trying. The second patient has coped very well on the diet (family D). Family B said: “Our 13 years-old has tried 15-20 different medications, in different combinations, trying some together and some on their own. She was put on the ketogenic diet when she was younger but would not tolerate it. She was also put on steroids when she was younger, and this helped for 2 or 3 years with her seizures greatly reduced but sadly it stopped working.” Family C told us that their adult daughter has tried every medication available for epilepsy: “Some of them seem to work, but then she gets used to it and they stop. They go through cycles and we have gone through all of the drugs and been told there is nothing new on the horizon. With some drugs she got very aggressive and bad tempered, so we took her off these as we didn’t think they were doing her any good”. Family E said, “If the keppra dose is too high, his arms and legs move around and it comes across as if he’s angry, so keppra is kept at a lower dose. He sleeps a lot whilst on other medications.” Four of the seven patients were assessed for vagal nerve stimulation (families A, B, C and G), with three undergoing the procedure (families A, C and G). It had to be removed in one patient (family G). Two parents told us that the vagal nerve stimulation has had a positive impact on their children’s epilepsy and reduced the severity of seizures in both cases (families A and C). Family A told us that their daughter had undergone corpus callosotomy but it didn’t work.

	Five patients have been assessed or are undergoing assessment for epilepsy surgery (families B, D, E, F and G). One patient has had the surgery privately (family F). Two patients (families B and D) are awaiting surgery with one due to undergo the procedure in three weeks at the time of interview (September 2021) (family B). One patient is currently undergoing assessment (family E).
8. Is there an unmet need for patients with this condition?	When we asked people living with TSC and their families and carers to share the aspects of living with TSC that are not met by currently available treatments, all seven families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs. Family A told us that the aspect of TSC that they struggle most with their 16 years-old son are: "His rages, his temper, his shouting. His mood changes very suddenly. He still has seizures during the night." Another parent (family E) said: "Other things that are wrong with him are always blamed on the TSC. An MRI scan found that our son has cerebellar atrophy, which presents the same symptoms as TSC". The statements above are in line with typical manifestations of TSC. Epilepsy is the most common neurological feature of TSC, affecting approximately 84 per cent of people living with the condition (Kingswood et al, 2017). More than 50 per cent of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment (Wylie et al. 1993, Pellock et al. 2001). One in every two people living with TSC have learning disabilities such as intellectual impairment and problems with attention and memory (Gillberg et al. 1994; Harrison & Bolton, 1997; Joinson et al. 2003, Bolton et al. 2015). Around 30 per cent of these individuals have profound learning disabilities, and around 20 per cent have an IQ slightly below the normal range (De Vries et al. 2015). Fifty per cent of people living with TSC have an IQ in the same range as the general population (De Vries et al. 2015). Uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015).
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When we asked the families what they thought were the benefits of Epidyolex®, four out of seven mothers described the improvements to their loved one's epilepsy as 'life-changing'. Two families didn't notice any impact of Epidyolex®, and one family had to stop the treatment due to side effects such as diarrhoea, weight loss, loss of appetite, feeling sleepy, and not feeling quite themselves, despite some positive effects. Family F with a young child (aged 7) said: "Epidyolex® was life changing in terms of sleep. My husband and I were able to have an entire night's sleep. His behaviour was much better at school. Epidyolex® massively reduced

	seizures in combination with Clobazam. He was having nine seizures a day before starting the medicine, but within five months of taking it, he was having a total of seven seizures in a month. His seizures reduced in severity, he would only experience chin twitches. He was calm and happy, and slept much better. He said Epidyolex® tastes nice – like strawberry. Epidyolex® was a godsend." Despite these improvements, the child was taken off Epidyolex® due to adverse weight loss. Of the three patients still taking the drug, family A told us: "Epidyolex® has been life changing for our son (aged 16). It has unlocked a part of him that the family had lost. He now has an opinion, he is not as vulnerable, he asks for the toilet. He is more rounded. He is more alert. He says no to things he doesn't like or doesn't want to do. He has had no drop seizures and the Epidyolex® has reduced the frequency of other seizures, although he still has some seizures during the night. Epidyolex® has given him the energy to live in society and has unlocked the monkey in him." Family E told us their 12 year-old son took part in the clinical trial and is now receiving Epidyolex® on compassionate grounds: "Our son was seizure free for nine months at first, and he now has around 4-5 seizures a day. He has more emotions since taking Epidyolex®. If seizure frequency increases, then I take him to the GP as this usually means that he has some sort of infection. He is more awake, he sleeps less, and he is happier going to school." A third family (family G) told us: "It hasn't made much of a difference on his epilepsy on its own. I don't know whether that is because my expectation was so high because I hoped Epidyolex® was the wonder drug that was going to fix everything. But when combined with Clobazam, it made a massive impact on his seizures and he is almost seizure-free at the moment. Before he started on Clobazam combination, he was having over 10 seizures a day in a 24-hour period, on average at the moment it's down to two or three seizures a week." Another mother of a 12 year-old who has been taking Epidyolex® since January 2019 told us (family E): "My daughter's grandad used to baby sit during the 9-month seizure free period, so that my partner and I could go out for food. We usually take it in turns to go out and look after her. As she now has less seizures, this means we can go out for food together and socially it has made a huge difference for my family. It has been a huge weight off her siblings' shoulders. It's upsetting for them to watch their sister go through a seizure which usually lasts for 40-50 seconds, but it feels like two hours. Everyone's mood has lifted, and her siblings are not so worried all the time. Mental health wise, a huge cloud has lifted. The teachers in school were happy for her too." Her mum added: "Personally, I can't express how good Epidyolex® is, but we were lucky with the side effects. Some children we met at clinics had really bad side effects and had to stop treatment. I would 100% recommend anyone allowed to give it a go to give it a go, over any other epilepsy medication."

	Seven out of seven families answered yes to our question: If Epidyloex®, would (patient) prefer to try this treatment first, before trying other treatments? One mum said (family D): "We would have tried this first – even if it doesn't work it's well worth giving it a go." Family F said: "Yes as Epidyloex® has non-toxic side effects." Family B told us: "We have been asking for CBD for years, but it was never licenced." Family C also agreed that it is worth a try: "None of the other treatments have worked fully. Epidyolex® was no worse than anything else. It is worth a try – it could work well for others."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	With regards to any disadvantages of Epidyolex®, two families out of seven families reported no side effects as a result of Epidyolex® treatment. Five families reported various side effects, with two families having to stop the treatment as the negative side effects outweighed the positive impact of Epidyolex®. Commonly reported side effects included diarrhoea, weight loss, loss of appetite, feeling sleepy, and not feeling quite themselves. Family B reported that their 13 years-old reported bellyache, excess saliva, always hungry and eating a lot. One patient (family A) who is currently on the treatment has to have regular blood tests. His liver enzymes have increased. He is on 20mg of Epilim, and his markers have stabilised. His family say they would like to wean him off the Epilim. Family C had to stop the treatment of their adult daughter (aged 37) due to excessive diarrhoea: "Epidyolex® treatment started in February with a lower dose which was gradually increased to therapeutic dose by the third week. My daughter started getting diarrhoea which was so bad that the drug had to be stopped. It was all over the carpet, car and running down her legs. The treatment was stopped in March and the diarrhoea carried on even after stopping the treatment and finally stopped around mid-May. There was improvement at some point, then really bad seizures. The doctor sent us to the GP who did tests for suspected irritable bowel disease or inflammatory bowel disease. Our daughter has been tested for Crohn's Disease and her next appointment is in October. I think that she may have had Crohn's disease before going on Epidyolex® and it made it worse. I also think that the strong dose of Epidyolex® is the reason, with the therapeutic dose perhaps too high for her? If we had introduced it slower and stopped sooner, maybe we wouldn't have had the problems." Another family (family F) with a seven-year-old son told us: "He lost a lot of weight and was down to 17kg which is off the paediatric scale. He didn't want to eat and said he felt ill all the time."

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The people living with TSC who will benefit most are those with refractory epilepsy. It is possible that younger patients will derive extra benefits from getting their epilepsy under control at an early age, because uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015). Epilepsy is generally more difficult to control for individuals living with TSC who have moderate or severe learning disabilities. There is a wide range of severity in TSC. Some people living with TSC are so mildly affected that they experience few problems. Five out of every ten people with TSC have learning disabilities. Around three in ten people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Early onset of epilepsy has been associated with a higher frequency and severity of intellectual disability (Gupta at al, 2020) and a slower gain in intellectual ability, which has also been linked to seizure severity (Tye et al, 2020). People with TSC who have epilepsy have been shown to have lower health-related quality of life (HRQL) compared with those without epilepsy (Vergeer et al, 2019). All age groups will have a better quality of life and a lower risk of serious co-morbidity and mortality (such as SUDEP) if Epidyloex® can provide better seizure control.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Yes. One in every two people living with TSC have learning disabilities such as intellectual impairment and problems with attention and memory (Gillberg et al. 1994; Harrison & Bolton, 1997; Joinson et al. 2003, Bolton et al. 2015). Around 30 per cent of these individuals have profound learning disabilities, and around 20 per cent have an IQ slightly below the normal range (De Vries et al. 2015). Fifty per cent of people living with TSC have an IQ in the same range as the general population (De Vries et al. 2015). Uncontrolled epilepsy is believed to be a contributing factor to learning disabilities in people living with TSC (Bolton et al. 2015).

Other issues	
13. Are there any other issues that you would like the committee to consider?	Carers of people with TSC have significantly lower quality of life and higher anxiety and depressive symptoms (Rentz et al, 2015). Parents and carers have also reported anxiety regarding the unknown future for the person with TSC that they care for and the possibility of medical emergencies, new symptoms, repeated surgeries and side effects of treatments. The need for supervision and monitoring of patients with TSC due to seizures and TAND manifestations also contributes to the burden on carers and wider family members (MacDonald 2019). TSC can impact on the life of the whole family, with activities centred around the patient's needs and siblings consequently missing out on family time. We would like to highlight the improvement to quality of life for the whole family – including parents and siblings – when a loved one with TSC has epilepsy that is better controlled. In addition to the benefits highlighted in our response for treating epilepsy we would also like to highlight that those who responded to the TSA noted improvements to the physical and mental health of family members – both parents and siblings – as well as patients themselves as a result of treatment with Epidyloex®. We would also like to draw attention to the difference between Epidyolex® and Everolimus® which can also be prescribed for TSC-related epilepsy. In addition to being used as a treatment for TSC-related epilepsy, Everolimus® is a holistic treatment for TSC which is also licensed and recommended by NHS England for the treatment of TSC-related brain tumours called subependymal giant cell astrocytomas (SEGA) and the treatment of TSC-related kidney tumours called an angiomyolipoma (AML). The choice of preferred treatment and appropriate treatment pathway for people with TSC-related epilepsy may be different for each individual living with TSC depending on which organs in their body are being affected by TSC at any given time in their life.
14. How would you describe the variability of seizure severity and frequency in tuberous sclerosis complex? How would this affect the level of care required?	Epilepsy is the most common neurological feature of TSC, affecting approximately 84 per cent of people living with the condition (Kingswood et al, 2017). Epilepsy is also one of the most common causes of TSC-related mortality, particularly due to status epilepticus and sudden unexpected death in epilepsy (SUDEP) (Zöllner et al, 2020). More than 50 per cent of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment (Wylie et al, 1993; Pellock et al, 2001). Epilepsy is generally more difficult to control for individuals living with TSC who have moderate or severe learning disabilities. There is a wide range of severity in TSC. Some people living with TSC are so mildly affected that they experience few problems. Five out of every ten people with TSC have learning disabilities. Around three in ten

	people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Early onset of epilepsy has been associated with a higher frequency and severity of intellectual disability (Gupta at al, 2020) and a slower gain in intellectual ability, which has also been linked to seizure severity (Tye et al, 2020). People with TSC who have epilepsy have been shown to have lower health-related quality of life (HRQL) compared with those without epilepsy (Vergeer et al, 2019). All of the patients who spoke to the TSA had refractory epilepsy with only a partial response to treatment with epileptic drugs. One mum of a 19 years-old daughter who has TSC told us (family D): "The impact of my daughter's TSC on day-to-day life is huge. She was diagnosed at 16 weeks old after the onset of infantile spasms. She has had refractory epilepsy since this. She is not able to live independently, because of seizures. Her seizures have impacted her learning ability and have stopped her doing more. The frustrations have kicked in now that she's an adult. My daughter's seizures impact her ability to walk so she uses a walker and a wheelchair. She lives in constant fear of seizures and these are worse at night. She is verbal and understands enough to realise the importance of being seizure free and hopes that this is a possibility one day." "My daughter has a college placement as a residential student at an epilepsy college, which she started last September. She comes home regularly, most weekends and during the holidays. My family give all of our time to care for her when she is at home. She wakes a lot during the night, and frequently won't get to sleep until the early hours of the morning. This means she is not up and ready for her day until midday. She often doesn't want to go out anywhere, and we have to make lots of adjustments to accommodate her in our plans. She needs lots of warning about things, and our family have to plan everything in advance. All of our plans centre around our daughter." One mother with an adult daughter living with TSC (37 years old) told us (family C): "It affects everything; we take her out to a meal and she can have a seizure whilst waiting for food and then doesn't want to eat. Usually I go to the restaurant first, while her Dad waits in the car and they only go in when the food is on the table. Or if she has a seizure during the meal then you are rushing to get out to leave and don't bother eating. Everything you do, you have to think about how it's going to affect her. It's pointless going out as more often than not, she's had a seizure. She has broken every bone in her left foot through drop seizures, it's so swollen that it's difficult to get shoes. She has two people with her 24 hours a day because of seizures and behaviour." Another mum shared what it's like to care for her daughter (13 years old) who has TSC and TSC-related daily seizures, developmental delay and behaviour problems (family B): "Every seizure could be her last seizure – the

	first thing our family does in the morning is check to see if she is still alive. Our daughter is in mainstream school, but she is followed by two carers."

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Epilepsy is the most common neurological feature of TSC, affecting eight out of ten of people living with the condition. Over half of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment.
- Epilepsy is generally more difficult to control for individuals living with TSC who have moderate or severe learning disabilities. Five out of every ten people with TSC have learning disabilities. Around three in ten people have profound learning disabilities and need round-the-clock care and life-long support from their families or move into residential care to receive this high level of support. Early onset of epilepsy has been associated with a higher frequency and severity of intellectual disability and a slower gain in intellectual ability, which has also been linked to seizure severity.
- When we asked people living with TSC and their families and carers to share the aspects of living with TSC that are not met by currently available treatments, all seven families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs.
- Seven out of seven families answered yes to our question: If Epidyloex®, would (patient) prefer to try this treatment first, before trying other treatments? One mum said (family D): "We would have tried this first – even if it doesn't work it's well worth giving it a go." Family F said: "Yes as Epidyloex® has non-toxic side effects." Family B told us: "We have been asking for CBD for years, but it was never licenced." Family C also agreed that it is worth a try: "None of the other treatments have worked fully. Epidyolex® was no worse than anything else. It is worth a try – it could work well for others."
- Those who responded to the TSA noted improvements to the physical and mental health of family members – both parents and siblings – as well as patients themselves as a result of treatment with Epidyloex®.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Sofia Eriksson**
2. Name of organisation	**Association of British Neurologists (ABN)**

3. Job title or position	**Consultant neurologist, chair of the ABN epilepsy advisory group**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
4a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a not-for-profit membership association for Neurologists whose mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The organisation is funded by membership fees.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Prevention of seizures and their consequences. There are many other comorbidities in people with Tuberous Sclerosis Complex (TSC) and refractory seizures (cognitive impairment, behavioural difficulties etc), some of which may be partly influenced by seizure frequency. Patients with refractory epilepsy are also at risk of injury from seizures and falls and there is an increased risk of sudden unexpected death in epilepsy (SUDEP).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	The ideal is freedom from seizures, but this is rarely achieved with current treatments for this group of patients. Cessation of generalised tonic-clonic seizures (one type of seizure seen in this condition) has benefits, for example in reduction of risk of sudden death (SUDED). The commonly used measures of a 50% reduction

x cm, or a reduction in disease activity by a certain amount.)	in frequency of seizures, or types of seizures, though of undoubted help, should be acknowledged to be the arbitrary measure it is, and does not necessarily reduce risks (eg of sudden death) or improve quality of life 30% reduction in disabling seizures, that is focal seizures with altered awareness, generalised tonic clonic seizures, tonic or atonic, tonic, has been used as a measurement of sufficient treatment response to warrant continuing treatment with cannabidiol for Dravet syndrome and Lennox-Gastuat syndrome and it would be reasonable to apply the same threshold for the current patient group.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Many patients with tuberous sclerosis do not become seizure-free with currently available antiseizure medications.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Primary treatments: antiseizure medications (ASM) Ketogenic diets and vagus nerve stimulation are also considered as is epilepsy surgery if a single tuber is found to generate all or the majority of the seizures. A proportion of patients may be eligible for treatment with Everolimus but this is currently only available to a small group of patients.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE CG137 (Epilepsies: diagnosis and management) for the general care of epilepsy but with regards to TSC, this is only mentioned as part of infantile spams cohort in the 2012 issue - update awaiting publication following consultation. NHS England Reference: 170093P (Clinical Commissioning Policy: Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above)

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is not a well-defined pathway for all aspects of care. Patients will normally try several regularly used antiseizure medications. If seizures fail to respond to medication, patients should be referred for specialist review at a tertiary centre as per NICE guidelines. However, patients may often not continue to be seen at tertiary centres. Patients should be part of a multidisciplinary TSC service with, as a minimum, renal and epilepsy input. Patients may have been through epilepsy surgery investigations to assess suitability for surgery but that is not the case for many of the patients, particularly if it is clear that seizures are multifocal.
• What impact would the technology have on the current pathway of care?	An additional drug to be tried as adjunctive therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as another antiseizure medication.
• How does healthcare resource use differ between the technology and current care?	Patients may require slightly more frequent monitoring and blood tests, at least at the start of treatment but long-term, no major difference.
• In what clinical setting should the technology be used? (For example,	Secondary or tertiary neurology clinics. Patients should have been reviewed in specialist services to be deemed refractory. If that has been the case, they may be able to continue their care in specialist secondary care neurology clinics and may not require tertiary clinics for regular follow-up.

primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Increased support and systems for prescribing in hospitals, particularly if there is an increase in the number of patients referred for specialist follow-up and prescribing.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Although not all patients will respond, studies have found improved seizure control compared to placebo and it is likely that some patients will have a clinically meaningful improvement compared to current care.
• Do you expect the technology to increase length of life more than current care?	Yes, if seizure freedom is achieved.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, particularly if seizure freedom is achieved.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not apparent.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will require monitoring (eg of liver profile) and may require dose adjustments for co-prescribed ASM. Will require additional time for issuing prescriptions from hospitals unless GPs are able to continue prescriptions after initiation and also blood monitoring (see point 10). Easier to prescribe with less monitoring and less harmful than everolimus.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Blood tests are required before starting treatment as well as regularly during the initial phases of prescription. Stopping criteria should be failure to achieve 30% reduction in disabling seizures, after stable dosage for 6 months, compared to baseline.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Cannabidiol has sometimes been considered to improve alertness but so far limited data on this.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes by reducing seizure burden and associated seizure related risks for patients who are refractory to current treatment options.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No, it is another antiepileptic drug.
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects with cannabidiol have been reported, most commonly diarrhoea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests and these may necessitate drug withdrawal. Cannabidiol may also increase levels of other ASM that may in turn lead to side effects and necessitate dose adjustments.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes reasonably. Much of the evidence is from children but adults have been included in the studies as well.

• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Seizure reduction and adverse events. These were both measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In clinical use of cannabidiol (Dravet syndrome and Lennox Gastaut syndrome) it has become clear that concomitantly used ASM may be increased and reducing these may reduce overall side effects and enable continued treatment with cannabidiol as well as increasing the dose to try to achieve efficacy.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. How do data on real-world experience compare with the trial data?	See 18.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No. All patients with TSC should be considered for the treatment.
21b. Consider whether these issues are different from issues with current care and why.	Not different from current care issues.
Topic-specific questions	
22. When would everolimus be used in the pathway for tuberous sclerosis complex? Would everolimus ever be	Everolimus would be used if the patient has not responded to ASM (usually a multitude of drugs tried). Many will also have been discussed in an epilepsy surgery MDT but not deemed suitable for surgery. Everolimus is likely to be offered after cannabidiol considering the side effect profile and substantial need for monitoring.

offered at the same position as cannabidiol in clinical practice?	
23. How would you describe the variability of seizure severity and frequency in tuberous sclerosis complex? How would this affect the level of care required?	Some patients with TSC have seizures that respond well to treatment and their epilepsy is well controlled. Others have multiple daily seizures that may include drop seizures (atonic), tonic, focal seizures with or without loss of awareness and bilateral tonic-clonic seizures. The care required will depend on severity and frequency of seizures. Some patients will be fairly independent whereas others require help with all activities of daily living. May patients have additional disorders including intellectual disabilities that will affect care needs as well.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Cannabidiol adds to the treatment options for TSC
- Freedom from convulsive seizures is a valuable achievement in this syndrome
- Cannabidiol has not been compared directly to other ASM
- Cannabidiol needs to be considered and treated like any other ASM
- Cannabidiol has a more favourable side effect profile than everolimus but does not have the same impact on the syndrome itself and does not for example reduce size of tubers

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in collaboration with:

university of groningen

University Medical Center Groningen

Maastricht University

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with University Medical Center (UMC) Groningen, the Netherlands (NL) and Maastricht University Medical Centre (UMC+), NL

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Rider on responsibility for report

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Contributions of authors

Jeremy Howick acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Thea van Asselt acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa de Jong, Maarten Postma, Bram Ramaekers and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Mark Perry, Charlotte Ahmadu, and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Mark Perry also acted as deputy project lead. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Robert Wolff and Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AED	Anti-epileptic drug (also referred to as an anti-seizure-medication)
AES	American Epilepsy Society
AiC	Academic in confidence
ASM	Anti-seizure medication (also referred to as an anti-epileptic drug)
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CBD25	Cannabidiol 25 mg/kg/day
CBD-OS	Cannabidiol oral solution
CEA	Cost effectiveness analysis
CGIC	Caregiver Global Impression of Change
CGICSD	Caregiver Global Impression of Change in Seizure Duration
CI	Confidence interval
CIC	Commercial in confidence
CS	Company submission
CSR	Clinical study report
CYP3A4	Cytochrome P450 3A4
DS	Dravet syndrome
DSA	Deterministic sensitivity analysis
EAP	Expanded Access Programme
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
ERG	Evidence Review Group
EQ-5D	EuroQol five-dimension scale questionnaire
FE	Fixing errors
FV	Fixing violations
GP	General Practitioner
HCRU	Healthcare resource use
HRQoL	Health-related quality of life
HS	Health state
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICD	International Classification of Disease
IMP	Investigational medicinal product
ITC	Indirect treatment comparison
ITT	Intention-to-treat
kg	Kilograms
LGS	Lennox-Gastaut syndrome
max	Maximum
MeSH	Medical subject heading
mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
min	Minimum
MJ	Matters of judgement
ml	Millilitres
mTOR	Mammalian target of rapamycin
NA or N/A	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported

OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
S/CGIC	Subject/Caregiver Global Impression of Change
PICO	Population, intervention(s), comparator(s), outcome(s)
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
QOLCE	Quality of Life in Childhood Epilepsy
QOLIE	Quality of Life in Epilepsy
RCT	Randomised controlled trial
RFS	Relapse free survival
RoB	Risk of bias
ROBIS	Risk of Bias in Systematic Reviews
S/CGIC	Subject/Caregiver Global Impression of Change scale
SAEs	Serious adverse events
SD	Standard deviation
SE	Standard error
SEGA	Subependymal giant cell astrocytoma
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SUDEP	Sudden unexpected death in epilepsy
TAND	TSC-associated neuropsychiatric disorders
TLR	Targeted literature reviews
TSC	Tuberous sclerosis complex
TEAE	Treatment emergent adverse event
TOSCA	TuberOus SClerosis registry to increase disease Awareness
TTO	Time trade-off
UK	United Kingdom
UMC+	Maastricht University Medical Centre
UNC+	University Medical Centre Groningen
US	United States
USA	United States of America
VNS	Vagus nerve stimulation

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem. Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary is presented in Section 1.7.

Background information on the condition, technology and evidence and information on key issues as well as non-key issues are in the main ERG report, see Sections 2 (background), 3 (decision problem), 4 (clinical effectiveness) and 5 (cost effectiveness) for more details.

All issues identified represent the ERG's view, and not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1416	Summary of issue	Report Sections
1	The different population considered by the company may not be representative of the England National Health Service (NHS) setting and could have led to exaggeration of cannabidiol's benefits.	2.1
2	The quality-of-life instrument chosen lacks adequate justification and does not permit calculation of utilities, leading to uncertainties regarding cannabidiol's cost effectiveness.	2.4
3	The extent to which the usual care treatments in the GWPCARE6 trial were representative of the England NHS setting remains unclear, so the efficacy and safety estimates of cannabidiol could be misleading.	2.3 and 3.2.4
4	Usual care treatments including vigabatrin used as background treatments differed between groups leading to a biased estimate of cannabidiol's efficacy and safety.	3.2.4
5	The small number of patients recruited from UK sites makes generalisability to the England NHS setting questionable.	2 and 3.2.1
6	The systematic literature review did not present all relevant evidence for comparator treatments, making the relative efficacy and safety estimates of cannabidiol uncertain.	3.1.2 and 3.1.5
7	The systematic review had a high risk of bias, making its conclusions about the relative safety and efficacy of cannabidiol uncertain.	3.1.4
8	Because of small sample size, patient characteristics between age categories varied. This may have an impact on assumed weight and body surface area (BSA) which, in turn, determined treatment costs.	4.2.3
9	The company assumed a 12 mg/kg/day average dose in the model used to calculate the drug costs. However, a dose of 25 mg/kg/day was used to inform most other model inputs, and it is unclear whether an average of 12 mg/kg/day reflects clinical practice.	4.2.4

ID1416	Summary of issue	Report Sections
10	The way in which predicted seizure-free days per week were incorporated in the economic model to determine 'seizure-free over seven days' is not justified and may not be in line with clinical practice, especially for the usual care arm.	4.2.6
11	The impact of TSC-associated neuropsychiatric disorders (TAND) was modelled using many uncertain assumptions.	4.2.9
12	The Evidence Review Group (ERG) believes that the seizure-free health state utility value estimated in the vignette study for caregivers (0.905), is overestimated, leading to an over-estimation of cannabidiol's cost effectiveness.	4.2.12
13	The assumption to apply caregiver disutilities additively to two caregivers lacks justification. Additionally, unlike costs utilities were not corrected for patients being institutionalised.	4.2.12
BSA = body surface area; ERG = Evidence Review Group; NHS = National Health Service; TAND = TSC-associated neuropsychiatric disorders; TSC = tuberous sclerosis complex; UK = United Kingdom		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing QoL of the patient through a reduction in seizures
- Decreasing the loss in QoL of the caregivers through a reduction in seizures

Overall, the technology is modelled to affect costs by:

- Its higher treatment acquisition price compared to care as usual
- A reduction in health state costs because of a reduction in seizure frequency

The modelling assumptions that have the greatest effect on the ICER (based on the company's sensitivity analyses) are :

- the stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven per week
- the patient utility values for seizure-free patients
- response rates used to estimate the proportion of patients who benefit from a reduction in tuberous sclerosis complex (TSC) associated neuropsychiatric disorders (TAND) symptoms.

Company submission (CS) scenarios that have a substantial impact on the ICER are the following:

- Inclusion of wider societal costs: social and educational care resource use
- Applying benefit of TAND reduction to all age groups
- Reducing the cannabidiol dose from 12 to 10 mg/kg/day

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the CS is broadly in line with the final scope issued by NICE. However, the **population** considered by the company is somewhat different than the population specified in the final NICE scope (Table 1.2), and the QoL instrument used to measure a main **outcome** lacks justification (Table 1.3).

Table 1.2: Key issue 1. Different population considered by company unclear and possible not representative of target England UK population

Report Section	**2**
Description of issue and why the ERG has identified it as important	The different population considered by the company in the main trial (restricted to those for whom usual care is unsuitable or not tolerated) may not be representative of England NHS clinical practice setting and could have led to exaggeration of cannabidiol's benefits. This also has implication for the suitability of comparators (treatments received given refractory or unsuitable/not tolerated).
What alternative approach has the ERG suggested?	Use the population described in the final NICE scope.
What is the expected effect on the cost effectiveness estimates?	Uncertain, but possibly exaggerated effectiveness and cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	New analysis restricted to the population defined in the final NICE scope and greater clarity as to precisely the population that is to be considered for reimbursement in terms or treatments to which patients are refractory and which unsuitable or not tolerated.
ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence	

Table 1.3: Key issue 2. The choice of the S/CGIC Quality of Life questionnaire lacks adequate justification

Report Section	**2**
Description of issue and why the ERG has identified it as important	The choice of the Subject/Caregiver Global Impression of Change scale (S/CGIC) quality of life questionnaire lacks justification and leads to considerable uncertainty regarding utilities.
What alternative approach has the ERG suggested?	Addition of a quality-of-life instrument from which utilities can be estimated.
What is the expected effect on the cost effectiveness estimates?	Exaggerated effectiveness and cost effectiveness
What additional evidence or analyses might help to resolve this key issue?	Addition of a quality-of-life instrument from which utilities can be estimated.
ERG = Evidence Review Group; S/CGIC = Subject/Caregiver Global Impression of Change scale	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified four major concerns with the evidence presented on the clinical effectiveness:

- Usual care treatments in both arms differed between trial and relevant clinical setting leading to questionable generalisability (Table 1.4)

- Usual care treatments including vigabatrin used as background treatments differed between groups leading to a biased estimate of efficacy and safety (Table 1.5)
- The small number of UK patients make generalisability to the England NHS setting questionable (Table 1.6)
- The systematic literature did not include results for relevant comparators (Table 1.7)
- The systematic literature suffered from serious methodological problems (Table 1.8)

Table 1.4: Key issue 3. Usual care treatments may have differed between trial and relevant NHS setting

Report Sections	**2.3 and 3.2.4**
Description of issue and why the ERG has identified it as important	Usual care treatments in both arms may not have been representative of the England NHS setting, leading to a potentially biased estimate of cannabidiol's efficacy and safety.
What alternative approach has the ERG suggested?	Analysis that is adjusted for differences between (i) trial and (ii) England NHS setting.
What is the expected effect on the cost effectiveness estimates?	Added uncertainty
What additional evidence or analyses might help to resolve this key issue?	Analysis that is adjusted for differences between (i) trial and (ii) England NHS setting.
ERG = Evidence Review Group; NHS = National Health Service	

Table 1.5: Key issue 4. Usual care treatments may have differed between both groups

Report Sections	**2.3 and 3.2.4**
Description of issue and why the ERG has identified it as important	Usual care treatments including vigabatrin used as background treatments differed between groups leading to a biased estimate of cannabidiol's efficacy and safety.
What alternative approach has the ERG suggested?	Intention to treat (ITT) analysis that is adjusted for differences in usual care treatments.
What is the expected effect on the cost effectiveness estimates?	Added uncertainty.
What additional evidence or analyses might help to resolve this key issue?	ITT analysis that is adjusted for differences in usual care treatments.
ERG = Evidence Review Group; ITT = Intention to treat	

Table 1.6: Key issue 5. Patients in GWPCARE6 study not representative of England NHS patients

Report Sections	**2.1 and 3.2.1**
Description of issue and why the ERG has identified it as important	The small number of patients recruited from United Kingdom (UK) sites (n=11) makes generalisability to the England NHS setting questionable.
What alternative approach has the ERG suggested?	Analysis with UK patients.

Report Sections	2.1 and 3.2.1
What is the expected effect on the cost effectiveness estimates?	Added uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Exploratory analysis using the subgroup of UK patients or comparison of baseline characteristics of UK patients with patients that might be expected in the England NHS clinical setting.
ERG = Evidence Review Group; NHS = National Health Service; UK = United Kingdom	

Table 1.7: Key issue 6. Restricted systematic literature review results in submission

Report Sections	3.1.2 and 3.1.5
Description of issue and why the ERG has identified it as important	The systematic literature review (SLR) did not seem to present all relevant evidence for comparator treatments, making the relative efficacy and safety estimates of cannabidiol uncertain.
What alternative approach has the ERG suggested?	Presenting the full SLR results as per submission population intervention comparator outcome study design (PICOS).
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Indirect treatment comparison (ITC) feasibility assessment of placebo-controlled studies from full SLR.
ERG = Evidence Review Group; ITC = Indirect treatment comparison; PICOS = population intervention comparator outcome study design; SLR = systematic literature review	

Table 1.8: Key issue 7. Methodological problems with systematic review

Report Sections	3.1.2 and 3.1.5
Description of issue and why the ERG has identified it as important	The systematic review had a high risk of bias, making its conclusions about the relative safety and efficacy of cannabidiol uncertain.
What alternative approach has the ERG suggested?	Updated systematic review that addresses the methodological problems highlighted by the Evidence Review Group (ERG).
What is the expected effect on the cost effectiveness estimates?	Uncertainty regarding the relative safety and efficacy of cannabidiol.
What additional evidence or analyses might help to resolve this key issue?	Updated systematic review that addresses the methodological problems highlighted by the ERG.
ERG = Evidence Review Group	

1.5 The cost effectiveness evidence : summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique are in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the Tables below, and are:

- The modelled population may not be representative of the target population (Table 1.9)

- The small sample size made estimated treatment costs questionable (Table 1.10)
- The company's assumed average dose is unlikely to be representative of relevant clinical practice (Table 1.11)
- The impact of TAND was modelled using many uncertain assumptions (Table 1.12)
- The seizure-free health state utility value estimated in the vignette study for caregivers is overestimated (Table 1.13)
- The assumption to apply caregiver disutilities additively to two caregivers lacks justification (Table 1.14)

Table 1.9: Key Issue 8: Modelled population may not be representative of target population

Report Section	**4.2.3**
Description of issue and why the ERG has identified it as important	Because of small sample size, there is quite some variation in patient characteristics between age categories. This may have an impact on assumed weight and body surface area (BSA) which determine treatment costs. Also, patients aged 1 year were included in the trial and used to determine model parameters although treatment efficacy separately for the 1-year age group was unknown.
What alternative approach has the ERG suggested?	No specific approach was possible given lack of data.
What is the expected effect on the cost effectiveness estimates?	The effect is unknown but may be small.
What additional evidence or analyses might help to resolve this key issue?	Exploratory analyses varying weight and BSA would provide insight into the impact of these parameters. To single out the impact of the 1-year-old age group, separate data on the effectiveness of cannabidiol in this group would be needed.
BSA = body surface area; ERG = Evidence Review Group	

Table 1.10: Key Issue 9: The use of an average cannabidiol dose of 12 mg/kg/day

Report Section	**4.2.4**
Description of issue and why the ERG has identified it as important	The company assumed a 12 mg/kg/day average dose in the model, used to calculate the drug costs. However, a dose of 25 mg/kg/day was used to inform most model inputs, and there is no clear evidence from literature that an average of 12 mg/kg/day reflects clinical practice.
What alternative approach has the ERG suggested?	It is unclear what dose is a reliable representative for tuberous sclerosis complex (TSC)-associated epilepsy clinical practice, therefore the Evidence Review Group (ERG) cannot suggest a preference. However, the effect of this uncertainty should be tested by conducting several scenario analyses based on other average doses (e.g., 10, 15, 20, and 25 mg/kg/day).
What is the expected effect on the cost effectiveness estimates?	The incremental cost-effectiveness ratio (ICER) is expected to increase, which was shown after the inclusion of these scenarios in the model after clarification response.

Report Section	4.2.4
What additional evidence or analyses might help to resolve this key issue?	Future collection of real-world cannabidiol dosing in United Kingdom (UK) TSC-associated epilepsy patients might help to resolve this issue.
ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; TSC = tuberous sclerosis complex; UK = United Kingdom	

Table 1.11: Key Issue 10: Incorporation of seizure-free days in the model

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The way in which predicted seizure-free days per week were incorporated in the economic model to determine 'seizure-free over seven days' is not justified and may not be in line with clinical practice, especially for the usual care arm.
What alternative approach has the ERG suggested?	The ERG have included a scenario where the cut-off value for 'seizure-free over seven days' was set to actually seven days, instead of 6.5. This does however not resolve the issue that the proportion of seizure-free patients in both arms may, in the long run, not represent clinical practice.
What is the expected effect on the cost effectiveness estimates?	In the ERG scenario the ICER increased. The impact of using a different approach to estimating seizure-free days is uncertain, as there is no data available on the natural course of seizure-free days in usual care.
What additional evidence or analyses might help to resolve this key issue?	Long-term data on seizure-free days/periods, also in usual care.
ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; TSC = tuberous sclerosis complex; UK = United Kingdom	

Table 1.12: Key Issue 11: Questionable validity of approach to TAND impact

Report Section	4.2.9
Description of issue and why the ERG has identified it as important	The impact of tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders (TAND) was modelled using many assumptions, all of them being quite uncertain: the prevalence of TAND aspects based on external data, then the near consensus of the Delphi panel on the 47.5% response cut-off, using response percentages for all age categories to apply to the [redacted] category, and the assumption that the impact of the reduction in TAND would be over the complete lifetime of a patient. Also, part of the TAND impact on health-related quality of life (HRQoL) may already be captured in the HRQoL as determined through the vignettes.

Report Section	4.2.9
What alternative approach has the ERG suggested?	The Evidence Review Group (ERG) would prefer to exclude TAND from the analysis or include it using very conservative assumptions.
What is the expected effect on the cost effectiveness estimates?	Excluding TAND increases the incremental cost-effectiveness ratio (ICER), although the impact could be limited.
What additional evidence or analyses might help to resolve this key issue?	To resolve the issue completely, long-term data would be required on TAND impact, which will be very difficult to obtain. The ERG does appreciate these difficulties and thinks a more conservative approach is still indicated.
ERG = Evidence Review Group; HRQoL = health related quality of life; ICER = incremental cost-effectiveness ratio; TAND = TSC-associated neuropsychiatric disorders; TSC = tuberous sclerosis complex	

Table 1.13: Key Issue 12: Potential overestimation of caregiver utilities in seizure-free state

Report Section	4.2.12
Description of issue and why the ERG has identified it as important	The Evidence Review Group (ERG) believes that the seizure-free health state utility value estimated in the vignette study for caregivers (0.905), is potentially overestimated. The 0.905 is already higher than the general utility for a woman aged 43 (assumed to be the average age of the mother of a 13-year-old child). This difference increases with age of the carer and male gender. Moreover, tuberous sclerosis complex (TSC) is a severe disease which among epilepsy also causes other symptoms that may cause burden for the caregivers. Also, when a patient is seizure-free, the caregiver may still have many worries, so a utility score of 0.905 may overestimate carer health-related quality of life (HRQoL) for this health state. Also, the carer disutilities were not corrected for age-related decrements.
What alternative approach has the ERG suggested?	A lower utility score for the seizure-free state was used in the ERG analyses. As it is not straightforward to correct the carer utilities for ageing, the ERG did not adjust the model to address this issue.
What is the expected effect on the cost effectiveness estimates?	A lower carer utility in the seizure-free state would increase the incremental cost-effectiveness ratio (ICER). The impact of an age-related decrement for carer utility is uncertain.
What additional evidence or analyses might help to resolve this key issue?	For carer utilities, EQ-5D data (matched for seizure frequency categories) could be collected, also from observational studies. This would shed light on the appropriateness of the currently used utilities.
ERG = Evidence Review Group; EQ-5D = EuroQol five-dimension scale questionnaire; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio	

Table 1.14: Key Issue 13: Applying caregiver disutilities additively to two caregivers and no correction for institutionalization.

Report Section	**4.2.12**
Description of issue and why the ERG has identified it as important	The assumption to apply caregiver disutilities additively to two caregivers. Additionally, unlike costs utilities were not corrected for patients being institutionalised.
What alternative approach has the ERG suggested?	The Evidence Review Group (ERG) assumed an average of 1.8 caregiver in line with TA614 and TA615 and corrected utilities for institutionalisation in their base case analysis.
What is the expected effect on the cost effectiveness estimates?	Both corrections would decrease the incremental quality adjusted life years (QALYs), resulting in an increase of the incremental cost effectiveness ratio (ICER).
What additional evidence or analyses might help to resolve this key issue?	The ERG believes it would have helped to determine the number of caregivers alongside the clinical trial per age group. Long-term data of the trial would provide more insight in the changes in the number of caregivers per patient in time.
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year	

1.6 Other key issues: summary of the ERG's view

None.

1.7 Summary of the ERG's view

Table 1.15: Deterministic ERG base-case

Technologies	**Total costs**	**Total QALYs**	**Incremental costs**	**Incremental QALYs**	**ICER (£/QALY)**
CS base-case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,712
Fixing errors 1: Correction of general population mortality from age 97					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,712
Fixing violations 2: Inclusion of age-related utility cap for patients					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,713

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Fixing violations 3: Seizure-free health state utility for carers adjusted to general population utility					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,126
Matters of judgement 4: Exclusion of TAND-related management costs and utility increments					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£14,391
Matters of judgement 5: Number of caregivers adjusted to 1.8					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,451
Matters of judgement 6: Adjust utilities for institutionalization					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,696

CS = company submission; ICER = incremental cost-effectiveness ratio; TAND = TSC-Associated Neuropsychiatric Disorders; QALYs = quality-adjusted life years.

Table 1.16: Deterministic scenario analyses (conditional on ERG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£16,928
Scenario 1: Average cannabidiol dose based on 15 mg/kg/day					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£27,210
Scenario 2: Average cannabidiol dose based on 20 mg/kg/day					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£44,347
Scenario 3: Weight and BSA – 5% higher than base case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£18,949
Scenario 4: Weight and BSA – 5% lower than base case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£14,907
Scenario 5: Seizure freedom per week cut-off – 7 days					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£24,022

BSA = body surface area; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.

Table 1.17: Probabilistic scenario analyses (conditional on ERG base-case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Probability
ERG base-case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£19,820	[redacted]
Scenario 1: Average cannabidiol dose based on 15 mg/kg/day						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£29,949	[redacted]
Scenario 2: Average cannabidiol dose based on 20 mg/kg/day						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£50,759	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Probability
Scenario 3: Weight and BSA – 5% higher than base case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£21,750	[redacted]
Scenario 4: Weight and BSA – 5% lower than base case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£16,843	[redacted]
Scenario 5: Seizure freedom per week cut-off – 7 days						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£27,256	[redacted]

BSA = body surface area; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	People with tuberous sclerosis complex (TSC) whose seizures are inadequately controlled by established clinical management.	People with TSC whose seizures are inadequately controlled by current or prior established clinical management. People with TSC where usual care is unsuitable or not tolerated.	This is in line with recommendations in National Institute of Health and Care Excellence (NICE) Clinical guideline 137 (CG137).	The narrower population used by the company may not be generalisable to the England National Health Service (NHS) setting.
Intervention	Cannabidiol in addition to current clinical management.	Cannabidiol in addition to current clinical management ('usual-care').	N/A	None
Comparator(s)	Established clinical management without cannabidiol, such as: • Anti-seizure medications (ASMs) • Everolimus • Vagus nerve stimulation (VNS) • Ketogenic diet • Surgical resection	Established clinical management without cannabidiol, such as: • Anti-epileptic drugs (AEDs) (also known as ASMs) • VNS • Ketogenic diet • Surgical resection	In line with the NHS England Clinical Commissioning Policy (Everolimus for refractory focal onset seizures associated with TSC (ages 2 years and above) 2018), and the drug's safety/tolerability profile, everolimus is included in this submission as a later line treatment. Everolimus is not specifically an AED, but it may be considered as a last-line treatment option for people aged 2 years and older with refractory focal onset seizures associated with TSC (everolimus is *not*	The extent to which the usual care treatments in the GWPCARE6 trial are representative of United Kingdom (UK) clinical management remains unclear.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
		Everolimus is included in the submission as a later line treatment.	licensed for generalised onset seizures) who have not adequately responded to treatment with at least two different AEDs given at therapeutic doses, and where epilepsy surgery has failed or is unsuitable and where VNS has failed or is not considered appropriate by the patient, or their carer, in discussion with the treating clinician. Since everolimus is an immunosuppressant agent initially developed to prevent transplant rejection and for oncology indications, it is associated with a safety and tolerability burden, including non-infectious pneumonitis, increased infection risk, hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, myelosuppression and metabolic disorders. It should be noted that everolimus has a separate indication/dosing schedule in TSC that is not specifically related to seizures: for the treatment of subependymal giant cell astrocytoma (SEGA), a benign tumour of the brain, where it is used in adults and children whose brain tumour cannot be surgically removed. For this indication and dosage, it may be considered in TSC earlier in the pathway, but not specifically for the treatment of seizures.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Outcomes	The outcome measures to be considered include: • Change in frequency of seizures • Response to treatment • Adverse effects of treatment • Health-related quality of life (HRQoL)	The outcome measures to be considered include: • Change in frequency of seizures • Response to treatment • Adverse effects of treatment • HRQoL • Seizure-free days	Both seizure-free days and seizure frequency are important outcomes for patients with TSC-associated epilepsy. Previous submissions to NICE for cannabidiol in Dravet syndrome and Lennox–Gastaut syndrome explicitly modelled seizure-free days and seizure frequency.	The choice of the Subject/Caregiver Global Impression of Change scale (S/CGIC) Quality of Life questionnaire lacks justification and leads to considerable uncertainty regarding utilities.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Cost effectiveness of treatments will be expressed in terms of incremental cost per QALY. A lifetime time horizon for estimating clinical and cost effectiveness will be used. Costs will be considered from an NHS and PSS perspective.	N/A	None

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	Costs will be considered from an NHS and Personal Social Services (PSS) perspective.			
Subgroups to be considered	N/A	N/A	N/A	N/A
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	None

Based on Table 1 and pages 10 to 12 of the CS.[1]

AEDs = anti-epileptic drugs; CS = company submission; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; SEGA = subependymal giant cell astrocytoma S/CGIC = Subject/Caregiver Global Impression of Change scale; TSC = tuberous sclerosis complex; UK = United Kingdom; VNS = vagus nerve stimulation

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) **final scope** is:

- People with tuberous sclerosis complex (TSC) whose seizures are inadequately controlled by established clinical management.[2]

The population in the **decision problem** of the company submission (CS) is:

- People with TSC whose seizures are inadequately controlled by current or prior established clinical management," and "people with TSC where usual-care is unsuitable or not tolerated (CS, Table 1, page 9).[1]

The population included in the **identified trial evidence**, the GWPCARE6 study,[3] is:

- Children and adults aged 1 to 65 years with a clinical diagnosis of TSC and a well-documented clinical history of epilepsy not completely controlled by their current anti-epileptic drugs (AEDs). Taking one or more AEDs at a dose that had been stable for at least 1 month. At least eight TSC-associated seizures in the initial 28-day baseline period, with at least one seizure in at least three of the 4 weeks. All medications or interventions for epilepsy (including a ketogenic diet and vagus nerve stimulation, which were not counted as AEDs) stable for 4 weeks before screening.

According to the company the rationale for including a different population in their interpretation of the decision problem and their main trials was that their population is that it is in line with recommendations in NICE Clinical Guideline 137 (CG137).[4]

In their request for clarification,[5] the Evidence Review Group (ERG) asked the company to justify the difference between the population in the final NICE scope and the population considered by the company.[5] The company acknowledged that NICE CG137 did not explicitly make recommendations for people with TSC epilepsy. However, the company argued that the following text from the guideline implied that the guideline applied to patients with TSC-associated epilepsy: "Treatment should be reviewed at regular intervals to ensure that children, young people and adults with epilepsy are not maintained for long periods on treatment that is ineffective or *poorly tolerated.*"[4] The company also notes that sodium valproate is not suitable for women of childbearing age unless a pregnancy prevention programme is in place.[6]

The European Commission approved the marketing authorisation for Epidyolex® (cannabidiol) in seizures associated with TSC on 16 April 2021. The Medicines and Healthcare products Regulatory Agency (MHRA) approved the type II variation application for Epidyolex® (cannabidiol) as an adjunctive treatment of seizures associated with TSC, for patients 2 years of age and older, on 5 August 2021.

Also in their request for clarification,[5] the ERG asked the company to provide more details about what constituted usual care, and how unsuitability or intolerance to usual care was defined. The company replied that there is "*no standard of care once a patient is refractory…In the GWPCARE6 trial of cannabidiol, patients entering the trial were permitted to be taking any AEDs/other treatments (except those listed as exclusion criteria) as long as they were stable during baseline and during the trial.*"[6] As reasons for unsuitability, the company provided a number of reasons for classifying patients as unsuitability (teratogenicity, contraindications, patient/caregiver preference). As reasons for determining intolerability, the company cites side-effects as the main apparent reason. The company stated that the criteria for deciding whether usual care was unsuitable or intolerable was determined by

"*the clinician, in conjunction with the patient, the patient's caregivers and/or the multidisciplinary team responsible for the patient's care*."[6]

ERG comment:

- The ERG does not understand the company's rationale for considering a different population. NICE CG137 refers to the diagnosis and management of epilepsies and, with the exception of sodium valproate for a specific group of patients (women of childbearing age not on a pregnancy prevention programme) does not comment on the suitable populations for appraisals.
- The ERG believes that despite there appearing to be no standard of care (SoC) once a patient is refractory it is essential to establish precisely what the company is considering in the decision problem. For the group of patients who have become refractory it means specifying which treatments considered to be usual care they have become refractory to, but also, according to the decision problem, for the group 'where usual-care is unsuitable or not tolerated', which treatments were those which are unsuitable/not tolerated. It is only by knowing this that one can determine:
    - the population for which the reimbursement decision is to be made,
    - the comparator or comparators for each of these patient groups,
    - whether the population in the main trial reflects this population in the England NHS setting.

2.2 Intervention

The intervention (cannabidiol in addition to current clinical management) is in line with the scope.

Epidyolex® (cannabidiol) is a highly purified, plant-derived pharmaceutical medicine of cannabidiol, administered as an oral solution. For TSC, the recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/ day) for 1 week. After 1 week, the dose should be increased to a dose of 5 mg/kg twice daily (10 mg/kg/day) and the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/kg/day). Patients then remain at this maintenance dose for 12 weeks. Dose escalation for each patient is subject to the investigator's assessment of safety and tolerability. If a dose becomes poorly tolerated, the investigator could temporarily or permanently reduce the dose.

ERG comment: The ERG agrees that the intervention considered by the company matches that in the final NICE Scope.

2.3 Comparators

The description of the comparators in the NICE scope is as follows:

"Established clinical management without cannabidiol, such as:

- *Anti-seizure medications (ASMs)*
- *Everolimus*
- *Vagus nerve stimulation (VNS)*
- *Ketogenic diet*
- *Surgical resection*"[2]

The comparators used by the company are similar, with one main difference. Whereas the final NICE scope lists everolimus as a comparator, the company only use everolimus as a later line treatment rather than as a direct comparator.[1]

The comparator used in the main trial was a placebo which consisted of an oily solution of sesame oil containing anhydrous ethanol (79 mg/mL), added sweetener (0.5 mg/mL sucralose), and strawberry flavouring (0.2 mg/mL).[7]

The company's rationale for using everolimus as a later line therapy rather than a direct comparator is cited below:

"In line with the NHS England Clinical Commissioning Policy (Everolimus for refractory focal onset seizures associated with tuberous sclerosis complex (ages 2 years and above) 2018), and the drug's safety/tolerability profile, everolimus is included in this submission as a later line treatment.

Everolimus is not specifically an AED, but it may be considered as a last-line treatment option for people aged 2 years and older with refractory focal onset seizures associated with TSC (everolimus is not licensed for generalized onset seizures) who have not adequately responded to treatment with at least two different AEDs given at therapeutic doses, and where epilepsy surgery has failed or is unsuitable and where vagus nerve stimulation (VNS) has failed or is not considered appropriate by the patient, or their carer, in discussion with the treating clinician.

Since everolimus is an immunosuppressant agent initially developed to prevent transplant rejection and for oncology indications, it is associated with a safety and tolerability burden, including non-infectious pneumonitis, increased infection risk, hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, myelosuppression and metabolic disorders.

It should be noted that everolimus has a separate indication/dosing schedule in TSC that is not specifically related to seizures: for the treatment of subependymal giant cell astrocytoma (SEGA), a benign tumour of the brain, where it is used in adults and children whose brain tumour cannot be surgically removed. For this indication and dosage, it may be considered in TSC earlier in the pathway, but not specifically for the treatment of seizures."[1]

In their request for clarification,[5] the ERG asked the company to further justify the exclusion of everolimus as a comparator.[5] The company reiterated that everolimus was a later line therapy according to the company's interpretation of NHS England Clinical Commissioning Policy.[6, 8]

ERG comment: The ERG agrees that everolimus is not considered by the NHS Clinical Commissioning Policy to be a first line of treatment.[8] The NHS Clinical Commissioning Policy related to everolimus for seizures associated with TSC states that "*Everolimus may be given to patients aged 2 years and older with TSC-related seizures that have not adequately responded to treatment with at least 2 different AEDs given at therapeutic doses in addition to their current treatments and where surgical resection has already been considered,*" and "*Everolimus will not be routinely commissioned as a first-line treatment.*"[8] However, in the company's modified scope, they include patients who do not tolerate or are unsuitable for 'usual care;' the ERG believes that for these patients that everolimus could constitute usual care. In fact, given uncertainty in the population, as described above, it is unclear generally what is the composition of usual care in the England NHS setting.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- Change in frequency of seizures
- Response to treatment
- Adverse effects of treatment

- Health-related quality of life (HRQoL)

These were all considered in the company's interpretation of the decision problem and the main trial (the GWPCARE6 study). In addition to these, the company's interpretation of the decision problem and main trial added seizure-free days as an outcome. Their rationale was: "*Both seizure-free days and seizure frequency are important outcomes for patients with TSC-associated epilepsy. Previous submissions to NICE for cannabidiol in Dravet syndrome and Lennox–Gastaut syndrome explicitly modelled seizure-free days and seizure frequency.*"[1]

Section 5.5.2.5 of the clinical study report (CSR) states, "*Effects on quality of life were therefore measured using the QOLCE/QOLIE-31-P questionnaires which have good construct validity, internal consistency, test-retest reliability, and sensitivity to epilepsy severity*."[7] Section 10.1 of the CSR states: "*Furthermore, these patients had a poor quality of life based on the low mean overall QOLCE [Quality of Life in Childhood Epilepsy] and QOLIE-31-P [Quality of Life in Epilepsy] scores of approximately 44–50 at baseline*."[7] Yet, the company did not present detailed data for this outcome in their submission. In their request for clarification,[5] the ERG asked the company to provide all outcome data that reports results of the Quality of Life in Childhood Epilepsy/Quality of Life in Epilepsy (QOLCE/QOLIE)-31-P questionnaires. In their response to clarification questions, the company provided this information.[6]

The ERG also asked the company to clarify how the QOLCE/QOLIE-31-P questionnaire results were accounted for in the efficacy conclusions. The company did not provide a direct answer to this question, and instead claimed that there are no validated disease-specific instruments, and that the QOLCE/QOLIE-31-P instruments do not work well for severe epilepsy. Instead, they claim that the "*Subject/Caregiver Global Impression of Change (S/CGIC) [Subject/Caregiver Global Impression of Change scale], which captures an estimate of the effect of treatment on the patient's overall condition based on his/her entire seizure and comorbidity burden, thereby providing valuable information on the clinical meaningfulness of the therapy. Using S/CGIC, patients and caregivers reported an improvement in patients' overall condition in 69% of those receiving cannabidiol (25 mg/kg/day) plus usual-care versus 39% receiving placebo plus usual-care. However, the S/CGIC measure is not preference-based and therefore could not be used to derive utilities.*"

In their request for clarification,[5] the ERG asked the company for more information regarding how baseline measurements compared with measurements taken during the trial period.[5]

ERG comment:

- The ERG neither accepts that the appeal to another *appraisal (*cannabidiol in Dravet syndrome and Lennox–Gastaut syndrome) can be used as a rationale for adding this additional outcome, nor that doing so represents inconsistency. All appraisals need to be conducted independently, and more relevantly, for the charge of inconsistency to be validated, the different appraisals would have to be rigorously and completely compared to establish that they are the same in all relevant respects.
- The ERG does not understand the rationale for choosing S/CGIC measure of QoL instead of the QOLCE/QOLIE-31-P questionnaires. Despite alleged problems with the QOLCE/QOLIE-31-P questionnaires, it is not clear to the ERG that the company's choice of the S/CGIC measure represents a net benefit, not least because, as the company acknowledges the latter cannot be used to derive utilities.

2.5 Other relevant factors

Epidyolex® is a purified, plant-derived pharmaceutical medicine of cannabidiol, administered orally solution. It is the first cannabinoid in class, with a novel mechanism of action compared with other AEDs. The European Commission granted to GW Research Ltd, UK, orphan designation (EU/3/17/1959) on 17 January 2018 for cannabidiol for the treatment of tuberous sclerosis. The sponsorship was transferred to GW Pharma (International) B.V., the Netherlands, in April 2019.[9]

According to the company, cannabidiol for TSC is innovative for a number of reasons, especially those listed below.

1. It has a novel mechanism of action.
2. There are currently only a small number of treatments approved for TSC-associated epilepsy, and no drugs that are effective or well-tolerated in the majority of patients.
3. Seizure control in TSC-associated epilepsy remains inadequate: up to two-thirds of patients are refractory to currently available treatments.
4. Current guidelines recommend the use of AEDs developed more than 20 years ago, and up to two-thirds of patients are refractory to currently available treatments, while side-effects of current AED treatments can be severe.
5. First cannabidiol medicine reviewed by European Medicines Agency (EMA) for patients with TSC
6. Additional benefits of cannabidiol that are not captured in the economic analysis

This appraisal does not fulfil the end-of-life criteria as specified by NICE.

According to the company, no equality issues related to the use of cannabidiol for the treatment of patients with seizures caused by TSC.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the CS. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The ERG has presented only the major limitations of each search strategy in the report

Appendix D of the CS detailed the systematic literature review (SLR) undertaken to identify relevant literature relating to efficacy and safety of drug treatments used to treat seizures in TSC. These strategies were also designed to identify papers related to the epidemiology of TSC-related seizures; model parameters relating to the QoL and utility values of patients with TSC and seizures and their caregivers; costs and resource use associated with TSC; and existing economic models in TSC. Therefore, the following critique will also be applicable to Section 4.1.1. The searches were conducted in November 2021. A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Dates searched
Electronic databases			
MEDLINE	via Embase	Not reported	01/11/21
Embase	Proquest	Not reported	01/11/21
Cochrane Library	Wiley	Not reported	01/11/21
Heoro.com	www.heoro.com		01/11/21
NHS EED	CRD	1968-2015/05	01/11/21
HTA			01/11/21
Conferences			
ISPOR	https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	2017-2020	01/11/21
AES	https://www.aesnet.org/annual_meeting/abstract_search		01/11/21
WCN	https://www.jns-journal.com/issue/S0022-510X(17)X0010-5 https://www.jns-journal.com/abstracts2019	2017 & 2019	01/11/21
International epilepsy congress	http://www.epilepsycongress.org/32nd-international-epilepsy-congress/	2017 & 2019	01/11/21
European congress on Epileptology	http://www.epilepsyprague2016.org/abstracts.153.html; http://epilepsyvienna2018.org/	2016 & 2018	01/11/21

Resource	Host/Source	Date Ranges	Dates searched
International TSC Research Conference	http://online.fliphtml5.com/tosk/nrjl/#p=1 http://fliphtml5.com/tosk/dnah/basic/101-120 http://online.fliphtml5.com/tosk/ghir/#p=1	2017-2019	01/11/21
Additional searches			
NICE	https://www.nice.org.uk/		01/11/21
ANSM	https://www.ansm.sante.fr		01/11/21
SMC	https://www.scottishmedicines.org.uk/		01/11/21
PBAC	https://pbac.pbs.gov.au/		01/11/21
CADTH	https://www.cadth.ca		01/11/21
NCPE	http://www.ncpe.ie		01/11/21
AWMSG	http://www.awmsg.org/		01/11/21
AAN	https://www.aan.com/		01/11/21
Clinicaltrials.gov	www.clinicaltrials.gov		21.12.21
ScHARRHUD	http://www.scharrhud.org/		01/11/21
EuroQol	https://euroqol.org/search-for-eq-5d-publications/		01/11/21
Handsearching	Reference checking of existing systematic literature reviews was conducted for the main SLR, to identify additional relevant publications.		

AAN = American Academy of Neurology; AES = American Epilepsy Society; ANSM = Agence Nationale de sécurité du médicament et des produits de santé; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; HTA= Health technology assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCPE = Ireland National Centre for Pharmacoeconomics; NHS EED = National Health Service Economic Evaluation Database; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee, Australia; ScHARRHUD = University of Sheffield Health Utilities Database; SMC = Scottish Medicines Consortium; WCN = World Congress of Neurology

ERG comment:

- The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches.
- Searches covered a broad range of resources, including databases, clinical trials registry, conference proceedings and additional grey literature resources.
- A single set of searches was used to inform all areas of the submission including clinical and cost effectiveness. For Embase and MEDLINE, the strategy was structured as (Tuberous sclerosis AND epilepsy) OR (Tuberous sclerosis AND HRQoL/economic evaluation), all remaining searches looked for the keywords "Tuberous sclerosis".
- The ERG noted that the MEDLINE search strategy appeared to contain Emtree subject headings rather than Medical Subject Heading (MeSH) terms. The CS also stated that the MEDLINE search was conducted via Embase. At clarification, the ERG asked the company to confirm whether this was a search of the Embase database conducted on the understanding that it now contains all records from MEDLINE or a separate search of both resources using the same strategy. The company clarified that *"…we searched Medline via the Embase database, on the understanding that it now contains all records from Medline."*[6] Whilst the ERG accepts this single approach as being

adequate, the ERG considers it preferable to conduct a separate companion MEDLINE search in order to fully utilise the power of database specific study design filters developed to make the most of an individual databases subject headings. However, given the searches of additional bibliographic databases and grey literature resources reported by company, it is unlikely that this omission would have impacted on the overall recall of results.

- Strategies show limited use of synonyms for 'tuberous sclerosis'. However, any loss of recall may have been mitigated by the use of subject headings and the broad range of resources searched.
- Both the MEDLINE and Embase searches included a limit to only those records that contained abstracts. The Ovid search notes for Embase indicate that only about 60% of the documents in Embase contain abstracts.[12] Therefore, a more cautious approach might have been to remove unwanted publication types rather than limiting to abstracts, a limit which may exclude relevant non-English language or e-print papers which do not always carry abstracts. However, given the additional searches reported above this is unlikely to impacted on the overall recall of results.
- An additional search of both the NICE and Scottish Medicines Consortium (SMC) websites was reported in Section B.3.1.1 to identify studies evaluating cannabidiol or cannabis-derived therapies. A further targeted search of prior NICE submissions was undertaken to inform on model structures used in chronic disease areas which involve attacks of varying degrees of severity similar to those observed in TSC-associated epilepsy. The keywords and strategies for these searches were not fully reported therefore the ERG is unable to comment on these additional searches.
- As the main SLR did not identify any relevant HRQoL sources, Appendix H.2. of the CS provided details of an additional search: "*targeted literature review (TLR) with systematic searches was conducted to expand on the SLR and identify HRQL data for patients in the broader fields of epilepsy and refractory epilepsy*."[13] The search was undertaken on the 12 May 2020 and repeated on the 14 February 2022 on MEDLINE In-Process® via the PubMed interface. Whilst no MeSH terms appear to have been included, the strategy contained a good range of keywords for epilepsy and seizure severity plus terms for utilities and appeared appropriate. Additional manual searches of the bibliographies of included studies were also reported.

3.1.2 Inclusion criteria

As stated in Section 3.1.1, the company performed a SLR to identify relevant evidence on the clinical effectiveness (efficacy and safety) of medications used to treat seizures in TSC.

The ERG in its clarification letter asked the company to provide a table summarising the Population, Intervention, Comparator, Outcomes, Study design (PICOS) used as study eligibility criteria in the SLR. As part of the company's response to clarification, they provided a table summarising the SLR inclusion/ exclusion criteria, which has been presented in this report as Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Criterion	Inclusion criteria	Exclusion criteria
Population	• Efficacy and safety: seizures associated with tuberous sclerosis complex (TSC) • Economic and quality of life (QoL) studies: general population with TSC with or without seizures	All topics: exclude studies where the only outcomes of interest relate to non-epilepsy manifestations of TSC
Intervention	Any drug intervention or none	
Comparators	Any or none	

Criterion	Inclusion criteria	Exclusion criteria
Outcomes	Any clinically relevant topics relating to TSC-related seizures, including: • Epidemiology: incidence/prevalence, risk factors, biomarkers, diagnosis, mortality/survival • Efficacy and safety of interventions for seizures • Guidelines and treatment pathways • QoL, utilities, social impact • Economic evaluations • Cost and resource use • Impact on work and productivity, education and learning	Pharmacokinetic/ pharmacodynamic studies with no clinical outcomes
Study methodology	• Randomised controlled trials (RCTs) • Single-arm clinical trials • Retrospective or prospective observational studies including database/registry studies, case-control, cross-sectional studies • Systematic literature reviews of relevant studies to identify additional relevant publications • Narrative reviews on the epidemiology and burden of illness of TSC-associated epilepsy • Study protocols for relevant RCTs	Conference abstracts with a corresponding full-text publication and no additional data were excluded unless they related to efficacy RCTs.
Study size	RCTs: any Other studies: >5 participants	
Language	Epidemiology: English full texts only Other topics: Any	
Publication date	Any	
Adapted from clarification letter response.[6] QoL = quality of life; RCTs = randomised controlled trials; TSC = tuberous sclerosis complex		

ERG comment:

Study selection - The ERG in its clarification letter asked the company to provide more information on the study selection - if this process was conducted independently by multiple reviewers and how consensus was carried out. The company in its response to clarification stated that "*Two researchers independently screened each abstract and any discrepancies were agreed in discussion with the project leader. One researcher and the project leader independently screened each full text publication to confirm that it met the inclusion criteria, with any disagreements resolved by discussion.*"[6]

This response suggests that while initial screening of titles and abstracts was conducted independently by two separate reviewers, the process of consensus in the case of disagreements is less clear. Generally, the optimal method is that a third reviewer is asked to screen with this opinion typically providing a majority one way or the other. It is also a common although less robust method, that the two reviewers reach consensus on any disagreements after discussion and debate. It seems that in this case

discrepancies were agreed in discussion with the project leader. It is uncertain exactly how this occurred. It is unclear 1) if the project leader also performed screening of those articles which were not agreed upon or simply arbitrated after discussion, 2) had a discussion with one or both reviewers, or 3) in the case of both reviewers, whether it was at the same time or separately. While the process of study selection and screening at the title and abstract stage may have been conducted appropriately, there is a lack of detail in the reporting which means we must consider it may be susceptible to bias and error. Full text screening does appear to have been conducted independently by two reviewers (researcher and project leader) with discussion being used to resolve any disagreements.

Inclusion/exclusion criteria - The ERG noted that despite the broadness of the eligibility criteria in Section D.1.2 of Appendix D, no efficacy/safety studies on common AEDs such as valproate, lamotrigine, oxcarbazepine, vigabatrin, levetiracetam, etc., appeared to have been identified in the SLR. Thus, the ERG in its clarification letter asked the company to confirm if restrictions were placed on outcomes on interests, and for the company to clearly outline the PICOs used during the screening stages. The company in its response to clarification[6] stated that *"Abstracts and full texts were excluded if they did not report* [redacted]*. Studies were excluded if they only assessed non-seizure-related manifestations of TSC. No other restrictions were placed during abstract screening".* The company also stated that *"Old conference abstracts with no poster or additional data available were generally excluded for not reporting enough data to be useful, but those with useful data were included unless a corresponding full-text publication was available that reported the same outcome data as the abstract."* This response suggests that no additional restrictions were placed and in fact further reinforces a rather vague and wide-ranging provision which may include multiple particular outcomes. The company in their response to a request to provide details on their PICO had stated that "any clinically relevant topics relating to TSC-related seizures…" (see Table 3.2 above) which included epidemiological, efficacy, safety, and QoL outcomes amongst others were to be included. The ERG continues to note that no efficacy/safety studies on common AEDs were identified, and we do not consider that this response represents a clear enough explanation to account for this.

Relevant studies - The paucity of evidence in the SLR on the efficacy/safety of common AEDs prompted the ERG's Information Specialist to rerun the conditions facets (lines #1 to #3) from the Embase strategy reported in Appendix D, Table 1 of the CS. The strategy was run as closely as possible to the company's strategy using Ovid syntax and the same limits. A facet for anti-epileptics including the named drugs valproate (or valproic acid), vigabatrin, and lamotrigine was added and finally an RCT study design limit was applied (for full details see appendix 1). The screening results were substantial, prompting the ERG in its clarification letter to query if these 41 references identified as potentially relevant during title and abstract screening, were not identified by the company in their SLR searching, and if they were, why they were excluded at title and abstract screening. The company's response[6] detailed that, *"we conducted a full SLR to identify all relevant studies on the efficacy and safety of pharmacological interventions for TSC-associated seizures. However, our submission to NICE focused on those studies that were most relevant to the decision problem of the use of cannabidiol as add-on therapy to usual-care. The studies of standard anti-epileptic drugs were considered to be describing the efficacy and safety of usual-care interventions and so were not reported in the submission. We have included the details of these additional studies in a supplementary document for completeness."* The ERG examined the supplementary document and was satisfied that the company's searches had indeed retrieved these relevant studies. However, from the company's response, it is clear that although the PICOs for 'Comparator' stated 'Any or none' (see Table 3.2), this was not the case. A set of parameters

not disclosed in the clarification response were used to determine which comparators (although within the basket of established clinical practice without cannabidiol) 'were considered to be not directly relevant to the decision problem'. The ERG is not satisfied that multiple relevant publications identified in the company's full SLR were excluded from the SLR results presented in the CS. It is unclear what restrictions were placed on the full SLR screening results to result in the limited evidence presented. This remains a key issue.

In the NICE final scope, VNS is listed as a comparator of interest however in the company's response[6] to the ERG's query on a certain excluded publication on VNS in paediatric patients with TSC, they stated that, *"VNS is not an included intervention so was excluded from the submission."* It remains unclear what interventions in the NICE final scope the company have considered as relevant to this submission.

3.1.3 Critique of data extraction

As the company did not provide any information on the SLR data extraction process, the ERG in its clarification question asked the company to provide more information on how data extraction was conducted. The company in their response to clarification stated that,[6] "*One researcher extracted data from included papers into an Excel template and a second researcher validated the data extraction. Any areas of uncertainty were checked by the project leader during the report synthesis and sign-off process."* The optimal process is that two independent reviewers extract data separately and then when disagreement exists, a third reviewer performs independent data extraction to inform a decision. In this case, it appears that data was extracted by one reviewer, this data was then scrutinised by a second researcher, suggesting that a second data extraction was not completed, but instead the first and only extracted data sheet was checked over. The checking and validation of extracted data is often used but is more prone to error and bias than the process of two independent data extractions. In the case of disagreement between reviewers, which we understand from the following clarification response "*Any areas of uncertainty were checked by the project leader during the report synthesis and sign-off process*."[6] It appears that the project leader arbitrated and made a decision. However, further details would have been welcomed to describe this process. It remains unclear whether a discussion took place with either of the two researchers, whether the project leader performed an independent data extraction, or simply looked at the queried data and then referred to study and made a decision. Clarity and details on these processes would offer further reassurance that risk of bias and error were minimised appropriately.

An additional point to note from the company's response is in the use of the phrase… '*any areas of uncertainty.*'[6] While we understand this to include data disagreements because of data extraction and checking, the wording means it cannot be restricted to this and could potentially include issues where data was not extracted for reasons of complexity or unfamiliarity, with the project leader then making additions or amendments that reflected his experience. In this situation, it would not be possible to determine from this paragraph whether this had been checked and verified by an additional reviewer. The ERG notes that this is speculative, but the minimal description must be considered as we can only comment based on details that are provided. The lack of clarity in this response does not provide sufficient detail and description to convince us that this process has been conducted to appropriate standards.

3.1.4 Quality assessment

The company conducted a critical appraisal of the GWPCARE6 trial in Section D.3 of Appendix D in the CS. As the risk of bias (RoB) tool used was not stated, the ERG asked the company to state the RoB

tool used in the quality assessment of the GWPCARE6 trial, and in addition, provide brief justifications for domain decisions. The ERG also asked the company to provide more information on how the quality assessment process was handled, specifically, how many reviewers were involved at each stage, how consensus was carried out, and if a third reviewer was involved in resolving disagreements. The company in their response to clarification[6] stated that "*The quality assessment of the GWPCARE6 trial and other RCTs was completed using the Cochrane Risk of Bias (ROB2) tool. This was summarised in the submission and the full evaluation reported below, with further justifications for domain decisions for GWPCARE6 added."* The response also confirmed that *"Two researchers independently evaluated the risk of bias of each included study and the assessment was signed off by the project leader."* [6] The ERG notes that again, insufficient detail is provided to reassure us that risk of bias and error has been appropriately minimised. It is not clear how disagreements were resolved although the statement that the assessment was signed off by the project leader would suggest that this is a measure of validation. However, this does not inform as to whether this meant serving as a third reviewer or not. The ERG considers that full detail is not provided in this response and therefore we cannot confirm whether appropriate measures have been taken to minimise bas and risk. The results of the quality assessment for the GWPCARE6 trial have been discussed in Section 3.2.4 of this report.

The ERG assessed the risk of bias of the SLR using the Risk of Bias in Systematic Reviews (ROBIS) tool[14] for assessing bias in systematic reviews and concluded that the restricted SLR presented in the CS was at a high RoB and therefore that its results are not reliable (see Table 3.3).

Table 3.3: Summary of ROBIS risk of bias rating

ROBIS Domain	Risk of bias (low, unclear, high)	Summary of rationale
Overall risk of bias	High	The risk of bias in three of the four domains is high.
1. Study eligibility criteria	High	No pre-published protocol. There were criteria outlined for screening the literature, but these did not define any specific systematic review question. There was therefore freedom to define the details of any desired review question post-hoc, within the fairly wide degrees of freedom defined by the screening criteria.
2. Identification and selection of studies	Unclear	Reference lists of existing systematic reviews were checked for additional relevant publications. No publication date limits were applied. Some report of good practice: used two independent researchers for screening with any discrepancies solved by consensus with a third party.
3. Data collection and study appraisal	High	No information was provided on methodology of extracting or analysing data. No information provided for majority of papers. Only papers dealing with quality of life (QoL) utility data were detailed.
4. Synthesis and findings	High	Studies were excluded based on being non-United Kingdom (UK) studies. Although the screening 'protocol' pre-specified non-UK cost studies for exclusion, some non-UK studies appear to have been excluded that would have had clinical as well as cost results. No efficacy or safety analysis appear to have been carried out, despite four studies being identified as 'efficacy papers' in the

ROBIS Domain	Risk of bias (low, unclear, high)	Summary of rationale
		preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram. In the absence of a clear pre-hoc protocol it is difficult to be sure that decisions on inclusion and exclusion were made prior to knowledge of the data revealed in the sourced papers. For example, note the following paragraph from the systematic literature review (SLR) on page 54 of the appendix document states: "*Of the identified studies which reported on patient utilities, only two were identified as being relevant for review. The other studies in Table 7 were ruled out as they reported insufficient information on the association of HRQL and seizure frequency and therefore could not be used to inform the health states in the cost-effectiveness model" [13]*. This puts study selection at risk of bias (RoB) (selecting papers that are favourable and rejecting those that are not).
HRQL = health-related quality of life; QoL = quality of life; PRISMA = preferred reporting items for systematic reviews and meta-analyses; ROBIS = Risk Of Bias In Systematic Reviews; SLR = systematic literature review; UK = United Kingdom		

3.1.5 Evidence synthesis

The only study included in the SLR was the company's GWPCARE6 trial provided direct evidence for the NICE final scope intervention and comparator - the intervention being cannabidiol oral solution in addition to usual-care and the comparator as usual-care without cannabidiol (i.e., usual-care plus placebo). Therefore, a meta-analysis was not performed.

ERG comment: From the company's response to clarification, it is clear that the results of the full SLR and its secondary publication table were not provided in this submission. Multiple RCTs that could provide relevant comparator data were excluded as being irrelevant to the decision problem using a vague parameter of 'relevance to the submission'. As discussed in Section 3.1.2, the ERG identified multiple RCTs excluded from the SLR presented in this submission on this basis, in its clarification letter[5] to the company, and as the GWPCARE6 trial is placebo-controlled, it is very well likely that an indirect comparison could have been carried out. This remains an issue and the ERG would like to see an indirect treatment comparison (ITC) assessment of relevant studies from the full SLR.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In the abstract/title screening phase of the CS[1] SLR, 5,579 records were excluded and 113 were retained for full text screening. From these 113 papers, 31 articles were identified for inclusion. Of these, five were reports of clinical trials relevant to this section of the ERG report. Of the identified trials, only GWPCARE6 reported on the correct combination of interventions, comparators and population, as shown in Table 3.4. As such GWPCARE6 is the only study of relevance to this appraisal.

Table 3.4: Trials included/excluded

Trial	Paper reference	Treatments	Inclusion
GWPCARE6	Thiele E, Bebin M, Bhathal H, et al. Cannabidiol (CBD) Treatment in Patients with Seizures Associated with Tuberous Sclerosis Complex: A Randomized, Double-blind, Placebo-Controlled Phase 3 Trial (GWPCARE6). *Am Epilepsy Soc*. Published online 2019	Cannabidiol and usual care versus placebo and usual care	Yes
BATSCH trial	Van Andel DM, Sprengers JJ, Oranje B, Scheepers FE, Jansen FE, Bruining H. Effects of bumetanide on neurodevelopmental impairments in patients with tuberous sclerosis complex: An open-label pilot study. Mol Autism. 2020;11(1). doi:10.1186/s13229-020-00335-4	Bumetadine (single arm study)	No
GWPCARE6	Thiele, E.A., et al. (2021). "Long-term safety and efficacy of add-on Cannabidiol (CBD) for treatment of seizures associated with tuberous sclerosis complex (TSC) in an open-label extension (OLE) trial (GWPCARE6)." Developmental medicine and child neurology 63(SUPPL 1): 69-.	Cannabidiol and usual care versus placebo and usual care	Yes
GWPCARE6	O'Callaghan, F.J., et al. (2021). "Efficacy of add-on cannabidiol (CBD) treatment in patients with Tuberous Sclerosis Complex (TSC) and a history of Infantile Spasms: post hoc analysis of Phase 3 Trial GWPCARE6." Developmental medicine and child neurology 63(SUPPL 1): 71-.	Cannabidiol and usual care versus placebo and usual care	Yes
GWPCARE6	Saneto, R., et al. (2021). "Efficacy of add-on cannabidiol (CBD) Treatment in patients with tuberous sclerosis complex (TSC) and a history of infantile spasms (IS): post hoc analysis of phase 3 Trial GWPCARE6." Neurology 96(15 SUPPL 1).	Cannabidiol and usual care versus placebo and usual care	Yes

3.2.1 Details of the included trial: the GWPCARE6 trial

The CS[1] identified the GWPCARE6 trial as the only RCT evaluating cannabidiol and established clinical management against placebo and established clinical management. GWPCARE6 was a blinded, randomised phase III study. Primary sources are the CSR[7] and the published RCT by Thiele et al. (2020).[15] Eligible patients entered the trial at the screening visit (Day -35) and began a 7-day screening period. Patients who successfully completed this then began a 28-day baseline period on Day 28. Patients who satisfied all eligibility criteria were then randomised on Day 1 to four treatment groups (cannabidiol 25 mg/kg/day, cannabidiol 50 mg/kg/day, placebo 25 mg/kg/day dose-volume equivalent, or placebo 50 mg/kg/day dose-volume equivalent) at a 2:2:1:1 ratio. The placebo groups (placebo 25 mg/kg/day dose-volume equivalent, or placebo 50 mg/kg/day dose-volume equivalent) were pooled for the analyses of efficacy.

All trial medication was taken in addition to usual-care: 75 patients were randomised to 25 mg/kg/day cannabidiol plus usual-care, 73 patients to 50 mg/kg/day cannabidiol plus usual-care and 76 patients to placebo plus usual-care. For safety reasons, Marketing Authorisation has been granted in TSC-associated seizures for cannabidiol doses up to 25 mg/kg/day only, and so the CS[1] only provides data for 25mg/kg/day cannabidiol. Because the placebo 25 mg/kg/day and 50 mg/kg/day data were pooled

the trial is left with two arms in terms of outcome data. Table 3.5 summarises the clinical effectiveness evidence of the trial.

Table 3.5: Clinical effectiveness evidence

Study	**GWPCARE6/GWEP1521/NCT02544763[15 7]**
Study design	Phase III double-blind, randomised, placebo-controlled, multicentre, multinational study
Population	Children and adults aged 1 to 65 years* with a clinical diagnosis of tuberous sclerosis complex (TSC) and a well-documented clinical history of epilepsy not completely controlled by their current anti-epileptic drugs (AEDs). Taking one or more AEDs at a dose that had been stable for at least 1 month. At least eight TSC-associated seizures in the initial 28-day baseline period, with at least one seizure in at least three of the 4 weeks. All medications or interventions for epilepsy (including a ketogenic diet and vagus nerve stimulation (VNS), which were not counted as AEDs) stable for 4 weeks before screening.
Eligibility criteria for participants	Patients aged 1 year to 65 years with a well-documented history of epilepsy, and a clinical diagnosis of TSC according to the criteria agreed by the 2012 International TSC Consensus Conference. Taking one or more AEDs at a dose that had been stable for at least 4 weeks before screening. All medications or interventions for epilepsy (including a ketogenic diet and any neurostimulation devices for epilepsy) stable for 1 month before screening and the patient willing to maintain a stable regimen throughout the trial. Patients had experienced at least eight seizures during the first 28 days of the baseline period, with at least one seizure occurring in at least three of the 4 weeks. Patients were excluded if they had a history of pseudo-seizures, any clinically unstable medical conditions other than epilepsy, had an illness in the 4 weeks before randomization that could affect seizure frequency, had undergone general anaesthetic in the 4 weeks before screening or randomisation, had had epilepsy surgery in the 6 months before screening, were being considered for epilepsy surgery, had been taking felbamate for less than 1 year before screening, were taking an oral mammalian target of rapamycin (mTOR) inhibitor, had any known or suspected hypersensitivity to cannabinoids or excipients in the oral solution, had any history of suicidal behaviour or suicidal ideation in the month before or at screening, had used recreational cannabis in the 3 months before screening and were unwilling to abstain for the study duration, had a tumour growth that could affect the primary endpoint, had significantly impaired hepatic function, or had received an investigational medicinal product (IMP) within 12 weeks before the screening visit.
Intervention(s)	Cannabidiol 25 mg/kg/day in addition to usual care (n=75) Cannabidiol (and placebo) are oral solutions, administered orally by the patient or their caregiver twice each day. Patients titrated up to the required dose (or equivalent volume of placebo) over 4 weeks as per randomisation. Patients then remained at this maintenance dose for 12 weeks. Dose escalation for each patient was subject to the investigator's assessment of safety and tolerability. If a dose became poorly tolerated, the investigator could consider temporarily or permanently reducing the dose for the remainder of the study. Patients were on treatment for a total of 16 weeks. Patients not entering the OLE or who withdrew early down titrated over a period of 10 days.

Study	GWPCARE6/GWEP1521/NCT02544763[15] [7]
Comparator(s)	Placebo in addition to usual care (n=76)
Permitted and disallowed concomitant medication	Other AEDs and/or interventions for epilepsy (including a ketogenic diet and any neurostimulation devices for epilepsy) permitted but had to be stable for 1 month before screening and the patient willing to maintain a stable regimen throughout the trial. Excluded if other use of cannabis in past 3 months, or current use of felbamate for <1 year, or currently taking an oral mTOR inhibitor.
Reported outcomes specified in the decision problem **Note: the Decision Problem specified that the outcome measures to be considered include:** **Change in frequency of seizures** **Response to treatment** **Adverse effects of treatment** **Health-related quality of life**	Percent change in the number of TSC-associated seizures during the treatment period (16 weeks, comprising 4 weeks dose titration and 12 weeks dose maintenance) compared to baseline. Number of patients considered treatment responders during the treatment period, defined as those with a ≥50% reduction in TSC-associated seizure frequency. Change in number of TSC-associated seizure-free days. Number of participants with treatment-related adverse events (AEs). Serious treatment-emergent AEs (TEAEs) classified as severe and considered to be treatment-related. Change from baseline in Subject/Caregiver Global Impression of Change (S/CGIC) score at the participant's last visit. Changes in Quality of Life in Childhood Epilepsy (QOLCE) or Quality of Life in Epilepsy (QOLIE)-31-P score.
Other details	The GWPCARE6 trial included patients with TSC-associated epilepsy treated at 46 sites in six countries (United Kingdom (UK), Australia, Netherlands, Poland, Spain, and the United States of America (USA)). Patients titrated to 25 mg/kg/day or 50 mg/kg/day (or equivalent volume of placebo) over 9 or 29 days, respectively, and remained at this dose for the 12-week maintenance period. An interactive voice-response system was used daily to record information on seizures. A paper diary was used daily to record information on investigational medicinal product (IMP) usage, rescue medication, concomitant AEDs, and AEs. Following Day 1, further clinic visits took place on Days 15, 29, 43, 57, and 85. Additional safety telephone calls took place every 2 days during titration and on Day 71. Patients returned to the clinic for an end of treatment visit after 16 weeks of treatment (Day 113) or earlier if they discontinued IMP. Following end of treatment, patients who completed the trial were invited to continue in an open-label extension (OLE) trial under the same protocol. Patients who did not enter the OLE tapered IMP, with an end of taper period visit at Day 123. For patients who did not enter the OLE trial or who discontinued, this was followed by a safety follow-up visit or telephone call 28 days later.
Based on Tables 3 and 4 in CS document B[1] ; primary sources: Thiele et al. (2020),[15] CSR.[7] Note: *The approved indication for Epidyolex is in patients aged ≥ 2 years. *The GWPCARE6 trial included cannabidiol at doses of 25 mg/kg/day and 50 mg/kg/day. Both doses of cannabidiol reduced seizures associated with TSC. However, due to its more favourable risk-benefit profile (similar efficacy at both doses, but an increased rate of adverse reactions at the higher dose), only the 25	

Study	GWPCARE6/GWEP1521/NCT02544763[15 7]
mg/kg/day cannabidiol dose is approved for use in the Marketing Authorisation. For this reason, the data for the 50 mg/kg/day cannabidiol dose are not discussed in detail below. AED = anti-epileptic drug; AEs = adverse events; CS = company submission; CSR = clinical study report; IMP = investigational medicinal product; mTOR = mammalian target of rapamycin; OLE = open-label extension; QOLCE = Quality of Life in Childhood Epilepsy; QOLIE = Quality of Life in Epilepsy; TEAE = treatment-emergent adverse event; TSC = tuberous sclerosis complex; S/CGIC = Subject/Caregiver Global Impression of Change; UK = United Kingdom; USA = United States of America; VNS = vagus nerve stimulation	

In their request for clarification,[5] the ERG asked the company to discuss the generalisability of the study population to the target population (the England NHS setting). In their reply,[5] the company provided data for five of the seven UK based patients that were randomised in the GWPCARE6 trial (see Table 3.6). The company did not provide data for the two patients who received a 50 mg/kg/day dose. Also, in their response to clarification, the company noted that an health technology assessment (HTA) advisory board meeting,[16] as well as two clinical experts supported the generalisability of the results of the GWPCARE6 trial to the England NHS setting.[6]

ERG comment:

- The ERG is unclear regarding whether the GWPCARE6 population and the population expected in the England NHS setting are sufficiently similar to warrant generalisability. While the company provides data for five of the seven UK-based patients (see Table 3.6 below, they neither compare the characteristics of these patients to typical patients that might be expected in the England NHS setting, nor to the average patients in the GWPCARE6 trial itself.
- The ERG is not clear why the characteristics of the two UK-based patients who received a 50 mg/kg/day dose were not included.
- The ERG acknowledges the advisory board meeting which stated that two clinical experts had no concerns regarding the generalisability of the trial to clinical practice (in the UK). The ERG also notes that in the same document, a number of issues regarding generalisability were noted. These include (but are not limited to) the higher proportion of children than adults, and the difference in placebo response rates. In addition, the report noted the need to explore generalisability in a number of ways, described in the quotes from the report below:
    - to "*assess generalizability of vigabatrin use and the age of patients receiving this treatment. The assessment should include the line of treatment at which patients received vigabatrin*."[16]
    - "*to assess generalizability of vigabatrin use and the age of patients receiving this treatment. The assessment should include the line of treatment at which patients received vigabatrin*." [16]
- The ERG acknowledges the views of the two clinical experts contacted by the company regarding the generalisability of the GWPCARE6 trial. The ERG notes the value of independent experts to inform this issue.

Table 3.6: Characteristics of UK patients within the GWPCARE study

Patient	UK 1	UK 2	UK 3	UK 4	UK 5
Study arm	25 mg	25 mg	Placebo	Placebo	Placebo
Age (years)	16.16	29.87	8.79	3.02	18.18
Sex	F	F	M	M	F
Race	W/C	W/C	W/C	W/C	W/C

Patient	UK 1	UK 2	UK 3	UK 4	UK 5
Weight (kg)	56.0	59.1	22.6	14.7	90.7
Previous AEDs (n)	9	2	3	5	3
Current AEDs (n)	3	4	3	2	1
Taking clobazam?	No	Yes	No	No	No
Taking valproic acid?	Yes	No	No	No	No
Taking vigabatrin?	No	No	Yes	Yes	No
Taking levetiracetam?	No	Yes	Yes	No	No
Based on Clarification Response Table 1[6] AEDs = anti-epileptic drugs; F = female; M = male; W/C = White/Caucasian; UK = United Kingdom					

This constitutes a very small proportion of patients from the study (3.3%). Comparison of the baseline data with that of the overall cohort is difficult because of the small sample size from the UK sub-set, prohibiting any estimation of representativeness.

3.2.2 Statistical analyses of the GWPCARE6 trial

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in Table 3.7.

Table 3.7: Statistical methodology used

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
GWPCARE6	Primary null hypothesis: following 16 weeks of treatment there is no difference in effect between the 25 mg/kg/day cannabidiol treatment group and the placebo treatment group in terms of the change in number of tuberous sclerosis complex (TSC)-associated seizures during the treatment period compared to baseline.	Primary analyses used the intention-to-treat (ITT) analysis set. Only the primary and key secondary endpoints were analysed using the per protocol analysis set. Statistical hypothesis testing of the primary endpoint and key secondary endpoints for each dose was conducted hierarchically. The primary endpoint was analysed using a negative binomial regression model with the total	A total of 210 patients were planned for randomisation across four treatment groups (stratified by age group). It was assumed that patients in the placebo group would experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving cannabidiol would experience at least a 50% reduction in seizures and a common standard deviation (SD) of 60%, and therefore this sample size of 70 patients per	If a patient withdrew during the treatment period, then the primary analysis variable was calculated from all the available data, during the treatment period, including any data available after the patient withdrew.

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		number of TSC-associated seizures across the baseline period and treatment period as the response variable (a fixed effect for time was used to differentiate between the baseline and treatment periods).	group would be sufficient to detect a difference in response distributions with 90% power. This test was based on a two-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.	
Based on Table 6, in CS document B[1] ITT = intention to treat; SD = standard deviation; TSC = tuberous sclerosis complex				

ERG comment: The CS states that secondary endpoints were analysed using the per protocol analysis set. This indicated it was possible that that an intention-to-treat (ITT) analysis was not conducted for the key secondary endpoints. In response to our clarification question, asking if any of the outcomes were not ITT, the company replied that: "*We apologise if this caused confusion. In the Statistical Analysis section of Document B, the sentence reads "Primary analyses used the ITT analysis set. Only the primary and key secondary endpoints were analysed using the per protocol analysis set." The ITT analysis set was the primary analysis set for all efficacy endpoints".* The ERG takes this to mean that all of the efficacy outcomes presented in the trial use an ITT analysis.

It was unclear in the CS whether the trial was powered to show the superiority of cannabidiol to usual care as an add-on. However, the company clarified that the trial was powered the show the superiority of cannabidiol to usual care as an add-on.

3.2.3 Baseline characteristics of the GWPCARE6 trial

A total of 151 participants were allocated randomly to the two arms (see Section 3.2.1). A summary of the baseline characteristics of patients is presented in Table 3.8.

Table 3.8: Baseline characteristics of treatment groups in GWPCARE6

Characteristic	Placebo + usual care	CBD 25mg/kg/day + usual care
n	76	75
Median age, year (minimum, maximum)	11 (1, 56)	12 (1, 57)
Age group, n (%)		
1-6 years	22 (29)	21 (28)
7-11 years	18 (24)	18 (24)
12-17 years	16 (21)	16 (21)
18-65 years	20 (26)	20 (27)

Characteristic	Placebo + usual care	CBD 25mg/kg/day + usual care
Sex, n (%)		
Male	45 (59)	43 (57)
Race, n (%)*		
White/Caucasian	66 (88)	68 (91)
Number of AEDs, 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)
Baseline seizures per 28 days, median (Q1, Q3)		
Primary endpoint (TSC-associated seizures)	54 (26, 102)	56 (21, 101)

Based on Table 6, in CS document B[1]
AED, anti-epileptic drug; CBD, cannabidiol; CS = company submission; TSC, tuberous sclerosis complex

ERG comment: Comparability for most baseline variables is good, but there are almost 1.7 times as many people on vigabatrin in the cannabidiol group than the placebo group. This discrepancy could influence outcomes, although the direction of effect of any bias is unclear. Possibly more importantly, this anomaly raises an issue around the quality of randomisation. The probability of such a discrepancy arising by chance is very small (p=0.0024, using binomial analysis) which means that a discrepancy this extreme or more extreme would only be expected once in every 400 or so baseline variables. Given the relatively small number of baseline variables presented in this trial (approximately 10), the probability of such a result occurring by chance to any baseline variable presented in the trial is still probably smaller than one in 40. There may therefore be other more likely causes of this effect, the most likely of these being flawed randomisation. This feeds into our comments around the need for more details concerning allocation concealment procedures in the next Section.

This issue has been addressed in the clarification letter, where the company were asked to comment on the discrepancy between groups in vigabatrin use, and to explain how the potential threat to internal validity is accounted for in the analysis. The company responded by stating that: "*The company does not consider that there is a threat to internal validity. As stated in our submission, vigabatrin is recommended as first-line monotherapy for TSC-associated infantile spasms and/or focal seizures in children <1 year old. Vigabatrin is associated with irreversible visual field defects, including blindness in severe cases, and is therefore not suitable for all patients. As explained in question A9, refractory patients with TSC-associated epilepsy may cycle through many AEDs in an attempt to achieve seizure control. The majority of patients with refractory TSC-associated epilepsy in the GWPCARE6 trial had already tried and failed vigabatrin i.e., the drug did not lead to seizure control. The GWPCARE6 trial population had failed to achieve seizure control with a median of 4 AEDs prior to entering the study. Vigabatrin was among the most common of these AEDs, having already been tried and stopped by 43% of patients prior to entering the study. In addition, a further 33% of patients were taking vigabatrin on*

entering the study, meaning that, by definition, it was not working as they were not achieving adequate seizure control. Therefore, in total, >75% of the GWPCARE6 trial population had already failed to achieve seizure control with vigabatrin. The results of a pre-specified subgroup analysis show no effect on the primary endpoint whether the patient was taking or not taking vigabatrin (see figure [3.1] below)."[6]

Figure 3.1: Subgroup analysis of the primary endpoint

Subgroup	Interaction P-value	GWP42003-P (N)	Placebo (N)	Favors Placebo / Favors GWP42003-P	Ratio (95% CI)
Overall		75	76		0.699 (0.567, 0.861)
Age Group					
1–6 Years	0.9287	21	22		0.698 (0.472, 1.032)
7–11 Years		18	18		0.776 (0.504, 1.192)
12–17 Years		16	16		0.626 (0.394, 0.995)
18–65 Years		20	20		0.686 (0.453, 1.039)
Sex					
Female	0.4653	32	31		0.768 (0.554, 1.063)
Male		43	45		0.655 (0.498, 0.863)
Region					
USA	0.0813	36	42		0.583 (0.435, 0.781)
Rest of the World		39	34		0.846 (0.627, 1.141)
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)
Baseline TSC-associated Seizure Frequency					
≤ 36		29	29		0.800 (0.562, 1.137)

Based on Figure 1 from clarification response[6]

The ERG response to this is that regardless of how many AEDs patients had, the fact remains that there was a discrepancy between groups at the time of the trial in terms of the drug that was being used. This effect was beyond what would be expected by chance, thus invoking fears of flawed randomisation, and adverse effects on internal validity.

There are also concerns around external validity. It is unclear whether the baseline characteristics are representative of the UK population with this condition. The company was also asked to discuss the related question of the generalisability of the study baseline characteristics to the general UK population (with supporting documents). The company considered that "*the GWPCARE6 study baseline characteristics are generalisable to the general UK population*"[6] on the basis that:

- "*UK specialist clinicians agree that the participants with TSC-associated epilepsy in the GWPCARE6 trial broadly reflect the characteristics of people seen in their clinical practice in the UK National Health Service (NHS). This was noted in an HTA advisory board meeting and also confirmed in recent discussions (conducted to inform our responses to the ERG) with two UK clinical experts - consultant neurologists Professor Finbar O'Callaghan and Dr Sam Amin.*
- *The GWPCARE6 trial included UK patients.*
- *The diagnostic criteria for TSC-associated epilepsy in the trial were based on international guidelines, which are applicable to UK patients.*"[6]

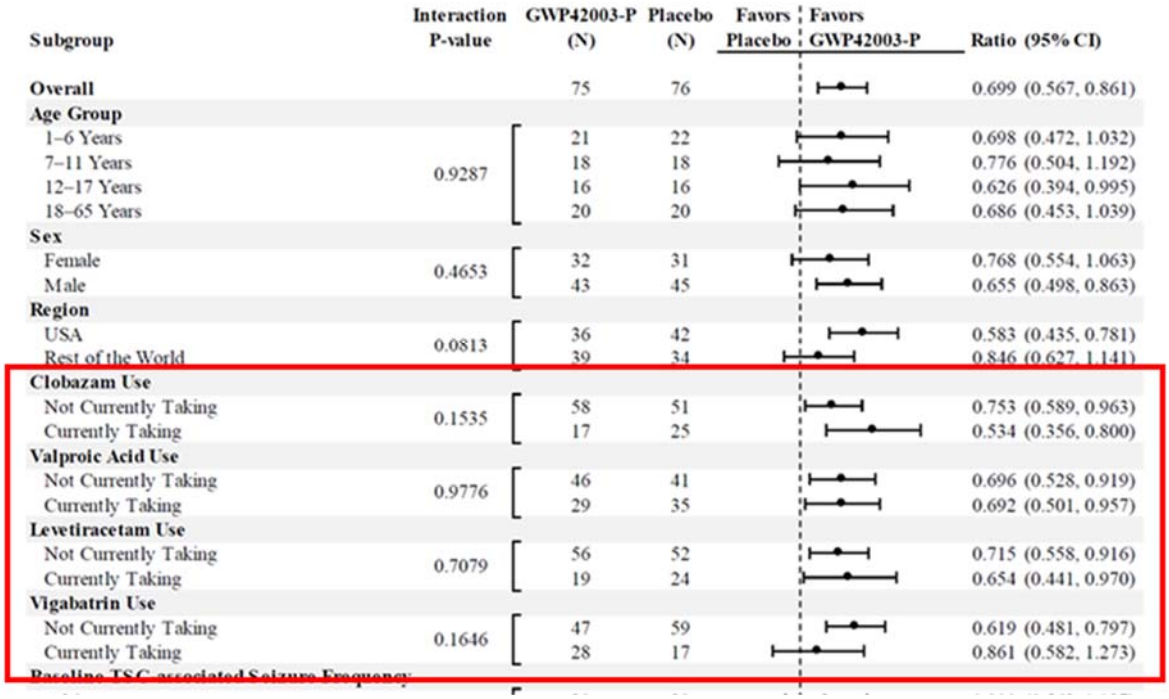
In terms of the first reason, we would prefer to have more objective documentary evidence of generalisability (as we had requested), such as that gained from published data. Without such evidence it is difficult to be confident that the evidence is indeed representative. We would also challenge the latter two reasons. Firstly, as stated, the proportion of UK patients was very small, and so they cannot confer UK representativeness upon the overall cohort. However, even if the trial had contained a majority of participants from the UK, it does not necessarily follow that the participants in the trial would have been similar to the UK population of patients with this condition anyway, as trial populations often differ from background patient populations within the same geographical region. Secondly, diagnostic criteria for a trial define people with the condition, but it is quite possible for a trial to have a sub-set of people with those same diagnostic criteria who also have other characteristics that are *not* representative of the general population of people with the condition. The ERG is therefore not satisfied that the question has been clarified.

Also, in relation to external validity, the ERG has requested sub-group analyses based on GWPCARE6 patients' prior and concomitant seizure interventions; and based on the presence and absence of drug-resistant TSC-associated epilepsy.

In relation to prior and concomitant seizure interventions the company response was: "*As outlined in questions A3.b and A9 above, in the GWPCARE6 trial of cannabidiol, patients entering the trial were permitted to be taking any AEDs/other treatments (except those listed as exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/combinations of treatments are what are referred to as 'usual-care' in our submission. Cannabidiol was an add-on to usual care.*

Refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control. As a result, 'usual-care' comprises many different AEDs/combinations of AEDs - there is no standard of care once a patient is refractory. This was seen in the GWPCARE6 trial population. Patients entering the GWPCARE6 trial had already failed to achieve seizure control with a median of 4 (and up to 15) AEDs prior to entering the study and were currently taking a median of 3 (and up to 5) AEDs. As discussed during the ERG clarification meeting, and as shown in Figure [1.1] above, the range of different drugs being taken, and thus the number of potential combinations, is huge. The pre-specified subgroup analysis (see Figure [3.2] below) provided here demonstrates that the main concomitant AEDs in the GWPCARE6 study (clobazam, valproic acid, levetiracetam and vigabatrin) have no impact on the efficacy of cannabidiol. This was similar for LGS and DS, and is why NICE decided for LGS and DS that the only relevant comparator was 'current clinical management' or 'usual-care.'"[6]

Figure 3.2: Subgroup analysis of the primary endpoint



Based on Figure 3 from responses to clarification questions [6]

The safety and tolerability profile of cannabidiol is consistent, well-defined and manageable, as demonstrated across five randomised controlled Phase III trials in severe refractory epilepsies, (including TSC-associated epilepsy, Dravet syndrome and Lennox-Gastaut syndrome), where patients had tried and failed various AEDs, or were taking numerous combinations of concomitant AEDs.

In GWPCARE6, most adverse events were mild to moderate, transient and resolved by the end of the trial. The safety profile of cannabidiol observed in the GWPCARE6 study was consistent with findings from previous studies, with no new safety risks identified."[6]

In relation to the presence and absence of drug-resistant TSC-associated epilepsy the company response was: "*All patients entering the trial had TSC-associated epilepsy that was not responding to their prior or current AEDs. One of the GWPCARE6 trial inclusion criteria was as follows: "Experienced at least eight seizures during the first 28 days of the baseline period with at least one seizure occurring in at least three of the four weeks."*[6]

3.2.4 Risk of bias assessment of the GWPCARE6 trial

A quality assessment of the GWPCARE6 trial was reported as low RoB in the CS.[1] The appendix reported the separate ratings for each criterion of RoB (see Table 3.9).

Table 3.9: Quality assessment for the GWPCARE6 trial[17]

Domain	Response
Randomisation appropriate?	Yes
Treatment concealment adequate?	Yes
Baseline comparability adequate?	Yes
Researcher blinding adequate?	Yes
Dropout imbalances?	No

Domain	Response
Outcome reporting selective?	No
Intention to treat?	Yes
Overall risk of bias?	**Low**

Based on Table 2 of document B of CS[1]
CS = company submission

ERG comment: Neither the CS document B[1] nor appendices appear to provide a rationale for the decisions made on the RoB rating, nor do they state the rating scale used. Furthermore, after review of the primary sources the ERG does not agree with the quality assessment in terms of the randomisation process. The allocation concealment process is very briefly reported and although the study protocol reports that the randomization schedule will be held centrally and not divulged to any other person involved in the study until the database has been locked and unblinding authorised by the relevant GW personnel, insufficient information is given to be certain that those recruiting participants were unaware of the allocation sequence. The company has been asked to clarify the rational for RoB decisions, and the response to the clarification letter was to confirm that the rating made by the company for 'allocation concealment being concealed until participants were enrolled and assigned to interventions' was 'probably yes'. This underlines the uncertainty of the company with the completeness of allocation concealment.

In terms of deviations from intended interventions, there are some uncertainties about the usual-care treatments used, as originally described in the CS. The company clarified in their response to the clarification letter that "*the usual-care interventions were not protocol-specified. Patients entering the GWPCARE6 trial were permitted to be taking any AEDs/other treatments (except those in the exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/combinations of treatments are what are referred to as 'usual-care' throughout our submission. Refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control. As a result, 'usual-care' comprises many different AEDs/combinations of AEDs - demonstrating that there is no standard of care once a patient is refractory… The patient's 'usual-care' was at the discretion of the clinician*".

The patients who did not receive usual care received other treatments, which were unclearly reported, further details of which were sought in the clarification letter. The company provided a table to summarise any non-usual care concomitant treatments (see Table 3.10).

Table 3.10: concomitant AEDs

Table 8.2-6 Concomitant Antiepileptic Medications (Excluding Rescue Medications) (Safety Analysis Set)				
Therapeutic Class Preferred Term	25 mg/kg/day GWP42003-P (N=75) n (%)	50 mg/kg/day GWP42003-P (N=73) n (%)	Pooled Placebo (N=76) n (%)	Total (N=224) n (%)
Patients taking any concomitant medications	**74 (98.7)[a]**	**73 (100)**	**76 (100)**	**223 (99.6)**
Barbiturates and derivatives	**3 (4.0)**	**3 (4.1)**	**2 (2.6)**	**8 (3.6)**
Phenobarbital	2 (2.7)	3 (4.1)	1 (1.3)	6 (2.7)
Primidone	1 (1.3)	0	1 (1.3)	2 (0.9)
Benzodiazepine derivatives	**25 (33.3)**	**30 (41.1)**	**32 (42.1)**	**87 (38.8)**
Clobazam	17 (22.7)	19 (26.0)	25 (32.9)	61 (27.2)
Clonazepam	6 (8.0)	9 (12.3)	4 (5.3)	19 (8.5)
Lorazepam	2 (2.7)	1 (1.4)	2 (2.6)	5 (2.2)
Midazolam	1 (1.3%)	0	1 (1.3%)	2 (0.9)
Clorazepate dipotassium	0	1 (1.4)	0	1 (0.4)
Nitrazepam	0	1 (1.4)	0	1 (0.4)
Carboxamide derivatives	**30 (40.0)**	**22 (30.1)**	**24 (31.6)**	**76 (33.9)**
Oxcarbazepine	13 (17.3)	12 (16.4)	10 (13.2)	35 (15.6)
Carbamazepine	11 (14.7)	9 (12.3)	6 (7.9)	26 (11.6)
Rufinamide	7 (9.3)	1 (1.4)	8 (10.5)	16 (7.1)
Eslicarbazepine acetate	2 (2.7)	0	1 (1.3)	3 (1.3)
Fatty acid derivatives	**42 (56.0)**	**50 (68.5)**	**46 (60.5)**	**138 (61.6)**
Valproic acid	29 (38.7)	36 (49.3)	35 (46.1)	100 (44.6)
Vigabatrin	28 (37.3)	29 (39.7)	17 (22.4)	74 (33.0)
Tiagabine hydrochloride	0	0	1 (1.3)	1 (0.4)
Hydantoin derivatives	**0**	**0**	**3 (3.9)**	**3 (1.3)**
Phenytoin	0	0	3 (3.9)	3 (1.3)
Other antiepileptics	**56 (74.7)**	**55 (75.3)**	**58 (76.3)**	**169 (75.4)**
Levetiracetam	19 (25.3)	22 (30.1)	24 (31.6)	65 (29.0)
Lamotrigine	17 (22.7)	15 (20.5)	18 (23.7)	50 (22.3)
Lacosamide	16 (21.3)	15 (20.5)	12 (15.8)	43 (19.2)
Topiramate	7 (9.3)	14 (19.2)	12 (15.8)	33 (14.7)
Zonisamide	9 (12.0)	2 (2.7)	7 (9.2)	18 (8.0)
Felbamate	6 (8.0)	3 (4.1)	4 (5.3)	13 (5.8)
Perampanel	4 (5.3)	5 (6.8)	1 (1.3)	10 (4.5)
Gabapentin	1 (1.3)	2 (2.7)	1 (1.3)	4 (1.8)
Pregabalin	0	2 (2.7)	1 (1.3)	3 (1.3)
Brivaracetam	0	1 (1.4)	1 (1.3)	2 (0.9)
Selective immunosuppressants	**1 (1.3)**	**0**	**1 (1.3)**	**2 (0.9)**
Everolimus[b]	1 (1.3)	0	0	1 (0.4)
Sirolimus[c]	0	0	1 (1.3)	1 (0.4)
Succinimide derivatives	**1 (1.3)**	**0**	**0**	**1 (0.4)**
Ethosuximide	1 (1.3)	0	0	1 (0.4)

Source: Table 3 from response to clarification questions[6]

Threat to internal validity: The ERG appreciates that both arms will receive usual care and non-usual care treatments and is aware of the argument that in a trial that is properly blinded to both clinical personnel and patients it shouldn't matter if patients are given additional treatments that vary in effectiveness. However, assumptions of perfect blinding are rarely tenable, and more importantly there appear to be differences in other concomitant usual care treatments between groups (table 3.9 above). These between-group differences alone are likely to have confounded the study.

Threat to external validity: An additional concern is that the usual care treatments used in the trial may have been so different to those used in UK practice that external validity may be reduced, regardless of any issues around internal validity. Independently of whether there are differences in the usual care and concomitant medications given to both groups (and even if the usual care/concomitant medications are distributed equally between groups), unless the usual care given in the trial is shown to be similar to what it would be in the England NHS clinical setting, the results of the trial may not be externally valid. Consider the following. If the usual care (in both groups) is so effective that it results in a complete response, there is no room for drug-induced improvement. And, contrariwise, if the usual care is very ineffective (relative to the England NHS setting), there is more room for drug induced improvement than there will be in actual practice.

The revised ERG quality assessment, using the Cochrane Risk of Bias-2 tool)[18], is presented in Table 3.11 for all three completed outcomes.

Table 3.11: ERG revised quality assessment of GWPCARE6 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome		
	RFS	HRQoL	AE
Randomisation process	Unclear	Unclear	Unclear
Deviations from the intended interventions	Unclear	Unclear	Unclear
Missing outcome data	Low	Low	Low
Measurement of the outcome	Low	Low	Low
Selection of the reported result	Low	Low	Low
Overall risk of bias	Unclear	Unclear	Unclear

AE = adverse event; HRQoL = health-related quality of life; RFS = relapse free survival

3.2.5 Efficacy results of the GWPCARE6 trial

The final NICE scope lists the following outcomes that need to be covered:

- Change in frequency of seizures
- Response to treatment
- HRQoL
- AEs of treatment

All were covered according to the CS.[1] In addition, the CS covered an additional outcome, 'seizure-free days', on the grounds that it is 'an important outcome'.

ERG comment: The ERG was concerned about including 'seizure-free days' in the ERG report because of the risk of double-counting with the primary outcome variable, 'change in frequency of seizures'. The company was therefore asked to provide evidence that seizure-free days is correlated with seizures. In its response, the company stated that "*Seizure-free days is … a clinically important outcome for patients and caregivers and a crucial element when considering the impact and efficacy of cannabidiol in patients with TSC-associated epilepsy. In the GWPCARE6 trial, patients taking cannabidiol (25 mg/kg/day) experienced an additional 2.8 seizure-free days per month vs the placebo group (p=0.0047). The previous models accepted by NICE for cannabidiol in DS and LGS included seizure-free days as an important aspect of quality of life. Auvin et al. reinforce the importance of seizure-free days as a specific outcome, concluding that, whilst fewer seizures and additional seizure-free days both improved quality of life in caregivers and patients, seizure-free days had the greatest impact on patient quality of life. As detailed in Document B, improvements in quality of life and patient wellbeing are linked to both*

the number of seizures experienced, as well as how these seizures are distributed over time. A period of seizure-free time (whether several hours in a day, or seizure-free days) has the potential to improve quality of life for patients and their families.

Additionally, feedback from clinicians and patient organisations also highlights the importance of seizure-free days:

- *Clinical experts at an advisory board meeting highlighted that seizure-free days matter more in terms of quality of life than a change in seizure frequency.*[16]
- *"Whilst reductions in convulsive seizures and drop seizures are of most medical benefit, other changes in seizure activity, including altering patterns of seizures leading to increased seizure-free days, should be viewed as clinically/statistically significant." - Epilepsy Action, comment on HTA for cannabidiol in DS and LGS.* [19, 20]

Therefore, it is clinically important to include seizure-free days as an outcome in the analysis.

We would expect to see a moderate negative correlation between seizure frequency and seizure-free days, i.e., a reduction in seizure frequency might lead to an increase in seizure-free days. However, although seizure frequency and seizure-free days may be moderately correlated, it is possible to experience a reduction in seizure frequency without a corresponding increase in seizure-free days and vice versa.

The NICE committee conclusion from the ACD for TA614 and TA615 considered it appropriate to capture the benefits of having more seizure-free days. However, the committee also considered that the approach used (categorisation into number of seizures, and then subdivision of these into number of seizure-free days) may have resulted in 'double-counting' the benefits of reducing the frequency of seizures.

To address this, the modelling approach used in the current submission allows for the separate modelling of seizure-free days and seizure frequency, whilst also accounting for the correlation between both. Firstly, a binomial regression model was used to predict the proportion of seizure-free days per cycle. Secondly, a fitted negative binomial model was used to predict the total seizure frequency on the non-seizure-free days per cycle. The correlation between both outcomes is therefore captured, as seizure frequency is only estimated for the days in each cycle when patients are expected to have seizures."[6]

As a result of this response, showing that double counting may be avoided, seizure-free days will now be covered in this ERG report as part of the 'response to treatment' outcome.

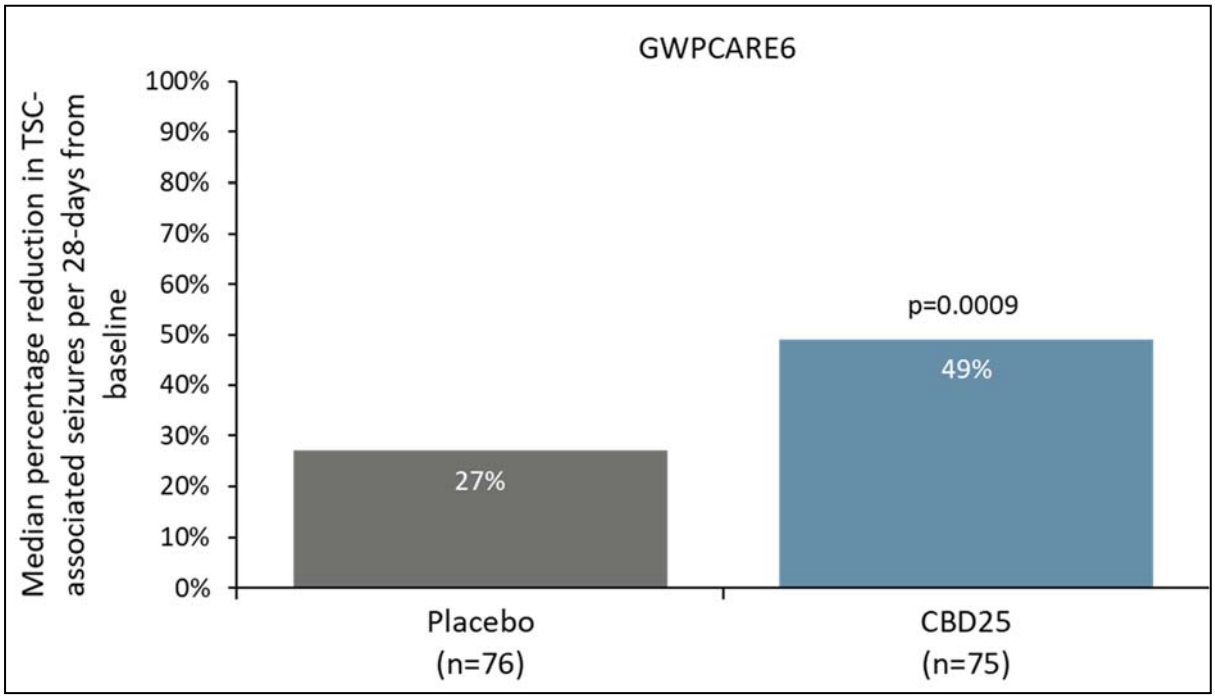
The first four of the NICE scope outcomes will now be evaluated in turn. Adverse outcomes will be evaluated in Section 3.2.6.

3.2.5.1 Change in frequency of seizures

In the GWPCARE6 study, the 'treatment period' lasted 16 weeks: a 4-week 'titration period' followed by a 12-week 'maintenance period'. The primary endpoint was the change in number of TSC-associated seizures during the treatment period compared to the baseline period (ITT analysis set).

A reduction from baseline in primary–end-point seizures of 48.6% (95% confidence interval (CI), 40.4% to 55.8%) was observed for the cannabidiol 25 mg group, and 26.5% (95% CI, 14.9% to 36.5%) for the placebo group during the treatment period.[15] The difference between cannabidiol and placebo groups in percentage reduction from placebo was 30.1% (95% CI, 13.9% to 43.3%; P=< .001).[15]

Figure 3.3: Change in TSC-associated seizures during the treatment period compared to baseline (ITT analysis set)



Based on Figure 6 in CS document B[1]
CS = company submission

During the maintenance period only of GWPCARE6 (i.e., the 12-week stable dosing period after titration), cannabidiol (25 mg/kg/day) plus usual-care demonstrated a 56% reduction in TSC-associated seizures versus 30% with placebo plus usual-care (p=0.0004).

ERG comment: In Thiele et al. (2020)[15] it is stated that: "*The primary end point, TSC-associated seizures, included countable focal motor seizures without impairment of awareness, focal seizures with impairment of awareness, focal seizures evolving to bilateral motor seizures, and generalized seizures (tonic-clonic, tonic, clonic, or atonic); this excluded absence, myoclonic, and focal sensory seizures and infantile/ epileptic spasms. A mean of 94% of patients' baseline seizures were classified as TSC-associated seizures. This functional definition and classification of the primary–end-point, TSC-associated seizures was reviewed and approved by the US Food and Drug Administration, the European Medicines Agency, and the Epilepsy Study Consortium independent committee of experts."* This clarifies that the outcome used was valid and appropriate.

Seizure frequency was measured by change from baseline. The ERG requested more information about how baseline measurements were taken compared with how measurements taken during the trial period. The CL response is, "*the measurements were the same during the baseline period baseline and the trial period. Eligible patients entered the trial at the screening visit (Day −35) and began a 7-day screening period. Patients who successfully completed this then began a 28-day baseline period on Day −28. Patients who satisfied all eligibility criteria were then randomized on Day 1. An interactive voice response (IVRS) system was used daily to record information on seizures. During the baseline period and the double-blind participation in the trial, the caregiver made daily calls into an interactive voice response system (IVRS) to log the seizures experienced by the subject within the previous 24 hours*." This response satisfied the ERG that the methodology of seizure frequency measurement at baseline was valid.

3.2.5.2 Responses to treatment

Although the CS refers to 'responses to treatment' in Table 1 of the CS,[1] it does not use this term thereafter and refers instead to key secondary endpoints.

Treatment responders (≥50% TSC-associated seizure reduction)

Thirty-six percent of patients taking cannabidiol (25 mg/kg/day) plus usual-care had ≥50% seizure reduction versus 22% with placebo plus usual-care (p=0.0692)

Treatment responders (≥75% TSC-associated seizure reduction)

Sixteen percent of patients taking cannabidiol (25 mg/kg/day) plus usual-care had ≥75% seizure reduction versus 0% with placebo plus usual-care (p=0.0003).

TSC-associated seizure-freedom

In the maintenance period of the trial (the 12-week period when patients had completed titration and were on a stable dose), TSC-associated seizure-freedom was achieved in four of the 75 patients (5.4%) taking cannabidiol (25 mg/kg/day) plus usual-care compared to none of the 76 patients in the placebo plus usual-care group (p=0.0354).

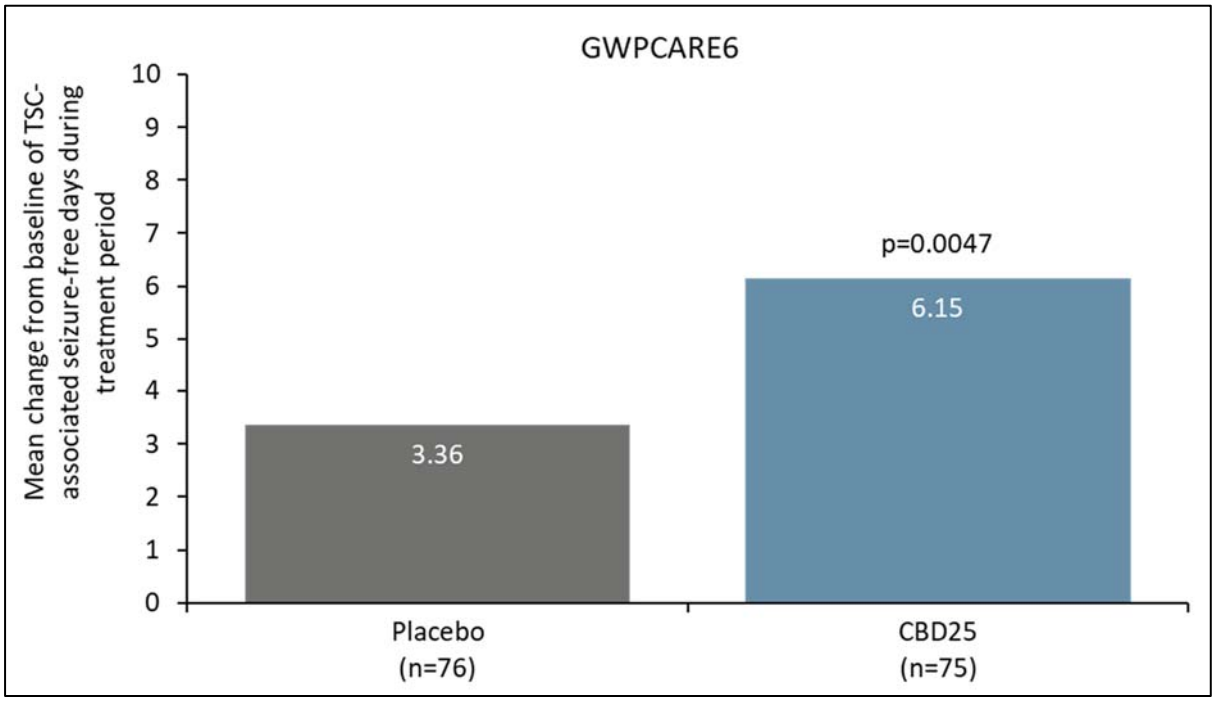
In the treatment period (the 16-week period including a 4-week titration followed by 12 weeks on a stable dose), one patient in the cannabidiol (25 mg/kg/day) plus usual-care arm achieved TSC-associated seizure-freedom versus none in the placebo plus usual-care arm (p=0.3173).

Overall, one patient in the cannabidiol (25 mg/kg/day) plus usual-care group, experienced *total* seizure-freedom (i.e., no seizures of any type) during the treatment period.

TSC-associated seizure-free days

Patients taking cannabidiol (25 mg/kg/day) plus usual-care demonstrated a nominally statistically significant percentage of improvement in TSC-associated seizure-free days. As shown in Figure 3.4, patients taking cannabidiol experienced an additional 2.8 seizure-free days per month versus the placebo group (p=0.0047)

Figure 3.4: Analysis of change from baseline in TSC-associated seizure-free days per 28 days during the treatment period (ITT Analysis Set)



Source: document B of CS[1], Figure 7.
CS = company submission

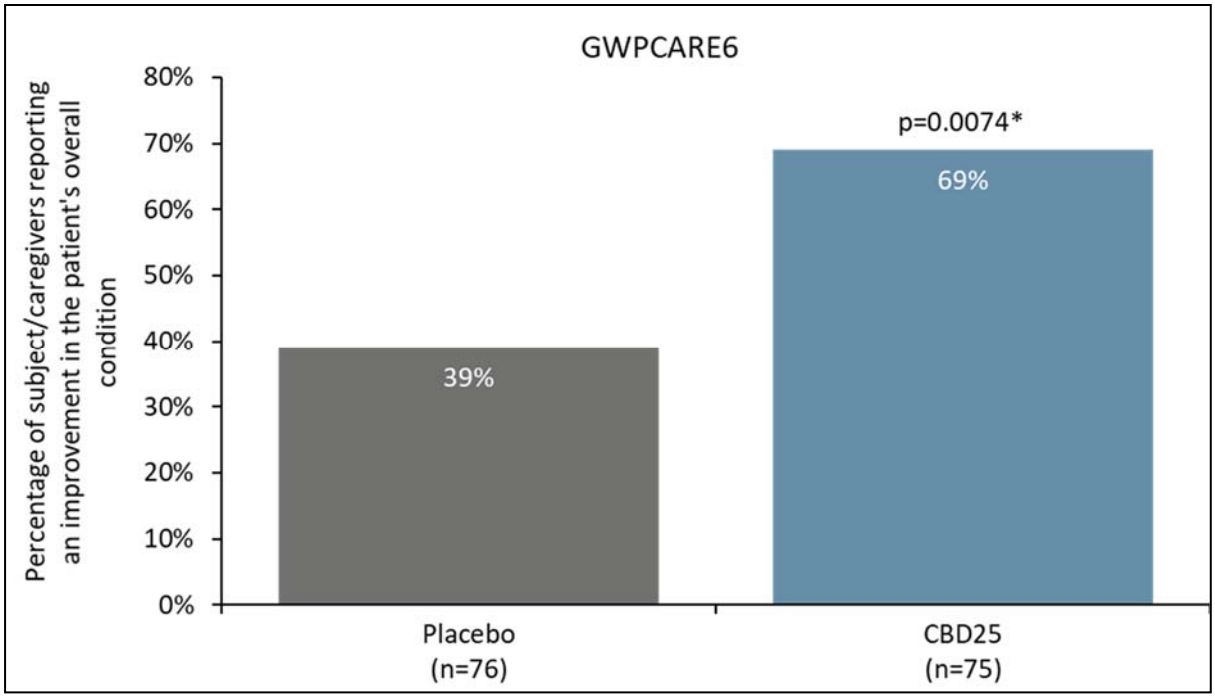
ERG comment: The results listed above all fit the outcome 'responses to treatment' and so have been included in the ERG report.

3.2.5.3 Quality of life

The GWPCARE6 study assessed patient-reported outcomes (PRO) and found no significant differences between cannabidiol 25 mg/kg/day plus usual-care and placebo plus usual-care using the QOLCE and QOLIE-31 P questionnaires. The CS[1] interpreted these results in terms of the challenges in collecting HRQoL data in clinical trials involving patients with severe and refractory epilepsies such as TSC-associated epilepsy. These challenges include the lack of validated disease-specific instruments, the fact that general epilepsy QoL instruments may not work well for severe epilepsy (for example, asking questions about school/work for a patient with TSC-associated epilepsy who has physical/learning disabilities that mean they do not attend school or go to work), and the consequent likelihood of missing data, making it difficult to draw meaningful conclusions. Detailed results were not provided in the main body of the CS[1], and were provided in the Appendix instead.

The CS[1] only reported detailed outcome data for the S/CGIC in the main clinical efficacy report. Patients and caregivers reported an improvement in patients' overall condition in 69% of those receiving cannabidiol (25 mg/kg/day) plus usual-care versus 39% receiving placebo plus usual-care (odds ratio (OR) 2.25 (95% CI, 1.24-4.07)).[15]

Figure 3.5: Subject/Caregiver Global Impression of Change from baseline



Source: document B of CS[1], Figure 7.
* Nominal p-value. CS = company submission

ERG comment: In the CS,[1] the company argues that the lack of any benefit for the cannabidiol group in terms of the QOLCE and QOLIE-31 P questionnaires is due to these being inappropriate measures for the target population. This appears to be a reason why the results are not provided in detail in the CS.[1] However, these two QoL measures (which appear to be valid measures for children with seizures) were originally planned to be used in the trial and so the opinion that they were unsuitable can only have been made after the results had been observed: it was hence a post-hoc, and thus potentially biased, decision. One possibility therefore, is that the measures were not presented in the main body of the CS[1] because they suggested that cannabidiol did not improve QoL. The company responded to our clarification question about QOLCE/QOLIE-31-P questionnaire results by re-stating what they had originally written in the CS[1]. The conclusion of the ERG is therefore that there were no good reasons for not presenting the data up-front in the CS[1] and that the QOLCE/QOLIE-31-P questionnaire results should be considered carefully as an integral part of the study data.

3.2.6 Adverse events

The GWPCARE6 study recorded adverse reactions reported by patients/caregivers, the number of withdrawals from the study and whether these were due to AEs. Most AEs were mild to moderate. The CS[1] report states that the majority occurred during initiation of treatment (2 to 4 weeks), were transient and resolved by the end of the trial.

The CS[1] states that the safety profile of cannabidiol observed in the GWPCARE6 study is consistent with findings from previous studies, with no new safety risks identified. Most patients (92.1%) experienced events that were of mild or moderate severity, and most (60.0%) had TEAEs that had resolved by the end of the trial. AEs were recorded in 93% of the 25 mg/kg/day group and 95% of the placebo group. The most common AEs were diarrhoea (31% of patients treated with 25 mg/kg/day cannabidiol: 25% of those in the placebo group), decreased appetite (20% and 12%, respectively), vomiting (17% and 9%, respectively) and somnolence (13% and 9%, respectively).

The AEs leading to discontinuation were described by the CS[1] as relatively low. Two patients in the placebo plus usual-care group and eight patients in the cannabidiol (25 mg/kg/day) plus usual-care group discontinued treatment due to an AE. A summary of TEAEs, including those leading to withdrawal from treatment, is provided in Table 3.12. The AEs reported with an occurrence in at least 10% of patients are summarised in Table 3.13.

Table 3.12: Summary of TEAEs (Safety Analysis Set) in GWPCARE6

Event	Cannabidiol 25 mg/kg/day (n=75) N (%)	Placebo (n=76) N (%)
Patients reporting any all-causality TEAEs	70 (93.3)	72 (94.7)
Patients reporting any treatment related TEAEs	52 (69.3)	40 (52.6)
Patients reporting any TEAEs leading to permanent discontinuation	8 (10.7)	2 (2.6)
Patients reporting any treatment related TEAEs leading to permanent discontinuation	8 (10.7)	2 (2.6)*
Patients reporting any serious TEAEs	16 (21.3)	2 (2.6)
Patients reporting any treatment related serious TEAEs	8 (10.7)	0

Based on Table 7 of CS Document B[1]
* The two patients in the placebo group with TEAEs leading to discontinuation of the investigational medicinal product (IMP) completed the double-blind phase of the trial and the IMP was discontinued within the open-label extension
CS = company submission; TEAEs = treatment emergent adverse events

Table 3.13: Adverse events recorded in GWPCARE6 by ≥10% of participants

Event	Cannabidiol 25 mg/kg/day (n=75) N (%)	Placebo (n=76) N (%)
Diarrhoea	23 (30.7)	19 (25.0)
Mild	**20 (26.7)**	**16 (21.1)**
Moderate	3 (4.0)	3 (3.9)
Severe	0	0
Decreased appetite	**15 (20.0)**	**9 (11.8)**
Mild	9 (12.0)	9 (11.8)
Moderate	6 (8.0)	0
Severe	0	0
Somnolence	**10 (13.3)**	**7 (9.2)**
Mild	10 (13.3)	6 (7.9)
Moderate	0	1 (1.3)
Severe	0	0
Vomiting	**13 (17.3)**	**7 (9.2)**
Mild	8 (10.7)	7 (9.2)
Moderate	4 (5.3)	0
Severe	1 (1.3)	0
Pyrexia	**14 (18.7)**	**6 (7.9)**
Mild	13 (17.3)	4 (5.3)

Event	Cannabidiol 25 mg/kg/day (n=75) N (%)	Placebo (n=76) N (%)
Moderate	1 (1.3)	2 (2.6)
Severe	0	0
Alanine aminotransferase increased	**9 (12.0)**	**0**
Mild	7 (9.3)	0
Moderate	2 (2.7)	0
Severe	0	0
Upper respiratory tract infection	**7 (9.3)**	**10 (13.2)**
Mild	6 (8.0)	8 (10.5)
Moderate	1 (1.3)	2 (2.6)
Severe	0	0
Aspartate aminotransferase increased	**8 (10.7)**	**0**
Mild	7 (9.3)	0
Moderate	1 (1.3)	0
Severe	0	0
Gamma-glutamyl transferase increased	**12 (16.0)**	**0**
Mild	11 (14.7)	0
Moderate	1 (1.3)	0
Severe	0	0

Based on Table 8, CS document B[1]
CS = company submission

Status epilepticus

The cannabidiol clinical trial patients were a highly refractory group with status epilepticus as part of their disease. In the GWPCARE6 study, status epilepticus was reported as a serious TEAE in three patients overall: two in the cannabidiol 25 mg/kg/day plus usual-care group and one in the usual-care group. The CS report states that all three serious events of status epilepticus were of moderate severity, and none were considered to be treatment related.

ERG comments: The follow-up period, and tools used for AEs reporting were not clear in the CS[1] so the company was asked to provide further information. The company response was:

"*a paper diary was used daily to record information on adverse events (AEs). All AEs (including serious AEs) observed by the investigator or reported by the patient/caregiver during the trial were recorded on the patient's Case Report Form at all trial visits, questioning the patient/caregiver further if necessary. An AE was defined as any new unfavourable/unintended signs/symptoms (including abnormal laboratory findings), or diagnosis or worsening of a pre-existing condition, which occurred following screening (Visit 1) and at any point up to the post-treatment safety follow-up visit (Visit 12, for patients who did not enter the OLE), which may or may not be considered related to the IMP. Any event that was the result of a trial procedure was to be recorded as an AE. Unless entering the OLE trial (in which case patients would have been monitored for AEs for the duration of the OLE) the trial required that patients be actively monitored for AEs up to 28 (+3) days after the last dose of IMP, until Visit 12.*"[6]

The metric used to classify the severity of AEs was also felt to be unclear. The company response was that "*For all AEs and serious AEs, the clinical trial investigators were required to assign severity and document this on the Case Report Form. The method is described in the trial protocol as follows: "when describing the severity of an AE, the terms mild, moderate, or severe should be used. Clinical judgment should be used when determining which severity applies to any AE. If the severity of an AE fluctuates day-to-day, e.g., a headache or constipation, the change in severity should not be recorded each time; instead, only the worst observed severity should be recorded with AE start and stop dates relating to the overall event duration, regardless of severity. A severe AE is not the same as a SAE. For example, a patient may have severe vomiting, but the event does not result in any of the SAE criteria above. Therefore, it should not be classed as serious." An AE was considered serious if it: (1) was fatal; (2) was life-threatening; (3) required inpatient hospitalization or prolonged existing hospitalization; (4) was persistently or significantly disabling or incapacitating; (5) was a congenital anomaly/birth defect; or (6) was a medically significant event that, based upon appropriate medical judgment, may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above."*[6]

In addition, it was unclear if the serious AEs (SAEs) were reported in all, or ≥10% of participants. This information was also sought in the clarification letter. The company response was that it was reported in all participants.

Although no studies have shown this specifically for cannabidiol, cannabis-based medications may have the potential to initiate drug-drug interactions that may lead to serious drug toxicities and side effects in real world practice.{Antoniou, 2020 #276} In the clarification letter, the company was asked to clarify if certain medications were disallowed during the trial to prevent these drug-drug interactions from occurring. The clarification letter response was "*The GWPCARE6 study protocol stated that "Care should be taken with drugs, or their metabolites, that are cytochrome P450 2C19 substrates, such as N-desmethylclobazam. Care should also be taken with drugs, or their metabolites, that are solely or primarily metabolized by UDP-glucuronosyltransferase 1A9 and 2B7." However, these medications were not disallowed during the study. As per the GWPCARE6 trial exclusion criteria, the following medications were prohibited for the duration of the trial: Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage; Recreational or medicinal cannabis or synthetic cannabinoid-based medications (including Sativex) within 3 months prior to or during the trial; Any other IMP taken as part of a clinical trial; Felbamate if taken for less than 1 year prior to screening; Oral mTOR inhibitor".*[6]

The company were also asked to clarify if the dosage of concomitant ASMs that patients were stable on for 1 month prior to screening, would have been modified by the investigator during the trial considering potential drug-drug interactions. The company responded with the statement: "*Throughout the duration of the trial, doses of concomitant AEDs and any non-pharmacological regimens for epilepsy were to remain stable. However, due to potential pharmacological interactions between cannabidiol and other concurrently administered drugs, the doses of concomitant AEDs could be adjusted following discussion with the GW medical monitor(s) if there were any clinical symptoms indicative of a safety concern. If, during the blinded phase, plasma concentrations of concomitant AEDs were found to be altered following administration of IMP, or if there were side effects suspected of being related to an elevation in the concomitant AED concentration, the investigator was to contact the GW medical monitor to discuss best management. Decisions were to be based on clinical symptoms and not plasma levels of AEDs*."[6]

Based on these responses, the ERG is satisfied that Cytochrome P450 3A4 (CYP3A4)-related drug-drug interactions were probably avoided in the trial, but the ERG also thinks that avoidance of such AEs in real-world practice depends on how well this risk is managed. In relation to this, the company stated that "*as stated clearly in the SmPC, it will be the decision of the prescribing clinician as to whether dose adjustments to other medicinal products used in combination with cannabidiol should be made in real world practice:*

"A physician experienced in treating patients who are on concomitant antiepileptic drugs (AEDs) should evaluate the need for dose adjustments of cannabidiol or of the concomitant medicinal product(s) to manage potential drug interactions"."

In relation to this response, the ERG would state that these are statements of good practice, but do not, of course, ensure that this will happen in practice.

The GWPCARE6 CSR states that, "*The use of rescue medication was allowed when necessary… Overall, 78 patients (34.8%) were recorded as taking rescue medications*." The company has been asked for further information in the clarification letter. The company stated that "*The most common class of rescue medication was benzodiazepine derivatives. These included diazepam, clonazepam, midazolam, midazolam hydrochloride, lorazepam, clobazam and clorazepate dipotassium. The most common rescue medication was diazepam.….Similar proportions of patients across the treatment groups were recorded as taking rescue medications: 25 patients [33.3%] in the 25 mg/kg/day cannabidiol group, and 26 patients [34.2%] in the placebo group"*. Based on this response, the ERG is satisfied that the use of rescue medication does not affect the internal validity of the trial.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparisons were carried out by the CS.[1]

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Not applicable.

3.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The company's main trial, the GWPCARE6 trial, was a phase III double-blind, randomised, placebo-controlled, multicentre, multinational study. The participants were children and adults aged 1 to 65 years with a clinical diagnosis of TSC. In the trial, cannabidiol 25 mg/kg/day in addition to usual care. (n=75) was compared with usual care and placebo (n=76). The results of the trial suggested that cannabidiol was more effective than placebo for decreasing the frequency of seizures, and for improving subject/caregiver global impression of change score. These positive findings need to be interpreted in the light of some limitations in the trial methodology. Vigabatrin, the first line concomitant drug, was much more prevalent in the cannabidiol arm. The low probability of a difference this large existing by chance does suggest that random allocation to groups may not have been optimally carried out. If so, this suggests that selection bias may be a serious underlying problem, preventing the assumption that unmeasured covariates, as well as measured covariates, are comparable. Another limitation was the failure to fully present two of the QoL indices in the main submission document, on the grounds that they were inappropriate for the study population, even though they had been part of the pre-hoc study plan. The failure of these two outcomes to demonstrate a benefit for the intervention may be the more

likely reason for the decision to not report them fully, an example of outcome reporting bias. Overall, therefore, although it appears that cannabidiol is more effective than placebo, the methodological limitations do imply that the true magnitude of effectiveness may not be quite as large as the data suggest.

The safety analysis suggested that cannabidiol does not cause major AEs and that any adverse effects are generally transient and manageable. However, although this has not been evaluated in cannabidiol itself, cannabis-based medications may have the potential to initiate drug-drug interactions that may lead to serious drug toxicities and side effects in real world practice.{Antoniou, 2020 #276}

The company also conducted a systematic literature review on the clinical effectiveness (efficacy and safety) of medications used to treat seizures in TSC. Their conclusion was that the only potentially relevant trial of interest was the GWPCARE6 trial. However, the ERG identified several problems with the SLR, ranging from unclear inclusion/exclusion criteria and potentially biased methods for data extraction to missing studies that could provide relevant comparator data. The ERG's independent appraisal of the SLR found that it was at a high RoB, and therefore that its results are not reliable.

The CS[1] and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify relevant literature relating to efficacy and safety of drug treatments used to treat seizures in TSC. Searches were conducted in November 2021. Searches were transparent and reproducible and covered a broad range of resources, including databases, conference proceedings, HTA organisations and other grey literature resources.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

A SLR was performed with the objectives to identify and select relevant 1) efficacy and safety studies in TSC (CS Appendix D); 2) cost effectiveness analysis (CEA) studies in TSC (CS Appendix G); 3) HRQoL studies in TSC (CS Appendix H); and 4) costs and healthcare resource use studies in TSC (CS Appendix I). Study selection criteria were listed in CS appendix D[13].

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the CS.

A single set of searches were designed to inform both the clinical and cost effectiveness sections of this review, please refer to Section 3.1.1 for the ERG critique of these methods.

4.1.2 Inclusion/exclusion criteria

Inclusion criteria for the review on cost effectiveness studies, HRQoL studies and costs and resource use studies are presented in Table 4.1. These inclusion criteria also applied to the SLR for effectiveness studies. When inclusion criteria were different for cost effectiveness, HRQoL or resource use this is mentioned as an addition. No exclusion criteria were listed.

Table 4.1: Inclusion criteria for the systematic literature reviews

	Inclusion criteria
Disease	- Seizures associated with tuberous sclerosis complex (TSC) - For costs and quality of life (QoL) only: general TSC with or without seizures (excluding studies specifically in other, non-neurological manifestations of TSC)
Population	Adults or children
Intervention	Any or none
Comparator	Any or none
Topics	Efficacy and safety of interventions for seizures - QoL studies with utility values - Economic evaluations - Cost and resource use in the United Kingdom (UK)
Study type	- Primary research reports of any relevant methodology - Systematic reviews of relevant studies - Narrative reviews on the burden of illness in seizures related to TSC (costs, QoL, economics) - Study protocols for efficacy/safety studies
Study size	>5 participants
Publication date	Any
Publication language	Any

Based on Appendix D of the CS[13]
Cs =company submission; QoL = quality of life; TSC = tuberous sclerosis complex; UK = United Kingdom

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies. The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, HRQoL and resource use and costs studies, but no specific conclusion was formulated.

ERG comment: See comments in Section 3.1.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.2: NICE reference case checklist

Element of HTA	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with National Institute for Health and Care Excellence (NICE) reference case
Perspective on costs	National Health Service (NHS) and Personal Social Services (PSS)	In line with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	In line with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in quality adjusted life years (QALYs). The EuroQol five-dimension (EQ-5D) questionnaire is the preferred measure of health-related quality of life (HRQoL) in adults.	QALYs derived via a vignette study. The EQ-5D was considered insufficiently sensitive in patients with severe epilepsy and not able to capture impact of small changes in seizure frequency.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	A vignette study was used as no suitable measure was identified to collect data directly from patients via a survey and trial data was unsuitable for use.

Element of HTA	Reference case	ERG comment on CS
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	In line with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	In line with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with NICE reference case

CS = company submission; EQ-5D = EuroQol five-dimension questionnaire; HRQoL = health-related quality of life; HTA = health technology assessment; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; NICE = National Institute for Health and Care Excellence; UK = United Kingdom

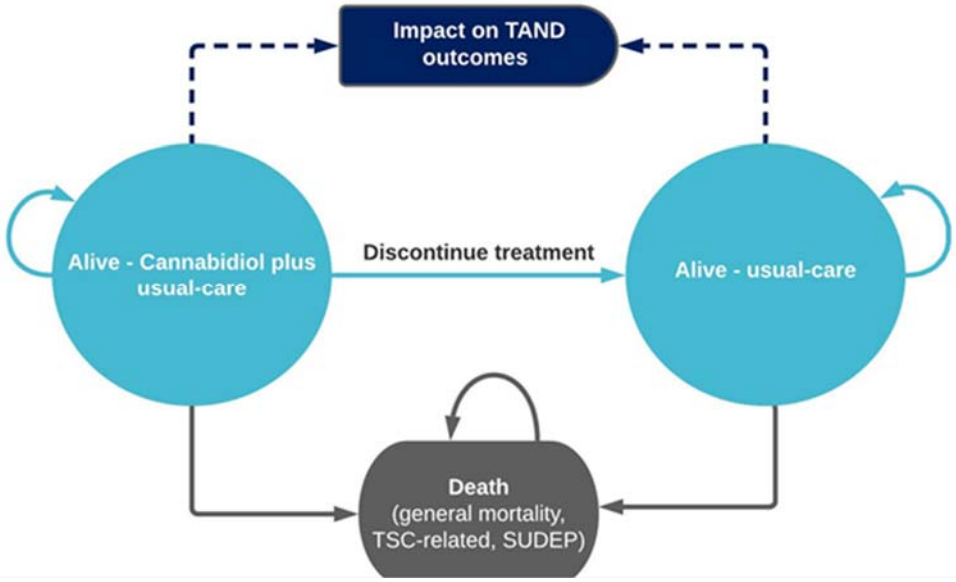
4.2.2 Model structure

The company developed a cohort-level model predicting the expected probability of seizure-free days and associated seizure frequency. The model was developed in Microsoft Excel™ and consists of three main health states: 'Alive and on treatment with cannabidiol plus usual-care', 'Alive and on treatment with usual-care only', and 'Death'. Figure 4.1 shows the model structure. All patients enter the model in either one of the 'alive' health states. Patients in the 'cannabidiol plus usual-care alive' health state move to the 'usual-care alive' health state if they discontinue treatment. Patients in both arms can move to the 'death' health state at any stage due to general mortality, TSC-related mortality, or sudden unexpected death in epilepsy (SUDEP). The effect of treatment in early childhood on TAND outcomes was modelled indirectly based on changes in seizure frequency.

Figure 4.2 summarises the model process. To model the healthcare resource use (HCRU) and HRQoL associated with differential seizure frequency and seizure-free days, the 'alive' health states were divided into sub-health states. Different seizure frequency categories were defined for HRQoL and HCRU. HRQoL were based on categories of seizure frequency per day and HCRU were based on the number of seizures per week. To distribute the cohort amongst sub-health states representing different seizure frequency categories within the 'alive' health states, the company applied two independent regression models sequentially to the GWPCARE6 individual patient-level data to produce coefficients that were used to predict the seizure-free days and seizure frequency associated with each treatment per patient per 7-day model cycle.[7, 15, 21] Firstly, they used a binomial regression model to predict the proportion of seizure-free days per 7-day cycle; secondly, they used a fitted negative binomial model to predict the total seizure frequency on the non-seizure-free days per cycle. This approach allowed for the correlation between seizure frequency and seizure-free days to be captured, as seizure frequency is only estimated for the days in each cycle when patients are expected to have seizures (non-seizure-free days). The regression coefficients were applied to each patient's baseline seizure frequency at each model cycle of 7 days to predict seizure-free day and seizure frequency distributions. Once patients

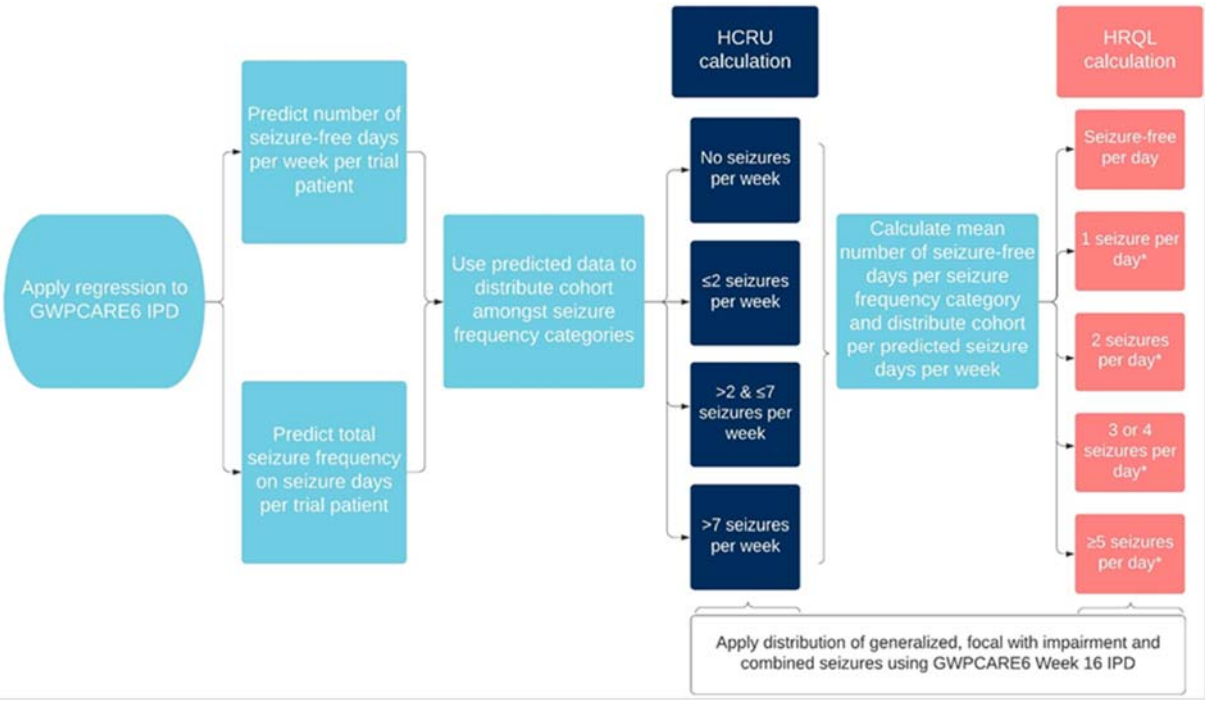
were assigned into sub-health states based on seizure frequency, the split between generalised seizures, focal with impairment of awareness seizures, or a combination of both seizure types per cycle is applied for each state to calculate per cycle HCRU and HRQoL. The company used the week 16 GWPCARE6 trial data to estimate the distribution.[7, 15, 21]

Figure 4.1: Model structure



Source: Based on Figure 12 of the CS[1]
CS = company submission; SUDEP = sudden unexpected death in epilepsy; TSC = tuberous sclerosis complex; TAND = tuberous sclerosis complex-associated neuropsychiatric disorders

Figure 4.2: Model process diagram

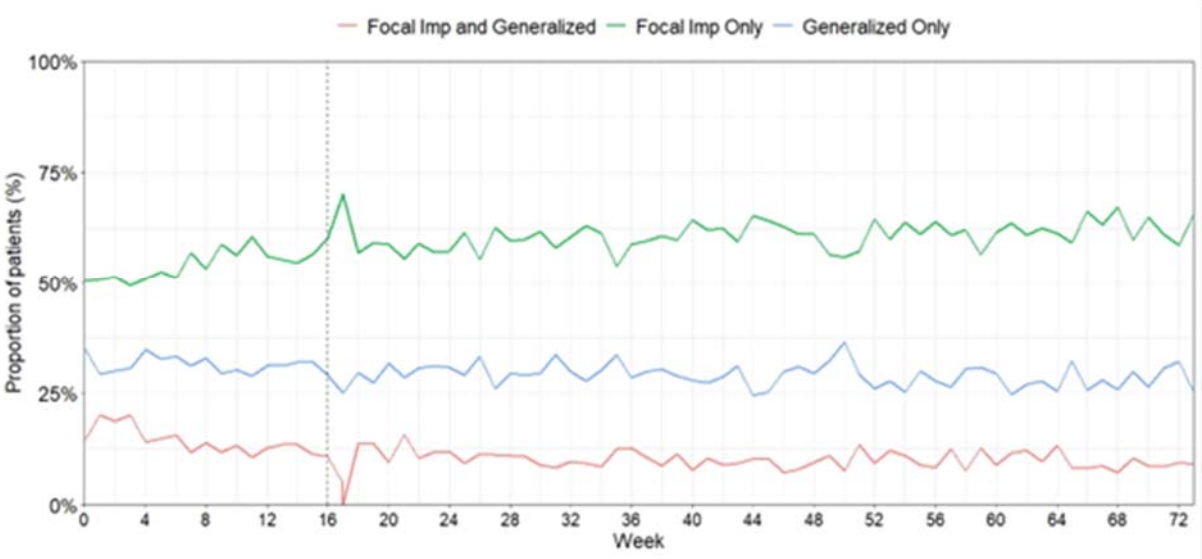


Source: Based on Figure 13 of the CS[1]
CS = company submission; IPD = individual patient-level data

ERG comment: The main concerns of the ERG relate to: a) use of week 16 data for distribution of seizure type instead of average; b) the assumption of seizure type distribution remaining stable over time.

a) The proportions for seizure type (generalised, focal with impairment, or combined) were based on week 16 data from the GWPCARE6 trial and were assumed to be constant over time. The company justified the use of week 16 data instead of the average over the 16-week trial period by the fact that the proportions change minimally over time and therefore the base case analysis uses the week 16 data as this was the point of completion of the core trial period and is expected to reflect the distribution of seizure types following treatment over a longer time horizon more accurately. The ERG agrees that the proportions of seizure types at week 16 better reflects the distribution of seizure type in the OLE study compared to an average of the initial 16-week trial period (see Figure 4.3). However, particularly in the first 16 weeks of the trial, the proportions for seizure type vary over time, with initially relatively more patients experiencing generalised or combined seizures. Since generalised and combined seizures are more severe than focal with impairment only, the ERG believes that assuming a constant distribution of seizure type based on week-16 data would potentially have led to an overestimation of the ICER, though it is unclear to what extent.
b) The company assumed that constant proportions of seizure types based on week-16 data throughout the time horizon of the model. The company justified this assumption by the fact that during the OLE trial period the seizure type proportions are consistent over time (Figure 4.3) and was supported by UK clinical expert option who confirmed that seizure type proportions are generally stable over time. Based on the observed data from GWPCARE6 core trial period and OLE, and with no data available on the seizure type distribution beyond the OLE trial period, the ERG believes this is a reasonable assumption.

Figure 4.3: Observed proportion of patients by seizure type: GWPCARE6 core trial period and OLE



Based on Figure 5 of the clarification response.[6]

4.2.3 Population

In line with its licenced Marketing Authorisation, the population considered in the company's economic model was people with TSC-associated epilepsy 2 years of age and older whose seizures are inadequately controlled by established clinical management.[9] This is in line with the final scope issued by NICE.[2]

The GWPCARE6 trial population consisted of children and adults aged 1 to 65 years with a clinical diagnosis of TSC and a well-documented clinical history of epilepsy not completely controlled by their current AEDs.[22] Baseline demographic characteristics such as mean age, weight, proportion female, concomitant AED use, and disease severity (i.e., baseline seizure frequency and seizure frequency per week and per day per seizure type) were obtained from GWPCARE6 ITT analysis. The ITT analysis included nine children (three on the cannabidiol 25 mg/kg/day arm and six on the placebo arm) aged 1 year-old. The characteristics were assumed to be the same for the entire cohort of patients entering the model, i.e., assumed to be treatment independent.

The key baseline patient characteristics in the economic model are listed in Table 4.3 below.

Table 4.3: Key baseline patient characteristics used in the economic model based on the GWPCARE6 trial

	2 – 6 years	7 – 11 years	12 – 17 years	≥18 years
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]
% female (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean body weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Mean BSA, m2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Age distribution (%) of cohort at baseline	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 12 of the CS and Table 8 of the clarification response.[1, 6]
BSA = body surface area; CS = company submission; SD = standard deviation

ERG comment: The main concerns of the ERG relate to: a) efficacy inputs, discontinuation rates, treatment response rates, and baseline characteristics are based on ITT population including 1-year-olds, b) variation in the proportion female between the age groups.

a) In response to clarification question B2, the company explained that the GWPCARE6 ITT population - including nine patients aged 1 at baseline - was used to inform efficacy inputs (regression analysis), discontinuation rates, treatment response rates, and baseline characteristics. The company noted that although all these inputs were based on the ITT population including 1-year-olds, the patient characteristics used to calculate the drug costs exclude patients aged 1 year-old. The ERG believes that including 1-year-olds in the ITT population creates uncertainty in the model, as it is unclear whether the efficacy, discontinuation rate, treatment response, and baseline characteristics for this population are representative of the model population (i.e., people with TSC-associated epilepsy 2 years of age and older). Therefore, the ERG asked the company to provide data separately for 1-year-olds from the ITT population or to perform a scenario analysis excluding 1-year-olds from the ITT population in estimating model inputs. However, the company only provided baseline characteristics for patients <2 years of age (see Table 7 of the clarification response), but did not provide any efficacy data, discontinuation rates, or treatment response rates for this

population. This was justified based on the argument that it is reasonable to assume that the outcomes in the <2-year-olds would be similar to the overall trial outcomes as all but two of the patients who were <2 years old at the screening visit had reached age 2 by the end of the trial. However, it is not clear to the ERG why these data could not be provided (while the company did provide the baseline characteristics for 1-year-olds separately) and without these data the ERG cannot make any conclusions on the effect of inclusion of data for 1-year-olds on the ICER.

b) The proportion of female patients varies between the age groups. In particular, the percentage of females in patients aged 18 years and older appears relatively low compared to the other age groups. Although the company mentions that the percentage of female input by age group is not directly used in the cost effectiveness analysis (CEA), the mean weight and BSA (which are sex-dependent) are used to calculate the drug costs (weight for cannabidiol and AEDs, BSA for subsequent treatment with everolimus). The proportion of patients aged 18 years and older is [redacted]% at the start of the model and increases in time as patients age (i.e., after a time horizon of 17 years, all patients are aged 18 years or older). The ERG is concerned that the weight and BSA of this age group might be overestimated given the relatively low proportion of patients being female. On the other hand, the model assumes that the weight and BSA for patients aged 18 years-and-older (mean age [redacted], SD [redacted]) remains stable over time. The ERG is concerned this may not reflect real-life, although it is unclear what the effect of this assumption is on the ICER.

4.2.4 Interventions and comparators

Intervention

In the licensed indication for TSC-associated epilepsy, cannabidiol oral solution is recommended to be administered by means of a starting dose of 2.5 mg/kg twice daily (5 mg/kg/day) increased to a maintenance dose of 5 mg/kg/day (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/kg/day).[23]

In the CS, the base case analysis utilises an average dose of 12 mg/kg/day as the company assumes that, across a cohort of patients in clinical practice, there will be a spectrum of doses ranging from ≤10 mg/kg/day to the maximum of 25 mg/kg/day. In the GWPCARE6 trial,[7, 15, 21] efficacy of cannabidiol was examined in two different dosages, i.e., 25 mg/kg/day and 50 mg/kg/day. Due to the comparable efficacy between the arms but more favourable risk-benefit profile of the 25 mg/kg/day dose, the summary of product characteristics (SmPC) recommends up to a maximum dose of 25 mg/kg/day. Therefore, the company based all treatment efficacy calculations on the population of the GWPCARE6 trial who received 25 mg/kg/day.

Comparator

According to the company, cannabidiol is positioned as an adjunctive treatment in the current treatment pathway, which includes pharmacologic treatment with AED, non-pharmacologic therapies (i.e., VNS, ketogenetic diet, and surgical resection), and everolimus if VNS or surgery has failed and only in refractory focal onset seizures (not licenced for generalised seizures).[24] The comparator defined in the NICE scope was established clinical management without cannabidiol, such as: AED, everolimus, VNS, ketogenetic diet, and surgical resection.

The comparator considered in the company's economic model was usual care (or current clinical management) consisting of a combination of AED (no non-pharmacologic treatments or everolimus). The proportion of AED usage was informed by the AED included in the GWPCARE6 trial with a minimum of 10% usage in either paediatric or adult population at baseline and were assumed to be treatment independent.[7, 15, 21] The company did not include ketogenetic diet, VNS, or resective surgery as comparators in the economic model, as they assume these are an established part of the treatment pathway in TSC-associated epilepsy, and therefore are also part of the usual-care mix into which cannabidiol would be added rather than being a comparator. Eligibility criteria for the GWPCARE6 trial did allow for patients who receive or received ketogenetic diet or VNS and were able to continue this throughout the treatment period.[7, 15, 21] Patients who had undergone surgery for epilepsy in the 6 months before screening or were being considered for epilepsy surgery during the blinded phase of the trial were excluded. However, there were patients in the trial across the treatment arms who had already undergone surgery.

Everolimus was also not included as comparator, but as later line treatment. The company justifies this given that, according to the current treatment pathway, everolimus should be used as last resort option, as it has an indication that is not specifically related to seizures (i.e., SEGA) and can only be used in patients with refractory focal onset seizures (not generalised seizures) who failed resective surgery and VNS.

ERG comment: The main concerns of the ERG relate to: a) company's justification for the use of an average dose of 12 mg/kg/day cannabidiol in the base case; b) no use of ketogenetic diet, VNS, or resective surgery as part of usual care (deviation from NICE scope); no use of everolimus as part of usual care but as subsequent treatment option (deviation from NICE scope).

a) The company assumed a fixed average dose of 12 mg/kg/day in the model. However, in the GWPCARE6 - which was used to inform most model inputs - patients were titrated up to 25 mg/kg/day. The company argued that in clinical practice it is to be expected that the dose will be lower than 25 mg/kg/day. From the GWPCARE6 trial and open-label extension (OLE) it is unclear what the average dose was in the patients. All patients entered the OLE study taking 25 mg/kg/day. However, investigators may decrease the dose if a patient experiences intolerance or increase the dose to a maximum of 50 mg/kg/day if required for better seizure control, until the optimal dose is found. The CS does not include any data that records the doses that patients actually had. Therefore, it is not possible to verify whether the fixed average of 12 mg/kg/day used in the model reflects the average in the pivotal trial. In response to clarification question B5a, the company explains that by using an average dose of 12 mg/kg/day case in the model, we can account for the range of doses seen in clinical practice across a cohort of UK patients with TSC-associated epilepsy, as clinicians aim to optimise the dose for individual patients. As stated in our original submission, in real-world clinical practice, there will be a spectrum of doses ranging from ≤10 mg/kg/day to the maximum of 25 mg/kg/day. The company says this is supported by a German dispensing database (INSIGHTS) on real-life dosing which showed that from a total of 118 TSC patients, the observed median dose was 12.21 mg/kg/day in children (inter-quartile range 6.67) and 7.77 mg/kg/day (IQR: 5.68) in adults, and discussions with expert clinicians which suggested that the average dose in real-world clinical practice will be around or below 12 mg/kg/day. Moreover, the company argued that the efficacy data from the GWPCARE6 trial would still be representative for a lower average dose in clinical practise, as the totality of the evidence in the cannabidiol clinical programme in refractory epilepsies to date does not support a clear response above 10 mg/kg/day. This was also concluded by the EMA in setting the maintenance dose of 10 mg/kg/day for Dravet syndrome (DS) and Lennox-

Gastaut syndrome (LGS).[25] However, it is unclear to the ERG why - if this is also the case for TSC-related epilepsy - did not recommend a maintenance dose of 10 mg/kg/day for these patients as well. The ERG believes there is limited evidence for the dose of 12 mg/kg/day being representative as an average dose for clinical practice. This causes uncertainty in the model. Additional to the scenario analysis conducted by the company based on an average of 10 mg/kg/day, the ERG asked for an option to explore average doses of 15, 20, and 25 mg/kg/day (clarification question B5b). This showed to have a considerable impact on the incremental costs, resulting in an increase of the ICER.

b) The comparator considered in the company's economic model was usual care consisting of a combination of AED. Ketogenetic diet, VNS, resective surgery, and everolimus were not included in the model as part of usual care. The ERG considers the exclusion of ketogenetic diet, VNS, and resective surgery not an issue it is reasonable to assume this would be equal for both arms and since there is no effect of cannabidiol on mortality, this would not impact the ICER. However, this is also the case for AED treatment, which is also assumed to be treatment independent in the current model. However, the ERG believes that in clinical practice it would be possible to receive everolimus before cannabidiol as the prior use of cannabidiol is not a condition for the use of everolimus. Therefore, everolimus could be considered as part of usual care. However, since it is unknown for what proportion of patients this would be the case, the effect on the ICER remains unclear.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and PSS perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 1 week with a lifetime time horizon (100 years). Half-cycle correction is not applied.

ERG comment: The ERG considers perspective, time horizon and discounting to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators are the data from the treatment period (weeks 1-16) and the OLE period (weeks 17-88) of the GWPCARE6 trial.

Baseline patient characteristics and modelled age categories

The trial population was split into four age groups, aligned to the age groups used for stratification during randomization in the GWPCARE6 trial. The proportion of patients and weight distribution for each age category as observed in GWPCARE6 was presented in Table 4.3 of Section 4.2.3

To account for the changing proportion of patients in each group over time, the baseline age for all patients in GWPCARE6 was simulated to increase by 1 year (per year in the model) until all patients were aged ≥ 18 years.

The age at which patients transition from childhood to adulthood was determined at [redacted] years by consensus in a two-round Delphi panel study.[26] This age was used in the base case analysis to model when patients would move from paediatric to adult management services (and associated health care resource use and costs). The same Delphi panel study resulted in the estimate that 31% of patients would require support such as assisted living or live-in residential units, and that the transition age to these services would be approximately 27 years of age.[26]

Clinical efficacy

In the economic model, clinical efficacy was expressed as a change in frequency of TSC-associated seizures, and a change in the number of TSC-associated seizure-free days. The economic analysis considered two seizure types: generalised seizures and focal with impaired awareness seizures. As GWPCARE6 data from the blinded trial period (weeks 1-16) had demonstrated that treatment efficacy was consistent across the population regardless of age, clinical efficacy and safety outcomes were modelled using the full GWPCARE6 patient population. The average baseline seizure frequency per week (for generalised and/or focal with impaired awareness seizures) from GWPCARE6 was 17.80 (SD 21.82).

Regression models

No well-fitting regression models to predict seizure-free days and seizure frequency for each seizure type separately could be found. Therefore, the company chose an approach using mixed effects regression models to predict seizure-free days and seizure frequency (on days with seizures) for both types of seizure types combined.

The two mixed effect models considered here were:

- A binomial regression to estimate seizure-free days
- A negative binomial regression to estimate seizure frequency

Two levels of random effects were applied in the model:

- Random intercept, reflecting the assumption that each patient may have a different intercept (baseline) value
- Random slope, reflecting the assumption that each patient may have a different rate of change over time

The company argued that correcting for prognostic factors or treatment effect modifiers was not required because patients in GWPCARE6 were randomised and subgroup analysis found no statistically significant treatment effect modifiers. Nevertheless, the following covariates were included in the regression:

- Treatment - cannabidiol plus usual care versus placebo plus usual care.
- Treatment cycle - as a proxy for time. A log transformation was performed to prevent improvement to occur indefinitely which was not considered plausible.
- Treatment * cycle interaction – to capture the treatment effect of cannabidiol versus placebo over time
- Average baseline seizure frequency per week. Although baseline seizure frequency was not a treatment modifier explored in a pre-specified subgroup analysis, it was still included as a covariate to, as the company stated, ‘explicitly model the range of seizures within and between patients, to accurately capture the patient population’. To be able to include baseline seizure frequency as a covariate in both regression models, the covariate includes days where patients had no seizures.

In addition to covariates and random effects included in the negative binomial analysis, an ‘offset’ term was included for the number of seizure days each patient experienced. This offset term was intended to account for patients having different numbers of seizure days per week.

Model evaluation

For the binomial model, the inclusion of covariates for cycle and baseline seizure frequency, in addition to treatment, improve model fit (based on AIC/BIC). Although the contribution to model fit of the interaction term (treatment * cycle) was ambiguous (better AIC, worse BIC), it was still included in the model, since the company considered including changes in efficacy over time to more likely reflect clinical practice.

For the negative binomial model, goodness of fit statistics showed similar results. Details can be found in Appendix M of the CS.[13]

Observed versus predicted

The predicted values from the fitted models were compared to the observed values in the GWPCARE6 trial. The predicted values for seizure frequency were plotted against values from the blinded study period (weeks 1-16) and the OLE (weeks 17-88) in Figures 15 and 16 of the CS, respectively. The proportion of seizure-free days predicted by the model could only be compared to values from the blinded study period (Figure 14 of the CS[1]) since in the OLE no data on seizure-free days was available.

Deriving efficacy inputs for the cost effectiveness model

The coefficients of the selected binomial and negative binomial fitted models are presented below in Table 4.4 and 4.5, respectively.

Table 4.4: Selected binomial seizure-free day model coefficients

	Estimate	SE	p-value
Intercept	-0.9216*	0.2364	<0.001
Treatment = Placebo (Ref = Cannabidiol 25 mg/kg/day)	-0.5183	0.328	0.114
Log (cycle)	0.5358*	0.116	<0.001
Baseline seizure rate (scaled)	-2.8032*	0.2484	<0.001
Treatment (Placebo) * log (cycle)	-0.2411	0.1611	0.135

Source: Table 13 of the CS[1]
CS = company submission; SE = standard error; Ref = reference treatment; * = statistically significant

Table 4.5: Selected negative binomial seizure frequency model coefficients

	Estimate	SE	p-value
Intercept	0.8659*	0.05132	<0.001
Treatment=Placebo (Ref = Cannabidiol 25 mg/kg/day)	-0.0107	0.06919	0.877
Log (cycle)	-0.0621	0.02466	0.0118
Baseline seizure rate (scaled)	0.4937*	0.02901	<0.001
Treatment (Placebo) * log (cycle)	0.0519	0.03226	0.1074

Source: Table 14 of the CS[1]
CS = company submission; SE = standard error; Ref = reference treatment; * = statistically significant

From these coefficients for the seizure-free day model, it can be seen that there is a non-significant trend that patients on placebo have an increasingly lower odds of achieving seizure-free days over time (negative coefficient for treatment * log(cycle)). A higher baseline seizure rate also lowers the odds of achieving seizure-free days (negative coefficient). For the seizure frequency model, there is a non-significant trend for the placebo group to have increased seizure frequency over time (positive coefficient for treatment * log (cycle)). Also in this model, baseline seizure frequency is statistically significant, indicating higher baseline seizure frequency would be associated with higher seizure frequency overall.

In both models, treatment was not statistically significant. The company state this to possibly be a consequence of a lack of power since the modelling approach used for the economic model estimates seizure-free days and seizure frequency across two models rather than one (as in the clinical trial). The company performed a sensitivity analysis for the regression analysis, using a single negative binomial regression for seizure frequency on all days. In this sensitivity analysis, the treatment effect was statistically significant. Therefore, the company states, the p-values should be treated with caution.

The company also emphasised that the differences in statistical treatment effects predicted for the trial and the economic model were not unexpected, as the economic model considered 16 weekly periods where the analysis of primary endpoint of the trial included two periods (baseline and treatment).

Importantly, although not described as such in the company submission, the model applies a cut-off of 6.5 days to define a patient as 'seizure-free over seven days' (one cycle in the model). At baseline, in both arms, 0% of patients are seizure-free over seven days. In the usual care arm, none of the patients become seizure-free in the first 16 weeks, and this is sustained over the full time horizon of the model. In the cannabidiol arm, from week 10 onwards, a proportion of patients has >6.5 seizure-free days per week and is therefore counted as being 'seizure-free over seven days', which is then assumed to be sustained over the full time horizon of the model, whilst on treatment. However, when the cut-off value is set to seven days, none of the cannabidiol patients are 'seizure-free over seven days', as the maximum predicted number of seizure-free days with the binomial regression model is 6.62. The 'seizure-free over seven days' proportion has an impact on other elements in the analysis, for instance, on how patients are divided over the other seizure-frequency categories, on healthcare resource use, and on discontinuation rates.

Long term efficacy

The base case analysis assumed that the relative treatment effect obtained at 16 weeks is consistent and maintained over the entire model time horizon, whilst patients are on cannabidiol plus usual-care treatment. To sustain this assumption, the company describe a number of sources:

- GWPCARE6 OLE study. An interim analysis (at 72 weeks) of the OLE data reported a median reduction of 53-75% in seizure frequency. At least 6% of patients remained seizure-free during the 12-week windows.[27]
- GWPCARE5 OLE study.[28, 29] Demonstrated a sustained reduction in drop seizures/total seizures (for patients with LGS) and in convulsive/total seizures (for patients with DS) over 156 weeks of follow-up.
- United States (US) Expanded Access Programme (EAP)[30] providing cannabidiol to patients at 25 US epilepsy centres. Four-year data of the EAP in 34 patients with TSC-associated epilepsy demonstrated a continued response to treatment.

ERG comment: The main concerns of the ERG relate to: a) the cut-off of 6.5 days applied to define 'seizure-free over seven days'; b) patients in the usual-care arm cannot be seizure-free over the full time horizon of the model; c) regression analysis including baseline seizure frequency as most important predictor while this was not a pre-defined subgroup analysis in the trial; d) interaction term did not increase fit but was included; and e) the assumption of a sustained treatment effect whilst on treatment.

a) The ERG considers the cut-off of 6.5 days to define 'seizure-free over seven days' to be not well justified. As was apparent from the model, the binomial regression model predicted that no patient in the GWPCARE6 trial would have a seizure-free period of seven days. By setting the cut-off to 6.5 days, the proportion of patients counted as 'seizure-free over seven days' is artificially increased for the cannabidiol arm. Given that the situation at 16 weeks is assumed to be continued over the full time horizon of the model, this cut-off value has a substantial impact on the effectiveness and quality of life associated with cannabidiol in the model.
b) Related to the issue above, since the binomial model predicted none of the patients in the usual care arm to have more than 6.5 days without seizures, the model assumed that no patient in the usual-care arm will ever be seizure-free for a week. In response to the ERG's clarification question on how likely this would be in clinical practice, the company replied that in the GWPCARE6 Phase 3 clinical trial, patients had tried and discontinued up to 15 AEDs (median 4) in order to try to achieve seizure control, with some taking up to 5 AEDs concurrently (median 3) and still not gaining control of their seizures. The company therefore considered it to be highly unlikely that a patient who is already refractory would become seizure-free just by continuing on their existing usual-care treatment.[6] The ERG wants to emphasize that when the median number of AEDs that patients have tried is four, there will also be patients that have tried only one or two and may still benefit from trying more options. The ERG considers that by incorporating the results of the binomial regression in the way the company did, that is optimistically setting the cut-off for seizure-free over seven days at 6.5 days (see point a. above) , and then assuming the situation obtained at 16 weeks will remain constant until end of life whilst on treatment, the contrast between the two arms may be biased in favour of cannabidiol.
c) In both regression models, the baseline seizure frequency turned out to be the most important predictor (apart from the intercept in the seizure frequency model). Although baseline seizure frequency was not a treatment modifier explored in a pre-specified subgroup analysis, it was still included as a covariate to, as the company stated, 'explicitly model the range of seizures within and between patients, to accurately capture the patient population'. Treatment nor treatment*time interaction was statistically significant in either model. Although the ERG appreciates the explanation of the company for the lack of statistical power, the regression models seem to have been constructed in a potentially selective way. For the seizure frequency model, it is reassuring that model predictions seem to be line with observation from the OLE study, but seizure-free days were not registered in the OLE study and so there is no long-term validation for the binomial model.
d) Related to the previous issue, the ERG considers the justification for inclusion of the interaction term of treatment*time (log cycle) to be weak. Although contribution of this covariate to model fit was ambiguous, the company considered including changes in efficacy over time to more likely reflect clinical practice. No clinical expert opinion was provided to support this assumption.
e) The company assumes that whilst patients are on treatment, the benefit of cannabidiol may potentially last for a lifetime. This assumption was supported by observations in external

datasets, and in the OLE study (be it that follow-up was limited there). In the clarification phase, the ERG requested the company to provide scenarios where the effect of cannabidiol would wane even while on treatment. The company implemented this as an extra 16 cycles of treatment cost to patients that would discontinue because of loss of response (see response to clarification, question B8d[6]). This way of implementing a treatment waning effect had a relatively small effect on the ICER, potentially because most patients discontinue the use of cannabidiol anyway at some point because of a loss of response – the company indicated in response to the same clarification question that after 20 years, less than 6% was still on treatment. The ERG considers this issue to be of limited importance to overall uncertainty.

Although the ERG has concerns on the justifications for selection of certain covariates in the regression models, the models may predict seizure-free days and seizure frequency in a sufficiently accurate way. However, the way in which seizure-free days were incorporated in the model to predict 'seizure-free over seven days' is not justified and may not be in line with clinical practice, especially for the usual care arm.

4.2.7 Adverse events

The main source of evidence on treatment AEs used for cannabidiol and usual-care is the 16-week GWPCARE6 trial.[7, 15, 21] The company's model included all serious TEAEs classified as severe. Mean exposure in days was used to calculate the incidence rate per cycle and was applied to patients in the 'alive on cannabidiol plus usual care' health states. The AE transition probability was assumed to remain constant for the duration of the time horizon.

ERG comment: The main concerns of the ERG relate to: a) the selection of AEs for the model (serious TEAEs that were classified as severe) and b) the justification of using 16-week (and not OLE study) data to inform the incidence of AEs.

a) From the CS it was unclear how serious and severe TEAE was defined. In response to clarification question B15a, the company explained that in the GWPCARE6 trial, an AE was considered serious if it: 1) was fatal; 2) was life-threatening; 3) required inpatient hospitalisation or prolonged existing hospitalisation; 4) was persistently or significantly disabling or incapacitating; 5) was a congenital anomaly/birth defect; or (6) was a medically significant event that, based upon appropriate medical judgment, may have jeopardised the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above. For all AEs and serious AEs, the clinical trial investigators were required to assign and document severity (mild, moderate, severe), based on clinical judgement. The ERG believes that in terms of costs and utilities serious events are most relevant to the economic model. However, only serious TEAEs classified as severe were included, while mild and moderate events resulting in one of the serious AE criteria described above could also affect costs and utilities. However, the ERG does not believe this is a major issue given that the impact of AEs in the economic model is minimal.
b) The AE-related transition probabilities in the model were based on 16-week AE data from the GWPCARE6 trial. However, AE data from the extended OLE study was also available. In response to clarification question B15c, the company explained that this is a conservative approach, since the incidence of serious AE was [redacted]% in the 16-week initial GWPCARE6 trial, while the incidence decreased to [redacted]% in the OLE study. The ERG agrees that with correction for the decreased serious AE incidence from the OLE study, the ICER would be lower, although the impact of AEs in the economic model is minimal.

4.2.8 Mortality

Cannabidiol is not expected to have direct or indirect effects on non-epilepsy related TSC or non-TSC related mortality risk. Patients are at risk of mortality though because of their epilepsy (SUDEP), non-epilepsy-related TSC manifestations (mostly cardiac, respiratory, and renal), and non-TSC-related risks – general mortality.

As no SUDEP was observed in the GWPCARE6 trial, the expected survival benefit of cannabidiol in reducing SUDEP risk is not included in the model.

Background mortality was included to reflect the age-adjusted mortality risk for all patients in the model. Patient age distributions (in the GWPCARE6 trial, baseline age ranged from 1 to 57) were used to calculate the average annual age-adjusted probability of mortality, which is then converted into a per cycle probability.

To inform background TSC-related mortality, an SLR study from 2020 by Zöllner et al. (2020)[31] was used. This review included seven studies providing information on TSC-related mortality. The company assumed all seven studies were equally robust and pooled the data to obtain an excess TSC-related mortality rate of 0.736% per year.

Mortality risk associated with SUDEP was based on a study by Amin et al.[32] reporting causes of death in a UK cohort of 284 TSC patients. Over an 8-year time period, 16 patients had died, and four of those had died from SUDEP. This resulted in a 0.176% mortality risk per year. This risk is applied to both arms in the model. To avoid double counting, the SUDEP mortality risk was subtracted from the excess TSC-mortality risk per cycle and applied separately in the model.

ERG comment: The main concerns of the ERG relate to an error in the model causing the general population mortality to be 0% from age 97.

4.2.9 TSC-associated neuropsychiatric disorders (TAND)

TAND manifestations are common in patients with TSC throughout their lifetime. Commonly reported TAND disorders include cognitive issues, behavioural problems, and psychiatric disorders. A review of the TOSCA registry by de Vries et al.[33] found that intellectual disability was identified in 55% of patients, ASD in 21% of patients, and attention deficit hyperactive disorder (ADHD) in 19% of patients. The company presents qualitative evidence in LGS and DS that while on treatment with cannabidiol, patients have improvements in cognitive function, behaviour, communications, and emotional functioning,[34] and express the belief that a positive relation exists between effective treatment reducing seizures and an improvement in neuropsychiatric disorders. In the absence of sufficient evidence to definitively demonstrate the relationship between seizure frequency and TAND, clinical expert opinion - as part of the two-round Delphi panel - was used to inform the model.

Six aspects of TAND were considered, with their prevalence derived from a study by de Vries et al. based on the TOSCA registry.[33] As the age categories reported by de Vries et al. differed from those used in the model, they were matched as shown in Table 4.6 below.

Table 4.6: Proportions of patients with TAND aspects assumed in the cost effectiveness analysis

Age bands used by de Vries et al	≤2 and >2 to ≤5	>5 to ≤9 and >9 to ≤ 14	>14 to ≤18	>18 to ≤40 and >40
N[a]	584	642	184	806
Age bands used in cost effectiveness model	2–6 years	7–11 years	12–17 years	≥ 18 years
TAND aspects per age band				
Delayed development	8.4%	56.1%	52.7%	28.4%
Behavioural issues[b]	54.8%	100.0%	100.0%	88.7%
Intellectual disability[c]	5.5%	11.8%	12.8%	18.8%
Autism Spectrum Disorder	11.5%	22.0%	20.7%	8.4%
ADHD	10.4%	22.3%	12.5%	5.1%
Anxiety disorders	1.5%	7.2%	7.1%	8.1%

Based on Table 18 of the CS[1]

[a] Age groups combined (≤2 and >2 to ≤5 mapped to 2–6 years, >5 to ≤9 and >9 to ≤14 mapped to 7–11 years, >14 to ≤18 mapped to 12–17 years and >18 to ≤40 and >40 mapped to ≥18 years)

[b] Issues considered: overactivity, sleep difficulties, impulsivity, anxiety, mood swings, severe aggression, depression mood, self-injury, obsessions, psychosis and hallucinations. Patients can have more than one issue. Patients may experience more than one of the items per aspect. To avoid double costing resources, the proportion of patients for those aspects was capped at 100%

[c] Percentages calculated considering individuals with IQ assessment available in each age group: 2–6 years (n=202); 7–11 years (n=322); 12–17 years (n=263); ≥18 years (n=234)

[d] The authors of the de Vries et al study suggest that the low rates of ASD and ADHD observed in adults may be due to a cohort effect where adults were not assessed for developmental disorders in the past decades

ADHD = attention deficit hyperactivity disorder; CS = company submission; TAND = TSC-associated neuropsychiatric disorders; TSC = tuberous sclerosis complex.

The Delphi panel came to a 'near consensus' that the reduction in seizure frequency would have to be 47.5% to reduce the progression of TAND aspects. This was rounded to 50% in the model and incorporated by applying the benefit of reducing the progression of TAND to the proportion of patients who experienced a reduction in seizure frequency of at least 50% at 6 months following treatment initiation. In a scenario, the required reduction in seizure frequency was set to 75%.

The benefit was incorporated in the model as a reduction in resource use and an increase in HRQoL and was only applied to patients aged [redacted] as the Delphi panel suggested that earlier treatment may be more beneficial than treatment at any age. In a scenario, the benefit was applied to all age groups. In another scenario, the benefit of reducing the progression of TAND symptoms was applied for a 5-year time horizon only.

ERG comment: The main concerns of the ERG relate to: a) potential double counting of the effect of cannabidiol directly on HRQoL and indirectly via TAND; b) the fact that the responder percentage also for the base case was taken from the full model population instead of only the [redacted] age category; and c) the multiple uncertainties in every step of the calculation of the TAND benefit.

a) The ERG has concerns over the fact that the impact of TAND may be counted double in the model. Seizure frequency has an impact on resource use and HRQoL, but also on TAND which

in turn has again impact on resource use and HRQoL. Although the TAND aspects have a distinct impact on resource use and HRQoL, there may also be overlap with aspects already captured in the vignettes for instance. In their response to clarification, the company stated that although their approach to modelling the impact of TAND was not ideal, they have made their best efforts with the limited available evidence. The company also pointed towards the fact that in the model there was minor sensitivity to TAND. The ERG acknowledges the difficulty in modelling TAND with the data available but does not fully agree that the model is not sensitive to TAND assumptions. When excluding TAND altogether, the ICER would increase quite substantially. And so, the ERG considers the approach to TAND to introduce uncertainty in the results.

b) In their response to a clarification question on how the ≥50% TAND responder percentages were derived, the company stated that because of limited sample size in the [redacted] age category, they used percentages of TAND responders based on all age categories for the base case analysis (which modelled TAND benefits only for the [redacted] age category). From table 24 of the response to clarification[6] it is apparent that in the [redacted] year age category, the total percentage of responders is actually lower in the cannabidiol group than in the placebo group, so when these responder percentages would have been used in the base case, this would have increased the ICER. The ERG appreciates the issues associated with the low sample size, but considers the approach taken here to favour the cannabidiol arm without proper justification other than small sample size.

c) Related to the issues above, the ERG considers the approach taken to incorporate TAND into the analysis to be based on many assumptions, all of them being quite uncertain. First the prevalence of TAND aspects based on external data, then the near consensus (so not full consensus) of the Delphi panel on the 47.5% responder, then using responder percentages for all age categories to apply to the [redacted] category, then the assumption that the impact of the reduction in TAND would be over the complete lifetime of a patient. And there is also the matter of double-counting for HRQoL. All in all, the ERG is not convinced that the calculation of TAND impact in the model is valid.

4.2.10 Treatment discontinuation and stopping rules

The company's model includes discontinuation rates to reflect patients discontinuing treatment during the 16-week GWPCARE6 blinded trial and the follow-up OLE study (period of 72 weeks) (Table 4.7). A long-term discontinuation rate is also applied post the OLE period to reflect patients discontinuing therapy due to non-response and other factors over the long-term. In the absence of longer-term discontinuation data beyond the 72-week OLE, the long-term discontinuation rate agreed during the NICE TA615 appraisal for LGS was used.[23]

Table 4.7: Treatment discontinuation rate per 1-week cycle per seizure frequency category

	Clinical trial period	Open-label extension period	Long-term[23]
	Up to Week 16	Week 17 – Week 88	From Week 89
Seizure-free (per week)	[redacted]	[redacted]	0.04%
≤2 seizures per week	[redacted]	[redacted]	0.77%
>2 ≤7 seizure per week	[redacted]	[redacted]	0.77%
≥7 seizures per week	[redacted]	[redacted]	0.77%

Based on Table 17 of document B of the CS[1]
CS = company submission

In line with the previous submissions for cannabidiol in DS and LGS (TA614 and TA615),[23, 35] the company has applied a stopping rule every 6 months for 2 years if seizure frequency has not fallen by at least 30% from baseline in the base case analysis. The proportion of patients who would be expected to stop treatment at 6 months and at 12 months is based on the treatment period and the OLE study (72-week follow-up).[17, 27] The proportions of patients who would be expected to stop treatment at 18 months and at 24 months were assumed to be the same as at 12 months, as the OLE did not have sufficient follow-up data to calculate rates at 18 and 24 months (see Table 4.8). After stopping cannabidiol treatment, patients were assumed to receive other AED as subsequent treatment and therefore patients moved to the 'alive on treatment with usual care only' health state.

Table 4.8: Proportion of patients stopping per seizure frequency category (≤[redacted]%)

	At 6 months	At 12, 18 and 24 months
≤ [redacted]% response rate		
Seizure-free (per week)	[redacted]	[redacted]
≤ 2 seizures per week	[redacted]	[redacted]
> 2 ≤ 7 seizure per week	[redacted]	[redacted]
≥ 7 seizures per week	[redacted]	[redacted]

Based on Table 16 of document B of the CS[1]
CS = company submission
Note: [redacted]

ERG comment: After the correction in response to clarification for the inconsistency of the proportion of patients stopping with a seizure frequency of >2 ≤7 seizure per week at week 12, 18, and 24 months, the ERG considers the treatment discontinuation and the stopping rule to be appropriate.

4.2.11 Subsequent treatment

Everolimus was considered as a subsequent treatment in the model for 7.7% of the cohort based on the TuberOus SClerosis registry to increase disease Awareness (TOSCA) registry.[36] Patients in the cannabidiol arm receive everolimus after discontinuation of cannabidiol, patients in the placebo arm are assumed to receive everolimus at 2 years after the trial period. In both arms it was assumed that patients would receive everolimus for 2 years.

ERG comment: The main concerns of the ERG relate to the lack of justification for start everolimus treatment 2-year after trial period and the fact that the 7.7% is based on external data. This causes uncertainty in the model.

4.2.12 Health-related quality of life (HRQoL)

The utility values were estimated for every sub-health state based on seizure frequency per day (i.e., seizure-free per day, one seizure per day, two seizures per day, three or for seizures per day, and ≥5

seizures per day) and by seizure type (i.e., focal, generalised, or combined seizures) (see Figure 4.3). The utility values were treatment independent.

4.2.12.1 Health-related quality of life data identified in the GWPCARE6 trial

Health utilities were estimated in the GWPCARE6 trial with the QOLCE and QOLIE-31 P questionnaires.[7, 15, 21] However, the company did not use these measures to inform the CEA since these measures are not validated in TSC-associated epilepsy, the high level of missing data, and the lack of appropriate mapping methods. The S/CGIC questionnaire was also estimated, and though unlike the QOLCE and QOLIE-31 P results it was possible to draw conclusions on the HRQoL based on this questionnaire, the company did not use this measure for the CEA as it is not a preference-based measure.

4.2.12.2 Health-related quality of life data identified in the review

According to the CS,[1] the SLR identified only two relevant studies on HRQoL for patients and two for caregivers. However, the company concluded that these studies were not suitable for use in the cost effectiveness model. Additionally, two targeted literature reviews (TLRs) were conducted specifically to identify HRQoL data for patients in the broader fields of epilepsy and refractory epilepsy. The TLR for patient burden in refractory epilepsy identified six studies reporting HRQoL data associated with seizure frequency. However, none of the studies were used by the company as they stated that the studies showed inconsistency in the reported values across health states, seizure frequency categories that are not representative of patients with TSC-associated epilepsy, or the mean utility values were not linked to seizure frequency. None of the studies identified in the TLR for caregiver burden in rare epilepsies reported HRQoL data per seizure frequency and were therefore deeded unsuitable for use in the CEA.

4.2.12.3 Health state patient utility and caregiver disutility values (based on vignette study)

As neither the GWPCARE6 trial or literature reviews identified any suitable data to inform the CEA, and EQ-5D and other generic or condition specific preference-based measures used in patients or caregivers were also deemed unsuitable, the company conducted a vignette study using time trade-off (TTO) methodology in UK general population to value the patient's and caregiver's utilities per health state (based on seizure type and frequency). Table 4.9 shows the TTO weights for the health states assessed in the company's vignette study.

Table 4.9: TTO weights for TSC-associated epilepsy health state vignettes for patients (N=100) and caregivers (N=100)

Patients				
Seizure type and frequency		**Mean (SD)**	**SE**	**95% CI**
Generalised seizures	Focal seizures with impaired awareness			
Seizure-free		0.725 (0.253)	0.025	0.674, 0.775
-	1–2 per day	0.504 (0.371)	0.037	0.431, 0.578
-	3–4 per day	0.282 (0.535)	0.053	0.176, 0.388
-	5–14 per day	0.074 (0.551)	0.055	-0.036, 0.183
1 per day	-	0.183 (0.569)	0.057	0.070, 0.296
2 per day	-	0.089 (0.538)	0.054	-0.018, 0.196
3–14 per day	-	-0.113 (0.592)	0.059	-0.231, 0.004

3–14 per day	5–14 per day	-0.234 (0.560)	0.056	-0.345, 0.122
Caregiver				
Seizure-free		0.905 (0.083)	0.008	0.890, 0.921
-	1–2 per day	0.791 (0.171)	0.017	0.757, 0.825
-	3–4 per day	0.638 (0.365)	0.037	0.565, 0.710
-	5–14 per day	0.431 (0.494)	0.049	0.332, 0.529
1 per day	-	0.546 (0.395)	0.039	0.467, 0.624
2 per day	-	0.476 (0.453)	0.045	0.386, 0.566
3–14 per day	-	0.319 (0.481)	0.048	0.223, 0.414
3–14 per day	5–14 per day	0.221 (0.530)	0.053	0.115, 0.326

Based on Table 20 of document B of the CS[1]
CI = confidence interval; CS = company submission; SD = standard deviation; SE = standard error; TTO = time trade-off; TSC = tuberous sclerosis complex

The health states of the vignette study did not match the health states in the economic model and therefore it was necessary to calculate the utility for other possible combinations of seizure type and frequency. The company used various calculations to estimate the utilities of combined seizures with different frequencies. The interpolated TTO weights for seizure type and frequency combinations are shown in Table 4.10. Caregiver disutility values were applied additively to the patient's health state utilities. The company used the seizure-free health state utility for caregivers from the vignette study as the reference value in the calculation and all other caregiver utilities were subtracted from this value (Table 4.11).

Table 4.10: Interpolated TTO weights for seizure type and frequency combinations for TSC-associated epilepsy health states

Seizure type and frequency		Calculated mean
Generalised seizures	**Focal seizures with impaired awareness**	
Patient		
1 per day	1–4 per day	0.123
2 per day	1–4 per day	0.029
1 per day	5–14 per day	0.062
2 per day	5–14 per day	-0.174
3–14 per day	1–2 per day	-0.113
3–14 per day	3–4 per day	-0.174
Caregiver		
1 per day	1–4 per day	0.43
2 per day	1–4 per day	0.43
1 per day	5–14 per day	0.45
2 per day	5–14 per day	0.34
3–14 per day	1–2 per day	0.32

Seizure type and frequency		Calculated mean
3–14 per day	3–4 per day	0.27
Based on Table 21 of document B of the CS[1] CS = company submission; TTO = time trade-off; TSC = tuberous sclerosis complex		

Table 4.11:Calculated caregiver disutility TTO weights for seizure type and frequency combinations for TSC-associated epilepsy health states.

Seizure type and frequency		Calculated mean
Generalised seizures	**Focal seizures with impaired awareness**	
Seizure-free		[redacted]
-	1–2 per day	[redacted]
-	3–4 per day	[redacted]
-	5–14 per day	[redacted]
1 per day	-	[redacted]
2 per day	-	[redacted]
3–14 per day	-	[redacted]
1 per day	1–4 per day	[redacted]
2 per day	1–4 per day	[redacted]
3–14 per day	1–2 per day	[redacted]
3–14 per day	3–4 per day	[redacted]
1 per day	5–14 per day	[redacted]
2 per day	5–14 per day	[redacted]
3–14 per day	5–14 per day	[redacted]
Based on Table 22 of document B of the CS[1] CS = company submission; TTO = time trade-off; TSC = tuberous sclerosis complex		

The final patient utility and caregiver disutility values used in the economic model were calculated based on the TTO weights described above, weighted by the proportion per seizure type and frequency combinations reported in the GWPCARE6 trial at week 16 (Appendix L of CS).[7, 15, 21] The GWPCARE6 trial were extrapolated long-term in the model as the company argues that the seizure type distributions are not expected to change over time. The final calculated health state patient utility and caregiver disutility values are presented in Table 4.12.

Table 4.12: Health state utility values for patients and disutility values for caregivers used in the economic model.

Health state	Utility value	Reference
Patient utility		
Seizure-free per day	[redacted]	Lo et al., (2021)[37]
1 seizure per day	[redacted]	Vignette study by the company, adjusted to account for seizure type distribution
2 seizures per day	[redacted]	

Health state	Utility value	Reference
3 or 4 seizures per day	[redacted]	
5 or more seizures per day	[redacted]	
Caregiver disutility		
Seizure-free per day	[redacted]	Lo et al., (2021)[37]
1 seizure per day	[redacted]	Vignette study by the company, adjusted to account for seizure type distribution
2 seizures per day	[redacted]	
3 or 4 seizures per day	[redacted]	
5 or more seizures per day	[redacted]	
Based on Table 23 of document B of the CS[1] CS = company submission		

4.2.12.4 Adverse event-related disutility value

Adverse event-related disutility values related to SAEs classified as severe and treatment-related sourced from the GWPCARE6 trial were applied in the model.[7, 15, 21] There was no AE-related disutility value available from the GWPCARE6 trials and the company did not identify any literature on disutility values specifically for cannabidiol treatment. Therefore, a study by de Kinderen et al. that reported a disutility (-0.061) for epilepsy TRAE was used to inform the model.[38] This value was calculated using vignettes elicited from a convenience sample of the Dutch population using TTO methodology and was deemed suitable for use by the ERG in previous appraisals for other cannabidiol indications DS and LGS (TA614 and TA615).[23, 35]

4.2.12.5 TAND-related health utility increment values

Based on the company's argument that impact of TAND on QoL have not been fully captured in the Vignette study, a utility increment associated with delaying the progression of TAND is applied in both model arms to the proportion of patients who at 6 months following treatment initiation had a 50% reduction in seizure frequency. Based on a study on the TOSCA registry by de Vries et al.,[33] the company applied an average TAND-related increment calculated based on the proportion of TAND aspects reported in de Vries et al. by age group (Table 18 of the CS). The company assumed a reduction of 50% of the TAND-related symptoms and therefore applied a 50% reduced TAND-related utility increment. TAND-related health utility increment values used in the economic model are summarised in Table 4.13.

Table 4.13: TAND-related health utility increment values.

Age group	Weighted average utility increment per cycle	
	Base case	Scenario
Ages (2–6)	0.072	0.041
Ages (7–11)	0.173	0.099
Ages (12–17)	0.165	0.093
Adult (≥ 18 years)	0.128	0.071
Source: Based on Table 24 of the CS[1] CS = company submission; TAND = tuberous sclerosis complex-associated neuropsychiatric disorders		

ERG comment: The main concerns of the ERG relate to: a) patient utilities were not corrected for age- and gender-matched population norms; b) caregiver baseline utilities may be overestimated and not corrected for age related decrements; c) both caregivers are assumed to have an equally large utility decrement; and d) caregiver disutilities are not corrected to the fact that part of the patients will be institutionalized at some point.

a) In their response to clarification,[6] the company added a general population utility value cap on the patient utility values, ensuring that utilities do not exceed the age- and gender-matched population norms, into the model. The ERG requested this because in the original model, utilities for health states could exceed population norms. The company did not incorporate this change into their updated base case though, which the ERG considers unjustified.
b) The ERG believes that the seizure-free health state utility value estimated in the Vignette study for caregivers (0.905), which was used as a base for calculating the carer disutilities in the non-seizure free health states, is overestimated. As the company explains in their response, the seizure-free utility value for carers based on the Vignette study (0.905) is already higher than the general utility for a woman aged 43 (based on Office for National Statistics (ONS) data this is the average age of a mother of a 13-year-old child). This difference increases with age of the carer and male gender. Moreover, TSC is a severe disease which among epilepsy also causes other symptoms that may cause burden for the caregivers. This is support by a study by Vyas et al.,[39] which showed that overall time spent caring for patients with TSC is 128 hours per week, of which 11 hours per week seizure specific. This implies that when a patient is seizure-free, the caregiver may still have many worries, so a utility score of 0.905 may overestimate carer HRQoL for this health state. The carer disutilities were not corrected for age-related decrements, while carers also age. However, the inclusion of an age-related utility cap for caregivers is not as straightforward as with patient utilities (which were included in response to clarification question B17), since care might be taken on by other caregivers when the carer is not capable of caring for the patient (e.g., due to high age).
c) Caregiver disutilities were assumed to apply additively to two caregivers. However, it is unlikely that both caregivers provide equal care to the patient. For example, Vyas et al.[39] showed that all household members together spent a total of 11 seizure-specific hours per week, of which 7 hours were spent by the primary caregiver. This indicates that disutilities might also differ between caregivers. Also, in TA614[35] and TA615[23] the committee concluded linearly extrapolating to two caregivers was not preferable. In response to clarification question B18a, the company explains that the vignette study specifically assessed caregiver QoL in the context of the respondent being one of two primary caregivers. The company, therefore, concluded it is reasonable to assume that the caregiver utility estimates are representative of an individual's QoL decrement where another carer was present. The company also explains that including disutilities for two carers also reflects the impact of TSC-associated epilepsy on the QoL of the wider family (including siblings, grandparents, etc.). The ERG agrees TSC-associated epilepsy has a considerable impact on caregivers and family and agrees that the vignette study corrected for the fact that the participant was one of two carers. However, it is not specified in the Vignette study whether the care is equally distributed over the caregivers. Moreover, there is uncertainty around the number of caregivers in time and the exact effect of the disease on other family members.
d) The caregiver disutilities were not corrected for the fact that a part of the patients will be institutionalised at a certain point (according to the Delphi panel study, [redacted]% of patients would be institutionalised at an average age of [redacted] see also Section 4.2.6). Especially in adult patients, parents or siblings may not always be able to continue caring for them, and it may need extra

help from institutions, or the patient will be institutionalised. Costs for additional support and institutionalisation (residential care) were included in the model for adult patients, but carer utilities were not corrected for this.

4.2.13 Resources and costs

The cost categories included in the model were treatment acquisition costs, monitoring costs, health state unit costs and resource use, and costs of managing TAND and AEs.

Unit prices were based on the NHS reference cost schedule 2019-2020, Personal Social Services Research Unit (PSSRU) 2021, Monthly Index of Medical Specialities (MIMS), and electronic Market Information Tool (eMIT).[40, 41, 42,, 43]

Resource use and costs data identified in the review

According to the CS, the SLR identified four studies reporting UK relevant resource use and cost information (see Table 25 of the CS). However, none of these studies reported resource use based on seizure frequency. As the company expected HCRU to differ with low and high seizure frequencies, the papers were considered unsuitable to inform model resource use.

Treatment costs (with PAS)

Dosages for all AEDs and cannabidiol were based on the approved licensed dose for epilepsy. When approved licensed dose varied for adults and children, the paediatric dose was used to estimate the drug resource use for patients aged up to 17 years, and the adult dose was used for patients aged ≥18 years. Detailed information on dosages for paediatric and adult patients is presented in Tables 35 and 36, respectively, of Appendix S of the CS.[13]

Table 34 of Appendix S of the CS shows details of drug unit cost[13]. Unit costs for AEDs were sourced from MIMS and eMIT.[40, 41] NHS prescription cost analysis data[44] was used to estimate a weighted average for each AED given the multiple available doses and formulations. The list price for cannabidiol is £850.29 per 100 ml bottle. Unit costs for cannabidiol in the model were based on the PAS price of [redacted] per 100 ml bottle ([redacted] per mg).

To account for variation in patient weight, the per cycle treatment cost for AED, the per cycle average treatment costs were based on the age group distribution from the GWPCARE6 clinical trial.[7] For patients aged 2-6, 7-11, 12-17 and ≥18 years, the mean weight at baseline in each age group was used to calculate the correct dose. Table 4.14 shows the resulting treatment acquisition costs per cycle and per age category as used in the health economic model.

Costs for AEDs per cycle for subsequent treatment are assumed to be the same as for initial treatment and are detailed in Appendix S of the CS.[13] The base case analysis includes a one-off cost for everolimus as a subsequent treatment (see Table 4.14). The mean BSA from the GWPCARE6 trial (baseline per age group) was used to calculate the appropriate dose. Subsequent treatment with everolimus is applied as a one-off cost for 7.7% of the patients (based on the TOSCA registry[36]), on discontinuation for cannabidiol in the cannabidiol arm and 2 years post the trial in the placebo arm.

Table 4.14: Treatment acquisition cost per cycle (including PAS for cannabidiol)

Age group	AED cost per cycle	Cannabidiol cost per cycle	Subsequent treatment (everolimus), one-off
Ages (2–6)	£12.80	[redacted]	£5,922.06

Age group	AED cost per cycle	Cannabidiol cost per cycle	Subsequent treatment (everolimus), one-off
Ages (7–11)	£27.51	[redacted]	£7,047.18
Ages (12–17)	£32.94	[redacted]	£10,267.75
Adult (≥ 18 years)	£16.80	[redacted]	£12,462.81
Based on Tables 37 and 38 of Appendix S of the CS[13] and Table 27 of Document B of the CS[1] AED = anti-epileptic drug; CS = company submission; PAS = Patient Access Scheme			

No treatment administration costs were included as all drugs are administered orally. Therefore, also vial sharing does not apply. A scenario was run where the costs of concomitant AED medication was reduced by 10% as data from the US EAP for LGS and DS showed that 52% of patients taking valproate reduced their dose while taking cannabidiol.[45]

Monitoring costs

As the costs for liver monitoring associated with AEDs were assumed to balance across the arms, the company only included the additional liver function tests associated with cannabidiol, every 3 months for 1 year, at a cost of £1.91 per test.[42]

Health state unit costs and resource use

Annual HCRU was elicited by conducting a two-round Delphi panel involving 10 clinical experts. To frame the questions for the Delphi panel, seizure frequency categories were defined, informed by the GWPCARE6 trial, the predicted seizure frequency distributions and clinical feedback. In this way, four weekly seizure frequency categories were defined:

- Seizure-free (no seizures per week)
- Low seizure frequency (fewer than two seizures per week)
- Medium seizure frequency (more than two and no more than seven seizures per week)
- High seizure frequency (more than seven seizures per week)

Consensus in the Delphi panel was defined as 70% (so seven out of 10) of the respondents agreeing.

The main findings of the Delphi panel study were:[46]

- General Practitioner (GP) visits, physician visit, psychiatry or mental health visits, speech and language outpatient visits and epilepsy nurse visits were considered to have the same annual visit frequency regardless of the type of seizures
- Patients experiencing only focal seizures with impairment of awareness would have lower hospital related HCRU and rescue medication compared to those also experiencing generalised seizures
- The mean age at which patients transition from paediatric to adult services is [redacted] years
- HCRU increased consistently for all categories with increased seizure frequency

The results of the Delphi panel study were validated with values reported in a study by Shepherd et al.[47] which collected HCRU in patients with TSC-associated epilepsy, and the results were also discussed with a clinical expert.[26] HCRU elicited by the Delphi panel study was comparable to HCRU reported by Shepherd but the Delphi panel reported higher resource use in the paediatric population. This may have been caused by new UK guidance as of 2018[34] since the Shepherd study was based on a retrospective cohort using data from up to 2013.

The resulting total health state resource use costs are presented in Table 4.15. As the model predicts combined seizure frequency for generalised seizures and focal with impairment of awareness seizures, the distribution of seizure types from the week 16 GWPCARE6 trial data were used to calculate the weighted average patient costs per model cycle. In the model, when patients experience a combination of generalised seizures and focal with impairment of awareness seizures, the HCRU is assumed to be reflective of a generalised seizure, as this has the higher impact on resource use.

Additional support costs (educational, day care, homecare) were not included in the base case but their addition was explored in a scenario.

Details of resource use and unit costs were specified in Appendix T of the CS.[13]

Table 4.15: Total healthcare resource use per cycle

Health state	Generalised seizures		Focal with impairment seizures	
	Paediatric	Adult	Paediatric	Adult
Seizure-free	£53.37	£540.85	£39.97	£533.46
≤ 2 seizures per week	£143.30	£594.36	£99.16	£568.99
>2 - ≤ 7 seizures per week	£288.90	£716.21	£195.20	£631.29
> 7 seizures per week	£700.17	£993.55	£427.93	£768.14

Based on Table 26 of document B of the CS[1]
CS = company submission

Adverse event costs

Serious AEs which were defined as 'requires or prolongs hospitalization' as per the GWPCARE6 protocol were assumed to require a hospitalisation at a cost of £802.39. Serious AEs which were defined as 'other medically important' were assumed to be treated by a visit to an epilepsy specialist nurse at a cost of £51. Costs were applied per cycle. Detailed AE costs can be found in Table 53 of Appendix T.[13]

TAND treatment costs

Costs for managing TAND were sourced from a pan-European study of brain disorder costs by Gustavsson et al. dating from 2011,[48] where six TAND aspects were matched to the International Classification of Disease (ICD) codes in the study. See Table 28 of the CS for details on the matching and associated annual costs.

In the base case analysis, the cost of TAND is applied to both arms. The model applies a weighted average TAND cost by age group. The reduction in management costs is applied for a lifetime horizon to the proportion of patients aged ≤6 years who, after 6 months of treatment, had a 50% reduction in seizures compared to baseline. In a scenario, the reduced cost is applied for 5 years only. See Table 4.16 for average TAND costs and reduced TAND costs as applied in the model.

Table 4.16: TAND cost by age group

Age group	Weighted average cost of TAND per cycle	Reduced cost of TAND per cycle applied to treatment responders
Ages (2–6)	£50.47	£25.24
Ages (7–11)	£134.06	£67.03

Age group	Weighted average cost of TAND per cycle	Reduced cost of TAND per cycle applied to treatment responders
Ages (12–17)	£122.39	£61.19
Adult (≥ 18 years)	£86.05	£43.02
Based on Table 29 of document B of the CS[1] CS = company submission; TAND = TSC-related neuropsychiatric disorders; TSC = tuberous sclerosis complex		

ERG comment: The main concerns of the ERG relate to: a) the fact that all healthcare resource use data to inform the model were obtained from the Delphi panel study; and b) treatment acquisition costs for age 18+ was based on average weight and BSA of this age group in the trial, where the average age was [redacted]

a) Healthcare resource use estimates for the health states were based solely on a Delphi panel. Validation was performed with one published study by Shepherd et al.[47] The company stated that for paediatric resource use, the Delphi panel reported higher values. The ERG could not verify this by inspection of the Shepherd study, as the definition of the HCRU categories was not fully comparable and the Shepherd study did not report resource use by seizure frequency. But, for instance, the number of GP visits reported by Shepherd (24 GP clinic visits over a 3-year period) did not seem to be lower than the number resulting from the Delphi panel (ranging from 2.5 to 8.4 depending on seizure frequency). The ERG is concerned by this and considers the validation with the report by Shepherd to be of little value.
b) Related to the issue mentioned in Section 4.2.3 (population), costs of treatment acquisition were based on average weight (for cannabidiol and AEDs) and BSA (for everolimus). For the 18+ age category, which applies for the larger part of the model cycles, the weight and BSA is based on average weight and BSA as observed in the 18+ group in the GWPCARE6 trial. The ERG has concerns on whether this group is representative for the whole of the adult TSC population. For instance, the average age of this group is [redacted] with a standard deviation of [redacted], and the percentage of females is [redacted] - which is lower than in all other age categories in the GWPCARE6 trial. This implies that in the model, as soon as a patient turns 18 years of age, they are assumed to have the weight and BSA associated with a [redacted]-old (and '[redacted]female'). Also, from that time, the weight and BSA is assumed to remain constant for the rest of the time horizon. Although it is difficult to say whether weight and BSA accurately represent the population, and how likely it is that no changes will occur over time, the ERG would like to see the impact of these variables on the ICER explored and therefore included scenarios varying weight and BSA at age 18.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CS base case cost effectiveness results (probabilistic) indicated that cannabidiol is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than current care amounting to an ICER of £14,196 per QALY gained (Table 5.1). Figure 5.1 shows the cost effectiveness plane. The cost effectiveness acceptability curve shows that the probability of cannabidiol being cost-effective compared to placebo, at a threshold of £30,000 per QALY gained, is 89% (Figure 5.2).

Table 5.1: Company's probabilistic base case results

Technologies	Total costs (£)*	Total QALYs*		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo + usual care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]			
Cannabidiol + usual care	[redacted]	Patient QALY	[redacted]			
		Caregiver QALY decrement	[redacted]			
		Total	[redacted]	[redacted]	[redacted]	£14,196

Based on the updated company model[6]
ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years
Note: *Discounting is applied to QALYs and cost

Figure 5.1: Company's cost-effectiveness plane

[redacted]

Source: Figure 20 of the CS[6]

CS = company submission; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year
Note: The difference in the probabilistic sensitivity analysis and deterministic results and the skew in the cost effectiveness plane is driven by the non-linearity of the regression analysis

Figure 5.2: Company's cost effectiveness acceptability curve

Source: Figure 21 of the CS.[6]
CS = company submission; ICER = incremental cost-effectiveness ratio

Overall, the technology is modelled to affect QALYs by:

- Increasing QoL of the patient through a reduction in seizures
- Decreasing the loss in QoL of the caregivers through a reduction in seizures

Overall, the technology is modelled to affect costs by:

- Its higher treatment acquisition price compared to care as usual
- A reduction in health state costs because of a reduction in seizure frequency

ERG comment: The main concerns of the ERG relate to the difference between the deterministic and probabilistic ICER. The company states this difference, and also the skewness in the cost effectiveness plane, to have its source in the non-linearity of the regression analysis. The ERG was not able to confirm this.

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses.

Figure 5.3: Company's tornado diagram of one-way deterministic sensitivity analyses (DSA)

Source: Figure 22 of the CS[6]
CS = company submission; CBD = cannabidiol; ICER = incremental cost-effectiveness ratio; HS = health state; pw = per week; TAND = TSC-associated neuropsychiatric disorders; UC = usual-care

Figure 5.4: Top 10 most influential scenario analyses

Source: Figure 23 of the CS.[6]

AED = anti-epileptic drug; CS = company submission; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; SmPC = summary of product characteristics; SUDEP = sudden unexpected death in epilepsy; TAND = TSC-associated neuropsychiatric disorders; UC = usual-care

The parameters that have the greatest effect on the ICER (based on the company's sensitivity analyses, Figure 5.3) are:

- the stopping rule assessment rate applied at 6 months for patients with a seizure frequency greater than seven per week
- the patient utility values for seizure-free patients
- response rates used to estimate the proportion of patients who benefit from a reduction in TAND symptoms

The CS scenarios that have a substantial impact on the ICER are the following:

- inclusion of wider social costs: social and educational care resource use
- applying benefit of TAND reduction to all age groups
- reducing the cannabidiol dose from 12 to 10 mg/kg/day

ERG comment: The main concerns of the ERG relate to the fact that the cannabidiol dose was only varied to 10 mg (a lower value compared to the base case of 12 mg) in the scenario, while there was uncertainty both ways as discussed in Section 4.2.4. The company did include an option in the model to increase dose as well though. Also, the number of carers was only varied in one direction in the scenario analyses (up to three) while the base case value of two carers is already higher than the 1.8 carers that the committees in TA614 and TA615 preferred[23, 35] as discussed in Section 4.2.12.

5.3 Model validation and face validity check

5.3.1 Face validity and technical assessment

All parameters and assumptions applied in the economic model were externally validated by an independent health economist. The model concept, structure, and key assumptions were validated by three health economists and two clinical experts. Once the model was finalised, internal modellers conducted quality control checks, and a programmer checked formulae and labelling. In addition, an external group of modellers performed a detailed review of formula, labelling and model assumptions.

Validity of the regression models was checked by comparing observed versus modelled seizure frequencies and seizure-free days, as also discussed in Section 4.2.6 of this report.

5.3.2 Comparisons with other technology appraisals

The technology appraisals for DS and LGS[23, 35] were referred to in many instances, and the current appraisal applied many of the same assumptions. In Appendix G of the CS, published cost effectiveness studies and their relevance to the current appraisal were discussed.

5.3.3 Comparison with external data

The HRQoL data collected via the Vignette study were validated to published EQ-5D and HUI data.[49] Both these studies were limited however and were not suitable for use in the base case.

The HCRU data as collected via the Delphi panel study were compared to the Shepherd study. The company concluded that results were broadly robust and comparable. A clinical expert noted that differences observed may be due to changing treatment practice.

ERG comment: The ERG considers the validation against EQ-5D and HUI data and the Shepherd report not to be proper external validation (see also discussion in Section 4.2.13 on the Shepherd report) but appreciates the fact that little external data is available for this purpose.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020[50]:

- Transparency (e.g., lack of clarity in presentation, description, or justification)
- Methods (e.g., violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g., particularly wide CIs, small sample sizes, or immaturity of data)
- Bias and indirectness (e.g., there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g., lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the ERG base case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base case. This base case included multiple adjustments to the original base case presented in the previous sections. These adjustments made by the ERG form the ERG base case and were subdivided into three categories (derived from Kaltenthaler 2016)[51]:

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base case

Adjustments made by the ERG, to derive the ERG base case (using the CS base case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base case. The 'FE' adjustments were combined, and the other ERG analyses were performed also incorporating these 'FE' adjustments given the ERG considered that the 'FE' adjustments corrected unequivocally wrong issues.

Fixing errors

1. Correction of general population mortality from age 97 (Section 4.2.8)

Fixing violations

2. Inclusion of age-related utility cap for patients (Section 4.2.12)
3. Issue 12 (Section 4.2.12)
   Seizure-free health state utility for carers adjusted to general population utility

Matters of judgement

4. Issue 11 (Section 4.2.9)
   Exclusion of TAND-related management costs and utility increments

5. Issue 13 (Section 4.2.12)
   Number of caregivers adjusted to 1.8
6. Issue 13 (Section 4.2.12)
   Adjust caregiver utilities for institutionalisation

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base case.

Exploratory scenario analyses:

1. Average cannabidiol dose based on 15 mg/kg/day (Issue 9 Section 4.2.4)
2. Average cannabidiol dose based on 20 mg/kg/day (Issue 9 Section 4.2.4)
3. Weight and BSA – 5% higher than base case (Issue 8 Section 4.2.3)
4. Weight and BSA – 5% lower than base case (Issue 8 Section 4.2.3)
5. Seizure freedom per week cut-off – 7 days (Issue 10 Section 4.2.6)

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 6.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
Because of small sample size, patient characteristics between age categories varied. This may have an impact on assumed weight and BSA which, in turn, determined treatment costs.	4.2.3	Transparency and unavailability; data for 1-year-olds separately were not provided by the company and small sample size	Conduct regression analysis for effectiveness based on trial population aged 2-years and older or provide data for 1-year-olds separately	+/-	No, however, impact of uncertainty around weight and BSA were explored in ERG scenarios 3 and 4	Compare effectiveness in 1-year-olds to patients aged 2 years and older
The company assumed a 12 mg/kg/day average dose in the model used to calculate the drug costs. However, a dose of 25 mg/kg/day was used to inform most other model inputs, and it is unclear whether an average of 12 mg/kg/day reflects clinical practice.	4.2.4	Transparency	Explore impact of higher average dose	+	No, however, impact of higher average cannabidiol dose was explored in ERG scenarios 1 and 2. Average dose in GWPCARE6 and OLE study trial was unknown to the ERG	Data on average cannabidiol dose in GWPCARE6/OLE study and real-world
The way in which seizure-free days as predicted by the binomial regression were incorporated in the economic model to	4.2.6	Bias and indirectness, the cut-off value of 6.5 days is not justified	Using a cut-off of 7 days.	+	Partly in ERG scenario 5, by exploring an alternative cut-off value. This may not	Long-term real-world data on seizure-free days (which was not available from the OLE study) or structuring the model in

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
predict 'seizure-free over 7 days' is not justified and may not be in line with clinical practice, especially for the usual care arm.					resolve the issue however, as with a cut-off of 7 days 0% of all patients would be seizure-free, which may not be reflective of clinical practice.	a way that does not rely on seizure-free days.
The impact of TAND was modelled using many uncertain assumptions.	4.2.9	Unavailability	Remove effect on TAND from the model due to lack of data	+	Yes, TAND was excluded in ERG base case (MJ 4).	Long-term data on effect of cannabidiol on TAND is required
The ERG believes that the seizure-free health state utility value estimated in the vignette study for caregivers (0.905), is overestimated, leading to an over-estimation of cannabidiol's cost effectiveness.	4.2.12	Bias & indirectness as utility may not be appropriate to the carer's health state in question	Correct carer disutilities for age, correct for remaining worries caregiver after patient being seizure-free	+	Partly, in ERG base case (MJ 3)	Data on carer age and/or EQ-5D survey data for validation of vignette utilities.
The assumption to apply caregiver disutilities additively to two caregivers lacks justification. Additionally, unlike costs utilities were	4.2.12	Unavailability data on number of carers per age category, bias because of design vignette study, and utilities were not corrected for institutionalization)	Number of carers aligned with previous TAs of cannabidiol (1.8), and adjust for institutionalisation	+	Yes, in ERG base case (MJ 5 and 6)	Not applicable

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
not corrected for patients being institutionalised.						

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored

BSA = body surface area; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; OLE = open-label extension; MJ = matters of judgement; ICER = incremental cost effectiveness ratio; TA = technical appraisal; TAND = TSC-associated neuropsychiatric disorders

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base case was presented, which was based on various changes compared to the company base case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3 deterministically and Table 6.4 probabilistically. These are all conditional on the ERG base case. The analyses numbers in Tables 6.2, 6.3, and 6.4 correspond to the numbers reported in Section 6.1. The cost effectiveness acceptability curves of the ERG base case and the exploratory scenario analyses are presented in Figures 6.1 to 6.6. The submitted model file contains technical details on the analyses performed by the ERG (e.g., the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,712
Fixing errors 1: Correction of general population mortality from age 97					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,712
Fixing violations 2: Inclusion of age-related utility cap for patients					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£12,713
Fixing violations 3: Seizure-free health state utility for carers adjusted to general population utility					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,126
Matters of judgement 4: Exclusion of TAND-related management costs and utility increments					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£14,391

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matters of judgement 5: Number of caregivers adjusted to 1.8					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,451
Matters of judgement 6: Adjust utilities for institutionalisation					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£13,696
CS = company submission; ICER = incremental cost-effectiveness ratio; TAND = TSC-associated neuropsychiatric disorders; QALYs = quality-adjusted life years					

Table 6.3: Deterministic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£16,928
Scenario 1: Average cannabidiol dose based on 15 mg/kg/day					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£27,210
Scenario 2: Average cannabidiol dose based on 20 mg/kg/day					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£44,347
Scenario 3: Weight and BSA – 5% higher than base case					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£18,949
Scenario 4: Weight and BSA – 5% lower than base case					
Cannabidiol + usual care	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£14,907
Scenario 5: Seizure freedom per week cut-off – 7 days					
Cannabidiol + usual care	[redacted]	[redacted]			
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£24,022
BSA = body surface area; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years					

Table 6.4: Probabilistic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Probability
ERG base case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£19,820	[redacted]
Scenario 1: Average cannabidiol dose based on 15 mg/kg/day						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£29,949	[redacted]
Scenario 2: Average cannabidiol dose based on 20 mg/kg/day						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£50,759	[redacted]
Scenario 3: Weight and BSA – 5% higher than base case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£21,750	[redacted]
Scenario 4: Weight and BSA – 5% lower than base case						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£16,843	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Probability
Scenario 5: Seizure freedom per week cut-off – 7 days						
Cannabidiol + usual care	[redacted]	[redacted]				
Placebo + usual care	[redacted]	[redacted]	[redacted]	[redacted]	£27,256	[redacted]
BSA = body surface area; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years						

Figure 6.1: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual care based on ERG base case

ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio

Figure 6.2: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual based on scenario 1

ICER = incremental cost-effectiveness ratio

Figure 6.3: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual based on scenario 2

ICER = incremental cost-effectiveness ratio

Figure 6.4: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual based on scenario 3

ICER = incremental cost-effectiveness ratio

Figure 6.5: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual based on scenario 4

ICER = incremental cost-effectiveness ratio

Figure 6.6: Cost effectiveness acceptability curve of cannabidiol + usual care versus placebo + usual based on scenario 5

ICER = incremental cost-effectiveness ratio

6.3 ERG's preferred assumptions

The estimated ERG base case ICER (deterministic), based on the ERG preferred assumptions highlighted in Section 6.1, was £16,928 per QALY gained. The probabilistic ERG base case analyses resulted in an ICER of £19,820 per QALY gained and indicated a cost effectiveness probability of [redacted]% at a willingness-to-pay threshold of £30,000 per QALY gained. The most influential adjustments were exclusion of TAND-related management costs and utility increments, assuming 1.8 caregivers and adjusting the utilities for institutionalisation. The ICER increased most in the scenario analyses with alternative assumptions regarding average cannabidiol dose, followed by the scenario where the cut-off for 'seizure-free over 7 days' was set to 7-days.

6.4 Conclusions of the cost effectiveness section

The company developed a de novo health economic model to determine the cost effectiveness of cannabidiol plus usual care compared to usual care for treating seizures caused by TSC. Health states in the model were centred around seizure-free days and seizure frequency. The evidence to populate the model was mostly derived from the GWPCARE6 trial. Data from this trial was used to develop two regression models predicting seizure-free days and seizure frequency. The QoL in patients and carers, and also health state costs were dependent on these seizure categories. The company base case assumed that each patient has two carers that spend an equal amount of time and have an equal impact on their QoL. The ERG argues that, despite alternative wording in the vignette study, a number of 1.8 may be more appropriate and in line with previous appraisals (Issue 13). The ERG also corrected for the fact that part of patients would be institutionalised at some point, making care by family members less prominent (Issue 13). Also, the baseline utility assigned to caring for a seizure-free patient seems overestimated (Issue 12). The incorporation of TAND in the model was based on a sequence of assumptions, of which most were not supported by evidence or solid justifications (Issue 11). These issues were all partly resolved in the ERG base case analyses.

The dosage of 12 mg/kg/day used in the model was not supported by data, as the average dose of cannabidiol in the GWPCARE6 trial of the OLE study was not reported (Issue 9). As increasing the dosage had a substantial impact on the ICER, the ERG considers the absence of information on actual provided dosage to be a source of uncertainty and potential bias. There was also uncertainty on how representative the population in the trial was of the target population, in terms of age, weight, and BSA (Issue 8). It would be useful to have information on the effect of cannabidiol separately for the group of 1-year olds that were included in the trial (but are not officially part of the target population), and on the average weight and BSA of an adult population with TSC.

Lastly, the fact that the economic model used a cut-off of 6.5 days to define 'seizure-free over 7-days' was not justified by the company. When using a cut-off of 7-days, which would seem to be the correct definition of a week, none of the patients in either arm would have a seizure-free week over the entire time horizon of the model (Issue 10). This raises doubts on the validity of the approach taken to model seizure-free days in the economic analysis, and the ERG has concerns over the uncertainty associated with this, which could not be fully captured by the scenario analysis.

7 END-OF-LIFE

The company does not claim that the intervention meets the NICE end-of-life criteria.

ERG comment: The ERG agrees that the intervention does not meet the NICE end-of-life criteria.

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Appendix 1: ERG search strategies

Embase (Ovid): 1974-2022/03/28
Searched 29.3.22

TSC + Epilepsy (facets translated from CS search) + Antiepilepsy drugs + RCTs

1 exp tuberous sclerosis/ (11636)
2 ("tuberous sclerosis" or "tuberous sclerosis" or tsc).ti,ab. (13780)
3 1 or 2 (16489)
4 exp epilepsy/ (255168)
5 exp seizure/ (161718)
6 (epilepsy or seizure or 'generalized epilepsy' or 'focal epilepsy' or epilepsy or epilept$ or seizure$ or convuls$ or fit$ or spasm$ or attack$ or atonic or myoclonic or dropi or tonic or clonic or partial or focal or absence).ti,ab. (2526805)
7 or/4-6 (2617012)
8 3 and 7 (5622)
9 limit 8 to (abstracts and human) (4366)
10 exp anticonvulsive agent/ or (anti?convulsive$ or anti-epileptic$).ti,ab,ot. (453345)
11 valproic acid/ or (Absenor or apilepsin or attemperator or convulex or convival chrono or "ct 010" or ct010 or delepsine or depacon or depakene or depakin$ or depalept or deprakine or diplexil or dipropylacetate or diprosin or dyzantil or epilam or epilex or epilim or episenta or epival cr or ergenyl or espa valept or everiden or goilim or hexaquin or "kw 6066 n" or labazene or leptilan or leptilanil or micropakine or mylproin or orfiril or orlept or petilin or propymal or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproat$ or valprodura or valprosid or valprotek or valsup or vupral or valproic acid).ti,ab,ot. (71130)
12 vigabatrin/ or (vigabatrin or Sabril or sabrilex or vigadrone or "rmi 71890" or "rmi 71754" or "mdl 71754" or kigabeq).ti,ab,ot. (8719)
13 Lamotrigine/ or (Lamotrigine or bw 430 c or bw 430c or bw 430c78 or bw430c or bw430c78 or crisomet or labileno or lambipol or lamepil or Lamictal or lamictin or lamodex or lamogine or lamotrigine or lamotrix or medotrigin or neurium or seizal).ti,ab,ot. (27763)
14 or/10-13 (454520)
15 9 and 14 (1163)
16 Randomized controlled trial/ (702100)
17 Controlled clinical study/ (465327)
18 random$.ti,ab. (1770953)
19 randomization/ (93410)
20 intermethod comparison/ (281424)
21 placebo.ti,ab. (338633)
22 (compare or compared or comparison).ti. (560699)
23 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2470094)
24 (open adj label).ti,ab. (95596)
25 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (254815)
26 double blind procedure/ (193593)
27 parallel group$1.ti,ab. (29115)
28 (crossover or cross over).ti,ab. (115447)
29 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (376037)
30 (assigned or allocated).ti,ab. (442819)
31 (controlled adj7 (study or design or trial)).ti,ab. (403350)

32 (volunteer or volunteers).ti,ab. (266156)
33 human experiment/ (570149)
34 trial.ti. (354414)
35 or/16-34 (5711491)
36 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8906)
37 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (303698)
38 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (19605)
39 (Systematic review not (trial or study)).ti. (204791)
40 (nonrandom$ not random$).ti,ab. (17666)
41 "Random field$".ti,ab. (2669)
42 (random cluster adj3 sampl$).ti,ab. (1421)
43 (review.ab. and review.pt.) not trial.ti. (978416)
44 "we searched".ab. and (review.ti. or review.pt.) (41113)
45 "update review".ab. (122)
46 (databases adj4 searched).ab. (49582)
47 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1143667)
48 Animal experiment/ not (human experiment/ or human/) (2400670)
49 or/36-48 (3923915)
50 35 not 49 (5060795)
51 15 and 50 (167)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	Geoffrey Wyatt
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	GW Research Ltd. (manufacturer of Epidyolex®)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's population may not be representative of the NHS setting.	No	The ERG stated that "The different population considered by the company in the main trial (restricted to those for whom usual care is unsuitable or not tolerated) may not be representative of England NHS clinical practice setting" (ERG Report, page 12). We would like to clarify that the population used in our submission and modelling is not a 'different population' but is *exactly the same population* as in the final scope issued by NICE. The population in the submission/modelling is as follows: "People with TSC whose seizures are inadequately controlled by current or prior established clinical management. People with TSC where usual-care is unsuitable or not tolerated." We added the wording "where-usual care is unsuitable or not tolerated" for clarification purposes only, as it is in line with the definition of a refractory patient from the International League Against Epilepsy (ILAE). Refractory epilepsy has been defined by the ILAE as failure of adequate trials of two *tolerated*, *appropriately chosen and used* anti-epileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom. Thus, patients may 'fail' an AED due to lack of efficacy and/or lack of tolerability. In addition, for some patients, certain AEDs may be unsuitable (e.g. sodium valproate is associated

		with a risk of teratogenicity, so it is often deemed to be unsuitable for women of childbearing age). Since we have used the exact population defined in the NICE scope in our submission/ modelling (simply adding the wording above for clarity, not to restrict the population), we do not consider it appropriate to conduct further analysis to inform the decision problem.
Issue 2: The quality-of-life instrument chosen lacks adequate justification and does not permit calculation of utilities.	No	The ERG stated that "The choice of the Subject/Caregiver Global Impression of Change scale (S/CGIC) quality of life questionnaire lacks justification and leads to considerable uncertainty regarding utilities" (ERG Report, page 13). Based on this statement from the ERG, we would like to make it clear that there may have been a misunderstanding regarding the source of the utilities used in the economic model: • Although the S/CGIC is a standard PRO measure used in clinical trials (and is a reasonable choice of outcome measure as it is considered to be a proxy for quality of life), it is not a preference-based measure and, as stated in our submission, it cannot be used (and was not used) to derive utilities. • As clearly described in our submission, the economic model uses utilities calculated from vignettes elicited using time trade-off (TTO) methods in a general population. It does *not* use the S/CGIC. • Taking on board the NICE/ERG feedback from previous appraisals of cannabidiol in DS and LGS (TA614 and TA615), the vignettes used TTO methodology, a preference-based measure, to value the health states in a representative sample of the general population. The vignette descriptions were designed to accurately capture the HRQL profile of people with TSC-associated epilepsy and their caregivers. In conclusion on this point, since S/CGIC is not used to derive utilities in the economic modelling, there is no uncertainty regarding the utilities or cannabidiol's cost-effectiveness based on S/CGIC. Later in the report, the ERG stated that "The ERG does not understand the rationale for choosing S/CGIC measure of QoL instead of the QOLCE/QOLIE-31-P questionnaires. Despite alleged problems with the QOLCE/QOLIE-31-P questionnaires, it is not clear to the ERG that the company's choice of the S/CGIC measure represents a net benefit, not least

		because, as the company acknowledges the latter cannot be used to derive utilities" (ERG Report, page 29). Please see the statements directly above explaining that the S/CGIC was *not* used to derive utilities for our model. The utilities used in the model were obtained from a robust vignette study in the general population using TTO methodology, in line with NICE DSU guidance. In terms of the results from the QOLCE/QOLIE-31-P questionnaires, we note the ERG's comment that these were not provided in detail in the company submission (ERG Report, page 56). We would respectfully like to point out that the results from QOLCE/QOLIE-31-P were provided in Appendix L of our submission, and also provided again at the ERG's request as part of our responses to the ERG Clarification letter. It was not our intention to hide the results from QOLCE/QOLIE-31-P, which showed that cannabidiol does not have a detrimental impact on a patient's QoL. Over the GWPCARE6 trial period, most differences in the QOLCE and QOLIE-31-P were in favour of cannabidiol, but none were statistically significant. However, missing or non-applicable items were an issue for both instruments. As stated in our Clarification responses (please see the detailed response to ERG question A12.b), although the QOLCE/QOLIE-31-P questionnaires are used in clinical trials involving patients with general epilepsy, there are significant challenges with them in trials involving patients with *severe and refractory* epilepsies such as TSC-associated epilepsy. For example, asking questions about social interactions for a patient who has physical/learning disabilities that mean they do not attend school, go to work, or have any social interactions is likely to be one of the main reasons for the missing data. In turn, the missing data make it difficult to draw meaningful conclusions from the results. This was why we conducted the vignette study in order to elicit the utility values for the model.
Issue 3: The extent to which the usual care treatments in the GWPCARE6 trial were representative of the England NHS setting remains unclear.	No	Epidyolex® (cannabidiol) for seizures associated with TSC has now been reviewed and approved for use by HTA bodies in Wales and Scotland (as well as by other countries in Europe, including Ireland). As part of the assessment process, these HTA agencies

consulted clinical experts independently of the company: these experts confirmed that the usual-care treatments from GWPCARE6 reflect their clinical practice in the UK NHS setting.

UK clinical experts consulted by the company also agree that the 'basket' of usual-care treatments from the GWPCARE6 trial is in line with the treatments they would use for their patients with TSC-associated epilepsy in the England NHS setting.

In the GWPCARE6 trial, cannabidiol was an add-on to usual-care. The usual-care interventions were not protocol-specified. Patients entering the GWPCARE6 trial were permitted to be taking any AEDs/other treatments (except those in the exclusion criteria) as long as they were stable during baseline and during the trial. These treatments/ combinations of treatments are what are referred to as 'usual-care' throughout our submission.

Refractory patients with TSC-associated epilepsy may cycle through numerous AEDs in an attempt to achieve seizure control. As a result, 'usual-care' comprises many different AEDs/combinations of AEDs and there is no standard of care once a patient is refractory. The table below demonstrates this.

GWPCARE6 – prior and concomitant AEDs

	Median number of prior medications	Median number of concomitant AEDs	Concomitant AEDs (5 most common)
Placebo	4 (up to 15)	3 (up to 5)	45% valproate 33% vigabatrin 29% levetiracetam 27% clobazam 22% lamotrigine
Cannabidiol 25 mg/kg/day	4 (up to 13)	3 (up to 4)	

The ERG suggested further analysis that is adjusted for differences between (i) trial and (ii) England NHS setting (ERG Report, page 13).

However, given the lack of a standard of care once a patient becomes refractory, the huge number of potential combinations of prior/concomitant AEDs (which UK clinical experts

		agree is representative of the treatments used in their NHS practice), and that cannabidiol has demonstrated efficacy as an add-on to this mix of usual-care treatments, we do not consider that this analysis would help to further clarify the decision problem.
Issue 4: Usual care treatments including vigabatrin used as background treatments differed between groups.	No	We reiterate our explanation given to the ERG during the Clarification process: the results of a pre-specified subgroup analysis of GWPCARE6 show *no effect on the primary endpoint* whether the patient was taking or not taking vigabatrin. This pre-specified subgroup analysis (Figure 3 in the company responses to the ERG Clarification letter) also demonstrates that the other main concomitant AEDs in the GWPCARE6 study (valproic acid, clobazam and levetiracetam) have no impact on the efficacy of cannabidiol. We acknowledge that there were slightly more patients taking vigabatrin as a 'current AED' in the cannabidiol 25 mg/kg/day arm of GWPCARE6 compared to the placebo arm (28 and 17 patients, respectively). However, we do not agree with the ERG that this led to "a biased estimate of cannabidiol's efficacy and safety" (ERG report, page 13). This is because the majority of patients with refractory TSC-associated epilepsy in the GWPCARE6 trial had already *tried and failed* vigabatrin i.e., the drug did not lead to seizure control. The GWPCARE6 trial population had failed to achieve seizure control with a median of 4 AEDs prior to entering the study. Vigabatrin was among the most common of these AEDs, having already been tried and stopped by 43% of patients prior to entering the study. In addition, a further 33% of patients were taking vigabatrin on entering the study, meaning that, by definition, it was not working as they were not achieving adequate seizure control. Therefore, in total, >75% of the GWPCARE6 trial population had already failed to achieve seizure control with vigabatrin.
Issue 5: The small number of patients recruited from UK sites makes generalisability to the England and Wales NHS setting questionable.	No	We would like to reiterate that TSC-associated epilepsy is an orphan disease, with the associated challenges in recruiting patients into clinical trials. The company considers that the GWPCARE6 study population baseline characteristics are generalisable to the UK population and the England NHS setting for the following reasons: • TSC-associated epilepsy is a rare disease. In order to recruit sufficient numbers of patients, the GWPCARE6 study was conducted across multiple sites including in the UK, Netherlands, Poland, Spain and the USA. The baseline characteristics of the study

		participants did not vary widely between the UK participants and those from other countries. • UK specialist clinicians agree that the participants with TSC-associated epilepsy in the GWPCARE6 trial broadly reflect the characteristics of people seen in their clinical practice in the UK NHS. This was noted in an HTA advisory board meeting (summary report provided with our submission) and also confirmed in recent discussions with two UK clinical experts - consultant neurologists Professor Finbar O'Callaghan and Dr Sam Amin. • The GWPCARE6 trial included UK patients (11 patients from the UK were screened, and 7 of the 11 were randomised). • The diagnostic criteria for TSC-associated epilepsy in the trial were based on international guidelines, which are applicable to UK patients. The ERG suggested an exploratory analysis using the subgroup of UK patients. However, given the similarity in baseline characteristics between the UK patients and the ITT population, as well as the small patient numbers, we do not consider that this analysis would help to inform the decision problem and/or the cost-effectiveness beyond the comprehensive analysis we have already provided.
Issue 6: The systematic literature review did not present all relevant evidence for comparator treatments.	No	We would firstly like to make it clear that the company engaged the services of a reputable expert third-party agency to conduct the SLR. This agency has many years of experience in conducting SLRs for HTA submissions, including NICE submissions. The ERG stated that "While the process of study selection and screening at the title and abstract stage may have been conducted appropriately, there is a lack of detail in the reporting…" (ERG Report, page 35). In our response to Clarification, we provided more detail on the methodology as follows: "Two researchers independently screened each abstract and any discrepancies were agreed in discussion with the project leader. One researcher and the project leader independently screened each full text publication to confirm that it met the inclusion criteria, with any disagreements resolved by discussion." This is the level of detail that is normally reported for a systematic review.

		However, given the ERG's remaining concerns, we would like to provide more detail: Firstly, we consider that some of the points made by the ERG are overly critical of our process. The ERG mentions that "The *optimal* process is that two independent reviewers extract data separately and then when disagreement exists, a third reviewer performs independent data extraction to inform a decision". We have stated that one researcher extracted data from each paper into an Excel spreadsheet template and all data extraction was checked by a second researcher with the project leader checking any areas of uncertainty. Thus, two researchers independently screened each abstract and the project leader was involved in deciding whether disputed abstracts were included or not. This is a methodology that has been accepted as adequate in multiple previous NICE submissions. NICE guidance for manufacturers does not state that double data extraction is required. The ERG stated that "the process of consensus in the case of disagreements is less clear" (ERG Report, page 34). To clarify further, in the case of disagreements, the project lead independently performed full-text screening of the disputed article(s) against the pre-specified inclusion/exclusion criteria (using her clinical experience and 20+ years of experience of interpreting data). The project lead then had a discussion with both researchers at the same time, in order to reach consensus. In the case of any remaining dispute, the project lead's decision (as the most experienced reviewer) was considered final. The ERG also stated that: "the results of the full SLR…were not provided in this submission" and "the ERG would like to see an indirect treatment comparison (ITC) assessment of relevant studies from the full SLR". We are unsure if our response to the factual accuracy check on both these issues has been considered (as it was indicated by the ERG that the points raised were not considered to be a factual inaccuracy), so we would like to reiterate some of the key points made: In addition to details of the cannabidiol RCT GWPCARE6, the full SLR summarised data from a total of 79 publications reporting on the efficacy and safety of anti-epileptic

		treatments in TSC, including: RCTs of everolimus and metformin; single-arm clinical trials of cannabidiol, vigabatrin, levetiracetam, valproic acid, bumetanide, rapamycin and everolimus; and observational studies of everolimus, vigabatrin, levetiracetam, anti-epilepsy surgery, mixed anti-epileptic drugs, ketogenic diet and vagus nerve stimulation. These studies were summarised in detail in a 122-page report that was sent to the ERG in response to its Clarification queries. The data were set out clearly in tables to show the populations, interventions, comparators, outcomes and study design (PICOS) from each study. The ERG ran a search that used more specific search terms than our SLR for anti-epileptic drugs and identified 41 references that were considered potentially relevant. We checked this list of references and found only one (a study of vagus nerve stimulation) that had been published at the time our search was run that had not been included in the full SLR, but would have met our inclusion criteria. Thus, the ERG has not demonstrated that any potentially relevant publication was omitted from our full SLR. Furthermore, the ERG has stated: "Of the identified trials, only GWPCARE6 reported on the correct combination of interventions, comparators and population...As such GWPCARE6 is the only study of relevance to this appraisal" (ERG Report, page 38). No ITC was conducted as this is not relevant to the decision problem of the efficacy and safety of cannabidiol as add-on therapy to standard of care involving multiple anti-epileptic drugs in any combination ("usual-care"). The only placebo-controlled trials identified were of cannabidiol, everolimus and metformin. We do not believe that conducting an ITC to compare these drugs would help clarify the decision problem. As described in our submission, everolimus is used later in the treatment pathway for seizures associated with TSC. Metformin is primarily an anti-diabetic drug being trialled in TSC as it is an mTOR inhibitor (although thought to be a less potent inhibitor of mTOR pathways compared to everolimus). Therefore, neither drug is relevant for an ITC.

Issue 7: The systematic review had a high risk of bias, making its conclusions about the relative safety and efficacy of cannabidiol uncertain.	No	As stated above, the company engaged the services of a reputable expert third-party agency to conduct the SLR. This agency has many years of experience in conducting SLRs for HTA submissions, including NICE submissions. Please see the response to Issue 6 above regarding the ERG's concerns about the SLR methodological reporting. We are unsure if our response to the factual accuracy check on the issue of potential bias has been considered (as it was indicated by the ERG that the points raised were not considered to be a factual inaccuracy), so we would like to reiterate some of the key points made: All systematic reviews, and all clinical trials, have the potential for bias but that does not mean that bias occurred. We acknowledge that we did not directly compare the efficacy and safety of add-on cannabidiol versus other specific anti-epileptic drugs via an indirect comparison. However, the justification for this was provided in detail in the submission and is also outlined above. In its report, we note that the ERG has agreed that: • The approach to conducting the searches was adequate and any additional efforts are unlikely to have impacted the overall recall of results (page 33). • Searches were transparent and reproducible and covered a broad range of resources, including databases, conference proceedings, HTA organisations and other grey literature resources (page 61). • The process of study selection and screening at the title and abstract stage may have been conducted appropriately (and the ERG reports no evidence to suggest that it was not, page 35). • "In the abstract/title screening phase of the CS SLR, 5,579 records were excluded and 113 were retained for full text screening. From these 113 papers, 31 articles were identified for inclusion. Of these, five were reports of clinical trials relevant to this section of the ERG report. Of the identified trials, only GWPCARE6 reported on the correct combination of interventions, comparators and population...As such, GWPCARE6 is the only study of relevance to this appraisal" (page 38).

		The ERG recommended updating the SLR to address its methodological concerns (ERG Report, page 14). However, we consider that an update to the SLR at this stage is unnecessary and not feasible within the timelines required by NICE. We acknowledge that the study protocol was not published before the SLR commenced and the inclusion criteria for a broad SLR were themselves broad. However, the ERG has failed to demonstrate that any aspect of the search strategy or inclusion criteria led to the exclusion of any study that should have been included, which would be the main consequence of bias in the SLR process. Based on the above, we consider that it is overly critical to suggest that the SLR is at high risk of bias. Furthermore, the ERG's own searches identified only one additional potentially relevant paper. This was for vagus nerve stimulation (VNS), and the ERG had already stated that it "considers the exclusion of ketogenetic diet, VNS, and resective surgery not an issue; it is reasonable to assume this would be equal for both arms and…this would not impact the ICER." (ERG Report, page 70). Therefore, we also disagree with the statement that the SLR, as conducted, would lead to uncertainty regarding the relative safety and efficacy of cannabidiol.
Issue 8: Because of small sample size, patient characteristics between age categories varied. This may have an impact on assumed weight and body surface area (BSA) which, in turn, determined treatment costs.	Yes – see Table B	As noted in our response to the ERG Clarification questions, the observed patient characteristics from the GWPCARE6 trial reflect the demographics of an orphan disease population. Observing variation across patient groups in a rare disease where there are small patient numbers is to be expected. The ERG queried the distribution of the percentage of females which differed across age groups, and the potential impact on assumed weight and BSA. As noted in our Clarification responses, the variation in % females across age groups (which may impact weight and BSA) is not significant (p-value: 0.453). However, in order to demonstrate the limited impact of any variation in patient characteristics across groups, we have now provided several scenarios to address these concerns. The results are presented in Table A below (note that a revised base case is being used in the scenario; further details on this are provided in Table 4).

In the scenarios, the percentage of females is fixed in each group, with weight and BSA changing as a result. Weight and BSA are adjusted up or down by reweighting the individual patient GWPCARE6 trial data. The impact of the percentage of females per age group was examined as outlined below:

- 41.7% to reflect the average percentage observed in the trial
- 35.0% to reflect the (minimum) percentage of females in the 18-plus age group
- 53.0% to reflect the (maximum) percentage of females in the 12-17 age group

The results show a minimal change in the ICER, demonstrating the limited impact of this parameter on the results.

We would also like to note that the ERG scenario analysis, which varied weight and BSA by an arbitrary ± 5%, demonstrated a minimal uniform (exact change in both directions) change in the ICER (±£2,021).

Based on the above, we consider that the overall impact of a variation in weight and BSA is minimal.

Table A: Scenario analysis results (PAS price)

	Scenario	ICER
Base case* (revised for Technical Engagement)	-	£14,594
Weight and BSA for each age group are adjusted if % female was fixed at:	41.7% (Average trial)	£14,562
	35.0% (Age ≥18 years old average)	£14,713
	53.0% (Age 12-17 years old average)	£14,306
Note: *A revised base case following Technical Engagement includes correction of error for mortality from age 97, the inclusion of general population cap on patient utility, update of caregiver seizure-free health state utility to the general population, and inclusion of TAND with more conservative assumptions.		

		Additionally, the ERG has raised concerns that the weight and BSA of patients aged 18 years and older is assumed to remain stable over time, which may not reflect real-life. The application of discontinuation and stopping rules means that the majority of patients do not receive treatment with cannabidiol over the longer term (≤9% remain on treatment at 10 years in the model). The average age of the model population at 10 years is 24 years old. At this age, the average general population weight is 72.6 kg and BSA is 1.85, which is comparable to the mean weight of 73.4 kg and BSA 1.84 for patients ≥ 18 years from the GWPCARE6 trial. Therefore, we consider that the assumption of stable weight and BSA is reasonable and can be expected to have a limited impact on the analysis. [Note: the average general population weight is weighted by the average percentage female from GWPCARE6 and based on adult weight for 16-24 years: 77.5 kg [male], 65.8 kg [female]), sourced from Health Survey for England data.[1] BSA is calculated based on the Du Bois calculation using weight and height (177 cm [male] and 163.5 cm (female), weighted average 171 cm).[2]] As cited in the ERG report as part of Issue 8 and discussed during the Technical Engagement call, the ERG have queried the impact of including patients aged less than 2 years on the analysis of effectiveness. As noted in the Clarification responses, due to the very small number of patients aged < 2 years in GWPCARE6 and considering that all except two patients had reached age 2 by the end of the trial, any impact is expected to be very low. This is supported by an analysis of the primary endpoint, comparing the ITT analysis to an analysis excluding patients < 2 years. As shown in Table B, the ratio to baseline of % reduction is comparable between the ITT population and patients aged ≥ 2 years. The treatment ratio is also comparable between the ITT population and patients aged ≥ 2 years, with a slightly better treatment ratio for patients aged ≥ 2 years. As noted in our Clarification response, the ITT patient population was used to inform model inputs including efficacy inputs, discontinuation rates and TAND response rates; patient characteristics for patients aged ≥ 2 years were used to inform inputs for weight and BSA. Excluding the small number of patients aged < 2 years would unnecessarily reduce patient numbers in an already small trial population (due to the orphan nature of the disease), break trial randomisation and increase model uncertainty by reducing sample size.

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<td>Additionally, as can be seen from Table B), the ITT population analysis is a conservative estimate of the cost-effectiveness of cannabidiol.
Table B: Primary Endpoint: Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)
<table>
<tr><th rowspan="2">Population</th><th rowspan="2">N (cannabidiol/ placebo)</th><th rowspan="2">Ratio to Baseline [% reduction] (cannabidiol/ placebo)</th><th colspan="2">Treatment ratio</th></tr>
<tr><th>[% reduction)</th><th>95% CI</th></tr>
<tr><td>All patients</td><td>75 / 76</td><td>0.514 [48.6%] / 0.735 [26.5%]</td><td>0.699 [30.1%]</td><td>0.567, 0.861</td></tr>
<tr><td>2+ years</td><td>72 / 70</td><td>0.499 [50.1%] / 0.719 [28.1%]</td><td>0.695 [30.5%]</td><td>0.560, 0.862</td></tr>
<tr><td colspan="5">Note: Treatment period is defined as Day 1 to Day 113.
Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction and factor by time by treatment interaction as fixed effects and subject as a random effect. Log transformed number of days seizures were reported by period is included as an offset.</td></tr>
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<td>Issue 9: The company assumed a 12 mg/kg/day average dose in the model used to calculate the drug costs. However, a dose of 25 mg/kg/day was used to inform most other model inputs, and it is unclear whether an average of 12 mg/kg/day reflects clinical practice.</td>
<td>Yes – see Figure 1</td>
<td>Average dose of 12 mg/kg/day in the model
Since the objective of the cost-effectiveness modelling is to represent a cohort in clinical practice in the NHS in England, a dose that represents this cohort has been used in the model, rather than considering the dosing of individuals. For this reason, the dose used in the model to calculate ICERs is an average dose.
According to the Epidyolex Summary of Product Characteristics (SmPC), for TSC-associated seizures, the dose should be increased to 10 mg/kg/day and then the clinical response and tolerability should be assessed. Based on individual clinical response and tolerability, each dose can then be further increased only if needed. Hence, the target dose for TSC-associated epilepsy is not 25 mg/kg/day (this is the maximum permitted dose) and,</td>
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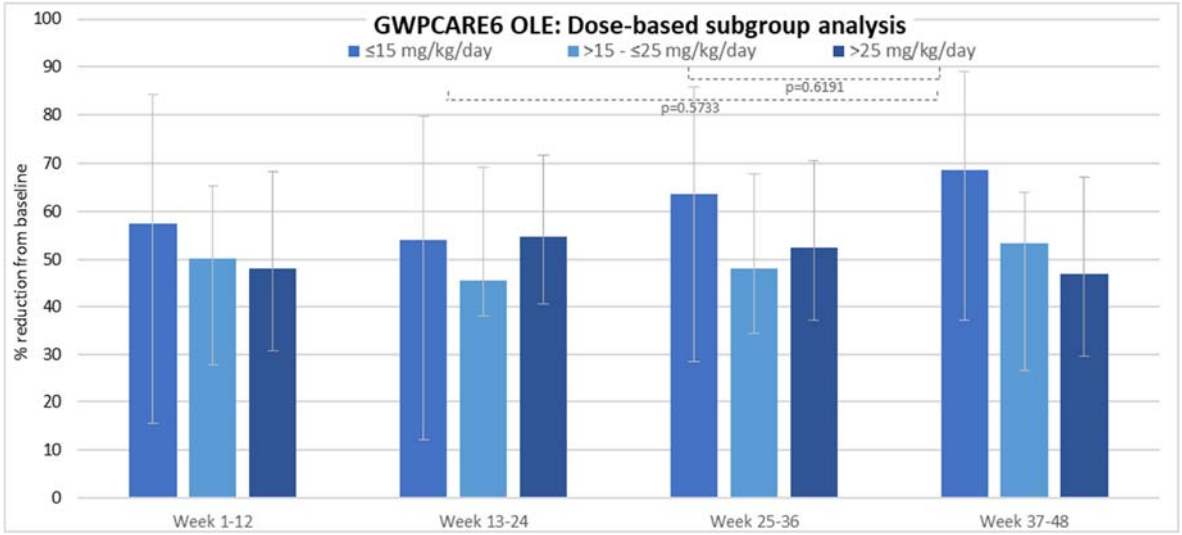
		across a cohort of patients in clinical practice, there will be a spectrum of doses in use ranging from ≤10 mg/kg/day to the maximum of 25 mg/kg/day. The SmPC clearly requires that a dose of 10 mg/kg/day be sought in the first instance. Clinicians should only escalate in an individual patient if they consider that the maximally effective dose might be higher, and can be tolerated. As such, it is reasonable to expect that the average dose in clinical practice will be much closer to 10 mg/kg/day than 25 mg/kg/day if the SmPC is followed. By using an average dose of 12 mg/kg/day in the model, we can account for the range of doses seen in clinical practice across a cohort of English patients with TSC-associated epilepsy, as clinicians aim to optimise the dose for individual patients. Feedback from clinical experts and real-world data support this assumption of using an average dose of 12 mg/kg/day in the model: • We have obtained data from a German dispensing database (INSIGHTS) on real-life dosing. The daily dose was estimated from a group of patients with Epidyolex prescriptions in 2021. The indication for the prescription was not available in the database, therefore a TSC diagnosis was inferred from a record of any use of vigabatrin or everolimus in the preceding 3 years. Body weight of patients was estimated from age and gender average weight in the German general population. From a total of 118 patients, the observed median dose was 12.21 mg/kg/day in children (inter-quartile range 6.67) and 7.77 mg/kg/day (IQR: 5.68) in adults. • Discussions across Europe with expert clinicians (including UK clinicians) who have experience of using Epidyolex in clinical practice suggest that the average dose in real-world clinical practice will be around or below 12 mg/kg/day. Lack of dose response Data from the clinical programme in all three approved indications for Epidyolex (LGS, DS and TSC-associated epilepsy) show that there is a lack of dose response for cannabidiol above doses of around 10 mg/kg/day.

		In the LGS and DS indications, the Phase 3 studies showed no numerical or statistical differences in efficacy between doses of 10 mg/kg/day and 20 mg/kg/day, leading to a recommended maintenance dose of cannabidiol in LGS and DS of 10 mg/kg/day by EMA. The GWCARE6 open-label extension (OLE) study protocol allowed patients to be maintained on a spectrum of doses, at the discretion of the investigator. A subgroup analysis by dose of the OLE study therefore allows for the correlation between efficacy and dose to be assessed directly. Across all timepoints in the study, seizure reductions from baseline were clinically similar between patients on ≤15 mg/kg/day and those on higher doses (see Figure 1 below). No statistically significant differences were seen between patients on lower vs. higher doses. These findings from the GWPCARE6 OLE are consistent with dose-response data observed in the longer-term open-label extension study, GWPCARE5, in DS/LGS. Efficacy versus baseline was the same irrespective of whether patients were on doses similar to the recommended maintenance dose of 10 mg/kg/day in LGS and DS, or higher doses. Based on the above, the company considers that the efficacy observed in the GWPCARE6 trial at a cannabidiol dose of 25 mg/kg/day is representative of the efficacy that would be expected to be observed in clinical practice in England for patients receiving the anticipated average real-world dose of 12 mg/kg/day. Conclusions • The average dose of 12 mg/kg/day used in our model is supported by real-world evidence and by feedback from clinical experts experienced in using Epidyolex in clinical practice. • Dose-based subgroup analyses of the GWPCARE6 OLE study suggest that the seizure outcomes observed in the GWPCARE6 trial at a cannabidiol dose of 25 mg/kg/day are likely to be consistent with those that would be expected in real-world clinical practice in England when patients are receiving the anticipated average dose of 12 mg/kg/day. • The objective of our cost-utility analysis was to model economic outcomes in the clinical setting. Based on the above, we consider that it is relevant to model an average dose of

		12 mg/kg day, and reasonable to estimate health benefits at this average dose from data in the 25 mg/kg/day arm of GWPCARE6 study. **Figure 1: Seizure reduction from baseline by modal dose in the GWPCARE6 OLE study**  Data is for the safety analysis set in patients who carried over into the GWPCARE6 OLE study from the cannabidiol arms in the GWPCARE6 study. The percentage reduction in 28-day average seizure count was estimated using a negative binomial regression model in the context of a general estimating equation for a generalised linear model. P-values between dose subgroups relate to the statistical significance of coefficient for dose as a factor in the model. p<0.05 for all timepoints in all dose subgroups vs baseline.
Issue 10: The way in which predicted seizure-free days per week were incorporated in the economic model to determine 'seizure-free over seven days'	No	As detailed in the factual accuracy response to the ERG report, the model uses a 6.5 cut-off for a seizure-free week, as the binomial regression predicts values on a continuous scale rather than predicting discrete integer values. In addition, within a binomial logistic regression, it is technically impossible to predict exactly 0 or 1, i.e., no days or 7 days, as the prediction asymptotes to the value of 0 or 1. As such, rounding is required.

is not justified and may not be in line with clinical practice, especially for the usual care arm.		As the ERG noted, the maximum predicted number of seizure-free days with the binomial regression model is 6.62. The 6.5 cut-off was chosen as it is the closest rounding cut-off point to 7 days without seizures. This is standard practice in the implementation of this type of regression model. As detailed in the ERG report, page 55 "*In the maintenance period of the trial (the 12-week period when patients had completed titration and were on a stable dose), TSC-associated seizure-freedom was achieved in four of the 75 patients (5.4%) taking cannabidiol (25 mg/kg/day) plus usual-care compared to none of the 76 patients in the placebo plus usual-care group (p=0.0354*)". These trial outcomes highlight that it is highly unlikely for a patient who is already refractory to achieve seizure-freedom by continuing on their existing usual-care treatment. The clinical plausibility of this was supported by feedback from recent discussions with two UK clinical experts, Professor Finbar O'Callaghan and Dr Sam Amin. Based on this, it was deemed important to reflect the trial outcomes in the model and we consider that a reasonable assumption was made. Additionally, long term data (from the GWPCARE6 Open Label Extension study) demonstrate that increasing seizure freedom is observed in patients continuing on cannabidiol (at 72 weeks, 19% of patients were seizure-free).[3] Therefore, the ERG scenario that applies a cut-off of 7, assuming no patients in the cannabidiol arm are seizure-free (per week), is clinically implausible. A scenario is provided in Table C (note that a revised base case is used in the scenario; further details are provided in Table 4), demonstrating the impact of using a cut-off of 6.61, which is very close to the maximum predicted threshold of seizure-free days by the binomial regression model (6.62). The scenario of assessing a cut-off close to the threshold of predicted seizure-free days demonstrates the limited sensitivity of the ICER to this change.

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Table C: Scenario analysis results (PAS price)
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<tr><th>Techno-logies</th><th>Total costs (£)*</th><th>Total QALYs*</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td colspan="6">Revised base case</td></tr>
<tr><td>Placebo + usual-care</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Cannabidiol + usual-care</td><td>[redacted]</td><td>[redacted]</td><td>£24,635</td><td>1.69</td><td>£14,594</td></tr>
<tr><td colspan="6">Scenario – 6.61 cut-off</td></tr>
<tr><td>Placebo + usual-care</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td>Cannabidiol + usual-care</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£16,386</td></tr>
<tr><td colspan="6">Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
Note: *Discounting is applied to QALYs and cost. A revised base case for technical engagement includes correction of error for mortality from age 97, the inclusion of general population cap on patient utility, update of caregiver seizure-free health state utility to the general population, and inclusion of TAND with more conservative assumptions.</td></tr>
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<td>Issue 11: The impact of TSC-associated neuropsychiatric disorders (TAND) was modelled using many uncertain assumptions.</td>
<td>No</td>
<td>The ERG has indicated that TSC-associated neuropsychiatric disorders (TAND) might be included in the analysis with very conservative assumptions (ERG Report, page 16).
Aspects of TAND can have a huge impact on the lives of patients with TSC-associated epilepsy and their caregivers. Therefore, we think it is important that TAND is included in the analysis. We acknowledge that there is currently limited long-term data supporting the impact of cannabidiol on the mitigation of TAND symptoms. We sought to address this by eliciting robust clinical input (via a two-round Delphi panel) to inform the assumptions used in the analysis.
As the ERG suggested that TAND mitigation benefits can be included using very conservative assumptions, we propose the inclusion of TAND in our revised base case (further details are provided in Table 4 below), but with the following conservative</td>
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		assumptions (some of which were previously provided as scenario analyses in Document B, Table 37): • TAND is included for patients aged 2-6 only, to reflect that the early control of seizures is more likely to lead to better outcomes on TAND in younger patients • The benefit on TAND is applied for a period of 5 years only, to reflect that the long-term lifetime outcomes are unknown, so a time-limited period of benefit is used • Only the minimum utility value (0.09) for TAND aspects is applied (rather than the higher values reported in the literature for some aspects of TAND).
Issue 12: Seizure-free health state utility value estimated in the vignette study for caregivers (0.905), is overestimated.	No	As detailed in our response to the ERG Clarification questions, the vignette study estimated a caregiver utility of 0.905 for the seizure-free health state value. Participants (as caregivers) were asked to consider the following: some worry, have some depressive or anxious thoughts, have some difficulty planning holidays and sometimes feel tired or exhausted amongst other aspects for the care of their child. A copy of the vignette health state description is provided in Figure 11 of the responses to the ERG Clarification questions. The vignette study was robustly designed, having taken on board the previous ERG and NICE feedback for the vignettes completed for the submissions to NICE for cannabidiol in LGS and DS.[5, 6] Additionally, as recommended by the latest NICE guidance[7], the vignettes used time trade-off (TTO) methodology, a preference-based measure, to value the health states in a representative sample of the UK general population aged ≥ 18 years. The carer seizure-free utility elicited via the vignettes was used in the cost-effectiveness analysis to minimise any biased adjustments. As noted in our response to the ERG Clarification questions, the utility estimated from the vignette study is broadly comparable to the utility for an adult (female) aged 43 (0.897). This utility value assumes that the primary caregiver is a parent of the child (mother). Based on ONS data, the average age of mothers at childbirth in 2019 was 30.7 years.[8] For a 13-year old child (as in the vignette), this implies an average parent age of 43 years. Therefore, the elicited utility value for the seizure-free health state (potentially over-estimated by 0.008 when compared to a 43 year old female) by the vignettes is reflective of a carer population in real-world practice.

		However, in light of the ERG's assertion that the carer utility may be overestimated, we are willing to accept the adjustment to the caregiver seizure-free health state utility value and have amended our base case (see Table 4 for further details) accordingly.
Issue 13: The assumption to apply caregiver disutilities additively to two caregivers lacks justification. Utilities were also not corrected for patients being institutionalised.	No	As detailed in our response to the ERG Clarification questions, we would like to reiterate that including utilities for two caregivers conservatively reflects the number of caregivers for a patient with TSC-associated seizures. In a severe and life-threatening disease such as TSC-associated epilepsy, patients are at a significant ongoing risk of injury and death from their seizures, have multiple co-morbidities and often require lifelong round-the-clock care from multiple caregivers. The number of caregivers was informed by a 2019 publication by Lagae et al., which reported on health and social care resource use, productivity and quality of life of caregivers of patients with another severe form of epilepsy, Dravet syndrome (DS).[9] The 2019 Lagae et al. study reported on HRQL collected for caregivers as part of the DISCUSS study (n=584), outlined in more detail in Document B, Section B3.4. The reported results indicated that the main respondent provided care 84% of the time. However, care from others (partner, other family members and/or friends) was high (cumulative at 121.6%), indicating that daily caregiving is shared among at least two caregivers who are family members or friends. The assumed number of caregivers is supported by a recent study exploring the role of seizures in the caregiver and family burden of TSC. A survey completed by 73 primary caregivers found that a mean of 2.3 household members were involved in care, including primary caregivers, their partners, parents, siblings, other child(ren) and other relatives. Caregivers and household members spent a substantial amount of time on care each week and highlighted the need to provide continuous care with only occasional respite (total and seizure-specific care time established).[10] The number of caregivers also reflects the context of the vignette study, where respondents evaluated utility in the context of being one of two primary caregivers. More broadly, two caregivers also reflects the impact of TSC-associated epilepsy on the quality of life of the wider family. Whilst we acknowledge that not every patient will have two primary caregivers (although many will need more than two), the company is aware that there are often many other people contributing to the care of the patient (for example,

siblings, grandparents, aunts, uncles, family friends). The cumulative impact on the quality of life of all these other caregivers more than compensates for any additive effect in the two main caregivers.

We note that there is precedent for caregiver disutility to be applied additively for each caregiver. The NICE submission for ataluren for Duchenne muscular dystrophy (DMD) applied disutility for three caregivers in a revised base case, which the committee considered better addressed patient organisations' concerns about the quality of life impact of the condition on caregivers.

Two UK clinical experts consulted as part of our response to the ERG Clarification questions indicated that having at least two caregivers was usual for patients with TSC-associated epilepsy.

The ERG base case assumes 1.8 caregivers. A scenario is provided in Table D, showing the minimal impact of this scenario on the company's revised base case (further details are provided in Table 4).

Table D: Scenario analysis results (PAS price)

Technol-ogies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised base case					
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	£24,635	1.69	£14,594
Scenario: 1.8 caregivers					
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£15,462
Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

		**Note: ***Discounting is applied to QALYs and cost. A revised base case for technical engagement includes correction of error for mortality from age 97, the inclusion of general population cap on patient utility, update of caregiver seizure-free health state utility to the general population, and inclusion of TAND with more conservative assumptions. We believe that including disutilities for a minimum of 2 caregivers reflects the quality of life impact of round-the clock care of a patient with TSC-associated epilepsy, but does not account for the impacts on the wider family, such as siblings. Each family carer has the burden, worry and psychological distress of caring for a patient at risk of injury and even death from their seizures. It would be expected that incorporating the full effect of TSC-associated epilepsy on the lives of all family members would result in a further reduction of the ICER. Institutionalisation Scenario The ERG made an adjustment for institutionalisation by assuming that, for 31% of patients aged ≥ 18 years, caregiver disutility is included for 0.5 caregivers, rather than the 2 caregivers allocated (in our submission) to the rest of the modelled population. No rationale was provided for the value used by the ERG. Although we agree that an adult patient being cared for in an institution may lead to some improvement in his/her primary caregivers' quality of life, we do not agree that the caregivers' quality of life improves as dramatically as in the ERG scenario above. Each caregiver still has the worry of their loved one being at risk of injury from their seizures, without the carer being there to provide assistance/comfort/support when this happens. 'Everyday life' is often still based around visiting the patient in the institution and accompanying them on trips to the doctor, hospital or even the emergency department. Patients may not settle in a particular home, resulting in worsening of their seizures, behaviour, or other aspects of TAND, all of which causes anxiety for their caregivers. Importantly, caregivers often continue to experience ongoing guilt about separating their loved one from their family, sibling(s), familiar surroundings and wider community, which can have a large impact on their own quality of life.

Based on the above, it is not expected that the caregivers' quality of life will significantly improve when adult patients are institutionalised. However, to allow for the fact that there may be some improvement in quality of life, we have provided a scenario below where we adjust for institutionalisation by assuming a 50% increase in caregiver utility. This, in effect, reflects an adjustment in the model where 1 caregiver is assumed for the 31% of patients who are institutionalised aged ≥ 18 years.

Table E: Scenario analysis results (PAS price)

Technol-ogies	Total costs (£)*	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Revised base case					
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£14,594
Scenario – institutionalisation					
Placebo + usual-care	[redacted]	[redacted]			
Cannabidiol + usual-care	[redacted]	[redacted]	[redacted]	[redacted]	£15,345

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Note: *Discounting is applied to QALYs and cost. A revised base case for technical engagement includes correction of error for mortality from age 97, the inclusion of general population cap on patient utility, update of caregiver seizure-free health state utility to the general population, and inclusion of TAND with more conservative assumptions.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Application of a disease severity modifier not mentioned	N/A – not included in the ERG report	No	The application of a disease severity QALY modifier reduced the revised base case ICER (of £14,594) by 16.7% to £12,162. The updated 2022 NICE methods guidance introduced new criteria to reflect, in exceptional circumstances, the severity of disease within decision making. The company is aware that this submission is being assessed under the old methods guidance (the invitation to participate was sent to us on 18th January 2022, two weeks before the guidance was introduced on 1st February 2022). However, given that the guidance was recently updated in order to support patients with severe diseases, we considered it appropriate to provide an indication of the severity of TSC-associated epilepsy and the impact of this on the economic analysis. As detailed in Document B, cannabidiol in a patient population with TSC-associated seizures satisfies the criteria laid out by NICE under the new methods for a severity of disease modifier. Given the severe impact of TSC-associated epilepsy, we consider that a QALY weight of 1.2 (applicable for the absolute loss of between 12 to 18 QALYs) should be applied in the context of decision making.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Correction of general population mortality from age 97 (ERG report Section 4.2.8)	There was a minor error in the model where patients from age 97 had 0% risk of general population mortality	The ERG correction made in the economic model	£12,712 (+£0)
Inclusion of age-related utility cap for patients (ERG Report Section 4.2.12)	An option to cap utility values for the general population was added in response to the ERG Clarification questions. However, the company base case was not updated to include this.	The option to cap utility values for the general population is selected as Yes	£12,712 (+£0)
Issue 12	The seizure-free health state utility value estimated in the vignette study for caregivers (0.905)	The ERG adjusted the caregiver utility for the seizure-free health state to that of an average adult aged 45. The company accepts this change.	£13,126 (+£414)

Issue 11	A TAND mitigation benefit was included in the submission, to patients (aged 2-6 years) with a 50% response rate at 6 months. The benefit was applied for a lifetime with patients experiencing a utility increment and a 50% reduced cost of TAND management. Utility values from the literature were applied for various aspects of TAND.	A more conservative TAND mitigation benefit is now applied to patients aged (2-6 years) with a 50% response rate at 6 months. The benefit is applied for 5 years only and the lowest reported utility (0.09) is used for all aspects of TAND.	£14,108 (+£1,395)
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	£14,594

Sensitivity analyses around the revised base case

We have provided additional scenario analysis around the revised base case related to Issues 8, 10 and 13. Text describing the scenarios and the results are provided above in Tables A, C, D and E above.

References

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2. Du Bois D; Du Bois EF. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine*. 1916; XVII(6_2):863-71.
3. Wheless J, Bebin EM, Filloux F, et al. Long-term Safety and Efficacy of Add-on Cannabidiol (CBD) for Treatment of Seizures Associated with Tuberous Sclerosis Complex (TSC) in an Open-Label Extension (OLE) Trial (GWPCARE6) (1127). *Neurology*. 2021; 96(15 Supplement):1127.
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9. Lagae L, Irwin J, Gibson E and Battersby A. Caregiver impact and health service use in high and low severity Dravet syndrome: a multinational cohort study. *Seizure*. 2019; 65:72-9.
10. Vyas KS, H.; Bowditch, S.; Dziadulewicz, E.; Hubig, L.; Lo, S.H. The Role of Epileptic Seizures in the Caregiver and Family Burden of Tuberous Sclerosis Complex (TSC) [IN PRESS]. *European Journal Of Paediatric Neurology*. 2022.

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Technical engagement response form

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	Dr Pooja Takhar
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Tuberous Sclerosis Association
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: The company's population may not be representative of the NHS setting.	No	Tuberous Sclerosis Complex (TSC) is a rare genetic condition. Every month around 10 babies are born with TSC in the UK. The TSA carried out interviews with seven people in the UK who care for someone living with TSC to inform our submission to NICE. The age range of the patients varies from 7 to 37 years; four male and three female patients who have all had access to Epidyolex®. Four out of seven patients received Epidyolex® due to a co-diagnosis of Lennox-Gastaut syndrome. Three out of seven patients received Epidyolex® as part of the recent clinical trial. All seven patients had refractory epilepsy with only a partial response to treatment with anti-epileptic drugs. We believe this is representative of TSC population in the NHS setting.
Issue 2: The quality-of-life instrument chosen lacks adequate justification and does not permit calculation of utilities.	No	When a TSC diagnosis is made, the whole family is affected both physically and mentally. TSC has a great impact on families' quality of life and on their ability to cope with the disease and support the child's ability to reach an acceptable level of well-being. Families and carers have reported the experience of losing control and

		feelings of despair and helplessness. They have shared their day-to-day struggles with their children's behaviour including what it's like to manage the rage, anger and mood swings. It not only affects their relationship with their child who has TSC but also their relationship with each other and the wider family circle including siblings who feel left-out and neglected as the parents focus on the needs of their child with TSC. In many instances, parents have had to give up work to become full time carers. There are additional costs for home improvements associated with TSC: the TSA Support Line receives regular calls from parents wishing to access our small family grants to purchase fridges to store medication or batches of ketogenic food, replace washing machines, tumble dryers, beds and bedding urgently needed to cope with the impact of urinary and faecal incontinence, and invest in improvements to make back gardens secure and safe for children with no sense of danger to play in.
Issue 3: The extent to which the usual care treatments in the GWPCARE6 trial were representative of the England and Wales NHS setting remains unclear.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 4: Usual care treatments including vigabatrin used as background treatments differed between groups.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 5: The small number of patients recruited from UK sites makes generalisability to the England and Wales NHS setting questionable.	No	As mentioned in issue 1 - The TSA carried out interviews with seven people in the UK who care for someone living with TSC who had access to Epidyolex®. The age range of the patients varies from 7 to 37 years; four male and three female patients. We believe this is representative of TSC population in the NHS setting.
Issue 6: The systematic literature review did not present all relevant evidence for comparator treatments.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Issue 7: The systematic review had a high risk of bias, making its conclusions about the relative safety and efficacy of cannabidiol uncertain.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 8: Because of small sample size, patient characteristics between age categories varied. This may have an impact on assumed weight and body surface area (BSA) which, in turn, determined treatment costs.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 9: The company assumed a 12 mg/kg/day average dose in the model used to calculate the drug costs. However, a dose of 25 mg/kg/day was used to inform most other model inputs, and it is unclear whether an average of 12 mg/kg/day reflects clinical practice.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 10: The way in which predicted seizure-free days per week were incorporated in the economic model to determine 'seizure-free over seven days' is not justified and may not be in line with clinical practice, especially for the usual care arm.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 11: The impact of TSC-associated neuropsychiatric disorders (TAND) was	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

modelled using many uncertain assumptions.		
Issue 12: Seizure-free health state utility value estimated in the vignette study for caregivers (0.905), is overestimated.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 13: The assumption to apply caregiver disutilities additively to two caregivers lacks justification. Utilities were also not corrected for patients being institutionalised.	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with tuberous sclerosis complex or caring for a patient with tuberous sclerosis complex. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **12.30am** on **30 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with tuberous sclerosis complex

Table 1 About you, tuberous sclerosis complex, current treatments and equality

My name is Lisa Suchet, I am a former charity CEO; I am now a mother and carer to my 8 year old son with TSC, mother to my 5 year old daughter who is thankfully healthy, and happily married to the father of my children. I have been a company director, charity trustee and am currently trustee of the Tuberous Sclerosis association (TSA).

TSC is a hideous condition combining an awful catalogue of ailments: benign tumours in every organ, learning and physical disabilities, facial disfigurements, autism, ADHD and epilepsy which is often intractable. Sufferers can be affected by some, all or none of these conditions. (I call them 'sufferers' as the reality is that this disease has caused my child and our family an inordinate amount of suffering, which never ceases.)

Todd is learning disabled, he cannot walk or run properly, he uses a buggy for long trips, he needs support on steps and uneven ground, he cannot speak properly (mostly via intonation), he can only eat puree (and currently only houmous), he can only drink from an open cup (not straws, water bottles), he needs help toileting. He has relatively high emotional intelligence, he is at mainstream primary school in a SEN classroom. He needs 1:1 support almost all of the time.

My son, Todd, was diagnosed with TSC at 5 weeks of age when he started having seizures. At this point he was having around 21 seizures a day. Todd was immediately put on Vigabatrin and then we introduced the ketogenic diet which stopped all visible seizures until he was 2yrs 2 months. His seizures gradually worsened over time and he was put on Sirolimus in Sept 2016. He was then briefly on Clobazam Sept 16 and Lamotrigine Sept 16. This stopped working and he then had drop-seizures. He was put on

Sodium Valproate, all the other drugs were weaned except for Sirolimus. He remains on these two today. By January 2019 his seizures worsened. We managed to privately source some CBD products. Our lives were instantly transformed by tiny doses. He was calm, happy, and his seizures reduced from 6 a day and 3 at night, to one a week, and he and would sleep through the night for the first time in years. We stopped being able to obtain these CBD products and he was put on Levetiracetum in winter 2019. He was depressed, apathetic and savagely attacked his little sister whilst I was driving us all in the car. His seizures persisted. His mainstream primary school said it could no longer cope and asked us to find a specialist setting. We stopped that drug. We then managed to get Todd diagnosed with atypical Lennox Gaustaut Syndrome in Jan/Feb 2020 and re-started Clobazam in April 2020 and Epidyolex in May 2020. This massively reduced his seizures (e.g. from 9 a day to 1-2 a week). He was also calm and happy and school reported the same, forgetting why they had asked us to move him. Sadly, over time, the high dose of the drug contributed to almost total loss of appetite and constant napping. We had to take him off it to get him eating again. He was anorexic. At 7yrs old he weighed just 17kgs. However we now also believe his new specialist school was not assisting him with his feeding as they should have been. We also believe we could have continued at a much reduced dose to ongoing benefit; however by this point we had found a doctor to prescribe CBD (full spectrum, not an isolate like Epidyolex) and THC privately on low doses which has given us our best results for Todd since the ketogenic diet which he grew out of.

Despite the benefits of CBD greatly reducing his seizures and improving his mood, as a family, we are all finding Todd, who is ever growing into a young man, and his regular meltdowns, almost too much to deal with. Grandparents, aunts and uncles who support us are getting older and are struggling to continue to help us. We are due to approach our local council for carer support. Todd's illness is compromising too much of every aspect of our lives. We can't do family day trips, or outings without Todd needing to go home very quickly. A trip to a local park or cafe is usually too much for him. Our determined attempts at family holidays are almost

unbearable. He becomes extremely unsettled and agitated in new places although does settle a bit after a few days. He likes routine and familiarity. We are pursuing an autism diagnosis at present. Todd has spent most of his life having and causing us, his parents, to have broken nights. CBD has been a big help with this.

Also see section 1 to 13 and part 2 below.

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1. Your name	Lisa Suchet
2. Are you (please tick all that apply)	☐ A patient with tuberous sclerosis complex ? ☐ A patient with experience of the treatment being evaluated? X A carer of a patient with tuberous sclerosis complex ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Tuberous Sclerosis Association
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) **X** Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement X I agree with it and **will be** completing

5. How did you gather the information included in your statement? (please tick all that apply)	X I am drawing from personal experience X I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with tuberous sclerosis complex ? **If you are a carer (for someone with tuberous sclerosis complex) please share your experience of caring for them**	I am mother and carer to my 8yrs old son. He is learning and physically disabled and has intractable epilepsy. We often have sleepless nights. Caring for him is exhausting and impacts me, my husband and daughter (5yrs old) constantly. We cannot live like a normal family due to Todd's condition.

7a. What do you think of the current treatments and care available for tuberous sclerosis complex on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Sirolimus/Everolimus is the drug of particular help to TSC sufferers. Todd has been on it since he was 2yrs and this is incredibly fortunate, most people are not put on it until later and usually not if brain or kidney surgery is an option. In my view, this is appalling. Why subject any family to the horror, risks and expense of brain surgery when a simple drug will do the job? It is also my view that all newly diagnosed children and adults should be put on a low dose of this drug immediately. I suspect this will be the case in the coming decades. Todd is on a very low dose (0.6ml) and it controls the growth of all his TSC 'tumours' (so far). Typical AEDs are terrifying owing to the list of side effects, and most do not work. Fellow TSC parents try to fight for Everolimus. Many want to to try CBD products. We all loathe the side effects of traditional AEDs.
8. If there are disadvantages for patients of current NHS treatments for tuberous sclerosis complex (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Brain surgery is the ultimate surgery risk. Its awful and traumatic for all involved, especially children/adults who do not have the IQ to understand what is happening to them. As above, it is often ineffective for TSC epilepsy and it does not stop new brain tumours forming (unlike sirolimus/everolimus). Most AEDS do not work on intractable epilepsy and the side effects are awful.

9a. If there are advantages of Cannabidiol over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Cannabidiol help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	It's more effective than half the AEDs we've tried in reducing seizures. Our son was happy on it as opposed to being depressed and angry. It caused our son to sleep through the night for the first time in years. I can not express to you enough the positive impact of a full nights sleep not only on Todd but also my husband and me. It's life changing. We are all healthier for it. Todd became calmer and happier Todd was able to cooperate better at school and learn more. Todd was easier to take out on day trips as he is calmer and less affected by seizures. Epidyolex tastes nice!
10. If there are disadvantages of Cannabidiol over current treatments on the NHS please describe these. For example, are there any risks with Cannabidiol ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are no more serious risks with cannabidiol than with other AEDs. The risks are sleepiness, and tummy sensitivity as I understand it. I also know from experience this can be remedied with lower doses. Todd is on low dose CBD and THC and has no tummy or weight issues now. He still has good seizure reduction. Another side effect is a full nights sleep - every TSC parents dream! I have no concerns about giving my child this drug at all. The side effects also cease when the drug is stopped or reduced.
11. Are there any groups of patients who might benefit more from Cannabidiol or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	It will benefit best those TSC patients with epilepsy as it has a positive impact on reducing numbers of severity of seizures. It will also help anyone with TSC who cannot sleep through the night. It might help with other aspects of the disease but I would not be able to know as Todd cannot speak well enough to tell us.

12. Are there any potential equality issues that should be taken into account when considering tuberous sclerosis complex and Cannabidiol ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	This drug should be made available to all sufferers of epilepsy, not a small cohort. To refuse it until all manner of other AEDS with their toxic side effects have been tried, or until brain surgery has been tried, is not abiding by the code of 'first do no harm'.
13. Are there any other issues that you would like the committee to consider?	Approving Epidyolex is the right next step in paving the way for CBD based products for epilepsy. I suspect that in a few decades time, England will finally have a better range of CBD products at its disposal for all manner of ailments, as in other countries. Once we get over the bizarre fear of CBD which is based on nothing scientific, we will be able to help our sick community far better or at least give them option of something new and non-toxic to try.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Cannabidiol absolutely has a positive impact on reducing numbers and severity of seizures.
- One of the most significant side effects is a positive one - sleepiness enabling a full nights sleep for sufferers and therefore carers - particularly when given at night.
- Cannabidiol has less negative side effects than many other AEDS e.g. it does not cause apathy, depression, suicidal thoughts
- Side effects are temporary e.g. stop/reduce as the drug is stopped/reduced
- Seizure reduction through this drug has been a lifeline for Todd and our family and it has completely transformed Todd's quality of life e.g. being unable to function at school to being able to function at school.

Thank you for your time.

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