NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine for treating Dravet syndrome [ID1109]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fenfluramine for treating Dravet syndrome [ID1109]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Zogenix

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Dravet Syndrome UK
   b. Epilepsy Action
   c. Association of British Neurologists *(endorsed by clinical expert Dr Sofia Eriksson)*
   d. British Paediatric Neurology Association
   e. Epilepsy Nurses Association

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

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

6. **Technical engagement response** from Zogenix

7. **Technical engagement responses from experts:**
   a. Dr Helen Cross – clinical expert, nominated by Zogenix
   b. Ms Amanda Hirst - clinical expert, nominated by Epilepsy Nurses Association
   c. Dr Sanjay Sisodiya– clinical expert, nominated by Association of British Neurologists

8. **Technical engagement response from consultees and commentators:**
   a. Dravet Syndrome UK response
   b. GW Pharmaceuticals

9. Evidence Review Group critique of company response to technical engagement prepared by by Kleijnen Systematic Reviews

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine for treating Dravet syndrome [ID1109]

Document B

Company evidence submission

August 2020

File name	Version	Contains confidential information	Date
ID1109_FINTEPLA_NICE_DOC_B_FINAL [ACIC Amended] (MAR2021)-REDACTED	**1.7**	**Yes**	**March 2021**

All text highlighted and underlined should be considered as commercial and/or academically confidential

Contents

Tables

Figures

Abbreviations

ADHD	attention-deficit hyperactivity disorder
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AWMSG	All Wales Medicines Strategy Group
BRIEF	Behaviour Rating Inventory for Executive Function
BRIEF-P	BRIEF scale preschool version used for children aged 2-4 years old
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol (refers to the pharmaceutical form Epidyolex® only)
CGI-I	Clinical Global Impression – Improvement
CLB	clobazam
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
ECHO	echocardiogram
EOS	end of study
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQOL–5 Dimensions–3 Levels scale produced by the European Quality of Life Group
EQ-5D-5L	EuroQOL–5 Dimensions–5 Levels scale produced by the European Quality of Life Group
FDA	(US) Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HTA	Health Technology Assessment
ILAE	International League Against Epilepsy
KD	ketogenic diet
kg	kilogram
MCSF	mean convulsive seizure frequency
mg	milligram
mg/kg/day	milligram per kilogram per day
mITT	modified intent-to-treat
mL	millilitre
NCSF	nonconvulsive seizure frequency
NICE	National Institute for Health and Care Excellence
PedsQL	Paediatric Quality of Life Inventory
PK	pharmacokinetic
PP	per protocol
QoL	quality of life
QOLCE	Quality of Life in Childhood Epilepsy
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SE	status epilepticus
SMC	Scottish Medicines Consortium
SMEI	severe myoclonic epilepsy of infancy
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
T+M	Titration plus Maintenance Periods
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
VNS	vagal nerve stimulation
VPA	valproate
ZX008	fenfluramine hydrochloride oral solution (FINTEPLA, FFA)

B.1 Decision problem, description of the technology and clinical care pathway

Dravet syndrome

- Dravet syndrome is a rare, genetic, life-limiting form of epilepsy, clinically considered to be one of the most severe forms of epileptic encephalopathy.
- It develops in early infancy and is characterised by frequent and severe convulsive seizures, often multiple times per day, that increase the risk of death due to Sudden Unexpected Death in Epilepsy (SUDEP), status epilepticus, and accidents; an estimated 15-20% of children with Dravet syndrome die before the age of 10 years and the risk remains elevated throughout life
- The high seizure frequencies experienced by people with Dravet syndrome are also associated with a profound impact on their cognitive and physical development, leading to significant comorbidities, learning difficulties and poor quality of life.
- The substantial burden of caring for patients with Dravet syndrome, arising from high seizure frequency and the wide range of comorbidities, has significant implications for the quality of life of parents who are responsible for delivering care, as well as wider family members.
- Seizures in Dravet syndrome are often intractable, despite the use of combination anti-epileptic drug (AED) therapy. Complete seizure freedom is rarely possible; however, increasing the number of seizure-free days by reducing the frequency of seizures substantially reduces the daily risk for accidental injury and death and improves the quality of life for patients and their carers.

Current treatment pathway

- NICE CG 137 recommends initial therapy with sodium valproate or topiramate, followed by add-on therapy with clobazam and/or stiripentol (Diacomit®). NICE TA614, published in December 2019, also recommends cannabidiol (Epidylex®) in combination with clobazam as an add-on therapy alongside stiripentol.
- The primary aim of therapy in Dravet syndrome is to reduce seizure frequency substantially, leading to more seizure-free days; however, seizures in Dravet syndrome are often resistant to combinations of existing anti-epileptic drug (AED) therapies, including those that are recommended by NICE.
- As other therapies used in general epilepsies may exacerbate seizures in Dravet syndrome, effective therapy options are limited. There is a significant unmet need for more effective and tolerable therapies that expand in a meaningful way the treatment options available to patients and clinicians.

Fenfluramine and its position in the treatment pathway

- Fenfluramine (Fintepla®) is a novel add-on AED. It has a different mode of action to other therapies used in Dravet syndrome and, in contrast to stiripentol and cannabidiol, which are only licensed for use in combination with clobazam, it is anticipated to be licensed for use with or without concomitant clobazam.
- This ability to use fenfluramine irrespective of clobazam use is a distinctive benefit that means it may be used at any point in the add-on therapy pathway, and has the potential to expand, in a meaningful way, the treatment options available to patients and clinicians.
- As cannabidiol (with clobazam) is the only NICE-recommended add-on therapy to have been formally appraised by NICE, and is accepted as a clinically and cost-effective option (alongside stiripentol) in the existing add-on therapy pathway, a primary clinical and economic comparison of fenfluramine against cannabidiol is the most appropriate, relevant and robust comparison to address the decision problem in this appraisal.

B.1.1 Decision problem

Dravet syndrome is a genetic, life-limiting form of epilepsy, clinically considered to be one of the severest forms of epileptic encephalopathy[1, 2]. With fewer than 500 diagnosed cases in the UK it is also one of the rarest. Starting in early infancy, it is a lifelong condition, characterised by frequent and severe convulsive (e.g. generalised tonic–clonic seizures) and non-convulsive (e.g. myoclonic and absence seizures) seizures that are intractable to existing antiepileptic therapies [1, 2]. As evident from the baseline characteristics of subjects enrolled in the fenfluramine registration trials (Study 1 [3] and Study 1504 cohort 2 [4]), patients typically experience a high seizure burden, with convulsive seizures on a daily basis, that increases their risk of death due to Sudden Unexpected Death in Epilepsy (SUDEP), status epilepticus, and accidents[5, 6]. An estimated 15-20% of children with Dravet syndrome die before the age of 10 years[5], and the risk remains elevated throughout adulthood.

As a direct or indirect consequence of frequent seizures, people with Dravet syndrome also experience a profound impact to their cognitive and physical development, morbidity and quality of life. Furthermore, the impact of Dravet syndrome not only directly impacts the patient's quality of life but extends to their parents, carers, siblings and the broader family unit [7, 8].

Complete seizure freedom is rarely possible for people with Dravet syndrome; however, increasing the number of seizure-free days by reducing the frequency of seizures, substantially reduces the daily risk of accidental injury, hospitalisation and death, as well as improving quality of life for the patient and their family. Reducing seizure frequency is therefore a primary aim of treatment for people with Dravet syndrome.

Despite polytherapy with antiepileptic drugs (AEDs), seizures in Dravet syndrome are often pharmaco-resistant and remain intractable to existing therapies. There are limited therapeutic options, as many AEDs used in general epilepsies can exacerbate seizures in Dravet syndrome [9]. There is therefore a significant unmet need for tolerable therapies that reduce the frequency of seizures and their wide impacts on patients and their families.

Fenfluramine hydrochloride (Fintepla®) is an add on therapy for the treatment of Dravet syndrome. This submission covers its full anticipated marketing authorisation: *for the treatment of seizures associated with Dravet syndrome as an add on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults* [10].

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal [11] and is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management. Based on its anticipated licensed indication, fenfluramine will provide an add on treatment option across the add-on treatment pathway, without reliance on the use of clobazam.	N/A
Intervention	Fenfluramine in addition to current clinical management.	Fenfluramine in addition to current clinical management.	N/A
Comparator(s)	Established clinical management without fenfluramine, which may include combinations of: • Sodium valproate • Topiramate • Clobazam • Stiripentol • Levetiracetam • Ketogenic diet • Vagus nerve stimulation • Cannabidiol with clobazam	Fenfluramine is anticipated to be licensed for use as an add-on therapy to a patient's established clinical management*. In the UK and in line with the licensed indication, fenfluramine, as an add on after first line AEDs is proposed for use as a: 2L add on treatment option after clobazam, or 1L add on treatment option in patients where clobazam or a clobazam-based regimen is undesired (Figure 2). In the absence of sufficient **stiripentol** data with which to make robust comparisons, the appropriate primary clinical and economic comparator for fenfluramine is: • **Cannabidiol (with clobazam)** The cost effectiveness of fenfluramine as an alternative 2L+ add on treatment option	Clobazam, stiripentol and cannabidiol (with clobazam) are recommended as add-on therapies in existing NICE guidance [9, 12]; however, as cannabidiol (with clobazam) is the only add-on therapy to have been formally appraised by NICE, and is accepted as a clinically and cost-effective option (alongside stiripentol) in the existing add-on therapy pathway, and is also the only therapy with sufficient trial data to permit a robust comparison, **a primary clinical and economic comparison of fenfluramine against cannabidiol (with clobazam) is the most appropriate, relevant and robust comparison to address the decision problem in this appraisal.** The available clinical data for stiripentol (and clobazam) precludes a robust comparison of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		(alongside **stiripentol and cannabidiol (with clobazam)**) at the same points in pathway), is inferred from the relative cost effectiveness of fenfluramine vs cannabidiol (with clobazam). Additional analyses, based on the robust and internally consistent fenfluramine RCT data versus **SoC AEDs,** support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. *The established clinical management of patients is typically formed of an individually tailored background of combinations of SoC AEDs, diet and devices, which may include: • SoC AEDs (e.g.): o Sodium valproate o Stiripentol o Clobazam o Topiramate o Levetiracetam • Ketogenic diet • Vagus nerve stimulation.	fenfluramine against other NICE-recommended add-on therapies, as accepted in the NICE appraisal of cannabidiol [12]). **In a 2L+ add-on therapy setting:** Cannabidiol is accepted as a cost-effective option alongside stiripentol. Conclusions on the cost effectiveness of fenfluramine as an add-on option at the same points in the add-on therapy pathway as cannabidiol (with clobazam) and stiripentol are recommended may therefore be inferred from the cost effectiveness of fenfluramine vs cannabidiol (with clobazam). **In a 1L add-on therapy setting:** We propose that fenfluramine would not be used as a direct alternative to clobazam but would be used where clobazam is not desirable or is not tolerated. The appropriate comparison would therefore be fenfluramine vs Soc AEDs, in a population of patients not receiving clobazam. However, most patients would receive fenfluramine as proposed in the 2L+ add on therapy setting Comparative analyses of fenfluramine as an add on therapy to background Soc AEDs that include or exclude stiripentol, or in patients not taking concomitant clobazam; support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Ketogenic diet and Vagus nerve stimulation are excluded from the economic model on the basis they are used in a minority of patients and would be used equally in both the fenfluramine and comparator arms of the model. Their exclusion will therefore not impact the estimated incremental cost effectiveness of fenfluramine and is consistent with the approach taken in the NICE appraisal of cannabidiol (TA614).
Outcomes	The outcome measures to be considered include: • Seizure frequency (overall & by type) • Response rate (overall & by type) • Seizure severity • Incidence of status epilepticus • Mortality • Adverse effects of treatment • Health-related quality of life.	The outcome measures included are: • Seizure frequency (overall & by type): o Convulsive seizures o Non-convulsive seizures • Response rate (overall & by type) • Seizure severity* • Seizure free intervals (days), over a defined period of time - Cumulative convulsive seizure-free days - Average longest convulsive seizure-free period - Convulsive seizure-freedom and near seizure freedom • Time to convulsive seizure event (relative between treatments) • Incidence of status epilepticus • Mortality • Adverse effects of treatment • Health-related quality of life: o Patient: ▪ PedsQL ▪ QOLCE	The primary and key secondary endpoints in the registration trials for fenfluramine measured measure reductions in convulsive seizure frequency. Whilst fulfilling standard regulatory requirements and providing a single metric of effect, these metrics alone have some limitations. For example, a 50% reduction from baseline seizures per month, would have different clinical, economic and QoL implications, if patients had experienced 2 or 60 seizures per month at baseline. Additional endpoints e.g. **seizure free intervals**, provide metrics more closely aligned with the goals of treatment and in having a meaningful impact on patient quality of life. As widely reported by patient groups, Dravet syndrome is associated with a significant caregiver burden [7]. Therefore, data on HRQoL from the caregiver perspective in addition to the patient's was formally collected in the Phase 3 fenfluramine clinical studies.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		▪ CGI-I o Caregiver/family: ▪ EQ-5D-5L ▪ PedsQL (family impact module).	Use of rescue medication and inpatient admission have been included, as valuable objective measures of the impact of seizure severity*, beyond patient/clinical experience alone.
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. 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.	As per the reference case.	N/A
Subgroups to be considered	N/A	This submission supports the use of fenfluramine within its full licensed indication, irrespective of clobazam use. Subgroup analysis are provided for completeness to demonstrate the clinical and cost effectiveness of fenfluramine at multiple points in the add-on therapy pathway, including in patients for whom clobazam is not appropriate or desirable, and before or after the use of stiripentol.	Dravet syndrome is rare disease with few effective treatment options available to patients. Seizures are also recognised as being inherently variable within and across patients, and over time, as is their response to different treatments. The goals of therapy are therefore tailored for each patient and comprise of a complex mix of treatments to address the needs of the patient at the time. Fenfluramine provides a new and needed clinical option for all patients in the 'add on therapy' pathway.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	NR	• Dravet syndrome is a very rare, genetic, life-limiting form of epilepsy that begins in infancy. • The severe convulsive and non-convulsive seizures are intractable to existing therapies and have a profound life-long impact on patients' cognitive and physical development, morbidity and mortality; 15-20% of children with Dravet syndrome die before reaching adulthood due to insufficiently controlled seizures. • As such, Dravet syndrome has a profound impact on the quality of life of patients, and their capacity to gain improvements in QALYs are limited. And due to the spectrum of comorbidities arising from frequent, severe convulsive seizures, the quality of life benefits of seizure reduction are muted. The benefits of treatment are therefore not fully captured in the QALY metric • Dravet syndrome also has a profound impact on the quality of life of patient caregivers and the wider family. • There are few licensed therapies available for Dravet syndrome and there remains a significant unmet need for more effective therapy options. Fenfluramine is an innovative orphan medicine that provides a step change in seizure reduction and, as it does not require concomitant use of clobazam, it	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		meaningfully extends the range of treatment options available for patients and their carers. • Older children and adult patients may not have received a definitive diagnosis of Dravet syndrome in there early years and so remain misdiagnosed and sub optimally treated. NICE should consider in its guidance how these older patients may be identified to ensure they are not overlooked by current care arrangements and are optimally treated	

AED = Antiepileptic Drug; CGI-I=Clinical Global Impression of Improvement; EMA = European Medicines Agency; EQ-5D-5L=Euroqol 5 Dimension, 5 Level Instrument; N/A = Not Applicable; NHS = National Health Service; NICE = National Institute for Health & Care Excellence; NR = Not Reported; PedsQL=Paediatric Quality of Life Inventory; QOLCE=Quality of Life in Childhood Epilepsy Questionnaire; SoC = Standard of Care

NICE TA614. Cannabidiol with clobazam for treating seizures associated with Dravet syndrome; 18 December 2019. Available at: https://www.nice.org.uk/guidance/ta614

NICE CG137. Epilepsies: diagnosis and management; updated 11 February 2020. Available at: https://www.nice.org.uk/guidance/cg137

Note: All reference to 'cannabidiol' within this submission refers to the licensed and NICE-recommended pharmaceutical form branded as Epidyolex®.

B.1.2 Description of the technology being appraised

Fenfluramine hydrochloride (Fintepla®) is a designated orphan medicine anticipated to be licensed in Europe early Q1 2021 for the treatment of seizures associated with Dravet syndrome as an add on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults [10].

Fenfluramine has a different mode of action to other therapies used in Dravet syndrome. In contrast to stiripentol (Diacomit®) and cannabidiol[1] (Epidyolex®), which are the only other therapies licensed for use in Dravet syndrome and are only licensed for use in combination with clobazam [13, 14], fenfluramine will be licensed for use with or without concomitant clobazam. Fenfluramine may therefore be used without restriction at any point in the add-on therapy pathway.

Having demonstrated a step change in seizure reduction when added to existing therapies [3, 4], fenfluramine is an innovative therapy that meaningfully extends the range of licensed therapy options for patients with Dravet syndrome. A summary of fenfluramine is provided in Table 2 with the draft Summary of Product Characteristics (SmPC); labelling, and package leaflet provided in the reference pack (see Appendix C).

Table 2: Description of Fenfluramine (Fintelpa®)

UK approved name and brand name	Fenfluramine hydrochloride (Fintepla®)
Mechanism of action	Fenfluramine is a serotonin releasing agent, and thereby stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C receptors, and also by acting on the sigma-1 receptor. The precise mode of action of fenfluramine in Dravet syndrome is not known.
Marketing authorisation/CE mark status	Fenfluramine is currently being reviewed for a European Market Authorisation by the European Medicines Agency (EMA) via a Centralised procedure. CHMP opinion is anticipated in late Q3 2020, with marketing authorisation approval (MAA) expected early Q1 2021. Fenfluramine was initially granted orphan drug designation (EU/3/14/1219) by the European Commission in 2014[15]. The designation is anticipated to be maintained at the time of MAA.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	**Indication (anticipated)** Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults. See the draft SmPC [10] for full details of contraindications, warnings and precautions for use.

[1] *Note: all reference to 'cannabidiol' within this submission refers to the licensed and NICE recommended pharmaceutical form branded as Epidyolex®.*

Method of administration and dosage	**Administration** Fenfluramine hydrochloride is presented as an oral solution containing 2.2mg/mL fenfluramine. It may be taken with or without food. **Dosage** **Patients who are not taking stiripentol:** • The starting dose is 0.1 mg/kg twice daily. • After 7 days, for patients who are tolerating fenfluramine, and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily. • After an additional 7 days, for patients who are tolerating fenfluramine, and require a further reduction of seizures, the dose can be increased to a maximum of 0.35 mg/kg twice daily (0.7mg/kg/day). • Do not exceed a total dose of 13 mg (6 mL) twice daily. **Patients who are taking stiripentol:** • The starting dose is 0.1 mg/kg twice daily. • After 7 days, for patients who are tolerating Fintepla, and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily (0.4mg/kg/day). • Do not exceed a total dose of 8.5 mg (4 mL) twice daily. When discontinuing fenfluramine, the dose should be decreased gradually.
Additional tests or investigations	**Details to be confirmed upon MAA and in accordance with the post marketing obligations in the risk management plans agreed with the EMA.** -Anticipated requirements for additional test and investigations based on the draft label- **Valvular heart disease and pulmonary hypertension** Because of reported cases of cardiac valvulopathy (and pulmonary hypertension) that may have been caused by fenfluramine at higher doses used to treat adult obesity, patients must undergo an echocardiogram (ECHO) to evaluate for regurgitant aortic or mitral valvular heart disease prior to starting treatment. Further cardiac monitoring must be performed using ECHO. In the controlled clinical studies of Fintepla, no valvular heart disease was observed. **Weight loss** Fenfluramine can cause weight loss. The decrease in weight appears to be dose-related. Most subjects resume weight gain over time while continuing fenfluramine treatment. The patients' weight should be monitored. See the draft SmPC for full details.

List price and average cost of a course of treatment	Fenfluramine is presented as an oral solution containing 2.2mg/ml. The maximum NHS list price (excluding VAT) submitted to the DHSC ([redacted]) is: • 60 mL bottle: [redacted] • 120 mL bottle: [redacted] • 250 mL bottle: [redacted] • 360 mL bottle: [redacted] Patients with Dravet syndrome experience seizures over the whole of their life-time. Treatment would be expected to be administered for the duration that their seizures persist and that they receive a clinical benefit. Consistent with the average weight of patients (30 kg) in the registration Phase 3 trials, the annual maintenance treatment cost, based on the NHS maximum list price of FINTEPLA (ex-VAT), is estimated as: [redacted] per patient not receiving concomitant stiripentol and [redacted] for patients concomitantly receiving STP. Based on the DISCUSS study patients with Dravet syndrome, approximately 58% of patients currently receive stiripentol in the UK [16]. **The average annual per 30kg patient price would therefore be estimated as [redacted] per patient.**
Patient access scheme (if applicable)	The proposed 'simple discount' Patient Access Scheme (PAS) price (excluding VAT): • 60 mL bottle: [redacted] • 120 mL bottle: [redacted] • 250 mL bottle: [redacted] • 360 mL bottle: [redacted] Based on the above assumptions, the annual maintenance treatment cost, based on the proposed PAS price (Ex-VAT) of FINTEPLA, is estimated as: [redacted] per patient not receiving concomitant stiripentol and [redacted] for patients concomitantly receiving stiripentol. **The average annual per 30kg patient price would therefore be estimated as [redacted] per patient.**

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Dravet syndrome

Dravet syndrome, previously known as severe myoclonic epilepsy in infancy (SMEI), is a severe, life-limiting, treatment-resistant form of epilepsy that affects children and adults. It is associated with *de novo* (non-inherited) mutations in the sodium channel α1 subunit gene *SCN1A* that is responsible for initiating action potentials in neurons and other excitable ion channels [17-19] [20], and is regarded as one of the most serious genetic epileptic encephalopathies [1].

Dravet syndrome was only recognised as a distinct epileptic syndrome around 40 years ago [2]. It typically presents in the first year of life with recurrent, prolonged convulsive seizures, often triggered by heat such as a mild fever or hot bath, in an otherwise healthy child. From around 1 to 5 years of age, patients experience a progressive worsening in their seizures, including more frequent seizures and prolonged convulsive seizures that may lead to status epilepticus (i.e., a state of continuous seizure that can cause permanent neurological damage, SE). Many patients experience several seizures per day. Additional seizure types, including non-conclusive seizures may also emerge, and everyday occurrences such as physical exertion, emotion, eating, bathing and flashing light may act as seizure triggers. During this worsening phase, developmental delay also becomes evident, together with a spectrum of comorbidities, including ataxia, which affects balance, co-ordination and speech, and learning difficulties. Patients may also begin to exhibit behavioural disorders, including autism and attention deficit hyperactivity disorder (ADHD), and experience sleep disturbances. In later childhood and adolescence, seizures may stabilise; however, seizure frequency and severity remain high and persist into adulthood, as do the associated developmental impacts and comorbidities [2, 7, 21-24].

At this time an ICD 9/10 code has not been assigned to Dravet syndrome. In the UK, the incidence of Dravet syndrome is estimated as 1 in 40,000 live births [11]. In a recent study of Dravet syndrome diagnosis that implemented improved genetic screening of children, the upper (theoretical) estimate of incidence has been estimated as 1 in 15,500 live births [25]. Therefore, in the year 2020, between 18 and 47 patients would be anticipated to be born with Dravet syndrome in the UK.

The prevalence of Dravet syndrome is estimated between 0.1 to 0.4 per 10,000 population [26-28]. This would indicate there are between 670 and 2,670 patients in the UK currently living with Dravet syndrome. However, many young adults and older adults remain undiagnosed due to their condition not being diagnosed in their early years. As patients transition into facilities for adult care, the number of patients with a known diagnosis of Dravet syndrome diminishes with the increasing age of the population. Alongside syndrome-related mortality, this may, in part, be due to the progressive burden of multiple comorbidities having a greater role in the focus of caring for complex patients on a day-to-day basis, as well as differing institutional practices towards seizures and their interest to seek out a diagnosis for an ‘undiagnosed seizure-characterised’ syndrome.

A recently conducted study of European patients and their carers, undertaken to characterise the syndrome, enrolled 584 patients, which was estimated to be 15% of all patients with Dravet syndrome in Europe [7, 8]. This included 72 patients in the UK [16]. On the basis of this representing 15% of the total UK population of patients, the total number of diagnosed Dravet

syndrome patients would be estimated to be 480. Therefore, the total number of Dravet syndrome patients is estimated between 480-2,670 in the UK.

B.1.3.1.2 Seizures in Dravet syndrome are resistant to existing antiepileptic drugs

Seizures in Dravet syndrome are resistant to treatment with existing antiepileptic drugs (AEDs) and sustained seizure freedom is rarely achieved [2, 29]. The DISCUSS study [7], indicated that patients have generally tried multiple prior therapies and take a mean of 3 concurrent AEDs in an effort to control their seizures. Despite this, fewer than 10% achieve seizure freedom lasting more than 3 months. The most frequent types of seizures are tonic-clonic (i.e. convulsive) seizures, which occur in 75-85% of patients, followed by myoclonic and absence (i.e. non-convulsive) seizures. These findings are consistent across all age groups from infancy through to adulthood [7].

In addition to the seizures proving highly resistance to currently available AED treatment, it is also of note that seizures in Dravet syndrome can actually be exacerbated by sodium channel modulator AEDs that are used in general epilepsies, such as carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin [2, 9, 29]. This significantly limits the available treatment options, compared with other epilepsies, and contributes to the considerable unmet medical need for these patients to have access to new, effective and well-tolerated therapies that reduce the frequency of seizures in Dravet syndrome.

B.1.3.1.3 High seizure frequency increases mortality risk

Dravet syndrome patients have a greater risk of premature mortality compared to both the wider population and the general epilepsy population [5, 6]. This is primarily due to Sudden Unexpected Death in Epilepsy (SUDEP: when a person with epilepsy during or following a seizure for no obvious reason dies [30]) and status epilepticus (SE: a prolonged seizure episode of >5 minutes), which are estimated to account for around a half and a third of premature deaths, respectively. Accidental deaths, such as drowning or fatal injury following a seizure, are also an important contributor to Dravet syndrome mortality [5, 6].

A published review of deaths observed in 100 consecutive patients followed for a median of 10 years estimated a Dravet-specific death rate of 15.84 per 1000 person years (approximately 15-16% of the cohort per 10 years), and a Dravet-specific SUDEP rate of 9.32 per 1000 person-years (9-10% of the cohort per 10 years) [575]. This would suggest that the other remaining Dravet syndrome deaths, primarily due to SE, occur at a rate of around 5-6% per 10 years.

Generally, a high seizure frequency is well recognised as a significant contributing risk factor for SUDEP [31]. A higher use of AED polytherapy, likely to be reflective of the pharmaco-resistive nature of the underlying condition, is also shown to be a major contributor to the risks of SUDEP. The most effective SUDEP prevention strategy is commonly accepted to be to reduce the frequency of seizures [32, 33].

Although there is a paucity of data linking rates of SUDEP to seizure frequency specifically in Dravet syndrome, there is little doubt that Dravet syndrome patients experience high seizure frequencies despite AED polytherapy. Patients enrolled in recently conducted clinical trials of Dravet syndrome, with characteristics reflective of patients in UK clinical practice, have convulsive

seizure frequencies in the range of four to several hundred per month [3, 4, 34, 35]. Given there is no correlation between the severity of the *SCN1A* mutation and SUDEP in Dravet syndrome [23], the high risk of death due to SUDEP observed in Dravet syndrome plausibly relates to the severity of the epilepsy, defined by the high frequency of seizures sufferers experience [6].

The presence of convulsive seizures is associated with a higher risk of premature death in epilepsy compared to other seizure types [32, 33]. Infants with Dravet syndrome typically present with prolonged convulsive seizures [2], and the DISCUSS study clearly demonstrates that convulsive seizures are the most common seizure type experienced by Dravet syndrome patients throughout life [7]. Furthermore, those with the highest convulsive seizure frequencies require significantly more emergency hospital admissions and ambulance assistance than those with the lowest convulsive seizure frequencies [7]. Although seizures may stabilise as patients age, convulsive seizures during adolescence and adulthood tend to occur mainly during sleep [2]. Nocturnal seizures are an independent risk factor for SUDEP [36]. Given these associations, it is clinically considered amongst experts that patients with Dravet syndrome are at a high risk of epilepsy-related death throughout their life, and that a reduction of convulsive seizure frequency is the most effective strategy to reduce death [32] and therefore a primary treatment goal to reduce that risk [5, 29].

B.1.3.1.4 High seizure frequency is associated with greater developmental comorbidities

In addition to refractory seizures, patients and their caregivers must manage a range of developmental comorbidities, including disturbance of motor skills and movement coordination, delayed speech development, attention-deficit hyperactivity disorder, behavioural problems, muscular hypotension and cognitive disorders [7, 37, 38]. Based on the DISCUSS study, over 90% of patients in the cohort had such comorbidities, including 88% with learning difficulties, 72% with motor impairment, and 64% with speech impairment (including 16% of patients over 5 years of age who were unable to speak at all) [7, 16]. Similar findings have been observed in other caregiver surveys [38].

These high rates of developmental problems have implications for independent living at all life stages [39, 40]. Young people may be unable to attend mainstream school, instead attending specialised or home schools, or not attending school at all [7], and in adults, partial or total dependency is a near-universal feature, with few people able to live independently without support [40] and many requiring 24-hour care [41]. This dependency exerts a substantial socioeconomic burden on families, with parents of Dravet syndrome patients often giving up paid employment to be full time caregivers with little respite from their carer responsibilities.[7, 8, 38, 42]. The profound, life-long caregiver burden was recognised and accepted by NICE in its appraisal of cannabidiol, affirming that patients with Dravet syndrome would typically require the equivalent of 1.8 caregivers [12].

The precise relationship between seizure frequency and the severity of developmental comorbidities has not been fully elucidated; however, clinical consensus is that the frequency and duration of convulsive seizures can have a large impact on developmental outcomes [43]. In the DISCUSS study, patients with the highest convulsive seizure frequencies had more comorbidities than those with the lowest convulsive seizure frequencies (81st vs 22nd centile, mean [SD] number of comorbidities: 4.08 [0.97] vs. 3.41 [1.28]). The number of patients (older than 2 years of age) that reported a motor (83% vs 53.8%;$p<0.001$) or speech impairment (including not talking at all; 89.4% vs 71.4% [$p<0.005$]) was also statistically significantly higher in patients with the highest frequencies of convulsive seizures compared with those with the lowest convulsive seizure

frequencies [7]. Furthermore, case series in adults with long-standing Dravet syndrome have reported cognitive improvements following improved seizure control [44]. There is, therefore, a clear association between higher seizure frequency and greater developmental comorbidities in Dravet syndrome throughout life, which highlights the importance of improving seizure control throughout life.

B.1.3.1.5 High seizure frequency reduces quality of life of patients and carers

The combination of seizure burden, and cognitive, motor, behavioural and sleep impairments in Dravet syndrome, significantly impairs the health-related quality of life (HRQoL) of patients [45]. Using the European Quality of Life-5 Dimensions 5-level scale (EQ-5D-5L) instrument, the DISCUSS study found the parent-rated mean value for all patients aged ≥2 years old to be 0.42 (SD 0.29), which is significantly lower than that in the general population. Those with the highest seizure frequencies (above the 80th centile) had lower HRQoL than those with the lowest frequencies (below the 21st centile) [7].

The substantial burden of caring for patients with Dravet syndrome, arising from refractory seizures and the wide range of comorbidities, has significant implications for the quality of life of parents who are responsible for delivering care as well as the wider family members [46]. In addition to the demands of care, which prevents carers from leading normal lives and spending time with their other children, anxiety associated with the spontaneous occurrence of seizures and the possibility of SE or death can be near constant (as best explained by parents of a child with Dravet syndrome – see Dravet UK: https://www.dravet.org.uk/families/dravet-stories/toby/). This constant demand for care and anxiety can significantly affect the mental wellbeing of all family members [12]. Fear, uncertainty, deterioration of relationships, and sleep disturbance are common [8, 42, 47, 48], and many Dravet syndrome patient caregivers suffer from depression, despite having no significant health issues themselves [49].

For these reasons, NICE concluded in its appraisal of cannabidiol that Dravet syndrome severely affects the quality of life of patients, families and carers to the extent that it is appropriate to capture the impact of both patients' and carer's quality of life within the estimates of cost effectiveness [12]. Based on the findings in a report published by the NICE Decision Support Unit in 2019, this has happened in fewer than 3% of appraisals [50], which signifies the gravity of the impact of Dravet syndrome compared to other conditions. Furthermore, whilst confirming that convulsive seizures have the biggest effect on quality of life in Dravet syndrome, NICE also concluded that, in addition to reducing frequency, reducing the duration of convulsive seizures and the occurrence of non-convulsive seizures are important factors for improving quality of life [12].

B.1.3.1.6 Reducing seizure frequency and increasing seizure-free days is key for patients and carers

Given the above, it is clear that patients that experience a high convulsive seizure frequency are at a greater risk of death and developmental comorbidities and have lower quality of life than patients with a lower convulsive seizure frequency. Reducing the frequency of seizures can increase the interval between seizures, and the greater the interval between seizures the greater the benefits to patients and carers [51]. The NICE final appraisal determination (FAD) for cannabidiol noted clinicians' views that, in addition to reducing convulsive seizure frequency, to increase the number of seizure-free days was also important, as fewer days with seizures means

fewer days in which patients are at risk of SUDEP [12]. From the perspective of patients and their families, increases in seizure-free days can also have a profound and direct impact on daily activities, including learning opportunities and planning for social interactions, as well as reducing the physical and emotional toll of the disease [51, 52].

Reducing convulsive seizure frequency, leading to more seizure-free days, therefore reduces the risk of patients experiencing SE or SUDEP, reduces the risk of developmental comorbidities, and improves patients' quality of life. In turn, increasing the number of convulsive seizure-free days is expected to reduce the physical burden, anxiety and fears experienced by caregivers, which improves their quality of life. Reducing seizure frequency, leading to increased seizure-free days is therefore a key therapeutic goal for patients with Dravet syndrome and their carers.

Whilst complete seizure freedom is the ambition for patients with Dravet syndrome, their carers and families, the resistance of seizures to AED therapy is a defining characteristic of Dravet syndrome. It is therefore rare for patients to achieve complete, sustained seizure freedom [2, 29]. However, complete seizure freedom is not necessary for patients, their families and caregivers to benefit significantly from treatment. Clinical trials typically employ a ≥50% reduction from baseline in convulsive seizure frequency to define a clinically meaningful reduction in seizures [3, 4, 34, 35], and re-analyses of fenfluramine trial data indicate that a 37.5-44% reduction in seizures from baseline was clinically meaningful when rated by caregivers and clinicians [53, 54]. The NICE FAD for cannabidiol indicates a 30% reduction in convulsive seizure frequency is sufficient patient-relevant benefit to warrant continued treatment [12], and in a UK Dravet syndrome pathway mapping project to explore physician, nurse and care givers views [redacted] on current management and outcomes in Dravet syndrome in the UK, participants reported [redacted] could be deemed meaningful for some patients [55].

As expressed in the patient expert submission to NICE in the appraisal of cannabidiol, given the context of the disease and its profound impact on patients, families and caregivers, any reduction in current seizures is of benefit [41]. Therefore, a therapy option that provides a substantial reduction in convulsive seizure frequency and increases seizure-free days compared with currently available therapy options, even if not providing complete seizure freedom, would still be considered a transformative step change to improving the day-to-day lives of patients, their families and caregivers.

B.1.3.2 Dravet syndrome clinical care pathway

B.1.3.2.1 Diagnosis of Dravet syndrome

The UK Strategy for Rare Diseases, published by the Government in 2013, highlights the importance of early diagnosis of rare diseases so that patients receive the most effective treatments [56]. This is particularly so in Dravet syndrome, where early diagnosis is critical to ensure avoidance of sodium channel blocking AEDs that can exacerbate seizures [29]. Although Dravet syndrome has recently been characterised as a genetic form of epilepsy associated with *de novo* mutations in the *SCN1A* gene, diagnosis is predominately based on clinical signs and symptoms, with mutations in the *SCN1A* gene considered as a supportive marker for the disorder [2, 7]. The initial presentation in young children is quite characteristic, but less so in older children and adults, and there are reports of sometimes extensive delays in patients receiving a definitive diagnosis [29]. The DISCUSS study observed that in one third of patients (32.9%), the time to diagnosis exceeded 4 years. This was heavily weighted by older patients' experiences of receiving

extensively delayed diagnosis. Dravet syndrome was instantly recognised in 45% of pre-school children, with 88% of infants receiving a definitive diagnosis within a year [7]. This suggests that physician awareness of Dravet syndrome has increased markedly over time alongside the implementation of improved genetic screening protocols for children presenting with undiagnosed Dravet syndrome. However, this also indicates that there are likely to be some older and adult Dravet syndrome patients who have not had an early definitive diagnosis and that would benefit from a diagnosis to ensure they are receiving appropriate clinical management and Dravet syndrome specific therapies.

B.1.3.2.2 Current treatment guidelines

In 2012, NICE issued clinical guideline 137*: Epilepsies: diagnosis and management* [9]. This provides specific recommendations on pharmacotherapy for Dravet syndrome, taking into account that sodium channel blocking agents should be avoided in Dravet syndrome, and the safety warnings on the teratogenic potential of sodium valproate:

First-line AED treatment:

- Consider topiramate for women and girls of current or future childbearing potential
- Consider sodium valproate or topiramate for boys, men and women not of childbearing potential.

Adjuvant (or 1st line 'add on') treatment:

- Consider clobazam or stiripentol.

These recommendations are broadly consistent with those of more recent published guidelines and consensus statements from several countries, available in the literature [29, 43, 57]. All agree that the primary aim of therapy should be to reduce seizure frequency and recognise that combinations of AEDs are necessary but rarely achieve complete seizure freedom [29, 43, 57].

As noted in the DISCUSS study, caregivers of Dravet patients report that patients on average take 3 concurrent AEDs in an effort to control their seizures [7]. Clinical expert opinion, sought by Zogenix to explore the management and outcomes in Dravet syndrome in the UK, indicates that clinicians would typically try up to 3 concurrent AEDs, with 4 concurrent AEDs used rarely [55]. This was reportedly due to physicians and carers being reluctant to withdraw therapies as it can be difficult to know which ones are not effective. In general, then, if first-line AED therapy (e.g. sodium valproate and/or topiramate) does not provide sufficient seizure control, another agent is added in (i.e. first line add-on therapy), and the majority of patients will also require a further add-on therapy (Figure 2).

The NICE scope for this current appraisal of fenfluramine references a specific combination of sodium valproate, stiripentol and clobazam [11], and UK data from the DISCUSS study indicates valproate is used by 68% of patients, with clobazam and stiripentol used in 74% and 58% of patients, respectively [16]. However, as noted in NICE CG 137, the ideal treatment strategy is personalised and considers a range of factors including the change in typical seizure patterns over time, seizure types, co-medications, comorbidities, adverse effects, lifestyles, and the personal preferences of patients, families and carers [9]. As different patients may respond to different therapies in different ways, it is important that a range of therapy options are available in order to tailor therapy to patients' individual needs. In 2019, NICE TA614 recommended cannabidiol (Epidyolex®) with clobazam as an additional add-on treatment option in patients with Dravet syndrome [12]. Its recommendation as a routine add-on treatment option within its full licensed

indication means that cannabidiol is recommended in the add-on therapy pathway alongside stiripentol, and it is included as a relevant comparator in the scope for this appraisal [11].

Non-pharmacological therapies included in other consensus guidelines and position statements include ketogenic diet and vagus nerve stimulation, which are only recommended after second- or third-line therapy in patients not achieving satisfactory response to pharmacological therapy and are not suitable for all patients [29, 57]; despite being recognised as therapy options for many years, only 6-7% of patients in the DISCUSS study were using ketogenic diet or vagus nerve stimulation [7, 8]. Given they would not be considered influential to the effectiveness of fenfluramine or the comparator treatments, and are likely to be used in similar proportions within background standard of care independently of the fenfluramine or a comparator treatment option selected, these approaches are not considered pertinent to the decision problem and are not further consider in this submission.

B.1.3.3 Key add-on pharmacological therapies

B.1.3.3.1 Clobazam

Clobazam is a benzodiazepine derivative. It is not specifically licensed for use in Dravet syndrome, but its use is well established in the treatment pathway. Although some guidelines recommend clobazam as a first-line option alongside sodium valproate [29, 43], NICE CG137 and other therapeutic positioning statements refer to clobazam as an add-on therapy when first-line AED is not providing sufficient seizure control [9, 57]. Despite being well established in the treatment pathway, the evidence for its use in Dravet syndrome is predominantly based on expert opinion and retrospective case series [43]; a Cochrane systematic literature review (SLR) published in 2017 found no RCTs evaluating the efficacy and safety of clobazam in Dravet syndrome [60]. The most common side effects of clobazam include somnolence (very common), sedation (common), dizziness (common) and ataxia (common) [43, 61]. Clobazam has not been formally appraised by NICE.

B.1.3.3.2 Stiripentol (Diacomit®)

Stiripentol was the first agent to be specifically licensed for use in the treatment of Dravet syndrome. It is licensed in Europe for use as an adjunctive treatment in combination with both clobazam and valproate, at a recommended dose titrated to 50mg/kg/day [13]. Stiripentol is an aromatic alcohol that inhibits cytochrome P450 enzymes and so increases the plasma concentrations of other agents, including clobazam and valproate. It may also inhibit uptake of GABA and modulate GABA receptors [13, 43].

Stiripentol was licensed on the basis of two placebo-controlled randomised controlled trials (RCTs) conducted 2 decades ago in children aged 3-18 years with Dravet syndrome who were already receiving valproate and clobazam (STICLO-France [n=41] and STICLO-Italy [n=23]) [62, 63]. Patients were treated for 8 weeks and the primary outcome was the proportion of patients achieving at least a 50% reduction (typically used in trials and by regulators to denote a clinically meaningful reduction) in the number of clonic or tonic-clonic seizures during the second month of therapy, which was increased significantly by around 60% compared with placebo [62-64]. Observational data suggest long term efficacy for this endpoint is maintained [65]. Of note, the STICLO trials did not assess other seizure types such as non-convulsive or focal seizures; and a recent Cochrane review found no benefit of stiripentol in people with treatment-resistant focal seizures [66]. The most common side-effects are reported to be drowsiness (very common),

anorexia, loss of appetite and weight loss (very common), insomnia (very common), and ataxia, hypotonia, and dystonia [13, 43]. Some adverse effects are due to increased serum concentrations of concomitant AEDs secondary to inhibition of their metabolism by stiripentol, which may necessitate their dose reduction [43].

Stiripentol has not been formally appraised by NICE. It has, however, been appraised and recommended for use by the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) [26, 64]. Of note, in the SMC appraisal, plausible sensitivity analyses resulted in incremental cost effectiveness ratios (ICERs) in excess of £30,000/QALY compared with standard of care therapy, and the incremental cost per QALY gained with stiripentol increased to over £40,000/QALY and over £60,000/QALY with 10% and 30% continued use in adulthood, respectively [64]. In the AWMSG appraisal it is noted that with 10% continued use into adulthood stiripentol is not cost effective at a £30,000/QALY threshold, and the ICER increases to £60,000/QALY with 30% continued use) [26]. In both the SMC and AWMSG appraisal processes, stiripentol appears to have benefited from the application of decision modifiers that allow for more flexible consideration of the cost effectiveness of therapies for rare diseases [26, 64].

B.1.3.3.3 Cannabidiol (Epidyolex®)

As mentioned above, cannabidiol is licensed for use only in combination with clobazam [14]. Its precise mode of action is unclear [14] but it is an inhibitor of cytochrome P450 enzymes, which increases plasma concentrations of clobazam and its active metabolite, similar to stiripentol. It may also alter neuronal excitability and have anti-inflammatory properties [14, 43]. Following a 1-week titration period (5mg/kg/day), the recommended maintenance dose is 10-20mg/kg/day [14].

Cannabidiol was licensed in Dravet syndrome on the basis of two placebo-controlled RCTs in which it was added to background standard of care therapy in patients aged 2-18 years (GWPCARE 2: doses of 10 and 20mg/kg/day; GWPCARE 1: dose 20mg/kg/day) [34, 35]. The restriction to use with clobazam was based on subgroup analyses that showed it offered insufficient benefit without concomitant clobazam [22]. The primary endpoint was percentage change from baseline in convulsive seizure frequency per 28 days, assessed over a 14-week titration and maintenance treatment period. In patients receiving a maintenance dose of 10mg/kg/day, the placebo-adjusted reduction with cannabidiol plus clobazam was statistically significant at 37% (GWPCARE2). In patients receiving a maintenance dose of 20 mg/kg/day, the placebo-adjusted reduction in seizures per 28 days was 31% (GWPCARE2) and 43% (GWPCARE1). The proportion of patients achieving at least a 50% reduction in convulsive seizures (typically used in trials and by regulators to denote a clinically meaningful reduction) also favoured cannabidiol versus placebo (48-63% for cannabidiol 20mg/kg/day [nominal $p<0.05$]; 56% for cannabidiol 10mg/kg/day [nominal $p=0.06$] versus 24-37% for placebo). However, the Summary of Product Characteristics notes that in its open-label extension (OLE) study the median decrease in convulsive seizures from baseline was reduced from 60% in Weeks 1-12 to 45% in Weeks 37-46 [14], which represents a 25% relative reduction in efficacy over less than a year of treatment, suggestive of a potential waning of effect over time. In addition, a published interim analysis of the OLE study, in which doses were titrated to 20mg/kg/day and could be increased or decreased based on response and tolerability, the mean modal dose received was 21mg/kg/day [67], suggesting that doses in practice may be more towards the upper rather than lower end of the recommended 10-20mg/kg/day dose range with potentially increased dosing being required over time to compensate for a loss of effect. The most commonly occurring adverse events are somnolence or sedation (very common), decreased appetite (very common), diarrhoea and vomiting (very common), fever, fatigue (very common) and decreased weight (common) [12, 14].

Cannabidiol was appraised by NICE and recommended for use with clobazam as an add-on therapy option in December 2019 [12]. The company compared cannabidiol as an add-on therapy to standard of care AEDs against standard of care AEDs alone, as per its clinical trials, and on the basis that there were insufficient robust data available to make formal indirect comparisons against stiripentol or other therapies. Since that appraisal, no further evidence has been developed for stiripentol or other currently available therapies that would permit a robust indirect comparison with cannabidiol (see section B.2.9).

A number of concerns were raised by the evidence review group and appraisal committee regarding the company's economic model, including: assumptions on long-term sustainability of the treatment effects; data underpinning the selected utility values; proportion of patients receiving a 10 or 20mg/kg/day dose; number of carers (and their quality of life) to include; and extrapolations of natural history over a life-time horizon with the sparsity of available data particularly in adult patients with Dravet syndrome. It was also noted that the heterogeneity in seizure-free days might have been more appropriately captured using a discrete event simulation modelling approach rather than the Markov cohort modelling approach used by the submitting company [12].

After revising a number of assumptions, including adoption of a mean dose of 12mg/kg/day and permitting the inclusion of carer burden in to the ICER estimate (incorporating quality of life decrements for 1.8 carers), the preferred ICER exceeded £30,000/QALY. However, when taking into account other benefits of treatment that were not captured in the ICER estimate, including: the impact of treatment on non-convulsive seizures; duration of convulsive seizures; and improvements in quality of life for siblings of Dravet syndrome patients, the committee concluded that cannabidiol was sufficiently cost effective when implemented with a confidential patient access scheme and treatment discontinuation criteria, to recommend within its full licensed indication [12] (Figure 1). Therefore, although it has not been compared either directly or indirectly against stiripentol in terms of its clinical or cost effectiveness, cannabidiol in combination with clobazam is recommended as an add-on therapy option alongside stiripentol in the current treatment pathway.

Cannabidiol (with clobazam) is included as a relevant comparator in the scope for this appraisal of fenfluramine [11]. At the point of the first appraisal committee meeting for this current appraisal of fenfluramine, cannabidiol (with clobazam) will have been an established treatment option for UK patients for over a year. Cannabidiol is also licensed by the EMA and recommended by NICE for use in Lennox-Gastaut syndrome [68]. With its recent reclassification from a Schedule 2 to a Schedule 5 controlled drug [58], which removes virtually all controlled drug prescribing requirements, access to and use of cannabidiol (with clobazam) is anticipated to increase [59].

Figure 1. NICE recommendation for cannabidiol with clobazam in Dravet syndrome

NICE recommendation: **Cannabidiol with clobazam for treating seizures associated with Dravet syndrome** *Technology appraisal guidance [TA614] Published date: 18 December 2019*

1.1 Cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome in people aged 2 years and older, only if:
- The frequency of convulsive seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment
- The company provides cannabidiol according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with cannabidiol, with clobazam, that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place before this guidance was published, until they and their NHS clinicians consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person, or the child or young person's parents or carers.

B.1.3.4 Proposed positioning of fenfluramine within the Dravet syndrome clinical pathway

As highlighted in Section B.1.3.1, Dravet syndrome populations are heterogenous in their seizure frequencies and treatment histories. The primary goal of treatment in Dravet syndrome is to reduce seizures; however, despite the availability of well-established and recently approved therapies, seizures in Dravet syndrome remain intractable for the vast majority of patients. There is therefore a significant need for further therapy options that provide a meaningful reduction in convulsive seizure frequency compared with currently available therapy.

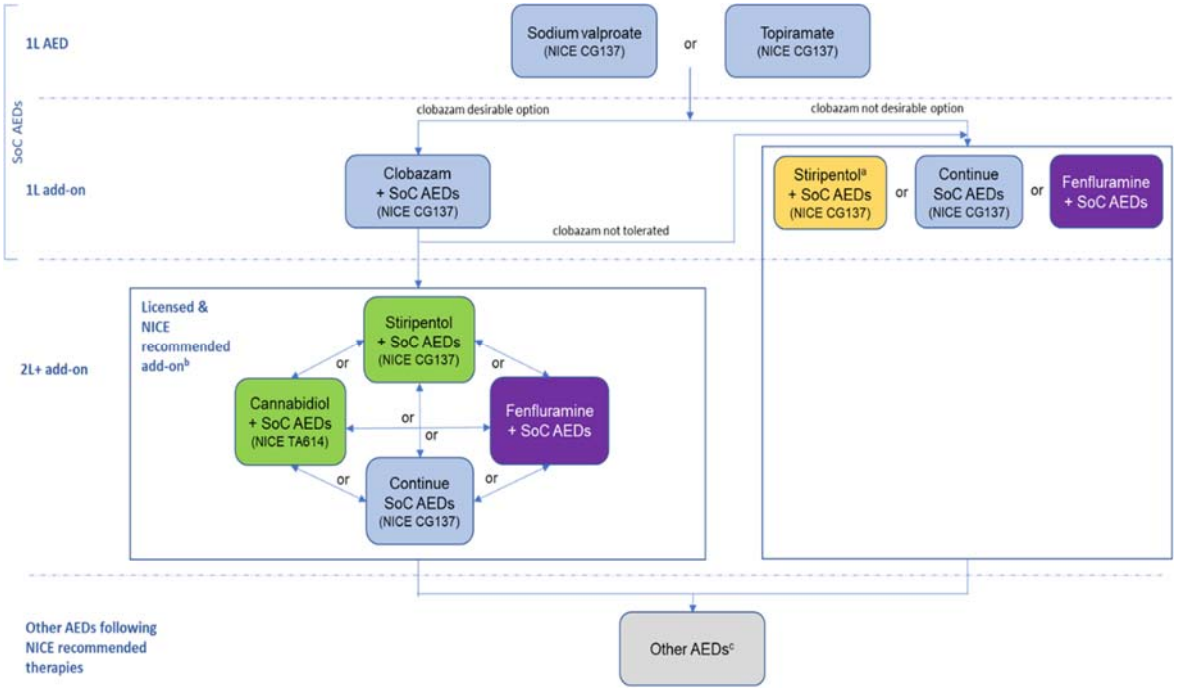
Fenfluramine is an innovative new therapy under review by the EMA for Dravet syndrome. The anticipated licensed indication is: *for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults* [10].

The clinical development programme for fenfluramine (detailed in section B.2) was therefore designed to accommodate this heterogeneity and confirm efficacy across the wide range of Dravet syndrome patients in clinical practice. In contrast to stiripentol and cannabidiol, fenfluramine is anticipated to be licensed for use both with or without concomitant clobazam. Fenfluramine, within its anticipated full licensed indication, will therefore meaningfully expand the therapy options available to patients and clinicians by being a potential treatment option at all points in the add-on therapy pathway.

The current add-on therapy pathway is complex. Based on existing NICE guidance in CG137 and TA614 and current clinical practice, the proposed positioning of fenfluramine in the treatment pathway for patients with Dravet syndrome is as outlined in Figure 2. We anticipate that, where clinicians feel clobazam is clinically a desirable first-line add-on therapy, this would be tried in preference to other options, including fenfluramine. However, fenfluramine could be a first-line add-on therapy option in patients for whom clobazam or clobazam-containing regimens are not a desirable option (or not tolerated, i.e., a second line add-on therapy), in which case, based on NICE CG137, unlicensed stiripentol or continued therapy with existing standard of care AEDs would be the appropriate comparators. NICE-recommended second- or subsequent line add-on therapy options following the addition of clobazam include stiripentol or cannabidiol (with clobazam). We anticipate that clinicians would generally select from these NICE-recommended options, optimise their doses (including increasing their dose to compensate for any waning of effect over time) and exhaust these options before considering continued ineffective therapy with existing standard of care AEDs, or addition of other AEDs that are experimental, unlicensed, and/or not NICE-recommended. The appropriate comparators for fenfluramine as a second- or subsequent line option in patients in need of an add-on therapy would therefore be stiripentol or cannabidiol (with clobazam). Continued therapy with existing standard of care AEDs could be relevant but only when NICE-recommended add-on therapies have been exhausted.

The introduction of fenfluramine in the treatment pathway aligns with typical clinical management and the existing treatments currently available for patients with Dravet syndrome. Patients will require an echocardiogram before starting treatment and periodically whilst maintained on treatment (section B.3.5.1.2; [10]); however, no other additional resource use or significant service redesign would be anticipated.

Figure 2: Proposed position of fenfluramine within the treatment pathway for Dravet syndrome



KEY: 1L, first-line; 2L+, second- and subsequent line AEDs; AEDs, anti-epileptic drugs; SoC AEDs, standard of care AEDs reflecting AEDs and add-on therapies continued from previous line

[a] Stiripentol is not licensed for use as 1L add-on therapy in Dravet syndrome without clobazam; however, NICE guidelines recommend considering stiripentol as an alternative to clobazam if seizure control not achieved on 1L treatment alone

[b] **We expect clinicians would select clinically appropriate options from this group, would optimise doses and would exhaust these options before considering moving to Other AEDs.**
Fenfluramine is proposed as an alternative 2L+ add on therapy option alongside cannabidiol (with clobazam) or stiripentol, and may be used before stiripentol (stiripentol-naïve) or after stiripentol (stiripentol-failures/experienced), as demonstrated in Study 1; or in addition to stiripentol, as demonstrated in Study 1504.
In the primary base case cost-effectiveness analysis, fenfluramine is presented as an alternative to cannabidiol (with clobazam) (see B.2.9 section and B.3)
Secondary analyses are presented to support decision-making for fenfluramine as a: 1L (or 2L) add-on therapy option in patients where a clobazam-based strategy (incl. stiripentol and cannabidiol) is not desirable, or as a 2L+ add-on therapy option for patients before, after, or on top of stiripentol

[c] Other AEDs licensed for general epilepsy and used in Dravet syndrome on an experimental or off-label basis

NOTE: In addition to AEDs, ketogenic diet and vagal nerve stimulation may also considered as additional adjunct treatments, but are used rarely and not further considered in this appraisal

Adapted from NICECG137 and NICE TA614

All patients in Study 1504 received stiripentol (and 95% received clobazam, in accordance with the licensed stiripentol indication)

B.1.4 Equality considerations

B.1.4.1 Older and adult patients, and those with undiagnosed Dravet syndrome

As highlighted in section B.1.3.1.1 and B.1.3.1.2, the diagnosis of Dravet syndrome was initially clinically characterised in the mid-1970s and has only relatively recently been confirmed with genetic testing alongside a clinical diagnosis. There is currently no ICD 9/10 code assigned to Dravet syndrome.

Today, an estimated 80-95% of incident cases of Dravet syndrome in children in the UK receive a genetic diagnosis; however, many young adults and adults who have Dravet syndrome remain undiagnosed due to their condition not receiving genetic testing in their early years. These vulnerable, older (mainly adult) patients may not be receiving optimal care or appropriate treatment

and may even receive treatments that exacerbate their condition and are contraindicated in patients with Dravet syndrome [9]. *NICE should consider in its guidance how these older patients may be identified and diagnosed to ensure they are not overlooked by current care arrangements and are optimally treated.*

The anticipated licensed indication spans patients with Dravet syndrome aged 2 years and older, including adults. From the age of 2 years, there is no evidence of significant differential effects on seizure reduction by age with fenfluramine therapy (see section B.2.6.1.1.1 and B.2.6.3). Furthermore, as demonstrated in section B.3.9.3, the cost effectiveness of initiation of fenfluramine in patients aged 18 years and above supports the use of fenfluramine in the whole Dravet syndrome population, regardless of age. *Access to fenfluramine therapy in patients aged 2 years and older should not be determined by age.*

B.1.4.2 Weighting a Dravet syndrome patient's quality of life

To ensure equality within NHS decision-making, the value of a Dravet syndrome patient's quality adjusted life year should be weighted to prevent underestimation of the true impact of seizures and to fully capture the benefits from a treatment on the patient's and their carer's quality of life.

i) **Coping with Dravet syndrome:** The burden from the high frequency of severe convulsive seizures associated with Dravet syndrome, and their profound impact on physical and cognitive development, exert a lifelong impact on patient and carer quality of life. However, the true burden on the patient and their carer's quality of life, relative to population norms is likely to be underestimated due to the need for patients and carers to adapt and cope with this lifelong and progressive condition.

ii) **Identifying the seizure-specific impact on quality of life within the overall complexity of Dravet syndrome:** In patients with Dravet syndrome, the seizure-specific component contributing to overall quality of life is difficult to identify due to the diversity of individual patient's seizures in combination with the spectrum of complex and progressive comorbidities. The specific impact of seizures (and their reduction) on patient quality of life is therefore likely to be underestimated (muted).

iii) **For decision-making purposes, the quality adjusted life year of Dravet syndrome patients should be normalised to ensure equality in their value:** Reducing seizure frequency reduces the immediate burden of seizures on quality of life and may reduce the risk of further developmental decline (and mortality); however, it cannot reverse the developmental decline that has already occurred and the future progression of existing comorbidities that contribute to the patient's overall quality of life. It should therefore be recognised that patients with Dravet syndrome and their carers will always have a reduced quality of life and a limited potential to improve that quality of life with therapy. The benefits from the significant and often profound reductions in convulsive seizure frequency with fenfluramine therapy are therefore likely to be muted (restricted) when measured on the quality of life scale. Consequently, the true benefits of fenfluramine therapy may not be fully reflected in the quality-adjusted life years (QALY) metric. When considering both the initial quality of life impact from reduced seizures, as well as the longer-term weighting of quality of life in surviving patients, the value of a Dravet syndrome patient's quality adjusted life year should be normalised to ensure equality within decision-making.

iv) **Dravet syndrome significantly impacts the quality of life of carers and broader family unit:** Given the profound impact of convulsive seizures on both the patient and carer quality of life, and hence the increase in quality of life for both patient and carer from a reduction in convulsive seizure frequency, it is appropriate to include the quality of life of both the patient and carers when considering the cost effectiveness of fenfluramine therapy, as was done in the appraisal of cannabidiol in NICE TA614 [12]. This is in line with the NICE reference case, which states that the perspective on outcomes should be all direct health effects, whether for patients or, where relevant, carers [69].

Assuming appropriate consideration of fenfluramine within its full licensed indication and the above technical points it is not anticipated that this appraisal will exclude from consideration any other people with characteristics protected by equalities legislation, or lead to a recommendation that has a different impact on people protected by equalities legislation than on the wider population, or lead to recommendations that have any adverse impact on people.

B.2 Clinical effectiveness

Summary of clinical effectiveness for fenfluramine

- Robust, high-quality RCT data from Study 1 and Study 1504 (cohort 2) clearly demonstrate that significant and clinically meaningful reductions in convulsive seizure frequency are achievable for most patients when fenfluramine is added to the most effective AEDs currently available.
- Significantly greater proportions of patients treated with fenfluramine had clinically meaningful (>50%) and profound (>75%) reductions in convulsive seizures compared to the placebo group, with numbers needed-to-treat of <2 and 2-3, respectively. From median baseline convulsive seizure frequencies of 14-20 per month, 25% of patients on fenfluramine in Study 1 and 12% in Study 1504 achieved near seizure freedom (<1 seizure during the 14-15 weeks of treatment, that included a 2-3 week titration period), compared with none treated with placebo.
- Reductions in convulsive seizures are consistent, irrespective of concomitant clobazam use, and if patients receive fenfluramine before, after, or in addition to stiripentol.
- The median longest convulsive seizure-free intervals were also significantly longer with fenfluramine 0.7mg/kg/day and 0.4 mg/kg/day (as an add on to stiripentol) than placebo in both Study 1 (25.0 days vs 9.5 days; p<0.0001) and Study 1504, cohort 2 (22.0 vs 13.0; p=0.004).
- The number of patients experiencing serious or severe treatment-emergent adverse events was low and similar in both the fenfluramine and placebo arms, and there was little difference in the number experiencing serious treatment-related adverse events between fenfluramine and placebo in either Study 1 [redacted] or Study 1504 ([redacted]). Few patients experienced adverse events leading to discontinuation (12.5% in Study 1 and 4.7% in Study 1504).
- Data from open-label extension and real-world observational studies clearly demonstrate that the significant and often profound reductions in convulsive seizure frequency, and the safety and tolerability, observed with fenfluramine in the phase 3 RCTs are durable and sustained with long-term treatment over several years.
- A robust indirect treatment comparison indicates clearly that fenfluramine is superior to cannabidiol (with clobazam) in reducing convulsive seizure frequency, with significantly greater proportions of patients achieving clinically meaningful reductions (≥50%) with fenfluramine. As cannabidiol (with clobazam) is accepted by NICE as a clinically (and cost-effective) option alongside stiripentol in the existing add-on therapy pathway, it is a reasonable expectation that fenfluramine would also be a clinically effective add-on therapy at the same points in the add-on therapy pathway as both cannabidiol and stiripentol.
- The clinical evidence base supporting fenfluramine is generalisable to UK practice, and supports its use across the add-on therapy pathway in line with its anticipated full licensed indication. Collectively, this clinical evidence base is more complete, robust and of a higher quality than the evidence supporting any of the existing NICE-recommended add-on therapies.
- **Dravet syndrome is characterised by severe, high frequency seizures that are typically resistant to existing AEDs; seizure freedom is rarely achieved. The significant and often profound reductions in seizure frequency achieved with addition of fenfluramine to existing AEDs are potentially life-changing for a high proportion of patients, their families, and caregivers.**
- **Combined with its ability to be used at any point in the add-on therapy pathway, without reliance on concomitant use of clobazam, fenfluramine is an innovative therapy that provides a step change in the treatment of Dravet syndrome.**

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was performed 28th June 2020 to identify clinical data relevant to the decision problem. This confirmed that the primary comparative clinical trial data for fenfluramine consists of two pivotal phase 3 RCTs (Study 1 [3] and Study 1504 cohort 2 [4]). Full details of the SLR methodology and results are provided in Appendix D.

Data from an open-label extension study that enrolled patients from these RCTs is also available (Study 1503 [70]), along with a number of observational studies ('Belgian RWE studies';[71, 72]) that provide real-world evidence and long-term data on the efficacy and safety of fenfluramine (*Table 3*). Brief data from a US expanded access program also provides additional supportive evidence of efficacy and safety [73], and initial details from the European expanded access programme and number of currently treated patient in the UK are also provided [74]. It is anticipated that further details on the European expanded access programme will be provided in confidence, as available, during the NICE appraisal.

B.2.2 List of relevant clinical effectiveness evidence

Details of the studies included in the fenfluramine clinical development are provided in Table 3.

Table 3: Clinical effectiveness evidence

Study	Study 1* (NCT02826863) [3, 75]	Study 1504 (cohort 2)* (NCT02926898) [4, 76]	Study 1503 Open-label extension study* (NCT02823145) [70]	Belgian RWE studies*: Prospective and retrospective analyses [71, 72, 77]
Study design	Phase 3, randomised, double-blind, parallel group, multicentre, placebo-controlled trial (completed)	Phase 3, randomised, double-blind, multicentre, placebo-controlled trial (completed)	Open-label, multicentre, long-term safety study (ongoing)	Open-label safety and effectiveness study (ongoing)
Population	Children and young adults with Dravet syndrome (n=119)	Children and young adults with Dravet syndrome (n=87)	Children and young adults with Dravet syndrome who have successfully completed 14 weeks of treatment in Study 1 or Study 1504 (n=330 at last analysis)	Children and adults with Dravet syndrome (n=9) Children and adolescents (n=12)
Intervention/ comparator (doses as free FFA)☐	• FFA 0.2 mg/kg/day (max 26 mg/day) + concomitant AEDs (n=40) • FFA 0.7 mg/kg/day (max 26 mg/day) + concomitant AEDs (n=39) • Placebo + concomitant AEDs (n=40) Most commonly used concomitant AEDs: VPA[a,] CLB, TPM, LVT	• FFA 0.4 mg/kg/day (max 17 mg/day) + STP + concomitant AEDs (n=43) • Placebo + STP + concomitant AEDs (n=44) Most commonly used concomitant AEDs: VPA[a,] CLB, TPM, LVT	• FFA 0.2–0.7 mg/kg/day (max 26 mg/day) + concomitant AEDs • FFA 0.2–0.4 mg/kg/day (max 17 mg/day + STP + concomitant AEDs Most commonly used concomitant AEDs: VPA[a,] CLB, STP, TPM, LVT, ZNS, ergenyl chrono	FFA doses approx.. 0.2–0.7 mg/kg/day (max 17 mg/day) + concomitant AEDs Most commonly used concomitant AEDs: VPA[a,] CLB, TPM
Supports marketing authorisation	Yes	Yes	Yes	Yes
Used in economic model	Yes	Yes	Supportive [b]	Supportive [b]
Rationale for use/non-use in the model	Pivotal phase 3 study in children and young adults with Dravet syndrome treated with the investigational product.	Pivotal phase 3 study in children and young adults with Dravet syndrome treated with the investigational product.	Extension of the pivotal phase 3 studies in children and young adults with Dravet syndrome treated with the investigational	Provides external evidence to support long-term extrapolations in patients with

Study	Study 1* (NCT02826863) [3, 75]	Study 1504 (cohort 2)* (NCT02926898) [4, 76]	Study 1503 Open-label extension study* (NCT02823145) [70]	Belgian RWE studies*: Prospective and retrospective analyses [71, 72, 77]
	Provides individual patient-level data	Provides individual patient-level data	product. Used to support extrapolation assumptions beyond trial periods	Dravet syndrome treated with FFA
Key outcomes (**bold = outcomes incorporated in the economic model**)	• **Convulsive seizure frequency** • Response rate • **Convulsive seizure-free days** • HRQoL o Patient (**PedsQL**, QOLCE, and CGI-I) o Caregiver/family (**EQ-5D-5L**, and PedsQL family impact module) • AEs of treatment	• **Convulsive seizure frequency** • Response rate • **Convulsive seizure-free days** • HRQoL o Patient (**PedsQL**, QOLCE, and CGI-I) o Caregiver/family (**EQ-5D-5L**, and PedsQL family impact module) • AEs of treatment	• Seizure frequency (convulsive) • Response rate • **Discontinuations** • AEs of treatment • Incidence of rescue medication usage • HRQoL o Patient (CGI-I)	• Change in frequency of major motor seizures • Response rate • AEs of treatment

Abbreviations: AE, adverse event; AED, anti-epileptic drug; CGI-I, Clinical Global Impression of Improvement; CLB, clobazam; DS, Dravet syndrome; EQ-5D-5L, European Quality of Life-5 Dimensions 5-level scale; HRQoL, health-related quality of life; LVT, levetiracetam; PedsQL, Paediatric Quality of Life Inventory; QOLCE, Quality of Life in Childhood Epilepsy; SE, status epilepticus; STP, stiripentol; TPM, topiramate; VPA, valproate

[a] Includes valproate semisodium, valproate sodium, and valproic acid

[b] Data from this study were not used explicitly in the economic model. Instead, results were used to support a number of model assumptions (see B.3.3 for further information)

☐ Dosing based on fenfluramine base equivalent doses, by request of the EMA and FDA. CSRs and early publications included doses based on fenfluramine hydrochloride salt e.g. 0.8mg/kg/day fenfluramine hydrochloride, which when converted based on the ratio of the molecular weight of the fenfluramine free base and the fenfluramine HCl salt (ratio = 0.864); the (rounded) base equivalent dose of fenfluramine is equivalent to 0.7mg/kg/day fenfluramine. To assist with interpretation and consistency in the reported doses of fenfluramine, this conversion has been used in some places (e.g. Belgian RWE).

* Further details of the individual study designs and their respective cohorts can be found in section B.2.3.1

Sources: CSR Study 1, August 2019; CSR Study 1504, December 2018; CSR Study 1503, December 2018

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

The Phase 3 clinical trial programme for fenfluramine includes two double-blind, randomised, placebo-controlled studies (Study 1 and Study 1504), and one long-term open label extension study (Study 1503), as summarised in Figure 3.

Study 1 represents a planned merged analysis of the first cohort of 119 consecutively enrolled patients from the two identical studies, Study 1501 and Study 1502, which was endorsed by the FDA after undertaking a review of the Statistical Analysis Plan and before unblinding of results and analysis [3, 78]. Study 1 evaluated fenfluramine as an add-on to standard of care therapy that excluded current stiripentol use. Study 2, comprising the remaining cohort of patients from study 1501 and 1502 is currently ongoing and remains blinded, these data are not yet available for analysis [78].

Study 1504 was a 2-part study; the first part (Cohort 1) was an open-label study in 18 subjects with Dravet syndrome to assess pharmacokinetics and safety to define the dose of fenfluramine to be used in the second part (Cohort 2), when fenfluramine was added to a regimen that included stiripentol. Cohort 2 was a double-blind, randomised, 2-arm, placebo-controlled study to evaluate fenfluramine in combination with stiripentol, valproate and/or clobazam [4, 78].

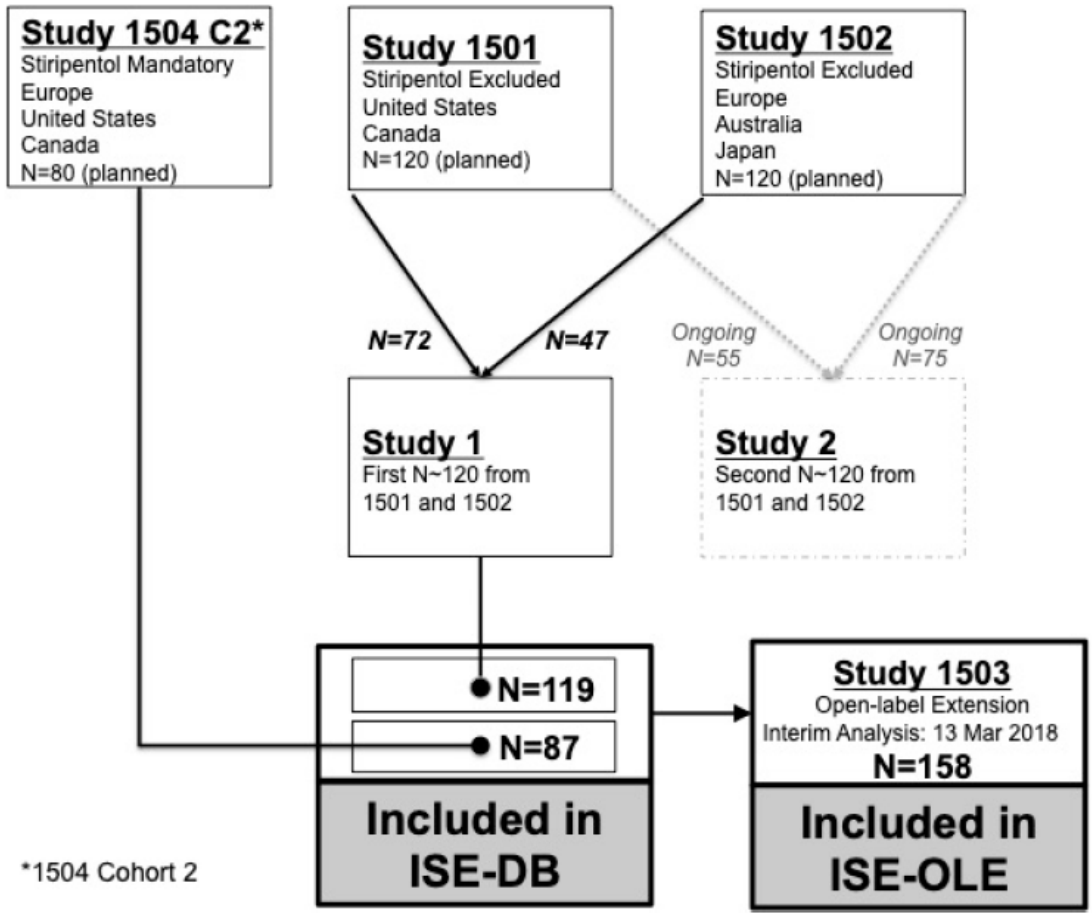
Study 1503 includes patients who completed Study 1 and Study 1504 and who elected to continue fenfluramine. As patients complete Study 2 (the remainder of patients completing from Study 1501 and 1502), they are also offered the opportunity to enrol in Study 1503, so to receive fenfluramine if they had previously received placebo, or to continue treatment with fenfluramine [70, 78]. As Study 2 is still ongoing and remains blinded, these data are not yet available for analysis.

In addition to the clinical trial programme, observational cohort studies from Belgium, including follow-up of patients for up 27 years [71, 72, 77, 78] formed part of the clinical development plan.

Data from a US early access programme [73] have also recently become available and are included for transparency. Initial details from the European expanded access programme and number of currently treated patient in the UK are also provided [74]. It is anticipated that further details on the European expanded access programme will be provided, as available, during the NICE appraisal.

A summary of the design and methodologies for the main studies is included in Table 4.

Figure 3: Fenfluramine clinical trial programme overview



Note: Patients from Japan were not included in Study 1 cohort 1 (only cohort 2)
Source: Integrated Summary of Efficacy, Figure 2, page 24

Table 4: Summary of study methodologies

Study name	Study 1* (NCT02826863) [3, 75]	Study 1504 (cohort 2)* (NCT02926898) [4, 76]	Study 1503 Open-label extension study* (NCT02823145) [70]	Belgian RWE studies*: Prospective and retrospective analyses [71, 72, 77]
Location	USA, Canada, Belgium, Denmark, Germany, Italy, Spain, United Kingdom, Australia	USA, Canada, France, Germany, Netherlands, Spain, United Kingdom	USA, Canada, France, Netherlands, Belgium, Denmark, Germany, Italy, Spain, United Kingdom, Australia	Belgium
Design	Phase 3, double blind, RCT (completed)	Phase 3, double-blind, RCT (completed)	OLE trial (ongoing)	Open-label RWE studies
Patient population	Children and young adults with DS Groups stratified by age: <6 years and ≥6yrs	Children and young adults with DS Groups stratified by age: <6 years and ≥6yrs	Children and young adults with DS who have completed 14 weeks of treatment from Study 1 and Study 1504 (and from Study 2[a])	Children and adults with refractory DS
Settings and locations where the data were collected	Secondary care	Secondary care	Secondary care	Secondary care
Key inclusion/exclusion criteria[b]	**Inclusion criteria Study 1, Study 1504 (cohort 2), and Study 1503:** • Age ≥2 to ≤18 years • DS with documented medical history with convulsive seizures not completely controlled by current AEDs • ≥4 convulsive seizures per 4-week period for 12 weeks prior to screening • All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulator/stimulation [VNS]) stable for at least 4 weeks prior to screening and expected to remain stable throughout the study • Subject approved by the Epilepsy Study Consortium • No cardiovascular or cardiopulmonary abnormality based on screening ECHO and ECG or physical examination and approved for entry by the central cardiac reader **Inclusion criteria Study 1, Study 1504 (cohort 2) only:**			**Inclusion criteria:** • Patients aged 6 months to 50 years • Uncontrolled despite AEDs **Exclusion criteria:** • Patients with cardiovascular pathology, hypertension treated with medication, glaucoma

	• Stable baseline with ≥6 convulsive seizures during the 6-week baseline period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks **Inclusion criteria Study 1504 (cohort 2) only:** • Current use of STP **Inclusion criteria Study 1503 only:** • Satisfactory completion of Study 1 or Study 1504 (or Study 2[a]) in the opinion of the investigator and the sponsor **Exclusion criteria Study 1, Study 1504 (cohort 2), and Study 1503:** • Pulmonary arterial hypertension • Current or past history of cardiovascular or cerebrovascular disease **Exclusion criteria Study 1 only:** • Current or had received STP in past 21 days prior to screening			
Trial drugs administration, dosing and schedule	FFA administered as an oral aqueous solution, divided into two equal daily doses with food, up to a max of 26 mg/d. Matching placebo was supplied as an oral solution. <u>Titration</u> (2 wk) Subjects randomised (1:1:1) in a double-blind manner to receive: • FFA 0.2 mg/kg/d (n=39) • FFA 0.7 mg/kg/d (n=40) • placebo (n=40). 0.7mg/kg/day group received 0.2mg/kg/day for 4 days, 0.4mg/kg/day for 4 days and then 0.7 mg/kg/d dose. Other groups received dummy titrations. <u>Maintenance</u> (12 wk) Randomised dose of FFA or	FFA administered as an oral aqueous solution, divided into two equal daily doses with food, up to a max of 17 mg/d. Matching placebo was supplied as an oral solution. <u>Titration</u> (3 wk) Subjects randomised (1:1) in a double-blind manner to receive: • FFA 0.4 mg/kg/d + STP + concomitant therapies (n=43) • Placebo + STP + concomitant therapies (n=44). 0.4mg/kg/day group received 0.2mg/kg/day starting dose, titrated gradually to 0.4mg/kg/day <u>Maintenance</u> (12 wk) Randomised dose of FFA or placebo BID in the morning and in the evening.	FFA administered as an oral aqueous solution, divided into two equal daily doses with food, up to a max of 26 mg/d (Study1) or 17 mg/d (Study 1504). <u>OLE Treatment period</u> (24 month) All subjects received 0.2 mg/kg/d for 1 month (n=330 at last analysis). <u>Dose escalation</u> to 0.7 mg/kg/d in subjects not receiving STP <u>Dose escalation</u> to 0.4 mg/kg/d in subjects receiving concomitant STP.	FFA administered as an oral capsule (a few patients had contents sprinkled prior to consumption) in concentrations of FFA HCl 2.5, 5, 10 and 20 mg/capsule twice daily (corresponding to approximate doses 0.2 to 0.7mg/kg/day of free FFA). <u>Baseline</u> (3 month): Observation period when subjects continued with current AEDs and assessed for baseline seizure activity based on recordings of daily seizure activity entered into an electronic diary. <u>Treatment</u>: Retrospective cohort (n=12, treated for up to 19 years) Prospective cohort (n=9, treated for up to 5 years)

	placebo BID in the morning and in the evening. Transition/taper period (2 wk) Subjects entering OLE study (Study 1503) or exiting study. Intermediate dose of 0.4 mg/kg/d used for 0.7 mg/kg/d dose.	Transition/taper period (2 wk) Subjects entering OLE study (Study 1503) or exiting study.		
Permitted and disallowed concomitant medication	**Concomitant therapies**: Subjects were required to take at least one concomitant AED during study participation.	**Concomitant therapies**: All subjects were required to take at a minimum STP plus CLB and/or VPA during the study.	**Concomitant therapies**: Subjects were required to take at least one concomitant AED during study participation.	**Concomitant therapies**: Subjects were required to take all current concomitant AED during study participation.
	Disallowed concomitant medications in Study 1, Study 1504 (cohort 2), and Study 1503: • AEDs that block sodium channels, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine, phenobarbital, or had taken any of these within the past 30 days, as maintenance therapy • Felbamate was prohibited as a concomitant medication unless the subject had been on felbamate for at least 18 months prior to screening, had stable liver function and haematology laboratory tests, and the dose was expected to remain constant throughout the study • Centrally-acting anorectic agents • Monoamine-oxidase inhibitors • Any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition • Any centrally-acting noradrenergic agonist such as atomoxetine • Cyproheptadine • Any form of marijuana, THC and THC derivatives, and cannabidiol products **Disallowed concomitant medications in Study 1 only:** • STP: Subjects must have been off STP for a minimum of 21 days prior to the screening visit **Disallowed concomitant medications in Study 1503 only:** • STP: Subjects who were not receiving concomitant STP, including subjects from the originating RCTs Study 1, Study 2, and Study 1504 cohort 1 (dose regimens 1 and 2 only), must have been off STP for a minimum of 21 days prior to them starting the study			**Disallowed concomitant medications**: NR

Primary outcomes[b]	Change between baseline and combined T+M period (14 weeks) in the mean CSF per 28 days for FFA 0.7 mg/kg/d vs placebo	Change between baseline and combined T+M period (15 weeks) in the mean CSF per 28 days for FFA 0.4 mg/kg/d vs placebo	Change in CSF per 28 days between the originating study pre-treatment baseline and OLE treatment period (up to 3 years) Endpoint 1 The difference in CSF per 28 days for the OLE treatment period (day 1 to EOS) compared to baseline (from the originating study) Endpoint 2 The difference in CSF for the month 2 to EOS (day 31 to EOS) time point compared to baseline (from the originating study)	Change from baseline in the frequency of major motor seizures (tonic, clonic, tonic-clonic, atonic and myoclonic seizures lasting >30 s)
Other outcomes[c]	*Key secondary outcomes* • Mean change in CSF per 28d (FFA 0.2mg/kg/d vs placebo) • Proportion of subjects who achieve ≥50% reduction from baseline in mean CSF (all groups) • Longest convulsive seizure free interval (all groups) *Additional outcomes:* • Number of convulsive seizure free days • Near-convulsive seizure freedom (0-1 seizures per 28 days; post hoc analysis)	*Key secondary outcomes* • Proportion of subjects who achieve ≥50% reduction from baseline in mean CSF • Longest convulsive seizure free interval *Additional outcomes:* • Number of convulsive seizure free days • Near-convulsive seizure freedom (0-1 seizures per 28 days; post hoc analysis) • Responder analyses– Proportion of subjects with ≥25% and ≥75% reduction from baseline in CSF	*Additional outcomes:* • CSF by age, and mean daily dose • Responder analyses– Proportion of subjects with ≥25%, ≥50%, ≥75%, and 100% reduction from baseline in CSF, and near convulsive seizure freedom • Incidence of rescue medication use • HRQoL/PROs (CGI-I, QOLCE, PedsQL)	Change in frequency of all major motor seizures during treatment compared to baseline period at specific time points: 3, 6, 9 and 12 months.

	• Responder analyses– Proportion of subjects with ≥25%, ≥75%, and 100% reduction from baseline in CSF • Change from baseline in non-convulsive seizures and total seizures • Incidence of rescue medication use, hospitalisation to treat seizures, and SE • HRQoL/PROs (CGI-I, QOLCE, PedsQL, EQ-5D-5L, HADS, BRIEF (safety endpoint))	• Change from baseline in non-convulsive seizures and total seizures • Incidence of rescue medication use, hospitalisation to treat seizures, and SE • HRQoL (CGI, QOLCE, PedsQL, EQ-5D-5L, BRIEF (safety endpoint))		
Exploratory analyses	Randomisation was stratified by age group, and primary and key secondary efficacy analyses included age as a factor. Age strata: <6 years, ≥6 years. Exploratory subgroup analyses from pooled Study 1 and Study 1504 data included: • baseline convulsive frequency as a categorical variable, • use of concomitant valproate and/or clobazam • CSF in Stiripentol naïve vs stiripentol experienced patients (Study 1 only) • Age <12 and ≥12 years	Randomisation was stratified by age group, and primary and key secondary efficacy analyses included age as a factor. Age strata: <6 years, ≥6 years. Exploratory subgroups from pooled Study 1 and Study 1504 data included: • baseline convulsive frequency as a categorical variable, • use of concomitant valproate and/or clobazam, • Age <12 and ≥12 years		n/a

Abbreviations: AEDs, anti-epileptic drugs; BID, twice a day; BRIEF, Behavioural Rating Inventory of Executive Function; CGI, Clinical Global Impression; CGI-I, Clinical Global Impression of Improvement; CLB, clobazam; CSF, convulsive seizure frequency; CSR, clinical study report; CRU, clinical research unit; d, day; DS, Dravet syndrome; ECG, electrocardiogram; ECHO, echocardiogram; EQ-5D-5L, EuroQOL – 5 Dimensions – 5 Levels scale produced by the European Quality of Life group; FFA, fenfluramine; HADS, hospital anxiety and depression scale; NR, not reported; PedsQL, Pediatric Quality of Life Inventory; PK, pharmacokinetics; OLE, open-label extension; QOLCE, quality of life in childhood epilepsy; RWE, real-world evidence; STP, stiripentol; TEAE, treatment-emergent adverse event; THC, tetrahydrocannabinol; T+M, treatment plus maintenance; VPA, valproate; sodium valproate; valproic acid; wk, week

[a] Study 2 includes the next 120 subjects from ZX008-1501 and ZX008-1502 randomized after database lock for Study 1, including subjects from Japan. Efficacy data for Study 2 are not included as the study is still ongoing and remains blinded.

[b] A comprehensive list of inclusion and exclusion criteria for Study 1, Study 1504 (cohort 2), and Study 1503 can be found in Appendix D.1.2.3

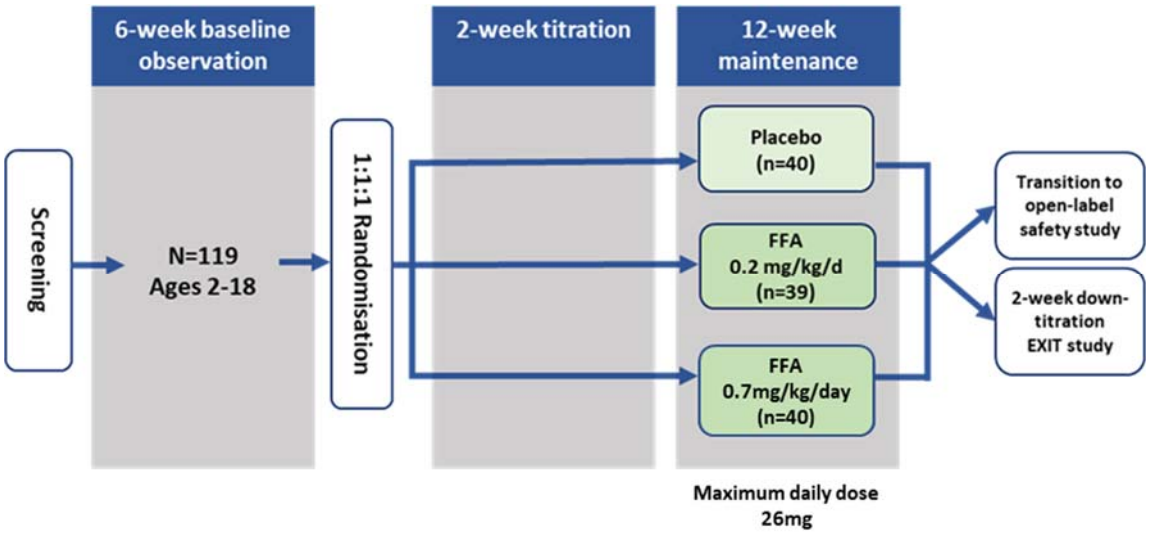
[c] Definitions of efficacy measures can be found in Appendix D.1.2.4

Sources: CSR Study 1, August 2019; CSR Study 1504, December 2018; CSR Study 1503, December 2018; publications listed in column heads

B.2.3.1.1 Study 1

Study 1 was a 20-week, double-blind, parallel group randomised placebo-controlled trial conducted in North America, western Europe and Australia to assess the efficacy, safety and PK of fenfluramine oral solution when used as adjunctive therapy to standard of care anti-epileptic treatment in children and young adults with Dravet syndrome (Figure 4) [3, 75].

Figure 4: Study 1 trial design



Abbreviations: d, day; FFA, fenfluramine
Source: Derived from CSR Study1, August 2019

Following screening (n=173), a 6-week baseline observation period was carried out to assess seizure activity before randomisation of eligible subjects (N=119) (1:1:1) to receive fenfluramine 0.2 mg/kg/day, fenfluramine 0.7 mg/kg/day; maximum dose 26 mg/day) or placebo. Randomisation was stratified by age (<6 years, ≥6 years), with a target of 25% of subjects in the <6 years age group [3, 75].

Subjects in the 0.7mg/kg/day group were titrated to their randomised dose over a 2-week titration period, with the other groups receiving dummy titration. The titration period was followed by a 12-week maintenance treatment period. For subjects who completed the full titration and maintenance periods (T+M), total treatment time was therefore 14 weeks. At the end of the maintenance period (or early discontinuation), all subjects underwent a 2-week blinded taper or transition period, depending on whether they exited the study or were enrolled in the subsequent long-term open-label extension (OLE) study (Study 1503) [70, 75].

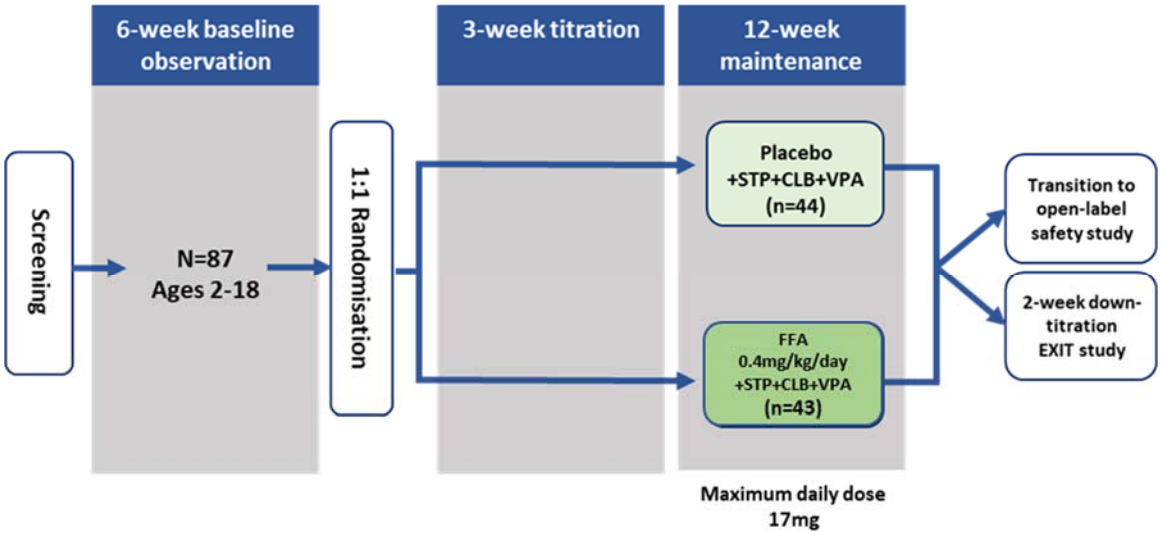
At screening, throughout the trial and at follow up (3–6 months following the last dose of study medication), cardiovascular safety assessments were undertaken, including electrocardiogram (ECG) and echocardiogram (ECHO) [75].

B.2.3.1.2 Study 1504

Study 1504 was a 2-part 21-week study. The first part (cohort 1), was an open-label study in 18 subjects to assess the pharmacokinetics and safety of fenfluramine oral solution. The second part (cohort 2) was a double-blind, RCT to evaluate fenfluramine as an adjunctive therapy to standard

of care anti-epileptic treatment which included stiripentol in children and young adults with Dravet syndrome. Data relevant to this submission and included as evidence relate only to Study 1504 cohort 2 [4, 76] (Figure 5).

Figure 5: Study 1504 (cohort 2) trial design



Abbreviations: CLB, clobazam; d, day; FFA, fenfluramine; STP, stiripentol; VPA, valproate
Source: Derived from Study 1504 CSR, December 2018

Following screening (N=115), a 6-week baseline observation period was carried out to assess seizure activity before randomisation of eligible subjects (N=87) (1:1) to receive fenfluramine 0.4 mg/kg/day (maximum dose 17 mg/day) with stiripentol or placebo with stiripentol. Randomisation was stratified by age (<6 years, ≥6 years), with the target of 25% of subjects in the <6 years age group [4, 76].

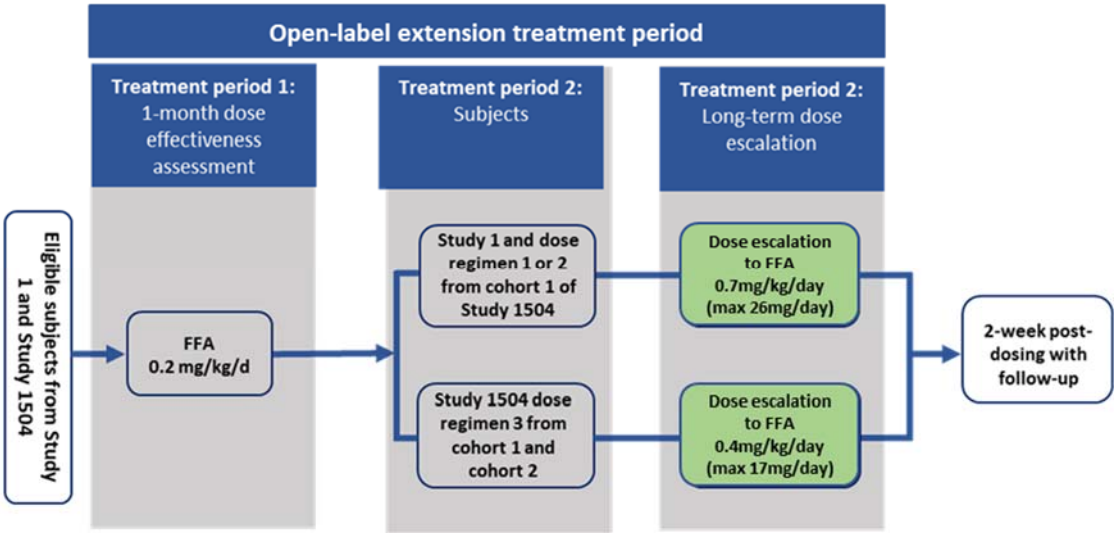
All subjects were titrated to their randomised dose over a 3-week titration period, followed by a 12-week maintenance period. For subjects who completed the full titration and maintenance periods (T+M), total treatment time was 15 weeks. At the end of the maintenance period (or early discontinuation), all subjects underwent a 2-week blinded taper or transition period, depending on whether they exited the study or were enrolled in the subsequent long-term open-label extension (OLE) study (Study 1503) [70].

At screening, throughout the trial and at follow up (3–6 months, and up to 24 months following the last dose of study medication), cardiovascular safety assessments were undertaken, including electrocardiogram (ECG) and echocardiogram (ECHO). [4, 76].

B.2.3.1.3 Study 1503

Study 1503 was a multicentre, open-label, long-term safety study of fenfluramine in children and young adults with Dravet syndrome who had successfully completed treatment in Study 1 or Study 1504 (cohort 2) or successfully completed Study 1504 (cohort 1) or Study 2 and were candidates for continuous treatment for an extended period of time [70](Figure 6). At the time of the last data cut (14 October 2019), 330 patients had been enrolled, with data available for up to 3 years of treatment [10, 70, 79].

Figure 6: Study 1503 trial design



Abbreviations: d, day; FFA, fenfluramine
Source: Derived from Study 1503 CSR, December 2018 and Integrated Summary of Efficacy

During treatment period 1, all subjects (including those previously receiving placebo, or fenfluramine 0.4mg/kg/day in Study 1504 or 0.7mg/kg/day in Study 1) were treated with fenfluramine at a 0.2 mg/kg/day dose for 1 month to assess effectiveness, safety, and tolerability. Dose adjustments could subsequently be made in treatment period 2 where patients who were not receiving stiripentol in their originating study could be given dose increments up to 0.7 mg/kg/day (not exceeding 26 mg/day), and subjects who were receiving stiripentol in their originating study could be given dose increments up to 0.4 mg/kg/day (not exceeding 17 mg/day) [70, 78].

At the end of their randomised control trial and before starting the OLE trial, throughout the OLE trial, and at follow up (3–6 months following the last dose of study medication), cardiovascular safety assessments were undertaken, including an electrocardiogram (ECG) and echocardiogram (ECHO) [70, 78].

B.2.3.1.4 Belgian RWE studies (observational cohorts)

The Belgian RWE studies were open-label, long-term studies (representing up to 30 years of daily treatment) that demonstrate the durable efficacy of fenfluramine in controlling seizures in patients with Dravet syndrome. A total of 21 patients from 6 months to 50 years of age fulfilling the diagnostic criteria for Dravet syndrome have been treated with fenfluramine in addition to their background therapies. Published data are available from a retrospective analysis in 12 children, with a prospective 5-year follow-up of 10 of these children from 2010 to 2014 [71, 77], and a prospective study in 9 children and adults [72].

In the prospective study of 9 children and adults, following a 3-month baseline period, fenfluramine was added to each patient's current AED regimen at doses up to a maximum of 17 mg/day. The daily dose was adjusted during the study based on efficacy or tolerability issues. Concomitant AEDs were kept stable during the first 3 months, with adjustments made thereafter if necessary. The incidence of major motor seizures (tonic, clonic, tonic-clonic, atonic and myoclonic seizures lasting >30 s) in both the baseline and treatment period was assessed via a seizure diary. Subjects

were treated for a median duration of 1.5 (range, 0.3–5.1) years, with periodic ECG examinations during the treatment period used to assess cardiovascular safety [72].

B.2.3.2 Eligibility criteria

The two registration, phase 3 RCTs (Study 1 cohort 1 and 2, and Study 1504, cohort 2) enrolled patients aged 2-18 years old with Dravet syndrome whose seizures had not been adequately controlled by their current regimens of AEDs or other therapies. Based on medical records or caregiver reports, patients must have had at least four convulsive seizures in a 4-week period during the 12 weeks before entering the screening (baseline) period of the trial. All medications or interventions for epilepsy must have been stable for at least 4 weeks before screening and were expected to remain stable throughout trial participation [3, 4]. Study 1 enrolled patients who were either stiripentol-naïve or experienced but excluded patients who were taking stiripentol or had taken stiripentol within 3 weeks of screening [3]. In contrast, for inclusion in Study 1504 (cohort 2) patients had to be receiving stiripentol as part of their AED regimen [4]. Key exclusion criteria included a history of pulmonary hypertension, cardiovascular or cerebrovascular disease, including aortic or mitral valve regurgitation as established by echocardiographic examination [3, 4].

A summary of eligibility criteria for Study 1 and Study 1504 (cohort 2), and for Study 1503, and the Belgian RWE cohorts is provided in Table 4. Full inclusion and exclusion criteria of the two registration phase 3 trials are provided in Appendix D.

Upon joining the studies, patients underwent a 6-week period to establish their baseline seizure frequency (and to ensure they maintained a stable baseline of: ≥6 convulsive seizures during the 6-week baseline period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks) before being randomised to receiving fenfluramine or matching placebo in a double blind manner [3, 4].

B.2.3.3 Endpoints

The primary and secondary efficacy endpoints for the two registration phase 3 RCTs (Study 1 and Study 1504 cohort 2) were agreed with regulatory authorities and appropriately focused on key seizure endpoints that drive patient morbidity and mortality, including: percentage change from baseline in monthly convulsive seizure frequency, responder analyses based on clinically meaningful (and regulatory agency determined) reductions in convulsive seizure frequency (≥50% (and 25%,75% and 100%) reduction from baseline) and longest convulsive seizure-free intervals. Convulsive seizures were defined as hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs. Total and non-convulsive seizure frequencies also have an impact on patient morbidity and were evaluated. Effects beyond seizure reduction, including impact of treatment on both patient and carer quality of life, were evaluated. Safety and tolerability of fenfluramine was assessed by recording adverse events and vital signs, and investigations of haematology, chemistry, echocardiogram, and electrocardiogram were conducted [3, 4].

These endpoint, and endpoints for the Study 1503 open-label extension study and the Belgian RWE studies, are further summarised in Table 4. Definitions of the endpoints used in the phase 3 RCTs are provided in Appendix D.

B.2.3.4 Baseline demographics and disease characteristics

Baseline characteristics of the patients enrolled in prospective studies (Study 1 and Study 1504 cohort 2 [3, 4], Study 1503 [70, 78] and the prospective Belgian RWE study [72]) are presented in Table 5.

Study 1 and Study 1504 recruited patients aged 2-18 years, with the mean age being approximately 9 years old. The majority of patients had confirmed *SCN1A* mutations, as would be expected. Patients in Study 1 were taking a mean of 2.4 AEDs at baseline, which most commonly included valproate (60%), clobazam (59%), and topiramate (25%) [3], and patients in Study 1504 were taking a mean of 3.5 AEDs at baseline, most commonly valproate (89%), clobazam (94%), and topiramate (24%), all in addition to stiripentol [4]. This use of AEDs in the trials is similar to AED use observed in clinical practice as demonstrated in the DISCUSS study, which reported patients take a mean average of around 3 AEDs [7, 16]. Despite this, patients in Study 1 were experiencing mean baseline convulsive seizure frequencies of 31 to 46 per 28 days (ranging from 3 to >600) [3], and patients in Study 1504 were experiencing mean baseline convulsive seizure frequencies of 22 to 28 per 28 days (ranging from 3 to >200) [4], reflecting the refractory nature of seizures in Dravet syndrome. Baseline characteristics were broadly similar between study arms. Approximately 12% of patients across these phase 3 RCTs were recruited from centres in the UK [78].

Baseline characteristics of patients enrolled into the Study 1503 open-label extension study were generally aligned with the characteristics of patients from the two registration phase 3 RCTs [78]. The prospective Belgian RWE study included children and adults, giving an age range of 1 to 30 years at the time of initiation of fenfluramine. The mean number of AEDs was 3.3 [72], which is aligned with patients in UK clinical practice [16].

Table 5: Summary of baseline characteristics of participants in the studies across treatment groups

Baseline characteristic	Study 1 [3, 75]			Study 1504 (cohort 2) [4, 76]		Study 1503 [79]	Belgian RWE Prospective cohort [72]
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)	FFA OLE ≤0.7 mg/kg/day (n=330*)	FFA ≤1¶ mg/kg/day (n=9)
Female, mean (SD)	19 (47.5)	17 (43.6)	19 (47.5)	17 (38.6)	20 (46.5)	150 (45.5)	3 (33.3)
Age in years, mean (SD)	9.2 (5.1)	9.0 (4.5)	8.8 (4.4)	9.4 (5.1)	8.8 (4.6)	9.0 (4.6)	13.5 (8.2)
Age group <6 years, n (%)	11 (27.5)	9.0 (23.1)	11 (27.5)	12 (27.3)	12 (27.9)	91 (27.6)	n/a
SCN1A mutation, n (%)	31 (77.5)	31 (79.5)	33 (82.5)	39 (88.6)	37 (86.0)	NR	9 (100)
Race, White, n (%)	31 (77.5)	33 (84.6)	34 (85.0)	29 (65.9)	23 (53.5)	245 (74.2)	n/r
Region/country, n (%)							
North America	24 (60)	24 (61.5)	24 (60.0)	14 (31.8)	15 (34.9)	150 (45.5	n/a
Europe/Australia	16 (40.0)	15 (38.5)	16 (40.0)	30 (68.2)	28 (65.1)	180 (54.5)	9 (100)
Baseline CSF, mean per 28 days (SD)	44.2 (40.2)	45.5 (99.8)	31.4 (30.6)	21.6 (27.7)	27.9 (36.9)	46.4 (179.2)	13.8 (NR)
Baseline CSF, median per 28 days (Min, Max)	27.3 (3.3, 147.3)	17.5 (4.7, 623.5)	20.7 (4.8, 124.0)	10.7 (2.7, 162.7)	14.0 (2.7, 213.3)	15.3 (2.7, 2719.3)	15 (0.4–37.9)
Number of concomitant AEDs*, Mean (SD)	2.5 (0.9)	2.6 (1.1)	2.3 (0.9)	3.4 (0.6)	3.6 (0.8)	2.9 (1.1)	3.1 (1.1)
Clobazam	22 (55.0)	24 (61.5)	24 (60.0)	42 (95.5)	40 (93.0)	239 (72.4)	3 (33.3)
Levetiracetam	11 (27.5)	11 (28.2)	4 (10.0)	5 (11.4)	6 (14.0)	80 (24.2)	1 (11.1)
Stiripentol	-	-	-	44 (100.0)	43 (100.0)	69 (29.1)	2 (22.2)
Topiramate	9 (22.5)	10 (25.6)	11 (27.5)	7 (15.9)	14 (32.6)	NR	8 (88.9)
Valproate (all forms)	8 (20.0)	7 (17.9)	11 (27.5)	9 (20.5)	8 (18.6)	235 (71.2)	9 (100.0)

AEDs, anti-epileptic drugs; CSF, convulsive seizure frequency; CSR, clinical study report; FFA, fenfluramine; NR, not reported; OLE, open-label extension; RWE, real-world evidence
* Study 1503 n =330 as of cut-off 15 February 2019. Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018; Study 1503 CSR, December 2018; Integrated Summary of Efficacy; Responses to Day 120 regulatory questions [Data on File]. ¶ Dose based on fenfluramine HCl - converts to fenfluramine <0.864mg/kg/day

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

This section relates only to the two registration phase 3 RCTs, Study 1 and Study 1504. Details for the Study 1503 open-label extension study the Belgian RWE cohorts are provided with the discussion of their results in section B.2.6.

B.2.4.1 Definition of study populations

The analysis sets used in Study 1, Study 1504 are defined in Table 6, with the patient numbers for each presented in *Table 7*. The modified intention-to-treat (mITT) and safety (SAF) population results are presented in this document, with additional results for the other analyses sets and sensitivity analyses provided in their respective Clinical Study Reports [75, 76].

Table 6: Analysis sets in Study 1 and Study 1504

Study population	Definition
Enrolled population	All subjects who signed the informed consent form (ICF). This population was used to present overall study disposition data and the number of subjects in each study population
Intention-to-treat (ITT) population	All subjects randomised to receive study treatment.
Safety (SAF) population	All randomised subjects who received at least 1 dose of fenfluramine or placebo. Subjects were analysed according to the treatment group to which they were randomised. All safety analyses were performed SAF population.
Modified intention-to-treat (mITT) population	All randomised subjects who received at least 1 dose of fenfluramine or placebo and for whom at least 1 week of diary data were available. Subjects were analysed according to the treatment group to which they were randomised. All efficacy analyses were performed using the mITT population.
Per protocol (PP) population	All randomised subjects who received at least 1 dose of fenfluramine or placebo, completed at least 4 weeks of the maintenance period, and had no major protocol deviations that would have a significant impact on clinical outcome.

Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018

Table 7: Trial population numbers in Study 1, Study 1504 (cohort 2) and Study 1503

	Study 1[75]				Study 1504 cohort 2[76]			Study 1503[70]
	Placebo	**FFA 0.2 mg/kg/day**	**FFA 0.7 mg/kg/day**	**Total**	**Placebo**	**FFA 0.4 mg/kg/day**	**Total**	**Total**
Enrolled population	n/a	n/a	n/a	n/a	n/a	n/a	115	330
Randomised population (ITT)	40	39	40	119	44	43	87	n/a
Modified ITT population	**40**	**39**	**40**	**119**	**44**	**43**	**87**	**n/a**
Per protocol population	35	34	33	102	41	32	73	n/a
Safety population	**40**	**39**	**40**	**119**	**44**	**43**	**87**	**330**

Abbreviations: FFA, fenfluramine; ITT, intention-to-treat
Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018; Study 1503 CRS, December 2018

B.2.4.2 Statistical analyses

A summary of the statistical methods used in Study 1 and Study 1504 (cohort 2) is provided in Table 8. The primary hypothesis was that the mean convulsive seizure frequency per 28-days for the fenfluramine 0.7 mg/kg/day (Study 1) or 0.4 mg/kg/day (Study 1504, cohort 2) was statistically significantly different from the mean convulsive seizure frequency per 28-days for the placebo groups in the respective trials. A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups among these primary and key secondary efficacy parameters.

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment group and age group (<6 years and ≥6 years) as factors and baseline frequency as a covariate. This was followed by analysis of the secondary endpoint of proportion of *subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency during the treatment and maintenance phase*, using a logistic regression model that incorporates the same factors and covariate as the ANCOVA model in the primary analysis. This was followed by analysis of the secondary endpoint longest interval (days) between convulsive seizures, which compared the groups using Wilcoxon rank sum test. In study 1, this was also repeated for comparisons of fenfluramine 0.2mg/kg/day against placebo.

Responder analyses (proportion of patients who achieved ≥25%, ≥75%, or 100% reduction in mean convulsive seizure frequency per 28 days) was assessed in the same way as the proportion of subjects who achieve a ≥50% reduction from baseline. For the Clinical Global Impression of Improvement, the proportion of patients who were rated as very much improved or much improved in each fenfluramine dose group was compared with placebo using the Cochran-Mantel-Haenszel test stratified by age group. Comparisons between treatment groups for the quality-of-life assessments were made using Wilcoxon rank sum tests.

The primary and all key secondary endpoint analyses were conducted on the modified intention-to-treat population, and were repeated in the per protocol populations [75, 76].

Table 8. Summary of statistical analyses in Study 1 and Study 1504 (cohort 2)

	Study 1 [3, 75]	Study 1504 cohort 2 [4, 76]
Hypothesis objective	The primary hypothesis was that the mean convulsive seizure frequency per 28-days for the fenfluramine 0.7 mg/kg/day group was statistically significantly different from the mean convulsive seizure frequency per 28-days for the placebo group.	The primary hypothesis was that the mean convulsive seizure frequency per 28-days for the fenfluramine 0.4 mg/kg/day group was statistically significantly different from the mean convulsive seizure frequency per 28-days for the placebo group.
Sample size, power calculations	The power analysis assumed that the SD of the percentage change in monthly seizure frequency was 55%, based on results from previous RCTs of stiripentol and cannabidiol for the treatment of seizures in patients with Dravet syndrome. Based on this assumption, a sample size of 40 patients per arm was determined to provide 90% power to detect a difference in mean change in monthly seizure frequency from baseline of 40%, using a two-sided t test at 0·05 significance.	
Missing data	There was no imputation of missing data for efficacy endpoints.	
Statistical tests	**Primary endpoint:** comparison of change in mean CSF per 28 days between the baseline period and the combined titration and maintenance periods in patients given fenfluramine 0.7 mg/kg/day (Study 1) or 0.4mg/kg/day (Study 1504) compared with placebo, analysed using an analysis of covariance (ANCOVA) model with treatment group and age group (<6 years and ≥6 years) as factors and baseline frequency as a covariate.	
	Key secondary endpoint: proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, analysed using a logistic regression model that incorporates the same factors and covariate as the analysis of covariance in the primary analysis	
	Key secondary endpoint: longest interval between convulsive seizures during the treatment and maintenance period, compared using a Wilcoxon rank sum test	
	Other secondary endpoints: **Responder analyses (proportion of patients who achieved ≥25%, ≥75%, or 100% reduction in mean convulsive seizure frequency per 28 days):** assessed in the same way as the proportion of subjects who achieve a ≥50% reduction from baseline. **Clinical Global Impression of Improvement:** proportion of patients who were rated as very much improved or much improved in each fenfluramine dose group was compared with placebo using the Cochran-Mantel-Haenszel test stratified by age group. **Quality-of-life assessments:** comparisons made using Wilcoxon rank sum tests.	
Statistical analysis procedure	A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups, among the primary and key secondary efficacy parameters: **Step 1:** The primary efficacy endpoint (mean convulsive seizure frequency per 28 days) was formally tested first between the fenfluramine 0.7 mg/kg and placebo group. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 2.	A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups across the family of the primary and key secondary efficacy parameters: **Step 1:** The primary efficacy endpoint (mean convulsive seizure frequency per 28 days) was formally tested first between the 0.4 mg/kg and placebo group. If the comparison was statistically significant at the α = 0.05 (2-sided) level, hypothesis testing proceeded to Step 2.

	Study 1 [3, 75]	Study 1504 cohort 2 [4, 76]
	Step 2: The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from Baseline in convulsive seizure frequency, was compared between the 0.7 mg/kg and placebo group. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 3. **Step 3:** The longest interval (days) between convulsive seizures was compared between 0.7 mg/kg and placebo. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 4. **Step 4:** The mean convulsive seizure frequency per 28 days was formally tested between the 0.2 mg/kg and placebo group. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 5. **Step 5:** The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from Baseline in convulsive seizure frequency, was compared between the 0.2 mg/kg and placebo group. If the comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to Step 6. **Step 6:** The longest interval (days) between convulsive seizures was compared between 0.2 mg/kg and placebo using a significance level of α=0.05 (2-sided). Additional secondary endpoints were analysed without correction for multiplicity.	**Step 2:** The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from Baseline period in convulsive seizure frequency, was compared between the 0.4 mg/kg and placebo group. If the comparison was statistically significant at the α = 0.05 (2-sided) level, hypothesis testing proceeded to Step 3. **Step 3:** The endpoint, the longest interval (days) between convulsive seizures was compared between 0.5 mg/kg and placebo using a significance level of α=0.05 (2-sided). Additional secondary endpoints were analysed without correction for multiplicity.

Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

In order to assess the risk of bias and generalisability to UK clinical practice of Study 1 and Study 1504 (cohort 2) studies, a quality assessment was conducted using guidance from 'Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination[80] (Table 9). This demonstrates that each study was completed to the highest standards possible in the context of this rare disease, and with an overall low risk of bias. The trials were double blind RCTs, randomisation and concealment of treatment allocation were appropriately conducted using an interactive web response system, all outcomes for which data were available are reported, and the efficacy analyses employed an ITT approach. The primary and key secondary endpoints were convulsive seizure endpoints, as these are the key drivers of morbidity and mortality, are most relevant to patients and carers, and are subject to less potential for reporting bias than non-convulsive seizures [3, 4].

Table 9: Quality assessment results for Study 1 and 1504 (cohort 2)

Trial name	**Study 1 [3]** (NCT02826863)	**Study 1504 cohort 2 [4]** (NCT02926898)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes: Baseline demographics, medical history and previous/concomitant therapies were generally balanced between the FFA and placebo study groups. There was variation in baseline CSF between groups. However, the mean baseline CSF was consistently high (>30 convulsive seizures per month) in all treatment groups. This reflects heterogeneity in patients in clinical practice	Yes: Baseline demographics, medical history and previous/concomitant therapies were generally balanced between the FFA and placebo study groups. Both treatment groups generally had comparable baseline CSF
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

Trial name	Study 1 [3] (NCT02826863)	Study 1504 cohort 2 [4] (NCT02926898)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Abbreviations: AEDs, Anti-epileptic drugs; CSF, convulsive seizure frequency; FFA, fenfluramine; ITT, Intention to treat; SD, standard deviation
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

Dravet syndrome populations are heterogenous in their seizure frequencies and treatment histories. Similarly, the patients enrolled in the fenfluramine trials had a wide range of seizure frequencies and a spectrum of treatment experiences. Of the patients enrolled in the trials, approximately 12% were recruited from centres in the UK [78], and across the whole trial populations the distribution of the major convulsive seizure type – tonic-conic seizures – at baseline were comparable to those of UK patients enrolled in the DISCUSS study [16] (Figure 7). The results of these trials are robust and reliable, are generalisable to the UK and are highly relevant to the decision problem.

Figure 7. Distribution of seizures in the fenfluramine trials and UK patients in the DISCUSS study

Sources: DISCUSS UK data set[16]; Pooled trial data

B.2.6 Clinical effectiveness results of the relevant trials

Summary of clinical efficacy

- Comprehensive efficacy data in support of fenfluramine are available from two robust, registration phase 3 RCTs and an open label extension (OLE) study providing efficacy data for up to 2 years of treatment. These data are further supplemented with real-world observational data in patients treated with fenfluramine for many years in Belgium, as well as a compassionate use, expanded access programme for patients in the US and Europe.
- The phase 3 RCTs met their primary and key secondary endpoints relating to reductions in convulsive seizure frequency:
  - The reduction in convulsive seizure frequency per 28 days for fenfluramine compared with placebo was 62.3% ($p<0.001$) in patient not taking stiripentol (Study 1), and 54.0% ($p<0.001$) in patients taking stiripentol (study 1504). Results in Study 1 were independent of concomitant use of clobazam or prior stiripentol use+.
  - Significantly greater proportions of patients treated with fenfluramine had clinically meaningful ($\geq$50%) and profound ($\geq$75%) reductions in convulsive seizures compared to the placebo group, with numbers needed-to-treat of <2 and 2-3, respectively.
  - From median baseline convulsive seizure frequencies of 14-20 per month, 25% of patients on fenfluramine in Study 1 and 12% in Study 1504 achieved near seizure freedom ($\leq$1 seizure during the 14-15 weeks of treatment, that included a 2-3 week titration period), compared with none treated with placebo.
  - The median longest convulsive seizure-free intervals were significantly longer with fenfluramine than placebo in both Study 1 (25.0 days vs 9.5 days; $p<0.0001$) and Study 1504 (22.0 vs 13.0; $p=0.004$).
  - Fenfluramine significantly increased the mean number of convulsive seizure-free days per 28 days, during which patients are at lower risk of experiencing SUDEP or status epilepticus: 20.8 days vs 15.2 days ($p=0.012$) in Study 1 and 21.6 vs 19.0 days ($p=0.001$) in Study 1504.
- Fenfluramine also reduced non-convulsive and total seizure frequencies, and showed directional improvements in patient and caregiver quality of life. Carers and clinicians independently rated significantly more patients on fenfluramine to be ”much” or “very much improved” compared with placebo.
- In the OLE study the reductions from baseline in convulsive seizure frequency were maintained for up to 2 years of treatment, with no evidence of a waning of effect. 63.3% of patients achieved a ‘clinically meaningful’ ($\geq$50%) and 40.5% a ‘profound’ ($\geq$75%) reduction from baseline.
- In the real-world, long-term observational studies in children and adults, 7 out of 10 patients that were prospectively followed up for 5 years had seizure-free intervals of at least 2 years, with 3 of the 10 patients being seizure-free for all 5 years.
- Similar, encouraging data is also emerging from the international expanded access programme, including patients from the UK.
- **Collectively, these data clearly demonstrate the significant and often profound reductions in convulsive seizure frequency in high proportions of Dravet syndrome patients when fenfluramine is added to the most effective AEDs currently available. Consistent results independent of concomitant clobazam use and prior stiripentol treatment support the use of fenfluramine across the add-on therapy pathway, including as an alternative non-clobazam based therapeutic option. Furthermore, this seizure control is maintained with long-term treatment**.

+All patients in study1504 received stiripentol (and 95% received clobazam, in accordance with the stiripentol licensed indication)

B.2.6.1 Double blind RCTs — Study 1 and Study 1504 (cohort 2)

Study 1 and Study 1504 (cohort 2) met their primary endpoints and all key secondary endpoints [3, 4]. Results of these and other secondary endpoints relating to seizures are summarised in Table 10. Results of other secondary endpoints relating to patients and caregiver health status ratings and quality of life are summarised in Table 11.

Table 10. Primary, key secondary and other secondary seizure-related efficacy endpoints from Study 1 and Study 1504 (cohort 2)

	Study 1 [3, 75]			Study 1504 [4, 76]	
Endpoints	**Placebo (n=40)**	**FFA 0.2 mg/kg/day (n=39)**	**FFA 0.7 mg/kg/day (n=40)**	**Placebo (n=44)**	**FFA 0.4 mg/kg/day (n=43)**
Median baseline CSF (range)	27.3 (3.3 to 147.3)	17.5 (4.7 to 623.5)	20.7 (4.8 to 124)	10.7 (3 to163)	14.0 (3 to 213)
Median T+M CSF (range)	22.0 (3 to 164.0)	12.6 (0 to 200.0)	4.7 (0 to 169.9)	11.4 (2.2 to 170.1)	5.2 (0 to 458.6)
Change from baseline in CSF, median (range); p-value vs placebo	-19.2 (-76.0 to 51.8) -	-42.3 (-100.0 to 197.6) p=0.2035	-74.9 (-100.0 to 196.4) p<0.0001	-1.1 (-82.8 to 435.1) -	-63.1 (-100.0 to 115.0) p<0.001
Primary endpoint					
Difference from placebo in CSF per 28 days, % (95%CI); p-value vs placebo	-	-32.4 (–6.2 to –51.3) p=0.0209	-62.3 (-47.7 to -72.8) p<0.001	-	-54.0 (-67.2 to -35.6) p<0.001
Key secondary endpoints					
50% reduction in convulsive seizure frequency, n (%); p-value vs placebo; Odds ratio (95% CI)	5 (12) - -	15 (38) p=0.0091 4.8 (1.5 to 15.0)	27 (68) p<0.0001 15.0 (4.5 to 50.0)	2 (5) - -	23 (54) p<0.001 26.0 (5.5 to 123.2)
Longest convulsive seizure-free interval, days Mean (SD); Median (range); Median treatment difference (95% CI) p-value vs placebo	10.6 (6.0) 9.5 (2 to 23) - -	26.0 (31.7) 15.0 (3 to 106) 4.5 (0 to 9) p=0.0352	32.9 (27.5) 25.0 (2 to 97) 15.5 (6 to 25) p<0.0001	13.4 (7.5) 13.0 (1.0-40.0) - -	29.7 (27.3) 22.0 (3.0 to 105.0) - p=0.004
Other secondary endpoints					
Convulsive seizure-free days, mean (SD); Difference from placebo in convulsive seizure free days, % (95%CI); p-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥25% reduction in convulsive seizure frequency, n (%); p-value vs placebo Odds ratio (95%CI)	14 (35) - -	26 (67) p=0.0041 4.1 (2 to 11)	36 (90) p<0.0001 22.3 (6 to 84)	12 (27) - -	30 (70) p<0.001 6.4 (2.5 to 16.5)

	Study 1 [3, 75]			Study 1504 [4, 76]	
Endpoints	**Placebo (n=40)**	**FFA 0.2 mg/kg/day (n=39)**	**FFA 0.7 mg/kg/day (n=40)**	**Placebo (n=44)**	**FFA 0.4 mg/kg/day (n=43)**
≥75% reduction in convulsive seizure frequency, n (%); p-value vs placebo Odds ratio (95%CI)	1 (2) - -	9 (23) p=0.0229 12.0 (1.4 to 102)	20 (50) p=0.0005 55.1 (6 to 526)	1 (2) - -	15 (35) p=0.003 23.7 (2.9 to 191.8)
Convulsive seizure freedom (0 convulsive seizures), n (%):	0	3 (8)	3 (8)	0	1 (2)
Near seizure freedom (≤1 convulsive seizure)*, n (%):	0	5 (13)	10 (25)	0	5 (12)
Non-convulsive seizure¶, % change from baseline, Mean (SD); Median (range); p-value vs placebo	22.2 (211.3) -55.6 (-100 to 723.6) -	-8.9 (151.2) -50.6 (-100.0 to 534.0) p=0.758	-60.5 (38.5) -76.0 (-100.0 to 69.2) p=0.046	1.68 (153.6) -49.67 (-100.0 to 529.4) -	36.7 (176.7)§ -0.47 (-100.0 to 611.2) p=0.182
Total seizures, % change from baseline, Mean (SD); Median (range); p-value vs placebo	18.6 (136.1) -16.2 (-77.6 to 600.7) -	-25.5 (77.1) -41.07 (-100 to 292.4) p=0.020	-61.1 (34.0) -68.3 (-100.0 to 35.6) p<0.001	12.7 (76.7) -5.9 (-73.8 to 375.6) -	-27.0 (60.4) -41.1 (-100.0 to 133.2) p=0.137
Incidence of status epilepticus+, n (%); p-value vs placebo	11 (27.5) -	11 (28.2) p=0.837	14 (35.0) p=0.461	8 (18.2) -	14 (32.6) p=0.128
Days of rescue medication use per 28 days, mean (SD); median (range); p-value vs placebo	3.1 (4.6) 1.7 (0 to 24) -	1.7 (2.9) 0.3 (0 to 16.0) p=0.082	0.9 (1.9) 0 (0 to 8) p<0.0001	1.2 (2.6) 0.3 (0 to 15) -	1.4 (2.2) 0.3 (0 to 9.0) p=0.248
Incidence of hospitalisations to treat seizures during treatment phase, n (%); p-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSF, convulsive seizure frequency; FFA, fenfluramine; SD, standard deviation

*Post hoc analysis.

¶Not all patients had non-convulsive seizures: Study 1 data based on n=21/40, 23/39 and 24/40 in the placebo, FFA 0.2mg/kg/day group and FFA 0.7 mg/kg/day group, respectively; Study 1504 data based on n= 22/44 and 17/43 in the placebo and FFA 0.4mg/kg/day group, respectively.

§Data skewed for Study 1504; both placebo and FFA experienced a decrease from baseline in median number of non-convulsive seizures: Placebo from 4.33 at baseline to 3.79 at end of treatment period, and FFA from 13.33 to 8.88.

+Status epilepticus incidence defined by seizures last >10mins, or requiring hospital treatment, or multiple episodes lasting >10 minutes in 24 hours and considered adverse events. The use of rescue medication may also provide a proxy indication of the emergence of SE events that were averted.

Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018

Table 11. Additional secondary efficacy endpoints relating to condition ratings and quality of life in Study 1 and Study 1504

	Study 1 [3, 75]			Study 1504 [4, 76]	
Efficacy Endpoints	**Placebo (n=40)**	**FFA 0.2 mg/kg/day (n=39)**	**FFA 0.7 mg/kg/day (n=40)**	**Placebo (n=44)**	**FFA 0.4 mg/kg/day (n=43)**
Patient condition rating and quality of life					
CGI-I rating very much/much improved by parent/caregiver, n (%); p-value vs placebo	4 (10) -	16 (41) p=0.0036	22 (55) p<0.0001	9 (21) -	14 (33) p=0.14
CGI-I rating very much/much improved by investigator, n (%); p-value vs placebo	4 (10) -	16 (41) p=0.0032	25 (62) p<0.0001	7 (16) -	19 (44) p=0.008
QOLCE – overall quality of life Change from baseline, mean (SD); p-value vs placebo	1.5 (8.7) -	0.8 (11.8) p=0.3683)	5.8 (11.7) p=0.2807	0.1 (8.5) -	-3.5 (10.3) p=0.191
PedsQL – total score Change from baseline, mean (SD); p-value vs placebo	-1.6 (10.4) -	6.8 (11.2) p=0.0029	5.9 (15.1) p=0.0198	-0.3 (12.4) -	-0.9 (11.8) p=0.618
Caregiver condition rating and quality of life					
EQ-5D-5L at end of study*					
Mobility – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Self-care – Problems (%)					
Usual activities – Problems (%)					
Pain/discomfort – Problems (%)					
Anxiety/depression – Problems (%)					
EQ-5D-5L – overall health status based on VAS, change from baseline; Mean (SD); Median (range); p-value vs placebo					
HADS – Total score , change from baseline, Mean (SD); Median (range); p-value vs placebo	[redacted]	[redacted]	[redacted]	NA	NA

CGI-I, Clinical Global Impression of Improvement; CSF, convulsive seizure frequency; EQ-5D-5L, EuroQOL – 5 Dimensions – 5 Levels scale produced by the European Quality of Life group; FFA, fenfluramine; HADS, hospital anxiety and depression scale; PedsQL, Paediatric Quality of Life Inventory (increases in total score indicates improvement); QOLCE, Quality of Life in Childhood Epilepsy (increases in total score indicates improvement); NA, Not assessed; SD, standard deviation; VAS, visual analogue scale (ranges 0-100, negative score indicates worsening, positive score indicates improvement in self-assessed overall health status)

* Dichotomised results; categories “moderate problems”, “severe problems” and “extreme problems” are collapsed into one response category “problems”.

The presented quality of life data (e.g. QOLCE, PedsQL, EQ-5D-5L (in carers)) reflect an unadjusted comparison of group means and medians. As highlighted in section B.3.4.2 (a linear mixed effect regression model and adjusted analysis of the PedsQL data), the underlying characteristics of the population, such as age and comorbidities have a significant impact on quality of life, and so should be considered in the interpretation of these data; as well as in the context of relative changes in seizures from baseline.

Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018

B.2.6.1.1 Primary Endpoint: Change in convulsive seizure frequency from baseline

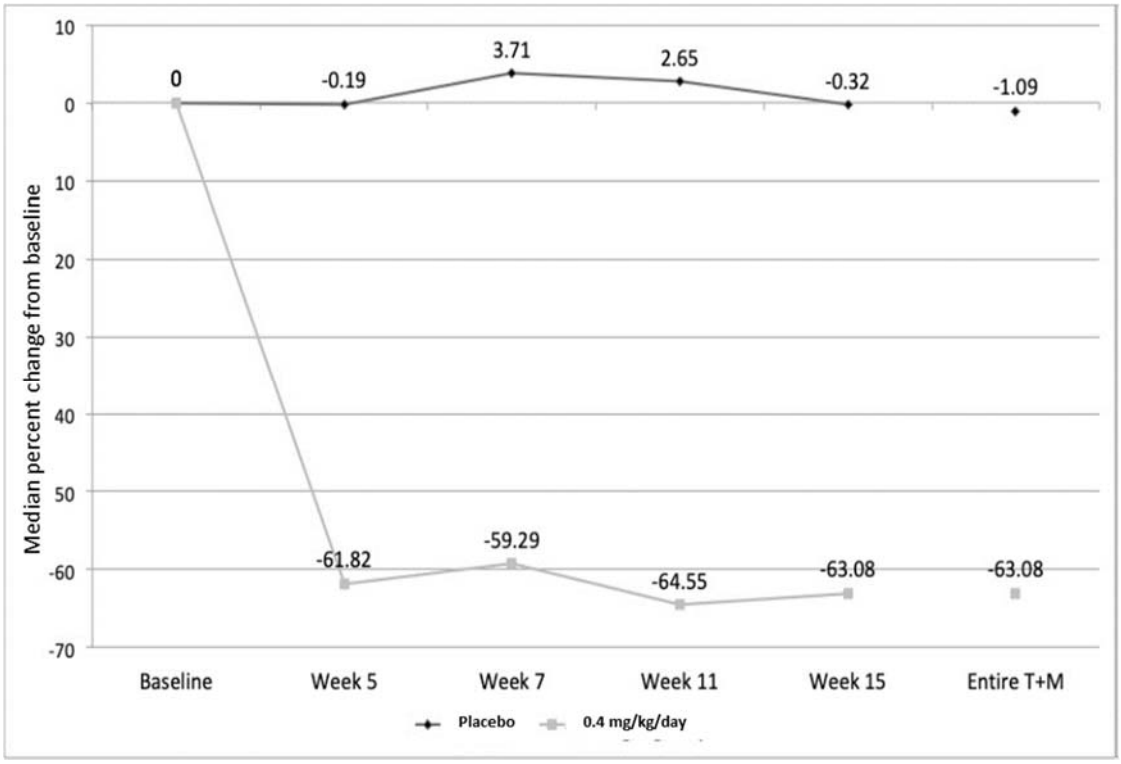
The primary endpoint was met in both Study 1 and Study 1504 (cohort 2) demonstrating that the addition of fenfluramine to standard of care AED regimens resulted in clinically and statistically significant reductions in convulsive seizure frequency in children and young adult Dravet syndrome patients, irrespective of concomitant use of stiripentol [3, 4].

In Study 1, the addition of fenfluramine 0.7 mg/kg/day to standard of care in patients not currently taking stiripentol resulted in a 62.3% reduction from baseline convulsive seizure frequency per 28 days, compared with placebo ($p<0.001$). By treatment group, patients receiving fenfluramine experienced a 75% median reduction from their baseline seizures per 28 days, compared with 19% for placebo patients (Table 10) [3]. In study 1504, addition of fenfluramine (0.4 mg/kg/day) to standard of care in patients receiving concomitant stiripentol resulted in a 54.0% reduction from their baseline convulsive seizure frequency per 28 days, compared with placebo ($p<0.001$). By treatment group, patients receiving fenfluramine experienced a 63% median reduction from their baseline seizures per 28 days, compared with a 1% reduction for placebo patients (Table 10) [4]. In both studies, the reduction in convulsive seizure frequency from baseline occurred rapidly with a treatment effect observed from the first visit and maintained throughout the 14-15 week study periods (Figure 8; Figure 9) [75, 76].

Figure 8. Median percent change from baseline in convulsive seizure frequency for fenfluramine 0.2mg/kg/day and 0.7 mg/kg/day, and placebo – Study 1

Source: Study 1 CSR, Figure 2; 28 Aug 2019

Figure 9. Median percent change from baseline in convulsive seizure frequency for fenfluramine 0.4mg/kg/day and placebo – Study 1504



Source: Study 1504 CSR, Figure 1; 21 Dec 2018

The primary efficacy analyses were conducted in the modified intention to treat population. Sensitivity analyses in the per protocol populations are consistent with the primary analyses [75, 76], confirming the results are robust.

B.2.6.1.1.1 Influence of patient characteristics and treatment history on the primary endpoint in the two registration trials (Study 1 and study 1504 cohort 2)

Fenfluramine is effective at reducing seizures in patients irrespective of their convulsive seizure frequencies

Exploratory integrated analyses of the primary endpoint from Study 1 and Study 1504 cohort 2 by categories of baseline convulsive seizure frequencies (<10; 10 to 50; >50 convulsive seizures per 28 days) are limited by the small sample sizes in each category; only 20% of trial participants were in the >50 convulsive seizures per 28 days at baseline category, and these patients had a range of 50 to 623.5 convulsive seizures per month [75, 76]. The results should therefore be interpreted with caution; however, they indicate that fenfluramine reduces convulsive seizure frequency in patients irrespective of their baseline frequencies [78] (Figure 10).

Figure 10. Percentage change in convulsive seizure frequency by baseline frequency compared with placebo

Source: Integrated summary of efficacy, Table 22

Fenfluramine is effective at reducing all convulsive seizure types

Convulsive seizures were defined in Study 1 and Study 1504 as generalised tonic-clonic (GTC), secondary GTC, tonic-clonic, tonic-atonic, hemiclonic, and focal with clear observable motor signs [78]. As sample sizes for each seizure type are small, integrated analyses of the effects of fenfluramine in the most common convulsive seizure types (occurring in >20% of patients at baseline: generalised tonic-clonic and focal with clear observable motor signs) were conducted (Figure 11). These data indicate that fenfluramine is effective at reducing seizure frequencies across all seizure types [78]. The effect on focal seizures is particularly noteworthy, given a recent Cochrane review highlighting that there was no evidence to support the use of stiripentol as an add on therapy for drug-resistant focal epilepsy [66](B.1.3.3.2).

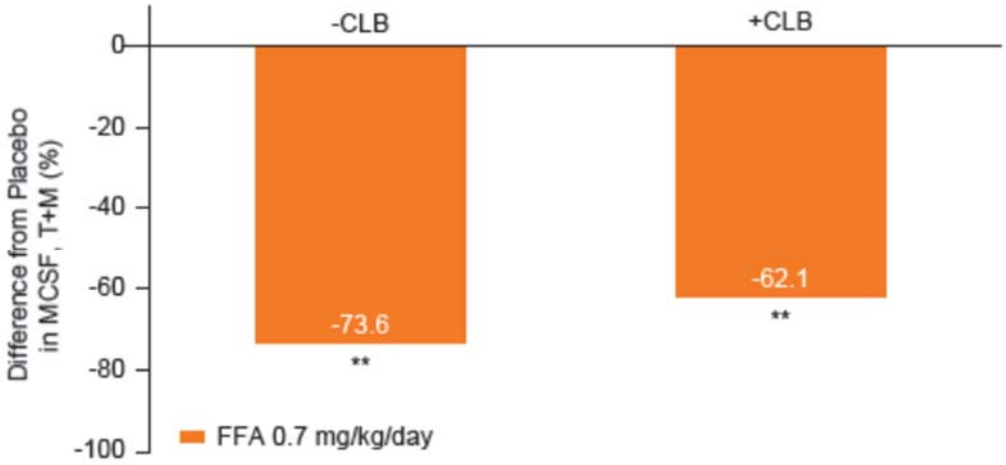
Figure 11. Median percentage change from baseline in convulsive seizure frequency per 28 days, by seizure type

Source: Integrated summary of efficacy, Table 16, Non-parametric analyses
FFA, fenfluramine; Note only 3 patients provide Secondary generalised tonic-clonic data in the FFA 0.4mg/kg/day group. The study was not powered to detect changes by seizure types.

Fenfluramine is effective at reducing seizures with or without concomitant clobazam.

Exploratory integrated analyses indicate that, although there were numerical differences, fenfluramine significantly reduced convulsive seizure frequencies both with or without concomitant use of clobazam in Study 1, with reductions in both groups of a similar order to that seen in the primary efficacy analysis (Figure 12). Similar results were also observed with or without concomitant valproate and/or clobazam [81]. These data highlight that fenfluramine may be an option for patients, independent of their underlying clobazam use and therefore offers patients a (simplified) non-clobazam-based therapeutic strategy where clobazam may not be desired (Figure 2). In accordance with their licensed indication, cannabidiol and stiripentol should be administered with clobazam [13, 14].

Figure *12*. Difference from placebo in monthly convulsive seizure frequency with fenfluramine with and without concomitant use of clobazam (Study 1 population)



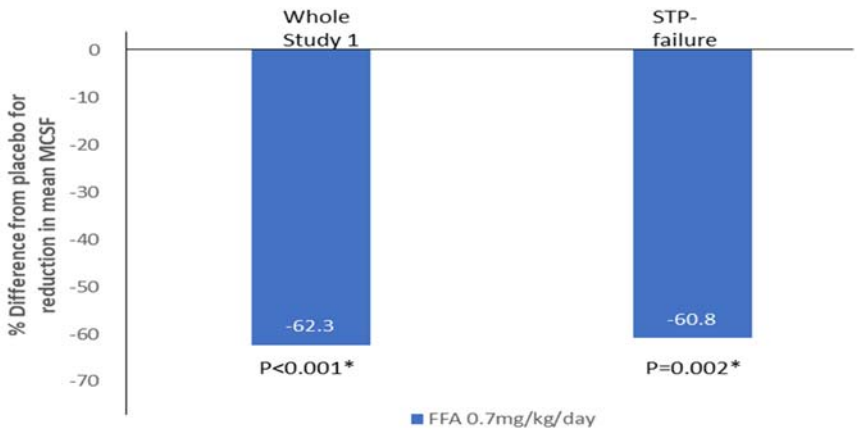
**P<0.001, difference from placebo. Patients receiving fenfluramine (0.7 mg/kg/day group) in the overall Study 1 population (+/- CLB) experienced a 62.3% reduction in convulsive seizure per 28 days compared to Placebo (*Figure 8*, *Table 10*)
CLB, clobazam; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods. Source: Knupp et al, 2019[81]

Fenfluramine is effective at reducing seizures in stiripentol failed and stiripentol naïve patients (Study 1) as well as an 'add on' to stiripentol (Study 1504, cohort 2).

In a post hoc analysis of patients in Study 1 that had previously failed on stiripentol treatment (48.7% of trial participants), the addition of fenfluramine 0.7mg/kg/day to standard of care AEDs statistically significantly reduced convulsive seizure frequency compared to placebo, and to a similar magnitude to that observed in the whole trial population (60.8% reduction from baseline over placebo; p=0.002) (Figure 13) [3, 82]. This indicates that fenfluramine is equally effective in patients who are stiripentol naïve or who have failed on prior stiripentol.

These data therefore support the use of fenfluramine in patients irrespective of their concomitant AEDs or prior treatment with stiripentol, which supports the proposed positioning for use of fenfluramine across all points in the current add-on therapy pathway (Figure 2).

Figure 13. Difference from placebo in mean monthly convulsive seizure frequency in patients previously failed on (experienced) stiripentol vs whole Study 1 population



*difference from placebo.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; STP, stiripentol
Source: Wirrell 2018; Lagae 2019

Fenfluramine is effective at reducing seizures in all age groups

Furthermore, to evaluate the potential efficacy of fenfluramine on convulsive seizures in older children and young adult patients with Dravet syndrome, a sub-group analysis on all patients ≥12 years of age across both Study 1 and Study 1504 (30.6% of trial participants) was performed. Patients receiving fenfluramine (all doses combined) achieved a reduction in mean convulsive seizure frequency of 63.9% compared with placebo, which is highly consistent with the effects seen in all patients in the trials and indicates that fenfluramine has comparable effects across all age groups [78].

B.2.6.1.2 Key secondary endpoint: ≥50% responder analysis (and ≥25% and ≥75% responder analyses)

Fenfluramine provides a statistically significant and clinically meaningful reduction in seizures

The key secondary endpoint of a ≥50% reduction in convulsive seizure frequency is considered a clinically meaningful reduction in convulsive seizure frequency [83], and the results for this endpoint support the primary efficacy endpoint in demonstrating the clinically meaningful improvement in seizure control achieved with fenfluramine when added to standard of care AED regimens.

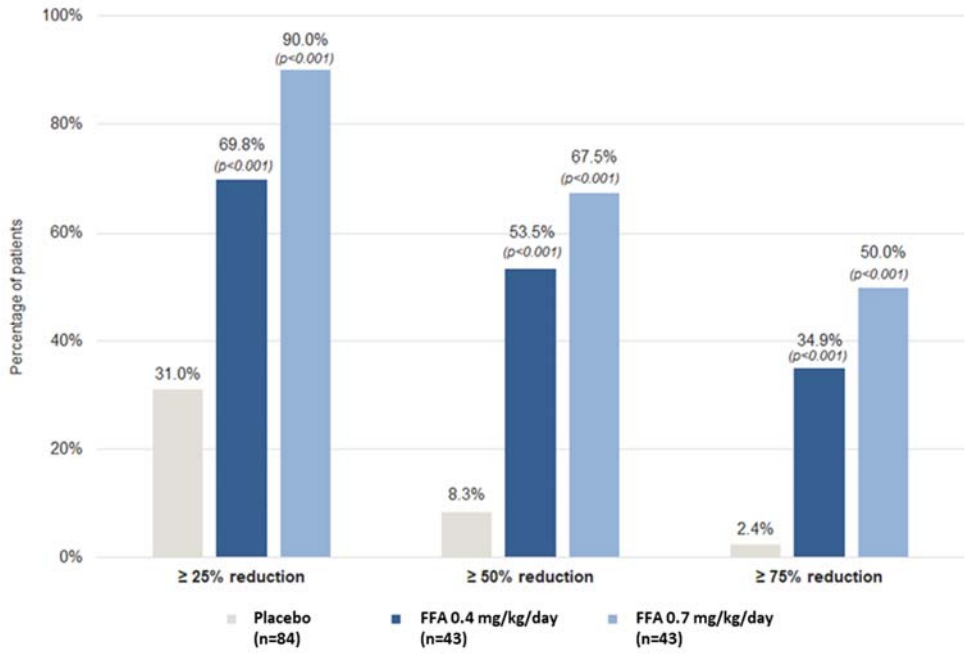
In both Study 1 and Study 1504 significantly more patients in the fenfluramine 0.7mg/kg/day and 0.4 mg/kg/day treatment groups achieved a ≥50% reduction from baseline in convulsive seizure frequency during the 14-15 week treatment periods compared with placebo; 68% vs 12% (odds ratio 15.0 [95% CI 4.5 to 50.0]; p<0.0001) in Study 1 and 54% vs 5% (odds ratio 26.0 [95% CI 5.5 to 123.2]; p<0.001) in Study 1504 (Table 10) [3, 4].

Fenfluramine provides a profound reduction in seizure frequency for a high proportion of patients

Additional secondary endpoints included a ≥25% and ≥75% reduction in convulsive seizure frequency, with the latter considered a profound treatment effect. In both Study 1 and Study 1504 significantly more patients in the fenfluramine treatment groups achieved a ≥75% reduction from baseline in convulsive seizure frequency during the 14-15 week trial periods compared with placebo; 50% vs 2% (odds ratio 55.1 [95% CI 6.0 to 526.0]; p=0.0005) in Study 1 and 35% vs 2% (odds ratio 23.7 [95% CI 2.9 to 191.8]; p=0.003) in Study 1504 (Table 10) [3, 4]. To put these figures into context, a profound reduction in monthly convulsive seizure frequency is achieved in one out of every 2-3 patients treated with fenfluramine rather than continued treatment with their current standard of care AED regimen, including in those currently taking stiripentol.

An integrated summary of these responder data from Study 1 and Study 1504 is provided in Figure 14 [78].

Figure 14: Percentage of patients who achieved a ≥25%, ≥50%, ≥75% reduction in monthly convulsive seizure frequency from baseline – integrated summary of Study 1 and Study 1504 data



Source: Integrated Summary of Efficacy, Table 19

The clinical meaningfulness of reductions from baseline in convulsive seizure has also been established in patients from Study 1 and Study 1504, on the basis of the degree of seizure frequency reduction associated with “Much improved” or “Very much improved” clinician and caregiver CGI-I ratings via receiver operating characteristic (ROC) analysis. The clinically meaningful threshold of seizure control was concordant among both clinician and caregivers. In Study 1504, a threshold of ≥37.5% reduction in monthly convulsive seizure frequency was defined as clinically meaningful [53]. In Study 1, a threshold reduction of ≥44% was established as being clinically meaningful [54].

Of note, these global Dravet syndrome-specific thresholds for clinically meaningful reductions in convulsive seizure frequencies appear lower than the conventionally accepted 50% threshold used by regulatory agencies [83] in general epileptic disorders and widely accepted as a threshold for meaningful seizure improvement, including by NICE in their general epilepsy guidance [9].

However, it is also of note that the NICE FAD for cannabidiol indicates a 30% reduction in convulsive seizure frequency is sufficient patient-relevant benefit to warrant continued treatment [12].

B.2.6.1.3 Key secondary endpoint: Longest convulsive seizure-free intervals (and seizure-free days and seizure-freedom)

Fenfluramine significantly increases the time interval between seizures

Given the intractable nature and high frequency of seizures in Dravet syndrome, prolonging the interval between convulsive seizures is important for patients and carers. The median longest convulsive seizure-free intervals were significantly longer with fenfluramine 0.7mg/kg/day and 0.4 mg/kg/day (as an add on to stiripentol) than placebo in both Study 1 (25.0 days vs 9.5 days; p<0.0001) and Study 1504, cohort 2 (22.0 vs 13.0; p=0.004) (Table 10) [3, 4, 51].

Fenfluramine significantly increases the number of seizure-free days

Related to this, the mean number of convulsive seizure-free days per 28 days, during which patients are at lower risk of experiencing SUDEP or status epilepticus, was significantly greater for fenfluramine 0.7 mg/kg/day and 0.4 mg/kg/day compared with placebo; [redacted] in Study 1 and [redacted]) in Study 1504 (Table 10) [75, 76]. Fenfluramine therefore provided an additional 5 convulsive seizure-free days per month (equivalent to an additional 2 months of seizure-free days per year) compared with non-stiripentol standard of care AED regimens, and an additional 2 convulsive seizure-free days per month (equivalent to nearly an additional month of seizure-free days per year) in patients who were receiving stiripentol as part of their standard of care AED regimens.

Complete, sustained seizure freedom (i.e. zero convulsive seizures) is the ambition for patients with Dravet syndrome; however, as Dravet syndrome is defined by intractable seizures, few patients ever achieve this outcome [2, 43]. In both Study 1 and Study 1504 (cohort 2), no patients in the placebo groups achieved complete seizure freedom throughout the 14-15 weeks of treatment. In comparison, from a median baseline convulsive seizure frequency of over 20 seizures per month in Study 1 and over 14 seizures per month in Study 1504 for patients randomised to fenfluramine, seizure freedom throughout the entire 14-15 week of treatment was achieved in 3 patients (8%) and 1 patient (2%), respectively.

Given the high baseline convulsive seizure frequency, near seizure freedom, defined as patients having at most 1 convulsive seizure during the 14-15 week of treatment, is also a meaningful outcome for patients with Dravet syndrome. No patients receiving placebo achieved near seizure freedom; however, 10 (25%) patients receiving fenfluramine 0.7 mg/kg/day in Study 1 and 5 (12%) patients receiving fenfluramine 0.4 mg/kg/day recipients in Study 1504 achieved this important outcome for patients, their carers and the broader family unit [3, 4]. These data (notably including both the titration and maintenance period of the treatment period), are further support by the OLE data that show that the benefits of fenfluramine continue to be maintained to at least 2 years on treatment and in the Belgian RWE long-term observational study where 7 out of 10 patients that were prospectively followed up for 5 years had seizure-free intervals of at least 2 years, and 3 of the 10 patients being seizure-free for all 5 years (see section B.2.6.2 and B.2.6.3).

Collectively, these data indicate that the impressive reductions in convulsive seizure frequency with fenfluramine treatment leads to significantly longer intervals between seizures and significantly increases the number of days in which patients are seizure-free. Fenfluramine

therefore significantly reduces the number of days in which patients are at risk of SUDEP and status epilepticus, and that in a substantial proportion of patients with previously high frequencies of convulsive seizures almost eliminates the number of days patients are at risk.

B.2.6.1.4 Non-convulsive seizure and total seizure frequency

Although convulsive seizures are associated with the most severe outcomes for patients with Dravet syndrome, non-convulsive seizures can also adversely impact daily activities such as learning, cognitive development and quality of life [2, 43].

In the two registration studies, while all subjects had convulsive seizures, the number of subjects with nonconvulsive seizures was approximately 50% in both studies. In addition, there was high variability in the number of non-convulsive seizures experienced by some subjects. For example, in Study 1504, subjects in the placebo group had nonconvulsive seizure frequencies of more than [redacted] per 28 days at baseline, including [redacted] with myoclonic seizures who had a frequency of over [redacted] seizures per 28 days [76]. In comparison, only [redacted] subjects in the fenfluramine 0.4 mg/kg/day group had more than [redacted] convulsive seizures per 28 days during the Baseline period, and the highest number of seizures experienced by any one subject in that group was [redacted] per 28 days [75].

The median percentage change from baseline in non-convulsive seizures was significantly greater with fenfluramine 0.7 mg/kg/day than with placebo in Study 1 (-76% vs -55.6%; p=0.046) [3]. In Study 1504, fenfluramine 0.4 mg/kg/day reduced non-convulsive seizures from a median of 13.33 at baseline to 8.88 at the end of the 15-week trial, compared with a change from 4.33 to 3.79 with placebo. The difference versus placebo in Study 1504 was not statistically significant **[4]**, but in the context of the heterogeneity in seizure frequency at baseline suggests a trend in favour of fenfluramine and confirms that the benefit of fenfluramine in reducing convulsive seizures is not at the expense of an increase in non-convulsive seizures.

Similar results were seen when considering total seizure frequency (convulsive and non-convulsive), with a statistically significant difference favouring fenfluramine 0.7 mg/kg/day over placebo in Study 1, and a non-significant difference between fenfluramine 0.4 mg/kg/day and placebo in Study 1504 (Table 10) [3] [4].

B.2.6.1.5 Incidence of status epilepticus, rescue medication use and hospitalisation

Status epilepticus (SE) is a condition in which a seizure lasts longer than 5 minutes or when seizures occur close together and the person does not recover between episodes [84]. It is an emergency condition that leads to use of rescue medication, emergency hospitalisation and is also a significant cause of death in Dravet syndrome [5].

In Study 1 and Study 1504 the seizure diaries captured seizures lasting < 2minutes, 2-10 minutes, or >10 minutes, rather than 5 minutes. Therefore, a composite endpoint was constructed to evaluate episodes of SE using the following definitions: cases captured as treatment at hospitals or other treatment centres, SE occurring more than once in a 24-hour period and entered as an adverse event per protocol, and as convulsive seizures lasting longer than 10 minutes from the seizure diary. A single seizure meeting more than 1 of these criteria was counted once [75, 76].

Up to 35% of patients experienced an SE event throughout the 14-15 weeks of treatment in Study 1 and Study 1504. There was no significant difference between fenfluramine and placebo in the incidence of SE, the probability of a seizure lasting < 2minutes, 2-10 minutes, or >10 minutes, [redacted]; however, the median number of days of rescue medication use per 28 days was lower in patients receiving fenfluramine 0.7 mg/kg/day than placebo in Study 1 (0 vs 1.7; p<0.0001) (Table 10) [75, 76].

B.2.6.1.6 Patient Reported Outcomes and Quality of Life

In addition to improvements in seizure-related outcomes, data from Study 1 and Study 1504 cohort 2 indicate a general pattern of improvement in patients' global health status and patients and carer quality of life with fenfluramine treatment.

These quality of life data should be viewed as underestimating the full impact of the condition and the value of a treatment. As highlighted in section B.1.4, there are a number of challenges in measuring the quality of life of patients with Dravet syndrome including: coping effects; difficulties in being able to delineate a seizure-specific contribution to quality of life within the overall complexities of Dravet syndrome; and the limited potential to achieve an improved quality of life with therapy as a consequence of the progressive nature of the condition.

B.2.6.1.6.1 Clinical Global Impression of Change - Improvement (CGI-I) rating

Parents/caregivers and study investigators independently rated their global impression of how patients' symptoms had improved or worsened relative to baseline using the Clinical Global Impression-Improvement (CGI-I) scale. This provides a global evaluation of a patient's response to treatment taking into consideration efficacy, safety and tolerability.

Parents/caregivers and investigator ratings were generally aligned and indicated more patients receiving fenfluramine were rated as "Very much" or "Much improved" than patients receiving placebo (Table 11). In Study 1, significantly more patients receiving fenfluramine 0.7 mg/kg/day were rated as "Very much" or "Much improved" by parents/caregivers (55%) and investigators (62%) compared with patients receiving placebo at the end of their treatment period (10%, both p<0.0001) [3]. In Study 1504, a non-significantly greater proportion of patients receiving fenfluramine 0.4 mg/kg/day were rated by parents/caregivers to be very much or much improved compared with patients receiving placebo (33% vs 21%; p=0.14), and a significantly greater proportion were rated by investigators to be very much or much improved compared with placebo (44% vs 16%; p=0.008) [4]. To put these data in context, in patients receiving placebo, or 10mg/kg/day or 20mg/kg/day of cannabidiol at the end of the GWPCARE2 trial, 14% (9 out of 65), 35% (23 out of 66) and 32% (21 out of 66) parents/caregivers of patients, rated that their overall condition was "Very much" or "Much improved"[35].

As stated in section B.2.6.1.2, these results demonstrate that fenfluramine provides a statistically significant and clinically meaningful reduction in seizures.

B.2.6.1.6.2 Quality of Life in Childhood Epilepsy Scale (QOLCE)

The Quality of Life in Childhood Epilepsy Scale (QOLCE) is an epilepsy-specific instrument to assess how epilepsy affects day-to-day functioning of children in various areas, including physical

activities, wellbeing, cognition, social activities, behaviour, and general health. The results for the QOLCE in the fenfluramine treatment groups did not show a consistent improvement in the overall score (Table 11). However, patients treated with fenfluramine 0.7 mg/kg in Study 1 were significantly improved from baseline compared with patients in the placebo arm for the Wellbeing/Anxiety subscale (p=0.018) [3, 75]. Furthermore, numerical improvements were observed in the 0.7 mg/kg group in several subscales, including physical restrictions, attention/concentration, language, other cognition, social interactions, and social activities, as well as the overall score [75].

B.2.6.1.6.3 Paediatric Quality of Life Inventory (PedsQL)

The Paediatric Quality of Life Inventory (PedsQL) generic core consists of 4 scales that measure physical, emotional, social, and school functioning. A psychosocial health summary score is comprised from the emotional, social, and school functioning scales, a physical health summary score is comprised of the physical functioning scale, and the total score is the sum of all the items over the number of items answered on all the scales [85].

The change from baseline in the total score was significantly greater with fenfluramine 0.7 mg/kg/day than with placebo (5.9 vs -1.6; p=0.0198) in Study 1 [3]. Based on a minimally clinically important difference of 5 points [86], these data suggest fenfluramine 0.7 mg/kg/day significantly improved patient quality of life compared with placebo in Study 1. Results in Study 1504 were not statistically significantly different from placebo [4](Table 11), and confirm that fenfluramine does not impair patient quality of life when added to standard of care AED regimens containing stiripentol.

Importantly, these data formed the basis of a linear mixed effect regression model to examine the relationship between convulsive seizures-free days and quality of life (PedsQL mapped to EQ-5D-Y), as a post-hoc analysis (section B.3.4.2 and Appendix M). When adjusting for age and underlying co-morbidities, a clear impact of seizures is observed to affect quality of life in patients (Figure 24, Figure 25); as well as to their carers (Figure 26).

B.2.6.1.6.4 Caregiver quality of life, anxiety and depression

Caregiver quality of life was assessed using the EQ-5D-5L instrument. The five rating levels for each domain were collapsed into two categories: ‘No problems’ (no problem rating), or ‘Problems’ (slight problems, moderate problems, severe problems, and extreme problems). Statistical comparisons were not calculated; however, at the end of the studies the general pattern of responses indicated fewer caregivers of patients receiving fenfluramine in Study 1 and Study 1504 reported ‘Problems’ across each of the five domains assessed by the instrument. Overall health status of caregivers assessed on the visual analogue scale (VAS) indicated numerical improvements from baseline for fenfluramine compared with placebo (Table 11) [75, 76].

Importantly, these data formed the basis of a linear panel regression model to examine the relationship between convulsive seizures-free days and quality of life (EQ-5D-5L mapped to EQ-5D-3L), as a post-hoc analysis (section B.3.4.2 and Appendix M). These results show a clear impact of seizures in affecting the quality of life of carers (Figure 26).

Caregiver levels of anxiety and depression were also assessed in Study 1 using the Hospital Anxiety and Depression Scale (HADS). At baseline, levels of anxiety were near the high end of the normal range and there were no notable levels of depressive symptoms. Caregivers of patients

receiving fenfluramine 0.7 mg/kg/day achieved a 1.0 point reduction in the median total anxiety and depression score compared with no reduction in caregivers of patients receiving placebo; however, there was no difference in the change from baseline in total score between fenfluramine and placebo (Table 11) [75].

B.2.6.2 Open Label Extension — Study 1503

B.2.6.2.1 Key efficacy endpoint: Change in convulsive seizure frequency from baseline

The key efficacy endpoint in the open-label extension (OLE) study was aligned with the primary endpoint in the two registration phase 3 RCTs (Study 1 and Study 1504 cohort 2); change in convulsive seizure frequency per 28 days between the originating study baseline and the OLE treatment period. To account for the use of a 0.2mg/kg/day fixed dose of fenfluramine for all patients during Month 1 of the OLE, two key convulsive seizure frequency related endpoints were evaluated [78]:

- **Endpoint 1**: Difference in convulsive seizure frequency per 28 days for the entire OLE treatment period (day 1 to end of study (EOS)) compared to baseline (from their originating double-blind study)
- **Endpoint 2**: Difference in convulsive seizure frequency for Month 2 to end of study (i.e day 31 to EOS) time point compared to baseline (double blind study).

In contrast to the originating RCT trials, which employed fixed fenfluramine dosing during the maintenance phase, the OLE permitted dose titration and adjustment after the first month. As of an interim analysis with a cut-off 13 March 2018 (n=232, including 158 patients with known prior treatment allocation in their originating RCTs (Study 1 and Study 1504, cohort 2)), the mean (min-max) daily dose of fenfluramine across all subjects in the OLE was [redacted]

In that interim analysis, fenfluramine demonstrated sustained, significant reductions in monthly convulsive seizure frequency over follow-up periods of up to 24 months, irrespective of originating study treatment assignment. From a median convulsive seizure frequency at baseline of [redacted] per 28 days, the median convulsive seizure frequency per 28 days for all patients during the OLE (Month 1 to Last Visit, Endpoint 1) was [redacted], which was a statistically significant reduction from baseline of [redacted] ($p<0.001$). Consistent results were observed for Month 2 to the Last Visit during OLE (Endpoint 2); during this period the median monthly convulsive seizure frequency was [redacted], which was a statistically significant reduction from baseline of [redacted] ($p<0.001$) (Table 12). The large, statistically significant reduction from baseline in monthly CSF was observed early, at Month 1 for all double-blind treatment groups, and was maintained for up to 24 months (the longest treatment OLE treatment duration included at the time of the interim analysis) (Figure 15) [78].

Table 12. Change from originating baseline in convulsive seizure frequency per 28 days – Study 1503 OLE study (data cut-off 13 March 2018)

Efficacy endpoint	FFA OL Placebo* (n=64)	FFA OL 0.2 mg/kg/day* (n=38)	FFA OL 0.4 mg/kg.day* (n=21)	FFA OL 0.7 mg/kg/day* (n=35)	FFA OL Total (n=158)
Baseline CSF in the originating study Mean (SD); median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint 1 – entire OLE treatment period					
% change in CSF from the originating study baseline, Mean (SD); Median (range); p-value vs baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endpoint 2 – Month 2 to end of study					
% change in CSF from the originating study baseline, Mean (SD); Median (range); p-value vs baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CSF, convulve seizure frequency per 28 days; FFA, fenfluramine; OL, open label; OLE, open-label extension; SD, standard deviation
*Assigned group in the originating studies; all patients received FFA during the OLE study, including those previously randomised to placebo in the originating studies
Source: Study 1503 CSR, December 2018

Figure 15. Reduction from baseline in convulsive seizure frequency – Study 1503 OLE study (data cut off 13 March 2018)

Source: Study 1503 CSR, December 2018, Figure 1

An updated analysis with data from 330 patients, including patients from the on-going Study 2 (data cut-off 14 October 2019) confirmed these reductions in convulsive seizure frequency with fenfluramine treatment are maintained for up to 3 years of treatment, with no evidence of a waning of treatment effect. The median percent reduction from baseline in convulsive seizure frequency for the overall OLE treatment period (Endpoint 1) was 64.48% ($p<0.001$), and for Month 2 to end of study (Endpoint 2) was 65.35% ($p<0.001$). The reduction with fenfluramine treatment for both Endpoint 1 and Endpoint 2 was statistically significant at each time period during the OLE [87].

B.2.6.2.2 Responder analysis

Interim analysis of responder rates in the 158 patients enrolled from the two registration phase 3 RCTs (Study 1 and Study 1504, cohort 2: data cut-off 13 March 2018) indicate the high responder rates with fenfluramine observed over 14-15 weeks in the Study 1 and Study 1504 RCTs persist with up to 24 months of treatment. Overall, [redacted] achieved a >25% reduction, [redacted] achieved a >50% (i.e. clinically meaningful) reduction and [redacted] achieved a >75% (i.e. profound) reduction in convulsive seizure frequency from their originating study baseline during the open-label treatment period [70].

Updated analysis with data from 330 patients, including patients from the on-going Study 2 (data cut-off 14 October 2019) confirmed these results with up to 3 years of treatment (Figure 16) [87], further supporting the long-term efficacy of fenfluramine, with no evidence of a waning of treatment effect.

Figure 16. Responder analyses in Study 1503 over time (data cuts 13 March 2018 and 19 October 2019)

Source: CSR Study 1503, December 2018; Responses to Day 120 regulatory questions

B.2.6.2.3 Additional endpoints

Based on the interim analysis of Study 1503 (data cut-off March 2018, n=158 with known treatment allocation in Study 1 and Study 1504), results for other endpoints in the OLE study were highly consistent with those observed in the originating Study 1 and Study 1504 RCTs. The large, statistically significant reductions from baseline in convulsive seizure frequency were consistent irrespective of age [78].

Analysis of the longest interval between convulsive seizures showed that patients had maximum intervals as long as , with the median interval for all patients being approximately In addition, CGI-I ratings of “Much improved” and “Very much improved” by parents/caregivers and investigators increased with increasing time in the OLE study, and quality of life assessment using QOLCE showed directional improvements across all domains at month 12 / last visit. Quality of life assessment using PedsQL showed directional improvements for all except those patients who had been randomised to fenfluramine which may be due to the shorter duration of time of these patients in the OLE compared with the other groups [78]. These data therefore confirm the sustained efficacy of fenfluramine in the longer term and suggest an increasingly positive impact on patient quality of life with sustained fenfluramine treatment and seizure control.

B.2.6.3 RWE of long-term effectiveness in children and adults

In addition to the RCT and OLE extension studies, which provide robust prospective evidence of efficacy in children and young adults for up to 3 years [3, 4, 87], fenfluramine is also supported by two European observational studies that provide real-world evidence of its long-term effectiveness in children and mature adults, representing up to 27 years of daily treatment [71, 72, 77], and a US [73] and European expanded access program [74]. Collectively, the findings of these real-world

evidence studies are consistent with the findings of significant and sustained seizure reduction and improvements in clinical status observed in the RCT and OLE studies. Addition of fenfluramine to standard of care AED regimens can provide profound reductions in seizure frequency in high proportions of patients with Dravet syndrome, which are sustained over many years with daily treatment, irrespective of age.

B.2.6.3.1 Belgian RWE studies

The first RWE study included 12 patients with Dravet syndrome (all displaying the core Dravet syndrome phenotype, and 11 with confirmed *SCN1A* mutation) aged between 1 and 16 years (mean age 8 years) at the time of initiating fenfluramine. All had seizures that were refractory to their existing AED regimen, and in the year before the start of fenfluramine treatment all had generalised tonic-clonic seizures, and five had frequent episodes of status epilepticus [77].

Fenfluramine was added to their existing AED regimen at doses of 8.5-17mg/day. The duration of exposure to fenfluramine ranged from 1 to 19 years at the time of evaluation in 2010, at which point their ages ranged 3-35 years. Seven patients who were still receiving fenfluramine at the time of the last visit had been seizure free for at least 1 year, and in total had been seizure-free for a mean of 6 years (range: 1 to 19 years) [77]. In a prospective further 5-year follow up of 10 of these patients, between 2010 and 2014, three patients were seizure-free for all 5 years with seizure-free periods lasting 15, 13, and 9.5 years. Four additional patients had seizure-free intervals of at least 2 years during the observation period and nine of the 10 patients had an average seizure frequency of <1 per month over the entire observation period [71].

The second study supports the findings in the first cohort. Nine Dravet syndrome patients (aged 1.2–29.8 years) were prospectively enrolled between January 2011 and December 2015. Following a 3-month baseline period, during which the median frequency of major motor seizures was 15.0 per month, fenfluramine was added to their existing AEDs at a dose of 0.2 to 0.8 mg/kg/day, with a maximum permitted dose of 17 mg/day. Over the entire treatment period (median duration of 1.5 years, range 0.3 to 5.1 years) all 9 patients experienced a reduction in seizure frequency, with a median reduction of 75% (range, 28 to 100%). Seven patients (78%) experienced a ≥ 50% reduction in major motor (tonic-clonic, tonic, clonic, atonic and myoclonic seizures) seizure frequency [72].

Several patients in the second study also experienced clinical benefits in addition to reductions in seizure frequency. At the most recent visit, mean sleep quality for patients and parents was 8.1/10 and 7.9/10, respectively (where 10 = very good), mean QoL scores were 7.4/10 and 7.6/10, respectively, and five parents indicated a “Much” or “Very much” improved global impression of their child [72].

B.2.6.3.2 US Expanded access program

The US expanded access program provides access to fenfluramine in patients who do not qualify for participation in the clinical trials. Data are available from 23 patients with a mean age of 6.8 years (range 2 to 22 years), treated with fenfluramine at doses of 0.7 mg/kg/day (without stiripentol) or 0.4 mg/kg/day (with stiripentol) for a median of 90 days (range 30 to 180 days). Fifteen (65%) patients were rated by physicians as experiencing meaningful global clinical improvement based on a rating of much/very much improved. Similarly, improvements in cognition, behaviour, or motor abilities were reported for 56%, 43%, and 48% patients, respectively [73].

B.2.6.3.3 European Expanded access program

The European Access Program (EAP) was launched in December 2018 to provide access to paediatric and adult patients with Dravet syndrome who lack other treatment options, including participation in clinical trials. The EAP is currently enrolling patients [redacted] As of April 2020 [redacted] patients have been enrolled [redacted] An additional [redacted] patients have discontinued treatment. The primary effectiveness assessment in this program is the clinician assessment of change in clinical status defined as: worse, unchanged, improved, and seizure-free [74].

Of the [redacted] adult patients currently being treated, [redacted] are also receiving concomitant stiripentol, and [redacted] are not. Treatment duration ranges from [redacted], with [redacted] treated for >12 months. The median fenfluramine dose as of April 2020 is [redacted]; dose ranges from 0.2 to 0.7 mg/kg/day, with [redacted] on 0.7 mg/kg/day compared to [redacted] on 0.2 mg/kg/day.

Effectiveness assessments are available for [redacted] adult patients and [redacted] paediatric patients, with similar outcomes achieved in each group Overall, ≥80% of adult and paediatric patients are improved or seizure free in the EAP (Table 13).

Currently in the UK, [redacted] patients are receiving treatment with fenfluramine in the EAP. There are also 7 UK patients with Dravet syndrome continuing to receive treatment on a long-term safety study of fenfluramine (Study 1601 – see section B.2.11).

Fenfluramine has been well tolerated in the EAP. No patient in the EAP in either age group has developed valvular heart disease or pulmonary arterial hypertension.

Table 13: Change in clinical status: European EAP

Status at Last Visit	Adults Patients (>18 years) n(%)	Paediatric Patients (0 to 17 years) n (%)
Worse	[redacted]	[redacted]
Unchanged	[redacted]	[redacted]
Improved	[redacted]	[redacted]
Seizure free	[redacted]	[redacted]

Source: Data on file. European EAP Progress Report

B.2.7 Subgroup analysis

As presented in section 2.6, the phase 3 Study 1 and Study 1504 RCTs demonstrate the large, clinically meaningful reductions in convulsive seizure frequency when fenfluramine is added to standard of care AED regimens, either with or without concomitant stiripentol. Exploratory analyses demonstrate this efficacy is robust irrespective of concomitant clobazam use, and irrespective of age. These data, and the data from the Study 1503 OLE study and long-term RWE studies, support the use of fenfluramine within its anticipated licensed indication as an option at all points in the add-on therapy pathway (see section B.1.3.4). No other subgroup analyses are considered.

B.2.8 Meta-analysis

Integrated efficacy analyses have been conducted for regulatory purposes but meta-analysis of the fenfluramine RCTs has not been undertaken.

B.2.9 Indirect and mixed treatment comparisons

- There are no direct comparative data between clobazam, stiripentol or cannabidiol (with clobazam) as existing NICE-recommended add-on therapies, nor for fenfluramine. Whilst the placebo-controlled trials of fenfluramine robustly demonstrate the efficacy and safety of its use in Dravet syndrome, they do not inform the comparative clinical and cost effectiveness of fenfluramine in patients in need of add-on therapy. Indirect treatment comparisons were therefore explored to provide the relevant comparative data for fenfluramine as an add-on therapy option alongside existing add-on therapies.
- Based on a systematic literature review there are no RCTs supporting clobazam specifically in the treatment of Dravet syndrome. Stiripentol is supported by 2 RCTs; however, a detailed ITC feasibility and quality assessment demonstrates these provide only low to moderate quality evidence and their endpoint data are incompatible with those of the trials of fenfluramine (and cannabidiol). Consistent with the acceptance by NICE of cannabidiol without an indirect comparison against stiripentol, the evidence limitations for stiripentol preclude a robust ITC of fenfluramine against stiripentol.
- **A robust ITC was possible for fenfluramine versus cannabidiol (with clobazam) and indicates clearly that fenfluramine is superior to cannabidiol (with clobazam) in reducing convulsive seizure frequency. The placebo-adjusted reduction in monthly convulsive seizure frequency was [redacted] with fenfluramine, compared with [redacted] with cannabidiol. With odds ratios in the range [redacted], and no overlap of 1.0 by the credible intervals, a significantly greater proportion of patients treated with fenfluramine achieve a clinically meaningful (≥50%) reduction in convulsive seizure frequency compared with cannabidiol (with clobazam).**
- Based on evidence from their open-label extension studies, there is no evidence of a waning effect of fenfluramine with up to 2 years of treatment; however, the SmPC for cannabidiol (with clobazam) reports OLE study data suggestive of a waning of effect of ~25% over the course of 1 year on treatment. The superior efficacy of fenfluramine over cannabidiol (with clobazam) observed in the ITC is therefore expected to persist with long-term treatment.
- Whilst it is not possible to make a robust ITC for fenfluramine against other NICE-recommended add on therapies, the comparison with cannabidiol (with clobazam) is highly relevant to the decision problem. Cannabidiol (with clobazam) was accepted by NICE as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway in 2019. At the point of the first appraisal committee meeting for this current appraisal, cannabidiol (with clobazam) will have been an established treatment option for UK patients for over a year. Given the need for new therapies in Dravet syndrome and the recent downgrading of its controlled drug prescribing requirements, use of cannabidiol (with clobazam) is anticipated to continue to increase.
- As the ITC provides robust evidence of the clinical efficacy of fenfluramine against cannabidiol (with clobazam) in similar patient populations, and confirms that fenfluramine is superior, it is anticipated that fenfluramine would be used as an alternative add-on therapy to cannabidiol (with clobazam), and by extension would an alternative to stiripentol.
- **A primary clinical and economic comparison against cannabidiol (with clobazam) is therefore the most appropriate comparison to determine the clinical and cost effectiveness of fenfluramine in the existing add-on therapy pathway.**

The proposed positioning of fenfluramine in the treatment pathway for patients with Dravet syndrome is as outlined in section B.1.3.4. We anticipate that, where clinicians feel clobazam is clinically a desirable first-line add-on, this would be tried in preference to other options, including fenfluramine. However, fenfluramine could be a first-line add-on therapy option in patients for whom clobazam is not a desirable option or when clobazam is not tolerated, in which case, based on NICE CG137, unlicensed stiripentol or continued therapy with existing standard of care therapy would be the appropriate comparators. As a second- or subsequent-line add-on therapy option after clobazam, the appropriate comparators would be stiripentol or cannabidiol as licensed and NICE-recommended therapies. Continued therapy with (ineffective) existing standard of care AEDs could be relevant but only when NICE-recommended add-on therapies have been exhausted.

As for the registration trials of stiripentol and cannabidiol, Study 1 and Study 1504 compared the addition of fenfluramine to standard of care AEDs against placebo plus continued therapy with standard of care AEDs. Whilst the placebo-controlled trials of fenfluramine robustly demonstrate the efficacy and safety of its use in Dravet syndrome, they do not inform the comparative clinical and cost effectiveness of fenfluramine in patients in need of add-on therapy. Indirect treatment comparisons were therefore explored to provide the relevant comparative data for fenfluramine as an add-on therapy option alongside existing add-on therapies.

B.2.9.1 Identification of relevant studies

The systematic literature review (SLR) described in Appendix D aimed to identify relevant clinical trial data for fenfluramine, and also for the key pharmacological therapies recommended in existing NICE guidance: clobazam, stiripentol and cannabidiol. The 2017 Cochrane SLR of AEDs in Dravet syndrome found only two published RCTs of stiripentol [60]; no RCTs of clobazam were identified and neither cannabidiol nor fenfluramine had published trial data available at the time of those Cochrane searches. Our SLR described in Appendix D (searches conducted 28th June 2020) confirmed there are no published RCTs available in support of clobazam specifically in Dravet syndrome, and identified two published primary RCTs each for fenfluramine [3, 4] and stiripentol [62, 63], and three RCTs for cannabidiol [34, 35, 88], as listed in Table 14.

On this basis it would not be possible to conduct an indirect comparison of fenfluramine against clobazam. The feasibility of conducting an indirect comparison of fenfluramine against stiripentol and cannabidiol trials is discussed below.

B.2.9.2 ITC feasibility assessment

As ITC methods rely on the assumption of exchangeability of studies, a key requirement of an ITC is that studies are comparable. In order to assess the feasibility of conducting an ITC for fenfluramine against stiripentol and cannabidiol it was therefore necessary to assess the comparability of their studies. Following the general approach outlined by Cope et al, 2014 [89], this was performed by first assessing the study designs and eligibility criteria, and the endpoints that were used to determine treatment effects. This was followed by assessment of baseline characteristics of patients enrolled in the trials to determine the degree of similarity in their baseline risks. In addition, quality assessment of the trials was conducted using guidance from '*Systematic reviews: CRD's guidance for undertaking reviews in health care'* (University of York Centre for Reviews and Dissemination) [80] to determine the risk of bias in study results.

B.2.9.2.1 Comparison of study designs, eligibility criteria and endpoint assessments

The comparability of the fenfluramine, stiripentol and cannabidiol study designs and eligibility criteria is summarised in Table 14. As convulsive seizures are associated with the most severe outcomes for patients with Dravet syndrome (see section B.1.3.1) assessment of comparability of the convulsive seizure reduction endpoints used as primary and key secondary endpoints in the trials was conducted. These included percentage reduction from baseline in convulsive seizure frequency compared with placebo and 50% responder rates (i.e., proportion of patients achieving at least a 50% reduction from baseline in convulsive seizure frequency). In addition to providing a robust measure of the clinical effects of the interventions, estimates of relative treatment effects in terms of reductions from baseline in convulsive seizures are required for the economic model (see section B.3).

Table 14. Comparability of study designs, eligibility criteria and endpoint assessment

	Study						
	Fenfluramine Study 1 [3]	**Fenfluramine Study 1504 [4]**	**Stiripentol STICLO-France [62]**	**Stiripentol STICLO-Italy [63]**	**Cannabidiol GWPCARE1 Part A [88]**	**Cannabidiol GWPCARE1 Part B [34]**	**Cannabidiol GWPCARE2 [35]**
Intervention and comparator	FFA 0.7mg/kg/day (max. 26mg/day) or FFA 0.2mg/kg/day or placebo	FFA 0.4mg/kg/day (max. 17mg/day) or placebo	STP 50mg/kg/day or placebo	STP 50mg/kg/day or placebo	CBD 5mg/kg/day or CBD 10mg/kg/day or CBD 20mg/kg/day or placebo	CBD 20mg/kg/day or placebo	CBD 10mg/kg/day or CBD 20mg/kg/day pr placebpo
Study design and size	Phase 3 placebo-controlled RCT (n=119)	Phase 3 placebo-controlled RCT (n=87)	Placebo-controlled RCT (n=41)	Placebo-controlled RCT (n=23)	Placebo-controlled RCT (n=34)	Phase 3 placebo-controlled RCT (n=120 in whole trial, but n=78 in the licensed subpopulation taking CLB)	Phase 3 placebo-controlled RCT (n=198 in the whole trial, but n=126 in the licensed subpopulation taking CLB)
Year(s) of conduct	2016–2018	2016–2018	1996-1998	1999-2000	2014-2015	2015	2015–2018
Study and treatment duration	6-week baseline, **3-week titration + 12-week maintenance**	6-week baseline, **2-week titration + 12-week maintenance**	1 month baseline, **2 months treatment**		4-week baseline, 3-week treatment (including titration)	4-week baseline, **2- week titration + 12-week maintenance**	
Eligibility	• Dravet syndrome • 2–18 years old • ≥4 convulsive seizures per 4- week period during previous 12 weeks prior to screening ≥6 convulsive seizures during 42-day baseline with ≥2 in first 3 weeks and ≥2 in last 3 weeks		• Dravet syndrome • 3–18 years old ≥4 generalised clonic or tonic-clonic seizures per month during baseline		• Dravet syndrome • 4-10 years old • <4 convulsive seizures during 4 week baseline	• Dravet syndrome • 2–18 years old ≥4 convulsive seizures during 28-day baseline	

	Study						
	Fenfluramine Study 1 [3]	**Fenfluramine Study 1504 [4]**	**Stiripentol STICLO-France [62]**	**Stiripentol STICLO-Italy [63]**	**Cannabidiol GWPCARE1 Part A [88]**	**Cannabidiol GWPCARE1 Part B [34]**	**Cannabidiol GWPCARE2 [35]**
Background medication	• No STP in the 21 days prior to screening • One or more stable AEDs • All other medications or interventions must be stable for ≥4 weeks prior to screening and are expected to remain stable throughout the study	• Receiving stable dose of CLB, and/or VPA, and 100% STP • All medications or interventions for epilepsy must be stable for ≥4 weeks prior to screening and are expected to remain stable throughout the study	• 100% receiving VPA + CLB		• One or more stable AEDs	• One or more stable AEDs • All medications or interventions must be stable for ≥4 weeks prior to screening and are expected to remain stable throughout the study	
Endpoints							
Convulsive seizure definition	Generalised tonic-clonic, tonic, clonic, tonic-atonic, hemiclonic, and focal seizures with an observable motor component		Generalised clonic or tonic-clonic		Tonic, clonic, tonic-clonic or atonic		
Reduction in convulsive seizures	% change in CSF between baseline and T+M periods (per 28 days) (primary endpoint) Parametric assessment of % reduction from baseline in convulsive seizure frequency per 28 days compared with placebo (i.e. the additional reduction over placebo)		% change from baseline in CSF after 1st month and after 2nd month of treatment period compared with baseline (secondary endpoint) **No assessment through whole treatment period** **No parametric assessment of % reduction from baseline in convulsive seizure frequency per 28 days compared with placebo (i.e. the additional reduction over placebo)**		NR	% change in CSF between baseline and T+M periods (per 28 days) (primary endpoint) Parametric assessment of % reduction from baseline in convulsive seizure frequency per 28 days compared with placebo (i.e. the additional reduction over placebo)	

	Study						
	Fenfluramine Study 1 [3]	**Fenfluramine Study 1504 [4]**	**Stiripentol STICLO-France [62]**	**Stiripentol STICLO-Italy [63]**	**Cannabidiol GWPCARE1 Part A [88]**	**Cannabidiol GWPCARE1 Part B [34]**	**Cannabidiol GWPCARE2 [35]**
50% responder rates (proportion achieving at least 50% reduction in convulsive seizure frequency	Reported on CSF over combined T+M period (per 28 days) (secondary endpoint)		Reported on CSF for 2nd month of treatment period compared with baseline (per 30 days) (primary endpoint) **No assessment through whole treatment period**		NR	Reported on CSF over combined T+M period (per 28 days) (secondary endpoint)	
Key: AED, antiepileptic drug; CBD, cannabidiol; CLB, clobazam; CSF, convulsive seizure frequency; FFA, fenfluramine; NR, not reported; RCT, randomized controlled trial; STP, stiripentol; T+M, titration and maintenance treatment period; VPA, valproate							

The GWPCARE1 Part A RCT of cannabidiol [88] met the inclusion criteria of the SLR (by virtue of its enrolled patient population, intervention and comparator, adverse event outcomes and trial design); however, it provides no efficacy data with which to compare against fenfluramine. This trial is therefore excluded from further consideration and the ITC.

The fenfluramine, stiripentol and remaining cannabidiol trial designs and eligibility criteria appear to be similar. All are placebo-controlled RCTs that assess the intervention as an add-on to standard of care AEDs, and so with this common comparator a network of evidence could potentially be formed. All trials recruited patients experiencing 4 or more convulsive seizures per month during their baseline assessment periods. Of note, the stiripentol trials were conducted 15-20 years earlier than both the fenfluramine and cannabidiol trials. The fenfluramine and cannabidiol trials were completed 2-5 years ago and may therefore reflect more contemporary clinical management of Dravet syndrome patients. Importantly, whilst the cannabidiol clinical trials enrolled patients taking cannabidiol with or without concomitant clobazam, cannabidiol was subsequently only licensed for use in combination with clobazam [14]; the relevant clinical evidence for comparing fenfluramine against cannabidiol should therefore be based on the relevant subgroup of the cannabidiol trials.

There are some differences across the studies in the reported definitions of convulsive seizures; all trials included tonic-clonic and clonic seizures but the fenfluramine trials also included focal seizures with a significant motor component among the included convulsive seizure types. However, integrated subgroup analyses indicate that, whilst fenfluramine clearly reduced the frequency of both focal seizures and generalised tonic-clonic seizures, the relative reduction in focal seizures compared with placebo was lower than the relative reduction in generalised tonic-clonic seizures compared with placebo [78] (see section B.2.6.1.1.1). The inclusion of focal seizures in the overall definition of convulsive seizures in the fenfluramine trials therefore suppresses the observed reduction in overall convulsive seizures observed with fenfluramine, and means that any indirect comparison of fenfluramine against stiripentol or cannabidiol, whose trials exclude focal seizures from the definition of convulsive seizures, will be conservative.

Convulsive seizures in all trials were assessed and recorded by caregivers of Dravet syndrome patients, which inevitably involves a degree of subjectivity; however, it seems reasonable to assume that the occurrence of convulsive seizures will have been recorded to a comparable extent across all studies. However, there are important differences in the assessment of convulsive seizure endpoints. Whilst the fenfluramine and cannabidiol trials were highly aligned in their assessment of convulsive seizure endpoints over the whole of their 14-15 week treatment periods, the stiripentol trials assessed convulsive seizure endpoints for only the last 4 weeks of only an 8-week treatment period. In addition, for the reduction in seizure frequency endpoint required for the economic model, the reported analyses in the stiripentol trials do not adjust for placebo. The stiripentol trial endpoint assessments are therefore not comparable with the endpoint assessments in the trials of fenfluramine and cannabidiol, and any attempt to compare their outcomes would be require strong assumptions in favour of stiripentol that would lead to biased results. These limitations in the stiripentol trial data therefore preclude a robust assessment of the convulsive seizure endpoints for fenfluramine compared with stiripentol.

B.2.9.2.2 Comparability of patient baseline characteristics

The baseline characteristics of patients enrolled in the fenfluramine, stiripentol and cannabidiol trials are presented in Table 15. Of note, the baseline characteristics of the cannabidiol trials relate to their full trial populations; the baseline characteristics of the subgroup receiving concomitant

clobazam (the subsequent licensed population) are not available in the primary cannabidiol trial publications or associated publications found in the SLR.

The trial patient characteristics are generally well balanced in terms of age, gender and number of concomitant AEDs received. Baseline convulsive seizure frequency per month is reasonably balanced across the studies. The placebo group in the fenfluramine Study 1 trial and both the stiripentol and placebo arms of the STICLO-Italy trial appear to have higher baseline convulsive seizure frequencies per month than the other arms and studies; however, some variation across the trial arms is to be expected given the heterogeneity of Dravet syndrome populations, and this is mitigated by the seizure endpoint assessments in the fenfluramine and cannabidiol trials, which estimate relative treatment effects for the interventions versus placebo as changes from baseline in convulsive seizure frequency. There are some differences in the proportions of patients receiving different concomitant AEDs, reflecting the eligibility criteria of the fenfluramine Study 1504 trial and the STICLO studies of stiripentol. However, the dose of fenfluramine is adjusted in Study 1504 to account for the pharmacokinetic interaction with stiripentol, and as each trial assesses the intervention as an add-on therapy to patients' individualised standard of care AEDs, a level of heterogeneity in the AEDs received is to be expected. Given the similarly high levels of baseline convulsive seizure frequencies across the different trials, and the fact each trial assesses relative treatment effects against standard of care, the assumption of a common standard of care effect irrespective of the individual components of that standard of care is justified. On this basis the numerical differences observed in the baseline characteristics of the trials do not preclude the use of these data in an ITC.

Table 15. Comparison of baseline characteristics across the fenfluramine, stiripentol and cannabidiol studies

	Study					
	Fenfluramine Study 1 [3]	**Fenfluramine Study 1504 [4]**	**Stiripentol STICLO-France [62]**	**Stiripentol STICLO-Italy [63]**	**Cannabidiol GWPCARE1 Part B [34]**	**Cannabidiol GWPCARE2 [35]**
N	119	87	41	23	120 (full population)	198 (full population)
Age – year (mean±SD)	9.0 ±4.65	9.1 ±4.80	~9.4	~9.0	9.8 ±4.8	9.3 ±4.4
Sex – no. (% male)	64 (54)	50 (57.5)	17 (41.5)	13 (6.5)	62 (52)	94 (47.5)
BMI – kg/m2 (mean±SD)	18.57 ±4.408	18.24 ±4.049	NR	NR	18.7±4.6	18.7±4.3
Race – no. (%)						
White	98 (82.4)	52 (59.8)	NR	NR	94 (78.3)	176 (88.9)
Black or African American	NR	3 (3.4)	NR	NR	4 (3.3)	5 (2.5)
Asian	7 (5.9)	3 (3.4)	NR	NR	1 (0.8)	5 (2.5)
American/Alaska Native	2 (1.7)	0 (0)	NR	NR	NR	1 (0.5)
Other/not reported/unknown	12 (10.1)	29 (33.3)	41 (100)	23 (100)	21 (17.5)	11 (5.6)
Region – no. (%)						
United States	70 (58.8)	22 (25.3)	0	0	72 (60)	93 (47)
Rest of world	49 (41.2)	65 (74.7)	41 (100)	23 (100)	48 (40)	105 (53)
No. of previous AEDs	NR	NR	NR	NR	4.6±3.8	Median 4
No. of concomitant AEDs	Mean 2.4	Mean 3.5	Mean 2.2	NR	Mean 2.9±1.0	Median 3

	Study					
	Fenfluramine Study 1 [3]	**Fenfluramine Study 1504 [4]**	**Stiripentol STICLO-France [62]**	**Stiripentol STICLO-Italy [63]**	**Cannabidiol GWPCARE1 Part B [34]**	**Cannabidiol GWPCARE2 [35]**
Convulsive seizures per 28 or 30 days	Per 28 days: FFA 0.2 mg/kg/day: median 17.5 (range 4.7– 623.5) FFA 0.7 mg/kg/day: median 20.7 (range 4.8–124.0) Placebo: median 27.3 (range 3.3–147.3)	Per 28 days: FFA 0.4 mg/kg/day: median 14.0 (range 2.7– 213.3) Placebo: median 10.7 (range 2.7–162.7)	Per 30 days: STP 50mg/kg/day: median 18 (IQR 4-73) Placebo: 19 (IQR 4-76)	Per 30 days: STP 50mg/kg/day: mean 27.4±28.6 Placebo: 33.6±28.2	Per 28 days: CBD 20 mg/kg/day: median 12.4 (range 3.9–1717) Placebo: median 14.9 (range 3.7–718)	Per 28 days: CBD 20 mg/kg/day: median 9.0 (range 3.9–661.2) (IQR 6, 21) CBD 10 mg/kg/day: median 13.5 (range 0–467.0) (IQR 6, 31) Placebo: median 16.6 (range 3.0–770.5) (IQR 7, 51)
AEDs – no. (%)						
Clobazam	70 (58.8)	82 (94.3)	41 (100)	23 (100)	78 (65)	126 (64)
Valproate, all forms	71 (59.7)	66 (75.9)	41 (100)	23 (100)	71 (59)	139 (70)
Stiripentol	0	87 (100)	0	0	51 (42)	71 (36)
Levetiracetam	26 (21.8)	10 (11.5)	0	0	33 (28)	54 (27)
Topiramate	30 (25.2)	21 (24.1)	0	0	31 (26)	46 (23)

Key: AED; antiepileptic drug; BMI, body mass index; CBD, cannabidiol; FFA, fenfluramine; NR, not reported; IQR, interquartile range; SD, standard deviation; STP, stiripentol.

B.2.9.2.3 Quality assessment of the trials

As a final assessment of the feasibility of conducting an ITC, quality assessment of the trials was conducted using guidance from '*Systematic reviews: CRD's guidance for undertaking reviews in health care'* (University of York Centre for Reviews and Dissemination) [80] to determine the risk of bias (Table 16).

The fenfluramine trials have been demonstrated to be at low risk of bias and provide high quality evidence of the benefits of fenfluramine, as discussed in section B 2.9.2.3. Assessment of the cannabidiol trials suggests these are generally also at low risk of bias. However, due to a lack of published baseline characteristics data in the subgroup of patients taking concomitant clobazam (i.e., the group in which cannabidiol is licensed) it is unclear whether the patients in the cannabidiol and placebo groups taking clobazam were similar at the outset of the study in terms of prognostic factors; the cannabidiol trials were not stratified by concomitant use of clobazam [34, 35]. Given that similar proportions of patients were taking clobazam in both the cannabidiol and placebo groups (60-68%) [34, 35], and the regulatory approval of cannabidiol based on these subgroup data [22], it is reasonable to assume that there were not significant imbalances that would significantly bias assessment of efficacy using the primary endpoint of reduction from baseline in monthly convulsive seizure frequency compared with placebo.

Quality assessment of the stiripentol trials indicates that these trials were at an unclear risk of bias. The STICLO-France study has been published in full [62] but lacks complete details on allocation concealment and patient withdrawal, and the STICLO-Italy study is published only as an abstract with limited details to determine the risk of bias. A Cochrane SLR published in 2017 (and used to inform this quality assessment of the stiripentol trials) notes discrepancies in the reporting of patient numbers for STICLO-Italy [60]. Both trials recruited small numbers of patients (21 patients treated with stiripentol in STICLO-France and 12 patients in STICLO-Italy), and therefore minor changes in patient numbers can amplify the relative treatment effects observed. In line with the conclusion of the Cochrane SLR, the evidence supporting stiripentol is of low to moderate quality due to an unclear risk of bias [60].

Table 16. Quality assessment of the fenfluramine and cannabidiol trials

Trial name	Fenfluramine Study 1 [3]	Fenfluramine Study 1504 [4]	Stiripentol STICLO-France [62]	Stiripentol STICLO-Italy [63]	Cannabidiol GWPCARE1 Part B [34]	Cannabidiol GWPCARE2 [35]
Was randomisation carried out appropriately?	Yes	Yes	Yes	Unclear: Abstract of study does not indicate randomisation, but an SLR by Kassai et al 2008 states was randomised.	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Unclear: computer generated list used for randomisation but no details of allocation concealment	Unclear: insufficient details in abstract	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes: Baseline demographics, medical history and concomitant therapies were generally balanced between the FFA and placebo study groups. There was variation in baseline CSF between groups. However, the mean baseline CSF (>30 convulsive seizures per month) was high in all treatment groups. Variation reflects heterogeneity in patients in clinical	Yes	Yes	Unclear: insufficient details in abstract	Yes: in full population Unclear: in the subgroup of patients taking concomitant CLB	Yes: in full population Unclear: in the subgroup of patients taking concomitant CLB

Trial name	Fenfluramine Study 1 [3]	Fenfluramine Study 1504 [4]	Stiripentol STICLO-France [62]	Stiripentol STICLO-Italy [63]	Cannabidiol GWPCARE1 Part B [34]	Cannabidiol GWPCARE2 [35]
	practice, and is mitigated by the approach to endpoint assessment that adjusts for baseline.					
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.	Unclear: trial was defined as "double-blind" with no further information	Unclear: trial was defined as "double-blind" with no further information	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.
Were there any unexpected imbalances in dropouts between groups?	No	No	Unclear: 4 patients on placebo and 1 patient on stiripentol dropped out during the double-blind period.	Unclear: 4 patients on placebo and 1 patient on stiripentol dropped out during the double-blind period	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	Unclear: published only as an abstract with few details	No	No

Trial name	Fenfluramine Study 1 [3]	Fenfluramine Study 1504 [4]	Stiripentol STICLO-France [62]	Stiripentol STICLO-Italy [63]	Cannabidiol GWPCARE1 Part B [34]	Cannabidiol GWPCARE2 [35]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Unclear: ITT analysis was stated, but 1 (4.5%) patient on stiripentol was excluded for non-compliance. No further details provided.	Unclear: published only as an abstract with few details	Yes	Yes

Abbreviations: AEDs, Anti-epileptic drugs; CLB, clobazam; CSF, convulsive seizure frequency; FFA, fenfluramine; ITT, Intention to treat; SD, standard deviation
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

B.2.9.2.4 Feasibility assessment conclusion

On the basis of the comparability of the fenfluramine and cannabidiol trials in terms of their trial designs, eligibility criteria and enrolled patient populations, their endpoint assessments, and the quality assessment that suggests a low risk of bias in their results, an ITC comparing fenfluramine against cannabidiol is judged to be feasible.

In contrast, due to substantial differences in the assessment of convulsive seizure reduction endpoints in the stiripentol trials, and also the unclear risk of bias that limits the quality of the stiripentol trial evidence, it is not feasible to conduct an ITC comparing fenfluramine against stiripentol. It is of note that the submitting company for the cannabidiol submission in NICE TA614 also concluded that it was not possible to conduct a robust ITC against stiripentol or other therapies [41] and the NICE appraisal committee, in making its positive recommendation for cannabidiol in the absence of either a direct or indirect comparison with stiripentol[12] has accepted this conclusion.

B.2.9.3 Methods of the ITC of fenfluramine versus CBD

B.2.9.3.1 Statistical methods

As relevant data are available from multiple trials of each intervention, the ITC was performed using network meta-analysis (NMA), rather than a simple Bucher ITC approach.

The ITC for percentage change from baseline in convulsive seizure frequency per 28 days compared to placebo (i.e., standard of care AEDs) aimed to evaluate relative treatment effects of fenfluramine and cannabidiol (with clobazam), and to provide efficacy inputs for the economic model. Therefore, an NMA was conducted for this endpoint. Frequentist and Bayesian approaches were considered and yielded consistent results; however, based on expert statistician advice, a Bayesian approach was deemed more technically correct to inform the economic model. This was conducted in the gemtc statistical package using R version 3.5.1. (using 4 chains, 20,000 iterations per chain) to provide relative treatment effects for fenfluramine and cannabidiol, using placebo as the reference. For the 50% responder rate endpoint (not used in the economic model) the aim of the ITC is to determine if there are significant differences between fenfluramine and cannabidiol in the proportion of patients achieving a meaningful (50%) reduction in convulsive seizures. As the dose of cannabidiol in the trials was titrated up to 10 or 20mg/kg/day and both a target dose of 10mg/kg/day and 20mg/kg/day was evaluated in the relevant clinical trials, the NMA provides odds ratios for fenfluramine against cannabidiol using two contrasts; one against cannabidiol 10mg/kg/day as the reference, and one against cannabidiol 20mg/kg/day as the reference. As the number of studies providing data is small and there is a lack of repetition of treatment comparisons in the network, fixed effect analyses were appropriately used.

B.2.9.3.2 Endpoint data used in the analyses

Table 17 summarises the relevant published data on the primary and key secondary endpoints of the fenfluramine and cannabidiol trials: percentage change from baseline in convulsive seizure frequency per 28 days, and the 50% responder rates. The cannabidiol data relate to the licensed subgroup receiving clobazam and are derived from the Epidyolex® Summary of Product Characteristics [14] in the absence of these data in the trial primary publications [34, 35].

For the percentage change from baseline in convulsive seizure frequency per 28 days the parametric analyses results were used, as the NMA requires inputs of the point estimates of the relative treatment effects and the standard errors for these effects – the standard errors are not available from the non-parametric analyses. As the published results of the parametric analyses are on the original scale, these were converted to log transformed relative rates prior to analysis (Table 17).

For the 50% responder rate data, the raw number of patients with a reduction in convulsive seizure frequency of at least 50% out of the total number of patients in the arm were included in the analysis.

Table 17. Endpoint data used in NMAs

Trial	Treatment	n	% change from baseline in CSF per 28 days		[redacted]	50% reduction in CSF (responder rate)	
			Median (range)	Parametric analysis (95% CI)		Number achieving (%)+	Odds ratio (95% CI)
Study 1 [3]	Placebo	40	-19.2 (-76.1–51.8)	Reference		5 (12.5)	Reference
	FFA 0.2 mg/kg/day	39	-42.3 (-100.0–197.6)	ANCOVA: -32.4 (-51.3, -6.2)a		15 (38.5)	4.8 (1.5, 15.5) d Unadj. 4.4 (1.4, 13.7)
	FFA 0.7 mg/kg/day	40	-74.9 (-100.0–196.4)	ANCOVA: -62.3 (-72.8, -47.7)a		27 (67.5)	15.0 (4.5, 49.9)d Unadj. 14.5 (4.6, 45.8)
Study 1504 [4]	Placebo	44	-1.1 (-82.8–435.1)	Reference		2 (4.5)	Reference
	FFA 0.4 mg/kg/day	43	-63.1 (-100.0–115.0)	ANCOVA: -54.0 (-67.2, -35.6)a		23 (53.5)	26.0 (5.5, 123.2) d Unadj. 24.2 (5.2, 112.6)
GWPCARE 1[b] [14]	Placebo w/ CLB	38	-18.9	Reference		9 (23.7)	Reference
	CBD 20 mg/kg/day w/ CLB	40	-53.6	Negative binomial regression: -42.8 (-60.4, -17.4)c		19 (47.5)	2.9 (1.1, 7.8)e Unadj. 2.9 (1.1, 7.7)
GWPCARE 2[b] [14]	Placebo w/ CLB	41	-37.6	Reference		15 (36.6)	Reference
	CBD 10 mg/kg/day w/ CLB	45	-60.9	Negative binomial regression: -37.4 (-54.5, -13.9)c		25 (55.6)	2.3 (1.0, 5.7)e Unadj. 2.2 (0.9, 5.1)
	CBD 20 mg/kg/day w/ CLB	40	-56.8	Negative binomial regression: -30.8 (-50.4, -3.6)c		25 (62.5)	3.3 (1.3, 8.3)e Unadj. 2.9 (1.2, 7.1)

Key: CBD, cannabidiol; CI, confidence interval; CLB, clobazam; CSF, convulsive seizure frequency; FFA, fenfluramine; Unadj., unadjusted

¶ [redacted]

+These data are used in the NMA for the 50% responder rates

[a] ANCOVA model with treatment group and age group (<6 years, ≥6 years) as factors, baseline CSF as a covariate and % change from baseline CSF during treatment period as response.

[b]Results for the subgroup of patients taking clobazam in Study 1504 taken from the Epidyolex® SmPC. Range around median not reported

[c]Negative binomial regression model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[d]Logistic regression model with treatment group and age group (<6 years, ≥6 years) as factors, log CSF at baseline as a covariate

[e]Logistic regression model.

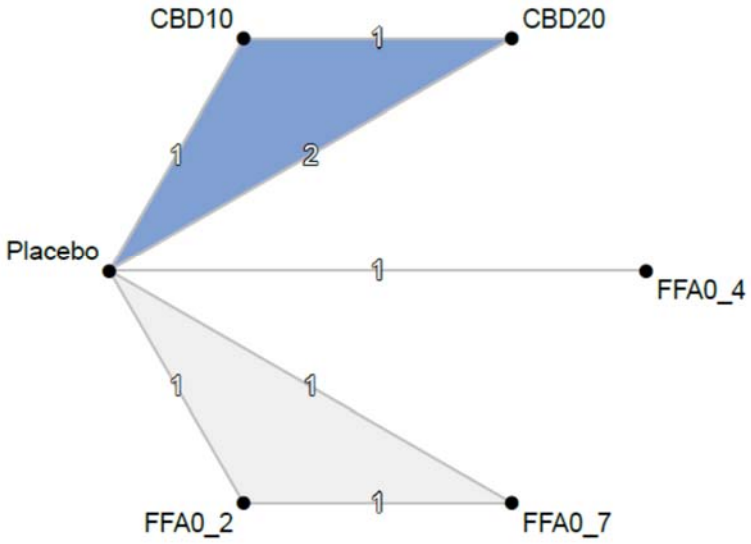
B.2.9.4 Results of the ITC of fenfluramine versus cannabidiol

B.2.9.4.1 Trial network and diagnostics

Figure 17 presents the plot of the four placebo-controlled trials forming the network for both endpoints considered in the ITC. Two trials (GPWCARE 1 and 2) provide data for cannabidiol 20mg/kg/day, with one trial providing data for cannabidiol titrated to 10mg/kg/day (GPWCARE 2) and one for each fenfluramine dose titration target (Study 1: fenfluramine 0.2mg/kg/day and 0.7mg/kg/day; Study 1504: fenfluramine 0.4mg/kg/day).

Given the small network, estimates of statistical heterogeneity are not possible/appropriate in these analyses; however, results (see B.2.9.4.2 and B.2.9.4.3) are consistent with expectations from the individual trial data and there is no evidence of inconsistencies between the direct and indirect evidence in the network. As the models converged sufficiently using the default settings of the gemtc R statistical package and are consistent with the expectations from the direct evidence, the results are sufficiently robust to draw conclusions on the relative treatment effects of fenfluramine versus cannabidiol, and to inform the relative treatment effects in the economic model (see section B.3.3.2.1).

Figure 17. Trial network for both outcomes



Key: CBD10, cannabidiol 10mg/kg/day with clobazam; CBD 20. Cannabidiol 20mgmg/kg/day with clobazam; FFA0_2, fenfluramine 0.2mg/kg/day; FFA0_4, fenfluramine 0.4mg/kg/day; FFA0_7, fenfluramine 0.7mg/kg/day

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B.2.9.4.2 Fenfluramine versus cannabidiol: percentage change from baseline in convulsive seizure frequency compared with placebo

Results of the NMA for the endpoint percentage change from baseline in convulsive seizure frequency are presented as relative rates on the log scale in Figure 18, with the back transformation to percentage reductions compared with placebo presented in Table 18. These results demonstrate that fenfluramine titrated to its anticipated licensed doses of 0.7mg/kg/day (maximum

26mg/day) when taken without concomitant stiripentol and 0.4mg/kg/day (maximum 17mg/day) when taken with concomitant stiripentol reduces the monthly frequency of convulsive seizures to a greater extent than cannabidiol at its licensed doses of 10-20mg/kg/day. The wide credible intervals for this endpoint preclude a claim of statistically significant differences, but the numerical differences clearly favour fenfluramine: the placebo-adjusted reduction in monthly convulsive seizure frequency was [redacted] with the recommended doses of fenfluramine, compared with [redacted] with cannabidiol.

Figure 18. NMA forest plot: Log-transformed relative rates of change from baseline in convulsive seizure frequency compared with placebo

Key: CBD10, cannabidiol 10mg/kg/day with clobazam; CBD 20. Cannabidiol 20mgmg/kg/day with clobazam; FFA0_2, fenfluramine 0.2mg/kg/day; FFA0_4, fenfluramine 0.4mg/kg/day; FFA0_7, fenfluramine 0.7mg/kg/day. Figure generated in MetaInsight to provide mean differences.

Table 18. NMA: Mean percentage change from baseline in convulsive seizure frequency compared with placebo (back transformed from logged relative rates to original scale)

Treatment	Mean (95%CrI) % change from baseline in CSF vs placebo*
Cannabidiol 10mg/kg/day	[redacted]
Cannabidiol 20mg/kg/day	[redacted]
Fenfluramine 0.2mg/kg/day	[redacted]
Fenfluramine 0.4mg/kg/day	[redacted]
Fenfluramine 0.7mg/kg/day	[redacted]

* Back transformed from logged relative rates as -100*(1-EXP(LogRR))
Note, small variations in probabilistic calculations with different runs of the MCMC generates small variations in estimates, compounded by back transformation of rounded results .
Results here are the values used in the economic model (see B.3.3.2.1)

B.2.9.4.3 Fenfluramine versus cannabidiol: 50% responder rates

Results of the NMA for the 50% responder rates endpoint using cannabidiol 10mg/kg/day and 20mg/kg/day as the reference are presented in Figure 19. With odds ratios in the range [redacted], and no overlap of 1.0 by the credible intervals, these analyses indicate that a statistically significantly greater proportion of patients treated with the anticipated licensed doses of fenfluramine achieve at least a clinically meaningful 50% reduction in convulsive seizure frequency compared with cannabidiol (with clobazam) at its licensed doses.

Figure 19. NMA forest plots: 50% responder rates

B.2.9.5 Long-term comparative effectiveness of fenfluramine versus cannabidiol

The ITC is appropriately based on the most robust RCT data available for fenfluramine and cannabidiol, which provide comparable assessment of endpoints over comparable treatment periods of up to 14-15 weeks. However, Dravet syndrome is a life-long disease requiring ongoing treatment.

Both fenfluramine and cannabidiol have longer-term data available from OLE studies. Whilst it is not possible to conduct formal, robust comparisons of these OLE data it is possible to consider the long-term data they each provide on a qualitative basis. Study 1503, the OLE study of the fenfluramine trials, demonstrates the reductions in convulsive seizure frequency with fenfluramine observed in Study 1 and Study 1504 over 14-15 weeks of treatment are maintained with long-term treatment; a median reduction from baseline of [redacted] over up to 2 years of treatment suggests no evidence of a waning of treatment effect with fenfluramine [78] (see section B.2.6.2). In contrast, the Summary of Product Characteristics (SmPC) for cannabidiol reports that, in the GWPCARE5 OLE study of the cannabidiol trials, the median percentage reduction from baseline in convulsive seizure frequency in the subgroup taking cannabidiol with clobazam was 60% during Week 1-12, but was 45% by Week 37-48 [14]. This represents a 25% relative reduction in efficacy over less than a year, suggesting a potential waning of effect of cannabidiol over time. The SmPC does not provide details on cannabidiol dosing over the course of the OLE in patients taking cannabidiol with clobazam (the licensed population). However, in a published interim analysis of the GWPCARE5 OLE study, in which patients recruited from both the GWPCARE1 and 2 studies (68% taking concomitant clobazam) were titrated to cannabidiol 20mg/kg/day, with doses reduced or increased up to 30mg/kg/day (outside the licensed dose) based on response and tolerance, the mean modal dose of cannabidiol over 48 weeks of treatment was 21.2mg/kg/day [67]. A waning of cannabidiol treatment effect and dosing towards the top end of the 10-20mg/kg/day dose range recommended in the SmPC [14] therefore seem plausible in practice.

Based on these data it is reasonable to conclude that the clear superior efficacy of fenfluramine over cannabidiol demonstrated in the ITC based on RCT data will be at the very least maintained over the long term, and it is plausible that the relative treatment effects of fenfluramine over cannabidiol may actually increase over time due to the waning of effects of cannabidiol.

B.2.9.6 Conclusions of the ITC

Based on the SLR described in Appendix D, there are no RCT data supporting the use of clobazam in the treatment of Dravet syndrome. Stiripentol is supported by 2 RCTs; however, a detailed ITC

feasibility and quality assessment indicates these provide only low to moderate quality evidence and their endpoints, which assess efficacy over only 4 weeks, are incompatible with those of the trials of fenfluramine (and cannabidiol). These data and evidence limitations for stiripentol and clobazam therefore preclude an ITC of fenfluramine against these therapies.

A robust ITC was possible for fenfluramine versus cannabidiol (with clobazam) and indicates clearly that fenfluramine is superior to cannabidiol in reducing convulsive seizure frequency. Given the evidence of sustained and durable efficacy with long-term fenfluramine treatment, the superior efficacy of fenfluramine versus cannabidiol is expected to persist over the long-term. Collectively, the comparative evidence supporting fenfluramine is more complete and of a higher quality than that for other therapies that are recommended by NICE and indicates that fenfluramine is superior in reducing convulsive seizure outcomes versus cannabidiol (with clobazam), the only other therapy with data to permit a robust ITC.

Whilst it is not possible to make a robust ITC for fenfluramine against other NICE-recommended add on therapies, the comparison with cannabidiol (with clobazam) is highly relevant to the decision problem. Cannabidiol (with clobazam) was accepted by NICE as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway in 2019. At the point of the first appraisal committee meeting for this current appraisal, cannabidiol (with clobazam) will have been an established treatment option for UK patients for over a year. Given the need for new therapies in Dravet syndrome (see section B.1.3.1.2), and the recent downgrading of its controlled drug prescribing requirements (see section B.1.3.3.3), use of cannabidiol (with clobazam) is anticipated to continue to increase. As the ITC provides robust evidence of the clinical efficacy of fenfluramine against cannabidiol (with clobazam) in similar patient populations, and confirms that fenfluramine is superior, it is anticipated that fenfluramine would be used as an alternative add-on therapy to cannabidiol (with clobazam), and by extension would an alternative to stiripentol. A primary clinical and economic comparison against cannabidiol (with clobazam) is therefore the most appropriate comparison to determine the clinical and cost effectiveness of fenfluramine in the existing add-on therapy pathway.

B.2.10 Adverse reactions

- Comprehensive safety and tolerability data are available from two phase 3 RCTs, an OLE study providing data for up to 3 years of treatment, and real-world observational data in patients treated with fenfluramine for up to 27 years
- In the phase 3 RCTs, the most common adverse events (of any severity) with fenfluramine were decreased appetite, diarrhoea, and weight loss >7%. Of note, weight loss was often regained with continued treatment, and decreased appetite and weight loss are listed as common/very common adverse events with stiripentol and cannabidiol in their respective SmPCs.
- The number of patients experiencing serious or severe treatment-emergent adverse events was low and similar in both the fenfluramine and placebo arms, and there was little difference in the number experiencing serious treatment-related adverse events between fenfluramine and placebo in either Study 1 ([redacted]) or Study 1504 ([redacted]). Few patients experienced adverse events leading to discontinuation (12.5% in Study 1 and 4.7% in Study 1504).
- There were no cases of mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension (adverse events of special interest) in the RCTs, or the open-label extension study in which 330 patients were treated for up to 3 years, or the prospective observational study of up to 5 years of treatment.
- A comprehensive risk management plan will specify requirements for echocardiogram and other measures to mitigate the potential for cardiorespiratory or other adverse events in patients in practice.
- **Collectively, the RCTs, OLE and real-world observation studies demonstrate that the efficacy of fenfluramine is achieved with good tolerability and few treatment-related adverse effects.**

Safety data are summarised in this section for the Study 1 and Study 1504 RCTs, Study 1503 OLE, and the Belgian RWE cohorts and US expanded access program. Collectively, these data support the short and long-term safety and tolerability of add-on treatment with fenfluramine. A comprehensive risk management plan has been developed to mitigate any residual potential risks based on its known adverse event profile when used at much higher doses than in Dravet syndrome.

B.2.10.1 Exposure data across RCTs, OLE and RWE studies

Across the phase 3 Study 1 and Study 1504 RCTs, 122 patients were exposed to fenfluramine for up to 16-17 weeks. In Study 1 the mean (SD) treatment duration for the fenfluramine arms was 103.3 (26.4) days and 113.1 (6.2) days for the 0.7 mg/kg/day and 0.2 mg/kg/day doses, respectively. In Study 1504, mean (SD) treatment duration with fenfluramine 0.4 mg/kg/day was 110.8 (29.9) days. In the placebo arms, the mean (SD) treatment duration was 107.2 (21.1) days and 117.9 (13.00) days for Study 1 and Study 1504, respectively [75, 76].

In the Study 1503 OLE study, which was prospectively designed to evaluate the long-term safety of fenfluramine, 330 patients have been exposed to target doses of fenfluramine for up to 3 years; the median duration of treatment exposure at the Day 120 Safety update cut-off (14 October 2019) was 631 days (range 7 to 1086) [87]. In observational real-world settings, exposure to daily treatment with fenfluramine ranged 1-27 years [71, 72, 77, 90]; in the cohort with the longest follow-up the mean total fenfluramine treatment duration was 16.1 years (range 6 to 27 years)[71].

B.2.10.2 Summary of Treatment Emergent Adverse Events (TEAEs)

Summary safety data across prospective studies are presented in Table 19. The number and percentage of subjects in each treatment group who experienced an adverse event that occurred in ≥5% of subjects, presented by system organ class and preferred term, are summarised in Appendix F.

Table 19: Summary of safety data for fenfluramine across prospective studies

Number[a] (%)[b] of subjects with safety event	Study 1 [3, 75]			Study 1504 [4, 76]		Study 1503 [87]	Belgian cohort [72]
	Placebo (N=40)	FFA 0.2 mg/kg/day (N=39)	FFA 0.7 mg/kg/day (N=40)	Placebo (N=44)	FFA 0.4 mg/kg/day (N=43)	FFA OLE 0.2-0.7 mg/kg/day (N=330)	FFA ≤17 mg/day (N=9)
Subjects with any TEAE occurring in ≥5%	26 (65.0)	37 (94.9)	38 (95.0)	42 (95.5)	42 (97.7)	[redacted]	9 (100)
Treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3 (33.3)
Serious TEAE	4 (10.0)	4 (10.3)	5 (12.5)	7 (15.9)	6 (14.0)	[redacted]	NR
Serious TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	0 (0.0)
Treatment-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Subjects with any AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Serious AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
AESI leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]	0 (0.0)
Treatment-related AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Treatment-related serious AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Adverse events leading to discontinuation	0 (0.0)	0 (0.0)	5 (12.5)	1 (2.3)	2 (4.7)	[redacted]	0 (0.0)
AESI leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)

Abbreviations: FFA, fenfluramine; TEAE, treatment emergent adverse event;
Sources: CSR Study 1, August 2019; CSR Study 1504, December 2018; Responses to day 120 regulatory questions (Data on file – Confidential), plus associated study publications

B.2.10.2.1 TEAEs in Phase 3 RCTs — Study 1 and Study 1504

The majority of patients experienced a treatment-emergent adverse events (TEAE) in both the fenfluramine and placebo arms of Study 1 and Study 1504. The most common (≥10%) TEAEs, irrespective of severity and whether treatment-related or not, are summarised in Table 20. There was a greater incidence of TEAEs among patients treated with fenfluramine, most noticeably decreased appetite and diarrhoea. The incidence of weight loss (>7% body weight) was also higher in patients receiving fenfluramine than placebo; however, there were few discontinuations due to decreased appetite, diarrhoea or weight loss [3, 4], and with continued treatment weight loss is often regained (see B.2.10.5.1).

Table 20. Non-cardiovascular adverse events occurring in ≥10% of patients in any study group – Study 1 and Study 1504

	Study 1 [3]			**Study** 1504 [4]	
TEAE, n (%)	**Placebo (n=40)**	**FFA 0.2 mg/kg/day (n=39)**	**FFA 0.7 mg/kg/day (n=40)**	**Placebo (n=44)**	**FFA 0.4 mg/kg/day (n=43)**
At least 1 TEAE	26 (65)	37 (95)	38 (95)	42 (96)	42 (98)
Decreased appetite	2 (5)	8 (20)	15 (38)	5 (11)	19 (44)
Diarrhoea	3 (8)	12 (31)	7 (18)	3 (7)	10 (23)
Fall	2 (5)	4 (10)	0	0	0
Fatigue	1 (2)	4 (10)	4 (10)	2 (5)	11 (26)
Lethargy	2 (5)	4 (10)	7 (18)	2 (5)	6 (14)
Nasopharyngitis	5 (12)	4 (10)	7 (18)	15 (34)	7 (16)
Pyrexia	8 (20)	7 (18)	2 (5)	0	0
Seizure	5 (12)	4 (10)	3 (8)	7 (16)	2 (5)
Somnolence	3 (8)	6 (15)	4 (10)	0	0
URTI/Bronchitis	5 (12)	8 (21)	0	2 (5)	5 (12)
Vomiting	4 (10)	4 (10)	3 (8)	0	0
Weight loss >7%	1 (2.5)	5 (13)	8 (20)	2 (4.5)	9 (20.9)

Abbreviations: FFA, fenfluramine; TEAE, treatment emergent adverse event; URTI, upper respiratory tract infection
Sources: CSR Study 1, August 2019; CSR Study 1504, December 2018; plus associated study publications

A greater proportion of patients receiving fenfluramine experienced TEAEs that were considered to be treatment-related compared with placebo; however, the number of patients experiencing serious or severe TEAE was low and similar in both the fenfluramine and placebo arms, and there was no real difference in the number experiencing serious treatment-related TEAEs between fenfluramine and placebo in either Study 1 [redacted] or Study 1504 [redacted] (Table 19) [75, 76]. On this basis, the addition of fenfluramine to standard of care AEDs does not appear to increase the number of difficult-to-treat or resource intensive adverse events.

B.2.10.2.2 TEAEs in Open label extension and RWE studies

As in the RCTs, the majority of patients receiving fenfluramine in the OLE study experienced a TEAE; however, only [redacted] of 330 patients treated for up to [redacted] years experienced a serious TEAE that was classed as related to fenfluramine treatment (Table 19) [87], confirming the long term-safety of ongoing treatment with fenfluramine.

In the prospective real world observational study in Belgium all 9 patients experienced TEAEs during up to 5 years of treatment, including somnolence (n = 5), anorexia (n = 4), fatigue (n = 3),

sleep difficulties (n = 2) and non-convulsive status epilepticus (n = 3) [72]. Several of these are generally recognised as adverse events with other AEDs that may have been used in the patients' treatment regimens and the extent to which these were fenfluramine treatment related is not stated. Similarly, in the US expanded access program, in 23 patients treated for up to 180 days, the most common adverse events included fever (30%), decreased appetite (17%), and emesis (13%). The majority were classed as mild-to-moderate in intensity and there is no indication of whether these are fenfluramine treatment-related [73].

B.2.10.3 Serious adverse events, treatment discontinuations and deaths

B.2.10.3.1 Phase 3 RCTs

The incidence of serious TEAEs in Study 1 and Study 1504 was low (10-15%) and was similar across their fenfluramine and placebo groups (Table 19), and few TEAEs led to treatment discontinuation.

In Study 1, 5 (12.5%) patients in the 0.7 mg/kg/day group had at least 1 adverse event leading to study discontinuation [redacted] compared to none in the other treatment groups [3, 75]. In Study 1504, 1 (2.3%) patient in the placebo group [redacted] and 2 (4.7%) patients in the fenfluramine 0.4 mg/kg/day group [redacted] had at least 1 TEAE that led to study drug discontinuation. No patients died in either study [4, 76].

B.2.10.3.2 Open label extension and RWE studies

During the Study 1503 OLE study, [redacted] out of 330 [redacted] %) experienced at least 1 serious TEAE during up to [redacted] years of treatment; however, only [redacted] experienced treatment-related serious TEAEs (Table 19), and only [redacted] patients discontinued due to a TEAE. [redacted]

In the Belgian prospective real-world observational study 3 patients experienced non-convulsive SE events that were considered serious TEAEs. One patient, who was hospitalised 11 times for SE before the addition of fenfluramine, experienced 4 separate episodes of SE with fever due to respiratory infection during the 4.7 years of treatment with fenfluramine. No patients were reported to have discontinued fenfluramine due to TEAEs, and there were no deaths reported [72]. Data on the number of severe TEAEs, discontinuations or deaths are not reported for the 23 patients in the US Expanded access program [73].

B.2.10.4 Adverse events of special interest (AESI)

Fenfluramine was previously marketed at significantly higher doses of 60-120mg/day as an appetite suppressant for the treatment of obesity but was withdrawn from the market over 20 years ago due to its reported association with valvular heart disease. Based on its known adverse event profile and mode of action, the incidence of adverse events of special interest (AESI) listed in Table 21 were identified for collection in the protocols of the phase 3 Study 1 and Study 1504 RCTs and the Study 1503 OLE study. Whilst there were numerical differences between fenfluramine and

placebo in the incidence of some AESIs in RCTs, none were found to be serious or led to study discontinuation. The OLE and real-world observational studies confirm the safety of tolerability of long-term treatment with fenfluramine.

Table 21. AESIs in the phase 3 RCTs and OLE study

Number[a] (%)[b] of subjects with safety event	Study 1 [75]			Study 1504 [76]		Study 1503 [87]
	Placebo (N=40)	FFA 0.2 mg/kg/day (N=39)	FFA 0.7 mg/kg/day (N=40)	Placebo (N=44)	FFA 0.4 mg/kg/day (N=43)	FFA OLE 0.2-0.7 mg/kg/day (N=330)
Subjects with any AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
Mitrial valve incompetence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
Tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations						
Blood glucose decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure diastolic increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure systolic increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood prolactin increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac murmur	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Echocardiogram abnormal[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AESI, adverse event of special interest; FFA, fenfluramine; NR, not reported; OLE, open-label extension.
a A subject with more than one TEAE with the same preferred term is counted once for that term. A subject with more than one TEAE under a system organ class is counted once for that class.
b Percentages are calculated based on the number of subjects in the safety population.
d All ECHO abnormalities were limited to trace regurgitation [redacted]

Sources: Study 1 CSR, August 2019; Study 1504 CSR, December 2018; Responses to day 120 regulatory questions (Data on file – confidential)

B.2.10.4.1 Phase 3 RCTs

The number of patients reported to have had at least 1 AESI during treatment in the phase 3 trials is summarised in Table 21. In Study 1 patients treated fenfluramine 0.7 mg/kg/day patients treated with fenfluramine 0.2 mg/kg/day experienced at least one AESI, compared with of patients receiving placebo. In Study 1504, there was no difference in the overall incidence of AESI between the fenfluramine and placebo arms patients in each arm). None of the AESIs in the fenfluramine arms in either study was rated as serious and none led to study discontinuation [75, 76].

Where differences in the incidence of AESIs existed between fenfluramine and placebo these are primarily due small differences in the numbers of patients experiencing and Of note, the observed with fenfluramine in Study 1 was not observed with fenfluramine in Study 1504; indeed, the incidence of in Study 1504 was higher with placebo than with fenfluramine, and the incidence with placebo in Study 1504 was similar to the incidence with fenfluramine in Study 1. For abnormal echocardiogram findings, the incidence was numerically higher with fenfluramine than with placebo in both studies; however, all were limited to trace regurgitation (which is not a pathological finding) except for who discontinued and was later found to have had pre-existing There were no cases of mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension observed in any patients at any time during the studies [3, 4, 75, 76].

B.2.10.4.2 Open label extension and RWE studies

The overall incidence of AESIs in 330 patients treated with fenfluramine for up to 3 years was comparable with that seen in the phase 3 RCTs (Table 21). The most frequently reported AESIs included v v No unexpected findings or new or concerning safety signals were observed [87].

In the prospective real-world observational study in Belgium, there was no evidence of change in cardiac valve structure or function nor were there any echocardiogram findings suggestive of pulmonary arterial hypertension in any patient during up to 5 years of treatment [72], and in the US Expanded access program no patient developed valvular heart disease or pulmonary arterial hypertension during up to 180 days of treatment [73]. Collectively, these data support the general and cardiovascular safety of long-term treatment with fenfluramine.

B.2.10.5 Other observations related to safety and tolerability

B.2.10.5.1 Weight loss

Weight loss occurred more frequently in subjects randomised to the fenfluramine treatment groups in the RCTs, Interpretation of these data is complicated by the fact that other AEDs list weight loss amongst their adverse effects, including stiripentol (very common) [13] and cannabidiol (common) [14], and there is some evidence to suggest that Dravet syndrome may be associated with reduced weight growth

independently of AED therapy [91]. Importantly, [redacted] of patients who experienced weight loss in the trials recovered or resolved weight loss by the time of the data cut of the OLE study, with time to resolution ranging from [redacted]

B.2.10.5.2 Suicidal ideation

The Columbia-suicide severity rating scale (C-SSRS) was administered at every visit to children and adults over 7 years in all studies of psychoactive agents. In patients who were capable of completing the rating scale, [redacted] Study 1 reported an instance of suicidal ideation and suicidal behaviour as per the C-SSRS. In Study 1504, [redacted] in the fenfluramine 0.4 mg/kg/day group [redacted] reported to engage in self-injurious behaviour on the C-SSRS without suicidal intent-SSRS, at baseline and through the study [75, 76]. In Study 1503, of the [redacted] who completed the C-SSRS at baseline (Visit 1 of OLE) and during the OLE period, [redacted] during Visit 1 of OLE and at subsequent study visits. [redacted]

B.2.10.5.3 Cognition and executive function

Behaviour Rating Inventory of Executive Function (BRIEF) and the preschool version (BRIEF-P) instruments, which measure multiple aspects of executive functioning, were assessed by the parent/caregiver during Study 1 and Study 1504. Based on Inhibitory Behavioural Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC) there was no significant worsening in cognition and executive function with addition of fenfluramine to standard of care AEDs; indeed, in Study 1, fenfluramine treatment resulted in significantly improved ratings for BRI and GEC compared with placebo [75, 76]. There was no deterioration or worsening in cognition and executive function with longer-term treatment in the OLE study [70].

B.2.10.6 Risk management plan

Given the mode of action and known adverse event profile of fenfluramine when used at much higher doses than used in Dravet syndrome, a comprehensive risk management plan is expected to specifically address the risks of weight loss, valvular heart disease, and pulmonary hypertension. Details are to be confirmed and will be provided if they become available during the appraisal process.

B.2.11 Ongoing studies

Ongoing studies of fenfluramine include:

- **Study 1503:** This open-label extension study is currently ongoing, with additional data cuts expected throughout 2020.
- **Study 2:** This is the second cohort from the double-blind 1501 and 1502 studies is currently ongoing, with final study results expected in 2H 2020.

- **Study 1601:** This is an international, multicentre, open-label, long-term safety study of fenfluramine in patients with epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Dravet syndrome patients currently enrolled in Study 1503, or in any other company-sponsored study by invitation, are eligible to participate. The study commenced in April 2019, will provide safety and efficacy data for up to a further 3 years of treatment. Primary completion is expected in 2023 [92].

B.2.12 Innovation

Fenfluramine is a novel add-on AED. It has a different mode of action to other therapies used in Dravet syndrome and, in contrast to stiripentol (Diacomit®) and cannabidiol (Epidylex®), which are only licensed for use in combination with clobazam [13, 14], it is anticipated to be licensed for use with or without concomitant clobazam. This ability to use fenfluramine irrespective of clobazam use means it may be used at any point in the add-on therapy pathway. As patients with Dravet syndrome have fewer treatment options available than patients with other epilepsies, this distinctive benefit has the potential to expand, in a meaningful way, the treatment options available to patients and clinicians.

Dravet syndrome is a very rare, severe orphan disease, with seizures that are refractory to existing AED therapies [2, 43]. Despite this context, fenfluramine at its recommended maintenance doses has been demonstrated robustly in phase 3 clinical trials to provide substantial reductions in mean convulsive seizure frequency, of the order of 62.3% over and above placebo when added to standard of care AEDs without stiripentol, and 54% over and above placebo when added to standard of care AEDs containing stiripentol. Significantly more patients on fenfluramine than placebo achieved a 50% responder rate (i.e., a clinically meaningful reduction in convulsive seizures) and, in a robust ITC, statistically significantly greater proportions of patients treated with fenfluramine achieved this endpoint than did patients treated with cannabidiol (see Section B.2.9). Furthermore, a third to a half of patients treated with fenfluramine achieved a 75% responder rate (i.e. a profound reduction in convulsive seizures). From high baseline convulsive seizure frequencies, fenfluramine treatment provided 12-25% of patients with near-complete seizure freedom (<1 convulsive seizure per month), and significantly increased their number of seizure-free days [3, 4]. Data from open-label extension and real-world observational studies confirm these benefits are durable and sustained in the long-term, with good tolerability and safety [71-73, 76, 78].

Given the clear relationships between convulsive seizure frequency, patient morbidity and mortality, and patient and caregiver quality of life, the dramatic reductions in convulsive seizure frequency demonstrated with the addition of fenfluramine to the most effective AEDs currently available are potentially life-changing for a high proportion of patients, their families and caregivers. Combined with its ability to be used at any point in the add-on therapy pathway, without reliance on the use of concomitant clobazam, fenfluramine provides a step change in the treatment of Dravet syndrome that qualify it as an innovative therapy.

B.2.13 Interpretation of clinical effectiveness evidence

Dravet syndrome remains one of the most difficult to treat childhood-onset epilepsy syndromes, with patients suffering frequent, severe, intractable, and prolonged convulsive seizures. The aim of current treatment is to reduce the overall frequency and increase the time between convulsive

seizures, thereby lowering the risk of hospitalisations and mortality, reducing the impact of seizures on developmental comorbidities, and improving patient and caregiver quality of life. Despite the availability of licensed add-on therapies in Dravet syndrome – stiripentol and cannabidiol – treatment options remain limited, and many patients remain refractory to treatment, with a high seizure burden.

There is a clear unmet need in Dravet syndrome for new treatment options that minimise the frequency of convulsive seizures, increase the number of seizure-free days, whilst maintaining a favourable safety and tolerability profile.

B.2.13.1 Summary of clinical evidence base

Despite the challenges of the rarity of the disease and heterogeneity that is inherent in small, difficult to manage patient populations, the clinical efficacy and safety of fenfluramine as an add-on therapy to standard of care AEDs in Dravet syndrome has been established through a robust clinical development programme. This includes two high-quality phase 3 RCTs providing efficacy and safety data through 16-17 weeks of treatment exposure in children and young adults (Study 1 [n=119]) [3] and Study 1504 [n=87] [4]), an OLE study (Study 1503) providing long-term efficacy and safety data in 330 children and young adults with treatment periods up to 3 years [70, 79], two real-world observational studies providing efficacy and safety data in 21 children and adults, some treated with fenfluramine for up to 27 years [71, 72, 77], and expanded access programs [73, 74].

B.2.13.1.1 Efficacy and safety in phase 3 RCTs

Fenfluramine at its recommended maintenance doses provided substantial, significant reductions in mean convulsive seizure frequency: 62.3% over placebo when added to standard of care AEDs without stiripentol (Study 1), and 54% over placebo when added to standard of care AEDs containing stiripentol (Study 1504). The reduction in convulsive seizure frequency was achieved rapidly, within 1 to 2 weeks of reaching the assigned dose of fenfluramine, and was consistent over the entire treatment period in both studies [3, 4]. Exploratory and *post hoc* analyses indicate fenfluramine provided similar, significant reductions in convulsive seizures irrespective of age [78]. Furthermore, results were consistent irrespective of concomitant AEDs (with or without clobazam or valproate) [78, 81] or prior use of stiripentol treatment [78, 81, 82]. These data therefore support the initiation and use of fenfluramine across all age groups, and at any point across the current add-on therapy pathway.

Significantly more patients on fenfluramine than placebo achieved a clinically meaningful reduction in convulsive seizures of at least 50% in both RCTs: 68% vs 12% in patients not receiving stiripentol, and 54% vs 5% in patients receiving concomitant stiripentol. Furthermore, a third to a half of patients treated with fenfluramine achieved a 75% responder rate, indicating that a profound reduction in monthly convulsive seizure frequency is achieved in one out of every 2-3 patients treated with fenfluramine rather than continued treatment with their current standard of care AED regimen, including in those currently taking stiripentol. From high baseline convulsive seizure frequencies, fenfluramine treatment provided 12-25% of patients with near-complete seizure freedom (<1 convulsive seizure per month), and significantly increased their number of seizure-free days. [3, 4]. Fenfluramine therefore provided dramatic, clinically meaningful improvements in convulsive seizure control in high proportions of Dravet syndrome patients who were inadequately controlled on combinations of the most effective AEDs currently available.

Fenfluramine also reduced the frequency of non-convulsive and total seizures in the trials. Although the change from baseline was statistically significant in Study 1 only, the numerical benefit in non-convulsive seizure reduction in Study 1504 confirms that the benefit of fenfluramine in reducing convulsive seizures is not at the expense of an increase in non-convulsive seizures.

In addition to improvements in seizure-related outcomes, data from Study 1 and Study 1504 indicate a general pattern of improvement in patients' day-to-day functioning and both patients' and carers' quality of life with fenfluramine treatment [3, 4, 75, 76]. Results from the CGI-I, a holistic assessment of the overall clinical status of patients, showed that more patients taking fenfluramine vs placebo were rated by their parent/caregiver and the study investigator as 'very much' or 'much improved', ratings that represent clinically meaningful changes. These positive effects were reflected in directional improvements in disease specific (QOLCE, PedsQL) measures of patient quality of life, and in caregiver quality of life assessed using the EQ-5D-5L instrument [75, 76].

Fenfluramine was generally well tolerated in the RCTs. There was a greater incidence of decreased appetite, as may be expected with an agent previously used at higher doses as an anorectic, and diarrhoea. The incidence of weight loss (>7% body weight) was also higher in patients receiving fenfluramine than placebo; however, there were few discontinuations due to these or other TEAEs [3, 4] and, importantly, initial weight loss was often regained. There was no real difference between fenfluramine and placebo in the number experiencing serious treatment-related TEAEs in either study, which indicates the addition of fenfluramine to standard of care AEDs does not appear to increase the number of difficult or resource intensive adverse events. There were no cases of mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension observed in any patients at any time during the studies [3, 4, 75, 76]. Assessment using the BRIEF instrument indicated that fenfluramine treatment did not worsen cognition and executive function, and in Study 1 fenfluramine treatment actually resulted in significantly improved ratings for behavioural regulation and global executive function indices compared with placebo [75, 76].

B.2.13.1.2 Long-term efficacy and safety

Data from the open-label extension and real-world observational studies clearly demonstrate that the dramatic improvements in seizure control and the safety and tolerability of fenfluramine observed in the phase 3 RCTs are durable and sustained with long-term treatment over several years.

Based on the interim analyses of Study 1503 (data cut-off March 2018, n=158 with known treatment allocation in Study 1 and Study 1504), the significant reductions in convulsive seizure frequency and responder rates were maintained for up to 2 years of therapy. The median interval between convulsive seizures for all patients was approximately [redacted] which given median convulsive seizure frequencies at baseline in the trials ranged 10-27 per month is a profound increase in seizure-free interval. All patients had [redacted] of rescue medication use at Month 12 compared to their pre-double-blind baseline and Month 1 of the OLE. In addition, CGI-I ratings of much/very much improved by parents/caregivers and investigators [redacted] and quality of life assessment using QOLCE showed [redacted] across all domains [70].

Updated analyses in 330 patients, with treatment duration up to 3 years (data cut-off 19 October 2019) [10], and real world observational analyses with fenfluramine treatment in some patients for up to 27 years, provide consistent conclusions that response to treatment with fenfluramine is durable and long-lasting, with no evidence of a waning of effect over time [71, 72]. The real-world

observational studies include both children and adult initiators of fenfluramine, supporting the initiation and continued use of fenfluramine in all age groups, including adults. Fenfluramine was well tolerated with long-term use and no patients appear to have developed mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension.

B.2.13.1.3 Comparative evidence versus NICE-recommended add-on therapies

Current NICE-recommended add-on therapies include clobazam, and stiripentol and cannabidiol [9, 12], which based on their licensed indications should be taken with clobazam [13, 14]. However, only cannabidiol has been formally appraised by NICE, and was recommended for use without any comparative data beyond placebo [12].

There are no RCTs supporting clobazam in Dravet syndrome, and the RCTs in support of stiripentol assess outcomes over only 4 weeks and provide only low to moderate quality evidence [60]. A robust ITC was therefore only possible for fenfluramine versus cannabidiol. As cannabidiol is accepted by NICE as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway, and as it is not feasible to provide an ITC for fenfluramine against any other NICE-recommended therapy, a primary clinical and economic comparison against cannabidiol is the most appropriate comparison to address the decision problem in this appraisal.

The ITC indicates clearly that fenfluramine is superior to cannabidiol in reducing convulsive seizure frequency, with significantly greater proportions of patients achieving clinically meaningful reductions with fenfluramine than cannabidiol (see section B.2.9). Based on the available long-term OLE data, it seems reasonable to conclude that the clear superior efficacy of fenfluramine over cannabidiol demonstrated in the ITC based on RCT data will be at least maintained over the long term, and it is plausible the relative treatment benefit of fenfluramine over cannabidiol may actually increase over time due to the waning of effects of cannabidiol (see section B.2.9.5).

B.2.13.1.4 Collective evidence supporting the proposed positioning of fenfluramine

The proposed positioning of fenfluramine (see section B.1.3.4, Figure 2) is aligned with its anticipated full licensed indication, as an option at all points across the add-on therapy pathway. This includes use as a first line add-on therapy option where clobazam is not a desirable option or is not tolerated, and as a second or subsequent line option alongside existing NICE recommended add-on therapies.

The most appropriate comparative data for this appraisal are from the ITC which shows clearly the superior efficacy of fenfluramine compared with cannabidiol – the only NICE-recommended therapy with sufficient clinical data to permit a robust comparison. However, the placebo-controlled fenfluramine RCTs (Study 1 and Study 1504) also provide robust data demonstrating the addition of fenfluramine to standard of care AEDs provides dramatic and significant reductions in convulsive seizure frequency compared with standard of care AEDs, irrespective of concomitant AEDs. Together, these robust RCT and ITC data clearly support the proposed positioning of fenfluramine across the add-on therapy pathway, as summarised in Table 22.

Of note, the RCT evidence supporting stiripentol is insufficient to permit an ITC for fenfluramine against stiripentol (see section B.2.9.2); however, as cannabidiol is accepted by NICE as a clinically and cost effective add-on therapy alongside stiripentol, and as fenfluramine is robustly

demonstrated to more effective than cannabidiol, it is a reasonable expectation that fenfluramine would also be a clinically effective add-on therapy at the same points in the add-on therapy pathway as both cannabidiol and stiripentol. This is further supported by consistent evidence of fenfluramine's effects before, after and in addition to the use of stiripentol (see section B.2.6.1).

Table 22. Evidence supporting the positioning of fenfluramine across the add-on therapy pathway

Positioning across the add-on therapy pathway	Relevant comparators	Evidence supporting fenfluramine positioning	Justification
1L add-on where clobazam is not desirable 2L add-on when clobazam is not tolerated	• Stiripentol + SoC AED (unlicensed) • **Continued SoC AED**	• Study 1 subgroup analysis: fenfluramine + SoC AED reduces CSF significantly compared to SoC AED both with or without concomitant clobazam (see section B.2.6.1.1.1)	• Stiripentol data are insufficient to permit an ITC (as per NICE TA614; see section B.2.9.2) • Stiripentol has not been appraised by NICE and its use in this positioning is off label • **SoC AED is therefore a relevant clinical comparator to demonstrate the efficacy of fenfluramine in this positioning**
2L+ add-on alongside NICE recommended add-on therapies – **before** use of stiripentol 2L+ add-on alongside NICE recommended add-on therapies – **after** use of stiripentol	• **Cannabidiol + SoC AED** • Continued SoC AED	• ITC: fenfluramine is superior to cannabidiol for reduction in CSF and 50% responder rates (see section B.2.9.4) • Study 1: fenfluramine + SoC AED excluding stiripentol is superior to SoC AED in patients not taking concomitant stiripentol (see section B.2.6.1) • Study 1 subgroup analysis: fenfluramine + SoC AED reduces CSF significantly compared with Soc AED to same extent in stiripentol naïve and stiripentol experienced patients (see section B.2.6.1.1.1)	• Cannabidiol (with clobazam) is a NICE-recommended treatment option in this positioning (as per TA614). • **The ITC supports the superior efficacy of fenfluramine compared with cannabidiol and is the primary comparative clinical data.** • Study 1 demonstrates the dramatic reductions in CSF from addition of fenfluramine to SoC AED • Subgroup analyses of Study 1 demonstrate consistent effectiveness of fenfluramine irrespective of prior use of stiripentol (and irrespective of prior use of clobazam)

Positioning across the add-on therapy pathway	Relevant comparators	Evidence supporting fenfluramine positioning	Justification
2L+ add-on as an alternative to stiripentol	• Stiripentol + SoC	• Insufficient evidence for stiripentol to permit a robust comparison (see B.2.9.2.4)	• ITC feasibility assessment. Aligned with Appraisal committee acceptance of cannabidiol without comparison against stiripentol in NICE TA614 .
2L+ add-on alongside NICE recommended add-on therapies – **in addition to** stiripentol	• **Cannabidiol + SoC** • Continued SoC AED	• ITC: fenfluramine is superior to cannabidiol for reduction in CSF and 50% responder rates (see section B.2.9.4) • Study 1504: fenfluramine + SoC AED including stiripentol is significantly superior to SoC AED including stiripentol (see section B.2.6.1)	• Cannabidiol (with clobazam) is a NICE-recommended treatment option in this positioning (as per TA614). • **The ITC supports the superior efficacy of fenfluramine compared with cannabidiol and is the primary comparative clinical data.** • Study 1504 demonstrates the dramatic reductions in CSF from addition of fenfluramine to SoC AED containing stiripentol
1L, first line; 2L+, second and subsequent line; CSF, convulsive seizure frequency; ITC, indirect treatment comparison; SoC AED, standard of care antiepileptic drugs			

B.2.13.2 Generalisability and relevance of the clinical evidence base

The clinical evidence base for fenfluramine is demonstrably generalisable to UK clinical practice and is therefore the appropriate and relevant data to use to address the decision problem.

B.2.13.2.1 Patient populations

The phase 3 RCTs enrolled Dravet syndrome patients aged 2-18 years, with a mean age of approximately 9 years. The populations were stratified by age to ensure an appropriate balance of younger patients (<6 years of age) and older patients (≥ 6 years of age). Patients at baseline had a history of multiple prior AEDs and were taking a mean average of 2.4 standard of care AEDs (Study 1) and 3.5 standard of care AEDs (Study 1504). The most common AEDs among their standard of care regimens were valproate, clobazam and stiripentol (0% in Study 1 and 100% in Study 1504) [3, 4]. Around 12% of trial participants were recruited from UK centres.

These trial population characteristics are well aligned with the real world patients contributing to the DISCUSS study, the largest survey of Dravet syndrome patient caregivers to date that covered approximately 15% of all Dravet syndrome patients in Europe, including patients in the UK. The

mean age of patients contributing to the DISCUSS study was 10.6 years (median 9 years), and patients were taking a mean of 3 AEDs, most commonly valproate, clobazam and stiripentol [7].

Of note, 22% of patients contributing to the DISCUSS study were adults [7]. Although the fenfluramine phase 3 RCTs recruited patients up to 18 years of age, patients in practice and in the clinical trials obviously continue treatment into adulthood. Subgroup analyses of the RCTs in patients aged >12 years indicate that outcomes with fenfluramine are comparable in the subgroup of adolescent and young adult patients and the whole trial populations [78], and real world observational data demonstrate consistent, sustained benefits in child and adult initiators [72].

Collectively, there is no reason to believe that Dravet syndrome patients enrolled in the phase 3 RCTs and the long-term observational studies are systematically different to patients in clinical practice in the UK. Furthermore, there is no evidence to suggest that the outcomes observed in the RCT populations would differ in adult initiators and users of fenfluramine in practice.

B.2.13.2.2 Intervention

The phase 3 RCTs evaluated fenfluramine as an add-on to standard of care AEDs at the doses and dosing schedules aligned with its anticipated license. The dose in both RCTs reflected their anticipated use in practice.

B.2.13.2.3 Comparator

The phase 3 RCTs compared fenfluramine against placebo as an add-on therapy to standard of care regimens [3, 4]. At the time of trial design and initiation, cannabidiol was not a licensed product in any jurisdiction and stiripentol was not licensed or in widespread use in the US but was available and in widespread use in Europe and elsewhere. Given the need for dose reduction with fenfluramine and other AEDs used in combination with stiripentol, and the limited patient population from which to enrol patients, the phase 3 RCTs were designed to specifically exclude (Study 1) or include (Study 1504) stiripentol as a concomitant AED and placebo was used as the appropriate comparator. Consequently, as is the case for both stiripentol (STICLO-FR and STICLO-IT) and cannabidiol (GWPCARE 1 and 2), there are no direct comparative RCT data for fenfluramine.

In order to generate comparative effectiveness data for fenfluramine, indirect treatment comparisons (ITCs) were explored. Due to significant limitations with the RCT data available for stiripentol it was not possible to conduct a robust ITC for fenfluramine vs stiripentol. However, sufficient data were available to enable a robust ITC for fenfluramine vs cannabidiol (see section B.2.9).

Although cannabidiol was not compared directly or indirectly against stiripentol, it is recommended by NICE within its full licensed indication as a treatment option alongside stiripentol in the current adjunctive treatment pathway [9]. Cannabidiol is therefore a relevant comparator in the decision problem and it is therefore appropriate to use the ITC of fenfluramine vs cannabidiol as the primary evidence of comparative effectiveness on the use of fenfluramine in the current adjuvant treatment pathway.

B.2.13.2.4 Outcomes

The primary and secondary efficacy endpoints for the phase 3 RCTs (Study 1 and Study 1504 cohort 2) appropriately focus on key seizure endpoints that drive patient morbidity and mortality, including percentage change from baseline in monthly convulsive seizure frequency, responder analyses based on clinically meaningful reductions in convulsive seizure frequency and longest convulsive seizure-free intervals and seizure-free days. Evaluations of non-convulsive seizure reductions, patient health status and patient and carer quality of life were also pre-specified, as were safety endpoints [3, 4]. These are all outcomes that matter to patients and carers, several are used in clinical practice to assess patient response to treatment, and most are listed as outcomes in the scope of this appraisal [11]. The outcomes assessed are therefore highly relevant to clinical practice and to the decision problem in this appraisal.

B.2.13.3 Strengths and limitations of the clinical evidence base

B.2.13.3.1 Strengths

Despite the rarity of the disease and heterogeneity that is inherent in small, difficult-to-manage patient populations, the clinical evidence base for fenfluramine is comprehensive and robust. Quality assessment of the two phase 3 double-blind RCTs indicates the trials are at low risk of bias, their results are robust, and they are highly generalisable to UK clinical practice (see section B.2.5 and B.2.13.2). Combined with the ITC data for fenfluramine versus cannabidiol (see section B.2.9), the comparative trial-based evidence for fenfluramine is more complete, robust and of a higher quality than the evidence supporting any of the existing NICE-recommended add-on therapies.

These comparative trial-based data are supported by an OLE study, which provides confirmation that the dramatic and often profound improvement in seizure outcomes with fenfluramine, and the safety and tolerability demonstrated in the phase 3 RCTs, are durable and sustained through up to 3 years of treatment. In addition, real-world observational data in patients with extensive treatment with daily fenfluramine for up to 27 years are consistent with these findings.

B.2.13.3.2 Limitations

Although the fenfluramine clinical development programme provides robust clinical effectiveness data, there are some limitations. The phase 3 RCTs involved a treatment duration of 14-15 weeks and overall duration of 20-21 weeks. This is similar to the treatment duration in the phase 3 cannabidiol RCTs [34, 35] and somewhat longer than the 8 weeks treatment duration in the stiripentol RCTs [62, 63]; however, it is relatively short in relation to the lifelong disease course of Dravet syndrome. This is mitigated to a large extent for fenfluramine by the OLE study that provides effectiveness data for up to 3 years in patients who successfully completed treatment in phase 3 RCTs, and the real-world observational data that provide much longer follow-up; however, these long-term studies do not include a control arm.

As in the RCTs for stiripentol and cannabidiol, the fenfluramine RCTs were placebo-controlled and do not provide direct comparative data for fenfluramine and potential comparators. Due to data limitations for stiripentol it was not possible to conduct a robust ITC to compare fenfluramine versus stiripentol; however, a robust ITC versus cannabidiol was possible, and as cannabidiol (with

clobazam) is accepted by NICE as a clinically and cost effective therapy in the existing add-on care pathway, this provides the most appropriate comparison to address the decision problem.

Seizure endpoints in the RCTs were recorded by parents/caregivers inputting patient daily seizure activity into an electronic diary. Such reporting of seizure activity is subjective and may be open to recall bias. The primary and key secondary endpoints were based on convulsive seizures that are easier to detect than non-convulsive seizures; however, as non-convulsive seizures are harder to detect, they may be underreported in the trials. The methods for reporting the duration of individual seizures or repetitive seizures, known as seizure clusters, and the definition of SE events may also lead to underreporting of relevant seizure events. These issues are likely to be the same across the fenfluramine, cannabidiol and stiripentol trials.

Finally, the phase 3 RCTs excluded adult patients over 18 years of age, which may be perceived to limit the generalisability of the RCT data to adult patients in practice. However, subgroup analyses stratified by age did not indicate a reduced efficacy as patients reached adolescence, the OLE study includes a cohort of patients who have reached adulthood during the study and continued to receive treatment benefit with fenfluramine, and the real-world observational data include children with treatment continuation in to adulthood and adult initiators of fenfluramine, with consistent benefits across all ages.

B.2.13.4 Conclusions from the clinical evidence

Robust, high-quality RCT data clearly demonstrate dramatic, clinically meaningful improvements in convulsive seizure control in high proportions of Dravet syndrome patients when fenfluramine is added to the most effective AEDs currently available. Based on an OLE study and real-world observational data, this efficacy is durable and sustained over long-term treatment, with good tolerability and few treatment-emergent adverse effects. A robust ITC further demonstrates that fenfluramine is clearly superior in reducing convulsive seizure frequency compared with cannabidiol, the only other add-on therapy to have been appraised by NICE. Collectively, the clinical evidence base supporting fenfluramine is more complete, robust and of a higher quality than the evidence supporting any of the existing NICE-recommended add-on therapies, and supports its use across the add-on therapy pathway in line with its anticipated full licensed indication.

Dravet syndrome is characterised by severe, high frequency convulsive seizures that are typically resistant to AED therapy. Given the clear relationships between convulsive seizure frequency, patient morbidity and mortality, and patient and caregiver quality of life, the significant and often profound reductions in convulsive seizure frequency demonstrated with fenfluramine as an add-on therapy are potentially life-changing for a high proportion of patients, their families and caregivers. Combined with its ability to be used at any point in the add-on therapy pathway, without reliance on concomitant use of clobazam, fenfluramine is an innovative therapy that provides a step change in the treatment of Dravet syndrome.

B.3 Cost effectiveness

Summary of cost effectiveness evidence for fenfluramine

- A patient-level simulation model was developed to determine the cost effectiveness of fenfluramine as an add-on therapy in the existing add-on therapy pathway. The simulated population is reflective of the Dravet syndrome population in the UK.
- **A primary base case comparison has been conducted of fenfluramine plus SoC versus cannabidiol (with clobazam) plus SoC as this is the most appropriate comparison to determine the cost effectiveness of fenfluramine in the existing add-on therapy pathway**. Cannabidiol (with clobazam) is the only NICE-recommended add-on therapy to have been formally appraised by NICE. It was accepted as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway in 2019 and its use is anticipated to continue to increase with recent de-regulation of its controlled drug prescribing requirements. It is also the only NICE-recommended add-on therapy with sufficient RCT data to permit a robust indirect comparison against fenfluramine.
- Secondary, supportive analyses of fenfluramine versus SoC are provided for completeness and transparency.
- The number of convulsive seizures per 28-day cycle is modelled using patient-level data from the placebo arms of the fenfluramine registration studies and is used to calculate the number of seizures and seizure-free days for each 28-day cycle, to determine the impact of add-on treatment on resource use, costs, mortality and HRQoL. The relative treatment effect of fenfluramine and cannabidiol (with clobazam) are derived from the robust ITC described in section B.2.9. Dravet-specific utilities for patients and carers are incorporated appropriately and in line with the NICE reference case, and UK-specific health care resource use data are derived from a detailed UK Pathway study.
- **Using the most robust data sources possible and highly conservative assumptions, the ICER for fenfluramine compared with cannabidiol (with clobazam) is £31,773/QALY.** In a secondary analysis, in patients for whom clobazam is not a desirable option or is not tolerated, the ICER for fenfluramine compared with continued SoC therapy is £38,102/QALY.
- Deterministic and probabilistic sensitivity analyses demonstrate that the results of the base case analysis are robust to parameter uncertainty. The mean probabilistic ICER of £31,887/QALY is highly consistent with the deterministic base case ICER of £31,773/QALY.
- The probability of the ICER being below £30,000/QALY is 35%; however, there is an 80% probability that the ICER is below £35,000/QALY. The homogeneity of these results with 95% CI: £28,979-£41,746 would suggest that fenfluramine would represent a reasonably cost-effective (£31,887/QALY) intervention across all patients in this rare disease.
- Scenario analyses further demonstrate that the base case analysis is highly conservative; under plausible alternative assumptions on cannabidiol dosing, fenfluramine dominates cannabidiol (with clobazam).
- **In the context of this devastating, rare disease, with few effective and tolerable treatment options, fenfluramine, as an innovative add-on therapy, is a cost-effective alternative to current NICE-recommended add-on therapies. Fenfluramine should therefore be recommended within its full licensed indication as a clinically and cost-effective alternative to existing NICE-recommended add-on therapy options.**

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) was performed to identify and evaluate any existing economic evaluations of anti-epileptic treatments in Dravet syndrome (see Appendix G). The SLR found no previous economic evaluations of fenfluramine in Dravet syndrome. However, it identified several relevant economic evaluations of other add-on AEDs used in Dravet syndrome, including five HTAs and a published cost utility analysis. One HTA (NICE TA614) compared cannabidiol (with clobazam) plus standard of care (SoC) against SoC [12], and the others compared stiripentol plus SoC against SoC [26, 93, 94]. All models were either Markov cohort models or budget impact models based on simplistic cost listing. A summary of the cost effectiveness studies identified in the SLR is presented in Appendix G.

B.3.2 Economic analysis

The SLR identified no previous economic evaluations of fenfluramine in the treatment of Dravet syndrome. A *de novo* economic analysis was developed to determine the cost effectiveness of fenfluramine as add-on therapy to SoC, i.e. other anti-epileptic drugs (AEDs). The primary base case comparison is against cannabidiol (with clobazam) plus SoC. Cannabidiol (with clobazam) is the only NICE-recommended add-on therapy to have been formally appraised by NICE. It was accepted as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway in 2019 and its use is anticipated to continue to increase with recent de-regulation of its controlled drug prescribing requirements (see B.1.3.3.3). It is also the only NICE-recommended add-on therapy with sufficient RCT data to permit a robust indirect comparison against fenfluramine (see B.2.9). This is therefore the most appropriate comparison to determine the cost effectiveness of fenfluramine in the existing add-on therapy pathway.

B.3.2.1 Patient population

The patient population in the economic evaluation reflects the decision problem; people with Dravet syndrome whose seizures are inadequately controlled by established clinical management (referred to as SoC throughout this submission). The patient population is also consistent with the anticipated licensed indication for fenfluramine; treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults [10].

Two Phase 3, randomised, placebo-controlled studies (Study 1 and Study 1504 [cohort 2]) underpin the registration of fenfluramine as a licensed treatment for Dravet syndrome by the EMA (see section B.2.3.1 for methodology and B.2.6.1 for results). Study 1 relates to the use of fenfluramine in patients not taking stiripentol as a concomitant AED, and Study 1504 cohort 2 relates to the use of fenfluramine in patients taking stiripentol as a concomitant AED (Table 23). Together, the registration studies support the positioning of fenfluramine across the add-on therapy pathway for patients with Dravet syndrome, ranging from before concomitant stiripentol use through to after concomitant stiripentol use (as described in section B.2.13.1).

Neither of the fenfluramine registration studies recruited adult Dravet syndrome patients; however, data from the OLE study, European and US EAP and Belgian RWE studies indicate that fenfluramine is similarly effective and well tolerated in patients who transition treatment into adulthood and in adult initiators as it was in the RCTs (see section B.2.13.2 and B.2.6.3).

Table 23: Fenfluramine registration studies

Study	Study 1 (n=119)[3]	Study 1504 cohort 2 (n=87)[4]
Population	Dravet syndrome patients aged ≥2 to ≤18 years whose convulsive seizures were not completely controlled by current AEDs	
Intervention	• FFA 0.2 mg/kg/day (max 26 mg/day) + concomitant AEDs not including stiripentol (n=40) • FFA 0.7† mg/kg/day (max 26 mg/day) + concomitant AEDs not including stiripentol (n=39)	• FFA 0.4† mg/kg/day (max 17 mg/day) + concomitant AEDs including stiripentol (n=43)
Comparator	• Placebo + concomitant AEDs not including stiripentol (n=40)	• Placebo + concomitant AEDs including stiripentol (n=44)

Abbreviations: AEDs, anti-epileptic drugs; FFA, fenfluramine.† Maintenance dose (draft SmPC).

B.3.2.2 Model structure

B.3.2.2.1 Seizure frequency and seizure-free days

The seizure burden associated with Dravet syndrome is lifelong and severe, with Dravet syndrome patients rarely seizure-free for a significant period of time [7, 38].

As described in section B.1.3.1.6, both seizure frequency and seizure-free days determine patient outcomes, including survival, health-related quality of life (HRQoL) and associated resource use and costs.

Heterogeneity in seizure frequency and seizure-free days (as depicted in Figure 20 and Figure 21) in patients with Dravet syndrome is observed, and reflects the significant variation in seizure burden. In addition, the disease has a spectrum of physical and behavioural comorbidities that appear both progressive with increasing age and associated with increasing seizure frequency.

Figure 20. Number of seizures per individual patient in patients not on stiripentol (Study 1) at baseline (42 days)

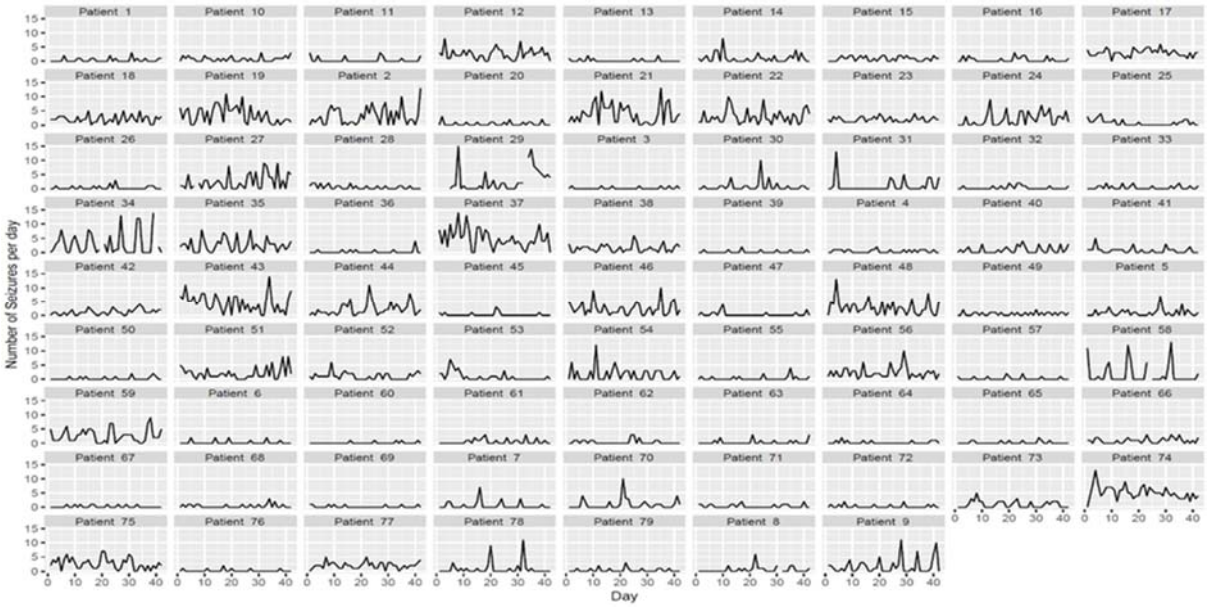
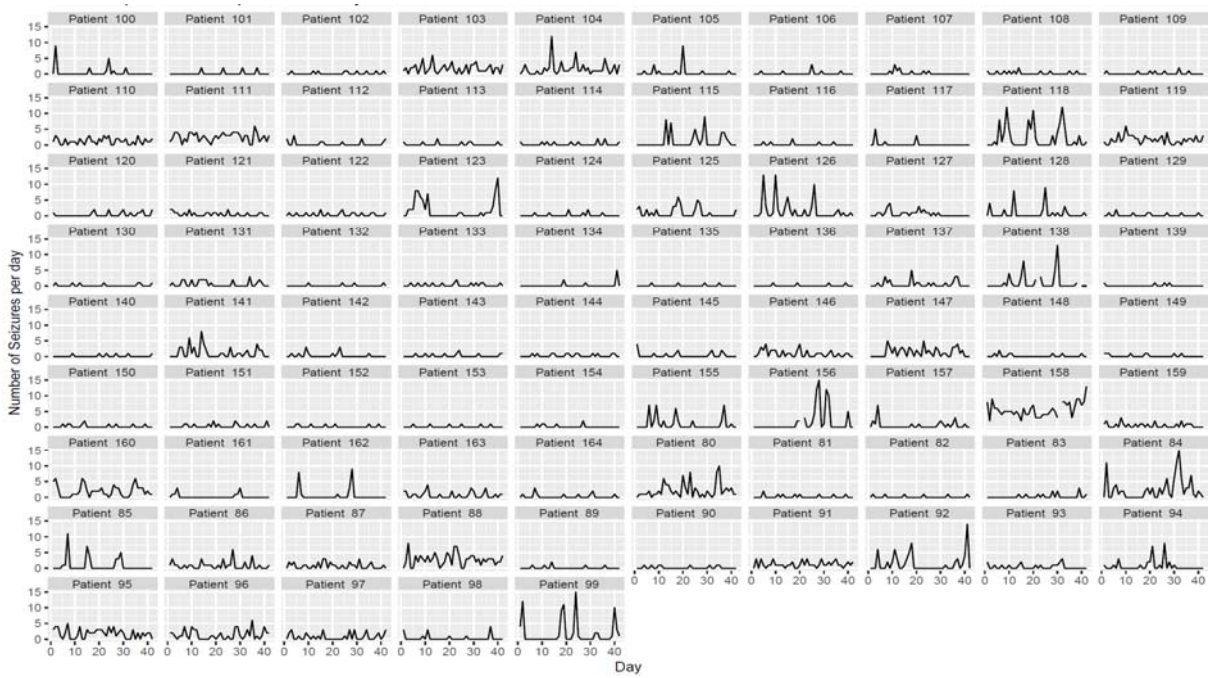


Figure 21: Number of seizures per individual patient in patients on concomitant stiripentol (Study 1504 cohort 2) at baseline (42 days)



B.3.2.2.2 Choice of modelling approach

Previous economic models in Dravet syndrome and other similar conditions have adopted a Markov cohort modelling approach (see Appendix G). However, as noted by the NICE committee in the appraisal of cannabidiol (TA614), a simulation-based modelling approach may be more

appropriate to capture the benefits of treatment in patients with different numbers of seizure-free days[12].

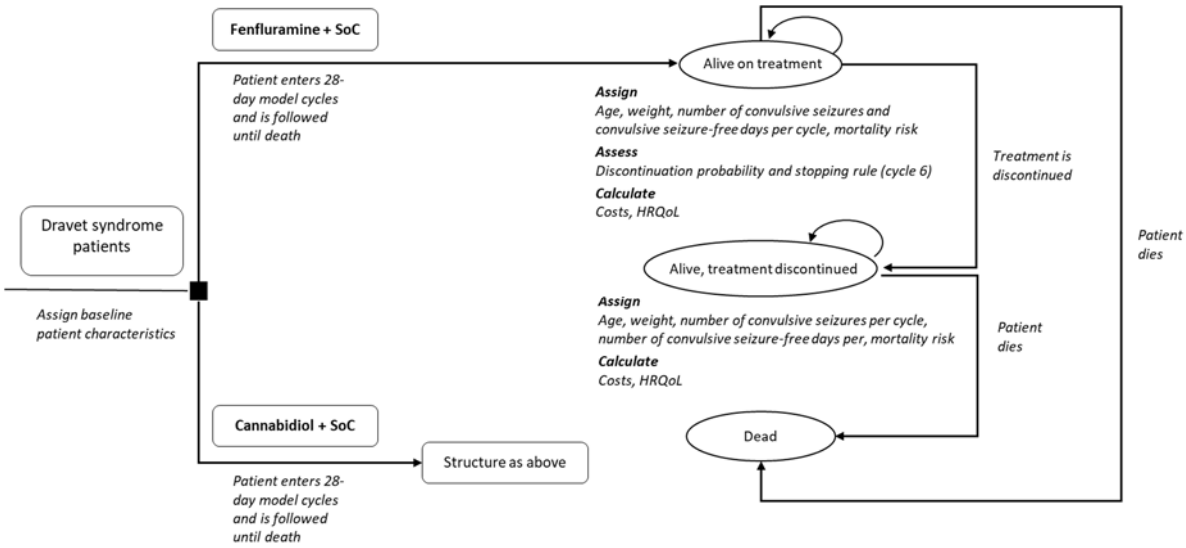
Therefore, to more appropriately account for patient heterogeneity, and in line with the suggestions of the committee in TA614, a patient-level simulation model was developed to evaluate the cost effectiveness of fenfluramine. The model, developed in R (version 3.5.2), simulates a realistic cohort of patients in England, with characteristics such as co-morbidities and seizure frequency based on patient-level data from the fenfluramine registration studies. Seizures observed in the trial are assumed to be representative of that observed in the UK for both the fenfluramine and cannabidiol trials, and are therefore generalisable to a UK population, with adjustments to reflect what is known in terms of treatment in UK clinical practice.

Patients are assigned to either fenfluramine + SoC or cannabidiol + SoC in the base case. Patients are modelled over time, with different events occurring based on patients' seizure patterns and characteristics. These events include treatment discontinuation, ongoing and emergency care, and death. Patients' seizures are modelled to reflect the placebo arm of the fenfluramine trials with a treatment effect added for both strategies. To simplify the modelling approach and due to insufficient data, only the primary intervention in each strategy is considered, and if patients discontinue treatment, they do not switch to another different intervention (e.g. fenfluramine to cannabidiol), but instead return to their baseline SoC. More details are given in the following sections for each of these components.

B.3.2.2.3 Model overview

A schematic diagram of the patient-level simulation model is provided in Figure 22.

Figure 22: Schematic diagram patient-level simulation model



Abbreviations: HRQoL, health-related quality of life; SoC, standard of care.

B.3.2.2.3.1 Data sources used in the modelling

The primary data sources for the model are the individual patient-level data from the two fenfluramine registration studies (Study 1 and Study 1504 cohort 2; see section B.3.3 for details of the studies) and published RCTs. In addition, ongoing discontinuation rates (after the fenfluramine

registration study periods), were taken from the open-label extension (OLE) studies of fenfluramine and cannabidiol (study 1503[70, 78] and GWPCARE5 [67], respectively).

Other data sources are listed in Table 24.

Table 24: Key data sources used in the model

Data	Source
Patient characteristics	Study 1 and Study 1504 cohort 2 [3, 4], Royal College of Paediatrics and Child Health [95]
Seizure frequency and seizure free days per 28-day period	Study 1 and Study 1504 cohort 2 [3, 4] GWPCARE1 and GWPCARE2[34, 35]
Mortality	Office for National Statistics[96], Cooper et al[5], Nilsson et al [31]
Discontinuation	Study 1 and Study 1504 cohort 2 [3, 4], Study 1503 [70] and GWPCARE5 [67]
Cost of AEDs	British National Formulary [97], Prescription Cost Analysis [98]
Utilities (patient and carer)	Study 1 and Study 1504 cohort 2 [3, 4]
HCRU	NHS Reference costs [99], Unit Costs of Health and Social Care [100], UK Pathway research study [55]

Abbreviations: AEDs, anti-epileptic drugs; HCRU, health care resource use.

B.3.2.2.3.2 Model population

Two populations of patients are run through the model; one in which the patient receives fenfluramine + SoC (referred to throughout as the intervention strategy) and one in which the patient receives cannabidiol + SoC (referred to throughout as the comparator strategy). The population receiving the intervention is comprised of patients on concomitant stiripentol (58%) or not (42%), representing the use of stiripentol observed in UK patients in clinical practice in the DISCUSS study [16]. To determine the ICER, the costs and QALYs were combined for the simulated patients on concomitant stiripentol or not for the intervention and comparator strategies, and then the incremental costs and QALYs for this merged population were calculated.

B.3.2.2.3.3 Cycle length

A cycle length of 28 days was defined for ease of computation and to align with the clinical data (the time period used in the fenfluramine clinical studies to measure convulsive seizure activity).

B.3.2.2.3.4 Baseline characteristics

Each patient in both model strategies were assigned a set of baseline characteristics (gender, age, weight, concomitant medication and motor impairments [none, ataxia, or severe]). Further detail is provided in section B.3.3.1.

B.3.2.2.3.5 Convulsive seizures

As detailed in section B.1.3.1.6, reducing convulsive seizure frequency, leading to more seizure-free days, reduces the risk of mortality, reduces the risk of developmental comorbidities, and improves patients' and carers' quality of life. For this reason, the model and all outcomes are driven by convulsive seizures and the ability of treatment strategies to influence convulsive seizure frequency.

To simulate convulsive seizures for each patient in both the intervention and comparator strategies, the number of convulsive seizures were modelled per 28-day cycle, using patient-level data from the placebo arm of the fenfluramine registration studies for the first 14/15 weeks (titration and maintenance periods). The number of convulsive seizure free days per 28-day cycle was also modelled using patient level data from the placebo arm of the fenfluramine registration per 28-day cycle. A treatment effect of either fenfluramine or cannabidiol was then applied, dependent on which model strategy the patient was in. After the first 14/15 weeks, the number of convulsive seizures was simulated in each cycle by bootstrapping the placebo arm of the fenfluramine registration studies and applying a treatment effect until discontinuation. Further detail is provided in section B.3.3.2.1.

B.3.2.2.3.6 Treatment discontinuation

Treatment discontinuation due to lack of efficacy or for other reasons, e.g. due to adverse events (AEs), was applied in both the intervention and comparator strategies using the treatment data from the fenfluramine registration studies. There are no published discontinuation data for the subgroup of patients receiving cannabidiol with clobazam, so this was assumed to be the same as in the fenfluramine studies. Ongoing discontinuation (i.e. after the study period) was also applied using the treatment data from the OLE fenfluramine and cannabidiol studies. Further detail is provided in section B.3.3.5.

B.3.2.2.3.7 Future convulsive seizures (after discontinuation)

Following treatment discontinuation in the intervention and comparator strategies, the convulsive seizure frequencies of the simulated patients are assumed to return to their baseline seizure frequencies experienced in their corresponding study. Further detail is provided in section B.3.3.5.1.

B.3.2.2.3.8 Mortality

In addition to background mortality (independent of seizures), total mortality in the model includes the key drivers of mortality in Dravet syndrome: sudden unexpected death in epilepsy (SUDEP), status epilepticus (SE) mortality and accidental mortality (e.g. drowning, injury) [5, 6]B.1.3.1.3). Further detail of the implementation of mortality in the model is provided in sectionB.3.3.3.

B.3.2.2.3.9 Other model variables

Other model variables include non-convulsive seizures (NCS) and SE events. Further detail is provided in section B.3.3.2.3 and B.3.3.2.4.

B.3.2.2.3.10 Healthcare resource utilisation

In the model, HCRU was split between ongoing resources to maintain routine management of patients with Dravet syndrome, and emergency resources that are required when severe seizure events occur. Further detail is provided in section B.3.5.

B.3.2.2.3.11 Health-related quality of life

The Paediatric Quality of Life Inventory (PedsQL) was used to collect patient HRQoL data in the fenfluramine registration studies. PedsQL data from the studies were mapped to EQ-5D-Y, to provide patient utility scores for use in the base case.

The NICE reference case states that the perspective on outcomes should be all direct health effects, whether for patients or, where relevant, carers [69]. In line with the acceptance by NICE of the inclusion of carer disutility in the cost effectiveness analysis of cannabidiol in TA614 [12], carer utility values are included in the analysis. In both fenfluramine registration studies, EQ-5D-5L data was collected directly from carers/parents. Consistent with the NICE reference case, these data were mapped to EQ-5D-3L. The carer impact of Dravet syndrome was incorporated in the base case. Further detail is provided in section B.3.4.

B.3.2.2.3.12 Time horizon, perspective and discounting

The base case analysis assumes a lifetime time horizon, with costs considered from an NHS and PSS perspective and an annual discount rate of 3.5% applied to both costs and QALYs, as per the NICE reference case [69].

B.3.2.2.3.13 Summary of model features

Key features of the economic analysis are provided in Table 25. These are compared to the company submission for cannabidiol in NICE TA614 [12], with justification for differences in approach.

Table 25: Features of the economic analysis (base case)

	Previous NICE appraisals	Current appraisal	
Factor	**Cannabidiol (TA614)**	**Chosen approach**	**Justification**
Model mathematical framework	Markov-state transition model (cohort-based)	Patient-level simulation	In line with the suggestions of the appraisal committee in TA614[12]. Allows the heterogeneity of the disease, patient population and

	Previous NICE appraisals	Current appraisal	
			response to treatment to be representatively modelled and is more appropriate than a cohort model to capture the benefit of seizure-free days.
Categorisation of patient seizure frequency	Banded into 4 seizure frequency categories, with the number of seizure free days as sub-categories per 3-month cycle	Absolute number of convulsive seizures and seizure-free days per cycle explicitly modelled for each individual and a treatment effect applied	The range in number of seizures per cycle experienced by patients is very large. Categorisation may lead to distortions; by modelling explicitly, all costs and benefits are more accurately and appropriately captured
Baseline seizure characteristics	No changes	Convulsive seizures and seizure-free day frequency adjusted to ensure the seizure frequency in the intervention and comparator strategies are the same at baseline	Ensures the comparison of populations with the same disease severity
Discontinuation	Patients discontinue back to an average seizure frequency	Patients discontinue to their own seizure frequency in the baseline trial period	Removes the treatment effect but ensures patients with a high seizure frequency are not discontinuing to lower average seizure frequency, and vice versa
Perspective	NHS/PSS	NHS/PSS	In line with the NICE reference case
Time horizon	15 years	Lifetime	Dravet syndrome is a lifelong condition, with a risk of premature mortality. Patients are expected to remain on active treatment for seizures into adulthood
Discounting	3.5% applied to all costs & utilities	3.5% applied to all costs & utilities	In line with the NICE reference case
Cycle length	3 months	28 days	Aligns to the time period used to measure frequency of patient seizures in the fenfluramine registration studies (see section B.2.3)
Treatment waning	Not included	Not included in the base case. Explored in scenario analyses, by testing the sensitivity of the model when CBD doses are optimised (increased) to compensate for a loss of effect over time, and in line with doses in OLE study.	The fenfluramine OLE (Study 1503) study data do not show any indication of treatment waning over up to 24 months of treatment. In contrast the cannabidiol OLE study (GPWCARE5) shows a 25% relative reduction in efficacy over 48 weeks of treatment [14], and doses at the top end of the licensed dose range [67] (see B.2.9.5)

	Previous NICE appraisals	Current appraisal	
Source of utilities	Online study whereby patients and/or carers of DS or epilepsy patients were asked to complete a quality of life questionnaire and score patient vignettes (representing the health states used in the cost-utility model) using a VAS scale. 1.8 carers included in the base case.	Fenfluramine registration trials Patient: Mapping PedsQL data from the registration studies to EQ-5D-Y Carer: Mapping EQ-5D-5L data from the registration studies to EQ-5D-3L An alternative EQ-5D source of patient utilities (Teneishvili et al) was tested in scenario analysis	PedsQL data from the double-blind studies can be mapped to the EQ-5D-Y using the algorithm developed by Khan et al [101]. Dravet syndrome presents a significant burden to carers and the wider family. In line with NICE TA614, caregiver utility is included in the base case (1.8 carers). EQ-5D-5L data from the trials is mapped to the EQ-5D-3L (in line with the NICE reference case), using the van Hout et al. 2012 value set [102].
Source of resource use and costs	NHS reference costs 2016/17 PSSRU 2017 NHS Electronic Drug Tariff 2018 Published literature Expert opinion	NHS reference costs 2018/2019 PSSRU 2019 BNF March 2020 Expert opinion	In line with the NICE reference case

Abbreviations: BNF, British National Formulary; CBD: cannabidiol; NHS, National Health Service; OLE, open-label extension PedsQL, Paediatric Quality of Life Inventory; PSS, Personal and Social Services; PSSRU, Personal Social Services Research Unit; RWE, real world evidence.

B.3.2.3 Intervention technology and comparators

As cannabidiol (with clobazam) is the only existing add-on therapy to have been appraised by NICE, and was accepted as a clinically and cost-effective option alongside stiripentol in the existing add-on therapy pathway, a primary clinical and economic comparison against cannabidiol (with clobazam) is the most appropriate comparison to address the decision problem in this appraisal. The base case model therefore estimates the cost effectiveness of fenfluramine + SoC vs cannabidiol (with clobazam) + SoC.

The modelled doses for fenfluramine align to those in the draft SmPC and reflect the doses used in the registrational trials; a daily maintenance dose of 0.7 mg/kg (maximum daily dose not to exceed 26 mg) when used without stiripentol (as per registration Study 1 [3]), and a daily maintenance dose of 0.4 mg/kg (maximum daily dose not to exceed 17 mg) when used with stiripentol (as per registration Study 1504 cohort 2 [4]).

The cannabidiol SmPC recommends a maintenance dose of 10-20mg/kg/day [14]; however, the dose of cannabidiol assumed in the base case is 12 mg/kg/day, to reflect the dose preferred by the appraisal committee in NICE TA614, (i.e. 80% of patients on a dose of 10 mg/kg/day, and 20% of patients on a dose of 20 mg/kg/day)[12].

Concomitant AED usage in the fenfluramine registration studies is summarised in Table 26. Data on the concomitant AEDs in the relevant subgroup of patients taking cannabidiol with clobazam in the cannabidiol registration studies (GWPCARE1 [34] and GWPCARE2 [35]) are not available.

Therefore, the percentage use of each SoC AED sourced directly from the fenfluramine registration studies (Table 26) is applied to patients in both model strategies, with the exception of stiripentol and clobazam. The percentage of patients receiving concomitant stiripentol which informs the weighting of Study 1 and Study 1504 cohort 2 in the base case, was taken from the DISCUSS study UK dataset (58% of patients on concomitant stiripentol) reflecting the use of stiripentol in clinical practice in the UK [16]. All patients in the comparator strategy were assumed to be on concomitant clobazam as per the licensed indication for cannabidiol [14].

Concomitant AEDs in the fenfluramine registration studies that were not listed in the NICE final scope (clonazepam, zonisamide and ergenyl chrono) were excluded from the analysis. The SoC AED medications used in the model are representative of UK clinical practice as confirmed by clinical experts in the UK pathway research study (section B.3.11).

Table 26: Concomitant AEDs used in the fenfluramine registration studies at baseline (total study populations)

Concomitant AEDs	Fenfluramine double-blind studies	
	Number of patients on each AED (percentage applied in the model)	
	Study 1[3] (N=119)	Study 1504 cohort 2[4] (N=87)
Clobazam†	71 (60%)	82 (94%)
Levetiracetam	29 (24%)	11 (13%)
Topiramate	30 25%)	21 (24%)
Valproate (semisodium & sodium)	57 (48%	50 (57%)
Valproic acid	18 (15%)	16 (18%)

Abbreviations: AED, anti-epileptic drug.
† Applied in the intervention strategy only. All patients in the comparator strategy were assumed to be on concomitant clobazam as per the cannabidiol licensed indication.

B.3.3 Clinical parameters and variables

The primary data sources for the economic analysis are the Phase 3 registration studies for fenfluramine (Study 1 [3] and Study 1504 cohort 2 [4]). These provide the patient characteristics (motor impairment [none, ataxia or severe]) and concomitant medication (excluding stiripentol), and are used in the simulation of clinical outcomes (number of convulsive seizures per 28-day cycle, number of seizure-free days per 28-day cycle and treatment discontinuation rates, except ongoing discontinuation) for both the intervention and comparator strategies.

B.3.3.1 Baseline patient characteristics

Each patient was assigned a set of baseline characteristics (Table 27) and run through both model strategies as depicted in Figure 22; each characteristic was sampled independently from the sources described in Table 27. These characteristics were used to inform mortality, HCRU and HRQoL.

Table 27: Baseline patient characteristics

Characteristic	Input	Source
Gender (male)	55%	
Age	Patients' ages at the start of the model reflect the age distribution in the UK dataset of the DISCUSS study; age is increased in every cycle	DISCUSS UK dataset [16]
Weight	Increases with age in line with average English weight – 12 kg at age 2 increasing to 78 kg at age 25 at which age weight plateaus through adulthood	Royal College of Paediatrics and Child Health (RCPCH)[95] and the NHS health survey for England [103] (see section B.3.5.1.1)
Motor impairments	Patients are assigned motor impairment categories of none, ataxia and severe, based on the placebo arms of the fenfluramine registration studies	Study 1 and Study 1504 cohort 2 [3, 4]
Concomitant medication	Blended mix of AEDs (percentages calculated from the fenfluramine registration studies). The percentage of patients on concomitant stiripentol was taken from the DISCUSS (UK dataset) to represent UK use. All patients in the comparator strategy were assumed to be on clobazam as per the licensed indication for cannabidiol [14]	Study 1 and Study 1504 cohort 2 [3, 4] DISCUSS UK dataset [16]

Abbreviations: AEDs, anti-epileptic drugs.

The baseline characteristics were selected based on an analysis of covariates that significantly influence HRQoL (see Appendix M – regression model). These were confirmed in an internal modelling workshop (12 February 2020) with the project team including experts in modelling and epilepsy, and . They were also informed by a UK Pathway research study (qualitative and quantitative) with physicians and nurses involved in the treatment and management of Dravet syndrome patients in England [55] (see section B.3.11 for further detail), and .

Whilst age and weight are correlated, there was no indication that the other baseline characteristics are correlated with each other. Gender, concomitant medication, and motor impairments were assumed to be constant over the patient's lifetime, with age and weight increasing over time. In reality, and as reported in the UK Pathway research study report [55], concomitant medications and motor impairments are unlikely to remain static. Motor impairments are likely to progressively increase over time as patients age and/or without effective therapeutic control of seizures. In practice, as it was reported that the tendency is to add rather than remove concomitant AEDs [55], the number of available alternative therapeutic options would decrease as the patient becomes increasingly pharmaco-resistant to the limited number of AED options.

B.3.3.2 Treatment effectiveness

B.3.3.2.1 Convulsive seizures

In the intervention and comparator strategies, individual patients were assigned a number of convulsive seizures per 28-day cycle at baseline (based on patient-level data from the placebo arm of the respective fenfluramine registration studies) to ensure that the number of convulsive seizures per 28-day cycle were the same at baseline in both strategies.

For the first 14/15 weeks in the model (titration and maintenance period for Study 1 and Study 1504 cohort 2, respectively), the number of convulsive seizures after randomisation in the placebo strategy were used and a treatment effect applied. Beyond this time period the convulsive seizures from the placebo arm of the fenfluramine registration studies were extrapolated and a treatment effect applied (see Appendix L for further detail).

Three methods (bootstrapping, a share frailty model and fitting a Poisson distribution for each patient) for the extrapolation of convulsive seizures after the first 14/15 weeks were tested and validated against the seizure characteristics recorded in the registration studies and the OLE dataset (Study 1503, see section B.2.6.2). The bootstrapping method most closely replicated the study data and was chosen for use in the model. Further details on the bootstrapping method and validation is provided in Appendix L.

An indirect treatment comparison (ITC) was conducted, using the fenfluramine registration studies [3, 4] and subgroup analyses of the cannabidiol registration studies in patients taking concomitant clobazam [14] to quantify the treatment effects of fenfluramine and cannabidiol (with clobazam), in terms of percentage change in convulsive seizure frequency between baseline and the titration and maintenance periods compared to placebo (see section B.2.9). Based on the results of the ITC a treatment effect was then applied to the percent change (reduction) in convulsive seizures per 28-day cycle from baseline for each individual (Table 28). The number of convulsive seizures was calculated using this percent change.

Table 28: Convulsive seizure frequency percentage change from baseline (ITC results)

Treatment	Convulsive seizure frequency percentage change (reduction) from baseline vs placebo (95% credible intervals)
Cannabidiol 10 mg/kg	[redacted]
Cannabidiol 20 mg/kg	[redacted]
Cannabidiol 12 mg/kg/day (weighted)	[redacted]
Fenfluramine 0.4 mg/kg	[redacted]
Fenfluramine 0.7 mg/kg	[redacted]

A worked example is provided below:

- A patient experiences a reduction from 22 to 20 convulsive seizures per 28 days in the placebo arm from baseline to maintenance period (i.e. ~10% reduction) in the fenfluramine Study 1 trial.

- In the model, with cannabidiol treatment (10 mg/kg/day dose) the same patient experiences a [redacted] reduction in convulsive seizures [redacted] reduction with placebo plus an additional [redacted] see Table 28), resulting in [redacted] convulsive seizures (when rounded).
- In the model, with fenfluramine treatment (0.7 mg/kg/day dose) a patient experiences a 63% reduction in convulsive seizures ([redacted] reduction with placebo plus an additional [redacted], see Table 28), resulting in 8 convulsive seizures (when rounded).

Seizure frequency in the model is driven by convulsive seizures observed in patients on concomitant stiripentol or not taken from the fenfluramine registration trial, which recruited patients aged 2-18 years [3, 4]. As the literature indicates that seizure frequency may decline as patients age [23], and the fenfluramine registration trials provide limited information on seizure frequency in patients beyond 18 years of age, the frequency of seizures in patients aged 18 and over were halved, and seizure free days doubled. This reflects the decrease in seizures reported by clinicians in adults as reported in the UK Pathways research study [55].

B.3.3.2.2 Seizure-free days

The same methodology as described previously for simulating convulsive seizures per 28-day cycle (see B.3.3.2.1) was used to simulate seizure-free days per 28-day cycle, i.e. patient-level study data was used to determine the number of days on which a convulsive seizure occurred during the titration and maintenance treatment period. The reduction in convulsive seizure days in the placebo arm between the baseline and maintenance period was calculated and a treatment effect applied.

For the first 14/15 weeks of the model the study data was used; beyond this time period the study data was extrapolated. Due to a lack of available data on reduction in convulsive seizure days in the cannabidiol studies (increase in seizure-free days), it was assumed that the percentage reduction was the same for convulsive seizure days as for convulsive seizures compared to the placebo arm, in both strategies to ensure consistency (Table 28). The number of convulsive seizure days was calculated using the same percent reduction from baseline as observed for convulsive seizures and subtracted from 28 to calculate the number of seizure-free days in each 28-day cycle.

B.3.3.2.3 Non convulsive seizures

Although convulsive seizures are associated with the most severe outcomes for patients with Dravet syndrome, non-convulsive seizures (NCS) can also adversely impact daily activities such as learning, cognitive development and quality of life [2, 43]. However, the recording of NCS frequency is challenging in the study datasets for a number of reasons: these seizures are often short and are in general less noticeable, so harder to record; as seizures are harder to record there will be variability of recording between patients (i.e. some might try to record every small myoclonic jerk, others might only record more obvious atonic drops); and defining clusters vs single events is more difficult. These challenges in recording the number of NCS in the registration trial is shown through the variability in the frequency, with counts ranging from [redacted] NCS a day. Many patients in the trial recorded very few NCS and it is therefore expected that the true frequency of NCS is underreported. For these reasons, in line with the approach taken in the NICE appraisal of cannabidiol [12], the model excludes NCS from the estimation of costs, QALYs and the ICER.

Given the adverse impact NCS have on quality of life, and the observation in the registrational trials that fenfluramine reduces NCS (see section B.2.6.1.4), this is a conservative approach.

B.3.3.2.4 Status epilepticus

Status epilepticus (SE) is a significant contributor to overall mortality in Dravet syndrome [5, 6]. The fenfluramine registration studies were not powered adequately for SE events; however, the literature indicates that SE events increase as convulsive seizures increase [104]. Therefore, the model includes SE events as a proportion of convulsive seizures ([redacted]based on data from the fenfluramine registration studies. As SE is proportional to convulsive seizures, treatment will have an effect on SE in the model.

B.3.3.2.5 Waning of treatment effect

The OLE (Study 1503) trial data with up to 24 months of treatment [78] and data from the Belgian RWE study (observational cohort) with up to 5 years of treatment [71] do not show any indication that the treatment effect of fenfluramine wanes over time. Therefore, waning of treatment effect is not included for either the fenfluramine or the cannabidiol (with clobazam) strategy in the base case. However, as the cannabidiol Summary of Product Characteristics includes OLE study data suggestive of a 25% waning in cannabidiol efficacy over 48 weeks of treatment [14], and published data from the OLE study suggests doses at the top end of the licensed 10-20mg/kg/day dose range [67] (see section B.2.9.5) this is a conservative assumption. Therefore, a scenario analysis has been conducted to explore the impact of the plausible use of higher doses of cannabidiol that may be needed in practice to maintain efficacy(section B.3.9.3).

B.3.3.3 Mortality

Dravet syndrome patients have a greater risk of mortality compared to both the wider population and general epilepsy patients, with SUDEP, SE and accidents such as drowning or injury being the main causes of death [5, 6]. High convulsive seizure frequency increases these risks of mortality, and reducing convulsive seizure frequency, leading to more seizure-free days, therefore reduces the risk of mortality (see section B.1.3.1.3).

In the model, total mortality for each cycle is composed of background mortality (non-seizure related) and convulsive seizure related mortality (SUDEP, SE and accidental mortality). The trials of fenfluramine and cannabidiol were not powered to assess mortality, and over their 14-15 week treatment periods only 1 death was recorded. Mortality estimates were therefore taken from published data, as described below.

B.3.3.3.1 Background mortality

The background mortality for a normal population by gender and age was taken from the Office of National Statistics (ONS) [96].

B.3.3.3.2 SUDEP mortality

It is well accepted that SUDEP is related to convulsive seizure frequency; however, there is a paucity of data on the association between convulsive seizure frequency (which drives the economic model) and SUDEP mortality specifically in Dravet syndrome. A study by Cooper et al. (2016) retrospectively studied mortality rates in a cohort of 100 Dravet syndrome patients over 14 years. The SUDEP mortality rate was 9.32 per 1,000 person-years. Furthermore, 59% of deaths were probable or definite SUDEP, 24% were SE and 18% were accidental [5]. However, no information was available in the Cooper study with which to model SUDEP by seizure frequency.

Therefore, a study by Nilsson et al. (1999) in general epilepsy was used to inform the estimate of the risk of SUDEP based on seizure frequency in Dravet syndrome [31]. Nilsson et al. conducted a study to determine the risk factors for SUDEP in general epilepsy and calculated the relative risk (RR) of SUDEP by annual seizure frequency (Table 29).

Table 29: Relative risks of SUDEP by annual seizure frequency (Nilsson et al.)[31]

Seizure frequency during last year	RR (95% CI)
0–2	1.00
3–12	7.21 (2.52–20.60)
13–50	8.64 (2.88–25.93)
>50	10.16 (2.94–35.18)
Unknown	15.04 (4.26–53.12)

The Nilsson et al study [31] provides estimates of RR of SUDEP by seizure frequency in a general epilepsy population, which are applied in the model to the background general population mortality. However, there is a marked difference between general epilepsy and Dravet syndrome in the number of seizures that patients experience, with Dravet syndrome patients often experiencing several seizures per day instead of a few seizures per year. To account for this, the RRs by seizure count reported in Nilsson were linearly extrapolated up to a seizure count equivalent to the 75th percentile of seizures observed in the fenfluramine trial data ([redacted] seizures annually, to accommodate the fact that Dravet syndrome patients often experience multiple seizures per day), after which the RR of mortality was assumed to remain constant. As each seizure event carries an acute hazard of mortality, and longer-term damage to the brain (e.g. due to hypoxia), it is reasonable to apply the hazard of mortality to each event. The application of the cap on the relative risk of SUDEP by seizure frequency is therefore a conservative approach.

The SUDEP mortality rate from Cooper et al. [5] suggests that the mortality rate in Dravet syndrome patients is much higher than Nilsson predicts in the general epilepsy population. Therefore, the Nilsson et al mortality was calibrated to the expected mortality from Cooper et al observed over a 10-year period. This was achieved by comparing the expected mortality based on Nilsson et al data in the simulated patient population against the expected 9.32% SUDEP mortality after ten years seen in with the Cooper et al [5]. From this, it was determined that a multiplier of 8.38 needed to be applied to the Nilsson relative risks in order to align the simulated patient population's mortality risk with the Dravet specific mortality risk observed in Cooper et al.

The resultant SUDEP mortality for the simulated patients in the model is consistent with available literature on Dravet syndrome mortality that reports a large percentage of deaths occurring before the age of 20 years [5, 105]. There is no evidence to suggest this does not reflect reality, although

it needs to be acknowledged that additional factors may have contributed to the observed higher mortality rate in younger patients versus older patients (e.g. underdiagnosis of Dravet syndrome in older patients as the syndrome was not characterised until the mid-1970's, the introduction of genetic testing only recently, and lack of follow up in older patients), which would skew the age of death to a younger age. Scenario analyses exploring alternative mortality assumptions have therefore been conducted (see section B.3.9.3).

B.3.3.3.3 SE-related mortality

A flat rate of SE mortality from Cooper et al. (0.0029 probability per cycle) [5] was applied to patients in the model experiencing an SE episode, as this was the only available data for patients with Dravet syndrome.

B.3.3.3.4 Accident-related mortality

Whilst the published data in the literature indicates that patients who experience seizures are at greater risk of accidental death [106], data on the risk of accidental death by seizure frequency are lacking. Clinical experts in the UK Pathway research study (section B.3.11) noted that they presumed that seizure frequency (particularly generalised tonic clonic seizures) would be a driver of accidental mortality, although there are no data to substantiate this. Due to a lack of data on this, accidental death was applied as 24% of SUDEP and SE deaths as reported in Cooper et al. [5], i.e., an indirect effect of treatment on accidental mortality was modelled via the effect on SUDEP and SE.

B.3.3.3.5 Total mortality

The resulting total mortality (including background, SUDEP, SE-related and accident related) observed in the simulated patient population assuming a patient starting at age 2 years is shown in Figure 23. Background mortality and mortality without the calibration of SUDEP to Cooper et al are also shown for comparison. These curves reflect mortality in the simulated population without a treatment effect of fenfluramine or cannabidiol (with clobazam) applied. In the model mortality with fenfluramine or cannabidiol (with clobazam) is estimated using the convulsive seizure frequencies, from which the probability of SUDEP, the probability of SE, and the proportional impact on accidental mortality is estimated. Mortality assumptions were validated as described in section B.3.11.

Figure 23: Mortality curve showing Dravet syndrome mortality in the model with all cause background mortality and estimated general epilepsy mortality for reference

B.3.3.4 Adverse events

Treatment emergent adverse events (TEAEs) which could be medically important or expected due to the mechanism of the drug were considered for inclusion in the model. Data on the placebo and treatment arms of the fenfluramine registration studies indicated that there was an increase in TEAEs of all grades in the fenfluramine arms. However, the incidence of serious TEAEs was low and similar across the fenfluramine and placebo arms, and there was little difference in the number experiencing serious treatment-related adverse events between fenfluramine and placebo in either Study 1 ( ) or Study 1504 cohort 2 ( ) (see section B.2.10). On this basis, the addition of fenfluramine to standard of care AEDs does not appear to increase the number of difficult-to-treat or resource intensive adverse events and would not be expected to adversely affect patient quality of life. Adopting a pragmatic assumption that the same would be true for cannabidiol (with clobazam), adverse events are therefore excluded from the model.

B.3.3.5 Treatment discontinuation

Three types of treatment discontinuation were applied in the intervention and comparator strategies in the base case (lack of efficacy, other discontinuation and ongoing discontinuation). In addition, a stopping rule is applied at 6 months after treatment initiation.

B.3.3.5.1 Discontinuation due to lack of efficacy, and other reasons

Lack of efficacy and other discontinuation data was taken directly from the treatment arm of the fenfluramine registration studies for both strategies in the model; the data from the fenfluramine registration studies was applied to both strategies as discontinuations in the subgroup of patients receiving clobazam in the cannabidiol trials was not available. Ongoing discontinuation data was taken from the OLE studies for fenfluramine (Study 1503) and for cannabidiol (GWPCARE5 – sub group of patients on concomitant clobazam) and applied in the respective strategies of the model. For each of these, the discontinuation of patients due to lack of efficacy was relatively applied to the lowest performing patients; other discontinuation and ongoing discontinuation were randomly applied across the population:

i) **Lack of efficacy discontinuation**, applied to mirror the percent of patients that discontinued in the fenfluramine registration studies due to a lack of drug efficacy in the titration or maintenance periods. There were no discontinuations in the titration period across both arms in both studies. Discontinuation in the maintenance period was applied during cycles 2–4 for the intervention and comparator strategies. Those that discontinued for this reason in the model were all individuals that saw only a small reduction (<15%) or no reduction in convulsive seizures.

ii) **Other discontinuation** during the study period (titration and maintenance), i.e. discontinuation due to AEs, withdrawal by patient/physician decision, and other discontinuation not due to lack of efficacy, were applied to the first four cycles to mirror the trial durations.

iii) **Ongoing discontinuation** after the study period. Rates of discontinuation (not due to lack of efficacy) were taken from the OLE periods of the fenfluramine and cannabidiol studies (study 1503 and GWPCARE5 -subgroup of patients receiving concomitant clobazam, respectively) for the relevant treatment arm and applied from cycle five onwards to replicate the longer term impact.

The discontinuation probabilities are provided in Table 30. A principle of discontinuation was applied to both the intervention and comparator strategies to ensure symmetry in patient handling between strategies. Patients discontinued from either arm based on their respective experience in the studies. Patients discontinuing in the model reverted to the seizure frequency seen in the baseline period for that individual, without progression of their disease or further deterioration in health (seizure related or otherwise). Returning each patient to their own baseline seizure frequency, rather than to an average seizure frequency, ensured that discontinuation did not lead to a decrease/increase in the seizure frequency for that individual patient compared with what they had experienced at baseline.

Table 30: Discontinuation probabilities

Discontinuation	Arm in study	Trial period	Probability per model cycle
Lack of efficacy	Fenfluramine + SoC and cannabidiol + SoC	Titration	[redacted]
	Fenfluramine + SoC and cannabidiol + SoC	Maintenance	[redacted]
Other	Fenfluramine + SoC and cannabidiol + SoC	Titration	[redacted]

Discontinuation	Arm in study	Trial period	Probability per model cycle
	Fenfluramine + SoC and cannabidiol + SoC	Maintenance	[redacted]
Ongoing	Fenfluramine + SoC	Post-maintenance	[redacted]
Ongoing	Cannabidiol + SoC	Post-maintenance	[redacted]

Abbreviations: SoC, standard of care.

B.3.3.5.2 Treatment stopping rule

Although the EMA has not proposed a "stopping rule" for fenfluramine on the basis of efficacy, it is expected that clinicians would stop fenfluramine and cannabidiol treatment if there was insufficient improvement in seizure frequency at 6 months. A treatment stopping rule was applied in the base case for fenfluramine and cannabidiol in patients not achieving at least a 30% reduction in convulsive seizure frequency at 6 months compared with the patient's baseline seizure frequency prior to starting treatment, in line with the NICE recommendation for cannabidiol in TA614 [12]. As the base case assumes no waning of effect of fenfluramine or cannabidiol over time, this eliminates the need for application of the stopping rule every subsequent 6 months.

B.3.3.5.3 Subsequent treatment following discontinuation

Due to a lack of specific data and for pragmatic reasons, the economic analysis does not model any subsequent add-on strategies following discontinuation; patients remain on their existing SoC treatment following treatment discontinuation. This is a conservative approach, as the superior efficacy of fenfluramine demonstrated in the ITC (see section B.2.9) means that treatment discontinuations due to a lack of efficacy would occur more frequently with cannabidiol (with clobazam) than with fenfluramine, which would return patients on cannabidiol (with clobazam) in the model to their less costly SoC treatment more quickly.

B.3.3.6 Clinical expert opinion

Details are provided in section B.3.11.

B.3.4 Measurement and valuation of health effect

As per the NICE reference case, the economic analysis measures health effects in the form of QALYs. The SLR, described in Appendix H identified a range of HTAs and a published cost utility analysis of Dravet syndrome therapies. These resorted to using utility values obtained in patients with Lennox-Gastaut syndrome [26, 64, 94, 107], or else a visual analogue scale for Dravet syndrome patients/carers to estimate utilities rather than a NICE-preferred approach [12]. No studies specifically reporting health state utility values for Dravet syndrome patients as a function of seizure-free days were identified through the SLR (see Appendix H). Therefore, given there were Dravet syndrome-specific patient and carer HRQoL data available from the fenfluramine trials, these were used to estimate utilities for the economic model.

B.3.4.1 Health-related quality of life data from clinical trials

As described in section B.2.6.1.6, the fenfluramine double-blind studies and the OLE study, data was collected for the following patient and caregiver HRQoL measures:

- Patient - Quality of life in childhood epilepsy (QOLCE-16)
- Patient - Paediatric Quality of Life Inventory (PedsQL) Version 4 Generic Score Scale
- Carer - EuroQoL-5 Dimensions five-level (EQ-5D-5L)

Significant improvements in HRQoL using the generic PedsQL instrument were observed with addition of fenfluramine 0.7mg/kg/day to SoC in Study 1[3], and there was no evidence of a significant decrease in HRQoL with addition of fenfluramine to SoC including stiripentol in Study 1504 cohort 2 [4]. In terms of carer reported HRQoL, there was a directional improvement across each domain of the EQ-5D-5L (for the carer) when patients experienced a reduction in seizure frequency, irrespective of treatment arm (i.e. intervention or comparator).

B.3.4.2 Mapping

B.3.4.2.1 Patient utilities

To obtain patient EQ-5D utility values for use in the model, PedsQL data from the registration studies was mapped to EQ-5D-Y using the Kahn et al. (2014) algorithm [101], the only published and validated mapping algorithm available to estimate patient utility scores from these data. The QOLCE data from the trails could not be used as no published mapping algorithms are available to convert the QOLCE scores into EQ-5D utilities. PedsQL data were available for three timepoints in the fenfluramine registration studies; visit 3 (randomisation), visit 8 (end of titration period) and visit 12 (end of maintenance period or discontinuation). Complete PedsQL data for all visit times was available for most patients (196 of the 206 patients) in the studies [75, 76].

A linear mixed effect regression model was developed to quantify the relationship between patient EQ-5D-Y and clinically relevant variables. The final model included the following covariates:

- Age group (<6 years, 6-11 years and ≥12 years)
- 28-day frequency of number of seizure-free days
- Motor impairment (none, ataxia, severe)
- Study ID (Study 1, Study 1504 cohort 2)

Subject ID and visit ID (visit 3, 8, 12) formed the two random effect components of the model. Further information on the statistical analyses conducted is provided in Appendix M.

With the quantified relationship between patient characteristics and patient EQ-5D-Y calculated through the regression analysis, this relationship was used to predict a patient's utility score in each 28-day cycle of the model. This accounted for the number of seizure-free days experienced in that cycle, age in that cycle (based on age bands used within the studies (<6, 6-11 or ≥12 years), motor impairment (none, ataxia, severe) and which study an individual was in (Study 1 or Study 1504 cohort 2). This generated a predicted patient utilities table.

A graphic depicting this table is presented in Figure 24 and Figure *25* for Study 1 and Study 1504 cohort 2, respectively. To obtain the utilities per cycle for each patient, their age group, level of

motor impairment and number of seizure-free days in that cycle were used. For example, if a patient in study 1 had 10 seizure-free days in a cycle (read off y axis), was <6 years old age and had no motor impairments the corresponding utility value for that cycle would be [redacted] (read off x axis). Figure 24 and Figure 25 show that patients with severe motor impairments have lower utility values than those with less severe impairments and utility values increase as the number of convulsive seizure-free days increases as would be expected.

Regression coefficients, standard errors and p-values for all fixed effects covariates in the patient regression model are provided in Table 31.

Figure 24. EQ-5D marginal means for patients not on concomitant stiripentol (Study 1)

Figure 25: EQ-5D marginal means for patients taking concomitant stiripentol (Study 1504 cohort 2)

Table 31: Regression coefficients, standard errors and p-values for all fixed effects covariates in the patient regression model

Covariate	Coefficient†	Std. Error	p-value
28-day frequency of seizure free days	[redacted]	0.1517	<0.001
Study 1	[redacted]	2.869	0.70
Age 6-11 years	[redacted]	3.504	0.06
Age >12 years	[redacted]	3.810	0.11
Motor impairments: Ataxia	[redacted]	2.920	<0.05
Motor impairments: Severe	[redacted]	7.821	0.07

† Coefficients refer to a 0-100 scale. All utility values predicted using these coefficients were divided by 100 before being used in the model.

B.3.4.2.2 Carer utilities

The severe needs of many people with Dravet syndrome can have a major impact on the personal life of parents and carers (see section B.1.3.1.5). Therefore, in line with the approach adopted in the NICE appraisal of cannabidiol [12], and in line with the NICE reference case that states the perspective for modelled outcomes should be all direct health effects, whether for patients or, when relevant, carers [69], carer utilities were included in the base case. EQ-5D-5L data was collected directly from the carers in the registration studies at two time points: visit 3 (randomisation) and visit 12 (end of maintenance period). As per the NICE position statement on use of the EQ-5D-5L [108], all data were mapped from EQ-5D-5L onto EQ-5D-3L using the UK value set (updated October 2019), developed by van Hout et al. (2012) [102]. A linear panel regression model with fixed effects was developed to estimate carer utility values. The following covariate was retained in the final model:

- 28-day frequency of number of seizure-free days

Further information is provided in Appendix M.

With the quantified relationship between patient characteristics and carer EQ-5D-3L calculated through the regression analysis, this relationship was used to predict the carer utility score in each 28-day cycle, taking into account the number of seizure-free days experienced by the patient in that cycle. This generated a predicted carer utilities table. A graphic depicting this table is presented in Figure 26. To obtain the utilities per cycle for each carer the number of convulsive seizure-free days that the patient experienced in that cycle were used. If a patient in study 1 had 10 seizure-free days in a cycle, the corresponding utility value for the carer is [redacted](read off x axis).

Regression coefficients, standard errors and p-values for all fixed covariates in the patient regression model are provided in Table 32.

The cost-effectiveness model considers the utilities of 1.8 carers per patient in the base case as accepted in the cannabidiol NICE appraisal [12]; the carers' utility values are removed from the model when the patient dies.

Figure 26: EQ-5D marginal means for carers (Study 1 and Study 1504 cohort 2)

Table 32: Regression coefficients, standard errors and p-values for the fixed effect covariate in the carer regression model

Covariate	Coefficient	Std. Error	p-value
28-day frequency of seizure free days	[redacted]	0.3862	<0.001

† Coefficients refer to a 0-100 scale. All utility values predicted using these coefficients were divided by 100 before being used in the model.

Excel spreadsheets containing the patient and carer utility values are provided as embedded files in Appendix M.

B.3.4.3 Health-related quality of life studies

An SLR was performed to identify HRQoL and health-state utility data relevant to patients and carers with Dravet syndrome. Full details on the search strategy, methodology, PRISMA flow diagram and relevant extracted data from the SLR are outlined in Appendix H.

There were 16 published studies identified that reported data on health-related quality of life in Dravet syndrome, and an additional four HTAs (AWMSG; CADTH; SMC and NICE) and a published cost utility analysis of Dravet syndrome therapies that make reference to health state utility values (see Tables 20 and 21 in Appendix H, section H.1.2). As per section B.1.3.1.5, the studies reporting HRQoL data confirmed that Dravet syndrome has a significant impact on both patients and carers and that the frequency of seizures has a negative impact on HRQoL.

The HTAs and the published cost utility analysis have used utility values taken from LGS patients [26, 64, 94, 107], with the exception of the NICE appraisal of cannabidiol that derived utility values from Dravet syndrome patients and carers using a visual analogue scale, rather than the NICE-preferred EQ-5D, but results are redacted as confidential [41]. No previous HTAs or published cost effectiveness analyses were identified that reported health state utility values for Dravet syndrome patients and their carers that could be used in our model. Therefore, utility values were

appropriately mapped from the HRQoL data collected in the fenfluramine trials (see section B.3.4.2).

Of note, several of the HRQoL studies reporting quality of life are aligned with the findings of our mapping exercise; e.g. Dunwoody et al 2020 and Sinoo et al 2019 report that younger patients have lower quality of life measured by PedsQL [109, 110] in line with the results from our analysis (Figure 22 and 23) where we identified that individuals >6 years of age had a significantly worse QoL in comparison to those <6 years of age.

B.3.4.4 Adverse reactions

As AEs were not included in the model, no specific AE utility values are assumed.

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

The health-related quality of data used in the model are detailed in B.3.4.2.

B.3.5 Cost and healthcare resource use identification

A systematic literature review was conducted to identify relevant resource use and cost data for patients with Dravet syndrome. Full details on the search and results are outlined in Appendix I.

There were 31 studies that reported data on the healthcare resource use and costs from publications globally (see Tables 27-29 in Appendix I, section I.1.1.3). This included studies from Germany, France, Netherlands, Denmark, USA, and Canada. For this review, only data from the subset reporting on resource use and cost from patients/caregivers in the UK were extracted (9 publications), as the others are less relevant to a UK population.

While several of the studies reported on the use and associated costs of drugs, routine and emergency care in the UK, none of them did so at the level of detail needed for the patient-level simulation model.

In the absence of the detailed published data required, estimates of ongoing and emergency HCRU were obtained from a UK Pathway research study conducted in physicians and specialist epilepsy nurses in England involved in the management and treatment of Dravet syndrome patients [55] (section B.3.11). Resource use is likely to be lower for patients who can achieve clinically meaningful reductions in seizure frequency, particularly emergency admissions and ongoing care associated with seizure and disease management. The costs associated with resource use were obtained from the British National Formulary (March 2020) [97], NHS schedule of reference costs (2018/19) [99] and the PSSRU Unit Costs of Health and Social Care (2019) [100].

B.3.5.1 Intervention and comparators' cost and resource use

The base case analysis limited intervention and comparator costs to drug acquisition costs only. Given that most AEDs are administered orally by the parent/caregiver, the model assumed no treatment administration cost.

B.3.5.1.1 Drug acquisition costs and resource use

The dose of fenfluramine and other AEDs changes over a patient's lifetime are based on patient's weight (determined as a function of age). For each cycle, average daily doses and costs were calculated using the recommended BNF dose for patients with Dravet syndrome or epilepsy, by age and/or weight as applicable. The total cost of concomitant SoC AEDs was calculated by weighting the daily cost of each AED by the percentage of patients receiving each concomitant AEDs in the fenfluramine trials for those drugs recommended by NICE (Table 26); the weighting for each AED was dependent on concomitant stiripentol usage.

Limited data is available on patient weight in patients with Dravet syndrome. However, clinical opinion suggests that there should be limited discrepancy in weight between Dravet patients and the general population of a similar age [55], which is supported by the weights of patients within the studies. Therefore, average weight by age data from the general population is used to model Dravet syndrome patient weight in the model.

To account for changes in a patient's weight over time, the model has derived estimates of weight by age using general population data provided by the Royal College of Paediatrics and Child Health (RCPCH) [95] and the NHS health survey for England [103]. The model assumes an average patient weight of 12 kg at 2 years, the earliest age to start treatment with fenfluramine based on its anticipated licensed indication [10], with a continuous linear weight function to estimate weight as patients age applied to all doses of AEDs. The model assumes a patient's weight reaches a maximum of 78 kg and then plateaus at age 25 years in line with the RCPCH data average weight of adults in the UK (Figure 27). The dose of certain drugs is based on a patient's weight. As applicable, a maximum capped dose was applied to those drugs (Table 33).

The assumed doses for SoC AEDs and rescue medications were based on the individual product doses as reported in the BNF/CBNF (March 2020), the draft SmPC for fenfluramine and the preferred appraisal committee dosing assumption for cannabidiol in NICE TA614 (Table 33). The committee in the NICE cannabidiol appraisal (TA614) felt that 20% of patients would have the maximum cannabidiol daily dose of 20 mg/kg/day and 80% of patients would have the minimum daily dose of 10 mg/kg/day [12]. As a result, the average daily dose of cannabidiol preferred by the committee was 12 mg/kg/day. Therefore, this dose is used in the model. As the cannabidiol trial data do not suggest a significant difference in efficacy between the 10mg/kg/day dose and the 20mg/kg/day dose, both the cost and the treatment efficacy of cannabidiol reflect this 12 mg/kg/day dose.

Figure 27. Linear function for age versus weight (model and trial data). The model weight is extrapolated to reach plateau at the average UK adult weight at age 25 (green dot)

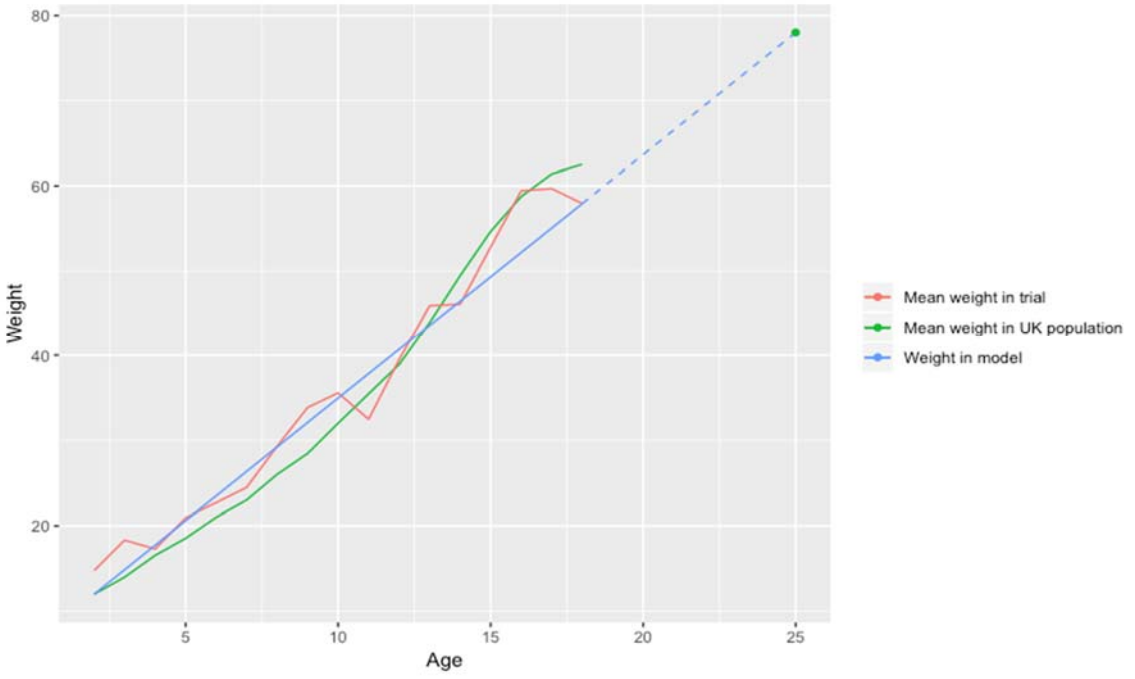


Table 33: Average and maximum drug doses by age group per day

	Age 1-5 years			Age 6-11 years			Age 12-17 years			Age 18+ years		
Drug	**Avg dose mg/kg/d**	**Avg dose mg/d**	**Max dose mg/d**	**Avg dose mg/kg/d**	**Avg dose mg/d**	**Max dose mg/d**	**Avg dose mg/kg/d**	**Avg dose mg/d**	**Max dose mg/d**	**Avg dose mg/kg/d**	**Avg dose mg/d**	**Max dose mg/d**
Intervention												
FFA with stiripentol†	0.4	–	17	0.4	–	17	0.4	–	17	0.4	–	17
FFA without stiripentol†	0.7	–	26	0.7	–	26	0.7	–	26	0.7	–	26
Comparators												
Cannabidiol‡	12	–	–	12	–	–	12	–	–	12	–	–
Concomitant AEDs												
Clobazam	0.5	–	30	0.65	–	60	0.65	–	60	–	25	60
Levetiracetam	40	–	–	40	–	–	40	–	–	–	2000	3000
Stiripentol	50	–	–	50	–	–	50	–	–	50	–	–
Topiramate	7	–	400	7	–	400	7	–	400	–	300	400
Valproate (sodium and semisodium)	27.5	–	–	27.5	–	–	–	1500	2500	–	1500	2500
Valproic acid	27.5	–	–	27.5	–	–	–	1500	2500	–	1500	2500
Rescue medications												
Diazepam	–	7.5	20	–	7.5	20	–	15	40	–	15	40
Midazolam	–	5	10	–	7.5	–	–	10	20	–	10	20

Abbreviations: AEDs, anti-epileptic drugs; Avg, average; d, day; FFA, fenfluramine; min, minimum; max, maximum.

† Fenfluramine dose is only adjusted with stiripentol use i.e. not with any other concomitant AEDs.

‡ Preferred dosing assumption by the committee in TA614.

Drug costs were taken from the drug tariff price as reported in the March BNF [97](Table 34), except the list price of cannabidiol which was taken from an alternative source as it is not reported in the BNF. For drugs that had different formulations, a weighted average cost per mg was calculated using the volume of prescriptions dispensed in England from the Prescription Cost Analysis (PCA) by Pharmacy and Appliance Contractors in England (November 2019) [98] (Table 34).

Table 34: Drug acquisition costs used in base case analysis

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
Intervention								
Fenfluramine	OS	60ml	2.2mg/ml	132	[redacted]	[redacted]	N/A	N/A
		120ml		264	[redacted]			
		250ml		550	[redacted]			
		360ml		792	[redacted]			
Comparators								
Cannabidiol (list price)	OS	100 ml	100 mg/1 ml	10000	£850.29	£0.0850	N/A	N/A
Concomitant AEDs								
Clobazam	OS	150 ml	1 mg/ml	150	£90.00	£0.6000	30.6%	£0.2537
			2 mg/ml	300	£95.00	£0.3167	20.1%	
	Tablet	30	10 mg	300	£3.82	£0.0127	49.3%	
Levetiracetam	Tablet	60	250 mg	15000	£3.35	£0.0002	19.2%	£0.0003
			500 mg	30000	£7.21	£0.0002	27.9%	
			750 mg	45000	£6.34	£0.0001	5.3%	
			1000 mg	60000	£8.90	£0.0001	9.9%	
	Granules	60	250 mg	15000	£22.41	£0.0015	0.2%	
			500 mg	30000	£39.46	£0.0013	0.2%	
			1000 mg	60000	£76.27	£0.0013	0.1%	
	OS	300 ml	100 mg/ml	30000	£7.69	£0.0003	37.2%	
	Solution for infusion	5 ml	100 mg/ml	500	£127.31	£0.2546	0.0%	
Stiripentol	Capsules	60	250 mg	15000	£284.00	£0.0189	19.4%	£0.0180
			500 mg	30000	£493.00	£0.0164	15.0%	
	Powder	60	250 mg	15000	£284.00	£0.0189	41.4%	
			500 mg	30000	£493.00	£0.0164	24.2%	

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
Topiramate	Tablet	60	25 mg	1500	£5.69	£0.0038	39.2%	£0.0063
			50 mg	3000	£11.59	£0.0039	27.7%	
			100 mg	6000	£19.72	£0.0033	17.6%	
			200 mg	12000	£44.67	£0.0037	2.9%	
	Capsules	60	15 mg	900	£14.79	£0.0164	1.9%	
			25 mg	1500	£16.02	£0.0107	4.3%	
			50 mg	3000	£36.45	£0.0122	3.6%	
	OS	150 ml	10 mg/ml	1500	£129.00	£0.0860	1.7%	
		280 ml	20 mg/ml	5600	£195.69	£0.0349	0.9%	
Valproate (sodium and semisodium)	Tablet	100	100 mg	10000	£5.60	£0.0006	3.0%	£0.0007
	MR tablet	100	200 mg	20000	£11.65	£0.0006	16.8%	
			300 mg	30000	£17.47	£0.0006	7.7%	
			500 mg	50000	£29.10	£0.0006	16.9%	
	GR tablet	100	200 mg	20000	£9.67	£0.0005	0.0%	
			500 mg	50000	£23.27	£0.0005	0.0%	
	MR capsule	100	150 mg	15000	£7.00	£0.0005	0.2%	
			300 mg	30000	£13.00	£0.0004	1.2%	
	MR granules	100	50 mg	100000	£41.00	£0.0004	0.0%	
			100 mg	100000	£41.00	£0.0004	0.3%	
			250 mg	100000	£41.00	£0.0004	0.1%	
			500mg	100000	£41.00	£0.0004	0.3%	
			750 mg	100000	£41.00	£0.0004	0.1%	
			1000 mg	100000	£41.00	£0.0004	0.1%	
	OS	300 ml	40 mg/ml	12000	£9.77	£0.0008	53.3%	
	Solution for injection	5 amp	100 mg/ml	1500	£35.00	£0.0233	0.0%	

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
	Powder + solvent for injection	1 vial	400 mg	400	£13.32	£0.0333	0.0%	
Valproic Acid	GR capsule	100	150 mg	15000	£3.68	£0.0002	11.1%	£0.0002
			300 mg	30000	£7.35	£0.0002	27.3%	
			500 mg	50000	£12.25	£0.0002	61.6%	
Rescue medications								
Diazepam	Enema	5	5 mg	25	£5.90	£0.2360	44.9%	£0.1875
			10 mg	50	£7.40	£0.1480	55.1%	
Midazolam (hydrochloride)	Oromucosal solution	4	5 mg/1 ml	20	£85.50	£4.2750	17.4%	£2.9851
			7.5 mg/1.5 ml	30	£89.00	£2.9667	14.4%	
			10 mg/2 ml	40	£91.50	£2.2875	57.1%	
Midazolam (maleate)	Oromucosal solution	1	10 mg/1 ml	10	£45.76	£4.5760	11.1%	

Abbreviations: Amp, ampoule; Avg, average; MR, modified-release, GR, gastro-resistant, N/A, not applicable; OS, oral suspension.
The manufacturer of cannabidiol (Epidyolex) has agreed a confidential commercial agreement (Patient Access Scheme) with NHS England. The published list price for cannabidiol, as for all drug prices, has been used for the cost-utility analysis. The price of fenfluramine reflects the simple [redacted] discount price proposed to NHS England and excludes VAT.
A scenario analysis (Figure 32) has been provided to allow insight into the sensitivity of the model to varying % discounts applied to the published list price.

B.3.5.1.2 Monitoring costs

Additional costs (Table 35) are included in the model for echocardiograms to confirm the absence of valvular heart disease or pulmonary hypertension in line with the draft SmPC for patients on fenfluramine as follows [10]:

- An initial echocardiogram prior to starting treatment
- Subsequent echocardiograms every six months for the first two years and annually thereafter
- A final echocardiogram on discontinuing fenfluramine treatment

These costs are for the echocardiogram procedure, and we assume that this would be done at a routine ongoing care appointment, so no further costs are included for monitoring.

Table 35: Fenfluramine monitoring costs by age group

Resource	Average Cost†	Reference
Echocardiogram (age ≤5 years)	£53.27	NHS Reference Costs 2018/19 Simple echocardiogram, 5 years and under (RD51C); Service Codes IMAGDA, IMAGOP, IMAGOTH
Echocardiogram (age 6-18 years)	£53.28	NHS Reference Costs 2018/19 Simple echocardiogram, between 6 and 18 years (RD51B); Service Codes IMAGDA, IMAGOP, IMAGOTH
Echocardiogram (age 19+ years)	£72.57	NHS Reference Costs 2018/19 Simple echocardiogram, 19 years and over (RD51A); Service Codes IMAGDA, IMAGOP, IMAGOTH

† Average cost = weighted average of number of attendances and unit cost across codes. An echocardiogram would be performed as part of a routine visit.

B.3.5.2 Health state unit costs and resource use

Estimates of resource use were elicited from physicians and nurses involved in the management and treatment of paediatric and adult patients with Dravet syndrome as reported in the UK Pathway research study [55] (see section B.3.11 for further detail).

In the model, HCRU was split between ongoing resources to maintain routine management of patients with Dravet syndrome, and emergency resources that are required when severe seizure events occur. As these resources vary according to a patient's age and seizure burden, they are both considered variable rather than fixed costs.

B.3.5.2.1 Ongoing resource use

Patients diagnosed with Dravet syndrome have ongoing care for their condition, in primary, secondary and/or tertiary (and in some cases quaternary) care institutions. As reported by clinical experts in the UK Pathway research study [55], a patient's age and the amount of seizure control measured by the number of seizures influence the ongoing care for patients. Typically, as patients

age after initial diagnosis, they require less frequent ongoing care as carers are better able to manage their condition.

Whilst seizures are not defined as high or low frequency in the model, for the purpose of determining ongoing resource use, resource use was categorised based on the average monthly number of convulsive seizures a patient experienced. Ongoing resource use would be regular visits at specific intervals, which can be thought of as ongoing SoC care resource use alongside drug therapies.

In the model, the annual resource use was weighted by the percentage of patients accessing each type of care in the relevant age and seizure frequency group. Annual resource use was assumed to happen at equal intervals throughout a year and therefore annual resource use was divided by the number of cycles a year to determine the resource use per 28-day cycle.

Table 36: Definition of seizure frequency to determine ongoing resource use (UK Pathway research study)

Frequency	Average seizures per month	
	2-17 years	18+ years
High (minimum number of seizures / month)	[redacted]	[redacted]
Low (maximum number of seizures / month)	[redacted]	[redacted]

Note: medium frequency is between the defined low and high cut-offs.

Table 37: Annual ongoing resource use (number of visits) in the presence of high seizure frequency by age group (UK Pathway research study)

	Total % of patients accessing	Number of annual visits by patient age group (years)						
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary care GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F2F, face-to-face.

Table 38: Annual ongoing resource use (number of visits) in the presence of medium seizure frequency by age group (UK Pathway research study)

	Total % of patients accessing	Number of annual visits by patient age group (years)						
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary care GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F2F, face-to-face.
Note: the medium group are those patients who have seizures between the low and high frequency.

Table 39: Annual ongoing resource use (number of visits) in the presence of low seizure frequency by age group (UK Pathway research study)

	Total % of patients accessing	Number of annual visits by patient age group (years)						
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary care GP visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Secondary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tertiary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Consultant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quaternary non-F2F Nurse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: F2F, face-to-face.

B.3.5.2.2 Emergency resources

Emergency resources are directly incurred due to individual seizure episodes. These resources are therefore directly linked to the number of seizures in a cycle that would trigger rescue medication, emergency care, including ambulance call outs, ambulance conveyance to hospital, A&E visits, and general ward or ICU admissions.

Rescue medications are fast-acting sedatives given ‘as needed’ in specific situations and serve to reduce brain activity. These are commonly benzodiazepines (e.g. diazepam and midazolam). According to the UK Pathway research study [55], physicians who manage Dravet syndrome patients reported that rescue medication would be administered for all SE events, and also in other cases (e.g. clusters of seizures, extended focal seizures, etc). In the model it was assumed that a percentage of seizures will be severe enough to warrant a patient taking rescue medication; it was conservatively estimated that they would be given this rescue medication just for SE events.

The number of rescue medications given per month was estimated by multiplying a patient’s probability of SE by their total 28-day seizure frequency (assumes that for all SE events rescue medications are given). The cost of rescue medication was estimated in the same way as that of other AEDs (see section B.3.5.1.1 and Table 33 and Table 34).

Of those taking rescue medication, a proportion have ambulance call outs, and a percentage of ambulance call outs are then conveyed to hospital and seen in A&E. A percentage of patients seen in A&E will then be discharged, or admitted to inpatient care on either a general ward or ICU. Of those admitted to the ward for inpatient care on a general ward, a percentage will be seen and discharged in one day and the remainder will be kept in hospital for a given length of stay. The estimates for emergency resource use are based on patient’s age, as reported by UK clinical experts [55].

Patients with epilepsy and Dravet syndrome have high rates of accidents and injury that may require emergency resource use (61% of patients in Strzelczyk et al., 2019) [38]; however, there are no data to link this with seizure frequency. Therefore, the model conservatively excludes emergency resource use due to accidents. Annual emergency resource use by age group is summarised in Table 40.

Table 40: Annual emergency resource use by age group (following rescue medication)

Patient age (years)	% call ambulance	% attend A&E (of those that call an ambulance)	From A&E % admitted on general ward or ICU		Length of stay (days)	% discharged same day
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient age (years)	% call ambulance	% attend A&E (of those that call an ambulance)	From A&E % admitted on general ward or ICU		Length of stay (days)	% discharged same day
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: A&E, accident and emergency; ICU, intensive care unit.

B.3.5.2.3 Ongoing and emergency resource use costs

Unit costs for ongoing and emergency resources and length of stay for inpatient admissions on a general ward were taken from established sources, namely the PSSRU 2019 [100] and the NHS schedule of reference costs 2018/19 [99] (Table 41 and Table 42).

Table 41: Ongoing resource use costs applied in the model

Resource	Average Cost†	Reference
GP visit	£37.40	PSSRU 2019 GP visit for ongoing monitoring (includes direct cost with qualifications, per consultation)
Consultant outpatient visit F2F (paediatric)	£207.94	NHS Reference Costs 2018/19 Consultant led (paediatric epilepsy): 1. Non-Admitted Face-to-Face Attendance, Follow-up (WF01A), 2. Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up (WF02A)
Consultant outpatient visit non-F2F (paediatric)	£76.12	NHS Reference Costs 2018/19 Consultant led (paediatric epilepsy): Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF01C)
Nurse outpatient visit F2F (paediatric)	£153.18	NHS Reference Costs 2018/19 Non-consultant led (paediatric epilepsy): 1. Non-Admitted Face-to-Face Attendance, Follow-up (WF01A), 2. Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up (WF02A)
Nurse outpatient visit non-F2F (paediatric)	£93.12	NHS Reference Costs 2018/19 Non-consultant led (paediatric epilepsy): Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF01C)
Consultant outpatient visit F2F (adult)	£176.15	NHS Reference Costs 2018/19 Consultant led (general medicine): 1. Non-Admitted Face-to-Face Attendance, Follow-up (WF01A), 2. Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up (WF02A)
Consultant outpatient visit non-F2F (adult)	£133.92	NHS Reference Costs 2018/19 Consultant led (general medicine): 1. Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF01C), 2. Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF02C)
Nurse outpatient visit F2F (adult)	£109.32	NHS Reference Costs 2018/19 Non-consultant led (general medicine): 1. Non-Admitted Face-to-Face Attendance, Follow-up

Resource	Average Cost†	Reference
		(WF01A), 2. Multiprofessional Non-Admitted Face-to-Face Attendance, Follow-up (WF02A)
Nurse outpatient visit non-F2F (adult)	£69.12	NHS Reference Costs 2018/19 Non-consultant led (general medicine): 1. Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF01C), 2. Multiprofessional Non-Admitted Non-Face-to-Face Attendance, Follow-up (WF02C)

† Average cost = weighted average of number of attendances and unit cost across codes, where applicable.

Table 42: Emergency resource use costs applied in the model

Resource	Average Cost†	Reference
Ambulance call out (all ages)	£209.38	NHS Reference Costs 2018/19 Ambulance attendance (see and treat or refer - code ASS01)
Convey to hospital in ambulance (all ages)	£47.95	NHS Reference Costs 2018/19 Cost to convey patient to hospital for those who have an ambulance attendance (cost difference between ASS02 see and treat and convey (£257.34) - ASS01 see and treat or refer)
Non-admitted patient A&E (all ages)	£144.48	NHS Reference Costs 2018/19 Non-admitted patient A&E episodes (service codes T01A, T02A, T03A, T04A; currency codes VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z, VB11Z)
Admitted patient A&E (all ages)	£260.92	NHS Reference Costs 2018/19 Admitted patient A&E episodes (service codes T01NA, T02NA, T03NA, T04NA; currency codes VB01Z, VB02Z, VB03Z, VB04Z, VB05Z, VB06Z, VB07Z, VB08Z, VB09Z, VB11Z)
Non-elective inpatient general ward (adults) >1 day length of stay	£530.28	NHS Reference Costs 2018/19 Non-elective (>1 day) episodes; Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+ (AA26C, AA26D, AA26E, AA26F, AA26G, AA26H)
Non-elective inpatient general ward (adults) 0 day length of stay	£436.89	NHS Reference Costs 2018/19 Non-elective (same day discharge) episodes; Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-15+ (AA26C, AA26D, AA26E, AA26F, AA26G, AA26H)
ICU admission (paediatrics)	£1,725	NHS Reference Costs 2018/19 Service codes CCU04 - Paediatric intensive care unit (paediatric critical care patients predominate), CCU16 - Ward for children and young people, CCU17 - High dependency unit for children and young people, and Paediatric Critical Care currency codes XB01Z- XB05Z (Advanced Critical Care 1-5), XB06Z (Intermediate Critical Care), XB07Z (Basic Critical Care), XB09Z (Enhanced Care)
ICU admission (adults)	£1,506	NHS Reference Costs 2018/19 Service codes CCU01 - Non-specific, general adult critical care patients predominate, CCU05 -

		Neurosciences adult patients predominate, across Adult Critical Care, 0-6 or more organise supported currency codes XC01Z-XC07Z

† Average cost = weighted average of number of attendances and unit cost across codes, where applicable.
Note: number of bed days and average length of stay are from the 2017/18 NHS reference costs as these are not reported 2018/19 NHS reference costs.

B.3.5.3 Adverse event unit costs and resource use

AEs were not included in the model (see SectionB.3.3.4).

B.3.5.4 Miscellaneous unit costs and resource use

Non-seizure related healthcare costs for Dravet patients, which includes speech therapy, behavioural therapy and remedial help, were not included in the model. This is because there is limited data available to quantify a relationship between seizure frequency and the severity of comorbidities in Dravet syndrome patients. No additional costs or resource use items were included in the model that have not already been reported elsewhere.

B.3.6 Uncertainty analysis

A number of uncertainty analyses were performed to assess the robustness of the model results to a range of structural and parametric assumptions.

B.3.6.1 Probabilistic sensitivity analysis

The impact of parameter uncertainty in the model was explored through a probabilistic sensitivity analysis. For each parameter in the model for which there was a measure of variance, we drew a new value based on an appropriately defined statistical distribution with shape and scale parameters of that distribution determined from the variance of the data (where possible and appropriate). A complete list of all parameters varied, the assumed distribution for each, SD, shape and scale parameters are provided in Appendix N. 1000 independent sets of these parameters were drawn and the model re-run for 1000 realisations. An overview of the parameter types that were varied and respective distributions assumed in the PSA are presented in Table 43. For a complete list of all parameters defined individually, please see Appendix N.

Table 43: Summary of the parameter group evaluated, and distribution type assumed in the PSA

Parameter group	Number of parameters in each group [+]	Distribution type assumed
Seizure category (costs cat only)	6	Uniform
Discontinuation	8	Uniform
Adverse events	3	Uniform

Parameter group	Number of parameters in each group [+]	Distribution type assumed
Costs of other AEDs	8	Gamma
Probability an individual is on another AED not on stiripentol	8	Beta
Probability an individual is on another AED on stiripentol	8	Beta
Cost of rescue medication	2	Gamma
Ongoing healthcare costs	14	Gamma
Emergency healthcare resource use costs	8	Gamma
Proportion of adults and paediatric patients that visit primary, community, secondary, tertiary or quaternary care, by age group	10	Beta
Frequency of attendance at different health care settings, by age group	294	Uniform
Probability of calling an ambulance by age group	7	Beta
Probability of going to A&E after an ambulance has been called, by age group	7	Beta
Probability of being admitted as in inpatient after attending A&E, by age group	7	Beta
Probability of same day discharge as an inpatient, by age group	7	Beta
Days spent in hospital, by age group	7	Uniform
Probability of being admitted to ICU after A&E attendance, by age group	7	Beta
Probability of SE	1	Uniform
Proportion of patients with each of the 3 comorbidities	3	Uniform
Treatment effect of fenfluramine and cannabidiol	8	Posterior samples from Bayesian regression
Patient utilities	5	Perturbed coefficients using Cholesky decomposition of the covariance matrix [111]
Carer utilities	1	Perturbed coefficients using Cholesky decomposition of the covariance matrix

[+] Number of parameters within each group is defined but draws for all parameters in each group were done independently.
Note: The specifications for the shape and scale of each parameter's distribution, the SD and min and max are provided in Appendix N. Abbreviations: AED, anti-epilepsy drug; A&E, Accident & Emergency; ICU, intensive care unit; SE, status epilepticus.

B.3.6.2 Deterministic sensitivity analysis

To understand the impact of variance in individual parameters, and determine whether any parameter (or groups of parameters) was a substantial driver of the ICER, deterministic sensitivity

analysis was performed. This was conducted by varying each parameter (or parameter group) to its lower and upper bounds of its variance. Parameters that were similar were grouped together and varied simultaneously, e.g. probability of calling an ambulance was assigned for 7 age groups (2-3 years, 3-5 years, 5-8 years, 8-14 years, 14-18 years, 18-25 years and 25+ years) as such these 7 parameters were varied simultaneously. Parameters that were distinct from one another were varied independently. For base values that were taken from the UK Pathways research study [55], minimum and maximum values that were reported were used as the lower and upper bounds for the DSA values. Discontinuation rates were varied by +/- 10% as per the approach taken for cannabidiol in NICE TA614. For averaged costs where a minimum and maximum were available these were used as the lower and upper bounds, or where no range of values were available, we varied the base values +/- 20%. However, for the proportion of individuals with different co-morbidities, these were varied above and below the base values but ensuring that they still summed to one and for the probability of status epilepticus we varied the minimum to 0 and also doubled the base value. Detailed reporting of the base values and absolute minimum and maximum values for every parameter within each of the groupings are reported in Appendix N.

B.3.6.3 Scenario analyses

Uncertainty around structural and parametric assumptions in the base case model was tested in the scenario analyses detailed in Table 44. In addition, scenario analyses have been conducted exploring the positioning of fenfluramine at various points in the add-on therapy pathway, as described in Table 45 and in the context of Figure 2. As cannabidiol was recommended by NICE under a confidential patient access scheme [12], the impact of a range of discounts on the cannabidiol list price is also separately explored in B.3.9.3

Scenario analyses around base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Fenfluramine+ SoC vs. cannabidiol +clobazam +SoC	[redacted]	[redacted]	**31,773**
1: Patients' seizure frequency remains constant throughout life	[redacted]	[redacted]	32,468
2: Population at start of the model are all aged under 18	[redacted]	[redacted]	39,722
3: Population at start of model are all aged over 18 (i.e. adults only)	[redacted]	[redacted]	8,532
4: Disease-specific mortality risk is assumed to be the same as 'general epilepsy', (i.e. seizure-risks only, not Dravet syndrome)	[redacted]	[redacted]	57,990
5: General epilepsy mortality risk partially calibrated to Dravet syndrome	[redacted]	[redacted]	40,865
6: No carer utility	[redacted]	[redacted]	104,835
7. Alternative utility values (EQ-5D) for patients taken from Teneishvili et al study, based on French Dravet syndrome patients	[redacted]	[redacted]	30,224
8: Cannabidiol dose: 15mg/kg/day (the mid-dose between licensed 10 and 20mg/kg/day)	[redacted]	[redacted]	14,355

Scenario analyses around base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
9: Cannabidiol dose: 20mg/kg/day (upper end of the licensed dose range)	[redacted]	[redacted]	Cannabidiol dominated*

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

* [redacted]

With the exception of the adjustment highlighted for a specific scenario, all other parameters and assumptions are held consistent with the base case.

Figure 32

Table 44: Summary of the scenario analyses explored and comparison to the base case

Scenario number	Scenario explored	Definition	Base case
1	Patients seizure frequency remains consistent throughout their lifetime	At the age of 18 seizure frequency remains consistent	At the age of 18 seizure frequency halves
2	Population at start of the model is all aged under 18 years	Patient age at start of model reflects the distribution of ages under 18 seen in the DISCUSS study	Patient age at start of model reflects the distribution of ages seen in the entire DISCUSS study (2-34 years)
3	Population at the start of model are all aged over 18 years (i.e adults only)	Patient age at start of model reflects the distribution of ages over 18 seen in the DISCUSS study	Patient age at start of model reflects the distribution of ages seen in the entire DISCUSS study (2-34 years)
4	Disease-specific mortality risk is assumed to be the same as 'general epilepsy'	SUDEP mortality rates based on relative risk of mortality per seizure from general epilepsy population reported in Nilsson et al (1999).	SUDEP mortality risk based on general epilepsy mortality risk per seizure calibrated to Dravet syndrome SUDEP mortality
5	General epilepsy mortality risk partially calibrated to Dravet syndrome	SUDEP mortality rates based on relative risk of mortality per seizure from Nilsson et al (1999), calibrated to halfway between general epilepsy mortality and Dravet syndrome mortality (Figure 28)	SUDEP mortality risk based on general epilepsy mortality risk per seizure calibrated to Dravet syndrome SUDEP mortality
6	No carer utility	Carer utility not included in the model	Utility values for 1.8 carers included in the model, as accepted by NICE in TA614
7	Alternative utility values (EQ-5D) for patients taken from	Patient utility values modelled as a regression, with convulsive seizures, age and motor	Patient utilities are modelled using a linear regression from pivotal fenfluramine trial data

Scenario number	Scenario explored	Definition	Base case
	Teneishvili et al study, based on French Dravet syndrome patients	impairments as discussed in Appendix M.	
8	Cannabidiol dose: 15mg/kg/day (the mid-dose between licensed 10 and 20mg/kg/day)	Cannabidiol dose, cost and efficacy reflects a 15mg/kg /day dose applied to all patients at the start of treatment.	Cannabidiol dose, cost and efficacy reflects a 12mg/kg/day dose
9	Cannabidiol dose: 20mg/kg/day (upper end of the licensed dose range)	In line with approach to modelling fenfluramine dosing, the cannabidiol dose, cost and efficacy reflects the maximum licensed cannabidiol dose of 20mg /kg/day, applied to all patients at the start of treatment.	Cannabidiol dose, cost and efficacy reflects an estimated proportional usage of 10 and 20mg/kg/day dosing in UK practice to derive an average 12mg/kg/day dose, as accepted by NICE in TA614

Abbreviations: SUDEP, sudden unexpected death in epilepsy;
With the exception of the adjustment highlighted for a specific scenario, all other parameters and assumptions are held consistent to the base case.

Table 45. Scenario analysis to inform the proposed position of fenfluramine within the treatment pathway for Dravet syndrome

Positioning analyses	Comparator
Base case: 2L+ add-on as an alternative to cannabidiol (with clobazam)	**Cannabidiol + clobazam + SoC** [1]
1L add-on when clobazam is not desirable	SoC without clobazam (nor stiripentoln or cannabidiol)[2]
2L add-on when clobazam is not tolerated	
2L add-on before stiripentol use	**Cannabidiol + clobazam + SoC** [1†]
	SoC (stiripentol naïve)[3]
2L add-on as an alternative to stiripentol	Analysis not possible – insufficient stiripentol data[4]
2L+ add-on in addition to stiripentol	**Cannabidiol + clobazam + SoC** [1†]

Positioning analyses	Comparator
	SoC (including stiripentol)[5]
2L+ add-on after stiripentol failure	**Cannabidiol + clobazam + SoC** [1☐]
	SoC (excluding stiripentol)[6]

Abbreviations:1L, first-line; 2L, second-line; 2L+, second- or subsequent-line; SoC, standard of care AEDs
☐ Assumption of subgroup effects and costs consistent with the base case due to lack of subgroup and/or patient-level data for cannabidiol (with clobazam)
Clinical evidence supporting positioning analysis:

1. Indirect treatment comparison for fenfluramine + Soc vs cannabidiol +SoC (including clobazam) (see B.2.9.6)
2. Study 1 subgroup analysis in patients with / without concomitant clobazam use (see B.2.6.1.1.1)
3. Study 1 subgroup analysis in patients stiripentol experienced vs whole population (see B.2.6.1.1.1)
4. Insufficient evidence for stiripentol to permit a robust indirect treatment comparison against fenfluramine (see B.2.9.2.4)
5. Study 1504 trial; all patients receiving concomitant stiripentol (see B.2.6.1.1)
6. Study 1 subgroup analysis in patients stiripentol experienced vs whole population (see B.2.6.1.1.1)

Figure 28: Mortality assumption applied in scenario 2 (general epilepsy partially calibrated to mortality seen in Cooper et al), compared to all-cause mortality, general epilepsy mortality and the mortality assumption applied in the base case model

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base case analysis inputs

A summary of the model parameters used for the base case analysis is presented in Table 46.

Table 46: Summary of key model parameters used in the base case analyses

	Base case assumption	Range explored in DSA	Reference to section in submission
Model settings			
Time horizon	Lifetime	N/A	B.3.2.2.3
Cycle length	28 days	N/A	
Discount rate: costs	3.5%	0-6%	
Discount rate: utilities	3.5%	0-6%	
Cohort definition			
Baseline demographics			
Starting age (years)	Age distribution based on UK DISCUSS population	2-9	B.3.3.1
Weight at age 2 (kg)	12	6-18	
Gender, male	55%	N/A	
Motor impairments	30% Ataxia	N/A (scenario analysis)	
	20% Severe motor issues		
	50% None		
Treatment discontinuation			
Other discontinuation* Cycle 1	[redacted]	+/-10%	B.3.3.5
Lack of efficacy discontinuation Cycles 2 - 4	[redacted]		
Other discontinuation* Cycles 2 - 4	[redacted]		
Long term discontinuation FFA**	[redacted]		
Long term discontinuation CBD**	[redacted]		
Stopping rule	Discontinuation if <30% decrease in seizures 6 months after initiating treatment compared to baseline	N/A	
Costs			
Treatment			
Cannabidiol £/mg	£0.09	N/A	B.3.5.1
Fenfluramine £/mg	[redacted]	N/A	
Proportion of people on other AEDs	Varies based on underlying RCT population and proportion of stiripentol use	+/- 20%	
Monitoring costs for fenfluramine	Based on age	+/- 20% for a single fixed cost or minimum and maximum values from the range where a cost was an average	
Treatment effect (% reduction in convulsive seizure frequency vs placebo)			
Fenfluramine 0.4 mg/kg	[redacted]	N/A	B.3.3.2

	Base case assumption	Range explored in DSA	Reference to section in submission
Fenfluramine 0.7 mg/kg	[redacted]	N/A	
Cannabidiol 10 mg/kg	[redacted]	N/A	
Cannabidiol 20 mg/kg	[redacted]	N/A	
Cannabidiol 12 mg/kg/day (weighted)	[redacted]	N/A	
Utilities			
Patient***	[redacted]	Coefficients perturbed using Cholesky decomposition of the covariance matrix	B.3.4
Carer***	[redacted]		
HCRU			
Ongoing costs	Varies based on seizure frequency and age	+/- 20% for a single fixed cost or minimum and maximum values from the range where a cost was an average	0
Emergency costs	Varies based on seizure frequency and age		

Abbreviations: FFA, fenfluramine, CBD, cannabidiol
* Discontinuation recorded that were not due to lack of efficacy, e.g. patient or physician decision
** Discontinuation recorded in the trial after the maintenance period
*** Estimated base regression coefficients used to generate the predicted utilities values are provided in Table 31 and 32 for patients and carers respectively

B.3.7.2 Assumptions

The assumptions applied in the base case of the economic analysis are described in Table 47.

Table 47: Key assumptions used in the model (base case)

Model input and cross reference	Source/Assumption	Rationale/Justification
Time horizon B.3.2.2.3.12	Lifetime	Dravet syndrome is a chronic disease and this approach is consistent with the NICE reference case [69]
Perspective B.3.2.2.3.12	NHS/PSS	Consistent with the NICE reference case [69]
Seizure frequency B.3.3.2.1 B.3.3.2.3	Model is driven by convulsive seizure frequency. Non-convulsive seizure frequency does not contribute to the ICER	As detailed in section B.1.3.1.6, reducing convulsive seizure frequency, leading to more seizure-free days, reduces the risk of mortality, reduces the risk of developmental comorbidities, and improves patients' and carers' quality of life. For this reason, the model and all outputs are driven by convulsive seizures and the ability of treatment strategies to influence convulsive seizure frequency. Non-convulsive seizures are more challenging to record and may be underreported in the trials. Therefore, and in line with the approach taken in the NICE appraisal of cannabidiol [12], non-convulsive seizures do not contribute to the ICER. As non-convulsive

Model input and cross reference	Source/Assumption	Rationale/Justification
		seizure can adversely impact daily activities and quality of life, this is a conservative approach.
	Seizure frequency halves in patients over 18	Seizure frequency in the model is driven by seizures observed in Study 1 and Study 1504 cohort 2, which recruited patients aged 2-18 years [3, 4]. Literature indicates that seizure frequency may decline as patients age [23], which was supported by the UK Pathways research study [55]. The frequency of seizures in patients aged 18 and over were therefore halved, and seizure free days doubled to reflect decline. This assumption is further assessed in scenario analyses (B.3.9.3).
Dosing and posology B.3.2.3 B3.5.1.1	Patients receive fenfluramine at 0.7 mg/kg/day with a maximum dose of 26 mg (without stiripentol), or 0.4 mg/kg/day with a maximum dose of 17 mg (with stiripentol)	These are the anticipated recommended maintenance and maximal doses for fenfluramine as stated in the draft SmPC [10]
	Patients receive stiripentol at the recommended maintenance dose of 50 mg/kg/day	This is the recommended dose of 50 mg/kg/day is based on the available clinical study findings and was the only dose of stiripentol evaluated in the pivotal studies [13]
	Patients receive cannabidiol at 12 mg/kg/day	As per the appraisal committee preferred dosing assumption in the NICE cannabidiol appraisal [12] and is further assessed in scenario analyses (B.3.9.3).
	A continuous linear function using general population data is used to capture weight-based dose increases for all drugs as patients get older	Limited data is available on body weights of patients with Dravet syndrome. However, clinical opinion suggests that there should be limited discrepancy in weights between Dravet patients and children of a similar age, which is supported by the weights of patients within the trial. Therefore, data from the general population is considered a suitable proxy measure
Cannabidiol is given with clobazam B.3.2.3	Patients on cannabidiol receive concomitant clobazam	Consistent with the license requirements for the use of cannabidiol [14].
Treatment stopping rule B.3.3.5.2	Patients discontinue fenfluramine or cannabidiol if the change in seizure frequency after 6 months of treatment is <30% compared to seizures prior to starting treatment	Consistent with the stopping rule specified in the NICE recommendation for cannabidiol [12], the stopping rule is also adopted for fenfluramine.
Treatment following discontinuation B.3.3.5.3	Patients discontinuing active treatment due to lack or loss of efficacy would revert back to their SoC treatment	Given limited existing treatment options for Dravet syndrome patients, there are limited further add-on therapy options, and no robust evidence with which to model complex treatment sequencing. This (potentially conservative) approach is consistent with the approach taken in the NICE appraisal of cannabidiol [12]

Model input and cross reference	Source/Assumption	Rationale/Justification
Seizure frequency following discontinuation B.3.3.5.1	Patients discontinuing in both the intervention and comparator strategies revert back to their individual seizure characteristics recorded in their baseline period	This ensures that any treatment effect is removed when a patient discontinues fenfluramine or cannabidiol, and ensures patients in the model return to their individual seizure frequencies.
Waning of effect B.3.3.2.5	Treatment waning is not included for patients receiving fenfluramine or cannabidiol in the base case.	Two-year follow data from the fenfluramine OLE study [78], and five-year data from the Belgian RWE study [71] indicate the treatment effect with fenfluramine is sustained and durable, with no evidence of waning of effect with fenfluramine with long-term use (See B.2.6.2 and B.2.6.3). As the 48-weeks data for cannabidiol (with clobazam) presented in its SmPC is suggestive of a potential waning effect with long-term use of cannabidiol [14], this is a conservative assumption.
Use of stiripentol B.3.2.3	58% of patients were assumed to be on concomitant stiripentol	In line with the percentage of patients in the UK on concomitant stiripentol in the DISCUSS study [16]
Status epilepticus B.3.3.2.4	Status epilepticus was modelled as a proportion of convulsive seizures	Status epilepticus events happened too rarely in the trials to determine how frequently they occur, however literature shows that there is an association between the number of convulsive seizures and the number of status epilepticus episodes [104]
Utilities B.3.4.2.1 B.3.4.2.2	Patient quality of life is associated with number of seizure free days per cycle, co-morbidities, age and concomitant stiripentol	Based on regression analyses of quality of life data from Study 1 and Study 1504 cohort 2. This assumption is further assessed in scenario analyses with the use of an alternative source of utility values (EQ-5D) from Dravet syndrome patients in France (B.3.9.3).
	1.8 carer utilities were included in the model, with the carer removed from the model when the patient dies	The NICE reference case states that the perspective on outcomes should be all direct health effects, whether for patients or, where relevant, carers [69]. 1.8 carers is in line with the assumption accepted by the NICE appraisal committee for the appraisal of cannabidiol in NICE TA614 and the substantial burden placed on carers, parents, siblings and the broader family unit of affected people with Dravet syndrome [12]. This assumption is further assessed in scenario analyses (B.3.9.3).
Mortality B.3.3.3.2	Patients were assumed to have an increased risk of mortality with increased convulsive seizures per cycle, above the risk conveyed by general epilepsy	Increased mortality risk with increasing seizure frequency is in line with published literature [31], and the increased risk of mortality in Dravet syndrome over general epilepsy has been reported in a number of sources [5, 6, 105].
Resource use and costs B.3.5.1	Resource use is directly related to convulsive seizure frequency. Resource use by seizure frequency based on UK Pathway research study	Model requires resource use by seizure frequency; however, published resource use and cost data did not provide this detail. UK Pathway research study with 16 UK clinicians experienced in management of Dravet syndrome confirms resource use is directly related to convulsive seizure frequency and

Model input and cross reference	Source/Assumption	Rationale/Justification
		provides UK-specific emergency and ongoing resource use data [55]
Adverse events (AEs) B.3.3.4	Specific AEs are not included in this model	Data on the placebo and treatment arms of the registration studies indicated that there was no meaningful difference in the overall number of treatment-related AEs that would have an impact on resource use or quality of life not otherwise covered by the HCRU and QALY assignments to treatment and SoC in the model (B.2.10.2). Therefore, additional specific AEs are excluded from the model.

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

The results per patient from the model base-case analysis for fenfluramine + SoC vs cannabidiol (with clobazam) + SoC are presented in Table 48.

Over the lifetime time horizon, the total number of accrued (discounted) QALYs was [redacted] and 20.54 for fenfluramine + SoC and cannabidiol + SoC, respectively. This resulted in an incremental QALY gain of [redacted] for patients receiving fenfluramine + SoC. In terms of total overall costs, these were estimated at [redacted] in the fenfluramine + SoC strategy and £255,759 in the cannabidiol + SoC strategy, representing an incremental (discounted) cost of [redacted] for patients receiving fenfluramine + SoC.

The overall ICER for fenfluramine + SoC compared with cannabidiol (with clobazam) + SoC in the model base-case is estimated at £31,773 per QALY gained.

Table 48: Base-case results (deterministic, discounted) – fenfluramine + SoC versus cannabidiol (with clobazam + SoC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. Costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Cannabidiol +clobazam + SoC	255,759	17.02	20.54	-	-	-	-
Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**31,773**

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, Standard of care
Total costs, LYG and QALYS are per patient

The clinical outcomes and disaggregated results from the model are provided in Appendix J.

B.3.9 Sensitivity analyses

B.3.9.1 Probabilistic sensitivity analysis

Table 49: Results of the base case for the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Cannabidiol + clobazam + SoC	257,530	16.99	20.55	-	-	-	-
Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**31,887**

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The combined uncertainty in parameter values is represented on the cost effectiveness plane for 1000 simulations, with the dashed line representing a willingness to pay threshold of £30,000/QALY (Figure 26). The probabilistic ICER of £31,887/QALY (95% CI: £28,979 - £41,746) is highly consistent with the base case deterministic ICER estimate of £31,773/QALY. This, and the steep gradient of the cost effectiveness acceptability curve (Figure 30) indicates that there is little uncertainty in the ICER arising from parameter uncertainty. The probability of the ICER being below £30,000/QALY is 35%; however, there is an 80% probability that the ICER is below £35,000/QALY. The homogeneity of these results with 95% CI: £28,979-£41,746 would suggest that fenfluramine would represent a reasonably cost-effective (£31,887/QALY) intervention across all patients in this rare disease.

Figure 29: Cost-effectiveness plane for adjunct fenfluramine + SoC versus cannabidiol + clobazam + SoC alone (dashed line represents an ICER of £30,000)

Figure 30: Cost effectiveness acceptability curve for fenfluramine + SoC versus cannabidiol + clobazam + SoC.

B.3.9.2 Deterministic sensitivity analysis

Table 50 provides an overview of the parameter groups that were varied independently in the DSA, and the resulting ICER range obtained when the lower and upper bounds of each parameter group were assumed. Detailed reporting of the base values and absolute minimum and maximum values for every parameter within each of the groupings are reported in Appendix N.

The tornado diagram showing the parameters with the greatest impact on the ICER (Figure 31) indicates that the most influential parameter is the utility values for carers. There is little impact on the ICER arising from uncertainty around other parameter value estimates, and suggests the model is robust. Structural uncertainty is explored in scenario analyses in B.3.6.3.

Table 50: Deterministic sensitivity analysis results

Parameter	Lower bound	Upper bound	Reference	Resulting ICER range (£/QALY)
Base case	**-**	**-**	**-**	**£31,773**
Carer utilities	NA	NA	Perturbed coefficients using Cholesky decomposition of the covariance matrix	24,222 - 45,972
Patient weight (collective variables)	-20%	+20%		[redacted]
Patient utilities	NA	NA	Perturbed coefficients using Cholesky decomposition of the covariance matrix	30,454 - 33,204

Parameter	Lower bound	Upper bound	Reference	Resulting ICER range (£/QALY)
Long term discontinuation (after the RCT period)	-10%	+10%	Approach taken in company submission for NICE TA614 [41]	30,357 – 31,550
Short term discontinuation (within the RCT period)	-10%	+10%	Approach taken in company submission for NICE TA614 [41]	32,439 - 32,548
Frequency of ongoing HCRU appts	NA	NA	Min and max of interview data*	31,244 - 32,197
Prop. of ongoing HCRU appts	NA	NA	Min and max of interview data*	31,606 - 32,068
Seizure frequency for HCRU bands	NA	NA	Min and max of interview data*	31,603 - 31,964
Prop. on different CM AEDs	-20%	+20%	Assumption of reasonable range to explore	31,642 - 31,904
Seizure frequency for HCRU bands	NA	NA	Min and max of interview data*	31,603 - 31,964
Cost of outpatient visits	NA	NA	Min and max of composite costs	31,636 - 31,843
Cost of ongoing HCRU	NA	NA	Min and max of composite costs	31,692 - 31,843
Prob. of ambulance	NA	NA	Min and max of interview data*	31,743 - 31,814
Prob. of A&E visit	NA	NA	Min and max of interview data*	31,744 - 31,801
Cost of emergency HCRU	NA	NA	Min and max of composite costs	31,740 - 31,788
Prob. of being an inpatient	NA	NA	Min and max of interview data*	31,755 - 31,790
Prob. of same day inpatient discharge	NA	NA	Min and max of interview data*	31,468 - 33,366
Length of inpatient stay	NA	NA	Min and max of interview data*	31,771 - 31,774
Prob. admitted to ICU	NA	NA	Min and max of interview data*	31,759 - 31,779
Cost of rescue medication	-20%	+20%	Approach taken in company submission for NICE TA614 [41]	31,771 - 31,773
Prob. of SE	0	0.034	0 – 2 x base value	31,772 - 31,772

Abbreviations. NA, is defined for the upper and lower bounds for parameter types where multiple parameter values were varied in the group simultaneously; HCRU, health care resource use; prop., proportion; CM, concomitant; AEDs, anti-epileptic drugs; prob., probability; A&E, Accident & Emergency; ICU, intensive care unit; SE, Status Epilepticus. Full details of exact base, lower and upper values assumed for every parameter are reported in Appendix N.

*Min and max of values suggested by clinicians in the UK Pathway research study [55]

Figure 31: Tornado plot: deterministic sensitivity analyses for fenfluramine + SoC versus cannabidiol (with clobazam) + SoC

NOTE: The dashed line represents the base case ICER of £31,773. For the minimum and maximum long-term discontinuation values the estimated ICERs were both lower than the base ICER so are plotted separately as long-term discontinuation (min) and long-term discontinuation (max). For the maximum and minimum short-term discontinuation values the estimated ICERs were both higher than the base ICER so are also plotted separately as short-term discontinuation (min) and short-term discontinuation (max).

B.3.9.3 Scenario analysis

The impact of structural assumptions in the base case model was tested in scenario analyses detailed in Table 44, with the results given in Table 51. As cannabidiol was recommended by NICE in the context of a patient access scheme [12], the impact of a range of discounts on the cannabidiol list price is also separately explored in Figure 32.

Table 51: Results of the scenarios explored in the economic analysis

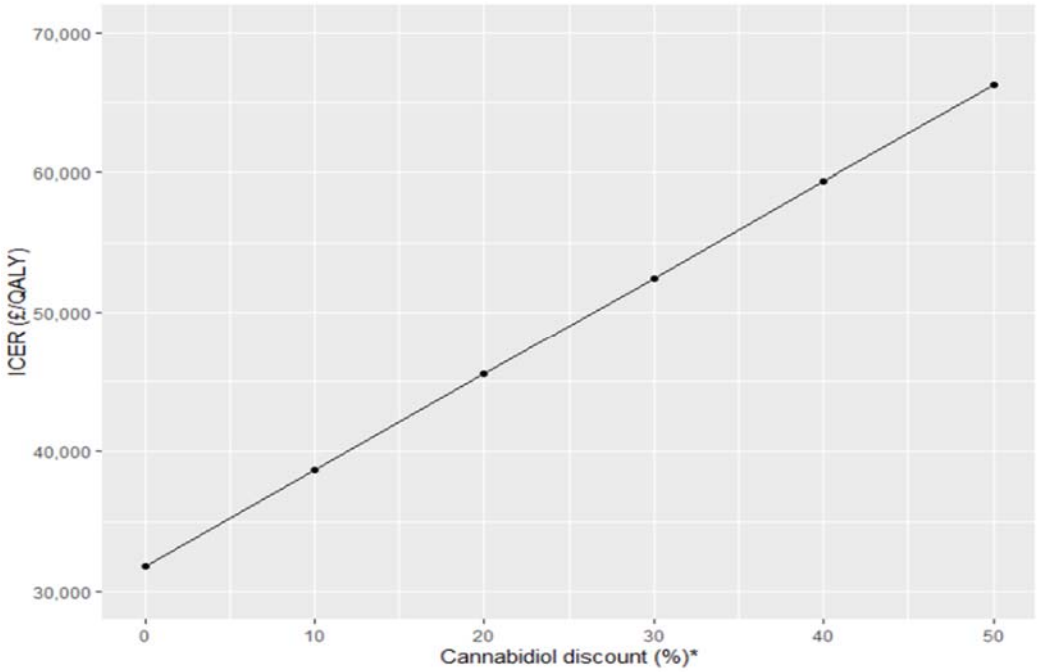
Scenario analyses around base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: Fenfluramine+ SoC vs. cannabidiol +clobazam +SoC	[redacted]	[redacted]	**31,773**
1: Patients' seizure frequency remains constant throughout life	[redacted]	[redacted]	32,468
2: Population at start of the model are all aged under 18	[redacted]	[redacted]	39,722
3: Population at start of model are all aged over 18 (i.e. adults only)	[redacted]	[redacted]	8,532
4: Disease-specific mortality risk is assumed to be the same as 'general epilepsy', (i.e. seizure-risks only, not Dravet syndrome)	[redacted]	[redacted]	57,990
5: General epilepsy mortality risk partially calibrated to Dravet syndrome	[redacted]	[redacted]	40,865
6: No carer utility	[redacted]	[redacted]	104,835
7. Alternative utility values (EQ-5D) for patients taken from Teneishvili et al study, based on French Dravet syndrome patients	[redacted]	[redacted]	30,224
8: Cannabidiol dose: 15mg/kg/day (the mid-dose between licensed 10 and 20mg/kg/day)	[redacted]	[redacted]	14,355
9: Cannabidiol dose: 20mg/kg/day (upper end of the licensed dose range)	[redacted]	[redacted]	Cannabidiol dominated*

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

* [redacted]

With the exception of the adjustment highlighted for a specific scenario, all other parameters and assumptions are held consistent with the base case.

Figure 32: The impact of discounted cannabidiol price on the base case ICER.



*Discount applied to list price of cannabidiol in the base case model, assuming 12mg/kg/day average dose. Patients in practice may receive higher doses (up to 20mg/kg/day)

Additional scenario analyses exploring the positioning of fenfluramine at various points in the add-on therapy pathway (Figure 2) are presented in Table 52.

Table 52. Results of positioning scenario analyses

Positioning analyses	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: 2L+ add-on as an alternative to cannabidiol (with clobazam)	**Cannabidiol + clobazam + SoC** [1]	[redacted]	[redacted]	**31,773**
1L add-on when clobazam is not desirable	SoC without clobazam (and without stiripentol, or cannabidiol)[2]	[redacted]	[redacted]	38,102
2L add-on when clobazam is not tolerated				
2L add-on before stiripentol use	**Cannabidiol + clobazam + SoC** [1]	[redacted]	[redacted]	**31,773**
	SoC (stiripentol naïve)[3]	[redacted]	[redacted]	50,947
2L add-on as an alternative to stiripentol	Analysis not possible – insufficient stiripentol data[4]			

Positioning analyses	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
2L+ add-on in addition to stiripentol	**Cannabidiol + clobazam + SoC [1]**	[redacted]	[redacted]	**31,773☐**
	SoC (including stiripentol)[5]	[redacted]	[redacted]	51,365
2L+ add-on after stiripentol failure	**Cannabidiol + clobazam + SoC [1]**	[redacted]	[redacted]	**31,773☐**
	SoC (excluding stiripentol)[6]	[redacted]	[redacted]	39,676

Abbreviations:1L, first-line; 2L, second-line; 2L+, second- or subsequent-line; SoC, standard of care AEDs
☐ Assumption of subgroup effects and costs consistent with the base case due to lack of subgroup and/or patient-level data for cannabidiol (with clobazam)
Clinical evidence supporting positioning analysis:

1. Indirect treatment comparison for fenfluramine + Soc vs cannabidiol +SoC (including clobazam) (see B.2.9.6)
2. Study 1 subgroup analysis in patients with / without concomitant clobazam use (see B.2.6.1.1.1)
3. Study 1 subgroup analysis in patients stiripentol experienced vs whole population (see B.2.6.1.1.1)
4. Insufficient evidence for stiripentol to permit a robust indirect treatment comparison against fenfluramine (see B.2.9.2.4)
5. Study 1504 trial; all patients receiving concomitant stiripentol (see B.2.6.1.1)
6. Study 1 subgroup analysis in patients stiripentol experienced vs whole population (see B.2.6.1.1.1)

B.3.9.4 Summary of uncertainty analysis results

A comprehensive range of sensitivity analyses indicates that the base case ICER estimate for fenfluramine + SoC vs cannabidiol (with clobazam) + SoC is robust to plausible ranges of parameter values. The deterministic sensitivity analyses indicate that the ICER is most sensitive to the uncertainty around the carers' utility values. However, the probabilistic sensitivity analysis, which considers the combined uncertainty across all parameter values, produces a probabilistic ICER of £31,887/QALY (95% CI £28,979 - £41,746) which is highly consistent with the base case deterministic ICER of £31,773/QALY, with the 95% CI indicating there is little uncertainty in the ICER arising from parameter uncertainty. The probability of the ICER being below £30,000/QALY is 35%; however, there is an 80% probability that the ICER is below £35,000/QALY. The homogeneity of these results with 95% CI: £28,979-£41,746 would suggest that fenfluramine would represent a reasonably cost-effective (£31,887/QALY) intervention across all patients in this rare disease.

The deterministic sensitivity analyses indicate that long-term discontinuation created a small decrease in the ICER for both the minimum and maximum values explored, and varying the short term discontinuation created a small increase in the ICER for both the maximum and minimum values. This seemingly odd result is explained by the influence of the plausible maximum and minimum values of these parameters on the individual components of the overall modelled population. Minimum discontinuation increases time on effective treatment and so increases life years, QALYs and costs, whilst maximum discontinuation has the opposite effect. When comparing between the two strategies, the 'net effect' of varying discontinuation in this life-time analysis, is that maximal discontinuations favour cannabidiol in the short-term (due to removing the number of patients receiving a less cost-effective therapy), whereas minimal discontinuation favours fenfluramine in the long-term (due to patients receiving relatively greater health gains from treatment and increasing the number of patients that receive the most cost effective strategy). The oddity in the DSA for discontinuations is therefore an artefact of this net effect over time, whereby

cost effectiveness improves for cannabidiol (with clobazam) when fewer patients are retained on treatment (see Appendix N, Table 35 for values). Importantly, the time dependency of discontinuations had minimal impact on the ICER at the extremes of the ranges explored.

Scenario analyses around the base case comparison against cannabidiol (with clobazam) indicate that the approach to modelling mortality has a significant influence on the resulting ICER. Adopting the mortality observed in general epilepsy patients increases the ICER to £57,990/QALY; however, the literature clearly indicates a greater risk of mortality in Dravet syndrome than in general epilepsy [5, 6, 105], and the mortality curve in the base case is compatible with the statistic quoted in the NICE scope for this appraisal – 20% of Dravet patients die before adulthood, with most of these deaths occurring before the age of 10 years [11]. The base case mortality assumption is therefore more appropriate than the alternative scenarios.

The exclusion of carer utilities from the model increases the ICER to £104,835/QALY; however, the NICE reference case states that the perspective on outcomes should include all direct health effects, whether for patients or, when relevant, carers [69]. As the NICE appraisal of cannabidiol (with clobazam) (TA614) included carer utility in the committee's preferred analysis [12], the inclusion of carer utility in the base case analysis of fenfluramine plus SoC versus cannabidiol (with clobazam) plus SoC is relevant and appropriate, and in line with the NICE reference case. The base case analysis is therefore more appropriate than the scenario analysis that excludes carer utility.

The base case analysis assumes cannabidiol is administered at a dose of 12mg/kg/day, in line with the appraisal committee's preferred assumption in NICE TA 614 [12]. However, as noted in B.2.9.5, a waning of cannabidiol treatment effect and dosing towards the top end of the 10-20mg/kg/day dose range recommended in the SmPC [14] seem plausible in practice. Scenario analysis assuming a plausible cannabidiol dose of 15mg/kg/day (mid-point of the licensed dose range) rather than 12mg/kg/day reduces the ICER to £14,355/QALY and at a plausible cannabidiol dose of 20mg/kg/day fenfluramine dominates cannabidiol (with clobazam). The base case analysis is therefore plausibly highly conservative, as are all of the above scenario analyses that are also based on this base case cannabidiol dose. The scenario analysis exploring PAS discounts on the cannabidiol list price of up to 50% (Figure 32) demonstrates the sensitivity of the ICER to the price of cannabidiol assumed in the model; however, this is also based on assuming a highly conservative 12mg/kg/day cannabidiol dose. If the PAS discount was to be applied to the list price-based cost of a plausible cannabidiol dose of 20mg/kg/day, the economic dominance and relative cost effectiveness of fenfluramine would hold across the range of discounts explored in Figure 32.

As discussed in B.1.3.1.1, there is a notion that in later childhood and adolescence seizures may stabilise; however, seizure frequency and severity remain high and persist into adulthood, as do the associated developmental impacts and comorbidities [2, 7, 21-24]. The base case therefore included a reduction in seizure frequency at age 18 years, as patients transition into adulthood. A scenario analysis explored the influence of removing this assumption and maintaining a constant seizure frequency through adulthood. This had only a marginal impact, increasing the ICER to £32,468/QALY.

Exploration of initiating fenfluramine in patients above the age of 18 years produced an ICER of £8,532/QALY, confirming not only the clinical and equalities-based rationale (B.1.4.1) for initiating fenfluramine in adults, but also a strong rationale based on cost effectiveness. Therefore, access to fenfluramine therapy in patients aged 2 years and older should not be determined by age. In consultation with clinical experts, the assumptions used in the base case were confirmed to be conservative.

Results of the positioning scenario analyses are discussed in B.3.12.

B.3.10 Subgroup analysis

The submission relates to the full licensed indication of fenfluramine, for which cannabidiol (with clobazam) is the most appropriate clinical and economic comparator. Analyses of fenfluramine plus SoC against comparative SoC alone at different points in the add-on therapy pathway are provided in Table 52 for completeness. These data support the use of fenfluramine within its full licensed indication. No specific subgroup of the licensed indication is proposed.

B.3.11 Validation

B.3.11.1 UK Pathway research study

A qualitative and quantitative UK Pathway research study was undertaken with clinical experts to gain further understanding of Dravet syndrome treatment pathways and disease concepts (e.g. seizure-free days), to inform modelling, and to estimate resource use for the economic analysis.

Sixteen face-to-face semi-structured interviews were conducted with physicians and specialist nurses involved in the management and treatment of paediatric and adult patients with Dravet syndrome across 8 of the 9 regions in England. A self-completion validation exercise (quantitative and free text questionnaire) was subsequently conducted to substantiate and robustly quantify the interview data, including the resource use data adopted in our model and the concept of seizure-free days (Table 53).

These results have been summarised into a summary report, which is provided as an academic-in-confidence reference [55].

Table 53: Expert opinion interviews in the UK Pathway research study

	Description
Total face-to-face interviews	16 (8 treating adults and 8 treating paediatrics), from 8 of 9 regions in England
Roles	Consultant neurologist, paediatrician (epileptologist), consultant epileptologist/ neuropsychiatrist, epilepsy specialist nurses
Types of service	Secondary, tertiary and quaternary
Total validated interviews	9 (5 treating adults and 4 treating paediatrics)

B.3.11.2 Model approach and data validation

The model methods, e.g. bootstrapping, were tested and validated against the seizure characteristics recorded in the fenfluramine registration studies and the OLE study (study 1503) as a predictor of accuracy (see section B.3.3.2.1 and Appendix L).

To validate the mortality assumptions in the model, the mortality seen in the placebo arms of the fenfluramine registration trials was compared with an equivalent time period in the model. During the first four cycles of the model 0.43% of the population died compared to 0.49% of the trial population, indicating that the mortality assumptions in the model reflects the mortality seen in the

fenfluramine studies. Comparison of convulsive seizure frequency and convulsive seizure-free days at baseline and throughout the trial period are also highly consistent, indicating the patient simulation model is modelling the trial data accurately (see Appendix J, section J.1.1).

In addition to the UK pathway research study, model methodology, input parameters and assumptions were explored and agreed in an internal modelling workshop with the project team including internationally-respected, senior academic experts in modelling and health economics.

The final economic model and regression models were quality checked by a modeller and statistician not involved in the development, to ensure the models were reliable, including:

- Audit of all the code in the models (line by line)
- Quality check of all input parameters
- Validation of the base case results against the predicted results (e.g. comparison of mortality to mortality observed in fenfluramine registration trials, comparison of mortality to published literature)
- Internal consistency and plausibility of all results.

B.3.12 Interpretation and conclusions of economic evidence

B.3.12.1 Summary of the evidence of cost effectiveness

Fenfluramine is an innovative add-on therapy for Dravet syndrome that provides a step change in seizure control and is anticipated to be licensed for use with or without concomitant clobazam. This unique benefit means it may be used throughout the add-on therapy pathway (see B.2.13.4).

The primary base case analysis demonstrates the cost effectiveness of fenfluramine in its licensed indication as an add-on therapy against cannabidiol in its licensed indication as an add-on therapy. As cannabidiol is the only NICE-recommended add-on therapy to have been formally appraised by NICE, and to have sufficient RCT data against which to make a robust comparison for fenfluramine add-on therapy, this is the most appropriate comparator to demonstrate the cost effectiveness of fenfluramine in the add-on therapy pathway.

Based on a PAS discount on the list price of fenfluramine the base case ICER is £31,773/QALY. In line with the appraisal of cannabidiol (NICE TA614) [12] and the NICE reference case [69], this appropriately includes the profound impact of Dravet syndrome on the quality of life of both patients and their carers. However, it excludes the influence of non-convulsive seizures on quality of life, and the impact of Dravet syndrome across patient siblings, both of which were recognised in NICE TA 614 as omissions that, if included, would further reduce the ICER [12]. Furthermore, due to a lack of specific data and for pragmatic reasons, the economic analysis does not model any subsequent add-on strategies following treatment discontinuation; this is a conservative approach, as the superior efficacy of fenfluramine demonstrated in the ITC (see section B.2.9) means that treatment discontinuations due to a lack of efficacy would occur more frequently with cannabidiol (with clobazam) than with fenfluramine, which would return patients on cannabidiol (with clobazam) in the model to their less costly SoC treatment more quickly.

Deterministic and probabilistic sensitivity analyses demonstrate that the results of the base case analysis are robust to parameter uncertainty. The probability of the ICER being below £30,000/QALY is 35%; however, there is an 80% probability that the ICER is below £35,000/QALY. The homogeneity of these results with 95% CI: £28,979-£41,746 would suggest that fenfluramine

would represent a reasonably cost-effective (£31,887/QALY) intervention across all patients in this rare disease.

Scenario analyses further demonstrate that the base case analysis is highly conservative; whilst the maximum dose of fenfluramine is assumed in the base case, the dose of cannabidiol (12mg/kg/day) is assumed to be towards the lower end of its recommended 10-20mg/kg/day maintenance dose range. Given evidence of a waning effect of cannabidiol and doses towards the upper end of its recommended dose range in its OLE study (see B.2.9.5) it is plausible that effective doses in practice could be towards the upper end of its recommended dose range. Assuming the maximum doses for both fenfluramine and cannabidiol, fenfluramine dominates cannabidiol.

Additional, supportive scenario analyses of fenfluramine plus SoC against comparative SoC alone across all points of the add-on therapy pathway have been provided for transparency and completeness (Table 52). It should be noted that, as an add-on therapy, the most appropriate comparator for fenfluramine would be a NICE-recommended add-on therapy. For a patient in need of new additional treatment, continued therapy with SoC alone would not be clinically appropriate. The comparison of fenfluramine plus SoC against cannabidiol (with clobazam) plus SoC, therefore remains the most appropriate comparison to demonstrate the cost effectiveness of fenfluramine in the current add-on therapy pathway. The exception to this is when fenfluramine is used as a first-line add-on therapy in patients for whom clobazam is not a desirable option, or as a second-line add-on therapy when clobazam is not tolerated. In these cases, in the absence of sufficiently robust data for stiripentol (unlicensed for use without clobazam) to permit an indirect comparison, SoC (without clobazam) is the appropriate comparator. The ICER for fenfluramine plus SoC versus SOC (without clobazam) is £38,102/QALY; however, this is a conservative estimate, given that patients in the SoC arm would have few, if any, remaining therapy options available and therefore would be exposed to an accelerated progression of the syndrome. Furthermore, this excludes the quality of life impact of an additional active therapy on non-convulsive seizure reduction and the benefits to patients' siblings.

B.3.12.2 Strengths and limitations of the cost effectiveness evidence

Strengths of the cost effectiveness evidence include the development and use of a patient level simulation model to account for heterogeneity in Dravet syndrome patient characteristics, in line with the suggestions of the appraisal committee in NICE TA614[12]. The simulated population is based on the placebo arms of the phase 3 fenfluramine RCTs, which are representative of Dravet syndrome patients in the UK (see B.2.5). In contrast to several previous cost effectiveness analyses, including analyses of cannabidiol in NICE TA614, utility values specific to Dravet syndrome based on robust data meeting the NICE reference case have been used in the model. A Dravet syndrome UK Pathway research study provides granular detail on health care resource use, informed by 16 clinicians experienced in the management of Dravet syndrome patients in the UK [55]. The base case analysis compares fenfluramine against the most appropriate comparator based on a collective comparative evidence base that is more complete and more robust than the evidence supporting any of the existing NICE-recommended add-on therapies (see B.2.13.3.1). A comprehensive range of sensitivity and scenario analyses demonstrate that the results are robust and that conservative structural assumptions have been adopted in the base case analysis.

A limitation for the cost effectiveness evidence is the inability to make a comparison of fenfluramine as an alternative to stiripentol. This is due to a lack of sufficient RCT evidence for stiripentol (see B.2.9.2.4). Despite this, we have nonetheless looked to inform the appraisal by providing analyses of the use of fenfluramine before, after, and on top of stiripentol, recognising the limitations in

drawing conclusions from these analyses. Cannabidiol (with clobazam) has been accepted as a clinically and cost effective add-on therapy option alongside stiripentol in the existing add-on therapy pathway (see Figure 2). This was without a comparison against stiripentol or any other add-on therapy within the pathway [12]. The cost effectiveness of fenfluramine compared against cannabidiol (with clobazam), as a NICE-recommended standard in the add-on therapy pathway, therefore provides a reliable estimate of the cost effectiveness of fenfluramine in the existing pathway.

A further limitation is that the economic analysis does not model any subsequent add-on therapies following treatment discontinuation; however, as explained above, this is a pragmatic and conservative approach that favours cannabidiol (with clobazam) in the primary analysis. Across all analyses, the impact of treatment on non-convulsive seizures and sibling quality of life is excluded, and the full quality of life benefit from the significant and often profound reduction in convulsive seizures observed with fenfluramine add-on therapy is likely to be muted, as explained in B.1.4.2. The QALY metric is therefore unlikely to have captured the full incremental benefit of fenfluramine therapy.

B.3.12.3 Conclusions from the economic evidence

Given the clear relationships between convulsive seizure frequency, patient morbidity and mortality, and patient and caregiver quality of life, the significant and often profound reductions in convulsive seizure frequency demonstrated with fenfluramine as an add-on therapy are potentially life-changing for a high proportion of patients, their families and caregivers. Combined with its ability to be used at any point in the add-on therapy pathway, without reliance on concomitant use of clobazam, fenfluramine is an innovative therapy that provides a step change in the treatment of Dravet syndrome.

Based on a rigorous cost effectiveness analysis, using the most robust data sources possible and highly conservative assumptions, the ICER for fenfluramine compared with cannabidiol (with clobazam) – the most appropriate comparator – is £31,773/QALY. In a secondary analysis, in patients for whom clobazam is not a desirable option or is not tolerated, the ICER for fenfluramine compared with continued SoC therapy is £38,102/QALY.

In the context of this devastating, rare disease, with few effective and tolerable treatment options, fenfluramine, as an innovative and clinically meaningful add-on therapy, should be considered a reasonably cost-effective alternative to current NICE-recommended add-on therapies. Fenfluramine should therefore be recommended within its full licensed indication as a clinically and cost-effective add-on therapy.

References

1. Connolly, M., *Dravet Syndrome: Diagnosis and Long-Term Course.* Can J Neurol Sci., 2016. **43**: p. S3-S8.
2. Dravet, C., *The core Dravet syndrome phenotype.* Epilepsia, 2011. **52 Suppl 2**: p. 3-9.
3. Lagae, L., et al., *Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial.* Lancet, 2020. **394**(10216): p. 2243-2254.
4. Nabbout, R., et al., *Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial.* JAMA Neurol, 2019. **77**(3): p. 300-8.
5. Cooper, M.S., et al., *Mortality in Dravet syndrome.* Epilepsy Res, 2016. **128**: p. 43-47.
6. Shmuely, S., et al., *Mortality in Dravet syndrome: A review.* Epilepsy Behav, 2016. **64**(Pt A): p. 69-74.
7. Lagae, L., et al., *Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey.* Dev Med Child Neurol, 2018. **60**(1): p. 63-72.
8. Lagae, L., et al., *Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study.* Seizure: European Journal of Epilepsy, 2019. **65**: p. 72-79.
9. National Institute for Health and Care Excellence, *Epilepsies: diagnosis and management. Clinical Guideline 137.* 2012; updated 2020.
10. Zogenix International Ltd, *FINTEPLA Summary of Product Characteristics [DRAFT]; May 2020.* 2020.
11. National Institute for Health and Care Excellence, *Final scope: Fenfluramine for treating Dravet syndrome.* 2020.
12. National Institute for Health and Care Excellence, *Technology Appraisal 614: Cannabidiol with clobazam for treating seizures associated with Dravet syndrome. Final Appraisal Determination.* 2019.
13. Alan Pharmaceuticals, *Diacomit 250 mg powder for oral suspension in sachet Summary of Product Characteristics.* 2019.
14. GW Pharma Ltd, *Epidyolex 100 mg/ml oral solution Summary of Product Characteristics.* 2019.
15. European Medicines Agency, *Public summary of opinion on orphan designation. Fenfluramine hydrochloride for the treatment of Dravet syndrome (EU/3/14/1219).* 2014.
16. Pagano, K., et al., *The clinical and socioeconomic impact of Dravet syndrome in the UK.* Developmental Medicine & Child Neurology 2019. **61**((Suppl 1)): p. 61 (abstract 111).
17. Bayat, A., H. Hjalgrim, and R.S. Moller, *The incidence of SCN1A-related Dravet syndrome in Denmark is 1:22,000: a population-based study from 2004 to 2009.* Epilepsia, 2015. **56**(4): p. e36-9.
18. Depienne, C., et al., *Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients.* J Med Genet, 2009. **46**(3): p. 183-91.
19. Brunklaus, A., et al., *Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome.* Brain, 2012. **135**(Pt 8): p. 2329-36.
20. Claes, L., et al., *De novo SCN1A mutations are a major cause of severe myoclonic epilepsy of infancy.* Hum Mutat, 2003. **21**(6): p. 615-21.
21. Aras, L.M., J. Isla, and A. Mingorance-Le Meur, *The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome.* Epilepsy Behav, 2015. **44**: p. 104-9.
22. European Medicines Agency, *Europan Public Assessment Report: Epidyolex.* 2019.
23. Gataullina, S. and O. Dulac, *From genotype to phenotype in Dravet disease.* Seizure, 2017. **44**: p. 58-64.

24. Ragona, F., *Cognitive development in children with Dravet syndrome.* Epilepsia, 2011. **52 Suppl 2**: p. 39-43.
25. Symonds, J., et al., *Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort.* Brain, 2019. **142**(8): p. 2303-2318.
26. All Wales Medicines Strategy Group, *Stiripentol (Diacomit®) -Reference No. 3468.* 2017.
27. Gil-Nagel, A., et al., *Ascertaining the epidemiology, patient flow and disease management for Dravet syndrome in Spain.* Rev Neurol, 2019. **68**(2): p. 75-81.
28. Syvertsen, M., et al., *Prevalence and etiology of epilepsy in a Norwegian county-A population based study.* Epilepsia, 2015. **56**(5): p. 699-706.
29. Wirrell, E.C., et al., *Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel.* Pediatr Neurol, 2017. **68**: p. 18-34.e3.
30. SUDEP Action. *Sudden Unexpected Death in Epilepsy - SUDEP*. 2020 04/04/2020]; Available from: https://sudep.org/sudden-unexpected-death-epilepsy-sudep.
31. Nilsson, L., et al., *Risk factors for sudden unexpected death in epilepsy: a case control study.* Lancet, 1999. **353**(9156): p. 888-893.
32. Donner, E., P. Camfield, and L. Brooks, *Understanding Death in Children With Epilepsy.* Pediatric Neurology, 2017. **20**: p. 7-15.
33. Harden, C., et al., *Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors.* Neurology, 2017. **88**(17): p. 1674-1680.
34. Devinsky, O., J.H. Cross, and S. Wright, *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.* N Engl J Med, 2017. **377**(7): p. 699-700.
35. Miller, I., et al., *Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial.* JAMA Neurol, 2020. **77**(5): p. 613-621.
36. Lamberts, R., et al., *Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk.* Epilepsia, 2012. **53**(2): p. 253-257.
37. Brunklaus, A. and S.M. Zuberi, *Dravet syndrome--from epileptic encephalopathy to channelopathy.* Epilepsia, 2014. **55**(7): p. 979-84.
38. Strzelczyk, A., et al., *Burden-of-illness and cost-driving factors in Dravet syndrome patients and carers: A prospective, multicenter study from Germany.* Eur J Paediatr Neurol, 2019. **23**(3): p. 392-403.
39. Akiyama, M., et al., *A long-term follow-up study of Dravet syndrome up to adulthood.* Epilepsia, 2010. **51**(6): p. 1043-52.
40. Genton, P., R. Velizarova, and C. Dravet, *Dravet syndrome: the long-term outcome.* Epilepsia, 2011. **52 Suppl 2**: p. 44-9.
41. National Institute for Health and Care Excellence, *Technology Appraisal 614: Committee Papers.* 2019.
42. Campbell, J.D., et al., *Assessing the impact of caring for a child with Dravet syndrome: Results of a caregiver survey.* Epilepsy Behav, 2018. **80**: p. 152-156.
43. Wirrell, E.C., *Treatment of Dravet Syndrome.* Can J Neurol Sci, 2016. **43 Suppl 3**: p. S13-8.
44. Catarino, C., et al., *Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology.* Brain 2011: 134; 2982–3010, 2011. **134**: p. 2982–3010.
45. Nabbout, R., et al., *Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet Syndrome.* Epilepsy Behav, 2018. **78**: p. 232-242.
46. Knupp, K.G., et al., *Parental Perception of Comorbidities in Children With Dravet Syndrome.* Pediatr Neurol, 2017. **76**: p. 60-65.
47. Nolan, K.J., C.S. Camfield, and P.R. Camfield, *Coping with Dravet syndrome: parental experiences with a catastrophic epilepsy.* Dev Med Child Neurol, 2006. **48**(9): p. 761-5.

48. Desnous, B., et al., *Perceptions of fever and fever management practices in parents of children with Dravet syndrome.* Epilepsy Behav, 2011. **21**(4): p. 446-8.
49. Villas, N., M.A. Meskis, and S. Goodliffe, *Dravet syndrome: Characteristics, comorbidities, and caregiver concerns.* Epilepsy Behav, 2017. **74**: p. 81-86.
50. NICE Decision Support Unit, *Modelling health-related quality of life in technology appraisals and highly specialised technologies.* 2019.
51. Sullivan, J., et al., *ZX008 (Fenfluramine Hydrochloride Oral Solution) Reduces Seizure Burden by Significantly Increasing Number of Seizure-Free Days and Time Between Seizures in Patients With Dravet Syndrome (Poster 3.431)*, in *American Epilepsy Society (AES) Annual Meeting*. 2019: Baltimore, MD, USA.
52. Berg, A., et al., *Seizure burden in severe early-life epilepsy: Perspectives from parents.* Epilepsia open 2019. **4**(2): p. 293-301.
53. Gammaitoni, A., J. Sullivan, and D. Dlugos, *Defining a Minimal Clinically Important Difference in Seizure Frequency Using Data From a Phase 3 Clinical Study of Add-On, Low-Dose ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome Patients Receiving an Antiepileptic Drug Regimen Containing Stiripentol (Poster 44)*, in *48th Child Neurology Society (CNS) Congress*. 2019: Charlotte, NC.
54. Nabbout, R., et al., *What defines "clinically meaningful changes in seizure frequency?" Analysis of data from a phase 3 clinical trial of ZX008 in Dravet syndrome (Abstract 3.202)*, in *AES annual meeting*. 2018.
55. Aquarius Population Health, *Dravet Syndrome: UK patient pathways, and how syndrome features influence care and quality of life.* 2020.
56. Department of Health, *The UK strategy for rare disease.* 2013.
57. Cross, J., et al., *Dravet syndrome: Treatment options and management of prolonged seizures.* Epilepsia, 2019. **60**: p. S39-S48.
58. Advisory Council on the Misuse of Drugs, *Advice on Epidyolex*. 2020.
59. Pharmaceutical Journal. *Restrictions on Epidyolex prescribing reduced, as it is rescheduled*. 2020; Available from: https://www.pharmaceutical-journal.com/news-and-analysis/news/restrictions-on-epidyolex-prescribing-reduced-as-it-is-rescheduled/20208105.article?firstPass=false.
60. Brigo, F., S.C. Igwe, and N.L. Bragazzi, *Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy.* Cochrane Database Syst Rev, 2017. **5**(5): p. Cd010483.
61. Accord, *Clobazam Summary of Product Characteristics.* 2020.
62. Chiron, C., et al., *Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group.* Lancet, 2000. **356**(9242): p. 1638-42.
63. Guerrini, R., et al., *Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial (P496)*, in *5th ECE PRoceedings*. 2002, Epilepsia.
64. Scottish Medicines Consortium, *Re-Submission: stiripentol 250mg and 500mg hard capsule, 250mg and 500mg powder for oral suspension in sachet (Diacomit®) SMC No 524/08.* 2017.
65. Chiron, C., et al., *Do children with Dravet syndrome continue to benefit from stiripentol for long through adulthood?* Epilepsia, 2018. **59**(9): p. 1705-1717.
66. Brigo, F., S.C. Igwe, and N.L. Bragazzi, *Stiripentol add-on therapy for drug-resistant focal epilepsy.* Cochrane Database Syst Rev, 2020. **5**: p. Cd009887.
67. Devinsky, O., et al., *Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial.* Epilepsia, 2019. **60**(2): p. 294-302.
68. National Institute for Health and Care Excellence, *Technology Appraisal 615: Cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome.* 2019.
69. National Institute for Health and Care Excellence, *Guide to the methods of technology appraisal 2013.* 2013.

70. Zogenix International Ltd, *Study 1503 Interim CSR; 21 December 2018 [CONFIDENTIAL].* 2018.
71. Ceulemans, B., et al., *Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine.* Epilepsia, 2016. **57**(7): p. 129-134.
72. Schoonjans, A., et al., *Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients.* Eur J Neurol, 2017. **24**(2): p. 309-314.
73. Perry, M., et al., *Real-world Experience with ZX008 (Fenfluramine HCl) for the Treatment of Seizures in Dravet Syndrome: Initial Report from United States Expanded Access Program.* Neurology, 2020. **94**(15 supplement).
74. Zogenix International Ltd, *Data on File: European Expanded Access Programme: Update report [CONFIDENTIAL].* 2020.
75. Zogenix International Ltd, *Study 1 CSR; August 2019 CONFIDENTIAL.* 2019.
76. Zogenix International Ltd, *Study 1504 CSR; December 2018 CONFIDENTIAL.* 2018.
77. Ceulemans, B., et al., *Successful use of fenfluramine as an add-on treatment for Dravet syndrome.* Epilepsia, 2012. **53**(7): p. 1131-1139.
78. Zogenix International Ltd, *Data on File. Integrated Summary of Efficacy: Fenfluramine CONFIDENTIAL.* 2020.
79. Sullivan, J., et al., *Long-Term (2-Year) Safety and Efficacy of Adjunctive ZX008 (Fenfluramine Hydrochloride Oral Solution) for Dravet Syndrome: Interim Results of an Ongoing Open-Label Extension Study.* Neurology, 2020. **94**((15 suppl)).
80. Centre for Reviews and Dissemination, *Systematic Reviews: CRD's guidance for undertaking reviews in health care.* 2009.
81. Knupp, K., et al., *ZX008 (Fenfluramine Hydrochloride Oral Solution) Provides Clinically Meaningful Reductions in Seizure Frequency Irrespective of Concomitant AEDs Commonly Used in Dravet Syndrome: Pooled Analysis of Two Phase 3 Trials (Poster 3.430)*, in *American Epilepsy Society (AES) Annual Meeting*. 2019: Baltimore, MD, USA.
82. Wirrell, E., R. Nabbout, and L. Laux, *ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome: Effect on Convulsive Seizure Frequency in Subjects Who Failed Treatment with Stiripentol Prior to Study 1, a Phase 3 Trial*, in *2018 American Academy of Neurology (AAN) Annual Meeting*. 2018: Los Angeles, CA, USA.
83. European Medicines Agency, *Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders* 2010.
84. Trinka, E., et al., *A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus.* Epilepsia, 2015. **56**(10): p. 1515-23.
85. Varni, J. *The PedsQL(TM) Measurenment Model of the Pediatric Quality of Lfe Inventory*. 2020 04/08/2020]; Available from: https://www.pedsql.org/.
86. Varni, J., et al., *The PedsQLy* 4.0 as a Pediatric Population Health Measure: Feasibility, Reliability, and Validity.* Ambulatory Pediatrics 2003. **3**: p. 329-341.
87. Zogenix International Ltd, *Data on File. Response to Day 120 regulatory questions - CONFIDENTIAL.* 2020.
88. Devinsky, O., et al., *Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome.* Neurology, 2018. **90**(14): p. e1204-e1211.
89. Cope, S., et al., *A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer.* BMC Medicine 2014. **12**: p. 93.
90. Perry, M.S., et al., *Caregiver measures for seizure control, efficacy, and tolerability of antiepileptic drugs for childhood epilepsy: results of a preference survey.* Epilepsy Behav, 2011. **22**(3): p. 542-7.
91. Eschbach, K., et al., *Growth and endocrine function in children with Dravet syndrome.* Seizure, 2017. **52**: p. 117-122.

92. Zogenix Inc. *A Study to Investigate the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution in Children and Adults With Epileptic Encephalopathy Including Dravet Syndrome and Lennox-Gastaut Syndrome (NCT03936777)*. ClinicalTrials.gov 2019 04/08/2020].
93. All Wales Medicines Strategy Group, *Stiripentol (Diacomit®).* 2008.
94. CADTH, *Common Drug Review.Pharmacoeconomic Review Report. Stiripentol (Diacomit) (capsules and powder for suspension, 250 mg and 500 mg).* 2015.
95. Royal College of Paediatrics and Child Health. *UK-WHO growth charts - 2-18 years*. 2020 04/08/2020]; Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years.
96. Office for National Statistics. *National Life Tables: UK*. 2019 04/08/2020]; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
97. BNF. *British National Formular, July 2020*. Available from: https://bnf.nice.org.uk/.
98. NHS Business Services Authority. *Prescription Cost Analysis (PCA); November 2019*. 2019; Available from: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data.
99. NHS Improvement. *National Cost Collection for the NHS - National schedule of NHS costs 2018/19*. 2020; Available from: https://improvement.nhs.uk/resources/national-cost-collection/#ncc1819.
100. Curtis, L. and A. Burns, *PSSRU Unit Costs of Health and Social Care 2019*. 2019: https://kar.kent.ac.uk/79286/11/UCFinalFeb20.pdf.
101. Khan, K.A., et al., *Mapping EQ-5D utility scores from the PedsQL generic core scales.* Pharmacoeconomics, 2014. **32**(7): p. 693-706.
102. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15**(5): p. 708-15.
103. NHS Digital. *Health Survey for England 2018: Data tables.* 2019 04/08/2020]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2018/health-survey-for-england-2018-data-tables.
104. Ferna´ndez, I., et al., *Comparison of risk factors for pediatric convulsive status epilepticus when defined as seizures ≥5 min versus seizures ≥30 min.* Seizure, 2014. **23**: p. 692-698.
105. Sakauchi, M., et al., *Mortality in Dravet syndrome: Search for risk factors in Japanese patients.* Epilepsia, 2011. **52**(Suppl 2): p. 50-54.
106. Spitz, M., *Injuries and Death as a Consequence of Seizures in People with Epilepsy.* Epilepsia, 1998. **39**(8): p. 904-907.
107. Elliott, J., et al., *Economic Evaluation of Stiripentol for Dravet Syndrome: A Cost-Utility Analysis.* Pharmacoeconomics, 2018. **36**(10): p. 1253-1261.
108. National Institute for Health and Care Excellence. *Position statement on use of the EQ-5D-5L value set for England (updated October 2019)*. 2019 04/08/2020]; Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
109. Dunwoody, B., et al., *Long-term developmental outcomes, comorbidity and quality of life in SCN1A positive Dravet syndrome*, in *BPNA Annual Scientific Meeting*. 2020, DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY.
110. Sooni, C., et al., *Behavior problems and health-related quality of life in Dravet syndrome.* Epilepsy & Behavior 2019. **90**: p. 217-227.
111. Briggs, A., K. Claxton, and M. Sculpher, *Decision Modelling for Health Economic Evaluation* 2006: Oxford University Press.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine for treating Dravet syndrome [ID1109]

Clarification questions

August 2020

File name	Version	Contains confidential information	Date
ID1109 - Fenfluramine - Request for clarification_ERG_v2.0_to company [ACIC]_RESPONSES_ REDACTED(09Nov20)	**V1.2**	**Yes**	**09 Nov 2020**

Additional information to follow, as agreed during the discussions with the ERG on the 7th and 10th September 2020:

Response and supplement information / data to Questions: C23b; C26a, C26c, C32b

Attachments:
Appendix O
NMA files (including R gemtc code for ITC)
R code and CSV files for DSA and PSA scenarios
Confidentiality checklist

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Literature searching

General questions

A1. Priority question: All searches of MEDLINE report this database as being searched via Embase.com.

a. **Please confirm whether you are referring to a search of Embase conducted on the understanding that it now contains all records from MEDLINE and conducted at the same time as the Embase search. If not, was this a separate search of the MEDLINE database within the Embase.com interface?**

b. **If the Medline search was a separate search, please clarify the impact of including Emtree indexing terms rather than medical subject headings (MeSH) in the search?**

The search of MEDLINE was conducted on the understanding that Embase® now contains all records from MEDLINE and these were conducted at the same time as the Embase® search.

A2. Priority question: Please explain the rationale behind the English language limit used throughout the searches in Appendices D-I, discuss potential implications and provide a list of references excluded using that limit.

The searches were limited to English language for pragmatic reasons, and in line with the approach taken in the company submission for NICE TA614 (cannabidiol in Dravet syndrome). The exclusion of non-English language studies from the PubMed and Embase searches has no meaningful implications, and the NICE Appraisal Committee can be confident that our searches were comprehensive and are highly unlikely to have omitted any relevant evidence that would materially inform its decision-making, as discussed below.

Clinical Evidence searches

The searches of Clinical Evidence, described in Appendix D, focused on RCT evidence to ensure that all published fenfluramine RCTs were identified and also to identify and assess RCTs of potential comparators for inclusion in an ITC. The Embase® and PubMed searches were also accompanied by searches of the Cochrane Central Register of Controlled Trials (CENTRAL) database, which includes clinical studies identified from Embase® and PubMed *without* any language limitations (see https://www.cochranelibrary.com/central/about-central). The decision to limit the inclusion criteria to English language publications was made for pragmatic reasons and based on previous president established by a recent NICE appraisal in Dravet syndrome [TA614].

The limit to English language publications resulted in 19 (out of 354) hits being excluded from the Embase® search and 31 (out of 427) hits being excluded from the PubMed search (see Table 1 of Appendix D). The searches of the CENTRAL database identified only 1 non-English language study (*Thanh TN et al. Long-term efficacy and tolerance of stiripentol in severe myoclonic epilepsy of infancy (Dravet's syndrome). Archives de Pediatrie, 2002, 9(11), 1120-1127.*), which was then excluded due to being a non-English language publication. This study relates to stiripentol, which is a potential comparator for fenfluramine; however, this study is not an RCT and does not provide data that could be used in an ITC. Consequently, the exclusion of this study would not materially change the conclusions that may be

drawn from the evidence base for fenfluramine or for fenfluramine relative to other therapies.

As CENTRAL provided non-English language studies, and only 1 study was excluded on the basis of not being an English language publication, this strongly indicates that any excluded studies in the PubMed and Embase® searches due to being published as non-English language studies, would not have fulfilled the criteria for inclusion in the SLR, irrespective of the publication language (otherwise they would have been identified in the CENTRAL searches). On this basis, limiting the Clinical Evidence searches to English language in the PubMed and Embase® is highly unlikely to have resulted in omission of any relevant clinical evidence that would materially inform on the efficacy, relative efficacy, or safety of fenfluramine. To demonstrate this, we have re-run the Embase® and PubMed clinical evidence searches to isolate non-English language hits (see the Appendix to this document – referred to as Appendix O). The re-run of the Embase searches (re-run 08 September 2020) identified 19 non-English language hits (c.f. 19 non-English language hits in the original searches run 28 June 2020 – see Table 1, Appendix O). The re-run of the PubMed searches (re-run 04 September 2020) identified 32 non-English language hits (c.f. 31 non-English language hits in the original searches run 28 June 2020 – see Table 1, Appendix O). These references are listed in Table 2 of Appendix O. None of these relates to fenfluramine, and none are RCTs of potential comparators (see Table 2, Appendix O). The use of an English language limit on the Clinical Evidence searches therefore has no meaningful implications in presenting the evidence base for this STA.

Economic Evaluation / Cost-Effectiveness Analyses searches

The searches of cost effectiveness analyses or other economic evaluations, described in Appendix G, aimed to identify and evaluate existing cost effectiveness analyses or other economic evaluations of fenfluramine or other pharmacological therapies used as add-on therapies to standard of care anti-epileptic drugs in Dravet syndrome. In line with the suggestions of the Appraisal committee for NICE TA614, which concluded that a discrete event simulation model may better account for heterogeneity in the Dravet syndrome population than a Markov cohort-type model could, our intention was to develop a discrete event simulation-type model using

patient-level data from our clinical trials, and focused specifically on UK clinical practice. Given that it is highly unlikely that a non-English language publication would provide results of an economic evaluation of the use of fenfluramine or any other potential comparator in the UK setting, or that could appropriately reflect the cost effectiveness of use of fenfluramine or any other potential comparator in UK clinical practice, or could reflect this to a better extent than an English language publication could, we made a pragmatic decision to limit our Embase® and PubMed searches for Economic Evaluations to English language publications. As these searches were also accompanied by searches of appropriate HTA organisation websites, including those in the UK, we considered our searches would be sufficiently comprehensive to identify cost effectiveness evidence of relevance to the NICE decision-problem in the UK.

The limit to English language for Embase® and PubMed in the cost effectiveness analyses or other economic evaluations (Appendix G) resulted in 9 (out of 206) hits being excluded from the Embase® search and 16 (out of 256) hits being excluded from the PubMed search (see Table 10 of Appendix G). Based on the above we do not believe the exclusion of non-English language publications could have material implications on the evidence-base or conclusions of the cost effectiveness of fenfluramine in UK clinical practice, nor on the methodology we adopted for our patient-level simulation model. To demonstrate this, we have re-run the Embase® and PubMed Economic evidence searches to isolate non-English language hits. This re-run of the Embase® searches (re-run 08 September 2020, see Appendix O) identified 9 non-English language hits (c.f. 9 non-English language hits in the original searches run 29 June 2020 – see Table 3, Appendix O). This re-run of the PubMed searches (re-run 04 September 2020, see Appendix O) identified 16 non-English language hits (c.f. 16 non-English language hits in the original searches run 29 June 2020 – see Table 3, Appendix O). None of these hits relates to economic evaluations of fenfluramine, or potential comparators (see Table 4, Appendix O). The use of an English language limit on the Economic evaluations evidence searches therefore has no meaningful implications in presenting the evidence base for this STA.

Health-related Quality of Life searches

As noted above, our intention was to develop a discrete event simulation-type model using patient-level data from our clinical trials and focused specifically on the UK population and clinical practice. Given that it is highly unlikely that a non-English language publication would provide quality of life or utility values data that could appropriately reflect the quality of life of patients (and caregivers) in UK clinical practice, or which would better reflect the quality of life of patients (and caregivers) in UK clinical practice than would an English-language publication, we made a pragmatic decision to limit our Embase® and PubMed searches for quality of life and utility values data to English language publications. As these searches were also accompanied by searches of appropriate HTA organisation websites, including the UK, we considered our searches would be sufficiently comprehensive to identify any quality of life data of relevance to the NICE decision-problem in the UK. Given that we aimed to develop a patient-level simulation model, the likelihood of identifying quality of life/utility data that were more appropriate than that collected in our internally consistent, randomised and controlled clinical trials was expected to be low, and this was confirmed in the English-language studies we identified.

The limit to English language for Embase® resulted in 2 (out of 73) hits being excluded from the Embase® search. As the PubMed search identified only 21 hits before any language limit was placed on the searches, an English language limit was not actually applied for the PubMed searches (see Table 17 of Appendix H). Based on the above we do not believe the exclusion of non-English language publications could have material implications on the conclusions of the impact of Dravet syndrome on quality of life of patients and their carers in the UK, or the impact of treatment with fenfluramine or other relevant comparators on quality of life of patients and their carers in the UK, or on the methodology we adopted for inclusion of quality of life in our patient-level simulation model, or interpretation of the results of our cost effectiveness analyses. For completeness, however, we have re-run the Embase® searches to isolate non-English language hits (searches re-run 08 September 2020, see Appendix O). This re-run of the Embase® searches identified 2 non-English language hits (c.f. 2 non-English language hits in the original searches run 29 June 2020 – see Table 5, Appendix O). Neither of these hits are relevant to inform the decision-problem for fenfluramine (see Table 6, Appendix O). The use of an English

language limit on the Health-related Quality of life / utility value searches therefore has no meaningful implications in presenting the evidence base for this STA.

Healthcare Resources Use and Costs evidence searches

The Healthcare resource use and costs searches aimed to identify data with which to parameterise our UK-specific patient-level simulation model. Given that it is highly unlikely that a non-English language publication would provide healthcare resource utilisation and costs data that could appropriately reflect the healthcare resource utilisation and costs associated with the management of Dravet syndrome in UK clinical practice, or which would better reflect UK healthcare resource utilisation, medical practice, availability of standard of care treatments and costs than would an English-language publication, we made a pragmatic decision to limit our Embase® and PubMed searches for healthcare resource utilisation and costs data to English language publications. We considered our searches would be sufficiently comprehensive to identify any relevant UK-specific resource use and costs data for our patient-level simulation model, and any data of relevance to the NICE decision-problem in the UK. Of note, we also commissioned a specific UK pathway study to provide the granular detail on elements of health care resource use required for use in the economic model (see Document B, section 3.5).

The searches conducted for Healthcare resource use and costs data were based on the same searches run for economic evaluations (see Appendix I). As reported above, the limit to English language for Embase® and PubMed resulted in 9 (out of 206) hits being excluded from the Embase® search and 16 (out of 256) hits being excluded from the PubMed search (see Table 24 of Appendix I). Based on the above we do not believe the exclusion of non-English language publications would have excluded health care resource use and costs data that would have material implications on the conclusions of the cost effectiveness of fenfluramine in UK clinical practice, nor on the methodology we adopted for our patient-level simulation model. To demonstrate this, we have re-run the Embase® and PubMed Economic evidence searches to isolate non-English language hits. This re-run of the Embase® searches (re-run 08 September 2020, see Appendix O) identified 9 non-English language hits (c.f. 9 non-English language hits in the original searches run 29 June 2020 – see Table 3, Appendix O). This re-run of the PubMed searches (re-run 04

September 2020, see Appendix O) identified 16 non-English language hits (c.f. 16 non-English language hits in the original searches run 29 June 2020 – see Table 3, Appendix O). None of these hits relates to health care resource use or costs in the UK. One study, identified from Embase® and published in 2019 (*Kalski M et al. Clinical characteristics, resource utilization, quality of life and care situation for patients with Dravet syndrome in Germany. Zeitschrift fur Epileptologie (2019) 32:4 (326-338)*) relates to resource utilization associated with Dravet syndrome in Germany, and appears not to provide further or more granular information over the English language publications (several of which were also conducted in Germany, but have limited direct applicability in the UK) identified in our original searches. One study, identified from PubMed and published in 2000, was identified relating to economic costs of childhood epilepsy in Spain (*Argumosa, A et al. [Economic costs of childhood epilepsy in Spain]. Revista de Neurologia 2000; 30: 104-8*), but provides no Dravet syndrome-specific information (see Table 4, Appendix O). The use of an English language limit on the Economic evaluations evidence searches therefore has no meaningful implications in presenting the evidence base for this STA.

A3. Please confirm whether the European Paediatric Neurology Society (EPNS) 2019 conference abstracts are included in Embase.com as stated (Appendices D-I). The proceedings for 2019 are not currently included in Embase via the Ovid interface, but the Evidence Review Group (ERG) is unable to confirm whether they are in the database via the Embase.com interface.

Thank you for highlighting. We confirm that the 2019 EPNS conference abstracts appear not to be indexed in the Embase.com interface. We have therefore conducted an individual search of the EPNS 2019 conference abstracts (available at: http://www.epns2019.org/assets/EPNS_2019_ABSTRACT_BOOK_high_v5.pdf) to determine the impact of this omission from the searches.

The EPNS 2019 abstracts include 11 abstracts that make reference to Dravet syndrome, of which 2 abstracts could potentially have met the inclusion criteria for our SLRs (see Table 7 of the Appendix O); however, both related to fenfluramine data that were already captured in our original searches (*Lagae L et al. Efficacy and safety of Fenfluramine HCl oral solution in the treatment of Dravet Syndrome: pooled analysis of two Phase 3 clinical studies. Abstract OC004; Ceulemans B, et al.*

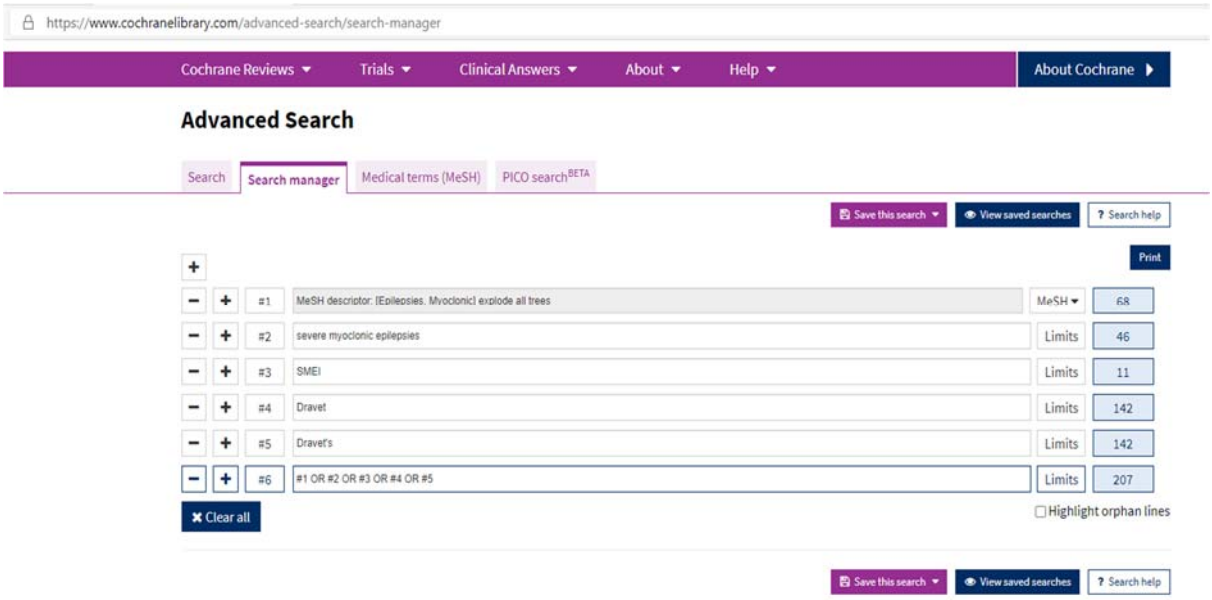
Fenfluramine HCl oral solution provides long-term, clinically meaningful (≥50%) reduction in seizure frequency in Dravet Syndrome: interim analysis of a long-term open-label extension study. Abstract P04-03) (see Table 4 of Appendix D). The omission of the EPNS 2019 abstracts from the Embase® searches therefore did not lead to the exclusion of data that could influence the conclusions on the efficacy, safety or cost effectiveness of fenfluramine or its relevant comparators.

Clinical effectiveness searches

A4. Please provide the name of the database host used for the Cochrane Database of Systematic Reviews (CDSR) and CENTRAL searches (Appendix D; Table 1). This does not appear to be the Cochrane Library website as stated in the company submission (CS; Appendix D; page 2).

The CDSR and CENTRAL were both searched from the Cochrane Library website as detailed in Appendix D. We have replicated the search (08 September 2020) and provided a screenshot below to demonstrate how this was conducted (**Figure *1***).

Figure 1. Screenshot of searches of Cochrane website

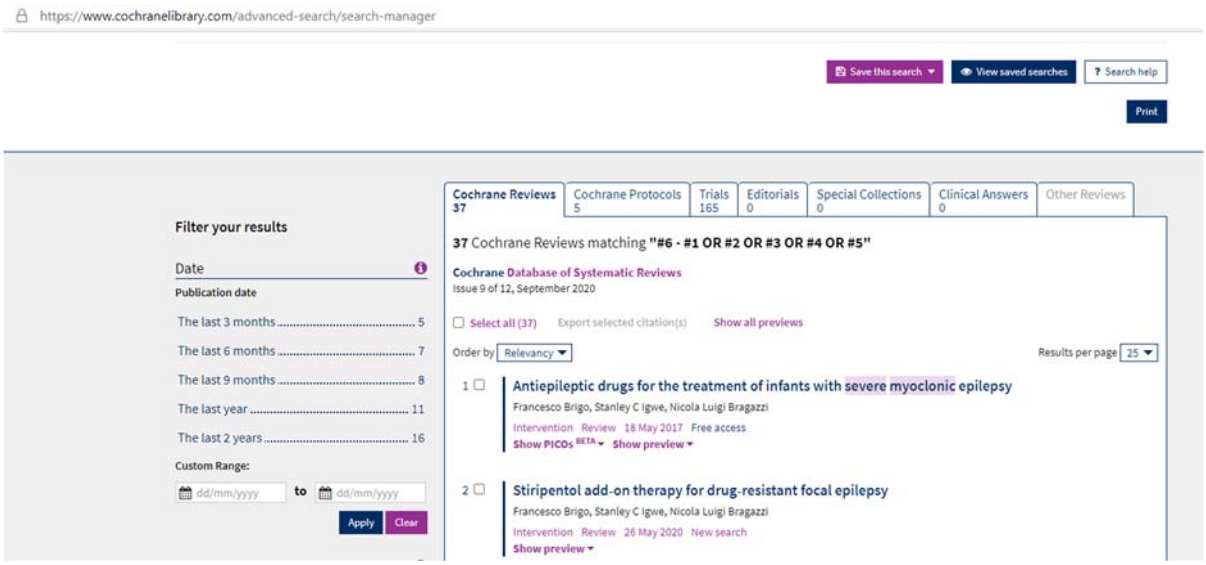


A5. Please provide full search results, with hits per line, for the CDSR and CENTRAL (Appendix D; Table 1).

Please see screenshot above in question A4 for the number of hits per line (search replicated for illustration 08 September 2020). The results of the searches are

provided by the different types of outputs of the Cochrane library, as illustrated in **Figure *2***.

Figure 2. Result reporting from Cochrane library searches



At the time of the original searches (28 June 2020) we recorded 37 Cochrane reviews and 167 CENTRAL records (Trials) that we subjected to screening.

A6. Please confirm the number of records retrieved by the search of CENTRAL for clinical evidence as there is a mismatch between search strategy and PRISMA flow diagram: 140 hits are shown as retrieved by the search strategy (Appendix D; Table 1), however the PRISMA flow diagram (Appendix D; Figure 1) lists a total of 167 hits for this database.

Apologies for this confusion. The PRISMA flow diagram reporting 167 records is correct.

Cost-effectiveness / Cost and healthcare resource use searches

A7. Please provide full search results, with hits per line, for the National Health Service (NHS) Economic Evaluations Database (EED) and health technology assessment (HTA) databases (Appendix G; Table 10 and Appendix I; Table 24).

Please see response to A8 below.

A8. Please explain the rationale behind excluding MeSH indexing terms from the NHS EED and HTA database searches (Appendix G; Table 10 and Appendix I; Table 24) when this could have retrieved additional records.

In constructing and testing our searches of the NHS EED and HTA database we observed that use of the MeSH search yielded fewer hits than use of the free-text searches we were testing. Furthermore, the MeSH search excluded a known HTA report for Stiripentol from CADTH. The CRD database interface appears not to permit the combined searching of MeSH terms and free-text terms. It was therefore decided that searches would be run using the free-text searches. In error, the description of the free-text searches of NHS EED and the HTA database were not updated when the final searches were decided upon and run, which has resulted in the incorrect description of the searches presented in Appendix G, Table 10, and in Appendix I, Table 24.

To clarify, the searches of the NHS EED and HTA database were conducted using the simultaneous free-text terms [all fields]: 'Severe myoclonic' OR 'Dravet syndrome' OR 'Dravet'. This resulted in 5 HTA database hits and 1 NHS EED database hit (as reported correctly in Appendix G, Table 10, and in Appendix I, Table 24). For completeness, we have run the search of the CRD database using the MeSH search (using "Epilepsies, Myoclonic" as the permuted search for Dravet syndrome). This yields no NHS EED hits and 4 HTA database hits (see Table 8 of the Appendix O). Of these 4 hits, 3 were already identified in the existing free-text searches; only 1 additional hit was identified, which was a review of Dentatorubral-pallidoluysian atrophy (DRPLA) that, as a different condition to Dravet syndrome, would be excluded from the SLR. Had the MeSH search been included in our original searches, this would therefore not have identified any additional economic evidence for inclusion in the SLR. The exclusion of the MeSH indexing term from the NHS EED and HTA database searches therefore has no meaningful implications in presenting the evidence base for this STA.

(For information, since our SLR was completed, a further HTA report for cannabidiol has been published. The SMC has issued its advice on Cannabidiol in NHS Scotland 7th September 2020. See:

https://www.scottishmedicines.org.uk/media/5365/cannabidiol-epidyolex-ds-final-august-2020docx-for-website.pdf).

A9. Please confirm the number of records retrieved by the NHS EED and HTA database searches. One record (NHS EED) and 5 records (HTA database) are shown as retrieved by the search strategy in Appendix G; Table 10 and Appendix I; Table 2, however the PRISMA flow diagram (Appendix G; Figure 4 and Appendix I; Figure 6) lists 6 and 4 records for these databases respectively.

Apologies for this confusion. The records retrieved by the NHS EED and HTA database searches were as reported in Appendix G, Table 10 and Appendix I, Table 24: there was 1 NHS EED record and 5 HTA database records identified. This discrepancy relates to an error in the reporting of hits and should have been corrected in the PRISMA flow diagrams before submission. This error does not impact on the final studies identified for inclusion in the review of cost effectiveness analyses and healthcare resource use and costs and has no meaningful implications in presenting the evidence base for this STA. Updated PRISMA flow diagrams are provided in Figures 1 and 2 in the Appendix to this document.

Health-related quality of life searches

A10. The PRISMA flow diagram in Appendix H shows the HTA database as having been searched for health-related quality of life (HRQoL) studies. Please confirm whether this database was searched, and if so, please provide the search strategy used.

The database searches for health-related quality of life studies were supplemented with reviews of the cost effectiveness analyses studies identified in Appendix G. The HTA database searches described in Appendix G identified 5 HTA reports (see response to A8 above), of which one was excluded upon initial screening on the basis it was not an English language report. This left 4 potential HTA reports that were available for screening to see if they contained relevant utility value data. These are the 4 HTA database reports that are listed in the PRISMA flow diagram in Appendix H. There was no additional search of the HTA database beyond the search conducted as described in response to question A8 above.

Section B: Clarification on effectiveness data

Decision problem

B1. Priority question: The final scope issued by the National Institute for Health and Care Excellence (NICE) defines the population of interest as *"people with Dravet syndrome whose seizures are inadequately controlled by established clinical management"*. According to section B.2.3.2 of the CS, the *"two registration, phase 3 RCTs* [randomised controlled trials] *(Study 1 cohort 1 and 2, and Study 1504, cohort 2) enrolled patients aged 2-18 years old with Dravet syndrome"*.

Please confirm that the results presented in the CS only apply to the narrower population, i.e. those aged 2-18 years. If not, please provide results for participants outside this age group.

The two phase 3 registrational RCTs (Study 1 and Study 1504) enrolled patients aged 2-18 years, and their results therefore relate to use in patients who initiated fenfluramine aged between 2 and 18 years. However, our submission also, appropriately, included results from the open-label extension study that enrolled patients from these two phase 3 registrational RCTs and included patients who continued fenfluramine into adulthood (Study 1503 - see Document B, section B.2.6.2) and additionally included long-term observational data from prospective and retrospective European RWE studies in patients who continued fenfluramine treatment into adulthood and also adult initiators (see Document B, section B.2.6.3.1). We also provided data (in confidence) from the ongoing European expanded access program, with efficacy assessments available from XX adults (see Document B, section 2.6.3.3).

Collectively, we believe these data demonstrate that both children and adults experience significant and often similarly profound reductions in convulsive seizure frequency with fenfluramine treatment. We note that the FDA has recently licensed fenfluramine for use in patients aged 2 years and above, i.e. in children and in adults, on the basis of the same clinical data and development program (see the US FINTEPLA label at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212102s000lbl.pdf). We

also note that, similar to the fenfluramine phase 3 trials, the phase 3 studies supporting cannabidiol (Epidyolex®) in the treatment of Dravet syndrome, which received a positive NICE recommendation for use within its full licensed indication in patients aged 2 years and older (i.e. in children and adults) in December 2019 (see NICE TA 614), were conducted in patients aged 2 to 18 years. On this basis, we do not believe the exclusion of patients aged >18 years from the phase 3 RCTs would preclude a recommendation for the use of fenfluramine within its anticipated full licensed indication.

B2. Priority question: In the decision problem and in Figure 2 of the CS fenfluramine is described as a potential first line (1L) add on therapy in patients where clobazam or a clobazam-based regimen is undesired.

a. **Please provide evidence as to what proportion of patients this might apply to (central estimate and range).**

We anticipate that use of fenfluramine as a first-line add on therapy in patients for whom clobazam is not a desirable option will account for a small proportion of the overall use of fenfluramine. As clobazam and several other antiepileptic drugs are used across a range of epilepsy types and is not specifically licensed for use in Dravet syndrome, it is challenging to derive a precise estimate of the proportion of patients in whom clobazam is and will remain a desirable first-line add-on option and therefore the proportion in whom clobazam will not be a desirable option. Data from the DISCUSS study, a large survey of Dravet syndrome patients and caregivers conducted in 2016, indicates that 74% of UK patients were taking clobazam at the time of the survey (Pagano et al, 2019[i]); however, the specific pattern of use of clobazam with other AEDs in that study is not clear. Although both stiripentol and clobazam are recommended as add-on therapy options in NICE clinical guideline 137, we anticipate that clobazam would be considered first where possible, based on acquisition costs, and the fact that stiripentol is only licensed for use in combination with clobazam (SmPC stiripentol[ii]). As clobazam is well established in the clinical pathway and clinicians managing people with Dravet syndrome are well experienced in the use of clobazam, we anticipate that clobazam would be considered as a first-line add-on in the vast majority of patients and assume it would be clinically suitable for the vast majority of patients. In our budget impact model, based on a number of

simplifying assumptions (see details in Appendix O), we have estimated that clobazam would not be a clinically desirable first-line add-on therapy in XXX of patients, of which possibly XXX XXX XXX of all Dravet patients in need of add-on therapy) would receive fenfluramine in the year 2024 onwards. Although this reflects a small proportion of use of fenfluramine, it is an important treatment option for patients and clinicians who otherwise have limited therapy options.

b. Why is it legitimate to consider Cannabidiol + standard of care (SOC; a second-line (2L) add-on therapy) as a legitimate comparator for a 1L add-on therapy?

We do not consider that cannabidiol + SoC is the relevant comparator for fenfluramine in the first-line add-on setting where clobazam is not clinically desirable. As stated in Document B, section B.1.3.4, we anticipate that, where clinicians feel clobazam is clinically a desirable first-line add-on therapy, this would be tried in preference to other options, including fenfluramine.

However, fenfluramine could be a first-line add-on therapy option in patients for whom clobazam or clobazam-containing regimens are not a desirable option (or not tolerated, i.e., a second line add-on therapy), in which case, based on NICE CG137, unlicensed stiripentol or continued therapy with existing SoC AEDs would be the appropriate comparators (Figure 2, Document B). As the clinical data available in support of stiripentol (without clobazam) are not sufficient to permit a robust comparison of add-on fenfluramine against unlicensed add-on stiripentol without clobazam (see response to question B3 below), it is not feasible to provide a cost effectiveness analysis of add-on fenfluramine against add-on stiripentol in this first-line add-on therapy setting (or indeed in any setting).

We have, however, provided a cost effectiveness analysis of add-on fenfluramine against continued SoC AEDs (without clobazam, and therefore stiripentol or cannabidiol), which would be a relevant comparator in this setting (see positioning scenario analyses in Document B, Table 52), since these patients have no other licensed treatments available to them, other than experimental or off-label options.

B3. Priority question: Stiripentol is included as a comparator in the scope. The company cite NICE clinical guideline (CG) 137 which recommends to *"discuss*

***with a tertiary epilepsy specialist if first-line treatments…in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam or stiripentol as adjunctive treatment"*. Trial 1504 compared fenfluramine to stiripentol as adjunct to clobazam plus sodium valproate. It is unclear whether the recommendation in NICE CG137 includes the possibility of clobazam and stiripentol being given together. However, the NICE scope specified as comparator *"established clinical management without fenfluramine, which may include combinations of…"* and then lists both stiripentol and clobazam. Furthermore, technology appraisal (TA) 614 stated that *"the clinical experts added that stiripentol is increasingly being used because of evidence that using valproate, clobazam and stiripentol together improves efficacy"*. Furthermore, a comparison between fenfluramine and stiripentol as adjuncts to clobazam might also be informative of a comparison between fenfluramine and stiripentol as adjuncts to other anti-epileptic drugs (such as sodium valproate) without clobazam. Therefore, the ERG requests:**

a. **an explanation as to why the comparison with stiripentol was not included in the network meta-analysis (NMA).**

As a point of clarification: The ERG states above that Trial 1504 compared fenfluramine to stiripentol as adjunct to clobazam plus sodium valproate. However, this is incorrect. As described in Document B, section B.2.3.1.2, Study 1504 (cohort 2) is a placebo-controlled trial in which patients were randomised to fenfluramine or placebo, each added on to a background of SoC AEDs that included stiripentol. Study 1504 therefore does not provide a comparison of add-on fenfluramine vs add-on stiripentol.

As detailed in Document B, section B.2.9, and in Appendix D, an objective of our SLR was to identify any RCTs of stiripentol (or cannabidiol or clobazam) that may permit an indirect treatment comparison (ITC) of add-on fenfluramine vs add-on stiripentol (or vs add-on cannabidiol or add-on clobazam). The SLR identified 2 placebo-controlled trials of stiripentol. We conducted a detailed assessment of these and the fenfluramine trials, including comparisons of enrolment criteria, study designs, the endpoints assessed, the baseline characteristics of enrolled patients,

and a quality/risk of bias assessment to determine if it was feasible to conduct an ITC. Due to substantial differences in the assessment of convulsive seizure reduction endpoints in the stiripentol trials, and also the unclear risk of bias that limits the quality of the stiripentol trial evidence, we determined it is not feasible to conduct an ITC comparing add-on fenfluramine vs add-on stiripentol (see Document B, section B.2.9.2.4). As there are no direct comparative data for add-on fenfluramine vs add-on stiripentol, and it is not possible to conduct a robust ITC, stiripentol was appropriately excluded from the NMA.

It is of note that the submitting company for the cannabidiol submission in NICE TA614 also concluded that it was not possible to conduct a robust ITC against stiripentol or other therapies (Committee papers for NICE TA614[iii]) and the NICE appraisal committee, in making its positive recommendation for cannabidiol in the absence of either a direct or indirect comparison with stiripentol (NICE FAD TA614[iv]) appears to have accepted this conclusion.

b. to add stiripentol as a comparator in the decision problem, including in the cost-effectiveness analysis (CEA) by using data from trial 1504.

Fenfluramine is anticipated to be licensed as an add-on therapy to SoC AEDs, and would therefore be used in patients requiring add-on therapy to their current SoC AEDs. To understand the cost effectiveness of add-on fenfluramine in the existing add-on therapy pathway, the most relevant comparison should be made against other add-on therapies where these are available; a comparison of add-on fenfluramine vs SoC AEDs would not reflect the cost effectiveness of the use of add-on fenfluramine therapy in patient requiring add-on therapy to SoC AEDs when other add-on therapies are available.

As stated in Document B, section B.1.3.4, the appropriate comparators for fenfluramine as a second- or subsequent line option in patients in need of an add-on therapy would be stiripentol (with clobazam) or cannabidiol (with clobazam). We have therefore acknowledged that stiripentol would be a relevant comparator in the decision problem. However, as detailed in Document B and in our response to question B3.a above, there are no direct comparative data for add-on fenfluramine vs add-on stiripentol, and due to limitations in the stiripentol RCT data it is not possible to conduct a robust indirect comparison of add-on fenfluramine vs add-on

stiripentol. It is therefore not possible to conduct a cost effectiveness analysis of add-on fenfluramine vs add-on stiripentol.

In contrast, cannabidiol has sufficient, contemporary RCT data available to permit a robust indirect comparison of add-on fenfluramine vs add-on cannabidiol (see Document B, section 2.9). Add-on cannabidiol is also the only add-on therapy recommended by NICE as a cost-effective option in the existing add-on therapy pathway alongside stiripentol, even though its cost effectiveness against stiripentol was not assessed. As both stiripentol and cannabidiol are now available as add-on therapy options, and it is only possible to make a robust comparison of add-on fenfluramine vs add-on cannabidiol, we have therefore compared add-on fenfluramine against add-on cannabidiol in a primary cost effectiveness analysis. This provides an estimate of the cost effectiveness of fenfluramine when added to SoC in the existing care pathway against a NICE-recommended add-on therapy. As cannabidiol is accepted as a cost-effective option alongside stiripentol, conclusions on the cost effectiveness of fenfluramine as an add-on option at the same points in the add-on therapy pathway as cannabidiol and stiripentol are recommended may therefore be inferred from the cost effectiveness of fenfluramine vs cannabidiol.

In addition, as it is not possible to compare the cost effectiveness of add-on fenfluramine vs add-on stiripentol, we have provided scenario analyses of the cost effectiveness of fenfluramine reflecting its use before stiripentol is used, after stiripentol is used and in addition to stiripentol, to demonstrate the clinical and cost effectiveness of fenfluramine with reference to stiripentol across the add-on therapy pathway (see Document B, Table 52).

B4. Row “Outcomes” in Table 1 of the CS states that *“additional endpoints e.g. seizure free intervals, provide metrics more closely aligned with the goals of treatment and in having a meaningful impact on patient quality of life”*.

Please provide a reference in support of this statement.

The text preceding this quote in Table 1 provides context for why the outcomes used as primary and secondary endpoints of the trials (and the outcomes stated in the NICE scope) may not alone be sufficient to capture the impact of Dravet syndrome on patients and the benefits of treatment, and therefore why additional outcomes

have been included beyond those in the scope: "*The primary and key secondary endpoints in the registration trials for fenfluramine measured measure reductions in convulsive seizure frequency. Whilst fulfilling standard regulatory requirements and providing a single metric of effect, these metrics alone have some limitations. For example, a 50% reduction from baseline seizures per month, would have different clinical, economic and QoL implications, if patients had experienced 2 or 60 seizures per month at baseline*."

Please also see section B.1.3.1.6 of Document B, which states: *"…The NICE final appraisal determination (FAD) for cannabidiol noted clinicians' views that, in addition to reducing convulsive seizure frequency, to increase the number of seizure-free days was also important, as fewer days with seizures means fewer days in which patients are at risk of SUDEP [12]. From the perspective of patients and their families, increases in seizure-free days can also have a profound and direct impact on daily activities, including learning opportunities and planning for social interactions, as well as reducing the physical and emotional toll of the disease [51,52]."*

Systematic literature review

B5. Priority question: Table 3 of Appendix D of the CS lists the eligibility criteria applied in the systematic review of clinical evidence. There are a number of discrepancies compared to the decision problem (Table 1 of the CS) which should be explained while missing results should be provided.

a. **The NICE scope lists ketogenic diet as well as vagus nerve stimulation as comparators. These are not included in Table 3.**

The scope for this appraisal lists the comparators as established clinical management without fenfluramine, which may include combinations of 8 different listed therapies, including vagus nerve stimulation (VNS) and ketogenic diet (KD). As it is unrealistic to expect a comparison against every possible permutation of these therapies, we have appropriately focused our comparisons against only the most relevant of therapies that in practice would be anticipated to be possible alternatives

to fenfluramine as add-on therapies to SoC. These are stiripentol, cannabidiol and continued SoC, as detailed in Document B, Table 1 (decision problem), and section B.1.3.4. We believe that VNS and KD may be components of the SoC to which fenfluramine may be added, but would not be a clinically relevant alternative to fenfluramine. This is consistent with the approach taken in the NICE appraisal of cannabidiol (TA614) and a broader clinical consensus by international expert physicians in developing both the fenfluramine studies and the cannabidiol trials, as neither VNS and KD were excluded as entry requirements for patients enrolled in the trials. For this reason, we noted in the footnote to Figure 2 of Document B that, in addition to 1st line AEDs, VNS and KD are adjunctive standard of care therapies and are rarely used and are excluded (as comparative interventions) from the submission. Accordingly, it was not necessary to include VNS and KD as comparators in our SLR, and their exclusion has no meaningful implications in presenting the evidence base for this STA.

b. Table 3 does not list severity of seizures, non-convulsive seizures, incidence of status epilepticus, and mortality as outcomes of interest.

The aim of the clinical SLR was to identify all relevant fenfluramine RCTs and studies of other relevant comparators that may be used in an ITC. The primary endpoints of the registration RCTs for fenfluramine, stiripentol and cannabidiol related to convulsive seizure frequency, and underpins the regulatory approval and agreed measure of benefit by European and the US regulators. Convulsive seizure endpoints therefore provide the most robust outcome measure in any of these trials and so was the focus of the endpoints for the ITC. There are important limitations to the outcomes that the ERG has noted were missing from the SLR inclusion criteria in Table 3, which when considered in the context of identifying relevant RCTs and conducting ITCs means that their exclusion from the SLR eligibility criteria has no meaningful implications in presenting the evidence base for this STA:

- **Severity of seizures** – this outcome is not well defined; it is unclear if or whether this relates to seizure type, seizure frequency, seizure duration or some other seizure characteristics. As this outcome is not well defined we do not believe this could be used to determine whether a study should be

included or excluded from the SLR, nor could it be used as an outcome measure for comparison of add-on therapies in an ITC.

- **Non-convulsive seizure** – whilst this outcome is often reported in clinical trials and is an important outcome for patients, there are particular issues that render this a less reliable outcome measure than convulsive seizures. These include the fact that non-convulsive seizures are less obvious and harder to detect than convulsive seizures, which would lead to a great possibility of differential subjective reporting across different trials (discussed in Document B, section B.2.13.3.2). On this basis we do not believe that non-convulsive seizures would be reported in a trial that did not also report convulsive seizures (which was an outcome of interest specified in Table 3), and we do not believe that non-convulsive seizure outcomes would provide a robust outcome measure for comparison of add-on therapies in an ITC.

- **Status epilepticus (SE**) – whilst this outcome is often reported in clinical trials and is an important outcome for patients, the duration of seizures that are used to define SE events may not be consistent between trials (SE-defining durations range from 5- 30 minutes in the literature – see https://www.ilae.org/journals/epigraph/epigraph-vol-20-issue-2-fall-2018/time-is-brain-treating-status-epilepticus and Glauser et al 2016[v]) Furthermore, irrespective of the precise definition, the frequency of SE events relative to the frequency of other seizure events is low. Given that the RCTs of Dravet syndrome therapies are of relatively short duration and typically involve relatively small sample sizes, the trials are not powered for detecting a difference SE events. On this basis we do not believe that SE events would be reported in a trial that did not also report convulsive seizures (which was an outcome of interest specified in Table 3), and we also do not believe that SE events would provide a robust outcome measure for comparison of add-on therapies in an ITC, given their low event rate frequency, variable definition across trials and non-statistical significance.

- **Mortality** – mortality is an important outcome; Dravet syndrome patients are at an elevated risk of mortality compared with both the general population and other epilepsy populations. However, it is thankfully a relatively rare event

compared to other seizure events. To our knowledge no Dravet syndrome RCTs report mortality as an efficacy outcome measure, and given that the RCTs of Dravet syndrome therapies are of relatively short duration and typically involve relatively small sample sizes, it is highly unlikely that an RCT in such a rare disease could reasonably, financially or feasibly/practically be expected to be adequately powered for mortality events. We also do not consider it likely that mortality events would be reported in a trial that did not also report convulsive seizures; or that mortality events could provide a robust outcome measure for comparison of add-on therapies in an ITC.

We have, of course, included data on non-convulsive seizures and SE events observed in the fenfluramine clinical trials in section B.2.6 of Document B; however, there are no “seizure severity” or mortality outcomes to report.

In summary, whilst efforts have been made to provide evidence in line with the scope, the exclusion of these outcomes from the eligibility criteria of the clinical SLR is highly unlikely to have resulted in the inappropriate exclusion of relevant evidence, and would not influence the conclusions that could be drawn on the efficacy of fenfluramine in its clinical trials or its efficacy relative to relevant add-on therapy comparators.

B6.The systematic review was limited to studies published in English only. At least one study appears to have been excluded on the basis of language. Were any relevant studies omitted due to this language restriction?

No relevant studies were omitted from the SLR as a result of limiting the publications to English language. Please see the response to question A2, which demonstrates this.

B7. How were the observational studies included in the CS identified as these would not meet the inclusion criteria for the systematic review? Were any relevant further observational studies available and excluded from the submission? Please provide relevant references.

The clinical SLR focused on identifying relevant RCTs of fenfluramine, and also identifying RCTs of relevant comparator add-on therapies to determine the possibility of conducting an ITC, as discussed in Appendix D. We did not aim to compare

observational data for fenfluramine against observational data for other possible comparators (not least because of the inherent methodological limitations in doing so) and therefore we did not employ a specific search filter for observational studies. The observational, long-term studies included in the submission (i.e. the two Belgian RWE studies) were included in the clinical development program and regulatory evidence package submitted to the EMA and FDA and provided the foundational data and supporting scientific basis of fenfluramine for the treatment of seizures in patients with Dravet syndrome (e.g. see the CSRs for Study 1, 1504 and 1503 provided as references to our submission).

B8. If open label extension studies were eligible for the systematic review, it is unclear why GWPCARE5, an extension study of cannabidiol, was not included. Please explain.

The GWPCARE 5 OLE study was included in our SLR. Please see Table 4 of Appendix D where multiple publications relating to this OLE study are listed (under column headed Combined analyses / OLE studies). It should be noted that the GWPCARE 5 OLE study publications listed in Table 4 of Appendix D may not relate to the specific licensed indication that stipulates cannabidiol must be used in combination with clobazam. Important data on this licensed subgroup of patients in GPWCARE 5 study (i.e. data suggesting a relative 25% reduction in efficacy over 48 weeks of treatment) are referenced in the cannabidiol SmPC.

Clinical trials

B9. Priority question: According to the CS, 12% of participants across the two randomised trials of fenfluramine were from the United Kingdom (UK).

a. **Please provide UK patients numbers by trial and treatment group.**

Please see **Table *1*** for these figures (reported for placebo and the fenfluramine dose groups).

Table 1. UK patient numbers by trial and licensed treatment group

Study	Arm	Number of patients
Study 1504	Placebo	9
Study 1504	0.4mg/kg/day	3
Study 1	Placebo	3
Study 1	0.7mg/kg/day	4
Study 1	0.2mg/kg/day	5

b. How generalisable to the population to be seen in NHS clinical practice are the patients in the two trials?

Generalisability of the trial populations and clinical evidence base to patients seen in NHS clinical practice is discussed in depth in Document B, section B.2.5 and B.2.13.2.

Dravet syndrome is a rare condition and patient populations are heterogenous in their seizure frequencies and treatment histories. The two phase 3 RCTs enrolled Dravet syndrome patients aged 2-18 years, with a mean age of approximately 9 years and a wide range of seizure frequencies. At baseline, patients had a history of multiple prior AEDs and were taking a mean average of 2.4 (Study 1) and 3.5 SoC AEDs (Study 1504). The most common AEDs among their SoC regimens were valproate, clobazam and stiripentol (0% in Study 1 and 100% in Study 1504). The SoC AEDs included in the trials were confirmed as being representative of UK clinical practice by clinical experts in our UK pathway research study and by comparison with UK data from the DISCUSS study, as described in Document B, section B.3.2.3, and in the response to question B16.a below.

In comparing the characteristics of these two RCT populations with the patients in the DISCUSS study – a large cross-sectional survey of Dravet syndrome patients and their carers conducted in Europe, including 72 patients from the UK –a broad degree of similarity between the trial populations and the identified patients in UK practice is observed. Of note, the distribution at baseline of the foremost convulsive seizure type, tonic-conic seizures, was comparable between the two RCTs and the UK patients reported in the DISCUSS study (see section B.2.5). The mean age of patients contributing to the DISCUSS study was 10.6 years (median 9 years), and

patients were taking a mean of 3 AEDs, most commonly valproate, clobazam and stiripentol (see B.2.13.2).

Although, the phase 3 RCTs excluded adult patients over 18 years of age, which may be perceived to limit the generalisability of the RCT data to adult patients in practice, subgroup analyses stratified by age did not indicate a reduced efficacy as patients reached adolescence (see Document B, section B.2.6.1.1.1 and the response to question B12 below). In addition, the OLE study includes a cohort of patients who have reached adulthood during the study and continued to receive a treatment benefit with fenfluramine. In real-world observational data of fenfluramine several children and adolescents continued/continue to receive a clinically meaningful reduction in seizures into adulthood; which was of a similar magnitude in benefit to those patients that initiated treatments with fenfluramine as an adult in these RWE studies. It is therefore considered that the type of seizures throughout studied ages; as well as the magnitude of benefit from fenfluramine achieved is consistent across all ages (see Document B, section B.2.13.2).

Notwithstanding the placebo effect inherent in all RCTs, on the basis of the above we have no reason to believe the treatment effects of fenfluramine observed in patients in the trials would differ in a systematic way in patients in clinical practice.

B10. Priority question: The inclusion criteria for Study 1, Study 1504 (cohort 2), and Study 1503 suggest that patients with cardiovascular or cardiopulmonary abnormality be excluded.

a. **Please provide numbers and proportions of patients excluded for these reasons. This is particularly relevant since fenfluramine has been associated with adverse outcomes at higher doses in an adult population.**

Please see response to B10b below.

b. **Alternatively, please confirm that fenfluramine should not be prescribed to patients who are at risk of cardiovascular or cardiopulmonary events.**

In the early 1960's, fenfluramine was marketed as an anorectic treatment to aid weight loss in obese adults. During this time on the market, cases of pulmonary arterial hypertension and cardiac valvulopathy were reported in patients who had

been treated with fenfluramine, often when administered in an off-label combination with phentermine. This led to its withdrawal from the US and European markets in the late 1990's [vi, vii, viii].

It is of note that the indicated dose of fenfluramine for use as an anorectic was 60mg/day[1]; although signs and symptoms of valvular heart disease were identified in patients receiving doses up to 220 mg/day (median 56.5 mg/day) in an off-label combination with phentermine [vi] It is also notable that the interpretation from the original studies, of an association of fenfluramine (and related drugs) with valvular heart disease, is confounded by the lack of echocardiograms obtained prior to initiating treatment with fenfluramine and a lack of controlling for other risk factors ix.

Since fenfluramine as a treatment to aid weight loss in obese adults was withdrawn from the market over 20 years ago, no other form of fenfluramine has been made commercially available, for any indication.

The current marketing authorisation application for fenfluramine (FINTEPLA) under review by the EMA, proposes that fenfluramine is indicated in an entirely different population of patients with Dravet syndrome - a rare, severe and life-limiting form of epilepsy that emerges in early infancy. The purpose of fenfluramine in the treatment of these vulnerable patients is for the reduction of life-threatening seizures that are frequent (often daily); are intractable to other antiepileptic therapies; and are associated with high morbidity and quality of life impacts to patients and their families.

The maximum clinical doses of fenfluramine for the treatment of Dravet syndrome are 0.7 mg/kg/day (0.4 mg/kg/day for patients receiving concomitant stiripentol), with a maximum total daily dose of 26 mg (or 17 mg, respectively). Therefore, regardless of a patient's weight, these doses are substantially lower than those previously used to treat obesity. The risk-benefit profile of fenfluramine (as FINTEPLA) in the treatment of Dravet syndrome is therefore completely different to the risk-benefit profile of the previously marketed fenfluramine product that was used and subsequently withdrawn for the treatment of obesity

[1] *Ponderax PACAPS UK Product Licence 0093/0013R*

As would be expected for an investigational medicine with a known adverse event profile at higher doses, additional and specific focus of the development programme (including non-clinical toxicity studies) was undertaken to scrutinise and investigate for potential cardiotoxicity, valvular heart disease and pulmonary arterial hypertension safety signals. Importantly, the data from the entirety of the programme have shown fenfluramine (as FINTEPLA), at the doses studies in Dravet syndrome patients, to be well tolerated with no serious cardiovascular, cardiopulmonary or notable other safety signals observed. In addition, in these studies (and as extensively detailed within the submission), FINTEPLA significantly demonstrates a robust effect on convulsive seizures that is clinically meaningful, highlighting a compelling risk-benefit profile for FINTEPLA in the treatment of seizures for patients with Dravet syndrome.

Although the label and SmPC for fenfluramine in Dravet syndrome is to be finalised by the EMA, it is anticipated that it will exclude the use of fenfluramine in patients with known cardiovascular or cardiopulmonary abnormalities, as per the RCT protocols and as reflected by the contraindications listed in the draft SmPC provided with our submission. The exclusion of patients with cardiovascular or cardiopulmonary abnormalities from the clinical trials is therefore aligned with the anticipated use of fenfluramine in clinical practice and has no meaningful implications on the conclusions of its demonstrated efficacy or observed safety profile to date.

B11. Table 5 of the CS presents details of the number of concurrent anti-epileptic drugs (AEDs) taken by patients.

Please also provide details of prior AEDs received by patients (mean, standard deviation (SD) and broken down by type).

Study 1 - Overall, the most commonly used prior AEDs (≥25% overall), were clobazam (83.2%), levetiracetam (79.0%), topiramate (68.9%), valproate semisodium/sodium (68.1%), stiripentol (48.7%), zonisamide (43.7%), phenobarbital (40.3%), lamotrigine (27.7%), cannabidiol (26.9%), clonazepam (26.9%), and valproic acid (31 subjects, 26.1%) (see CSR for Study 1, Table 14.1.4.3).

Study 1504 - Overall, the most commonly used prior AEDs (≥25% overall), were clobazam (94.3%), valproate semisodium/sodium (57.4%), and topiramate (25.3%) (see CSR for Study 1504, Table 14.1.4.3b).

The mean (SD) number of AEDs received by patients prior to enrolment in each of the trials requires reanalysis of the data and will be provided as soon as practicably possible.

B12. Why were the trials stratified at age <6 years and ≥ 6 years? Was there any expectation of differential effectiveness? If so, please provide details.

Dravet syndrome is a rare disease, which can pose challenges to trial recruitment. At the request of the regulatory agencies, the populations were stratified by age to ensure an appropriate balance of younger patients (<6 years of age) and older patients (≥ 6 years of age) in the trials (the studies targeted 25% of the trial population to be <6 years of age). There was no expectation of differential effectiveness by age.

This target was reached (26-27% of the trial populations were aged <6 years); however, efficacy analyses by age <6 years and ≥6 years are still subject to limitation due the low sample sizes. Nonetheless, these analyses suggest convulsive seizure reductions with the anticipated licensed doses of fenfluramine are similar across age groups (**Table *2***). Document B, section B.2.6.1.1.1 also reports results in patients aged ≥12 years, which are similar to the whole trial population.

Table 2. Percentage reduction from baseline in convulsive seizure frequency by age

	Placebo (median [min,max])	**Fenfluramine (median [min,max])**
Study 1 (fenfluramine dose 0.7mg/kg/day, max 26mg/day)		
<6 years	XXX	XXX
≥ 6 years	XXX	XXX
Study 1504 (fenfluramine dose 0.4mg/kg/day, max 17mg/day)		
<6 years	XXX	XXX
≥ 6 years	XXX	XXX

B13. In the maintenance phase of the randomised trials dosing was fixed. How does this reflect clinical practice in the UK?

The trial design specified initiation at a dose of 0.2mg/kg/day, with titration up to the maximum dose of 0.7 mg/kg/day (capped at 26mg/day) in Study 1 (patients not taking concomitant stiripentol) and titration up to the maximum dose of 0.4mg/kg/day (capped at 17mg/day) in Study 1504 (patients not taking stiripentol). The dose in the maintenance phase was stable.

In clinical practice, patients will initiate fenfluramine at the 0.2mg/kg/day and will be titrated up to these maximum doses; however, dose adjustment will, of course, be permitted to optimise efficacy and adverse events. The fact that patients were maintained on a stable dose in the trials does not imply that the relative efficacy and safety will be systematically different in clinical practice as a result of dose optimisation. The same approach was adopted in the cannabidiol RCTs.

It should be noted that, although we anticipate that patients will have their doses of fenfluramine optimised, which may include the use of less than maximum doses in clinical practice, we have nonetheless assumed the maximum dose (and cost) of fenfluramine throughout ongoing treatment in our economic model. In contrast, in our base case economic model we have assumed a dose (and cost) of cannabidiol of 12mg/kg/day, which is towards the lower end of its recommended 10-20mg/kg/day dose range and is a highly conservative assumption, particularly given that the GWPCARE 5 OLE study suggests a potential waning of effect of cannabidiol over 48 weeks of treatment and compensatory dosing that may plausibly be towards the upper end of the dose range (see section B.2.9.5). The SMC in its appraisal of cannabidiol published 07 September 2020 also notes that the average dose could plausibly increase further towards 20mg/kg/day, which has a significant impact on the estimated cost effectiveness of cannabidiol (See: https://www.scottishmedicines.org.uk/media/5365/cannabidiol-epidyolex-ds-final-august-2020docx-for-website.pdf).

B14. In Table 2 of the CS the dosage for fenfluramine is explained.

a. What proportion of patients are expected to receive the 0.2 mg/kg/day dose rather than the increased dose of 0.7mg/kg/day in the non-stiripentol group?

Fenfluramine will be initiated in all patients at a dose of 0.2mg/kg/day, irrespective of whether patients are taking concomitant stiripentol or not. In those not taking

concomitant stiripentol, the dose can be titrated up to a maximum of 0.7mg/kg/day (capped at 26mg/day), and in those who are taking concomitant stiripentol the dose can be titrated up to a maximum of 0.4mg/kg/day (capped at 17mg/day). The 0.2mg/kg/day dose is an initiation dose and we do not anticipate patients will be maintained on the 0.2mg/kg/day dose.

b. What are the corresponding proportions for patients taking stiripentol?

In the trials, due to their designs, no patients in Study 1 were taking concomitant stiripentol, and all patients in Study 1504 were taking concomitant stiripentol. In clinical practice, UK data from the DISCUSS study – a large survey of Dravet syndrome patients and caregivers – indicates that 58% of patients receive stiripentol. On this basis we have assumed that 58% of patients receive stiripentol in the population modelled in our economic analysis (see Document B, section B.3.2.2.3.2).

B15. In the CS it is stated that patients can progress to the open label extension study on 'satisfactory completion' of Study 1 or 1504.

How was 'satisfactory completion' defined?

At the end of the maintenance phase of treatment, patients from Study 1 or Study 1504 who remained eligible for treatment; willing to remain on treatment under trial conditions; and for whom the investigator, patients and/or caregiver determined continued treatment may provide continued benefit, were offered enrollment in the Study 1503 open-label extension study. Patients who discontinued study medication before completion of the 12-week maintenance phase of their core trial by definition did not complete the core study. Those who did not complete the 12-week maintenance period of the core study could have been, on a case-by-case basis, eligible for entrance into the OLE study after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a fenfluramine trial.

B16. Please justify whether the use of concomitant AEDs for patients in the two phase three trials are representative for UK clinical practice (Table 26 of the CS).

a. Provide evidence that the mix of concomitant AEDs is representative for the UK.

Dravet syndrome is a rare condition and patient populations are heterogenous in their seizure frequencies and their treatment histories. This is reflected in the clinical trial populations, and as each trial assessed fenfluramine as an add-on therapy to patients' individualised SoC AEDs, a level of heterogeneity in the AEDs received is to be expected.

Table 26 of Document B (replicated below in Table 3 for convenience) summarises the concomitant AEDs used in the overall study populations (a small number of patients were also taking clonazepam, zonisamide and ergenyl chrono but are excluded from this table). As reported in Document B, section B.3.2.3, these AEDs, which were included in our economic model, are representative of UK clinical practice as confirmed by clinical experts in our UK clinical pathway research study.

Table 3 Concomitant AEDs used in the fenfluramine registration studies at baseline (total study populations, excluding stiripentol)

Concomitant AEDs	Fenfluramine double-blind studies		DISCUSS
	Number of patients on each AED (percentage applied in the model)		UK cohort
	Study 1[3] (N=119)	Study 1504 cohort 2[4] (N=87)	N=72
Clobazam†	71 (60%)	82 (94%)	74%
Levetiracetam	29 (24%)	11 (13%)	NR
Topiramate	30 (25%)	21 (24%)	25%
Valproate (semisodium & sodium)	57 (48%)	50 (57%)	68%
Valproic acid	18 (15%)	16 (18%)	
Stiripentol*	0	87(100%)	58%
*Stiripentol use was not included in Table 26 of Document B. Added here for completeness based on the designs of Study 1 (which excluded concomitant use of stiripentol) and Study 1504 (in which all patients received stiripentol)			NR – not reported

Due to the design of the trials, no patients in study 1, and all patients in Study 1504 received stiripentol. Valproate, clobazam and stiripentol are therefore clearly the most commonly used AEDs across the trials.

In the DISCUSS study, 58% of UK participants reported current use of stiripentol. If we apply this 58% weighting to the concomitant AED use reported in the trials (i.e. 58% from Study 1504 and 42% from Study 1), the weighted average use of clobazam across the trials is 79% and the weighted average use of valproate (combined valproate and valproic acid) across the trials is 70%. This aligns closely with the reported use of clobazam (74%) and valproate (68%) in UK patients in the DISCUSS study. We therefore conclude that collectively the concomitant AEDs used in the trials are reflective of those reported to be used by UK patients, and furthermore the concomitant AEDs in Study 1 are likely to be reflective of those used in UK patients not taking stiripentol in practice, and the concomitant AEDs in Study 1504 are likely to be reflective of those used by patients taking stiripentol in UK practice.

In summary, both clinical expert opinion and available survey data from a significant proportion of UK patients indicate that the concomitant AEDs in the phase 3 trials are reflective of the AEDs received in clinical practice. Based on the above, there is no reason to believe that the mix of concomitant AEDs to which fenfluramine was added in the trials is not representative of the SoC AEDs to which fenfluramine will be added in clinical practice.

b. Please elaborate on the differences in concomitant AED use between the two phase III trials.

The difference in concomitant AEDs between the two phase 3 RCTs is due to the designs of the RCTs. Study 1 was conducted in patients who were not taking stiripentol among their concomitant AEDs, and Study 1504 was conducted in patients who were all taking stiripentol among their concomitant AEDs. By design, stiripentol use in Study 1 was therefore 0% in Study and was 100% in Study 1504.

This accounts for the difference in stiripentol use between the trials. However, as stiripentol is only licensed for use in combination with clobazam and valproate, use of valproate and clobazam is therefore higher among patients in Study 1504, as would be expected. The concomitant AEDs in Study 1 are likely to be reflective of those used in UK patients not taking stiripentol in practice, and the concomitant AEDs in Study 1504 are likely to be reflective of those used by patients taking stiripentol in UK practice (see response to question B16.a).

Analysis

B17. Priority question: Please provide the full R gemtc code including the relevant data so all NMAs, including any requested in the request for clarification, can be run by the ERG.

The full R gemtc code and data for the for the NMAs included in Document B is provided with this response.

B18. Priority question: Please clarify which convulsive seizure frequency (CSF) endpoint was used in the NMA. Table 17 provides a summary of the endpoint data used in the NMAs but the effect sizes provided for log-transformed mean values reflect those from the primary analyses presented in the clinical study reports (CSRs) which are from analyses of covariance (ANCOVA) of log-transformed CSF rates per 28 days and not the percentage change from baseline. For example, in Study 1, the primary endpoint parametric analysis results are in Table 20 of the CSR as mean difference from placebo in CSF rates on a Log scale XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX. These means and 95% confidence intervals (CIs) agree with the NMA results in Figure 18.

The ITC for convulsive seizure frequency compares fenfluramine against cannabidiol based on the primary endpoint of their registrational RCTs. This endpoint was the percentage change from baseline in monthly convulsive seizure frequency compared with placebo (with monthly referring to 28 days), which was analysed in parametric analyses, as is reported in the publications of the RCTs (see Lagae et al 2020[x] and Nabbout et al 2020[xi] for fenfluramine; Devinsky et al 2017[xii] and Miller et al 2020[xiii] for cannabidiol).

However, as the EMA concluded the efficacy of cannabidiol was insufficient to warrant licensing in patients not taking concomitant clobazam, cannabidiol is only licensed for use in combination with clobazam (see Epidyolex SmPC[xiv]). Data for this endpoint in the licensed subgroup are not available in the trial publications but are reported in the cannabidiol SmPC; the cannabidiol SmPC was therefore the source of these data for cannabidiol and the fenfluramine data were taken from the published RCTs. It should be noted that, in contrast to cannabidiol, the efficacy of

fenfluramine is generally consistent irrespective of concomitant clobazam use (see Document B, section B.2.6.1.1.1) and as there is no meaningful difference in the efficacy of fenfluramine based on concomitant use of clobazam we do not anticipate that the licensed indication will limit fenfluramine to use in combination with clobazam. Therefore, as effects of fenfluramine relative to cannabidiol would be generally consistent irrespective of clobazam use it is appropriate to use the full trial data for fenfluramine to preserve sample size in the ITC, and to use the licensed subgroup data for cannabidiol.

Based on independent academic and expert statistician advice, the theoretically correct approach to conduct the ITC for this endpoint is to conduct this on a log-scale. Whilst these same data analysed on the log scale are available for fenfluramine in our CSRs, we do not have access to the relevant subgroup data on the log scale for cannabidiol. We therefore took the reported percentage change from baseline data in mean monthly convulsive seizure frequency compared with placebo for fenfluramine from the published RCTs (Lagae et al 2020 and Nabbout et al 2020), and took the reported percentage change from baseline data in mean monthly convulsive seizure frequency compared with placebo for cannabidiol in the subgroup taking concomitant clobazam from the cannabidiol SmPC. These data were converted into relative rates, which were log-transformed for use in the ITC (as reported in Document B, Table 17, and in the spreadsheet provided in the response to question B19 below).

The fact that the log-based data for fenfluramine from Table 17 and used in the ITC are similar to the log-based data for this endpoint in the CSR is to be expected, given that the underlying data are the same. The CSR includes the results of the analysis on a log scale which has been transformed to the ordinary scale to provide the percentage change from baseline in monthly convulsive seizure frequency compared with placebo that is reported in the publications of the RCTs. We have taken these data on the ordinary scale and transformed back on to the log scale for the purposes of the ITC. We could in theory have taken the data directly from the CSR but felt it would be more transparent to use the publicly available data sources for both fenfluramine and cannabidiol and to handle these data identically.

B19. Priority question:

a. **In Table 17 please provide full details of how the log-transformed mean values used in the NMA were calculated, including the methods specified in the table footnote of how the percentage change in CSF was converted to relative rates.**

The data and its transformation to relative rates and on to the log scale are provided in a spreadsheet accompanying this response.

b. **Please provide all relevant data to enable the checking of the NMA input data or specify its location in the CSRs.**

The data and its transformation to relative rates and on to the log scale are provided in a spreadsheet accompanying this response.

B20. Please provide subgroup results for study 1 and study 1504 separately for the NMA outcomes for concomitant clobazam use as these data are not presented in section B.2.7 of the CS. Please also perform NMAs in the subgroups of patients on concomitant stiripentol (using Study 1504), clobazam and their combination where possible. The data used in the NMA for the cannabidiol trials are for the subgroup on clobazam but the current indirect treatment comparison (ITC) is using all patients from the fenfluramine trials, not the clobazam subgroup.

By design, all patients in Study 1504 were taking stiripentol. As shown in Table 26 of Document B and in our response to question B16 above, 94% of patients in Study 1504 were also taking concomitant clobazam. Study 1504 therefore already represents the use of fenfluramine with concomitant stiripentol and clobazam and, as demonstrated in the response to question B16, Study 1504 closely reflects the likely use of fenfluramine when added to stiripentol in clinical practice. As Study 1504 is included in the NMA as a separate and distinct study we feel that the ERG's request for NMAs in the subgroups of patients on concomitant stiripentol (using Study 1504), clobazam and their combination is already met in the NMA we submitted in Document B.

By design, no patients in Study 1 were taking stiripentol. As shown in Table 26 of Document B and in our response to question B16 above, 60% of patients in Study 1 were taking concomitant clobazam. Figure 12 of Document B presents results of the

primary endpoint analysis from Study 1 in patients on fenfluramine at the anticipated licensed dose of 0.7mg/kg/day by concomitant clobazam use. In comparing patients with or without concomitant clobazam, the percentage reduction from baseline in monthly convulsive seizure frequency when compared with placebo, was statistically significant different ($p<0.001$) in both groups, but was not significantly different between groups (Knupp et al 2019[xv]). Both groups achieved a comparable and profound reduction in seizures consistent with the effect size seen across all patients on fenfluramine at the anticipated licensed dose of 0.7mg/kg/day, irrespective of clobazam use (Lagae et al 2020). Given this effect size we concluded that it is appropriate to use the data from the whole trial arm, which preserves the sample size. We do not believe that use of the data from the subgroup would materially change the relative efficacy of fenfluramine vs cannabidiol estimated in the NMA and used in the economic model. We therefore, in line with the current views of the EMA and draft label, do not feel it is appropriate to conduct a separate NMA using the similar effect size in a much smaller sample for which the Study was not powered.

Given the similarity in results, irrespective of clobazam use, the NMA using Study 1 data from the whole 0.7mg/kg/day treatment group therefore reflects the anticipated efficacy of fenfluramine either with or without concomitant clobazam. These data are therefore appropriately used in the economic model for the comparison of add-on fenfluramine vs add-on cannabidiol, and for add-on fenfluramine vs continued SoC AEDs.

B21. According to section B.2.8 of the CS, *"integrated efficacy analyses have been conducted for regulatory purposes but meta-analysis of the fenfluramine RCTs has not been undertaken"*.

Please elaborate on this statement.

Integrated analyses have been conducted for regulatory purposes to explore effects in different subgroups by integrating across doses of fenfluramine when the sample size would otherwise be too limited to permit an analysis, but meta-analyses across the whole trial populations (of two registration phase III studies) have not been conducted. The NMA presented in Document B, section 2.9 appropriately includes both Study 1 and Study 1504 as separate studies.

Ongoing studies

B22. The open label extension study (study 1503) is ongoing. In the CS, two different data cuts are mentioned (13 March 2018 and 14 October 2019).

a. What is the end date of this trial?

Study 1503 is due to complete December 2020 (www.clinicaltrials.gov); but could be subject to changes with EMA market authorisation timelines.

b. What is the date of the latest data cut?

The latest publicly available data cut for efficacy was 14 October 2019.

c. Please provide results for the latest data cut (or refer to the relevant section of the CS).

Results from the latest data cut (14th October 2019) are presented in Document B, section B.2.6.2.1.

B23. When will data from study 2 (the remaining participants from 1501 and 1502) be available?

For information, top line results from the remaining participants of Study 1501 and Study 1502 have just been presented in a press release (9th September 2020 – see: https://zogenixinc.gcs-web.com/news-releases/news-release-details/zogenix-announces-positive-top-line-results-its-third-pivotal). These data, which include a cohort of Japanese patients for the purposes of filing fenfluramine in Japan, indicate that fenfluramine at a dose of 0.7 mg/kg/day (n=49) achieved a 64.8% greater reduction in mean monthly convulsive seizures compared to placebo (n=48) ($p<0.0001$). These data are highly consistent with the 62.3% greater reduction compared with placebo observed in Study 1 (see Document B, section B.2.6.1.1); however, they do not form part of the EMA registration package. Further details of this study and analyses will be provided when the CSR is made available to us (date tbc). (Please note: Study 2 (remaining participants of Study 1501 and 1502) has been renamed as Study 3 in the US and has been referred to as such in this press release.)

B24. Study 1601 is listed in the ongoing studies section of the CS. Are any data available from this study yet?

Please note that this study should be Study 1900 (NCT03936777, EudraCT Number: 2019-001331-31), rather than Study 1601. Apologies for this confusion. No data are available from Study 1900 at this time.

Section C: Clarification on cost-effectiveness data

Model structure

C1. As stated in the CS, the literature indicates that seizure frequency may decline as patients age and the fenfluramine registration trials provide limited information on seizure frequency in patients beyond 18 years of age. Hence, in the model, the frequency of seizures in patients aged 18 and over were halved, and seizure free days doubled.

a. In the CS, it is stated that this reflects the decrease in seizures reported by clinicians in adults as reported in the UK Pathways research study (reference 55 in the CS). However, this study does not seem to mention a decrease as strong as suggested by the company. Please elaborate on the clinical plausibility of this assumption.

Whilst there is little data on the absolute reduction in seizures as people with Dravet syndrome age, published data indicate that seizure frequency and duration decline with age and patients have a "*stabilisation phase*" (Gataullina & Dulac, 2017[xvi]; Dravet 2011[xvii], Chiron et al 2018[xviii]).

This was probed with UK clinicians in the Pathway Mapping study. Whilst clinicians were unable to offer an absolute quantification of seizure reduction, several noted that convulsive seizures reduce as children age, and that fewer convulsive seizures are observed in adults. While the report submitted did not include direct quotations from the interviews, some extracts of quotations from the recorded interviews have been inserted below to support this assumption.

In relation to early childhood to puberty:

> *“”…. You can see it becomes less frequent, they might be once every few months rather than having every couple of months earlier on. … Then maybe teenage years [aged] 14 [years] then you have predominantly nocturnal tonic seizures, that’s your predominant seizure burden…..” (Interview 3, Consultant, Paediatrics, Tertiary care)*

> *“… The one thing we always warn the later primary school, maybe early teens about is that, you know, seizures might literally be a bit better during the day but, they’re often much worse at night.” (Interview 15, ESN, Paediatrics, Tertiary care)*

In relation to adults:

> *“..I think the difficulty we have in adult services, [is] for kids, [the] parents usually are pretty aware of what’s going on at night. … So, convulsive seizures decrease with age. Focal seizures, although they’re reported we pick them up in our patients, so I think the literature isn’t very clear about how common these occur across the age range, but my suspicion is they stay fairly static or if they decrease, they don’t decrease as much as the tonic-clonics.” (Interview 5, Consultant, Adult, Tertiary care)*

In the registration phase III trials and the DISCUSS study, it is however notable that the proportion of patients experiencing convulsive seizures, particularly the tonic seizures associated with injury and SUDEP, do not appear to differ by age group (Figure 7, Document B).

b. Please perform a scenario analysis in which the seizure frequency was reduced with a smaller percentage (e.g. only 50% of the reduction observed in seizure frequency) to provide a range of plausible incremental cost-effectiveness ratios (ICERs) .

The base case ICER (£31,773/QALY) reflects a population in which the seizure frequency halves (on an individual patient basis) at age 18 onwards. As presented in the scenario analyses (Document B, section B.3.9.4), removing this inflection in seizure frequency so that a patient’s seizures remain constant throughout their life,

the ICER becomes £32,468/QALY. This indicates that when testing the bounds of this assumption between a 50% reduction, (which is thought to be clinically plausible) to 0% reduction in seizures at aged 18 years onwards, this only causes a small increase in the ICER. It is therefore considered that testing this assumption further and within these bounds will have a similar degree of influence on the ICER as previously indicated in Document B.

C2. Quality-adjusted life year (QALY) estimates were only informed by convulsive seizure-free days, i.e. not the CSF. Please justify why the convulsive seizure frequency per cycle is not incorporated in the QALY estimation.

The choice of using seizure free intervals was validated with clinicians in the UK Pathway Mapping study. When asked “if seizure free days were a meaningful metric?” and “what duration of increase in seizure free days might mean to patients and carers?” (see section 2 of the report for details); clinicians highlighted that to the patient and their caregivers, a greater value in reducing the burden and anxiety from day-to-day seizures would be more meaningful than could be ascribed to a specific seizure event itself, which may occur multiple times within a day. A greater value on quality of life was therefore considered to be had on the time between seizure events, rather than the disutility associated from a single event. Given a condition in which seizures are a frequent (almost daily occurrence based on the average seizures at baseline for the registration phase III RCTs); seizure free intervals was considered to have a greater value on quality of life to allow patients, their caregivers and the broader family unit a rest bite from the relentless stress and burden of seizures to be able to enjoy family life. These data also highlight the challenges in ascribing a single unit of disutility to a patient’s quality of life for a single seizure event, since patients can experience multiple seizures in a day, or clusters of seizures, and of different durations – An additive approach of applying a disutility on a seizure-by seizure basis was therefore considered less appropriate in reflecting a clinical reality.

Furthermore, when we analysed the data from the registration trials, we explored the relationship between reported PedsQL scores to both convulsive seizure frequency and seizure free days. In the analyses, there was a stronger association between seizure free days and quality of life, which is why this metric was selected for the

model. As we did not want to double count the change in QALYs with seizure change, we could only use one of the seizure metrics in the model; hence, we selected the metric which was deemed more meaningful by clinicians and also had the stronger relationship to quality of life.

Population

C3. Priority question: Cannabidiol was recommended for patients treated concomitantly with clobazam while fenfluramine + SoC is not limited to patients treated concomitantly with clobazam. NICE guidance for TA614 mentions that *"clinical experts stated that clobazam is currently used when two AEDs have not adequately controlled seizures, and that they would consider adding cannabidiol to clobazam"*. Moreover, concomitant treatment or prior AEDs is potentially a modifier of relative treatment effectiveness of fenfluramine.

a. **Please clarify that the population considered in the CS is broader than the population for which cannabidiol is recommended, i.e. people receiving clobazam.**

As stated in Document B, section B.1.1 (Decision problem) and section B.1.3.4 (Proposed positioning of fenfluramine within the Dravet syndrome clinical pathway), our submission covers the full anticipated marketing authorisation of fenfluramine: *for the treatment of seizures associated with Dravet syndrome as an add on therapy to other antiepileptic medicines in children aged 2 years to 17 years and adults* (See draft SmPC).

We have provided a primary economic analysis of add-on fenfluramine against add-on cannabidiol (with clobazam) for the reasons stated in Document B, Table 1, with secondary/scenario analyses against continued SoC AEDs with or without clobazam supporting the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. The licensed population anticipated to be treated with fenfluramine considered in the submission is therefore broader than the population for which cannabidiol is recommended and is not limited to use only in combination with clobazam.

b. **Cannabidiol is concomitantly given with clobazam. Fenfluramine may be given with or without clobazam. Given this difference, please elaborate on whether these patient groups are comparable, considering that cannabidiol would not be given when contraindications against clobazam exist.**

As discussed in our response to question B20 above, 94% of patients in Study 1504 were taking concomitant clobazam (alongside 100% use of stiripentol), the results of Study 1504 reflect use in patients who are taking concomitant clobazam.

In Study 1, 60% of patients were taking concomitant clobazam. Figure 12 of Document B presents results of the primary endpoint analysis from Study 1 in patients on fenfluramine at the anticipated licensed dose of 0.7mg/kg/day by concomitant clobazam use. The percentage reduction from baseline in monthly convulsive seizure frequency when compared with placebo, was statistically significant different ($p<0.001$) in both groups, but was not significantly different between groups (Knupp et al 2019). Both groups achieved a comparable and profound reduction in seizures consistent with the effect size seen across all patients on fenfluramine at the anticipated licensed dose of 0.7mg/kg/day, irrespective of clobazam use (Lagae et al 2020). Given the similarity in effect size irrespective of clobazam use, we conclude that the data from the whole 0.7mg/kg/day treatment group in Study 1 appropriately reflects the anticipated efficacy of fenfluramine when used with and without concomitant clobazam. These data are therefore appropriately used in the economic model for the comparison of add-on fenfluramine vs add-on cannabidiol, and for add-on fenfluramine vs continued SoC AEDs.

c. **Please provide an analysis for patients receiving clobazam, i.e. comparing fenfluramine in combination with clobazam (i.e. by using a subset of the trial data) with cannabidiol in combination with clobazam.** .

Please see the response to question B20 and C3.b above. Given the similarity in effect size in patients taking fenfluramine irrespective of concomitant use of clobazam, we concluded that it is appropriate to use the data from the whole trial arm of Study 1 in the NMA and the economic model, as this preserves the sample size. We do not believe that use of the data from the subgroup would materially

change the relative efficacy of fenfluramine vs cannabidiol estimated in the NMA and used in the economic model. We therefore do not feel it is appropriate to conduct a separate analysis using a similar (non-significantly different) effect size in a much smaller sample for which the study was not powered.

We have therefore provided a scenario analysis in which 100% of patients on fenfluramine are assumed to receive the costs of concomitant clobazam and retain the relative efficacy of fenfluramine as in the base case analysis on the basis this will reflect the clinical and cost effectiveness of fenfluramine in patients taking concomitant clobazam. The ICER in this scenario is £37,577/QALY.

d. **As the population considered in the CS is broader than patients receiving clobazam, please make comparisons with the appropriate comparators (as listed in the scope) and stratify by concomitant treatment and/ or prior AEDs (e.g. stiripentol or clobazam).** .

A proactive approach has been undertaken to provide insight into interactions (or modifiers) of fenfluramine effect on the basis of concomitant AEDs and/or their relative sequence of use; based on the findings from pharmacological (PK/PD) studies; or observed differences in clinical outcomes in the phase III registration RCTs; or other interactions/modifiers of interest identified by Regulatory agencies (EMA and FDA) when evaluating and forming their views on the approval of a licensed indication for fenfluramine. Essentially, the following interactions have been identified and previously provided as cost-effectiveness scenario analyses in Document B:

Pharmacological: The concomitant use of stiripentol, with an adjustment to fenfluramine dose.

Analyses presented in our submission have been stratified by concomitant stiripentol on the basis that 100% of patients in Study 1504 and no patients in Study 1 were taking concomitant stiripentol. As previously detailed in Document B, section 2.9.2, it is not possible to conduct a cost effectiveness analysis of fenfluramine (as an add on therapy to SoC) against stiripentol (as an add on therapy to SoC) due to significant limitations in the stiripentol trial evidence base.

Clinical outcomes: No significant differences in outcomes (e.g. reduction in monthly convulsive seizures frequency) have been identified with the use of fenfluramine with or without concomitant clobazam or valproate/clobazam in the phase III registration RCTs (Knupp et al 2019); or in PK/PD studies.

As noted in our response to question B20 and C3.c, and consistent with the regulatory agency (EMA and FDA) views, there is no meaningful difference in effect size with fenfluramine treatment based on concomitant use of clobazam. Unlike cannabidiol and stiripentol, fenfluramine therefore provides a clobazam independent benefit to all patients without a concomitant requirement for clobazam. In looking to assist the NICE review, we have however provided a scenario analysis assuming the costs of clobazam in 100% of patients and retaining the base case efficacy of fenfluramine on the basis this will reflect a comparative clinical and cost effectiveness assessment of fenfluramine in all patients taking concomitant clobazam, as per the licensed cannabidiol indication. The ICER in this scenario is £37,577/QALY.

Other interactions/modifiers of interest:

Previously, we also provided several scenario analyses in our submission comparing fenfluramine as add-on to SoC against continued SoC AEDs (see Table 52 of Document B). In addition, we have also provided in positioning scenario analysis; a comparison of fenfluramine as an add on therapy to SoC Vs Soc of alone in Study 1 patients that have had prior experience of stiripentol, but no longer taking it (Stiripentol experienced); as well as a similar comparative analysis in patients that have had no prior experience of stiripentol (stiripentol naive). See also question C4. below

These data are provided on the basis of identified interactions and/or modifiers within studies and during the Regulatory procedure. However, it is important to note that underpinning these analyses, there is an inherent diversity in the presentation of the syndrome within individual patients over time and across patient groups; as well as a spontaneous nature about seizures events, in a rare disease with few treatment options available. Furthermore, given the limitations in sample sizes and statistical under-powering of these types of analyses, care should be taken to not overinterpret

differences; a viewpoint that the committee agreed on during the recent appraisal of cannabidiol (with clobazam) in TA614.

Collectively, the analyses we have provided in Document B support the clinical and cost effectiveness of fenfluramine in its anticipated full licensed indication throughout the add-on therapy pathway, against the most appropriate comparators and using the most robust data possible.

C4. Priority question: Please clarify (with supporting evidence) whether concomitant treatment or prior AEDs is a modifier of relative treatment effectiveness for fenfluramine.

Concomitant treatment with stiripentol is a treatment effect modifier due to a pharmacokinetic interaction that increases exposure to fenfluramine. It is for this reason that the recommended dose of fenfluramine is lower in patients taking stiripentol (0.4mg/kg/day) compared with those not (0.7mg/kg/day). As this pharmacokinetic interaction had not been fully elucidated at the time of Study 1 initiation, patients taking concomitant stiripentol were excluded from Study 1. Study 1504 was therefore conducted to provide RCT data for fenfluramine specifically in patients on concomitant stiripentol.

There is no specific interaction between fenfluramine and clobazam that leads to an increase in fenfluramine exposure with concomitant clobazam. Whilst the available data are not sufficient to explore an interaction term in the regression model, exploratory subgroup analyses do not support a treatment modifier effect of concomitant clobazam upon fenfluramine (see Document B, section 2.6.1.1.1 and our response to question B20). This is supported by the fact that, in contrast to cannabidiol, the anticipated licensed indication for fenfluramine does not restrict it to use in combination with clobazam. As the subgroup analyses indicate that the effect size with fenfluramine is similar irrespective of concomitant use of clobazam, we feel it is appropriate that our NMA utilises the entire fenfluramine 0.7mg/kg/day arm data.

The draft SmPC for fenfluramine does not allude to any other AEDs that used concomitantly would be modifiers of fenfluramine treatment effectiveness. We do not foresee prior treatment as an effect modifier *per se* but acknowledge that patients with greater prior treatment experience may have disease that is more refractory

than other patients. We therefore provided scenario analyses in our submission relating to prior history of stiripentol use (stiripentol experienced and stiripentol naïve), as the only therapy recognised as a modifier of treatment effect and normally used as a 2L+ add-on therapy following insufficient response to 1L AEDs and 1L add-on therapy (see scenario analyses in Document B, Table 52 and Figure 2). Collectively, given the context of the rarity and heterogeneity of the disease, and the consequent availability of data, we have provided the most appropriate, robust and comprehensive range of analyses possible.

C5. The target population in the model is specified as patients with Dravet syndrome whose seizures are inadequately controlled by current or prior established clinical management. This is in line with the final scope issued by NICE. However, the two phase 3 trials all target children or adolescents ≤18 years old.

a. Please provide data from the open-label extension (OLE) study, European and US access programmes and Belgian real world evidence (RWE) studies which indicate that fenfluramine is similarly effective and well tolerated in patients who transition treatment into adulthood and in adult initiators as it was in the RCTs (as is stated in the CS). If possible, provide a breakdown of response rates by age group.

Belgian RWE studies – retrospective and prospective RWE data support the sustained and durable efficacy of fenfluramine over many years of use.

Celuemans et al 2012 reports on a retrospective analysis of 12 Dravet syndrome patients who initiated fenfluramine as children. At the time of analysis 6 had continued fenfluramine into adulthood. One of these 6 patients did not experience a reduction in seizures; however, the remaining 5 patients experienced reductions in seizures of 75-100%, with those achieving 100% reduction being seizure-free for periods ranging from 5 to 19 years.

Ceulemans et al 2016 reports on a 5-year extended, prospective follow up of 10 of the 12 Dravet syndrome patients above. Eight of these patients were >18 years of age at the time of analysis. Longitudinal analysis of their convulsive (tonic-clonic) seizure frequencies between 2010 and 2014 indicates that the profound reductions observed in the Ceulemans et al 2012 study were maintained, with 3 adults

completely seizure free in each of the 5 years and 5 adults seizure free in each of the last 2 years of follow up. Total treatment duration at the time of analysis in those continuing into adulthood ranged from 6 years to 27 years, with no patients developing any clinical signs or symptoms of cardiac valvulopathy or pulmonary hypertension.

Schoonjans et al 2016 reports a prospective follow up of nine patients with median frequency of major motor seizures of 15/month, of which 3 were adults at the point of fenfluramine initiation. Over treatment durations ranging from 0.3 to 1.57 years, these adult initiators experienced reductions in the monthly frequency of major motor seizures ranging from 28-75%. No evidence of cardiac valvulopathy or pulmonary hypertension was observed.

These data therefore support the efficacy and safety of fenfluramine when continued into adulthood or when initiated in adulthood.

Expanded access program (EAP) – the data currently available from the European EAP have been detailed in Document B, section B.2.6.3.3. This provided effectiveness assessments for [redacted]

OLE study – A breakdown of the OLE study data by adults/children are not currently available to us. As the core RCTs enrolled patients up to 18 years of age, and followed patients for up to 3 years, a proportion of the core trial patients will have continued treatment into adulthood.

As the OLE study confirms the long-term efficacy and safety of fenfluramine observed in the RCTs is maintained in the long-term across the trial populations, and the RWE studies confirm the significant reductions observed with fenfluramine treatment are maintained in the long-term, with no cases of clinical cardiovascular or pulmonary adverse effects in patients who continue treatment into adulthood, we conclude that collectively these data support the use of fenfluramine in adults, with efficacy and safety similar to that observed in the RCTs.

As demonstrated in the scenario analyses presented in Table 51 of Document B, fenfluramine is highly cost effective when initiated in adults, with an ICER <£10,000/QALY compared with cannabidiol (with clobazam).

C6. As stated in the CS, two populations of patients are run through the model; one in which the patient receives fenfluramine + SoC and one in which the patient receives cannabidiol + SoC. However, the population receiving the intervention is comprised of patients on concomitant stiripentol (58%) or not (42%), which is argued to represent the use of stiripentol observed in UK patients in clinical practice in the DISCUSS study. Therefore, the resulting economic model consists of a weighted average of two models (one in which the intervention consists of fenfluramine + SoC + stiripentol and one without stiripentol) to obtain final cost-effectiveness estimates.

a. The ICERs of the two separate models (model based on study 1 and the model based on study 1504, vary greatly, i.e. £38,974 per QALY gained for study 1 and £10,770 per QALY gained for study 1504). Please justify whether these two models should be combined and why they should not be presented as two separate models as these represent separate populations.

The efficacy of fenfluramine in patients on concomitant stiripentol and those not on concomitant stiripentol was assessed in separate trials (Study 1504 and Study 1, respectively). Based on the DISCUSS study, 58% of patients in the UK are on concomitant stiripentol (and 42% not on concomitant stiripentol) (Pagano et al 2019), with the number of patients taking stiripentol rising (as noted in TA 614). In this submission, these two populations are run through the same model, however for ease of use they are run through it separately, rather than differentiating between patients in the code and changing the treatment effect and cost for each. The patient population is presented as a whole instead of separately as it is more representative of the use of fenfluramine and other AEDs in the patient population in clinical practice in the UK, as required by the NICE scope. Furthermore, the merged population provides a more appropriate comparison with cannabidiol as the cannabidiol trials included patients who were and patients who were not taking concomitant stiripentol but results broken down by stiripentol use are not available in the public domain. To compare fenfluramine with cannabidiol, a population that

includes both patients on concomitant stiripentol and patients not on concomitant stiripentol is required.

b. Please provide all base case results and scenario analyses for the two cohorts/models separately.

The base case ICER and incremental costs and QALYs for the two separate populations are presented in **Table *4***:

Table 4, Base case ICER by concomitant stiripentol use

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental Costs (£)	Incre-mental LYG	Incre-mental QALYs	Incre-mental ICER (£/QALY)
Patients on concomitant stiripentol							
Cannabidiol +clobazam + SoC	354,599	18.32	22.10	-	-	-	-
Fenfluramine + SoC	XXX	XXX	XXX	XXX	XXX	XXX	**10,770**
Patients not on concomitant stiripentol							
Cannabidiol +clobazam + SoC	119,265	15.22	18.40	-	-	-	-
Fenfluramine + SoC	XXX	XXX	XXX	XXX	XXX	XXX	**38,874**

c. The two models are averaged according to the percentage patients on concomitant stiripentol (58%) or not (42%). These percentages are not subject to sensitivity analyses. Please provide scenario analyses in which these percentages are varied based on empirical estimates, e.g. reported upper and lower bounds in other studies.

The percentage of patients on stiripentol was taken from the UK cohort of the DISCUSS study (Pagano et al 2019). No other sources of data were found in the literature for the percentage of patients taking concomitant stiripentol in England. A European study conducted in 2015 (Aras et al, 2015) reports 42% of patients on concomitant stiripentol. As this study included patients receiving standard of care treatments and in a clinical practice setting not necessarily the same as the UK, it is

not appropriate to use in the base case. In the NICE appraisal of cannabidiol (with clobazam) (TA614) it was noted that stiripentol usage was increasing in England. This is likely a consequence of the NICE recommendation of stiripentol for use in patients with Dravet syndrome in the recently published Epilepsies: diagnosis and management clinical guideline (NICE CG137[xix], section 1.9.9.3). Therefore, to understand the sensitivity of the ICER results to the proportional use of stiripentol within SoC, and to incorporate the reported usage of stiripentol in Aras et al, and the increasing use of stiripentol in England, the percentage of patients on concomitant stiripentol has been varied by +/- 30% from the base case parameter (58% stiripentol use) to give results for a broad range of stiripentol usage in England (Table 5).

Table 5. Scenario analysis exploring impact of percentage use of stiripentol inn UK clinical practice

Scenario analyses around base case	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case: 58% of patients on concomitant stiripentol	XXX	XXX	**31,773**
78% of patients on concomitant stiripentol	XXX	XXX	26,973
41% of patients on concomitant stiripentol	XXX	XXX	34,788

C7. In the model, it is assumed that weight reaches a maximum of 78 kg and then plateaus at age 25 years.

Please provide a justification for this assumption and elaborate on the possible implications.

Available NHS data show that 78kg is the average adult weight in England, reached at age 25 years old (Royal College of Paediatrics and Child Health (RCPCH)). There were no data specifically available for Dravet syndrome patients, however the average trial weight aligns with the English average weight until age 18 years old (NHS health survey for England; the trial only included patients up to age 18) suggesting that the average England weight is representative of the Dravet population. In reality, there were patients weighing significantly above this across the RCTs (range 12kg to 110kg) so this maximum weight could be a conservative estimate. As fenfluramine reaches a capped maximum dose before 78kg (for both 0.4 and 0.7 dosage), this maximum weight will not affect the cost or effectiveness of

fenfluramine. However, other AEDs (cannabidiol and stiripentol) are weight dependent and have no maximum dose per day, therefore the higher the weight, the higher the cost of cannabidiol, which would decrease the ICER for fenfluramine. This is therefore a conservative assumption. The starting weight of an individual and the weight of plateau were both varied in the DSA. A lower bound on the starting weight was 9.6kg and the lower bound for the plateau weight was 62.4kg (20% below the baseline values), this resulted in an ICER of £[redacted]. The upper values of starting weight and maximum weight achieved were 14.4kg and 93.6kg respectively (20% above the baseline values) resulting in an ICER of £[redacted].

C8. The CS stated that baseline characteristics in the model were selected based on an analysis of covariates that significantly influence HRQoL, and that these were confirmed in an internal modelling workshop.

a. Details of the workshop are missing. Please present these to the ERG.

[redacted]

[redacted].

Given confidentiality agreements in place with participants, further details and minutes cannot be shared.

b. It appears as if the sentences in the paragraph of the CS in which the workshop is discussed (page 128 of the CS) are incomplete (i.e. “and .”). Please provide any missing information.

Apologies – this should have said: “These were confirmed in an internal modelling workshop (12 February 2020) with the project team including [redacted].

c. In the CS, it is stated that there was no indication that the other baseline characteristics are correlated with each other except weight and age. Please elaborate on the clinical plausibility that concomitant medication, motor impairments, and age (and maybe also weight) are not correlated and provide supporting evidence.

It could be clinically plausible that motor impairments and concomitant medication would be correlated to age, however the trial data shows that there is no correlation.

Table 6 shows the average number of concomitant AEDs by age.

Table 6. Average number of concomitant AEDs by age in the fenfluramine phase 3 RCTs

Age	Mean number of concomitant AEDs	Number of patients
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

In the Pathway Mapping study, the clinicians reported that physical impairments become worse as patients age and enter into adulthood, and that these are more likely to be the primary burden of the disease, rather than the seizures themselves as adults with Dravet syndrome. However, in the trial data, no correlation was seen (Figure 3) and as the seizure profiles were modelled using the trial data, no correlation was included.

Figure 3. Motor impairments by patient age in the fenfluramine trials

Intervention

C9. A treatment stopping rule was applied in the base case for fenfluramine and cannabidiol in patients not achieving at least a 30% reduction in convulsive seizure frequency at 6 months compared with the patient's baseline seizure frequency prior to starting treatment. However, the European Medicines Agency (EMA) has not proposed a "stopping rule" for fenfluramine on the basis of efficacy, as stated in the CS.

a. Please elaborate on the implications of this stopping rule on the results of the economics evaluation, e.g. how does this impact the ICER? .

Table 7 shows the ICERs when different stopping rules are applied to the fenfluramine arm. Note that in all of these scenarios a 30% stopping rule is applied to the cannabidiol arm, in line with its NICE recommendation in TA614. As the threshold for the stopping rule increases, the ICER decreases as more patients

discontinue treatment at 6 months, and therefore the cost of the overall treatment strategy decreases compared to cannabidiol which always has a 30% stopping rule implemented.

Table 7. ICERs when a range of stopping rules are implemented in the fenfluramine arm of the model

% convulsive seizure reduction required to continue on treatment after 6 months (stopping rule)	ICER	Rationale behind stopping rule
10	£39,861	Median placebo effect observed in the fenfluramine trials
30 (base case)	£31,773	Stopping rule implemented in NICE TA614
44	£23,405	Clinically significant reduction in CGI in the fenfluramine trials
50	£21,495	Accepted measure of clinical efficacy in epilepsies [NICE CG137] and regulatory response criteria [EMA][xx]

b. As the EMA has not proposed a "stopping rule" for fenfluramine on the basis of efficacy (as stated in the CS), please provide an analysis in which the stopping rule has been removed.

When the stopping rule is removed from both arms, the ICER is £19,898. The removal of a stopping rule in the fenfluramine arm (and keeping a 30% stopping rule in the cannabidiol arm) results in an ICER of £63,268. The reason the ICER increases from the base case is due to the unequal behaviour in the two arms, with about 58% of cannabidiol patients stopping treatment after 6 months, and no one in the fenfluramine arm. Cannabidiol and fenfluramine costs make up a large proportion of total costs in the analysis (32% and 25% of the cannabidiol arm and fenfluramine arm respectively), therefore removing patients from treatment in the cannabidiol arm gives it an advantage to the overall intervention strategy; but as highlighted in NICE TA614, this principle is considered counterintuitive to providing a clinically optimal and NICE recommended treatment.

Comparator

C10. Priority question: Contrary to the final scope issued by NICE, several AEDs / treatments were not considered as separate comparators. In addition, SoC (which is pluriform, as described in the scope) was also not included in the submission. Please provide a full incremental analysis of SoC and include the AEDs as separate comparators. At least, SoC based on the trial data should be included (e.g. by using the placebo arms). Please provide an updated model to calculate the base case and all sensitivity and scenario analyses, as well as the results of these analyses in tabular form. Stratify these analyses for different patient populations (e.g. with or without clobazam) if appropriate.

It is neither feasible nor clinically appropriate to provide comparisons of fenfluramine against all of the AEDs / treatments listed in the scope. Our submission therefore focuses on comparisons of fenfluramine added onto SoC AEDs against the most relevant comparator add-on therapies to SoC AEDs, which could be add-on stiripentol, add-on cannabidiol or, when these are not desirable or have been exhausted, continued SoC AEDs (see Document B, section B.1.3.4). As it is not possible to conduct a treatment comparison against stiripentol, due to significant limitations in the stiripentol RCT data (see Document B, section B.2.9.2) it is not possible to include stiripentol in the cost effectiveness analysis.

We have therefore provided a fully incremental analysis of SoC AEDs, add-on cannabidiol and add-on fenfluramine assuming the distribution of concomitant clobazam use (costs) as per our base case analysis (**Table 8**). This would reflect the licensed indications for both treatments. We also provide an analysis assuming that all patients are receiving concomitant clobazam in their SoC AEDs, in line with the cannabidiol licensed indication (**Table 9**). This would infer a direct comparison in treating patients eligible for cannabidiol (with clobazam), with fenfluramine as an alternative treatment option. These demonstrate that add-on cannabidiol is significantly less cost effective than add-on fenfluramine when compared against continued SoC AED therapy, and in these fully incremental analyses add-on cannabidiol is extendedly dominated by add-on fenfluramine. As add-on cannabidiol has been accepted by NICE in TA614 as cost effective in the add-on therapy

pathway, this would imply that add-on fenfluramine should also be considered cost effective in the add-on therapy pathway, and would be the economically preferred option.

Table 8. Fully incremental analysis – assuming the proportional use and costs of clobazam as per the base case analysis

Treatment	Cost (£)	QALYs	ICER compared to next most effective AED	ICER compared to underlying SoC AEDs
SoC AED (trial data)	X XXX	X XXX	-	-
Cannabidiol (with clobazam) + SoC AED	X XXX	X XXX	£69,478/QALY	£69,478/QALY (Extendedly dominated by fenfluramine + SoC AED)
Fenfluramine + SoC AED	X XXX	X XXX	£31,638/QALY	£50,968/QALY

Table 9. Fully incremental analysis – assuming all patients receiving clobazam amongst their SoC AEDs.

Treatment	Cost (£)	QALYs	ICER compared to next most effective AED	ICER compared to underlying SoC AEDs
SoC AED (trial data) including clobazam	X XXX	X XXX	-	-
Cannabidiol (with clobazam) + SoC AED	X XXX	X XXX	£64,271/QALY	£64,271/QALY (Extendedly dominated by fenfluramine + SoC AED)
Fenfluramine + SoC AED including clobazam	X XXX	X XXX	£37,577/QALY	£51,205/QALY

Effectiveness

C11. Priority question: The treatment effect does not seem to be related to patient characteristics. Please elaborate on the (clinically) appropriateness of this assumption.

Study 1 and Study 1504 showed no association between treatment effect and patient age, as shown in Figure 4:

Figure 4. The relationship between patient age (grouped) and the mean percent change in seizure frequency between the baseline and maintenance period in the trial and placebo groups in Study 1 and 1504 (grouped data).

Furthermore, any difference in treatment effect changes due to concomitant stiripentol are captured by the use of data from Study 1 and Study 1504. No other concomitant AEDs had a significant impact on treatment effect, as noted in our response to question C3,d.

C12. Priority question: As stated in the CS, in the intervention and comparator strategies, individual patients were assigned a number of convulsive seizures per 28-day cycle at baseline (based on patient-level data from the placebo arm of the respective fenfluramine registration studies) to ensure that the number of convulsive seizures per 28-day cycle were the same at baseline in both

strategies. The methods for generating / estimating the convulsive seizures per 28-day cycle (over time) are not entirely clear to the ERG.

a. **Please justify why only the placebo arm of the studies was used to generate patient profiles**.

To include the treatment effect of both cannabidiol and fenfluramine, an indirect treatment comparison was performed (Document B, section B.2.9). This allowed the treatment effect of both drugs to be compared to an adjusted (common) placebo arm for the trials. Therefore, the ITC calculated the effectiveness of cannabidiol and fenfluramine relative to the placebo effect. In order to apply this in the model, and to ensure that the heterogeneity of seizures profiles was still adequately captured, the placebo effect of each individual patient in the model was used and the treatment effect relative to this placebo effect was applied. As all treatment effect was relative to placebo, in order to model it only the placebo arm of the trial was used.

b. **In document B of the CS as well as appendix L, it is stated that, in order to perform the bootstrap procedure to develop individual patient seizures trajectories to be used in the model, a cohort of representative patients were identified from the trial population and bootstrapped. Please explain how these patients were identified, e.g. which patients were excluded/included**.

All patients in the placebo arm of the trial that continued into the maintenance arm of the trial were included in the population. Any patients that only had baseline data available were excluded, and any patients that discontinued during the titration period of the trial were excluded as the extent of the placebo effect would not be clear.

c. **It is unclear what time periods in the trial were used to obtain the bootstrapped individual patient seizure trajectories. What time period was used to obtain the baseline period and on-treatment period, and which patients were selected for the on-treatment period, e.g. patients with complete follow-up or patient with/without treatment discontinuation?** .

Seizure trajectories were taken from both the baseline and maintenance period of the trial. For patients on treatment, seizures were bootstrapped from the maintenance period of the trial, so that the placebo effect was captured (as the treatment effect calculated in the ITC is relative to the placebo effect). Upon discontinuation, seizures are bootstrapped from the baseline period of the trial, to ensure that all treatment and placebo effect is removed. It also ensures that the seizures of patients who have discontinued from treatment are the same in both the intervention and comparator arm, so there is no additional benefit or penalty in either arm for discontinuing.

d. **Please elaborate what (implicit) assumptions were used to extrapolate the (relative) treatment effectiveness, e.g. relative treatment effect is, on average, maintained over time**.

The model extrapolation of relative treatment effectiveness was based on the following assumptions. Firstly, the reduction in the proportion of days with seizures is proportionate to the reduction in frequency of seizures. Secondly, the proportionate reduction in days with seizures is independent of baseline seizure frequencies. Thirdly, the rate of seizure free days is constant over time. Fourthly, the proportionate treatment effectiveness is constant and maintained while patients are on treatment and end when patients stop treatment.

The indirect comparison made here assumes that treatment effects on seizure rates are consistent on a multiplicative scale. This is consistent with the specification of the analysis of seizure frequency used in the trial analyses.

e. **Please justify the use of the bootstrap method to extrapolate treatment effectiveness. If it is implicitly assumed that the treatment effect is, on average, maintained over time, this could also have been implemented using simpler methods, e.g. last observation carried forward. In this case, please provide an analysis in which simpler methods are used (in order to reduce random noise in the model)** .

Patients experience different numbers of seizures and seizure days during the trial (Figures 9 and 10, Appendix L and Figure 5 and Figure 6 below). In order to reflect this reality of Dravet Syndrome, seizures and seizure free days were bootstrapped from existing data. To use last observation carried forward would assume that patients are having the same seizures/seizure days over time and that the last observation is representative of this, which discounts the heterogeneity that each patient could experience over time. Given the availability of individual level data from the trial to be able to recreate seizures with such detail, bootstrapping seizures by day ensures that the complexity of seizures experienced by patients is fully captured.

Figure 5. Seizure events on a given day for patients in Study 1 (Green: 0.7mg/kg/day, Red: 0.2 mg/kg/day, black: Placebo). Day 0 is randomisation and data prior to this is from the baseline period of the trial. Crosses represent discontinuation or trial end

Figure 6. Seizure events on a given day for patients in Study 1504 (Red: 0.4 mg/kg/day, Black: Placebo). Day 0 is randomisation and data prior to this is from the baseline period of the trial. Crosses represent discontinuation or trial end

f. **The bootstrapped number of seizures or seizure-free days does not seem to be related to patient characteristics, e.g. motor impairments. Please elaborate on the clinical plausibility of this assumption**.

There was no association between patient characteristics such as motor impairments and seizure profile in the trial. Whilst data from the DISCUSS study (Lagae 2018[xxi]) report that there may be a relationship between seizure frequency (based on high vs low seizure bands) and co-morbidities, it is unclear if this is a causal relationship or what the clinical plausibility of this relationship may be. During the Pathway Mapping study, clinicians commented that they believe that greater seizure frequency may be related to worse motor impairment, but there is uncertainty and not much data to support the relationship. Given the complex natural history of Dravet Syndrome there are likely to be non-linearities between patient characteristics and seizure frequencies. Whilst it is possible that frequency of seizures or seizure

free days may be related to a patients characteristics, it is also possible that random accidents and events occur as a results of only a few seizures. These accidents may lead to long-term issues such as motor impairments but did not necessarily occur as a result of a high seizure frequency. Furthermore, patient characteristics such as motor impairments are likely to stay with patients throughout their lifetime and as such will not always be related to seizure frequency.

g. **It is unclear to the ERG how individual seizure frequency was related to seizure-free days in the same individual. If both are bootstrapped from the same patients, did the company account for clinically implausible combinations (e.g. a high seizure frequency with a low number of seizure-free days)? Please provide more details on how the model accounted for the correlation between both estimates**.

Number of convulsive seizures each day was bootstrapped from the patient level trial data (including 0 seizures on a day). The seizure frequency was then aggregated to 28 day cycles by summing the number of seizures for every day in that cycle.

If a patient had a convulsive seizure on any given day in the bootstrapped data, this was classed as a 'seizure day'. The 'day-level' (rather than 'cycle-level') data was then used to determine the number of days on which the patient had convulsive seizures in a given cycle (seizure days). As the number of seizure days was calculated directly from the number of seizures each day in the cycle, the association between seizures and 'seizure days' is inherently captured in the data.

As agreed in the model (code) walkthrough discussion with the ERG on 10/9/20, the bootstrapping code will be shared with NICE to demonstrate the methodology.

h. **In the model R-code, is it correct to assume that "placebo discontinuation data" is supposed to be the placebo baseline seizure frequency? Please justify and explain this terminology**.

The "placebo discontinuation data" is the placebo baseline seizure frequency data. The variable is named this as this data is used for patients that have discontinued off treatment, so that all treatment and placebo effects have been removed in both arms.

i. **Please provide the code used for generating patient seizure-frequency profiles as well as a description of how exactly each step of the bootstrap procedure was performed**.

Dummy data is being prepared to run with this code and the code and dummy dataset will follow shortly as agreed in the model (code) walkthrough discussion with the ERG on 10/9/20.

C13. Priority question: Clinical effects of drugs are frequently known to wane over time. For TA614, the committee concluded that the effectiveness of cannabidiol was likely to diminish over time (as with other AEDs). In the CS it is stated that the OLE (Study 1503) trial data with up to 24 months of treatment and data from the Belgian RWE study (observational cohort) with up to 5 years of treatment do not show any indication that the treatment effect of fenfluramine wanes over time. Hence, no treatment waning was assumed in the CS base case.

a. **Given that the OLE as well as the Belgian RWE studies are non-randomised and have 5 years of follow-up, which may still be considered relativity short compared to a life time horizon, please justify why no treatment waning was assumed for fenfluramine (with supporting evidence showing no treatment waning)** .

Dravet Syndrome is a very rare disease, and as such the ability to conduct large, long-term clinical trials to prove an absence of treatment waning is not viable. In order to prove an absence of treatment waning over time, a sizeable cohort of patients would need to be followed for their lifetime. However, despite the rarity of the disease, follow-up data of 5 years showing sustained treatment efficacy has been demonstrated and is a strong justification for not including treatment waning in this model.

Furthermore, long-term discontinuation in this model takes into account discontinuation due to lack of effect (even if non-randomised), as it is directly taken from the OLE trial data, and therefore if any patients that experienced treatment waning and discontinued will be inherently captured in the model.

It should be noted that the pharmacological action, absorption, distribution, metabolism and elimination of cannabidiol is very different to that of fenfluramine;

and so it does not necessarily follow that a waning of treatment effect (to the same extent observed with cannabidiol) would been seen with fenfluramine.

It is notable that stiripentol (another AED, used in the same condition), in long-term follow up studies, also does not appear to show signs of a waning in treatment effect[xviii], thereby, further substantiating a basis that not all treatments necessarily will have a waning of treatment effect.

Moreover, the OLE study data for cannabidiol (GWPCARE 5) presented in the Epidyolex® SmPC suggest a ~25% reduction in efficacy over 48 weeks of treatment (discussed in Document B, section 2.9.5). Given there is no evidence of such a waning of effect with fenfluramine in patients followed up for 5 years, we do not consider it appropriate to assume that because there is an apparent waning of effect with cannabidiol that the same must also apply to fenfluramine. We therefore feel that exclusion of a waning effect of fenfluramine in our base case analysis is justified, and the exclusion of a waning effect for cannabidiol is a conservative approach.

b. **Please add a scenario in which the efficacy of fenfluramine is assumed to decrease over time (consistent with the committee's preference for TA614, for which it was stated that: "*The committee agreed that the company had made a reasonable attempt to account for treatment waning. However, it would have preferred that the company's analysis had also accounted for a reduction in effect over time in patients before they stop cannabidiol.*")** .

As noted in our response to question C13.a, given the absence of evidence of a waning effect with fenfluramine treatment in long term OLE and RWE data (in contrast to positive evidence of a waning effect with cannabidiol), we feel that exclusion of a waning of effect of fenfluramine in our base case analysis is justified and the exclusion of a waning effect for cannabidiol in our base case is a conservative approach. We have therefore not provided a scenario analysis in which a waning effect of fenfluramine is assumed.

C14. Priority question: For TA614, the committee concluded that *"there is insufficient evidence to prove that cannabidiol prolongs life"*, i.e. there was

insufficient evidence to prove that cannabidiol, through reducing convulsive seizures, prolongs life.

a. **In the CS, the association between convulsive seizure frequency and death is based on assumptions. Please provide supporting (empirical) evidence of the association between convulsive seizure frequency and death for both epilepsy in general and specifically for Dravet syndrome.** .

General epilepsy trials are not typically powered for mortality outcomes – even the large SANAD studies (Arm A recruited 1,721 patients with partial epilepsy and provided 5,406 patient years of follow up [Marson et al. Lancet 2007; 369: 1000-1015]; Arm B recruited 716 patients with generalised epilepsy and provided 2,333 patient years of follow up [Marson et al. Lancet 2007; 369:1016-1026]) were not powered for and did not include mortality as an outcome. It is therefore unrealistic to expect that RCTs will provide data to prove that treatment with cannabidiol or fenfluramine or any other AED prolongs life in patients with Dravet syndrome. Consequently, there are significant challenges in providing empirical evidence linking mortality to convulsive seizure frequency in either general epilepsy or the much rarer Dravet syndrome.

In Document B, section B.1.3.1.3 we have discussed in detail how high seizure frequency increase mortality risk: "*Dravet syndrome patients have a greater risk of premature mortality compared to both the wider population and the general epilepsy population [5, 6]. This is primarily due to Sudden Unexpected Death in Epilepsy (SUDEP: when a person with epilepsy during or following a seizure for no obvious reason dies [30]) and status epilepticus (SE: a prolonged seizure episode of >5 minutes), which are estimated to account for around a half and a third of premature deaths, respectively. Accidental deaths, such as drowning or fatal injury following a seizure, are also an important contributor to Dravet syndrome mortality [5, 6].*

A published review of deaths observed in 100 consecutive patients followed for a median of 10 years estimated a Dravet-specific death rate of 15.84 per 1000 person years (approximately 15-16% of the cohort per 10 years), and a Dravet-specific SUDEP rate of 9.32 per 1000 person-years (9-10% of the cohort per 10 years) [575]. This would suggest that the other remaining Dravet syndrome deaths, primarily due to SE, occur at a rate of around 5-6% per 10 years.

Generally, a high seizure frequency is well recognised as a significant contributing risk factor for SUDEP [31]. A higher use of AED polytherapy, likely to be reflective of the pharmaco-resistive nature of the underlying condition, is also shown to be a major contributor to the risks of SUDEP. The most effective SUDEP prevention strategy is commonly accepted to be to reduce the frequency of seizures [32, 33].

Although there is a paucity of data linking rates of SUDEP to seizure frequency specifically in Dravet syndrome, there is little doubt that Dravet syndrome patients experience high seizure frequencies despite AED polytherapy. Patients enrolled in recently conducted clinical trials of Dravet syndrome, with characteristics reflective of patients in UK clinical practice, have convulsive seizure frequencies in the range of four to several hundred per month [3, 4, 34, 35]. Given there is no correlation between the severity of the SCN1A mutation and SUDEP in Dravet syndrome [23], the high risk of death due to SUDEP observed in Dravet syndrome plausibly relates to the severity of the epilepsy, defined by the high frequency of seizures sufferers experience [6].

The presence of convulsive seizures is associated with a higher risk of premature death in epilepsy compared to other seizure types [32, 33]. Infants with Dravet syndrome typically present with prolonged convulsive seizures [2], and the DISCUSS study clearly demonstrates that convulsive seizures are the most common seizure type experienced by Dravet syndrome patients throughout life [7]. Furthermore, those with the highest convulsive seizure frequencies require significantly more emergency hospital admissions and ambulance assistance than those with the lowest convulsive seizure frequencies [7]. Although seizures may stabilise as patients age, convulsive seizures during adolescence and adulthood tend to occur mainly during sleep [2]. Nocturnal seizures are an independent risk factor for SUDEP [36]. Given these associations, it is clinically considered amongst experts that patients with Dravet syndrome are at a high risk of epilepsy-related death throughout their life, and that a reduction of convulsive seizure frequency is the most effective strategy to reduce death [32] and therefore a primary treatment goal to reduce that risk [5, 29].”

On the basis that fenfluramine treatment has been shown to significantly, and often profoundly, reduce the frequency of convulsive seizures in patients with Dravet

syndrome, it is a reasonable and clinically plausible expectation that fenfluramine treatment will reduce the associated risk of premature mortality.

b. **Please justify the linear extrapolation procedure of the relative risk by seizure count reported by Nilsson et al., i.e. supporting the plausibility of this assumption by evidence and/ or expert opinion, similarly, for the assumed accidental death of sudden unexpected death in epilepsy (SUDEP) as well as status epilepticus deaths (extrapolated from Cooper et al.)** .

Given the challenges outlined above, there are limited data available on mortality in Dravet Syndrome. None of the studies on mortality in Dravet Syndrome reported the seizure frequency of patients and therefore the association cannot be taken directly from studies in Dravet Syndrome. It was therefore necessary to take data from general epilepsy. However, as there is evidence of increasing SUDEP with increased convulsive seizures (see response to C14a) and patients with Dravet Syndrome have a considerably higher seizure burden and higher mortality than those in general epilepsy (reported by Nilsson et al[xxii]), it is necessary to extrapolate the data from Nilsson et al. Due to a lack of data and evidence on what shape this extrapolation should take, a simple linear extrapolation was used. However, to be conservative, the relative risk was capped at the 75th percentile of seizures seen in the trial, so that patients with abnormally high seizure counts (100s per month) do not have improbably high mortality rates.

Both the probability of status epilepticus (SE) mortality and accidental mortality are taken directly from Cooper et al[xxiii] due to a lack of other available data sources. Although there is evidence that accidental death increases with convulsive seizure, the exact relationship is unclear, particularly as accidental death due to seizures is likely to have an element of randomness. Therefore, as Cooper showed that accidental deaths are generally 24% of SUDEP and SE deaths for patients with Dravet Syndrome deaths, this probability was applied in the model.

The evidence for the association between status epilepticus and mortality is also limited. Although there is literature available on mortality 30 days after SE events in general epilepsy, unlike SUDEP, it is unlikely that this is directly transferable to Dravet Syndrome as the rates reported are much higher than those seen in the

fenfluramine trials. It is likely that this is because those patients included in the SE mortality studies in general epilepsy are only the patients that are hospitalised due to SE, therefore capturing only the most severe patients. The SE events recorded in the trial (which is how SE was modelled), would include seizures that were much less severe than those reported in general epilepsy literature. For this reason, SE mortality was modelled using the rate directly from Cooper et al.

c. **Please justify the estimated risk reduction in SUDEP mortality for fenfluramine by linking seizure frequency to SUDEP mortality (as described in section B.3.3.3.2 of the CS), which results in incremental life years gained compared to cannabidiol in favour of fenfluramine**.

Please see the responses to question C14.a and C14.b above.

d. **Please explain in more detail and justify the calibration procedure, resulting in a multiplier of 8.38, as described in section B.3.3.3.2 of the CS**.

As described in answer C14b, modelling mortality in Dravet Syndrome is difficult due to limited data. However, as described above, SUDEP is strongly associated with seizure frequency and therefore a relative risk of SUDEP was applied to background mortality in the model. However, when this was applied, mortality was considerably lower than what would be expected from Dravet Syndrome (Figure 23 in Document B of the submission). In order to reflect the mortality seen in Dravet Syndrome, a calibration was applied to the Nilsson et al mortality value. The calibration number was calculated by running the baseline population through the model (so that no treatment effect was included), with background mortality and the rates from Nilsson et al paper. This was then compared to the expected 9% SUDEP mortality after 10 years seen in Cooper et al. and the multiplier was back calculated so that when the relative risk was applied to background mortality with the calibration, the mortality expected from Cooper et al. was seen.

e. **Please provide a tabulated overview of both the calculated SUDEP mortality and accident-related mortality by seizure frequency, as implemented in the economic model. If these are based on categorizations of number of convulsive seizure frequency per year, please provide the percentage of simulated patients belonging to each category separately for CBD and fenfluramine (if this is time-dependent, please present this at least for the first year)** .

In contrast to the cannabidiol cohort model in NICE TA614, which modelled convulsive seizure frequencies based on distinct categories of convulsive seizure frequencies, in our model convulsive seizure frequency is modelled continually on an individual patient level basis. As the relative risk of mortality applied to these data changes over time and for every different convulsive seizure frequency that an individual patient may experience in the model, it is not possible to tabulate mortality by seizure frequency.

f. **Please provide a scenario analysis assuming fenfluramine does not prolong life (i.e. does not result in positive incremental life years) through assuming mortality is independent of frequency and days without convulsive seizures**.

As discussed in the response to question C14a, there are strong associations between the occurrence and frequency of convulsive seizures and premature death due to SUDEP, SE and accidents. Given these strong associations, a reduction of convulsive seizure frequency is the most effective strategy to reduce death and is therefore a primary treatment goal to reduce that risk. This view appears to be aligned with the views of the experts expressed in the NICE TA 614 final appraisal determination for cannabidiol, where it is stated: "*The experts would welcome new treatment options, and noted that reducing the number of convulsive seizures is the main goal of treatment. They noted that an increase in the number of convulsive seizure-free days would also benefit people with Dravet syndrome. This is because it would mean having fewer nights with seizures, when there is a higher risk of sudden unexpected death in epilepsy.*"

As both fenfluramine and cannabidiol directly impact seizure frequency, and robust evidence indicates that the reduction in convulsive seizure frequency is meaningfully

greater with fenfluramine than with cannabidiol (see Document B, Section B.2.9.4), it would not be representative of clinical reality to assume that mortality is independent of seizure frequency and seizure free days, and further to assume that there is no mortality benefit from the meaningfully greater reduction in convulsive seizure frequency observed with fenfluramine compared with cannabidiol.

In our submission we presented scenario analyses exploring the impact of alternative assumptions on the mortality risk in Dravet syndrome, including reducing the mortality risk to align with the general epilepsy population (see Document B, Table 51); however, given the recognition that mortality risk is greater in Dravet syndrome compared with the general population and the general epilepsy population (Cooper et al 2016) we consider that the mortality risk we adopted in our base case remains the most plausible.

C15. Priority question: The company assumed that the percentage of reduction was the same for convulsive seizure days as for convulsive seizure frequency (reported in Table 28 of the CS). This does not seem to be based on empirical evidence.

a. **Please provide supporting evidence to justify this assumption**.

It would be intuitive and there is evidence from the fenfluramine trials that number of seizure free days is inversely associated with the number of seizures that a patient experiences in a cycle. Therefore, as seizures decrease on treatment, it is valid to assume that seizure free days would increase on treatment. However, there is no data on how seizure free days are impacted by cannabidiol. Therefore, in order to ensure that the neither arm of the trial is having an incremental benefit due to this lack of data, both arms were modelled so that the decrease in seizure frequency was also applied to the decrease in seizure days.

b. **Please provide a scenario analysis assuming the percentage of reduction for convulsive seizure days is half the percentage of reduction for convulsive seizure frequency**.

The ICER when the reduction in seizure days is half of the reduction in seizures is £46,844. This assumption however assumes patients experience more seizures on a seizure day than were observed in the trial over the treatment period as they cannot

be seen as fully independent parameters; which will infer a higher cost and mortality rate, alongside lower quality of life from life year gains than also seen in the trial and the UK population of patients anticipated to be treated with fenfluramine. The clinical plausibility and basis for this analysis is therefore unclear.

c. **Please provide a scenario analysis assuming the percentage of reduction for convulsive seizure days is treatment independent (i.e. equal for cannabidiol and fenfluramine)** .

Although not reported as a primary endpoint, the fenfluramine trials show that there is a treatment effect on seizure days. To model seizure days as treatment independent would therefore not capture the treatment effect (and benefit) of fenfluramine and would not be representative of what has been demonstrated in clinical trials.

C16. Priority question: The estimation of and assumptions related to time to treatment discontinuation are not clear to the ERG.

a. **Please elaborate and justify the methods and data used to estimate the discontinuation probabilities reported in Table 30 of the CS**.

The discontinuation probabilities are calculated by determining the rate of discontinuation during relevant periods of the trial, e.g. for titration period discontinuation, the duration of the titration period was used, the duration of the maintenance period was used for lack of efficacy and other types of discontinuation, and the total time of the OLE was used to determine the ongoing discontinuation. The rate was determined by the number of events over the total person days for that period. The rate was then converted to a probability per cycle (28 days) (or during the maintenance period for lack of efficacy discontinuation) (

Table *10*).

Table 10. Discontinuation probabilities

Type of discontinuation	Arm	Period	Number in pop	Number discontinued	Person days	Model probability (per cycle unless stated otherwise)
Lack of efficacy	Treatment	Titration	[redacted]	[redacted]		
	Placebo	Titration	[redacted]	[redacted]		
	Treatment	Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
Other	Treatment	Titration	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	Titration	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment	Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	Maintenance	[redacted]	[redacted]	[redacted]	[redacted]
All ongoing	Treatment	OLE	[redacted]	[redacted]	[redacted]	[redacted]

b. **Please justify the use of treatment dependent discontinuation probabilities for 'ongoing' discontinuation (based on non-randomized evidence) in contrast with short term discontinuation, i.e. 'lack of efficacy' and 'other' discontinuation**.

Discontinuation in the long term needs to capture all reasons for discontinuing, including lack of efficacy, adverse events and patient/physician choice, to ensure that the number of patients remaining on treatment is representative of what would happen in reality. As the OLE period is non-randomised, it is important that discontinuation due to lack of efficacy is captured in this period, and could be more representative of the discontinuation in the longer term than the randomised period of the trial. It is also recognised that patients that do not receive a benefit from treatment, or that experience an adverse event that requires discontinuation from treatment, tend do so early on in starting (any) new treatment. The rates of discontinuation within a cohort starting a new treatment are therefore likely to be higher at the beginning and then tend towards becoming lower over time, with a greater proportion of patients that do not discontinue treatment continuing to receive

a benefit. The actual reasons for discontinuation also change over the longer term and should be accordingly adjusted over time.

c. **Please provide a scenario analysis only using treatment independent discontinuation probabilities**.

The ICER when only treatment independent discontinuation is used is £31,943/QALY. In this scenario, the stopping rule has been implemented as per the base case.

d. **Please provide a scenario analysis only using the randomised trial data to estimate discontinuation probabilities for both treatments using an indirect comparison**.

The ICER when only trial discontinuation is applied (no ongoing discontinuation) is £25,067/QALY. In this scenario, the stopping rule has been implemented as per the base case.

e. **Please justify the use of discontinuation probabilities that are constant over time (i.e. time independent) other than the distinction between short term (i.e. 'lack of efficacy' and 'other') and long term (i.e. 'ongoing') discontinuation**.

There are no data from published sources other than the OLE to suggest that the discontinuation rate would change in the mid-longer term for fenfluramine. In particular, based on the Pathway Mapping study, experts reported that when patients take medications that are effective, they stay on them for very long periods, and generally only stop due to adverse reactions. Consequently, there is no basis or evidence to suggest that discontinuation rates would change as patients age; therefore in the model we assumed this rate is constant over time.

f. Please use parametric survival models (consistent with NICE Decision Support Unit (DSU) technical support document (TSD) 14) to estimate and extrapolate treatment discontinuation probabilities.

Figure ***7*** shows the percent discontinuation within each cycle of the OLE period. Given the limited long-term follow-up the rate of discontinuation for the last OLE cycle represents the best available data we have from the trial. However, it is not

appropriate to extrapolate the discontinuation from the last period of the OLE, as there does not seem to be an obvious pattern (the discontinuation rate increases, but appears to start decreasing again towards the end of the follow up period).

Figure 7. Percent of patients discontinuing during the OLE period.

g. **In TA614, treatment discontinuation was assumed to depend on seizure frequency, please implement this dependency in a scenario analysis**.

The use of a stopping rule ensures in the base case, that any patient that does not see a seizure reduction of ≥30% in the first six months discontinues. Therefore discontinuation is explicitly linked to seizure frequency.

Furthermore although in the long term, discontinuation is not explicitly linked to seizure frequency, it is modelled using the discontinuation from the OLE trial and therefore includes patients that discontinue for lack of efficacy, which is likely to be linked to their seizure frequency (if the treatment is not effective the patients seizure frequency has not changed). In the short term, lack of efficacy discontinuation is dependent on seizure frequency in this model. For these reasons the base case already includes discontinuation that is dependent on seizure frequency.

h. **In the committee discussion for TA614 it was mentioned that *"the model generates more favourable results for patients that stop cannabidiol than***

***would be expected"*. Please clarify that the current model does not have this limitation**.

Our model does not have this limitation. When a patient discontinues in this model, they return back to the individual seizure frequencies that they experienced at baseline (before treatment or randomisation) in the trial. By returning patients back to their own seizure frequency instead of an average, the model does not give an advantage to either arm, as if the same patient discontinues in both arms then they will have the same seizure frequency, and therefore the same costs and utilities.

i. **Please justify the assumption that after discontinuation patients revert to the baseline seizure frequency**.

There is no evidence to suggest that treatment has a long-term effect that continues after discontinuation. Therefore, by returning patients to their baseline seizure frequency it ensures that treatment and placebo effect are removed and that after discontinuation neither arm is benefitted.

There is evidence to suggest that increased seizures over a prolonged period of time has an impact on other aspects of Dravet Syndrome such as increasing motor or learning impairments [xviii]. If this is the case, then a patient with decreased seizures over a long period of time (due to effective treatment) might see a decrease in other impairments in the long term, which would mean that even in a discontinued patient there could be beneficial effect of treatment remaining (i.e. increased utilities due to fewer physical impairments). Due to the limited data on this, it wasn't implemented in the model and the assumption that patients return back to baseline is therefore conservative as effective fenfluramine treatment over a prolonged period of time could also decrease other impairments and further increase quality of life.

In the analysis of fenfluramine as a 1st line add on treatment, a further conservative assumption is made, in that patients receiving SoC (without clobazam) are considered to receive a placebo effect at the point of starting the interventions, but upon discontinuation revert to their baseline level of seizures. In reality, patients would be unlikely to experience this 'placebo effect' benefit for staying on their existing SoC, without a change to their existing treatment.

j. **Please assume that after discontinuation patients revert to the placebo arm (instead of baseline) seizure frequency in a scenario analysis**.

Only the placebo arm of the trial is modelled in this model, and those that discontinue do remain in the placebo arm, but use the seizure frequency during the baseline observational period of the trial. Reverting patients back to the seizure frequency seen in the maintenance period of the trial would mean that patients are still experiencing the benefit of the placebo effect, which would give an advantage to patients discontinuing sooner. It is therefore not appropriate to assume that after discontinuation patients revert back to the placebo arm instead of baseline seizures.

C17. In the model, the placebo effect is added to the treatment effect identified in the NMA. However, the ERG believes the placebo effect is part of the treatment effect and hence should be subtracted from the identified effects in the NMA. Please clarify why the placebo effect was added to the treatment effect in the first place and adjust the model as suggested by the ERG.

The NMA calculates the treatment effect of cannabidiol and fenfluramine relative to their respective placebo effects so that they can be compared to each other. This is because the placebo effect in the two sets of trials was slightly different so to directly compare percent reduction from baseline would not be an equal comparison. As the treatment effect in the NMA is only the difference between the 'placebo effect' and the 'treatment effect', and not the absolute change in the treatment arm from baseline, in order to calculate the full percentage change from baseline, the treatment effect must be added to the placebo effect.

E.g. If the average placebo effect in trial A is a 10% reduction from baseline seizures, and the average treatment effect is a 25% reduction from baseline seizures, the treatment effect relative to placebo would be 15%. Therefore, if the placebo effect is known from a different trial, (e.g. 5%) then the relative treatment effect (15%) can be added to this placebo effect to get the absolute percentage reduction from baseline seizures, which would be 20% in this example.

C18. In the CS, it is stated that the model excludes non-convulsive seizures (NCS) from the estimation of costs and QALYs, and that given the adverse impact NCS have on quality of life, and the observation in the registrational trials that fenfluramine reduces NCS, this is a conservative approach. However, from table 10 in the CS, it

appears as if NCS increased in the FFA 0.4 mg/kg/day group of study 1504. Please elaborate on the validity of the statement that excluding NCS results in a conservative estimate of the ICER.

In the NICE TA614 appraisal of cannabidiol the appraisal committee gave additional consideration to NCS in its decision-making on the basis that NCS was not adequately captured within the company's model. The adverse impact of NCS on patient and carer quality of life, and importance of reducing their occurrence, is therefore well recognised.

The ERG refers to Table 10 of Document B and states that it appears as if NCS is increased in the fenfluramine 0.4 mg/kg/day group of study 1504. We would like to draw the attention of the ERG to the footnote of Table 10, which explains that not all patients were reported to have non-convulsive seizures and therefore these data are based on less than half of the Study 1504 trial population (17/44 [39%] patients on fenfluramine 0.4mg/kg/day and 22/44 [50%] on placebo). It is also noted that the data in these small subgroups are skewed, and both the placebo and fenfluramine treatment groups actually experienced a decrease from baseline in the median number of NCS: placebo from 4.33 at baseline to 3.79 at end of treatment period, and fenfluramine from 13.33 to 8.88. This is also discussed in some depth in Document B, section B.2.6.1.4 (Non-convulsive seizure and total seizure frequency).

In the context of the heterogeneity in seizure frequency at baseline, these data suggest a trend in favour of fenfluramine 0.4mg/kg/day in Study 1504, and confirms that the benefit of fenfluramine in reducing convulsive seizures is not at the expense of an increase in NCS. It should also be noted that in Study 1 the median percentage change from baseline in NCS was significantly greater with fenfluramine 0.7 mg/kg/day than with placebo (-76% vs -55.6%; p=0.046). Collectively, these data suggest a decrease in NCS with fenfluramine treatment, and the exclusion of NCS from the model therefore does not capture the full benefit of fenfluramine treatment. The economic model therefore remains conservative.

C19. The NMA does not include the dosage of 12 mg cannabidiol (CBD). Instead the treatment effect of 12 mg CBD is based on a weighted average of the treatment effect of 10 and 20 mg CBD. Please justify the use of this weighted average (instead of using

the 10 mg CBD effectiveness for 80% of the individual simulated patients and the 20 mg CBD effectiveness for 20% of the individual simulated patients).

The use of a weighted cost and treatment effect vs assigning patients to a 10 or 20mg/kg/day dose of cannabidiol is unlikely to make a difference to the ICER, and is probably a conservative assumption as outlined below.

In reality, patients that increase their dosage of cannabidiol are likely to be those who do not see a treatment effect at 10mg/kg/day; however, in the cannabidiol trials, the 20mg/kg/day dosage had a lower efficacy compared to placebo than the 10mg/kg/day (mean percentage change of 35.91% and 39.07% for 20mg/kg/day and 10mg/kg/day, respectively [Epidyolex SmPC]). Therefore, if the most refractory patients were to increase cannabidiol dosage instead of discontinuing, this would lead to increased costs in the cannabidiol arm and no additional utilities (it is more beneficial in the cannabidiol arm to discontinue and remove treatment cost, than it is to continue treatment and accumulate utilities, as shown in response C.9b in which the stopping rule was removed from both arms of the model and the ICER was £19,898/QALY). Furthermore, if patients who were not seeing a treatment effect had an increased dosage, it is likely that the average dose of cannabidiol would be higher than the 12mg/kg/day that was deemed appropriate in TA614, as there are more than 20% of patients discontinuing at 6 months because they do not achieve a 30% reduction in seizures.

If the patients on 10mg/kg/day vs 20mg/kg/day dose were randomly assigned in the model, this would not reflect clinical practice. Furthermore the number of simulated patients would need to be significantly higher to ensure that the noise from this assignment was removed, which would add to an already lengthy run time (1+ hour, therefore for 1000 iterations for the PSA it would be untenable).

In light of the points raised above, and the previously provided scenario analysis of using a 15mg/kg/day (ICER: £14,223/QALY) or 20mg/kg/day (cannabidiol is dominated) presented in Table 51 of Document B, please advise if this analysis is required and if so, specify how the ERG would like to see this analysis undertaken.

Adverse events

C20. See also question B10. Adverse events (AEs) were not considered in the model. However, as stated in the CS, in study 1 12.5% of the patients experienced AE leading to discontinuation.

Please include the effects of (at least) the most frequently occurring adverse event in the model (e.g. treatment-emergent adverse events mentioned in Table 20 of the CS)

As agreed in discussions with the ERG during a clarification call on 7/9/20, given there were only minor differences in AEs reported between treatments and the clinical and economic implications from the consequences of the AEs and/ or treatment of the reported AEs were considered negligible (Document B, section B.2.10), at this time it was agreed that no further action or analyses is required to support clarification of this question.

Quality of life

C21. According to section 3.4.2.1. of the CS, mapping of PedsQL to EQ-5D-Y was used to generate utility values in the model. As mentioned by the authors of the mapping study of Kamran et al. 2014, this mapping process has some methodological weaknesses in that the performance of the algorithm becomes worst as the quality of life of the population under consideration becomes worse. The authors state: "*A caveat to the study findings is that although we used a fairly large sample for the mapping analyses, we encountered problems when attempting to use the response mapping approaches to generate predictions. This was because of the fact that our study population largely comprised healthy children with a mean EQ-5D-Y utility score of 0.89*". Next, the authors highlight: "*We have not tested the performance of the estimated models in populations of less healthy children*".

Please comment as to what might be the likely impact on utility and cost effectiveness estimates of using a mapping approach as an alternative to direct utility measurement.

Khan et al 2014[xxiv] noted that there were higher prediction errors at the lower end of the utility scale and that their study focused on mapping data that contained a high mean EQ-5D utility score of 0.89 (relative to Dravet syndrome patients). The authors reported that there were overpredictions for the lower end of the EQ-5D range

suggesting that the mapping tool may perform better when evaluating data for sicker individuals in comparison to more healthy ones. Therefore, this may suggest that the mapping algorithm may perform better (and more accurately capture the true PedSQL data) when used to map to a population with lower utility scores such as ours in this population. Based on the reports by Khan et al it is possible that the mapped utility values at the lower end of the range may actually be lower than currently predicted by our analysis. Meaning that if these lower values have been overpredicted, the gradient of the line may be less steep (i.e. less difference between the upper and lower bounds in quality of life, in having 0 seizures per day and a seizure every day, respectively). Thus, if this was the applied implication, an increase in the number of seizure free days on a cohort basis may lead to more substantial increases in the overall utility values for the cohort and thus improve the cost-effectiveness of a treatment strategy. The method presented in Khan 2014 et al is currently the only suitable mapping algorithm to convert PedSQL data to EQ-5D-Y to be best of our knowledge therefore despite limitations it was the only way to obtain the required indirect measurement of utility from PedSQL data.

C22. In line with the NICE appraisal of cannabidiol (TA614), carer utilities were included in the base case. A linear panel regression model with fixed effects was developed to estimate carer utility values based on the 28-day frequency of number of seizure-free days. Moreover, a total of 1.8 carers per patient were assumed.

a. The resulting lowest carer utility in the model is almost equal to the lowest patient utility, i.e. 0.356 for carers and 0.353 for patients. Please elaborate on the plausibility of this assumption.

Given the substantial burden placed on carers by Dravet syndrome patients it is possible that carers may well have a comparably poor quality of life to patients. Carers are more likely to be able to express exactly how they feel and the ways in which they are suffering when asked; this expression may be more difficult for patients. Carers may have a greater degree of consciousness around the life they have lost as well as observing a loved one suffer with Dravet syndrome. Carers may also experience anxiety, financial stress and guilt when caring for a patient. These factors in turn could lead to a carer having an equally poor QoL. Furthermore, the lower utilities value estimate of 0.356 is consistent with findings in the literature from

other studies reporting carer QoL. Campbell 2017 and 2018 report a lower EQ-5D index score for Dravet syndrome carers in the US of 0.31. In a study of UK care givers, a mean EQ-5D index of 0.382 (range: -0.17-0.88) was reported by Pagano 2019 and Lagae 2018 and Irwin 2017 reported a range of EQ-5D index between -0.35-1 for care givers of Dravet syndrome patients between 1-48 years, supporting the lower ranges of utility values reported in this study. All data were identified in the SLR reported in Table 21 of Appendix H.

b. Using the regression function to determine carer utilities, an increase in patients' health status results in an increase in carers' utility. In contrary to TA614, carer utilities are included for all patients whereas in TA614 they were only included for patients with the 2 health states reflecting the highest frequency of seizures. Please provide a more conservative scenario regarding carer utilities, e.g. in which carer utilities are only included in more severe patients instead of all patients to make it resemble what was done in TA614 as closely as possible.

Assessing the health state categorisations outlined by TA614 those who had >8 - ≤ 25 convulsive seizures a month and >25 convulsive seizures a month where the 2 health states considered with the highest frequency of seizures. We have re-run the analysis assuming that individuals who had >20 seizure free days a month would be given 0 carer utilities. The combined ICER across the two studies when this assumption was made was £44,042/QALY.

It is likely that solely looking at convulsive seizure frequency does not fully capture the true burden placed upon carers, as it is not just the immediate convulsive seizure burden that necessitates the need for carers. Patients may experience non-convulsive seizures, accidents may occur because of only 1 seizure, carers remain stressed and anxious throughout a patient's life. Patients may require ongoing care due to the accumulation of injuries and comorbidities throughout the course of their disease even if they currently have a lower convulsive seizure frequency. Thus it is important to still capture the burden on carers even when patient's convulsive seizure frequencies are lower. Furthermore, in comparison to TA614, we explicitly model the number of seizure free days per patient and do not aggregate the frequencies into groups, which more accurately reflects the burden on carers for

each convulsive seizure free day and avoids a blunting of the parameter (e.g. no quality of life impact to carers are assumed for 0-7 seizures; and the same quality of life impact is assumed for a carer with a patient that has 26 seizures per month to 623, as was seen in study 1 at baseline), as well as large step changes in the application of quality of life for patients moving from 7 to 8, or 25 to 26 seizures per month.

c. Carer utilities of 1.8 carers per patient are included in the model until the patient dies. Please elaborate on the appropriateness of assuming 1.8 carers per patient over the whole patient's lifetime. Please take into account that carer utilities do not necessarily assumed as additive (see: https://www.nice.org.uk/guidance/ta614/chapter/3-Committee-discussion#companys-economic-model) .

Caring for patients with Dravet syndrome has a substantial detrimental impact of the quality of life of their carer's, therefore including at least 1 carer was felt to be important. Based on evidence presented by Lagae 2017 it was reported that even if there was one primary carer within the family it was very likely that additional family members would also help to provide care and would live with the stress of dealing with the consequence of a seriously ill family member. Therefore, in line with Lagae 2017 and TA614, 1.8 carers was selected for the patient's lifetime. Given the evolving and complex nature of Dravet syndrome it is possible that patients may go through periods where their condition is more manageable and may require less care, however there will also be ongoing periods where additional care (above 1.8 carers) may also be required depending on the severity of disease. Given the progressive nature of the condition patients may require more carers as they age. However, to the best of our knowledge no long-term data on the number of carers required over a patient's lifetime and the resulting carer QoL impact is available. Equally, it was previously acknowledged that it would be challenging to estimate how much each additional carer reduced the burden of other carers, therefore the pragmatic assumption was made to value a fixed 1.8 carers over the patient's lifetime. Sensitivity of the ICER to the assumed number of carers over a patient's lifetime was explored. When no applied carer's utility was assumed the ICER was £104,835/QALY (Table 51, Document B). We have also now tested the impact of

assuming 3.6 carers per patient in the model, this resulted in an ICER of £7,058/QALY.

Please also consider the challenges in measuring and weighting quality of life in patients with Dravet syndrome as highlighted in the equality section of Document B (section B.1.4.2)

d. Please justify the applicability of the regression function to estimate carer utilities in adult patients, given that the estimation of the function was mainly based on carers of children in the registration studies. As mentioned in the CS, *"Typically, as patients age after initial diagnosis, they require less frequent ongoing care as carers are better able to manage their condition"* .

It was considered that the application of the regression function to estimate carer utilities in adult patients based on child patient data is still appropriate in the absence of detailed patient-level data on how seizure free days in adult patients impact a carers QoL. We used the full age range of data available (for patients up to age 18) and we felt it inappropriate to try and extrapolate outside of this range without additional data to support it. However, given the immense burden that this progressive condition places on carers, it was deemed important to still capture the impact that older Dravet syndrome patients have on carer QoL. Estimates of EQ-5D index values showed that patient QoL continues to decline with age (Lagae 2018 and Irwin 2017). The study from which our carer QoL life data was obtained captures at least some of the diversity in carer burden within the Dravet syndrome patient population over time and as patients enter into adulthood. The burden of caring for Dravet syndrome patients is by no means limited to seizure management. There will be ongoing phycological stress associated with dealing with such patients, ongoing anxiety about their health, managing other co-morbidities and dealing with the progressive long-term implications of seizures that occurred when patients were much younger can still place a considerable burden on carers as a patient's condition evolves. The accidents and injuries that accumulate before adulthood are likely to carry on into later life and means that patients are highly dependent on carers, and the burden remains high even if the condition can be managed better by carers following initial diagnosis. As patients age they may need to move to a care home, which may reduce the burden on a single carer but will increase the number

of carers that are required and so still has a relevant impact and a requirement for an assignment of utilities. Whilst the immediate burden on a single carer may be less, they will still have suffered irreversible damage and are unlikely to return to a normal QoL.

Costs and resource use

C23. Because of reported cases of cardiac valvulopathy (and pulmonary hypertension) that may have been caused by fenfluramine at higher doses used to treat adult obesity, patients must undergo an echocardiogram (ECHO) to evaluate for regurgitant aortic or mitral valvular heart disease prior to starting treatment. Further cardiac monitoring must be performed using echocardiograms. Additional costs (Table 35 of the CS) are included in the model for echocardiograms to confirm the absence of valvular heart disease or pulmonary hypertension in line with the draft SmPC for patients on fenfluramine.

a. Please explain why the results of these tests are assumed to be negative in 100% of cases (since no follow-up costs or disutilities associated with positive test results have been assumed) .

In Study 1 and 1504, only 2 patients out of 288 (0.69%) who received an ECHO during their pre-treatment screening did not continue to receive treatment with fenfluramine as a result of their findings (section 3.7 of the BIM document), Therefore, we assumed that the associated cost of failed ECHO screening would be negligible and have minimal influence on the ICER. The cost of an ECHO is estimated to be £53-73 (based on a patient's age; Table 35). We also have assumed a prevalence cohort of 480 people in the model, all of whom would be starting treatment with fenfluramine; it is of note that the actual incidence population for new patients starting fenfluramine treatment would be estimated to be much lower than this in practice (please see section 5 of the BIM document). In adding these costs to those participants who would receive an ECHO, but subsequently not receive treatment, an additional 0.01% to the total costs of the fenfluramine arm could be assumed, which is considered to have negligible influence on the overall ICER results.

We also assumed that there would be no disutility or follow-up cost that should be included in the analysis if an abnormal ECHO result were found, as patients would stay on their current AEDs. In clinical practice, in taking a perspective of the analysis to incorporate this earlier time point to receiving the comparative interventions (i.e. to include potential screen failures), the few patients not able to receive fenfluramine would likely receive cannabidiol instead. As a consequence, they may experience a lower treatment effect, which in turn would then have a lower associated utility with it, which arguably could be considered to be applied to either the fenfluramine or comparator (cannabidiol) strategy.

With regards to patients during the initial follow up period after starting fenfluramine, XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX; see B.2.10.4.1 Phase 3 RCTs and Table 21; and section 3.7 of the BIM document); XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX

b. Please provide scenarios whereby a proportion of test results lead to additional costs and/or disutility. Please justify the estimation of this proportion.

This analysis will be provided in follow up to this response, as soon as practically possible

C24. The ongoing resource use that patients receive in the primary, secondary and/or tertiary care institutions is based on their seizure frequency.

a. Please elaborate on how the chosen seizure frequency categories (high, medium and low), as illustrated in Table 36 of the CS, were determined.

In the UK Pathway Mapping study (validation portion), ongoing resource use was reported to vary by seizure frequency and age (CS section B.3.5.2.1 - Ongoing resource use). We therefore asked clinicians to define “high”, “medium” and “low” seizure bands based on what was considered meaningful to the patient and their experience of managing patients with Dravet syndrome, so as to be able to quantify and appropriately allocate resource utilisation in the model by seizure frequency and age. The reason for categorising them into seizure frequency bands rather than using a linear model, was that ongoing resource use was reported as tending not to increase in a linear fashion with seizure frequency; but rather with patients that are

less controlled being seen more frequently, and that this was determined on a centre by centre basis and with protocol thresholds for escalating or deescalating care and associated resources. In contrast to this, patients' emergency resource use is linked to the number of seizures that require rescue medication, so therefore would increase in a linear manner as seizure frequency increases.

b. Please provide more information on how and in which population resource use (as reported in Tables 37-40 of the CS) was derived. Please provide all supporting evidence.

The ongoing resource use for patients with Dravet syndrome was collected in the Pathway Mapping study (for full methods see the report). The wording for the question on the seizure frequency bands (also see question C24a) and for this one which generated the data in Tables 37-39 is given below, as taken from the validation exercise questionnaire:

> *"..5. We have divided seizure frequency into 'high/medium/low'. Please would you give your own definitions of what these bands mean to you in terms of convulsive seizure frequency (per month)? You may offer a range, if that is easier*
> - *Definition of **high** convulsive seizure frequency: (number of seizures per month)*
> - *Definition of **medium** convulsive seizure frequency: (number of seizures per month)*
> - *Definition of **low** convulsive seizure frequency: (number of seizures per month)"*
>
> *"6. We would like you to fill out the following tables as appropriate – showing how routine healthcare resources related to primary, community & secondary and tertiary medical consultations are used for patients who have different seizure frequencies, and at different age-bands. "*

The answers from all responses received in the validation exercise (Phase 3 of the study) were averaged and are reported in the CS Tables 37-39.

The emergency resource use was captured in the validation exercise as well. The question posed in the validation part of the project is copied below, and interviewees were asked to complete the following table:

7. Now thinking about paediatric emergency care resources, and how this might vary by age of patient, please could you fill out the below?

Patient Age	Of those given rescue medications, what % call an ambulance?	Of those who call an ambulance, what % go to A&E?	Of those who go to A&E, what % are:	Length of stay (avg. or range)
2 – 3 years*	%	%	Admitted: %	# days
			Admitted into ICU: %	# days
			Discharged:	

*Note this is repeated for all age groups

The answers from all responses received were averaged and are reported in the Document B, Table 40.

Respondents were also asked to enter the resources typically used for each admission, and consequences to secondary, tertiary or quaternary care. However, these were not well completed so were not used in the analysis.

Sensitivity analyses

C25. The R-code to run the deterministic sensitivity analysis (DSA) and the probabilistic sensitivity analysis (PSA) was not provided to the ERG.

a. Please provide the (annotated) R-code for the DSA as well as the PSA.

Commented R-code to run the DSA and PSA for each study has now been provided in the supplementary code folder [ID1109_FINTEPLA_DSA_PSA_code[ACIC] (Aug 2020)] in addition to the csv files that contain the parameter values assumed for each DSA and PSA run.

The scripts are:

PSA_study_1_ITC.R,
PSA_study_1504_ITC.R,
ITC_DSA_study1.R,
ITC_DSA_study_1504.R.

Scripts for the patient and carer QoL DSA are:
DSA_patientQol_study_1.R,
DSA_patientQol_study_1504.R,
DSA_CarerQol_study_1504.R,
DSA_carerQol_study_1.R.

The names of the csv files are:
PSA_test_vals_finaltest_ITC_last2.csv,
DSA_matrix_pars_ITCtest_FINAL_v3_edit.csv
(as listed in the scripts).

b. Please describe the methods used to perform the DSA and PSA in combination with the microsimulation, e.g. were nested loops used.

For both the DSA and PSA a csv table of new parameter values to be used were generated. The csv tables of new values were read into R and each parameter (where appropriate) was assigned a new value for that iteration. For the DSA 46 unique sets of values were run through (18 different groups of parameters with upper and lower values for each group). Therefore, the csv of new parameter values was looped through 36 times (per study). The same sets of parameter values were used for both studies. 1000 different sets of parameter values were recorded in a csv and read into R and each parameter was assigned a new value for that iteration. All 1000 rows of the table were looped through for the PSA. The tables of parameter values used for the DSA and PSA have been provided in the supporting information. The script which loops through the new sets of parameters can be found on lines 360-87 and 362-1212 in the DSA and PSA scripts respectively. In order to perform the DSA and patient and carer utilities the same approach was taken for the PSA. The model was re-run with 100 different patient and carer utility tables separately to obtain the upper and lower values for the DSA patient and carer utilities. For both studies 100 different tables were read in and looped through.

c. Please provide an indication of the runtime for the complete DSA (if automated) and PSA.

One full run of the model, and thus one iteration of the PSA and DSA analyses takes ~1 hour 20 minutes. For each study in the DSA a total of 18 different sets of parameters were varied. Upper and lower values for these sets of parameters were explored therefore 36 iterations for the DSA for one study takes ~ 50 hours. Results of the DSA for both studies were then merged. As with the DSA, each iteration and

full run of the model for the PSA also takes ~ 1 hour 20 minutes. For the PSA, 1000 iterations are required, thus ~ 1,333 computational hours are required to run the PSA. Results of the PSA for both studies were then merged. The DSA for patient and carer utilities takes ~122 hours.

Validation and transparency

C26. Priority question: In the model, 480 patients are simulated. However, it is not clearly stated in the CS why 480 patients were chosen.

a. **Please explain why 480 patients were chosen**.

The DISCUSS study identified 72 patients in the UK, which was estimated to be ~15% of the total Dravet syndrome population the UK (Document B, section B.1.3.11). In scaling up the identified 72 patients, the total number of Dravet syndrome patients in the UK is estimated as 480 patients. This number of patients in the model cohort therefore reflects a similar total to the population of patients with Dravet syndrome in the UK.

An analysis will be provided in follow up to supplement this response, as soon as practically possible

b. **In the model, more profiles are generated. Please elaborate on how the 480 profiles were selected in the model**.

The 480 profiles are made up of each of the 40/44 placebo patients bootstrapped 12/11 times (for Study 1/Study 1504, respectively – N.B. 8 patients randomly picked were bootstrapped 10 times in 1504, when other patients were picked this did not impact the results). All of these placebo patients completed the baseline and titration period of the trial and continued into the maintenance period of the trial.

c. **Please provide a justification for the use of only 480 simulated patients as it is unclear to the ERG whether 480 patients is enough to capture all stochastic uncertainty. Please provide diagnostics such as a figure demonstrating mean outcomes (costs, QALYs, and ICER) vs. the number of patients (i.e. visual inspection of stochastic uncertainty); and by means of a mathematical estimation**.

An analysis will be provided in follow up to supplement this response, as soon as practically possible

C27. Priority question: Please provide a definition of all parameters/vectors, data.frames and functions used in R code. For example, this could be in tabulated form:

An outline of files, functions and variables used in the model are provided below. Variables that are "well commented" within the model, "not in use" or are "cost variables" are not included as there are too many of them to include in this document; please see the source code in R.

R script name	Description / usage
Base case.R	Main file that reads in required scripts/inputs and saves results to working directory
Inputs_micro_4sf.R	Defines all inputs (Note: There are X dataframes outlined below that are read in separately)
population.R	Contains the function that assigns age, weight and concomitant stiripentol use to the model population
Costs.R	Contains the function that calculates the costs for each individual per cycle
characteristics.R	Contains the function that assigns the gender and comorbidities to the model population
Utilities_noNC.R	Contains the function that calculate patient utilities for each in individual per cycle
Utilities_carer.R	Contains the function that calculates carer utilities for each individual per cycle

Input file name	Description / usage	Source.
Utility_values_seizurefreedays.RData	A look up table of all the patient utility values	Regression model developed from clinical trial
Background_mortality.RData	A look up table of probabilities of background mort	
Carer_onlyseizures_plm.RData	A look up table of all the carer utility values	Regression model developed from clinical trial

Input file name	Description / usage	Source.
Seizuresseiz.RData	Number of seizures in maintenance period of each individual of the placebo arm per cycle	Bootstrapped from clinical trial data
Seizuredaysseiz.RData	Number of seizure days in maintenance period of each individual of the placebo arm per cycle	Bootstrapped from clinical trial data
baselineseizuresseiz.RData	Number of seizures in baseline period of each individual of the placebo arm per cycle	Bootstrapped from clinical trial data
baselineseizuredaysseiz.RData	Number of seizure days in baseline period of each individual of the placebo arm per cycle	Bootstrapped from clinical trial data
annualRRcappedUQR.csv	Look up for relative risk of SUDEP by number of annual seizures	Extrapolated from Nilsson et al
Drug_doses.csv	Look up for the dose of different AEDs	BNF/CBNF (March 2020) [97], draft SmPC for fenfluramine, preferred appraisal committee dosing assumption for cannabidiol in NICE TA614)
max_dose.csv	Look up for the maximum dose of different AEDs	BNF/CBNF (March 2020) [97], draft SmPC for fenfluramine

Variable name	Description / usage
ffareduc1	Seizure frequency reduction using fenfluramine relative to placebo in study 1
ffareducdays1	Seizure day frequency reduction using fenfluramine relative to placebo in study 1
ffareduc1504	Seizure frequency reduction using fenfluramine relative to placebo in study 1504
ffareducdays1504	Seizure day frequency reduction using fenfluramine relative to placebo in study 1504
CBDreduc	Seizure frequency reduction using cannabidiol relative to placebo
CBDreducdays	Seizure day frequency reduction using cannabidiol relative to placebo
agedist	Age distribution from 2-34 at start of model

Variable name	Description / usage
study	Whether the patients are on concomitant stiripentol (study <- 0 refers to fenfluramine clinical trial study 1, study <- 1 refers to fenfluramine clinical trial study 1504
stpexp	Whether the model patients are stiripentol experienced (1) or stiripentol naïve (0)
n.i	Number of individuals in the model
d.c	Discount rate for costs
d.u	Discount rate for utilities
n.t	Number of model cycles
OTHER.DISCON.RULE	Switch to turn on/off discontinuation during the cycles 2-4 (not including discontinuation due to lack of efficacy)
OTHER.DISCON.TITRATION	Switch to turn on/off discontinuation during the first model cycle
LoE.DISCON.RULE	Switch to turn on/off discontinuation in cycles 2-5 due to lack of efficacy
STOPPING.RULE	Switch to turn on/off stopping rule
Percent.stopping / percent.stoppingffa	The stopping rule – the percent reduction in seizures required for patients to continue treatment after 6 months for the comparator arm and fenfluramine arm respectively
CARER.UTILITY	Switch to include carer utility (TRUE = include carer utility)
NCSprop	Proportion of non-convulsive seizures compared to convulsive seizure
w.age	Age at which weight plateaus
w.plateau	Weight at plateaus

C28. The ERG would like to plan a separate meeting in which a walkthrough of the model is provided by the company.

A model walkthrough was held on the 10th September 2020.

C29. The “seizuredays.cycle” and “seizures.cycle” matrices in the model include the variable “STP”, which is either “FALSE” or “TRUE”.

a. Please explain what this variable entails.

STP is the flag for whether the patient is on concomitant stiripentol, i.e. whether they were in Study 1 or 1504.

b. If applicable, assuming the variable “STP” is short for stiripentol, please elaborate on whether patients in study 1 were also on concomitant stiripentol as the CS states that these patients were excluded in study 1.

Patients in Study 1 were not on concomitant stiripentol, and were given a ‘0’ flag for that variable (those in 1504 were given a ‘1’ flag to differentiate).

C30. The “seizuredays.cycle” and “seizures.cycle” matrices in the model include the variable “tx”, which has the levels “Placebo”, “ZX008 0.5 mg/kg/day”, or “ZX008 0.5 mg/kg/day”.

Please explain why these levels appear to refer to a different dosage than what was used in the CS.

The original dosages in the fenfluramine trials had the nomenclature 0.5mg/kg/day and 0.8 mg/kg/day. During the FDA submission this nomenclature was changed to 0.4 mg/kg/day and 0.7mg/kg/day. The active dosage of fenfluramine remained the same, and the reason for the change was the removal of the weight of the accompanying hydrochloride in the named dosage (please see footnote on Table 5 of Document B). Therefore, the actual dosage of fenfluramine and components of the compound remains the same, it is just the way the dosage is named was changed. In the clinical trial data the 0.5/0.8 nomenclature was used, and this dataset is modified directly from the clinical trial data which is why it has not been changed.

C31. The scenario in which age was set to only include adult patients has a large impact on the ICER (i.e. lower ICER). Please elaborate on this result and why this is to be expected.

Fenfluramine has a maximum dose of 17mg/day and 26mg/day depending on whether a patient is respectively receiving concomitant stiripentol or not. Cannabidiol does not have a maximum daily dose. Although the cost of fenfluramine per mg is more than the cost of cannabidiol per mg, once patients reach a weight whereby a cap in dose of fenfluramine is reached, the cost of fenfluramine becomes fixed (see BIM document, section 1.1). The daily cost of treatment with fenfluramine is therefore limited and provides some assurance in budget containment to the NHS,

however the costs of cannabidiol (and stiripentol) continue to increase with patient weight.

Assuming that 58% of patients take concomitant stiripentol (based on the UK DISCUSS study data) and therefore 58% of patients in practice would receive fenfluramine at a dose of 0.4mg/kg/day (and 42% would receive fenfluramine at a dose of 0.7mg/kg/day), and assuming an average daily dose of cannabidiol of 12mg/kg (based on the conservative assumption adopted in NICE TA 614) and its list price, the average cost of cannabidiol would be higher than that of fenfluramine once the typical patient (with a 58% of Stiripentol use) weight reaches XXX kg. Based on the relationship between age and weight in the model, XXX g is reached at age XXX years, and therefore for patients older than this (XXX XXX XXX XXX XXX XXX XXX XXX XXX), cannabidiol costs are greater than fenfluramine. In the DISCUSS study, 22% of UK patients were aged 18 years and older.

As fenfluramine/cannabidiol costs make up a large percentage of total costs (32% and 25% in the fenfluramine and cannabidiol arms, respectively), the weight, and therefore the age, of the patient population has a big impact on the ICER. In an adult only population, there are more patients for which fenfluramine costs less than cannabidiol and therefore the ICER is considerably lower.

C32. In section 3.11.2 of the CS, it is stated that a validation of the base case results against the predicted results (e.g. comparison of mortality to mortality observed in fenfluramine registration trials, comparison of mortality to published literature) was performed as well as an examination of internal consistency and plausibility of all results.

a. Please provide the corresponding results of this assessment, e.g. comparison of long-term mortality & discontinuation in the model to external data.

The mortality seen in the trial was 0.49% in the OLE period, and in a corresponding time period of 1 year, the mortality seen in the model was 0.43% (Appendix J in the submission). Note that over the OLE period, a number of patients discontinued and therefore would not have been taken into account in this population if they had died.

There are currently no externally available data on discontinuation rates for patients on fenfluramine. Therefore, the most suitable approach in the absence of externally available data was to ensure that the rates of discontinuation used were consistent with those identified in the trial populations. Rates of discontinuation from trials of other AEDs were not seen as appropriate external data sources to validate the plausibility of our results as reasons for discontinuation including efficacy and tolerability are likely to differ between other AEDs and fenfluramine. Thus, are not appropriate external validation sources.

b. To ensure internal validity of the model, please complete the TECH-VER checklist which is a verification checklist to reduce errors in models and improve their credibility (see: *Büyükkaramikli, N. C., Rutten-van Mölken, M. P., Severens, J. L., & Al, M. (2019). TECH-VER: A verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics, 37(11), 1391-1408*) .

As agreed in the model (code) walkthrough discussion with the ERG on 10/9/20, the TECH-VER checklist will follow shortly with the bootstrapping code, apologies for the delay.

Section D: Textual clarification and additional points

Clinical study reports

D1. Priority question: Three CSRs (study 1, study 1503, study 1504) have been provided as part of the CS. However, these appear incomplete, e.g. appendices are missing.

Please provide the missing appendices and all relevant files related to the CSR documents provided.

In the submission package provided to NICE the full body document of all relevant CSRs have been uploaded as references. The appendices that accompany the full body CSR document are in process for release and we will endeavour to provide these once we have confirmation in being able to provide these material. However, in the meantime, we can confirm that any references we have made to the CSRs in our submission have been to the data and information contained within the full body

documents we have already provided; we have not made reference to any of the CSR appendices. The ERG therefore has access to the data we have referenced in the CSRs.

D2. Please ensure that all 'data on file' references are provided. For example, we do not appear to have reference 78 of the CS. Is there a full report for reference 74? .

Reference 74 is data from the European Expanded Access Programme. These data are included in a larger regulatory document and are not available as a standalone full report. This and other data on file are in process for release and we endeavour to provide these once we have confirmation to be able to release these material as final versions.

D3. In Table 13 of the CS, do the figures quoted as 'seizure free' refer to 'total seizure free' or 'convulsive seizure free'? .

'Seizure-free' in Table 13 of Document B was as defined by the patient, but at a minimum would be considered to be convulsive seizure free.

References

[i] Pagano, K., et al., *The clinical and socioeconomic impact of Dravet syndrome in the UK.* Developmental Medicine & Child Neurology 2019. 61((Suppl 1)): p. 61 (abstract 111).

[ii] Alan Pharmaceuticals, *Diacomit 250 mg powder for oral suspension in sachet Summary of Product Characteristics.* 2019.

[iii] National Institute for Health and Care Excellence, *Technology Appraisal 614: Committee Papers.* 2019.

[iv] National Institute for Health and Care Excellence, *Technology Appraisal 614: Cannabidiol with clobazam for treating seizures associated with Dravet syndrome. Final Appraisal Determination.* 2019.

v Gluaser T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents 2016; 16: 48-61

[vi] Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. New Engl J Med. 1997;337(9):581-588. Erratum in: N Engl J Med. 1997;337(24):1783.

[vii] Wong J, Reddy SS, Klein AL. Anorectic drugs and valvular heart disease: a biological and clinical perspective. Cleve Clin J Med. 1998;65(1):35-41.

[viii] Center for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations, November 1997. Morbidity and Mortality Weekly Report. 1997;46(45):1061-1066.

ix Schoonjans AS, Marchau F, Paelinck BP, Lagae L, Gammaitoni A, Pringsheim M, et al. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population. Current medical research and opinion. 2017;33(10):1773-81.
[x] Lagae, L., et al., *Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial.* Lancet, 2020. 394(10216): p. 2243-2254.
[xi] Nabbout, R., et al., *Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial.* JAMA Neurol, 2019. 77(3): p. 300-8.
[xii] Devinsky, O., J.H. Cross, and S. Wright, *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.* N Engl J Med 2017;376:2011-20.
[xiii] Miller, I., et al., *Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial.* JAMA Neurol, 2020. 77(5): p. 613-621
[xiv] GW Pharma Ltd, *Epidyolex 100 mg/ml oral solution Summary of Product Characteristics.* 2019.
[xv] Knupp, K., et al., *ZX008 (Fenfluramine Hydrochloride Oral Solution) Provides Clinically Meaningful Reductions in Seizure Frequency Irrespective of Concomitant AEDs Commonly Used in Dravet Syndrome: Pooled Analysis of Two Phase 3 Trials (Poster 3.430)*, in *American Epilepsy Society (AES) Annual Meeting*. 2019: Baltimore, MD, USA.
[xvi] Gataullina, S. and O. Dulac, *From genotype to phenotype in Dravet disease.* Seizure, 2017. 44: p. 58-64.
[xvii] Dravet, C., *The core Dravet syndrome phenotype.* Epilepsia, 2011. 52 Suppl 2: p. 3-9.
xviii Chiron C, Helias M, Kaminska A, Laroche C, de Toffol B, Dulac O, Nabbout R, An I. Do children with Dravet syndrome continue to benefit from stiripentol for long through adulthood? Epilepsia. 2018 Sep;59(9):1705-1717. doi: 10.1111/epi.14536. Epub 2018 Aug 22.
[xix] National Institute for Health and Care Excellence, *Epilepsies: diagnosis and management. Clinical Guideline 137.* 2012; updated 2020.
[xx] European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. CHMP/EWP/566/98 Rev.3; 28 July 2018
[xxi] Lagae, L., et al., *Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey.* Dev Med Child Neurol, 2018. 60(1): p. 63-72
[xxii] Nilsson, L., et al., *Risk factors for sudden unexpected death in epilepsy: a case control study.* Lancet, 1999. 353(9156): p. 888-893.
[xxiii] Cooper, M.S., et al., *Mortality in Dravet syndrome.* Epilepsy Res, 2016. 128: p. 43-47.
[xxiv] Khan, K.A., et al., *Mapping EQ-5D utility scores from the PedsQL generic core scales.* Pharmacoeconomics, 2014. 32(7): p. 693-706.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fenfluramine for treating Dravet syndrome [ID1109]

Clarification questions – Addendum to responses

September 2020

File name	Version	Contains confidential information	Date
ID1109 - Fenfluramine - Request for clarification_ERG_v2.0_to company [ACIC]_RESPONSE_Addendum (09Nov)_REDACTED	**V1.2**	**Yes**	**09 Nov 2020**

Additional information following on from the previously provided responses to clarification questions (16September 2020) document; and discussions with the ERG on the 7th and 10th September 2020:

- Response and supplement information / data to Questions: C23b; C26a, C26c, C32b

Attachments:

- Please see page 2 for specific files and documents

Addendum to Responses to ERG Clarification Questions
- provided 21st September 2020

This Addendum provides the follow-on information to the original Response to ERG Clarification Questions document of 16th September 2020. It refers specifically to:

- Question C23.b
- Question C26.a
- Question C26.c
- Question C32.b

This Addendum should be read in conjunction with the original Response to ERG Clarification Questions document (16th September 2020)**.**

Attachments accompanying this Addendum:

- Bootstrapping code and dummy data
    - Code files: ENGINE- seizures bootstrapping.R, Bootstrapping_functions.R
    - Dummy dataset: dummydata.csv
- R code for scenarios provided in original response
    - All scenarios.R
    - Scenario_number.csv – Key of which scenario is which in the code for easy reference

    Note that additional dependencies are also included (Microsim function_x.R), but files that were included in the original submission have not been duplicated
- Patient and carer utility values used in DSA
    - Code to create the files: Qol_utility_files_generate.R
    - Utility files (carer): Carer_utilities_x.csv (x = 1-1000)
    - Utility files (patient): Patient_utilities_x.csv (x=1-1000)
- TECH-VERs checklist
    - TECHVER_submission.docx
- Confidentiality checklist

Section C: Clarification on cost-effectiveness data

Costs and resource use

C23. Because of reported cases of cardiac valvulopathy (and pulmonary hypertension) that may have been caused by fenfluramine at higher doses used to treat adult obesity, patients must undergo an echocardiogram (ECHO) to evaluate for regurgitant aortic or mitral valvular heart disease prior to starting treatment. Further cardiac monitoring must be performed using echocardiograms. Additional costs (Table 35 of the CS) are included in the model for echocardiograms to confirm the absence of valvular heart disease or pulmonary hypertension in line with the draft SmPC for patients on fenfluramine.

b. Please provide scenarios whereby a proportion of test results lead to additional costs and/or disutility. Please justify the estimation of this proportion.

In the base case analysis, we included an ECHO for all patients initiating and continuing fenfluramine on a 6-monthly basis in year 1 and year 2, followed by an ECHO on a 12-monthly basis thereafter.

In a follow-on analysis we have examined a scenario whereby we also include an additional cost of an ECHO for all fenfluramine recipients who discontinue treatment for any reason (excluding death). This changes the ICER marginally to £31,822/QALY (c.f. base case: £31,773/QALY), by adding an additional £45 per patient to the total costs, over the lifetime fenfluramine strategy. As mentioned in our response to question C23.a (original response to clarification questions, 16th September 2020), there would be no additional costs (aside from an ECHO), or disutility added; to those patients that might discontinue because of an abnormal ECHO (as no meaningful additional disutility is associated with an abnormal ECHO per se). The clinical, quality of life and economic implications of discontinuing treatment are however already accounted for within the SoC treatment strategy to which patient revert to, when discontinuing fenfluramine treatment.

It should be noted that the EMA has not made a final decision on the requirements for ECHO monitoring and that these assumptions are therefore in line with the draft SmPC to date.

Validation and transparency

C26. Priority question: In the model, 480 patients are simulated. However, it is not clearly stated in the CS why 480 patients were chosen.

a. **Please explain why 480 patients were chosen**.

The DISCUSS study identified 72 patients in the UK, which was estimated to be ~15% of the total Dravet syndrome population the UK (Document B, section B.1.3.11). In scaling up the identified 72 patients, the total number of Dravet syndrome patients in the UK is estimated as 480 patients. This number of patients in the model cohort therefore reflects a similar number to the total population of patients with Dravet syndrome in the UK. Furthermore, it was chosen as it provides enough profiles to remove noise generated in the model (see response to question C26.c below).

On the basis of 480 patients, each trial patient was simulated a minimum of 10 times. Care was taken to ensure a consistent simulation of patients across the starting trial profiles in both arms, i.e. the same patient (profile) was simulated in each arm. See also our response to question C26.b in our original response to clarification questions 16th September 2020.

c. **Please provide a justification for the use of only 480 simulated patients as it is unclear to the ERG whether 480 patients is enough to capture all stochastic uncertainty. Please provide diagnostics such as a figure demonstrating mean outcomes (costs, QALYs, and ICER) vs. the number of patients (i.e. visual inspection of stochastic uncertainty); and by means of a mathematical estimation**.

To confirm the stability of results using 480 patient simulations in the base case we explored if there are differences in the base case costs, QALYs and ICER generated using 2,000 patient simulations.

Using 2,000 simulated patients produced an ICER of £32,511/QALY, compared with £31,773/QALY using 480 simulated patients in our base case. The difference in costs and QALYs between 480 and 2,000 simulated patients varied by only 0.7%

(cannabidiol+clobazam+SoC strategy) and 2.6%(fenfluramine+SoC strategy) (Table 1). Given the similarity in costs, QALYs and ICER obtained using the 480 patient simulations and using 2,000 simulations, we concluded that 480 simulated patients provided a sufficient number to use in the base case model and sensitivity analyses.

Table 1. Base case model costs and QALYs using 480 simulated patients vs. 2,000 simulated patients

Technologies	Total costs (£)		% difference in total costs	Total QALYs		% difference in total QALYs
	N=480	N=2,000		N=480	N=2,000	
Cannabidiol +clobazam + SoC	255,759	253,938	0.7%	20.54	20.28	1.3%
Fenfluramine + SoC	[redacted]	[redacted]	2.6%	[redacted]	[redacted]	2.1%

It should be noted that the sensitivity analyses provided in our submission using 480 simulated patients had a run time of 1,333 computational hours (55.5 computational days), and was therefore undertaken by purchasing additional server capacity equivalent to at least 25 well-specified CPUs (computers). Although we tried to vectorise the code to improve the efficiency of the model runs, this did not decrease the run times. Conducting sensitivity analyses based around 2,000 simulated patients would therefore have more than quadrupled the run time / computational capacity required, which would not be feasible. Therefore, the use of 480 simulated patients provided a sufficient number for stable results in the base case whilst on a practical level also permitted the running of a comprehensive range of deterministic and probabilistic sensitivity analyses that would not have been possible with a greater number of simulated patients.

In order to deliver the results for the base case model, simulating 2,000 patients using internal CPUs took approximately a week to run alongside the other modelling requests. We apologise for the delay.

C32. In section 3.11.2 of the CS, it is stated that a validation of the base case results against the predicted results (e.g. comparison of mortality to mortality observed in fenfluramine registration trials, comparison of mortality to published literature) was

performed as well as an examination of internal consistency and plausibility of all results.

b. To ensure internal validity of the model, please complete the TECH-VER checklist which is a verification checklist to reduce errors in models and improve their credibility (see: *Büyükkaramikli, N. C., Rutten-van Mölken, M. P., Severens, J. L., & Al, M. (2019). TECH-VER: A verification checklist to reduce errors in models and improve their credibility. Pharmacoeconomics, 37(11), 1391-1408*) .

The TECH-VER checklist has been completed. This confirms that the modeling approach is robust, and verifies that the model performs in line with expectations.

The completed checklist accompanies this Addendum, along with the bootstrapping code, code of scenario analyses provided in response to the ERG clarification questions, and the dummy data we agreed we would provide.

Appendix O to ERG Clarification Responses

Re-run of SLR searches for Non-English Language Studies

Table 1. Clinical Evidence searches

Name of database	Search strategy	Original searches (28 June 2020)	Re-run searches for Non-English Language studies (08 Sept 2020)
• EMBASE® (via Elsevier) • MEDLINE ® (via Elsevier)	#1 'myoclonus epilepsy'/exp	6601	6656
	#2 (child OR childhood OR children OR infan*)	3798764	3847657
	#3 #1 and #2	3195	3225
	#4 “dravet syndrome”	1627	1677
	#5 “childhood epileptic encephalopathy”	50	53
	#6 “severe myoclonic epilepsy”	2282	2335
	#7 SMEI	292	295
	#8 Dravet*	2093	2152
	#9 "Dravet s syndrome"	77	80
	#10 “childhood epileptic encephalopathies”	32	32
	#11 “childhood epilepsy encephalopathies”	0	0
	#12 “childhood epilepsy encephalopathy”	0	0
	#13 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	5637	5745
	#14 random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	1798270	1827292
	#15 #13 AND #14	360	374
	#16 'animal'/exp NOT 'human'/exp	5449189	5487387
	#17 #15 NOT #16	354	367
	#18 #15 NOT #16 AND [english]/lim	**335**	**#18 NOT [english]/lim: 19**
Name of database	**Search strategy**	**Original searches (28 June 2020)**	**Re-run searches for Non-English Language studies (04 Sept 2020)***
• PubMed	#1 “Epilepsies, Myoclonic”[Mesh]	4627	4720
	#2 (child OR childhood OR children OR infan*)	3225849	3257427
	#3 #1 AND #2	2256	2283
	#4 “dravet syndrome”	940	970
	#5 “childhood epileptic encephalopathy”	30	31

	#6	“severe myoclonic epilepsy”	368	369
	#7	SMEI	171	173
	#8	Dravet*	1254	1286
	#9	"dravet's syndrome"	38	38
	#10	“childhood epileptic encephalopathies”	17	17
	#11	“childhood epilepsy encephalopathies”	6506	6588
	#12	“childhood epilepsy encephalopathy”	6506	6588
	#13 OR #12	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	9067	9188
	#14	randomized controlled trial [pt]	509383	513442
	#15	controlled clinical trial [pt]	596182	602412
	#16	randomized [tiab]	523366	531973
	#17	placebo [tiab]	214300	216283
	#18	clinical trials as topic [mesh: noexp]	341863	345436
	#19	randomly [tiab]	335824	340410
	#20	trial [ti]	219812	223831
	#21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	1378631	1394794
	#22	#13 AND #21	428	437
	#23	animals [mh] NOT humans [mh]	4712175	4731720
	#24	#22 NOT #23	427	436
	#25	English[lang]	26448823	26730168
	#26	#24 AND #25	**396**	**#24 NOT #25: 32**
• CENTRAL (via Cochrane library)			**167**	
• Cochrane Database of Systematic Reviews (via Cochrane library)	#1 #2 #3 #4 #5 #6	Epilepsies, Myoclonic[MeSH] severe myoclonic epilepsies: TI, AB,KY SMEI: TI, AB, KY Dravet: TI, AB, KY Dravet’s: TI,AB.KY #1 OR #2 OR #3 OR #4 OR #5	**37**	
*** Note: PubMed interface has changed since original searches were conducted end June/beginning July. Different number of hits for the re-run of searches may be due to both the later data of searches and the interface changes.**				

Table 2. Non-English Language Clinical Studies hit by searches

Non-English Language Clinical studies - Embase					
Authors	Title (translated)	Journal	Year	Volume	pg
Schulze-Bonhage A.	Orphan drugs in epileptology	Zeitschrift fur Epileptologie (2019) 32:4 (277-285). Date of Publication: 1 Nov 2019			
Klotz K.A.	Cannabinoids as orphan drugs	Zeitschrift fur Epileptologie (2019) 32:4 (286-291). Date of Publication: 1 Nov 2019			
Bast T.	Treatment of epilepsy in children and adolescents	Zeitschrift fur Epileptologie (2013) 26:3 (134-141). Date of Publication: August 2013			
Pezzella M., Errichiello L., Santulli L., Giudizioso G., Ferrari A., Prato G., Vari S., Mancardi M.M., Baglietto M.G., Striano S., Mainardi P., Striano P.	A pilot randomized, double-blind, placebo-controlled, cross-over trial of the whey protein alfa-lactoalbumin in chronic cortical myoclonus	Bollettino - Lega Italiana contro l'Epilessia (2012) :144 (125-127). Date of Publication: May 2012			
Arnold S., Kluger G.	News from the pharmacotherapy: Lacosamide, eslicarbazepinacetate, rufinamide, stiripentol	Nervenheilkunde (2010) 29:4 (191-198). Date of Publication: 2010			
Fröscher W.	Antiepileptic drug withdrawal - Why, when, how?	Nervenheilkunde (2010) 29:4 (204-208). Date of Publication: 2010			
Jaffré I., Bordes V., Dejode M., Dravet F., Classe J.-M.	Management of retroperitoneal lymphadenectomy in advanced epithelial ovarian cancer	Bulletin du Cancer (2010) 97:1 (65-71). Date of Publication: January 2010			
Janszky J.	Role of zonisamid in treating epilepsy, Parkinson disorders and other neurological diseases	Ideggyogyaszati Szemle (2009) 62:11-12 (383-389). Date of Publication: 30 Nov 2009			
Porta N., Vallée L., Boutry E., Auvin S.	The ketogenic diet and its variants: State of the art	Revue Neurologique (2009) 165:5 (430-439). Date of Publication: May 2009			
Schweizer S., Kuhn K.	Stiripentol (Diacomit®) - A new option in the treatment of Dravet syndrome (SMEI)	Zeitschrift fur Epileptologie (2008) 21:3 (135-141). Date of Publication: 2008			
Classe J.-M., Catala L., Marchal F., Ferron G., Dravet F., Pioud R., Descamps P.	Locoregional recurrence after ovarian cancer: Place of surgery	Bulletin du Cancer (2004) 91:11 (827-832). Date of Publication: November 2004			
Campos-Castellé J., Viñas J.M.P., García-Ribes A.	Idiopathic epilepsies: Some therapeutic aspects	Revista de Neurologia (2004) 38:2 (180-184). Date of Publication: 16 Jan 2004			
Nguyen Thanh T., Chiron C., Dellatolas G., Rey E., Pons G., Vincent J., Dulac O.	Long term efficacy and tolerance of stiripentol in severe myoclonic epilepsy of infancy (Dravet's syndrome)	Archives de Pediatrie (2002) 9:11 (1120-1127). Date of Publication: 1 Nov 2002			
Nieto-Barrera M.	Characteristics and indications of topiramate	Revista de Neurologia (2002) 35:SUPPL. 1 (S88-S95). Date of Publication: September 2002			
Poyen V., Labrunie P., Haddad V., Dravet F., Valeix B.	Primary angioplasty associated with systemic coronary stenting in acute myocardial infarction. Results at the end of the hospitalization period and at 24 months	Archives des maladies du coeur et des vaisseaux (2001) 94:3 (183-189). Date of Publication: Mar 2001			
Cenraud B., Chedru F., Cler J.-M., Cohadon S., Duhurt J., Feuerstein J., Garrel S., Gil R., Jallon P., Jogeix M., Latinville	Valproic acid or carbamazepine monotherapy in partial epilepsy	Epilepsies (1990) 2:1 (11-19). Date of Publication: 1990			

D., Legroux M., Loiseau P., Mauguiere F., Maupetit, Pasquier C., Remy C., Roger J., Dravet C.					
Bureau M., Guerrini R., Vigliano P., Dravet C.	Contribution of ambulatory EEG (A/EEG) in patients with epilepsy	Neurophysiologie Clinique (1989) 19:3 (219-230). Date of Publication: 1989			
Lund M., Reintoft H., Simonsen N.	Controlled sociologic and psychologic investigation of patients with juvenile myoclonus epilepsy	Nervenarzt (1976). Date of Publication: 1976			
Weinmann H.M., Willms E.	Experince of the effect of clonazepam as anticonvulsant in various forms of epilepsy	Acta Neurologica Scandinavica (1973) 47:53 Sup. (124-132). Date of Publication: 1973			
Non-English Language Clinical studies - PubMed					
Authors	Title (tanslated)	Journal	Year	Volume	pg
	[Topiramat in childhood epilepsy. A growing indication spectrum in everyday clinical practice. 2nd Congress of the European Pediatric Neurology Society, Maastrich, 9 October 1997]. Klinische Padiatrie	Klinische Padiatrie	1998	210	
Basnec, A.; Skarpa, D.; Barisić, N.; Jurin, M.; Mucić-Pucić, B.	[The risk of second seizure in children with benign childhood epilepsy with centrotemporal spikes without treatment--a prospective study]	Acta medica Croatica : casopis Hravatske akademije medicinskih znanosti	2005	59	59-62
Classe, J. M.; Catala, L.; Marchal, F.; Ferron, G.; Dravet, F.; Pioud, R.; Descamps, P.	[Locoregional recurrence of ovarian cancer: the place of surgery]	Bulletin du cancer	2004	91	827-32
Curatolo, P.; Bruni, O.; Brindesi, I.; Pruna, D.; Cusmai, R.	[Flunarizine in drug-resistant epilepsies of childhood and adolescence]	Rivista di neurologia	1986	56	25-38
Dai, J.; Han, L.; Wang, L.; Zhang, L. L.	[Levetiracetam therapy for childhood epilepsy: a systematic review]	Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics	2010	12	128-31
Dongier, M.; Dongier, S.; Gastaut, H.; Roger, J.	[Trial of a new anti-epileptic drug (PM 671, alpha-ethyl-alpha-methyl-succinimide) in children]	Revue neurologique	1961	104	441-6
Fanuele, G.; Rossi, U.	[Therapy of epilepsy in childhood. Clinical testing of a new combination of drugs]	La Pediatria	1969	77	189-216
Fröscher, W.; Eichelbaum, M.; Hildenbrand, G.; Hildenbrand, K.; Penin, H.	[Prospective studies on epilepsy therapy with carbamazepine]	Fortschritte der Neurologie-Psychiatrie	1982	50	396-408
Garcia-Penas, J. J.	[Autism spectrum disorder and epilepsy: the role of ketogenic diet]	Revista de neurologia	2016	62 Suppl 1	S73-8
Garzon, P.; Lemelle, L.; Auvin, S.	[Childhood absence epilepsy: An update]	Archives de pediatrie : organe officiel de la Societe francaise de pediatrie	2016	23	1176-1183
Hallfahrt, T.	[FLIP&FLAP educational program in epilepsy in childhood and adolescence]	Kinderkrankenschwester : Organ der Sektion Kinderkrankenpflege	2007	26	516-21

Huang, T. S.; Zhu, J. L.; Li, B.; Hu, Y.; Chen, L.; Liao, J. X.	[Valproic acid versus lamotrigine as a monotherapy for absence epilepsy in children]	Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics	2009	11	653-5
Ito, S.; Oguni, H.	[Ketogenic diet for intractable childhood epilepsy; as an early option as well as a last resort]	Brain and nerve = Shinkei kenkyu no shinpo	2011	63	393-400
Jaffré, I.; Bordes, V.; Dejode, M.; Dravet, F.; Classe, J. M.	[Management of retroperitoneal lymphadenectomy in advanced epithelial ovarian cancer]	Bulletin du cancer	2010	97	65-71
Janszky, J.	[Role of zonisamid in treating epilepsy, Parkinson disorders and other neurological diseases]	Ideggyogyaszati szemle	2009	62	383-9
Kaminska, A.	[New antiepileptic drugs in childhood epilepsies: indications and limits]	Epileptic disorders : international epilepsy journal with videotape	2001	3 Spec No 2	Si37-46
Kaminska, A.	[Eligibility for epilepsy surgery in children: review of the literature]	Revue neurologique	2004	160 Spec No 1	5s220-31
Knudsen, F. U.	[Febrile convulsions, Treatment and prognosis]	Ugeskrift for laeger	2001	163	1098-102
Loubier, D.; Dravet, C.; Soulayrol, R.	[Preliminary note of a therapeutical trial: thioridazine in epileptic children]	Revue de neuropsychiatrie infantile et d'hygiene mentale de l'enfance	1973	21	559-64
Mauri-Llerda, J. A.; Tejero-Juste, C.; Iñiguez, C.; Morales-Asín, F.	[Use of lamotrigine in the treatment of absence epilepsy crises]	Revista de neurologia	2001	32	247-50
Miranda, M. J.; Ahmad, B. B.	[Treatment of rolandic epilepsy]	Ugeskrift for laeger	2017	179	
Nagayama, T.; Takeshita, K.; Kurakawa, T.	[Treatment of personality and behavior disorders in childhood epilepsy with Neuleptil]	No to shinkei = Brain and nerve	1967	19	935-40
Nieto-Barrera, M.	[Characteristics and indications of topiramate]	Revista de neurologia	2002	35 Suppl 1	S88-95
Ohtsuka, Y.	[New antiepileptic drugs: characteristics and clinical applications]	Nihon rinsho. Japanese journal of clinical medicine	2014	72	931-8
Raffo, E.	[Long-term therapy in childhood epilepsy]	Revue neurologique	2004	160 Spec No 1	5s272-9
Rett, A.	[2 year experience of clonazepam in childhood cerebral spasm seizures]	Acta neurologica Scandinavica. Supplementum	1973	53	109-1
Schroll, M.; Naestoft, J.; Lund, M.	[Treatment of pyknoleptic petit mal epilepsy and juvenile myoclonic epilepsy with dipropyl acetate (Deprakine). A pilot study of therapy-resistant patients during control of plasma concentration]	Ugeskrift for laeger	1977	139	1073-7
Takeshita, K.; Kurokawa, T.	[S-500 (nitrazepam) in the treatment of myoclonic seizures of infancy and childhood]	No to shinkei = Brain and nerve	1968	20	1303-9
Thanh, T. N.; Chiron, C.; Dellatolas, G.; Rey, E.; Pons, G.; Vincent, J.; Dulac, O.	[Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome)]	Archives de pediatrie : organe officiel de la Societe francaise de pediatrie	2002	9	1120-7

Tich, S. N.; Péréon, Y.	[Cognitive impairment in childhood epilepsy: the role of antiepileptic drugs]	Epileptic disorders : international epilepsy journal with videotape	2001	3 Spec No 2	Si87-93
Willig, R. P.; Lagenstein, I.	[Therapeutic trial with a fragment of ACTH (ACTH 4-10) in early childhood epilepsy (author's transl)]	Monatsschrift fur Kinderheilkunde	1980	128	100-3
Yoo, H.; Kim, H. S.	[Development and evaluation of the Empowering A Self-Efficacy (EASE) program for children with epilepsy]	Journal of Korean Academy of Nursing	2015	45	54-63

Table 3. Economic evaluation searches / Health care resource use and costs searches

Name of database	Search strategy	Original searches (29 June 2020)	Re-run searches for Non-English Language studies (08 Sept 2020)*
• EMBASE® (via Elsevier) • MEDLINE ® (via Elsevier)	#1 'myoclonus epilepsy'/exp	6601	6656
	#2 child OR childhood OR children OR infan*	3798764	3847657
	#3 #1 AND #2	3195	3225
	#4 'dravet syndrome'	1627	1677
	#5 'childhood epileptic encephalopathy'	50	53
	#6 'severe myoclonic epilepsy'	2282	2335
	#7 SMEI	292	295
	#8 dravet*	2093	2152
	#9 'dravet s syndrome'	77	80
	#10 'childhood epileptic encephalopathies'	32	32
	#11 'childhood epilepsy encephalopathies'	0	0
	#12 'childhood epilepsy encephalopathy'	0	0
	#13 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	5637	5745
	#14 'economics'/de	239327	240325
	#15 'cost'/exp	351682	355131
	#16 'health economics'/exp	861173	870489
	#17 'pharmacoeconomics'/exp	206307	207936
	#18 'fee'/exp	41757	41982
	#19 'budget'/exp	28944	29213
	#20 (budgets:ti,ab OR economic*:ti,ab OR costs:ti,ab OR costly:ti,ab OR costing:ti,ab OR price:ti,ab OR prices:ti,ab OR pricing:ti,ab OR pharmacoeconomic*:ti,ab OR 'pharmaco	97371	99470

	economic*':ti,ab OR expenditure:ti,ab OR expenditures:ti,ab OR expense:ti,ab OR expenses:ti,ab OR financial:ti,ab OR finance:ti,ab OR finances:ti,ab OR financed:ti,ab OR 'value for money':ti,ab OR monetary) AND value*:ti,ab		
	#21 'economic model'/exp	2125	2194
	#22 economic AND model*:ti,ab	70421	72195
	#23 'markov chain'/exp	8988	9437
	#24 'monte carlo method'/exp	40161	40892
	#25 'decision theory'/exp	1722	1734
	#26 ((decision AND tree*:ti,ab OR decision) AND analy*;ti,ab OR decision) AND model*:ti,ab	101956	104682
	#27 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1262642	1278781
	#28 productivity:ti,ab OR 'resource use':ti,ab OR 'resource utilization':ti,ab OR 'cost of illness':ti,ab OR burden:ti,ab	394060	404106
	#29 #27 OR #28	1585418	1610094
	#30 #13 AND #29	206	214
	#31 #13 AND #29 AND [english]/lim	**197**	**#30 NOT [english]/lim 9**
• **Name of database**	**Search strategy**	**Original searches (29 June 2020)**	**Re-run searches for Non-English Language studies (08 Sept 2020)***
• PubMed	#1 “Epilepsies, Myoclonic”[Mesh]	4,672	4720
	#2 (child OR childhood OR children OR infan*)	3225849	3258139
	#3 #1 and #2	2,256	2283
	#4 “dravet syndrome”	940	970
	#5 “childhood epileptic encephalopathy”	30	31
	#6 “severe myoclonic epilepsy”	368	369
	#7 SMEI	171	173
	#8 Dravet*	1,254	1286
	#9 "dravet's syndrome"	38	38
	#10 “childhood epileptic encephalopathies”	17	17
	#11 “childhood epilepsy encephalopathies”	6,506	6589
	#12 “childhood epilepsy encephalopathy”	6,506	6589
	#13 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	9,067	9189
	#14 Economics[Mesh:NoExp] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab]	1153535	1172320

	OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab]		
	#15 (productivity[tiab] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "cost of illness"[tiab] OR burden[tiab])	267980	275043
	#16 #14 OR #15	1346785	1370822
	#17 #13 AND #16	256	262
	#18 English[lang]	26448823	26736885
	#19 #17 AND #18	**240**	**#17 NOT #18: 16**
NHS EED	#1 severe myoclonic: Any field	**1**	
HTA Database	#2 Dravet syndrome: Any field #3 Dravet: Any field #4 #1 OR #2 OR #3	**5**	

Table 4. Non-English Language Economic evaluation / Health care resource use and costs studies hit by searches

Non-English Language Economic evaluation / health care resource use and costs studies – Embase®					
Authors	Title (translated)	Journal	Year	Volume	pg
Kalski M., Schubert-Bast S., Kieslich M., Leyer A.-C., Polster T., Herting A., Mayer T., Trollmann R., Neubauer B.A., Bettendorf U., Bast T., Wiemer-Kruel A., von Spiczak S., Kurlemann G., Wolff M., Kluger G., Carroll J., Macdonald D., Pritchard C., Irwin J., Klein K.M., Rosenow F., Strzelczyk A., Kay L.	Clinical characteristics, resource utilization, quality of life and care situation for patients with Dravet syndrome in Germany	Zeitschrift fur Epileptologie (2019) 32:4 (326-338). Date of Publication: 1 Nov 2019			

Rasche T., Emmert D., Stieber C., Conrad R., Mücke M.	Cannabis and cannabinoids—easier access, hype and disappointment: What has been confirmed in therapy?	Internist (2019) 60:3 (309-314). Date of Publication: 1 Mar 2019			
Forest C., Fiumana E., Faggioli R., Suppiej A., Maggiore G.	Cannabis and epilepsy: Myth or reality?	Medico e Bambino (2019) 38:5 (303-309). Date of Publication: 2019			
Umeno J.	A survey on the utilization status of social welfare services for pediatric patients with epilepsy	No To Hattatsu (2019) 51:4 (234-239). Date of Publication: 2019			
Ohtsuka Y.	[New antiepileptic drugs: characteristics and clinical applications].	Nihon rinsho. Japanese journal of clinical medicine (2014) 72:5 (931-938). Date of Publication: May 2014			
Bast T.	Antiepileptics in children: An update	Monatsschrift fur Kinderheilkunde (2011) 159:8 (721-731). Date of Publication: August 2011			
Cappanera S., Passamonti C., Petrelli C., Zamponi N.	Vagal nerve stimulation in dravet syndrome	Bollettino - Lega Italiana contro l'Epilessia (2011) :142 (25-31). Date of Publication: April 2011			
Steinhoff B.J.	Rufinamide and stiripentol - Two new anticonvulsants and the first orphan drug approvals in epilepsy therapy	Zeitschrift fur Epileptologie (2008) 21:3 (120-122). Date of Publication: 2008			
Schweizer S., Kuhn K.	Stiripentol (Diacomit®) - A new option in the treatment of Dravet syndrome (SMEI)	Zeitschrift fur Epileptologie (2008) 21:3 (135-141). Date of Publication: 2008			
Non-English Language Economic evaluation / health care resource use and costs studies - PubMed					
Authors	Title (translated)	Journal	Year	Volume	pg
Aicardi, J.	[The role of new antiepileptic drugs in childhood epilepsies]	Revista de neurologia	1998	27	301-5
Argumosa, A.; Herranz, J. L.	[Economic costs of childhood epilepsy in Spain]	Revista de neurologia	2000	30	104-8
Auxéméry, Y.; Hubsch, C.; Fidelle, G.	[Psychogenic non epileptic seizures: a review]	L'Encephale	2011	37	153-8
Campos-Castelló, J.	[Role of generic antiepileptic drugs in the treatment of childhood epilepsy]	Medicina	2009	69	109-13
Caraballo, R.; Trípoli, J.; Escobal, L.; Cersósimo, R.; Tenembaum, S.; Palacios, C.; Fejerman, N.	[Ketogenic diet: efficacy and tolerability in childhood intractable epilepsy]	Revista de neurologia	1998	26	61-4
Dánová, J.; Göpfertová, D.; Príkazský, V.; Bobák, M.	[Failures to comply with the routine childhood immunization schedule due to contraindications and the use of alternative vaccines in children aged 0-4 years in the Czech Republic]	Epidemiologie, mikrobiologie, imunologie : casopis Spolecnosti pro epidemiologii a mikrobiologii Ceske lekarske spolecnosti J.E. Purkyne	2007	56	33-7
Devilat, M.; Chamorro, R.; Erazo, R.; Germain, L.; Mena, F.; Valenzuela, B.	[Juvenile myoclonic epilepsy. Life difficulties and response to treatment]	Revista chilena de pediatria	1990	61	99-102

Guihard, P.; Dravet, F.; Ricaud-Couprie, M.; Doutriaux-Dumoulin, I.; Classe, J. M.	[Surgical management of non-palpable breast lesions in ambulatory care]	Journal de gynecologie, obstetrique et biologie de la reproduction	1999	28	330-4
Herranz, J. L.; Argumosa, A.	[Prognosis of epilepsy and withdrawal of treatment: withdrawal of treatment in childhood and adolescents]	Revista de neurologia	2000	30	351-5
Karwautz, A.; Wöber-Bingöl, C.; Wöber, C.	[Idiopathic headache in childhood and adolescence]	Der Nervenarzt	1993	64	753-65
Lebon, S.; Campos-Xavier, B.; Bonafé, L.; Roulet-Perez, E.	[Genetics of childhood epilepsies: for who? how? why?]	Revue medicale suisse	2014	10	110-1
Mochizuki, Y.; Takeuchi, C.; Osako, M.; Minatogawa, M.; Shibata, N.	[Investigation of transition from pediatric to adult health care for patients with special health-care needs for neurological disease dating from childhood]	Rinsho shinkeigaku = Clinical neurology	2019	59	279-281
Rufo-Campos, M.	[Partial seizures in childhood]	Revista de neurologia	2001	32	962-9
Shapira, Y.; Sapir, S.; Amir, E.	[Management of the pediatric dental patient with seizure disorder: prevention and treatment of emergencies]	Refu'at ha-peh veha-shinayim (1993)	2003	20	6-10, 86
Weber, Y. G.; Lerche, H.	[Genetics of idiopathic epilepsies]	Der Nervenarzt	2013	84	151-6
Zubcević, S.; Gavranović, M.; Catibusić, F.; Uzicanin, S.; Buljina, A.	[Vigabatrin in childhood epilepsy--personal experience]	Medicinski arhiv	1999	53	63-5

Table 5. Health-related quality of life / utility searches

Name of database	Search strategy		Original searches (03 July 2020)	Re-run searches for Non-English Language studies (08 Sept 2020)
• EMBASE® (via Elsevier) • MEDLINE ® (via Elsevier)	#1	'myoclonus epilepsy'/exp	6604	6656
	#2	child OR childhood OR children OR infan*	3803079	3847657
	#3	#1 AND #2	3197	3225
	#4	'dravet syndrome'	1631	1677
	#5	'childhood epileptic encephalopathy'	50	53
	#6	'severe myoclonic epilepsy'	2284	2335

#7	SMEI	292	295
#8	dravet*	2097	2152
#9	'dravet s syndrome'	77	80
#10	'childhood epileptic encephalopathies'	32	32
#11	'childhood epilepsy encephalopathies'	0	0
#12	'childhood epilepsy encephalopathy'	0	0
#13 OR #12	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	5643	5745
#14	('socioeconomics'/exp OR 'quality of life'/exp OR 'quality of life':ti,ab OR 'quality adjusted life year'/exp OR 'quality adjusted life':ti,ab OR qaly*:ti,ab OR qald*:ti,ab OR qale*:ti,ab OR qtime*:ti,ab OR 'life year':ti,ab OR 'life years':ti,ab OR 'disability adjusted life':ti,ab OR daly*:ti,ab OR sf36:ti,ab OR sf) AND 36:ti,ab OR 'short form 36':ti,ab OR 'shortform 36':ti,ab OR 'short form36':ti,ab OR 'shortform36':ti,ab OR sf6:ti,ab OR 'sf 6':ti,ab OR 'short form 6':ti,ab OR sf6d:ti,ab OR 'sf 6d':ti,ab OR 'short form 6d':ti,ab OR sf8:ti,ab OR 'sf 8':ti,ab OR 'short form 8':ti,ab OR sf12:ti,ab OR 'sf 12':ti,ab OR 'short form 12':ti,ab OR sf16:ti,ab OR 'sf 16':ti,ab OR sf20:ti,ab OR 'sf 20':ti,ab OR 'short form 20':ti,ab OR hql:ti,ab OR hqol:ti,ab OR 'h qol':ti,ab OR hrqol:ti,ab OR 'hr qol':ti,ab OR hye:ti,ab OR hyes:ti,ab OR 'healthy year equivalent':ti,ab OR 'healthy years equivalent':ti,ab OR pqol:ti,ab OR qls:ti,ab OR 'quality of well being':ti,ab OR 'index of wellbeing':ti,ab OR qwb:ti,ab OR 'nottingham health profile':ti,ab OR 'sickness impact profile':ti,ab OR 'health status indicator'/exp OR 'health utility':ti,ab OR 'health utilities':ti,ab OR 'health status':ti,ab OR disutilit*:ti,ab OR rosser:ti,ab OR 'willingness to pay':ti,ab OR 'standard gamble':ti,ab OR 'time trade off':ti,ab OR 'time tradeoff':ti,ab OR tto:ti,ab OR hui:ti,ab OR hui1:ti,ab OR hui2:ti,ab OR hui3:ti,ab OR eq:ti,ab OR euroqol:ti,ab OR 'euro qol':ti,ab OR eq5d:ti,ab OR 'eq 5d':ti,ab OR euroqual:ti,ab OR 'euro qual':ti,ab OR 'duke health profile':ti,ab OR 'functional status questionnaire':ti,ab OR 'dartmouth coop functional health assessment':ti,ab OR (utilit*:ti,ab AND (valu*:ti,ab OR measur*:ti,ab OR health:ti,ab OR life:ti,ab OR estimat*:ti,ab OR elicit*:ti,ab OR disease:ti,ab OR score*:ti,ab OR weight:ti,ab)) OR (preference*:ti,ab AND (valu*:ti,ab OR measur*:ti,ab OR health:ti,ab OR life:ti,ab OR estimat*:ti,ab OR elicit*:ti,ab OR disease:ti,ab OR score*:ti,ab OR instrument:ti,ab OR instruments:ti,ab))	496909	510686
#15	#13 AND #14	73	75
#16	#13 AND #14 AND [english]/lim	**71**	**#15 NOT [english]/lim: 2**

Table 6. Non-English Language health-related quality of life studies hit by searches

Non-English Language Economic evaluation studies – Embase®					
Authors	Title (translated)	Journal	Year	Volume	pg
Dejode M., Bordes V., Jaffré I., Classe J.-M., Dravet F.	Oncologic, functional, and aesthetics results; evaluation of the quality of life after latissimus dorsi flap breast reconstruction. About a retrospective series of 450 patients	Annales de Chirurgie Plastique et Esthetique (2011) 56:3 (207-215). Date of Publication: June 2011			
Soulayrol R., Robaglia L., Dravet C., Roger J.	Treatment of epilepsy in children	CAH.MED. (1973) 14 (703-710). Date of Publication: 1973			

Table 7. EPNS 2019 abstracts referring to Dravet syndrome

Abstract	**Conclusions on relevance**
Lagae L et al. Efficacy and safety of Fenfluramine HCl oral solution in the treatment of Dravet Syndrome: pooled analysis of two Phase 3 clinical studies. Abstract OC004	Potentially meets the inclusion criteria of the clinical SLR; however, these data were already captured in our original searches (see Table 4 of Appendix D).
Brunklaus A et al. Death in SCN1A positive Dravet Syndrome – Findings from a 10-year follow-up of 141 cases. Abstract OC041	This study would not have met the inclusion criteria of any of our SLRs.
Brunklaus A et al. A novel tool to predict phenotype from genotype in SCN1A-related Epilepsies. Abstract OC100	This study would not have met the inclusion criteria of any of our SLRs.
Schoonjans AS, et al. Therapeutic drug monitoring of Fenfluramine and its metabolite Norfenfluramine in patients with Dravet Syndrome. Abstract P02-07	This study would not have met the inclusion criteria of any of our SLRs.
De Liso P, et al. Fatal Status Epilepticus in Dravet Syndrome: an acute Encephalopathy triggered by fever. Abstract P02-27	This study would not have met the inclusion criteria of any of our SLRs.
Ceulemans B, et al. Fenfluramine HCl oral solution provides long-term, clinically meaningful (≥50%) reduction in seizure frequency in Dravet Syndrome: interim analysis of a long-term open-label extension study. Abstract P04-03	Potentially meets the inclusion criteria of the clinical SLR; however, these data were already captured in our original searches (see Table 4 of Appendix D).
Ozturk Thomas G, et al. Ketogenic diet experience of our clinic in Epileptic Encephalopathy patients. Abstract P04-12	This study would not have met the inclusion criteria of any of our SLRs.
Perullli M et al. Potassium Bromide in Dravet Syndrome and Lennox-Gastaut Syndrome: an underutilized option? Abstract P04-21	This study would not have met the inclusion criteria of any of our SLRs.
Schoeler N, et al. Use of a medium chain Triglyceride-based food for special medical purposes in children with Epilepsy: compliance, tolerability and acceptability. Abstract P04-23	This study would not have met the inclusion criteria of any of our SLRs.
Critchley D, et al. Two phase 1 healthy volunteer trials investigating the potential effects of CYP3A4 and CYP2C19 inhibition or induction on Cannabidiol (CBD) Pharmacokinetics. Abstract P08-12	This study would not have met the inclusion criteria of any of our SLRs.
Prpic I. et al. DAT Questionnaire – Early detection of disorders associated with Dravet Syndrome (DS). Abstract P08-37	This study would not have met the inclusion criteria of any of our SLRs.

Table 8. NHS EED and HTA database searches (via CRD database interface available at: https://www.crd.york.ac.uk/CRDWeb/)

Additional MeSH search: Epilepsies, Myoclonic			**Existing Free-text searches [any field]: Severe myoclonic OR Dravet syndrome OR Dravet**	
NHS EED hits	**HTA data base hits**	**Relevance**	**NHS EED hits**	**HTA data base hits**
0	Mengarelli C, et al. [Stiripentol for the treatment of severe myoclonic epilepsy in infants (dravet's syndrome)] Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS). Documentos de Evaluación de Tecnologías Sanitarias, Informe de Respuesta Rapida No 522. 2017	Argentinian, Non-English language – was captured in existing searches and would be excluded from SLR upon screening	Heaney D C, et al. Cost minimization analysis of antiepileptic drugs in newly diagnosed epilepsy in 12 European countries. Epilepsia 2000; 41(Supplement 5): S37-S44	Mengarelli C, et al. [Stiripentol for the treatment of severe myoclonic epilepsy in infants (dravet's syndrome)] Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS). Documentos de Evaluación de Tecnologías Sanitarias, Informe de Respuesta Rapida No 522. 2017
	NIHR HSRIC. Fenfluramine for Dravet syndrome – first line. Birmingham: NIHR Horizon Scanning Research & Intelligence Centre. Horizon Scanning Review. 2016	Horizon scanning document – relates to first-line use – was captured in existing searches and would be excluded from SLR upon screening		NIHR HSRIC. Fenfluramine for Dravet syndrome – first line. Birmingham: NIHR Horizon Scanning Research & Intelligence Centre. Horizon Scanning Review. 2016
	Dentatorubral-Pallidoluysian Atrophy (DRPLA) Lansdale: HAYES, Inc.. Genetic Testing Publication. 2011	Not Dravet syndrome – additional hit not captured in existing searches but would be excluded from SLR upon screening		CADTH. Stiripentol (Diacomit — Biocodex SA) indication: severe myoclonic epilepsy in infancy (Dravet syndrome) Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). CDEC Final Recommendation; SR0360. 2014
	All Wales Medicines Strategy Group (AWMSG). Stiripentol (Diacomit®) for use in conjunction with clobazam and valproate in patients with severe myoclonic epilepsy in infancy. Penarth: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG). AWMSG Secretariat Assessment Report Advice No. 1608. 2008	Was captured in existing searches		All Wales Medicines Strategy Group (AWMSG). Stiripentol (Diacomit®) for use in conjunction with clobazam and valproate in patients with severe myoclonic epilepsy in infancy. Penarth: All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG). AWMSG Secretariat Assessment Report Advice No. 1608. 2008

				Generalized Epilepsy with Febrile Seizures Plus (GEFS+) Lansdale: HAYES, Inc.. Genetic Testing Publication. 2011

Figure 1. PRISMA flow diagram for the Economic evaluation SLR

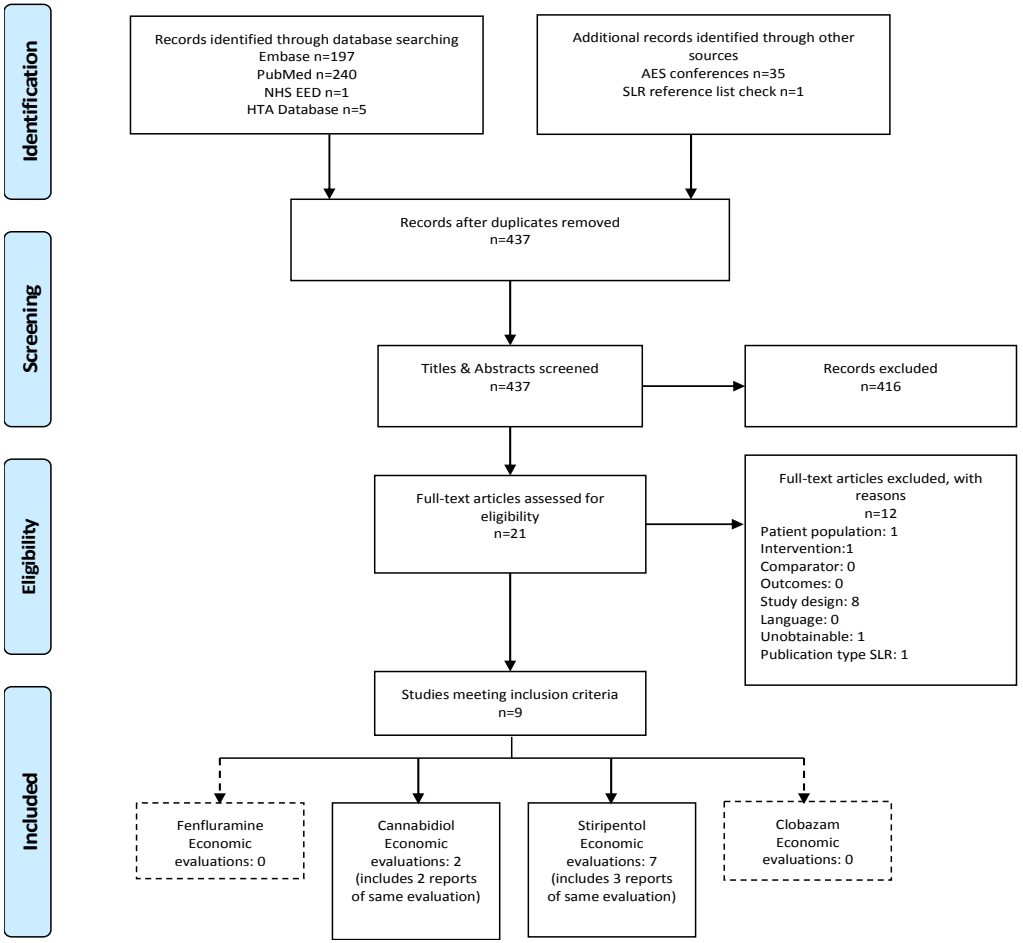
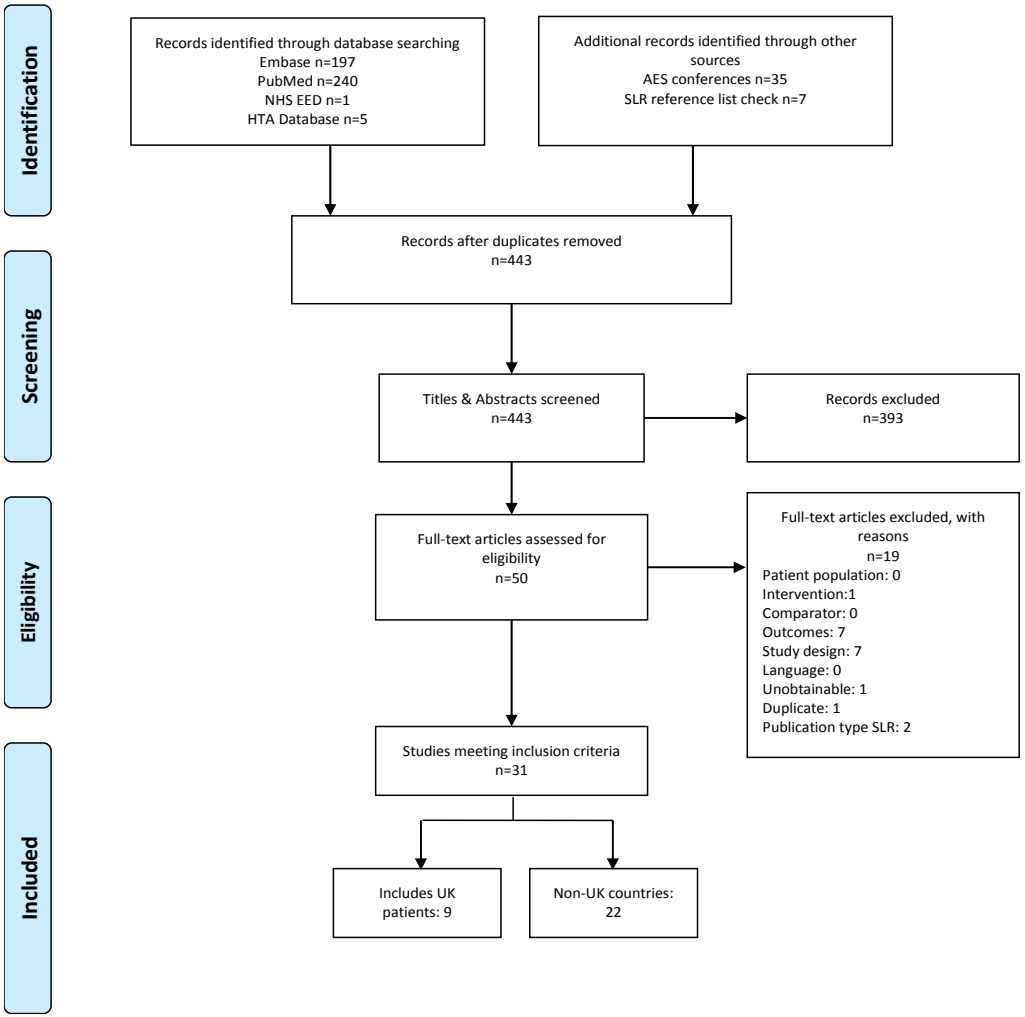


Figure 2. PRISMA flow diagram for the healthcare resource use and costs SLR



Estimation of proportion of patients in eligible for 1L fenfluramine when clobazam or a clobazam-based regimen is not desired

In the DISCUSS study, 58% of UK patients were currently receiving STP, and 11% had taken STP previously (data on file; related ref. No. 7 Pagano et al. 2019). On this basis, and in using STP as an indicator for a commonly first used '1st line add on therapy', >69% of patients would not be on their 1st line AEDs as they were either on or had received STP in the past (Figure 3).

However, it is not possible from these data (as treatments are not mutually exclusive), to fully identify the proportion of the <31% of patients that are receiving 1st line AEDs only and that are considered stable Vs. those that would be looking for a new add on therapy that may not be STP (i.e. CBD+CLB or FINTEPLA); or on a clinical trial. This is further challenged when considering the varied treatment goals desired for the patient, as well as the eligibility requirements and appetite for STP, CBD+CLB or FINTEPLA, as an offering for a new add on therapy.

In the DISCUSS study,74% of patients were receiving clobazam. A further 7% had previously tried clobazam and were no longer receiving it (Figure 3). Therefore, a total of 81% of UK patients have experienced CLB and 19% of patients had not tried clobazam yet (some of which may not have a desire to start it). [redacted] of the total Dravet syndrome patients may reasonably be expected to sit within the total "clobazam not desired" part of the schematic below. An estimated [redacted] of these patients would be anticipated to receive FINTEPLA by year 2024 onwards (ID1109_FINTEPLA_BIM_ FINAL_CIC (Aug 2020).

This would inform the basis of SoC in the total clobazam undesirable population. Depending on the chosen comparative analysis perspective, the remaining [redacted] of the total Dravet syndrome population could be relatively allocated to their various 1st line AEDs and 'add on therapy to AEDs' line positions, with >69% of the total Dravet syndrome population being considered to have SoC consistent with the presented FFA Vs CBD+CLB proposition.

Figure 3 Estimated percentage distribution of UK patients by line of therapy based on the DISCUSS study

NICE National Institute for Health and Care Excellence

Patient organisation submission

Fenfluramine for treating Dravet syndrome [ID1109]

About you	
1.Your name	[redacted]
2. Name of organisation	Dravet Syndrome UK
3. Job title or position	[redacted], DSUK
4a. Brief description of the organisation (including who funds it). How many members does it have?	Dravet Syndrome UK (DSUK) was registered with the Charity Commission of England and Wales in January 2009. DSUK is an independent UK charity dedicated to improving the lives of those affected by Dravet Syndrome through support, education and medical research. The charity operates with the following three main aims: 1. To support families affected by Dravet Syndrome emotionally, practically and financially. 2. To raise awareness and understanding of Dravet Syndrome among medical professionals 3. To fund medical research to increase understanding of Dravet Syndrome, improve its management, work towards better outcomes and to hopefully one day find a cure Approximately 486 parents/carers are now registered on the DSUK database. DSUK receives income from a range of different sources. DSUK's principle source of income is community fundraising with DSUK families and other supporters under-taking sponsored marathons, bike rides and the like to raise funds for the charity. In addition to community fundraising DSUK receives corporate sponsorship from XTX Markets, grants from trusts/foundations (Medicash and Boshier Hinton in 2019/20) and grants from industry (Zogenix and GW Pharma in 2019/20). DSUK also undertakes income generating activities through its online shop and the sale of tickets for its biennial DSUK Conference.

4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	The information provided here is gathered from parents/carers of individuals living with Dravet Syndrome (DS), who are registered with DSUK. Registration requires proof of a DS diagnosis. Information about the experiences of parents/carers has been gathered verbally, via email and via comments posted to our closed Facebook group. We can provide anonymised copies if required.
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?	Dravet Syndrome (DS) is a life-long, life-limiting, catastrophic disorder that places a huge burden on children/adults with the condition, their parents/carers and the entire family. As a spectrum disorder, DS is complex and unpredictable; every individual experiences the condition with varying degrees of severity and symptoms do not stay static for long. The key features of DS are treatment-resistant seizures, intellectual disability, autism, behavourial problems, and difficulties with speech, mobility, feeding and sleep. Seizure-related premature mortality is a major issue in DS. Prolonged, recurrent seizures usually start in the first year of life. As the condition progresses, other seizure types occur. 15% of individuals with DS die of SUDEP or status epilepticus before their 20th birthday. SUDEP is responsible for around half of all premature deaths in DS, with status epilepticus responsible for around one-third of these. The risk of SUDEP is up to 15 times higher in DS than other childhood-onset epilepsies and tends to occur at a younger age (73% before the age of 11). For more information on seizure-related mortality see Cooper et al, 2016, and Shmuely et al, 2016. While seizures are a central part of living with DS, it is important to recognise that this disorder is not limited to epilepsy and seizures. The comorbidities associated with DS can often be harder to manage than the seizures and, as children become older, these can lead to significant disabilities.

(continued from previous page)	Given the high seizure burden, high risk of mortality and associated comorbidities, many children/adults with DS require 24-hour supervision, and additional family support or home care is likely to be required. This combination of treatment-resistant seizures, debilitating comorbidities and the requirement for 24-hour monitoring causes DS to have a catastrophic impact, not only on health-related quality of life but overall quality of life - for the person with the condition, their parents/carers and the entire family. A recent longitudinal 10-year follow up study on patients with DS in the UK (conducted by A Brunklaus et al; publication ending) found: • 98% of parents/carers reported that their child/adult's condition had affected their own health • Over 90% of parents/carers reported mental health difficulties (depression, anxiety, stress disorders) • In over 90% of families, at least one parent had to quit their job or cut back on hours due to the burden of looking after a very unwell child; this has a significant financial impact on families For a more personal insight into the day-to-day impact of living with DS, please read the following statement from a parent: *'<redacted> is now 12 but is at the developmental stage of an 18-24 month old. His prolonged seizures have subsided, but he has seizures every night and is still awake for many hours each night. He is very onerous to care for and requires one-on-one care 24 hours a day, which is difficult to resource and relentless. We are very worried about how puberty will affect his seizures and behaviour and there is always lurking the latent risk of SUDEP…I would to add that the condition does change and is progressive in many cases. It is unpredictable, which makes caring very challenging. Living with the constant threat that your child might die, either from a seizure or SUDEP is terrifying and often the first thing a parent will do in the morning upon waking is to check that their child is still breathing. Living in a heightened state of emergency and never being able to switch off in case a seizure occurs, never knowing if it will be short, prolonged or fatal is something that no one will ever get used to.'* For more insights into how this condition affects the day-to-day lives of patients and their families, we would urge the committee to watch our 'Living with Dravet Syndrome' video, found here: https://www.dravet.org.uk/about-dravet-syndrome/living-dravet-syndrome.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	It is essential for parents/carers to have access to a range of effective and well-tolerated treatments for their child/adult with DS, if they are to have any hope of improving seizure control. The goal of seizure control is made extremely difficult by the fact that DS is one of the most treatment-resistant epilepsies, with around 90% of individuals resistant to existing treatment options (for example, a European survey among families living with Dravet Syndrome established that only 6.3% reported seizure freedom within a 3 month period, see Lagae et al, 2018). Moreover, because DS is a spectrum disorder, not all children/adults with DS respond in the same way to treatments. Most of the current treatments/treatment combinations are given on a trial and error basis to see which work best. This process is taxing on the children/adults with DS and their parents/carers. Good seizure control is rare and very few children/adults experience a seizure-free existence. Most children with DS are on three AEDs (these are sometimes described as 'the magic three', a term which many parents/carers tell us they dislike as in most cases they have limited success in controlling seizures). Each of the currently available AEDs brings with them side effects, such as suppression of appetite, aggression, insomnia, somnolence, etc. Side effects from treatments can also increase some of the symptoms associated with comorbidities. The recent approval of Epidyolex (cannabidiol) has been important in providing another treatment option for DS. However, whilst cannabidiol has undoubtedly improved seizure control for some individuals with DS, it does not work for all. Many have tried the Ketogenic diet and VNS with limited success, again dependent on the child. A significant proportion of the discussion on our closed Facebook group is from parents/carers sharing their experiences of different treatments, the different ways in which these might improve/worsen seizure control, the impact of side effects, and how the effects of medication change as children become older, or new comorbidities emerge.

8. Is there an unmet need for patients with this condition?	A treatment that improves seizure control and quality of life without a high burden of side effects continues to be desperately needed for people of all ages living with Dravet Syndrome. If seizure control can be achieved or improved, it affects the whole aspect of looking after a child/adult with this catastrophic condition, leading to significant improvements in overall outcomes for patients and their families. Very few children/adults experience a seizure-free existence with the currently available treatments (see answer to question 7, above). In addition, the combination of treatment-resistant seizures, debilitating comorbidities and the requirement for 24-hour monitoring cause DS to have a catastrophic impact, not only on health-related quality of life but overall quality of life (see answer to question 6, above). Another important unmet need in DS is to reduce the burden of status epilepticus, leading to emergency admissions and rescue medication. A European survey among 584 parents/carers of children/adults with DS found that half of these individuals required at least one emergency admission, and 46% needed at least one ambulance call within a 12-month period (see Lagae et al, 2018). Improved treatment of seizures will reduce the likelihood of status epilepticus and consequently reduce the time patients spend at hospital, with less need of emergency rescue medication. This improves quality of life for the whole family, including siblings (who frequently need to accompany their brother or sister to the hospital with their parents, as there is no one else who can look after them) as well as reducing the burden on in-hospital NHS resources.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There have been many very positive stories from our community about children becoming seizure-free or having dramatically improved seizure control due to receiving fenfluramine via a clinical trial or open access programme. In addition to improved seizure control, families have reported improvements with respect to comorbidities, burden of care and quality of life. The combination of these improvements has a huge impact on overall quality of life for families. Children/adults with DS participate more fully in family life and stress/worry is lessened for parents/carers, potentially improving their mental health.

(continued from previous page)	Below are four verbatim examples from our community of parents/carers: • *My daughter has been doing the trial for over two years and has been seizure free for 2 years. No hospital visits due to seizures. She is learning more e.g. recognising words, letters, number, can write her name. Her sleep pattern has improved due to no seizures* • *In 13 years we have tried many treatments, nothing has worked for us…This time last year <redacted> was fitted for a wheelchair her mobility was so bad, she would struggle just to walk…she had to have a special chair in order to sit safely. I was feeding her because she just couldn't manage to feed herself anymore and her appetite was very poor. She drooled constantly and her speech was very limited and slurred.…Our hearts broke as we watched her lose all her abilities and her quality of life reduce. Within 2 weeks of starting Fenfluramine her seizures were much reduced and even then they were mild mainly myoclonic, she regained her balance, her mobility and the drooling disappeared. She wanted to feed herself and and eat a varied diet. It was as if she was suddenly awake and alert and had a sparkle in her eyes we hadn't seen in a long time. She is happy all the time, full of life and learning new words and skills every day. In addition to all this we have not experienced any adverse side effects which usually come with treatments. She is 10 months on fenfluramine and it has transformed all of our lives in the most positive way.* • *'[he] went from having 5-6 tonic clonics a night to having maybe 1-2…We know we will never be seizure free, it's about getting a balance of seizures and life. Fenfluramine has enabled him to take part in days out, and be more involved in activities, no sleepiness in the day. We were very close to putting a lift in our house, he couldn't walk out the front door without getting in a wheelchair, he can know climb the stairs quite happily, stands more upright, walks and runs a small distance. It has helped the whole family feel better about enjoying things and less stressed parents. He does still have nights with maybe 3 seizures, but we know he'll get some nights with 1 or sometimes even none! His schoolwork is better, his overall happiness is better, as he's not being asked to do things when he's trying to recover from loads of seizures.* • *Having been on the drug for 2 years now I can honestly say it has transformed his quality of life tremendously…we were housebound and unable to leave due to <redacted> being so photosensitive to any kind of daylight. He had to wear sunglasses and a patch daily 24/7 even indoors, all blinds and curtains were drawn and some days switching on some lights was difficult…Since the first dose of fenfluramine his photosensitivity has disappeared. He is no longer affected by sunlight and can go outdoors and enjoy life again. His quality and our quality of life is night and day [compared to what it was]. He has responded so well to the drug we were able to take him on his first holiday abroad in the sun. The was the highlight of our whole experience as before the drug we couldn't even take him into the garden. To say it's been life changing for him is an understatement. Yes we have seizures and he's still on other drugs, however instead of counting seizures now from his photosensitivity we now count sunsets and feel incredibly lucky that we could change his quality of life.*

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There was some initial apprehension around fenfluramine due to the history of the drug as a diet pill (children/adults with Dravet Syndrome often have problems with eating) and its withdrawal for this use due to cardiac side effects. However, among families who have trialled fenfluramine these soon dissipated. Generally, fenfluramine appears well-tolerated and, anecdotally, side effects do not seem to have been an issue to date among our community of families. If cardiac monitoring is required, this does pose an additional burden, however, because parents/carers are in desperate need of treatments that improve Dravet-related seizures and other comorbidities, they will adhere to monitoring. It's also important to note that if fenfluramine does not have a noticeable benefit, parents/carers will not want to continue with an additional treatment given that their child/adult with Dravet Syndrome will already be on multiple medications.
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.	Any child/adult with DS whose seizures are not controlled could benefit from trying this new medication. Most of these children/adults have tried many drugs before and still have seizures. Any reduction in seizure activity is a benefit. For example, if you have a child who has five seizures a night and the medication reduced the number of seizures to three a night, that would be considered by a family to an improvement. Or if a child was having daily seizures and the medication reduced this to two seizures a week, then that would be considered a success. One factor that needs consideration is the reduction in length of seizure. For example, if a child has three seizures a week, and each seizure normally last five minutes; if after starting treatment they still have those three seizures week, but the length of seizures has reduced to one minute each, that is a huge difference. We have heard anecdotally from some parents/carers that treatment with fenfluramine has resulted in improvements in sleeping and alertness in their child/adult with Dravet Syndrome, suggesting that it could have a benefit on sub-clinical seizures (see answer to Q9, above).

Equality	
12. Are there any potential equality issues that should be taken into account?	No comments.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Dravet Syndrome is often described as a complex form of epilepsy. As the UK patient group for DS, we feel it is more accurate and complete to define DS as a life-long, life-limiting neurological condition. It is a spectrum disorder that causes severe, treatment-resistant seizures, intellectual disabilities, autism and behavioural problems, and difficulties with speech, walking, feeding and sleeping. In order to fully appraise the impact of a new treatment such as fenfluramine, it is important to recognise that DS is not limited to epilepsy and seizures. The comorbidities associated with DS can often be harder to manage than the seizures and, as children become older, these can lead to significant disabilities. Whilst DS is a spectrum disorder, it is rare that anyone with DS is able to live independently, adding to the long-term burden on families. Although comorbidities are in part due to the underlying causes of DS (a dysfunction in the sodium ion channel), good seizure control undoubtedly leads to better cognitive outcomes and improvements across the range of comorbidities (e.g. see H Cross et al, 2019). Improved seizure control affects the whole aspect of looking after a child/adult with this catastrophic condition, leading to significant improvements not only for the individual with Dravet Syndrome, but also the wider family, including siblings. Living with a brother or sister with Dravet Syndrome can have a huge impact on the well-being of siblings. Their routines are disrupted (e.g. via emergency hospital visits); they worry and wonder what is happening and if their sibling will be all right. Often their own time with parents/carers is limited by the complex needs of the child/adult with Dravet Syndrome, who needs 24/7 care.

(continued from previous page)	Respite options remain difficult to find and resource, while support (e.g. from extended networks of family or friends) are often limited because of the potential severity of seizures and complexity of needs. This can also impact quality of life and development, and as individuals with Dravet Syndrome become older, their world can become quite small.

Key messages

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

- Dravet Syndrome (DS) is a life-long, life-limiting, catastrophic disorder that places a huge burden on children/adults with the condition, their parents/carers, siblings and the entire family, with an urgent unmet need for treatment options to improve seizure control and quality of life.
- Dravet-related seizures are often frequent and prolonged, with less than 90% of individuals with DS achieving seizure control. Reducing both the frequency and length of seizures is a fundamental goal for individuals with DS
- DS is not just seizures - the comorbidities associated with DS can often be harder to manage than the seizures and, as children become older, these can lead to significant disabilities; good seizure control leads to better cognitive outcomes and improvements across the range of comorbidities
- Given the high seizure burden, high risk of mortality and associated comorbidities, many children/adults with DS require 24-hour supervision, and additional family support or home care is likely to be required.
- Most parents/carers of children/adults with DS have already tried multiple combinations of existing treatments, without gaining seizure-control. Because of this fact, families are aware that new treatments may not work for everyone and will not keep their children/adults on an additional medication, if it is not showing a benefit.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Fenfluramine for treating Dravet syndrome [ID1109]

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.

Information on completing this submission

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- 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	[redacted]

2. Name of organisation	Epilepsy Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Epilepsy Action is the UK's leading epilepsy organisation and exists to improve the lives of everyone affected by the condition. As a member-led organisation, we are led by and represent people with epilepsy, their friends, families and healthcare professionals. Epilepsy can affect anyone at any age and from any walk of life. Epilepsy Action is funded by individual donations from members and supporters. Epilepsy Action has around 10,000 members.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**Epilepsy Action previously engaged with parents and carers of people with Dravet syndrome as part of our response to NICE Single Technology Appraisal [ID1211] Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome.** **This engagement was in the form of email communications with relevant members and supporters and social media requests.** **Four parents and carers of people with Dravet syndrome provided detailed responses including around the impact of the condition on individuals as well as parents/ carers and wider families, and currently available treatment options.**

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?	Dravet syndrome is a rare and treatment-resistant epileptic encephalopathy. As such, the condition is inherently complex and people with the condition also often experience severe comorbidities associated with encephalopathy. The combined impact of frequent and often severe seizures and developmental and cognitive delays usually necessitates high and continuous care and support needs, presenting a high care burden for parents/ carers. Parent carer respondents highlighted the high care burden associated with caring for someone with the condition. In relation to seizures, these needs centre on the number and severity of seizures associated with Dravet syndrome. One parent carer noted that their son experiences a variety of seizure types up to 50 times day. 'He experiences tonic clonic, focal, partial and absent seizures (sometimes 30-50 of these per day)'. They went on to highlight the severity of some of these seizures and the associated risks – '[their son] is hospitalised every 5 weeks on average due to a prolonged seizure'. During these hospitalisations, their son will often have to be intubated and placed in PICU at the children's hospital. Another carer whose son has Dravet syndrome noted that he required '24 hour care and 24 hour monitoring for seizures'. People with Dravet often have a range of comorbidities that can have a major impact on their day-to-day lives. Many people with the condition also have a spectrum of learning disabilities with most being severe and many will also be on the autistic spectrum. Many people with Dravet will have difficulties with communication, some being non-verbal and unable to communicate at all. Sleep issues are a common problem with some having less than 2 hours a night. Those with Dravet syndrome have a spectrum of mobility issues, some have no mobility and use wheelchairs while others can have fairly good mobility but with balance issues. It is common to have a gait abnormality, which deteriorates over time. Feeding issues are also common, with some patients eventually having to be tube fed. Other comorbidities include ADHD, behaviour issues and incontinence

	Dravet also presents a significantly increased risk of associated injuries and ultimately death as a result of sudden unexpected death in epilepsy (SUDEP) or prolonged seizures. Injuries due to a fall during seizures can be severe, especially as patients get older. The risk of SUDEP was succinctly noted by a parent carer of a child with Dravet syndrome, 'SUDEP is never far from our thoughts'. A parent carer of a child with Dravet syndrome noted that their son required '24 hour care and 24 hour monitoring for seizures'. In light of the current low rates of seizure control and poor seizure management amongst people with Dravet, these care needs are likely to be constant throughout their lifetimes. Another parent carer noted the intense medication regime that their child required and the potential consequences if a mistake is made with administering the medications. 'Each morning, it's so important that we administer the correct AEDs [antiepileptic drugs] as we are aware of the consequences if this doesn't happen. Having 3 AEDs, morning and night, plus a 3-day course of antibiotics each week, is now set as a routine'. The severe needs of many people with Dravet syndrome can have a major impact of the personal life of parents, carers and other family members. These include financial pressures, strain on relationships and an impact of the health of parents and carers. One parent carer noted that 'the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially.' It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and family life noting that 'it has been a real toll on our health and family life'. This was echoed by other respondents, 'we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up.' The same parent carer went on to note that the burden of caring for their son has made them suicidal.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Dravet syndrome is one of the most resistant epilepsies to currently available treatments. Around 90% of people with Dravet syndrome will be resistant to existing treatment options. Gaining good control of seizures associated with Dravet is difficult and subsequently very rare. First line antiepileptic drugs (AEDs) for people with Dravet include sodium valproate and topiramate. It is often the case that people with Dravet will be prescribed multiple AEDs with a combination of three AEDs often providing the best seizure control. This combination is most commonly sodium valproate, stiripentol and clobazam. As with other medications, many AEDs have associated side-effects in monotherapy and these can be exacerbated in drug combination therapy through interactions between AEDs. A parent carer of a child with Dravet syndrome noted that current treatment options for people with the condition are 'limited'. They went on to note the risk and concern associated with trying alternative AEDs to improve seizure control, 'there is a worry that if you change med things will get worse'. A course of the steroid prednisolone can also be used if the condition is proving particularly problematic for a period of time. Emergency rescue medications such as buccal midazolam are used in some cases when prolonged seizures occur. Some people with Dravet are also recommended to adopt a ketogenic diet.
8. Is there an unmet need for patients with this condition?	Given the highly treatment-resistant nature of Dravet syndrome, with around 90% of people affected being resistant to existing treatment options, there is a clear unmet need for people with Dravet syndrome. This was echoed by a parent/ carer who noted that 'yes [there is an unmet need for patients with this condition] because it is rare and patients present differently.' Unmet needs include seizure freedom, a reduction in seizures or a reduction in length of seizures. Parent carers also noted a desire for improved cognition and for people with the condition to experience fewer side effects compared to current treatments.

	The treatment-resistant nature of Dravet syndrome means that risks associated with seizures, including SUDEP and status epilepticus, often persist despite current treatment options. This often leads to unplanned hospital admissions due to particularly serious or prolonged seizures.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	We were unable to speak to patients or carers with direct experience of fenfluramine. Instead Epilepsy Action have summarised the key potential advantages of fenfluramine as a treatment for Dravet syndrome. It is of note that one parent carer of a child with Dravet syndrome mentioned fenfluramine unprompted during a discussion about cannabidiol (Epidyolex) as a potential new treatment option for Dravet syndrome. They noted that their neurologist was interested in the potential benefits of fenfluramine as a treatment option for their child; “Their neurologist] was more interested in the trials of fenfluramine and the benefits that showed, and recommended that [their child] get on the first trial available.” Randomised, double-blind, placebo-controlled clinical trials of fenfluramine for the treatment of seizures associated with Dravet syndrome have shown the drug to provide significantly greater reductions in the frequency of convulsive seizures from baseline compared with placebo. Reducing the frequency of convulsive seizures for people with Dravet syndrome is likely to reduce the risk of status epilepticus for this patient group. Similarly, significant and sustained reduction of convulsive seizures is likely to improve the quality of life for people with Dravet syndrome and reduce the high care burden on parents, carers and others directly and indirectly involved with their care including siblings and wider family.

	It is of note that the Food and Drug Administration (FDA) in the United States recently approved fenfluramine as a treatment for Dravet syndrome in patients aged two and over. This decision was taken in light of data from two randomised control trials (RCTs) that demonstrated the safety and efficacy of fenfluramine for treating seizures associated with Dravet syndrome. In light of available clinical evidence, the frequency and severity of seizures, the increased risk of premature epilepsy related mortality and high care burden associated with Dravet syndrome, Epilepsy Action believes this technology should be made available on the NHS as an additional treatment option for seizures associated with Dravet syndrome.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We were unable to speak to patients or carers with direct experience of fenfluramine. Instead Epilepsy Action have summarised the relevant potential disadvantages of fenfluramine as a treatment for Dravet syndrome. The most common adverse effects associated with fenfluramine for seizures associated with Dravet syndrome include: decreased appetite, diarrhoea, fatigue, lethargy, somnolence and decreased weight. It was noted that fenfluramine was generally well tolerated. Fenfluramine has been associated with valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) in adult patients treated for obesity. This would require necessary consideration and monitoring as appropriate. It is of note that no VHD or PAH was observed during an RCT of fenfluramine for Dravet syndrome in the initial study period. Retrospective analysis and other research in this area also indicate a potentially lower risk of cardiac abnormalities associated with lower dose fenfluramine in patients with Dravet syndrome. The severe and treatment resistant nature of Dravet syndrome and the poor quality of life associated with the condition should also be considered when assessing the benefit-risk profile of fenfluramine for seizures associated with Dravet syndrome.

	It is important to consider the generally well tolerated common adverse effects of fenfluramine in comparison to those of existing treatment options, in both monotherapy and polytherapy. The association between Fenfluramine and VHD/ PAH also necessitates consideration with potential steps taken to monitor patients for cardiac abnormalities.
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.	N/a
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**N/a**

Other issues	
13. Are there any other issues that you would like the committee to consider?	N/a

Key messages

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

- Clear unmet need for this patient population – parent carer responses that have been used to inform this submission demonstrate a clear unmet need for this patient population. The frequency and severity of seizures associated with Dravet syndrome and associated comorbidities present a clear need for new potential treatment options.
- Severity of the condition and impact of parents, carers and families – these epilepsy syndromes are severe and very often resistant to current treatment options. Additional care and support needs are high and often remain so throughout patients' lives with an associated impact of patients, carers and families.
- Treatment resistant nature of the condition - current treatment options available on the NHS for seizures associated with Dravet syndrome are often unable to provide adequate seizure control.
- Some good quality clinical evidence of safety and efficacy - Randomised Control Trial (RCT) evidence of the safety and efficacy of Fenfluramine as a treatment option for seizures associated with Dravet syndrome.
- Potential adverse effects - due consideration should be paid to the potential adverse effects of Fenfluramine for seizures associated with Dravet syndrome including the association of the treatment with VHD, PHA and other cardiac abnormalities.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Fenfluramine for treating Dravet syndrome [ID1109]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists**

3. Job title or position	[redacted]
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):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a non 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.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
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,	Currently, the main aim is to improve seizure control. This in turn can lead to slowing, arrest or reversal of cognitive, motor and behavioural decline, and reduce the risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Important outcomes for people with Dravet syndrome and their families are individual, but include; 1. reduction of frequency of convulsive seizures, e.g. by 30% or more, and other seizure types that can be recorded e.g. non-convulsive seizures causing falls. 2. prevention of status epilepticus, or reduction in need for use of rescue medication, or reduction in hospital admission frequency 3. improved alertness, interaction, behaviour, sleep, use of language, feeding with weight gain, quality of life
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, absolutely. Existing treatments are often unsuccessful, with no options then being available.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	As per NICE guidelines, and in specialist practice including treatment with: valproate, clobazam, topiramate, levetiracetam, stiripentol, cannabidiol, perampanel, bromide, ketogenic diet
• Are any clinical guidelines used in the treatment of the	NICE Epilepsy Guidelines

condition, and if so, which?	
• 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.)	In specialist practice, yes.
• What impact would the technology have on the current pathway of care?	Improved seizure control, overall simpler to use than some other agents, e.g. stiripentol, cannabidiol
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	Only in terms of the probable additional need for annual echocardiography.
• In what clinical setting should the technology be	Specialist clinics

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None in specialist clinics, except provision of and access to echocardiography as a regular test, that should not require detailed explanation to the service provider.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes.
• Do you expect the technology to increase length of life more than current care?	Yes, if seizure freedom or improved control of seizures, especially convulsive seizures, is achieved.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, again mainly related to improved seizure control.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not as currently shown by the published data.
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.)	Its use will be comparable to many existing treatments, and may be easier than some, as there is likely to be a reduced burden for blood tests to monitor marrow and hepatic function. Its use will also probably necessitate annual echocardiography, which may be challenging for some people with Dravet syndrome, but is feasible as shown by the published trials.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that rules similar to those for cannabidiol, which has established a precedent, should be applied. For efficacy, these will not require additional testing. Additional testing will be needed for potential cardiac adverse events, at least until a larger body of evidence is available: the drug may need to be stopped for such events independently of seizure outcome.
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?	Yes. For example, with previous effective treatments in specific individuals and circumstances, we have seen substantial improvements in language use, from no spoken words in regular clinical appointment evaluation, to the use of many words. For people with Dravet, their families and carers, these are outcomes that are of enormous importance that may not be picked up by relatively unresolved QALY-related measures, or even standard neuropsychometry summary measures.
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, evidence to date suggests fenfluramine is innovative, with potential to make significant and substantial impact in a group of people for whom treatments currently are insufficient.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Available evidence suggests this may be the case: e.g. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B; FAiRE DS Study Group. Lancet. 2020 Dec 21;394(10216):2243-2254. doi: 10.1016/S0140-6736(19)32500-0. Epub 2019 Dec 17. PMID: 31862249 Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S; FAiRE, DS Study Group. JAMA Neurol. 2019 Dec 2. doi: 10.1001/jamaneurol.2019.4113. [Epub ahead of print]. PMID: 31790543
• Does the use of the technology address any particular unmet need of the patient population?	Yes, for many people with Dravet syndrome, currently available treatments, including cannabidiol, do not bring about seizure control.
17. How do any side effects or adverse effects of the technology affect the	The main adverse effect of concern is of cardiac valve structural change, which arose from previous use of the agent in combination with another drug for the treatment of obesity. However, available data suggest this is not an important issue for use of fenfluramine alone, at the doses currently recommended. The

management of the condition and the patient's quality of life?	adverse effect profile of fenfluramine does not otherwise raise specific concerns in comparison to other available treatments.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes. UK patients were included in the key trials in the FAiRE DS Study Group
• 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?	For an antiepileptic drug, rather than an agent intended to modify the underlying disease process (though that is a possibility that has not been excluded for fenfluramine: PMID: 32096222), the most important outcome is seizure control, which was measured in the trials.
• 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	Not currently.

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No
21. How do data on real-world experience compare with the trial data?	I consider the limited published real-world experience not to show major differences with the trial data.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Adults without capacity to consent on related matters must not be excluded.
22b. Consider whether these issues are different from issues with current care and why.	The only difference is that additional measures, such as ECG and echocardiography, may be needed for monitoring treatment that are not typically needed with other interventions for Dravet syndrome.
Topic-specific questions	
23. Would you consider that fenfluramine could be used at various stages of the treatment pathway? If yes, could it be used as a 1st line add on therapy following initial treatment with either valproate or topiramate; and as an alternative and/or add-on to	Yes, I think this may well emerge from clinical practice as clinicians gain confidence in its use and provided the results from trials are replicated in routine clinical practice. It is likely to prove easier to use than stiripentol and cannabidiol, and may prove more effective (there are no published comparator data to my knowledge).

stiripentol, cannabidiol with clobazam or clobazam?	

Key messages

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

Dravet syndrome is a rare, serious, life-threatening, epilepsy for which new treatment options are very much needed

- Fenfluramine represents one such option
- Existing data suggest good tolerability and efficacy
- Both adults and children should be able to benefit from the option of having fenfluramine available
- Formal national audit of its use would be of value

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Fenfluramine for treating Dravet syndrome [ID1109]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	The British Paediatric Neurology Association, a registered charity.

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X 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):
5a. Brief description of the organisation (including who funds it).	The British Paediatric Neurology Association (BPNA), a registered charity. The members include paediatric neurologists, paediatricians and paediatricians in Neurodisability and community paediatrics. The BPNA works in partnership with support groups for parents and children with epilepsy and Dravet syndrome. The BPEG has over 100 members who are paediatric neurologists or paediatricians from across the UK with a special interest in epilepsy.
5b. 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,	1. To prevent or reduce seizures. 2. To improve quality of life. 3. To support the development of cognitive, language and social communication.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A median of a 40% reduction in convulsive seizures.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Unmet needs: Seizure frequency and severity, SUDEP, impairments in neurodevelopment in children, including cognition, language, motor difficulties, the development of an autism spectrum disorder.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently there are several antiepileptic drugs that may reduce seizures: Stiripentol, clobazam, sodium valproate, clobazam, cannabidiol and also the ketogenic diet. Despite these treatments, children continue to have frequent and severe seizures and have an increased risk of SUDEP and associated neurodevelopmental abnormalities. The recent RCT for fenfluramine in patients with Dravet syndrome shows a positive response percentage for the control of tonic- clonic seizures that is higher than other anti-epileptic drugs.

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines: Cannabidiol with clobazam for treating seizures associated with Dravet syndrome, Epilepsies: diagnosis and management, and NICE Pathways: Anti-epileptic drugs to offer based on epilepsy syndrome.
• 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.)	Guidance states that children should be referred to a tertiary paediatric neurologist. Nice Pathways: Anti-epileptic drugs to offer based on epilepsy syndrome, sets out guidance on the treatment which paediatric neruologists follow.
• What impact would the technology have on the current pathway of care?	The above pathway would continue.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as an alternative anti-epileptic drug.
• How does healthcare resource use differ	The resource will remain the same.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Fenfluramine should be used by paediatric Neurologists working in partnership with secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The trial suggests that there will be improved seizure management.
• Do you expect the technology to increase length of life more than current care?	It is a possibility that the incidence of SUDEP could be less in those children receiving fenfluramine.
• Do you expect the technology to increase health-related quality of	The seizure response in the trial with a reduction in generalised tonic clonic seizures would be expected to improve health related quality of life with a reduction in seizure associated injuries, reduced administration of emergency treatment for seizures and reduced hospital attendances. The Pediatric Quality of Life

life more than current care?	Inventory showed improvement in both fenfluramine groups compared with placebo Lagae et al Lancet Vol 394 December 21/28, 2019
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Specifically, children with a diagnosis of Dravet syndrome.
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	The use will be similar to current medications with no specific monitoring needs.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Children with a clinical and genetic diagnosis of Dravet syndrome.
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?	The health related benefits need to be informed by parents/carers assessment of the child's quality of life.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Fenfluramine increases levels of serotonin in the brain which is a novel mechanism of action compared to other anti-epileptic drugs (AEDS) thus patients who have not responded to other AEDS may show a response.

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	The data available suggests fenfluramine may improve management above other AEDs.
• Does the use of the technology address any particular unmet need of the patient population?	To improve generalised tonic clonic seizures.
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?	Adverse effects are similar to other AEDs and clinical monitoring is required for these and the impact on quality of life.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trial Lagae et al Lancet Vol 394 December 21/28, 2019, provides data to support the use of fenfluramine in clinical practice.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	1. Seizure control. 2. Quality of life. Both of above measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Previously there was concern that fenfluramine was associated with valvular heart disease. Use over 30 years in Belgium with cardiac monitoring did not detect such changes. However, the trial duration may be too short to detect this adverse effect.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	No.
21. How do data on real-world experience compare with the trial data?	Long term use in Belgium appears similar to trial data- Schoonjans et al, Ther Adv Neurol Disord 2015, Vol. 8(6) 328–338 DOI: 10.1177/ 1756285615607726
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.

22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. Would you consider that fenfluramine could be used at various stages of the treatment pathway? If yes, could it be used as a 1st line add on therapy following initial treatment with either valproate or topiramate; and as an alternative and/or add-on to stiripentol, cannabidiol with clobazam or clobazam?	Yes, agree.
Key messages	

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

- Fenfluramine improves generalised tonic clonic seizures in children with Dravet syndrome
- Trial data suggests treatment may be associated with an improvement in quality of life.
- Serious adverse effects were not documented but consideration should be given to safety monitoring of possible cardiac adverse effects.
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-
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NICE National Institute for Health and Care Excellence

Professional organisation submission

Fenfluramine for treating Dravet syndrome [ID1109]

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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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Amanda Hirst**
2. Name of organisation	**ESNA**

3. Job title or position	**ESNA exec committee paediatric lead/Paediatric Epilepsy Specialist Nurse**
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):
5a. Brief description of the organisation (including who funds it).	ESNA - EpilepSy Nurses Association is a professional organisation whose membership consists of nurses and other health professionals working to support people with epilepsy in the fields of adults, learning disabilities and paediatrics. We work with our membership to raise the profile of epilepsy and to encourage a holistic and co-ordinated approach to care to enable our patients to reach the goal of self-management.
5b. 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,	To optimise seizure control & improve quality of life for patients with a diagnosis of Dravet syndrome

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Quality of life indicators Reduction in seizure burden Reduction in prolonged seizures resulting in status epilepticus Additional medication in treatment choices
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	New medications can always be of potential benefit to this patient group
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Dravet patients currently treated with Sodium valproate, steripentol & clobazam together Use of CBD recently approved for patients with Dravet Ketogenic diet also considered effective in some patients Bromide is also considered but this is a rarer treatment pathway

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Epilepsies: diagnosis & management NICE guidance CG137 Cannabidiol with clobazam for treating seizures with Dravet syndrome – NICE technology appraisal 614
• 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.)	Pathways seem consistent within the field of Paediatrics. The problem seem to be when these young people transition to adult care particularly around the use of Steripentol
• What impact would the technology have on the current pathway of care?	
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it would be potentially added into the clinical pathway for choosing pharmacological treatments
• How does healthcare resource use differ	

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Within specialist epilepsy clinics supported by Paediatric Neurology
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clear treatment/dose guidance Potential investigations/monitoring requirements eg :- bloods etc
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Potential to reduce seizure burden therefore potential to increase life expectancy due to risk of status epilepticus or SUDEP
• Do you expect the technology to increase health-related quality of	Yes as above

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
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	Prescribing - ? RAG rating within medicines management ie will it be a red drug as is Steripentol Investigations – any monitoring requirements

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
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?	
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 improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Additional treatment pathways are always of potential benefit to patients
• Does the use of the technology address any particular unmet need of the patient population?	Some children with Dravet are particularly resistant to current pharmacological options and therefore potentially this medication could be of benefit
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 are closely monitored by the family and clinical team and reported accordingly with the view of stopping medication if required.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Small number of studies seem to reflect current clinical practice and data/results seems to be able to be replicated in UK settings

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	50% seizure reduction in some patients No significant cardiac/pulmonary side effects reported
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Low dose fenfluramine has been used with no adverse cardiac problems. This seems to be linked to the fact that doses are considerably lower mg/kg than when the drug was used for obesity in adults.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator	

treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions	
23. Would you consider that fenfluramine could be used at various stages of the treatment pathway? If yes, could it be used as a 1st line add on therapy following initial treatment with either valproate or topiramate; and as an alternative and/or add-on to stiripentol, cannabidiol with clobazam or clobazam?	Fenfluramine could be considered as an add on to current pathways
Key messages	

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

- 50% seizure reduction
- Quality of life improvements
- Add on therapy for drug resistant epilepsy
- Precision therapy for complex epilepsy syndrome
- Increased life expectancy if seizures reduced

Thank you for your time.

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fenfluramine for treating Dravet syndrome

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

Authors
Debra Fayter, Systematic Reviewer, KSR Ltd., United Kingdom (UK)
Ben Wijnen, Health Economist, Maastricht University Medical Center+ (UMC+), The Netherlands
Bram Ramaekers, Health Economist, Maastricht UMC+, The Netherlands
Thomas Otten, Health Economist, Maastricht UMC+, The Netherlands
Willem Witlox, Health Economist, Maastricht UMC+, The Netherlands
Steve Ryder, Health Economist, KSR Ltd., UK
Pawel Posadzki, Reviews Manager, KSR Ltd., UK
Gill Worthy, Statistician, KSR Ltd., UK
Lisa Stirk, Information Specialist, KSR Ltd., UK
Manuela Joore, Health Economist, Maastricht UMC+, The Netherlands
Nigel Armstrong, Health Economics Manager, KSR Ltd., UK
Robert Wolff, Deputy Director, KSR Ltd., UK
Jos Kleijnen, Director, KSR Ltd., UK; Professor of Systematic Reviews in Health Care, Maastricht University, The Netherlands

Correspondence to Robert Wolff, Kleijnen Systematic Reviews Ltd.
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, UK
YO19 6FD

Date completed 13/10/2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number STA 12/78/99.

Declared competing interests of the authors
None.

Acknowledgements

The authors would like to acknowledge the clinical advice and expert opinion provided by

- Prof. Dr. Marian Majoie, Department of Neurology, Academic Centre of Epileptology Kempenhaeghe Maastricht UMC+, The Netherlands; School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands; School of Health Professions Education, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands
- Dr. Judith Verhoeven, Academic Center for Epileptology Kempenhaeghe/Maastricht University Medical Center, Heeze, The Netherlands

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Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
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This report should be referenced as follows:
Fayter D, Wijnen B, Ramaekers BLT, Otten T, Witlox W, Ryder S, Posadzki P, Worthy G, Stirk L, Joore MA, Armstrong N, Wolff R, Kleijnen J. Fenfluramine for treating Dravet Syndrome: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd., 2020.

Contributions of authors
Debra Fayter acted as clinical effectiveness project lead and systematic reviewer, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Ben Wijnen acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Bram Ramaekers, Thomas Otten, Willem Witlox and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Pawel Posadzki acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report, and provided general guidance. Robert Wolff 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. 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

1L	First-line
2L	Second-line
2L+	Second- and subsequent lines
A&E	Accident and emergency
ABN	Association of British Neurologists
AE	Adverse event
AED	Antiepileptic drug
AES	American Epilepsy Society
AESI	Adverse event of special interest
AiC	Academic in confidence
ANCOVA	Analysis of covariance
Avg	Average
AWMSG	All Wales Medicines Strategy Group
BC	Base-case
BID	Twice daily
BNF	British National Formulary
BPNA	British Paediatric Neurology Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CBD	Cannabidiol
CBD10	Cannabidiol 10 mg/kg/day with clobazam
CBD20	Cannabidiol 20 mg/kg/day with clobazam
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Central Register of Controlled Trials
CG	Clinical guideline
CGI-I	Clinical Global Impression – Improvement
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CLB	Clobazam
CM	Clinical management
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSF	Convulsive seizure frequency
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
d	Day
DALY	Disability-adjusted life year
DS	Dravet syndrome
DSA	Deterministic sensitivity analysis
ECE	European Congress on Epileptology
ECG	Electrocardiogram
ECHO	Echocardiogram
EED	Economic Evaluation Database
EMA	European Medicines Agency
EPNS	European Paediatric Neurology Society

EQ-5D	EuroQOL–5 Dimensions
EQ-5D-5L	EuroQOL–5 Dimensions–5 Levels scale produced by the European Quality of Life Group
EQ-5D-Y	EuroQOL–5 Dimensions–Youth scale produced by the European Quality of Life Group
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FE	Fixing errors
FFA	Fenfluramine
FV	Fixing violations
GR	Gastro-resistant
HADS	Hospital Anxiety and Depression Scale
HRCU	Health care resource unit
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICEGTCS	Intractable childhood epilepsy with generalised tonic-clonic seizures
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
IEC	International Epilepsy Congress
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KD	Ketogenic diet
KSR	Kleijnen Systematic Reviews
LVT	Levetiracetam
MCMC	Markov chain Monte Carlo
MeSH	Medical Subject Headings
mITT	Modified intent-to-treat
MJ	Matters of judgement
MR	Modified-release
MRI	Magnetic resonance imaging
NA	Not applicable; not assessed
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
OLE	Open-label extension
ONS	Office for National Statistics
OR	Odds ratio
OS	Oral suspension
PAS	Patient access scheme
PCA	Prescription cost analysis
PedsQL	Paediatric Quality of Life Inventory
PICOS	Population, Intervention, Comparator(s), Outcome(s), and Study design
PRISMA	Transparent Reporting of Systematic Reviews and Meta-analysis
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
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trial
RM	Rescue medication
RR	Relative risk; risk ratio
RWE	Real-world evidence
ScHARRHUD	School of Health and Related Research Health Utilities Database
SCN1A	Sodium Voltage-Gated Channel Alpha Subunit 1
SD	Standard deviation
SE	Status epilepticus
SF-36	Short form 36
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard of care
SoC AEDs	Standard of care antiepileptic drugs reflecting antiepileptic drugs and add-on therapies continued from previous line
STA	Single Technology Appraisal
STP	Stiripentol
SUDEP	Sudden Unexpected Death in Epilepsy
T+M	Treatment and maintenance
TA	Technology appraisal
THC	Tetrahydrocannabinol
TEAE	Treatment-emergent adverse event
TPM	Topiramate
UK	United Kingdom
UMC+	University Medical Center+
USA	United States of America
VAS	Visual analogue scale
VAT	Value-added tax
VNS	Vagus nerve stimulation
VPA	Valproate
wk	Week
WTP	Willingness to pay
ZNS	Zonisamide
ZX008	fenfluramine hydrochloride oral solution (FINTEPLA, FFA)

Table of Contents

Table of Tables

Table of Figures

1. Evidence review group report 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. 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 gives an overview of key model outcomes,
- Section 1.3 discusses the decision problem,
- Section 1.4 summarises issues related to the clinical effectiveness,
- Section 1.5 reviews issues related to the cost effectiveness,
- Section 1.6 lists other key issues, and
- Section 1.7 provides a summary of ERG's preferred assumptions and resulting ICERs

Background information on the condition, technology and evidence and information on 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, 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 the key issues

ID	Summary of issue	Report sections
1	Lack of evidence on adult patients with Dravet Syndrome	**Executive summary**: • Table 1.2 **Main report**: • Section 3.1 • Section 4.2.1 • Section 4.2.7 • Section 4.5
2	Not all relevant comparators have been fully investigated	**Executive summary**: • Table 1.3 **Main report**: • Section 3.3 • Section 4.1.2 • Section 4.5
3	Short-term nature of the included randomised trials	**Executive summary:** • Table 1.4 **Main repor**t: • Section 4.2.1 • Section 4.5
4	Adverse events and need for monitoring	**Executive summary**:

ID	Summary of issue	Report sections
		• Table 1.5 **Main report**: • Section 4.2.6 • Section 4.5
5	Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**Executive summary**: • Table 1.6 **Main report**: •Section 5.2.2
6	In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**Executive summary**: • Table 1.7 **Main report**: • Section 5.2.3 • Section 5.2.4
7	The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	**Executive summary**: • Table 1.8 **Main report**: • Section 5.2.4
8	The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**Executive summary**: • Table 1.9 **Main report**: • Section 5.2.6
9	In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**Executive summary**: • Table 1.9 **Main report**: • Section 5.2.6
10	Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	**Executive summary**: • Table 1.11 **Main report**: • Section 5.2.8
11	When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**Executive summary**: • Table 1.11 **Main report**: • Section 5.2.8
12	Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	**Executive summary**: • Table 1.13 **Main report**: • Section 6.3

ID	Summary of issue	Report sections
13	There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**Executive summary**: • Table 1.13 **Main report**: • Section 6.3
14	The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model.	**Executive summary**: • Table 1.13 **Main report**: • Section 6.3

1.2 Overview of key model outcomes

In the company base-case (probabilistic), the ICER amounted to £31,887 per QALY gained. However, the deterministic ICERs of the two separate models (model based on Study 1 and the model based on Study 1504), vary greatly, i.e. £38,874 per QALY gained for Study 1 and £10,770 per QALY gained for Study 1504. Incremental QALYs ([redacted]) were mainly driven by QALY gains resulting from carer utilities. Total costs were also higher for fenfluramine + SoC than for cannabidiol + clobazam + SoC. The incremental costs ([redacted]) mainly resulted from higher treatment costs. Moreover, when comparing the incremental costs and QALYs of cannabidiol in NICE TA614 to the incremental costs and QALYs for cannabidiol as estimated in the current appraisal a large discrepancy can be observed resulting in a substantially lower ICER for cannabidiol compared to SoC than what is shown in the current appraisal, with an ICER of £29,268 per QALY gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal. The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). However, the ERG considers that there remains substantial uncertainty about the presented cost effectiveness results.

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1 – Lack of evidence on adult patients

Report section	Sections 3.1, 4.2.1, 4.2.7, and 4.5
Description of issue and why the ERG has identified it as important	Although the decision problem in the NICE scope did not specify any age restriction and the expected licenced indication for fenfluramine includes children and adults, neither of the key trials used in the submission (Study 1 and Study 1504) included adult patients (over the age of 18 years). Therefore, adults with Dravet syndrome (DS) are not fully represented in the CS. The number of adults in the non-randomised studies was small and this evidence is at greater risk of bias. The committee will need to decide if is satisfied that fenfluramine will be equally suitable for adults with DS. Of note, the clinical experts consulted by the ERG agree with the company, i.e. that results are applicable to adult patients with DS.

Report section	Sections 3.1, 4.2.1, 4.2.7, and 4.5
What alternative approach has the ERG suggested?	If possible, future studies should include adult patients with DS.
What is the expected effect on the cost effectiveness estimates?	If convulsive seizure frequency and convulsive seizure days decrease in adults (as argued in the CS), the absolute decrease in seizures achieved by using fenfluramine (compared to children) would be smaller in adults and hence the incremental cost effectiveness ratio would increase.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence in adult patients with DS is needed. Unresolvable uncertainty with the current evidence.

Table 1.3: Key issue 2 – Not all relevant comparators have been fully investigated

Report section	Sections 3.3, 4.1.2, and 4.5
Description of issue and why the ERG has identified it as important	Unlike cannabidiol, where concomitant clobazam has to be given, fenfluramine can be given with or without concomitant clobazam. The company stated that a small proportion of patients would receive fenfluramine as a first-line add-on therapy in patients where clobazam or a clobazam-based regimen is undesired. Furthermore, the company stated that most patients would receive fenfluramine after clobazam as proposed in the second-line + add-on therapy setting. In this setting comparators are continuation of standard of care antiepileptic drugs (AEDs) reflecting AEDs and add-on therapies continued from previous line, cannabidiol + clobazam + standard of care (SoC) AEDs or stiripentol + SoC AEDs.
What alternative approach has the ERG suggested?	If possible, future studies should include relevant comparators.
What is the expected effect on the cost effectiveness estimates?	The comparison against cannabidiol + clobazam does not provide information regarding the cost effectiveness of fenfluramine against SoC. Although the ERG acknowledges the lack of evidence, the company could have incorporated the placebo + concomitant AEDs arm of the trial in their base-case model in order to produce a comparison with SoC.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence on all comparators is needed. Unresolvable uncertainty with the current evidence.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified two major concerns with the evidence presented on the clinical effectiveness, namely the short follow-up of the included randomised controlled trials (RCTs; see Table 1.4) as well as adverse events and the need for monitoring (Table 1.5).

Table 1.4: Key issue 3 – Short-term nature of the included randomised trials

Report section	Sections 4.2.1 and 4.5
Description of issue and why the ERG has identified it as important	The key randomised trials (Study 1 and Study 1504) were well-conducted, multinational trials including a number of patients from the United Kingdom. However, they only included a 12-week treatment maintenance period so cannot provide long-term data on Sudden Unexpected Death in Epilepsy (SUDEP)

Report section	Sections 4.2.1 and 4.5
	and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two RCTs. The extension study suggested that improvements in convulsive seizures could be maintained for up to three years. The two 'real world' observational studies in the CS were small and the lack of a control group is a major limitation.
What alternative approach has the ERG suggested?	If possible, future studies should have a longer follow-up.
What is the expected effect on the cost effectiveness estimates?	It adds to the overall uncertainty of the results, especially given that no treatment waning was assumed in the model (argued to be based on available evidence) and various assumptions regarding mortality (e.g. SUDEP and non-SUDEP related) which seemed implausible. A strong relation between seizure frequency and mortality and the lack of treatment waning in the model both favour fenfluramine.
What additional evidence or analyses might help to resolve this key issue?	Robust evidence with longer follow-up is needed. There is some uncertainty with the current evidence.

Table 1.5: Key issue 4 – Adverse events and need for monitoring

Report section	Sections 4.2.6 and 4.5
Description of issue and why the ERG has identified it as important	Although additional treatment-related adverse events occurred with fenfluramine these were mainly not rated as serious. However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients. Although cardiac adverse events did not appear to be serious, the committee should note the importance of ongoing cardiac monitoring. Decreased appetite and weight loss shown by fenfluramine also suggest a burden for monitoring.
What alternative approach has the ERG suggested?	The ERG does not suggest an alternative approach but wanted to highlight this issue.
What is the expected effect on the cost effectiveness estimates?	Adverse events were not considered in the model for both cannabidiol and fenfluramine. Hence, the impact on the ICER is unclear. The need for monitoring (which was only partially included in the model), does lead to higher costs for fenfluramine and would therefore increase the ICER. Given the evidence presented by the company (e.g. Gunning et al. 2020), the impact of this assumption is likely to be small.
What additional evidence or analyses might help to resolve this key issue?	More data will become available, however, for now monitoring of the issues described above might be warranted

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 7.4 of this report. The company's cost effectiveness results are presented in section 6, the ERG's summary and detailed critique in section 5, and the ERG's amendments to the company's model and results are

presented in section 7. The main ERG results are reproduced using confidential patient access schemes (i.e. for cannabidiol) in a confidential appendix. The key issues in the cost effectiveness evidence are discussed in Tables 1.6 to 1.13.

Table 1.6: Key issue 5 – Model structure

Report section	5.2.2 Model structure
Description of issue and why the ERG has identified it as important	Once patients discontinued treatment, they were assumed to revert to baseline seizure frequency (as observed during the observational period of the trial) and not to the placebo 'on-treatment' seizure frequency (as observed during the maintenance period of the trial). The ERG does not agree with this approach as this "placebo" effect (which could include other factors such as natural progress or regress of disease) may also be present in the fenfluramine and cannabidiol treated patients who are still on treatment (and hence is part of the demonstrated effects). Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment. Contrary to what would be clinically expected, it was possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation.
What alternative approach has the ERG suggested?	An approach which assumes a) that patients discontinue to the placebo 'on-treatment' seizure frequency and b) that patients do not improve after treatment discontinuation should be considered.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

Table 1.7: Key issue 6 – Population and intervention and comparators

Report section	5.2.3 Population and 5.2.4 Intervention and comparators
Description of issue and why the ERG has identified it as important	The license is anticipated to include fenfluramine for use both with and without concomitant clobazam (in contrast with cannabidiol). Nevertheless, in the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended). The company indicated that concomitant treatment with stiripentol was a treatment effect modifier due to a pharmacokinetic interaction or prior AEDs with fenfluramine. Given this interaction, the (cost) effectiveness of fenfluramine likely differs for patients with and without concomitant stiripentol. Therefore, the ERG preferred to report the results for these populations (based on concomitant stiripentol) separately.

Report section	5.2.3 Population and 5.2.4 Intervention and comparators
	In combination with the preceding comment, this resulted in three subpopulations that should be considered: • Patients without concomitant clobazam and stiripentol, • Patients with concomitant clobazam but without stiripentol, and • Patients with concomitant clobazam and stiripentol. The phase III fenfluramine trials targeted children or adolescents ≤18 years old. Nevertheless, the population considered in the company's base-case included children or adolescents that aged in adulthood as well as patients that initiated fenfluramine in adulthood. The methods to construct patient profiles were unclear and the correlations between patient characteristics incorporated in the bootstrapped patient profiles were limited.
What alternative approach has the ERG suggested?	Include all comparators listed in the scope, provide results for the three subpopulations listed above (including all relevant comparators per population), ensure the constructed patient profiles are plausible and focus on children or adolescents.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

Table 1.8: Key issue 7 – Intervention and comparators

Report section	5.2.4 Intervention and comparators
Description of issue and why the ERG has identified it as important	The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at six months. This stopping rule was not proposed by the European Medicines Agency (EMA) nor was it found in the scope provided by NICE.
What alternative approach has the ERG suggested?	Explore the impact of this stopping rule in more detail, e.g. conditional on the ERG or committee preferences. This could not be done by the ERG in the current model.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

Table 1.9: Key issues 8 & 9 – Treatment effectiveness and extrapolation

Report section	5.2.6 Treatment effectiveness and extrapolation
Description of issue and why the ERG has identified it as important	The company assumed that the relative treatment effect was constant and maintained over time while patients were on treatment. This assumption was mainly based on the open-label extension (OLE, study 1503) trial data as well as data from the Belgian real-world evidence (RWE) study (observational

Report section	5.2.6 Treatment effectiveness and extrapolation
	cohort). It should be noted that these are non-comparative studies and it is therefore difficult to infer from these sources that the relative treatment effectiveness does not wane over time (while on treatment). The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the NMA, for convulsive seizure frequency, i.e. assumed these two outcomes are proportional. Although it is evident that there is an association between these two outcomes, it is unclear whether it is plausible to assume proportionality. Moreover, particularly given that the cannabidiol Summary of Product Characteristics (SmPC) indicated that, compared with placebo, cannabidiol 10mg increased the convulsive seizure-free by 2.7 days while fenfluramine co-administered with stiripentol increased convulsive seizure-free days by two days. Given convulsive seizure-free days is the main driver of the incremental QALYs between the treatments, the current assumptions might result in an overly optimistic utility benefit for fenfluramine. The company did not incorporate non-convulsive seizures in the economic model and stated that this is conservative (both in the CS and in response to clarification question C18). This claim is, however, highly questionable, especially as this is based on a comparison with the placebo arm, while in the company's base-case fenfluramine is compared with cannabidiol. In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency. Given the strong assumptions the company was required to make leading to seemingly implausible estimates of relative risk, the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the preference of the committee working on TA614, the ERG preferred to remove the link between convulsive seizures and mortality. Due to the multiple issues related to the implementation of mortality, the ERG adjusted the approach to incorporate mortality in the economic model. Particularly, Dravet syndrome mortality was directly estimated based on reported SUDEP and non-SUDEP mortality (independent on convulsive seizures and not specifically incorporating status epilepticus (SE) mortality). This approach is consistent with TA614, i.e. the approach used by the ERG (except for the convulsive seizure-free health state) as well as the committee statement that *"there is insufficient evidence to prove that cannabidiol prolongs life"* indicating that the assumed link between convulsive seizures and mortality risk should be removed. The company assumed that the frequency of convulsive seizures in patients aged 18 years and over were halved, and convulsive seizure-free days doubled (compared with patients aged <18 years). However, there are little data to inform/quantify this improvement when patients become older.
What alternative approach has the ERG suggested?	Explore the impact of treatment waning (not performed by the company despite requested during the clarification phase), implement (reduction in) seizure-free days based on empirical

Report section	5.2.6 Treatment effectiveness and extrapolation
	evidence (instead of questionable assumptions), explore the impact of excluding non-convulsive seizures, remove the link between convulsive seizures and mortality (as done in the ERG base-case) and explore different assumptions for (relative) treatment effectiveness in adult patients.
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

Table 1.10: Key issues 10 & 11 – Health-related quality of life

Report section	5.2.8 Health-related quality of life
Description of issue and why the ERG has identified it as important	To generate utility values in the model, the company used the mapping study of Khan et al. 2014 to map Paediatric Quality of Life Inventory (PedsQL) to EQ-5D-Y (EuroQOL–5 Dimensions–Youth scale produced by the European Quality of Life Group). However, the authors of this mapping approach stated that it has some methodological weaknesses in that the algorithm performs worse as the quality of life of the population under consideration becomes worse. Therefore, the mapping function may not be suited to the population considered in the CS. In line with TA614, carer utilities were included in the company's base-case using a regression function based on carers of children and adolescents in the registration studies. However, contrary to TA614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month). Furthermore, the ERG questions whether the regression function based on carers of children and adolescents is also applicable to carers of adults and considers the assumption of 1.8 carer per patient over a whole lifespan to be high. The primary endpoint in the registration studies was the change in mean monthly convulsive seizure frequency. However, the company based the QALY estimates in the economic model only on convulsive seizure-free days, assuming proportionality between these two outcomes (Table 1.9). When a patient in the economic model died, the corresponding carer utility was also set to zero. This clearly overestimates the impact of mortality, given that the caregiver does not die together with the patient and its assumed utility value of 0 is therefore an implausible underestimation of the reality.
What alternative approach has the ERG suggested?	Alternative approach related to the implementation of carer utilities, consistent with TA614. Estimating health state utilities conditional on convulsive seizure frequency (not convulsive seizure-free days)

Report section	5.2.8 Health-related quality of life
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

Table 1.11: Key issues 12, 13 & 14 – Model implementation and validation

Report section	6.3 Model implementation and validation
Description of issue and why the ERG has identified it as important	• One iteration of the probabilistic sensitivity analysis (PSA) takes approximately 80 minutes. To run a PSA of 1,000 iterations would require >55 days and it was therefore not feasible for the ERG to run these analyses. • The company provided the R code which was used to run most of the scenario analyses. However, the scenario assuming that individuals who had >20 seizure-free days per month would be given 0 carer utilities was missing from the R code and the ERG was not able to replicate the ICER mentioned by the company. • In the model, 480 patients were simulated. However, it is not clearly stated in the CS why 480 patients were chosen. The ERG judged that the number of simulated patients should be dependent on diagnostics such as a figure demonstrating mean outcomes (costs, QALYs, and ICER) vs. the number of patients (i.e. visual inspection of stochastic uncertainty) rather than the estimated total population in the United Kingdom. • Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon. • Although the company referred to NICE TA614 for several methodological assumptions, the CS lacks cross-validation to that appraisal when looking at estimated outcomes of both models. When comparing total costs of cannabidiol in NICE TA614 to the total costs for cannabidiol, as estimated in the current appraisal, a large discrepancy can be observed, i.e. total costs of £393,521 per patient compared to £255,759 in the current appraisal. Moreover, the estimated QALYs gains for cannabidiol compared to SoC (or current clinical management as it is referred to in TA614 are notably larger in TA614 compared to the current appraisal, i.e. incremental QALY gain of 1.18 QALY in TA614 compared to 0.97 in the current appraisal. Both the difference in total costs and QALY gains in the TA614 appraisal result in a substantially lower ICER for cannabidiol compared to SoC as what is presented in the CS, with an ICER of £29,268 per QALY gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.
What alternative approach has the ERG suggested?	Explore origin of the aforementioned differences between TA614 and the current appraisal, justify that 480 patients is sufficient, ensure the model is internally valid and behaves as expected.

Report section	6.3 Model implementation and validation
What is the expected effect on the cost effectiveness estimates?	Could potentially have a substantial impact on the cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	This should be further explored by the company once the validity issues are resolved.

1.6 Other key issues: summary of the ERG's view

No other key issues were identified by the ERG.

1.7 Summary of ERG's preferred assumptions and resulting ICER

1.7.1 ERG new base-case

1.7.1.1 Fixing errors

1. Removal of the last cycle of bootstrapped patient data with convulsive seizure days and convulsive seizure frequency (cycle 131 of both data frames) as these data, seemed implausible to the ERG (section 5.2.3 - population).
2. Minor fixes:
    a. the ERG recalculated the SE mortality probability of 0.029% per cycle and considered that this is not a conditional probability (conditional on having SE) and thus should not be applied to SE patient only (rather the whole population, see section 5.2.6). This could not be easily adjusted in the model, but in order to incorporate treatment-independent mortality rates, this probability was set to 0 in the ERG base-case.
    b. the discontinuation probabilities used in the model were not in line with the probabilities mentioned in the CS. Hence, the discontinuation probabilities were adjusted to be in line with the CS, and
    c. in the CS, it was possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation. The ERG adjusted the post discontinuation convulsive seizure frequency and convulsive seizure-free days.

1.6.1.2 Fixing violations

3. The ERG added SoC as separate comparator in the model by incorporating results from the placebo arm of the trials by running the model twice (one in which a 0% reduction of cannabidiol was assumed, which essentially means that only the effectiveness of the placebo was included and the costs of cannabidiol were removed) and one with cannabidiol as per the CS base-case (section 5.2.4 – intervention and comparators).

1.6.1.3 Matters of judgment

4. The ERG decided to present their base-case for three subpopulations (section 5.2.3)
    a. No co-administered clobazam or stiripentol (including SoC and SoC + fenfluramine). For this population clobazam and stiripentol costs were set to 0 (and only the Study 1 cohort was considered).

   b. Co-administered clobazam without stiripentol, which includes SoC, SoC + cannabidiol, SoC + fenfluramine. For this population, clobazam costs were added to the fenfluramine arm and only the Study 1 cohort was considered.
   c. Co-administered clobazam with stiripentol, which includes SoC, SoC + cannabidiol, SoC + fenfluramine. For this population, clobazam costs were added to the fenfluramine arm and only the Study 1504 cohort (fenfluramine + stiripentol) was considered.
5. In the subpopulation that receives co-administered clobazam with or without stiripentol, clobazam was also added to the fenfluramine arm (to reflect the concomitant clobazam population). It should be noted that, similar to what was done in the company's scenarios, only costs were added assuming the effectiveness of the treatments remained similar.
6. The ERG preferred to remove the link between convulsive seizures and mortality (consistent with committee preferences for TA614). The ERG implemented DS mortality as reported by Cooper et al. for DS (section 5.2.6).
7. The ERG assumed no change when patients age (section 5.2.6).
8. The ERG assumed a carer utility of [redacted] (highest estimated utility by the company) for individuals with >20 seizure-free days a month (section 5.2.8).
9. In the ERG base-case reduction in convulsive seizure frequency × 0.4 was used to estimate the reduction in convulsive seizure days (section 5.2.6).

1.7.2 ERG scenarios

1. In TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility ([redacted] for >8 - ≤ 25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died. Hence, the ERG explored the impact of using carer disutilities from TA614.
2. The ERG assumed that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial instead of the observational trial period (section 5.2.2 Model structure).
3. The accidental mortality was increased to reflect all non-SUDEP mortality as reported by Cooper et al., for DS.
4. In response to the factual accuracy check, the ERG implemented a scenario in which discontinuation probabilities for lack of efficacy and other discontinuation for both the titration as well as the maintenance period were similar between CBD and fenfluramine (in line with table 30 of the CS).

1.7.3 Conclusion

The individual ERG adjustments had a large impact on the ICER, ranging from £19,863 per QALY gained to £162,886 per QALY gained in the merged population (population representing both with and without co-administered stiripentol and/or clobazam population Study 1 and Study 1504). It should be noted however that results between the three considered subpopulations, proposed by the ERG, vary greatly, with the ICER in the ERG base-case including all changes for the no co-administered clobazam or stiripentol population being £77,440 per QALY gained, for the co-administered clobazam without stiripentol population £82,865 per QALY gained and for the co-administered clobazam with stiripentol population fenfluramine was £121,216 per QALY gained compared with cannabidiol.

The ERG base-case ICER for the merged population was £83,426 per QALY gained compared to cannabidiol and £90,095 per QALY gained when comparing fenfluramine to SoC. Moreover, the ERG scenario using carer disutilities in line with TA614, resulted in lower ICERs for the three populations

as well as the merged population, with an ICER of £61,837 per QALY gained for the merged population and £88,183 per QALY gained when comparing fenfluramine to SoC. Additionally, the scenario with increased accidental mortality to reflect all non-SUDEP mortality resulted in an ICER of £74,789 per QALY gained compared to cannabidiol in the merged population and £100,117 per QALY gained when comparing fenfluramine to SoC.

Lastly, the ERG scenario in which it was assumed that once patients discontinue treatment, these patients would revert to the placebo seizure frequency as observed during the maintenance period of the trial instead of the observational trial period resulted in an ICER of £49,574 per QALY gained compared to cannabidiol in the merged population and £158,354 per QALY gained when comparing fenfluramine to SoC. It should be noted however, that this scenario should be interpreted with extreme caution as this scenario could not be easily implemented in the model as this change also impacted the placebo effect (which is added to the treatment effect and might include other factors such as natural progress or regress of disease) and therefore is likely to have an impact on other assumptions in the model, e.g. such as the stopping rule. This resulted in implausible survival estimates (survival benefit of fenfluramine compared to cannabidiol, whereas all mortality in the ERG should be treatment-independent). This underscores the validity issues related to the economic model that remain unresolved, even though multiple errors were fixed by the ERG.

It should be reiterated that some of the abovementioned potential biases (see for instance the model structure and validity sections) could not be explored by the ERG. Consequently, the ICERs reported are subject to great uncertainty. A summary of the ERG's base-case results is presented in Table 1.14.

Table 1.12: Summary of ERG's base-case results

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base-case; Treatments: • Intervention: Fenfluramine + SoC • Comparator: Cannabidiol + clobazam + SoC	[redacted]	[redacted]	£31,773
Deterministic ERG base-case – All changes – removal of effects of cannabidiol to mimic fenfluramine placebo arm. Treatments: • Intervention: Fenfluramine + SoC • Comparator: SoC	[redacted]	[redacted]	£77,440
Deterministic ERG base-case – All changes - Population with co-administered clobazam without stiripentol Treatments: • Intervention: Fenfluramine + SoC + clobazam • Comparator: Cannabidiol + clobazam + SoC	[redacted]	[redacted]	£82,865
Deterministic ERG base-case – All changes - Population with co-administered clobazam with stiripentol Treatments:	[redacted]	[redacted]	£121,216

Scenario	Incremental cost	Incremental QALYs	ICER
• Intervention: Fenfluramine + SoC + clobazam + stiripentol • Comparator: Cannabidiol + clobazam + SoC + stiripentol			
Deterministic ERG base-case – All changes – Merged population Treatments: • Intervention: Fenfluramine Comparator: • Comparator: Cannabidiol	[redacted]	[redacted]	£83,426
ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio, QALY = quality-adjusted life year; SoC = standard of care			

2. Background

In this report the Evidence Review Group (ERG) provides a review of the evidence submitted by Zogenix International Ltd. in support of fenfluramine hydrochloride, trade name (Fintepla®) for the treatment of patients with Dravet syndrome. In this section we outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken from section B.1.3 of the company submission (CS) with subsections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem

The underlying health problem in this appraisal is Dravet syndrome, a severe life-limiting form of epilepsy characterised by epileptic seizures as well as cognitive-behavioural impairment and motor disorders and affecting children and adults.[2] Dravet syndrome is a rare disease but it is regarded as one of the most serious genetic epileptic encephalopathies.[3] In the United Kingdom (UK), the incidence of Dravet syndrome ranges between 1 in 19,000 to 1 in 40,000 live births and according to the CS, *"there are between 670 and 2,670 patients in the UK currently living with Dravet syndrome"*.[1, 4]

The burden of Dravet syndrome was highlighted in the CS, i.e. *"the combination of seizure burden, and cognitive, motor, behavioural and sleep impairments in Dravet syndrome, significantly impairs the health-related quality of life (HRQoL) of patients"*.[1, 5] The company also detailed the substantial socioeconomic burden on families, i.e. *"parents of Dravet syndrome patients often giving up paid employment to be full time caregivers with little respite from their carer responsibilities"*.[1] The company cited a Dravet syndrome mortality rate between 15-20% with most deaths occurring before the age of 10 years, and the risk remaining elevated throughout adulthood.[1] The company further stated that patients with Dravet syndrome have a higher risk of Sudden Unexpected Death in Epilepsy (SUDEP) occurring at a rate of around 9-10% per 10 years and status epilepticus, which occur at a rate of around 5-6% per 10 years.[1] This is largely in line with a review that provided a breakdown of cause of death based on 177 deaths: 87 (49%) SUDEP, 56 (32%) status epilepticus.[6]

The company stated that *"high seizure frequency is well recognised as a significant contributing risk factor for SUDEP"* and that *"the presence of convulsive seizures is associated with a higher risk of premature death in epilepsy compared to other seizure types"*.[7-9]

ERG comment: The company provided a solid overview of the underlying health problem illustrating the seriousness of the condition and its burden on patients and their families. The ERG checked the references provided to support the statements in the CS and these were appropriately cited. However. clearer definitions and characterisations of seizures in Dravet are missing.[10] The clinical experts consulted by the ERG agreed with the statement by Dravet Syndrome UK in that it might be more *"accurate and complete to define DS as a life-long, life-limiting neurological condition"* rather than 'just' a *"severe form of epilepsy"*.[4, 11]

The role of genetic mutation in Dravet syndrome was mentioned in the CS but the prevalence of those mutations was missing. It should be noted that 79% of patients with Dravet syndrome tested positive for mutations of the SCN1A gene in a recent a prospective cohort study.[12]

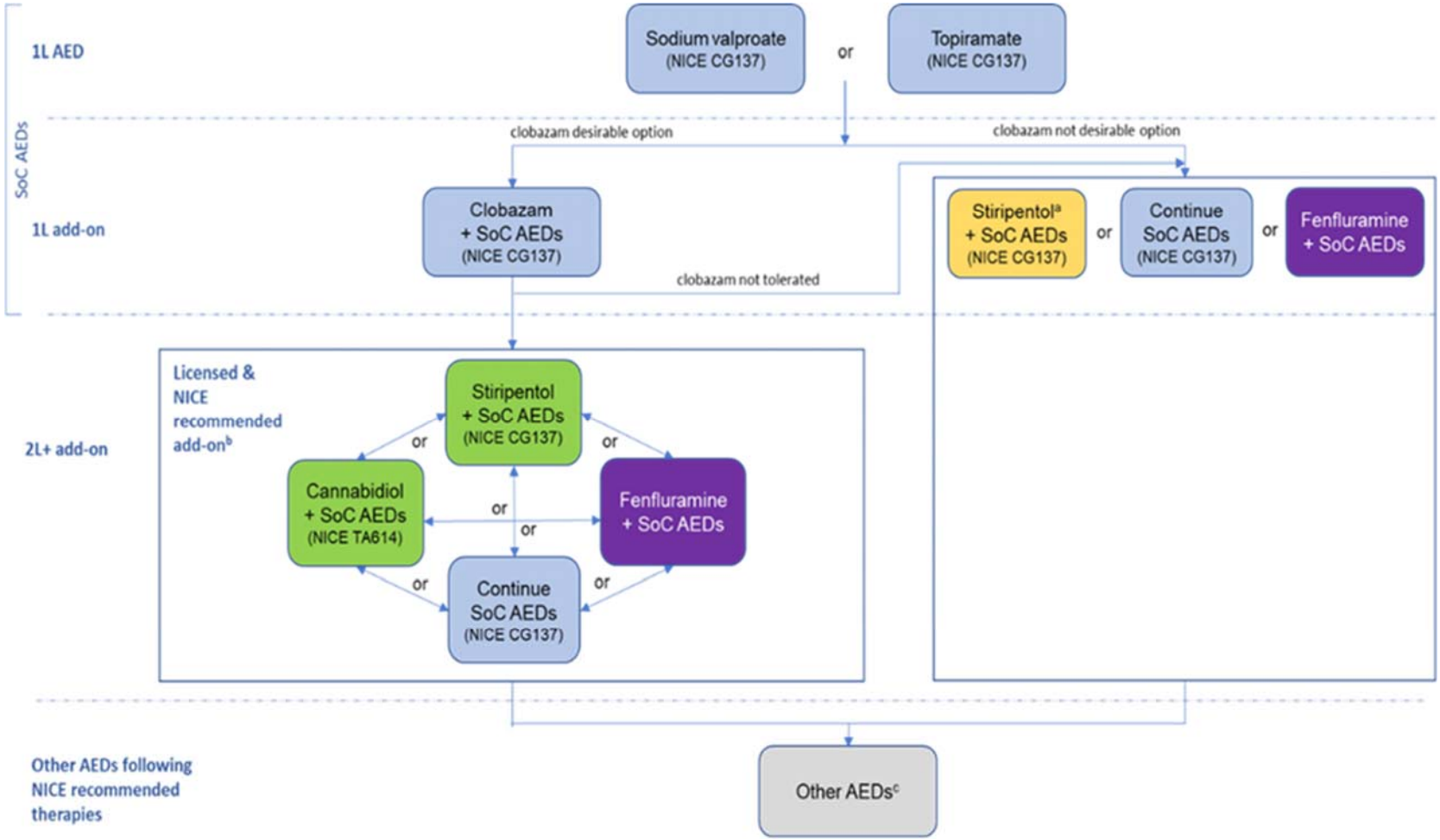
2.2 Critique of company's overview of current service provision

The main clinical guidance relevant to this submission is clinical guideline (CG) 137 and technology appraisal (TA) 614.[13, 14] These guidelines by the National Institute for Health and Care Excellence (NICE), referred to in the CS, recommend consideration of sodium valproate or topiramate followed by add-on therapy with clobazam and/or stiripentol for Dravet. The company highlighted a

distinctive benefit of the drug i.e., the ability to use fenfluramine irrespective of clobazam at any point in the add-on therapy pathway.[1] The company claims that safe and effective treatment options are limited for Dravet; and that there is an unmet need for more tolerable therapies that reduce the seizure frequency and improve the overall condition of patients with the disease.[1]

Figure 2.1 shows the proposed treatment pathway for fenfluramine for patients with Dravet syndrome.

Figure 2.1: Proposed position of fenfluramine within the treatment pathway for Dravet syndrome



Based on Figure 2 of the CS[1], adapted from NICECG137 and NICE TA614[13, 14]

1L = first-line; 2L+ = second- and subsequent line; AEDs = anti-epileptic drugs; CG = clinical guideline; CS = company submission; NICE = National Institute for Health and Care Excellence; SoC AEDs = standard of care AEDs reflecting AEDs and add-on therapies continued from previous line; TA = technology appraisal

a Stiripentol is not licensed for use as 1L add-on therapy in Dravet syndrome without clobazam; however, NICE guidelines recommend considering stiripentol as an alternative to clobazam if seizure control not achieved on 1L treatment alone; [b] We [the company] expect clinicians would select clinically appropriate options from this group, would

optimise doses and would exhaust these options before considering moving to other AEDs. Fenfluramine is proposed as an alternative 2L+ add-on therapy option alongside cannabidiol (with clobazam) or stiripentol, and may be used before stiripentol (stiripentol-naïve) or after stiripentol (stiripentol-failures/experienced), as demonstrated in Study 1; or in addition to stiripentol, as demonstrated in Study 1504. In the primary base-case cost effectiveness analysis, fenfluramine is presented as an alternative to cannabidiol (with clobazam). Secondary analyses are presented to support decision-making for fenfluramine as a: 1L (or 2L) add-on therapy option in patients where a clobazam-based strategy (incl. stiripentol and cannabidiol) is not desirable, or as a 2L+ add-on therapy option for patients before, after, or on top of stiripentol; [c] Other AEDs licensed for general epilepsy and used in Dravet syndrome on an experimental or off-label basis.

Of note: In addition to AEDs, ketogenic diet and vagal nerve stimulation may also considered as additional adjunct treatments but are used rarely and not further considered in this appraisal. All patients in Study 1504 received stiripentol (and 95% received clobazam, in accordance with the licensed stiripentol indication).

ERG comment: The company's overview of the current pathway is appropriate.

However, even though NICE CG 137 highlights that *"the ideal treatment strategy is personalised and considers a range of factors including the change in typical seizure patterns over time, seizure types, co-medications, comorbidities, adverse effects, lifestyles, and the personal preferences of patients, families and carers"* that personalised component is missing in the CS.[1, 13] For instance, the company insists that the ketogenic diet is rarely used and not considered in the appraisal (e.g. see footnote of Figure 2.1).[1] It should be noted that research shows that one year after starting the ketogenic diet, 77% of children had achieved a >75% decrease in their seizures.[15] Similarly, positioning of vagus nerve stimulation (VNS) in the current treatment pathway is also unclear or missing in the CS, however, research shows that VNS appears to reduce seizure frequency in patients with Dravet syndrome.[16] According to Figure 2 of the CS, first-line add-on therapy may consist of stiripentol + standard of care, which can also consist of stiripentol.[1] It is not clear which *"other AEDs licensed for general epilepsy and used in Dravet syndrome on an experimental or off-label basis"* the CS is referring to.[1]

The ERG notes a statement by Professor Sanjay Sisodiya, representing the Association of British Neurologists (ABN), according to which fenfluramine is *"simpler to use than some other agents, e.g. stiripentol, cannabidiol"*.[17] The clinical experts consulted by the ERG agrees with that statement.

3. Critique of company's definition of decision problem

As the company included a lot of detail in the decision problem table, we have broken it into several tables, each with their own critique.

3.1 Population

The population defined in the scope for this appraisal was *"people with Dravet syndrome (DS) whose seizures are inadequately controlled by established clinical management"*, see Table 3.1.[1] The company addressed this population, i.e. *"the submission relied, primarily, on two randomised controlled trials (RCTs) of fenfluramine (Study 1 and Study 1504)."*[18-20] Both trials were conducted in patients aged two to 18 years of age. Although the decision problem did not specify any age restriction and the expected licenced indication for Fintepla® is for patients two years of age and older, neither of the key trials used in the submission included adult patients (over the age of 18 years). Both trials included patients from the UK (24 participants).[21]

Table 3.1: The decision problem – Population

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management. Based on its anticipated licensed indication, fenfluramine will provide an add-on treatment option across the add-on treatment pathway, without reliance on the use of clobazam.	NA
Based on Table 1 of the CS[1] CS = company submission; NA = not applicable; NICE = National Institute for Health and Care Excellence		

ERG comment: Around 85% of people with Dravet syndrome can survive into adulthood.[22] Therefore a high proportion of those eligible for fenfluramine are not fully represented in the main trials given the inclusion of patients only up to age 18 years. Given the lack of randomised evidence for adults with DS, the company was asked to confirm that the results presented in the CS only apply to the narrower population, i.e. those aged 2-18 years. If not, the company was asked to provide results for participants outside this age group. The company responded that they believed that data from the open label Study 1503, real-world evidence studies program (see Section 4.2.7) and the ongoing European expanded access demonstrated that both children and adults "*experience significant and often similarly profound reductions in convulsive seizure frequency with fenfluramine treatment*".[21] However, numbers of adults in these studies are small and none of this constitutes randomised evidence. The committee will need to decide if is satisfied that fenfluramine will be equally suitable for adults with Dravet syndrome. Of note, the clinical experts consulted by the ERG agree with the company, i.e. that results are applicable to adult patients with DS.

3.2 Intervention

The intervention (fenfluramine hydrochloride (Fintepla®) in addition to current clinical management) is in line with the scope, see Table 3.2.[4] Orphan drug designation (EU/3/14/1219) was granted by the European Commission in 2014.[23] The company stated that the designation is expected to be maintained

at the time of market authorisation. A Committee for Medicinal Products for Human Use (CHMP) opinion is expected in late Q3 2020 with marketing authorisation approval anticipated in early Q1 2021.[1]

Fintepla® is indicated for the treatment of seizures associated with DS as an add-on therapy to other antiepileptic medicines in children aged two years to 17 years and adults, see appendix C of the CS.[24] It is described as a serotonin releasing agent which stimulates 5-HT receptor sub-types through the release of serotonin.[24] However, the precise mode of action of fenfluramine in DS is not known.

Fenfluramine hydrochloride is an oral solution which may be taken with or without food. The following details of dosage were presented in the CS[1]:

- *"Patients who are not taking stiripentol:*
    - *The starting dose is 0.1 mg/kg twice daily.*
    - *After 7 days, for patients who are tolerating fenfluramine, and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily.*
    - *After an additional 7 days, for patients who are tolerating fenfluramine, and require a further reduction of seizures, the dose can be increased to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day).*
    - *Do not exceed a total dose of 13 mg (6 mL) twice daily.*
- *Patients who are taking stiripentol:*
    - *The starting dose is 0.1 mg/kg twice daily.*
    - *After 7 days, for patients who are tolerating Fintepla, and require a further reduction of seizures, the dose can be increased to 0.2 mg/kg twice daily (0.4 mg/kg/day).*
    - *Do not exceed a total dose of 8.5 mg (4 mL) twice daily.*
    - *When discontinuing fenfluramine, the dose should be decreased gradually"*

The following anticipated requirements for additional tests and investigations were listed in the CS[1]:

"Valvular heart disease and pulmonary hypertension - Because of reported cases of cardiac valvulopathy (and pulmonary hypertension) that may have been caused by fenfluramine at higher doses used to treat adult obesity, patients must undergo an echocardiogram (ECHO) to evaluate for regurgitant aortic or mitral valvular heart disease prior to starting treatment. Further cardiac monitoring must be performed using ECHO. In the controlled clinical studies of Fintepla, no valvular heart disease was observed.

Weight loss - Fenfluramine can cause weight loss. The decrease in weight appears to be dose-related. Most subjects resume weight gain over time while continuing fenfluramine treatment. The patients' weight should be monitored."

Table 3.2: The decision problem – Intervention

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Fenfluramine in addition to current clinical management.	Fenfluramine in addition to current clinical management.	NA
Based on Table 1 of the CS[1] CS = company submission; NA = not applicable; NICE = National Institute for Health and Care Excellence		

ERG comment: Adverse effects of fenfluramine are discussed in more detail in section 4.2.6. The committee should consider the implications of the need for increased cardiac monitoring and weight monitoring**.** It should be noted that only costs for echocardiograms (ECGs) but not for weight monitoring were included in the model.

The company were asked what proportion of patients were expected to receive the 0.2 mg/kg/day dose rather than the increased dose of 0.7 mg/kg/day in the non-stiripentol group. The company replied that *"fenfluramine will be initiated in all patients at a dose of 0.2mg/kg/day, irrespective of whether patients are taking concomitant stiripentol or not. In those not taking concomitant stiripentol, the dose can be titrated up to a maximum of 0.7mg/kg/day (capped at 26mg/day), and in those who are taking concomitant stiripentol the dose can be titrated up to a maximum of 0.4mg/kg/day (capped at 17mg/day). The 0.2mg/kg/day dose is an initiation dose and we do not anticipate patients will be maintained on the 0.2mg/kg/day dose"*.[21]

3.3 Comparators

The final NICE scope suggested that the comparators for this appraisal are combinations of sodium valproate, topiramate, clobazam, stiripentol, levetiracetam, ketogenic diet, vagus nerve stimulation and cannabidiol with clobazam.[4] In practice, the clinical management of patients with DS is an individually tailored combination of antiepileptic drugs (AEDs), diet and devices, see Table 3.3. Figure 2.1 of this report described the potential place in the pathway for fenfluramine. The first-line treatment is sodium valproate or topiramate. Fenfluramine is proposed as a second-line add-on treatment option after clobazam, or as a first-line add-on treatment option in patients where clobazam or a clobazam-based regimen is undesired. The company stated that most patients would receive fenfluramine as proposed in the second-line + add-on therapy setting (where comparators are continuation of SoC AEDs (standard of care AEDs reflecting AEDs and add-on therapies continued from previous line), cannabidiol + SoC AEDs or stiripentol + SoC AEDs), see Table 3.3.[1]

The company considered that, in the absence of sufficient stiripentol data to make a robust comparison, cannabidiol (with clobazam) was the most appropriate primary clinical and economic comparator.[1] However, the company also provided comparative analyses of fenfluramine as an add-on therapy to background standard of care AEDs that included or excluded stiripentol, and in patients not taking concomitant clobazam.[1]

Table 3.3: The decision problem – Comparators

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Established clinical management without fenfluramine, which may include combinations of: • Sodium valproate • Topiramate • Clobazam • Stiripentol • Levetiracetam • Ketogenic diet • Vagus nerve stimulation • Cannabidiol with clobazam	Fenfluramine is anticipated to be licensed for use as an add-on therapy to a patient's established clinical management (see below). In the UK and in line with the licensed indication, fenfluramine, as an add-on after first line AEDs is proposed for use as a: 2L add-on treatment option after clobazam, or 1L add-on treatment option in patients where clobazam or a clobazam-based regimen is undesired. In the absence of sufficient stiripentol data with which to make robust comparisons, the appropriate primary clinical and economic comparator for fenfluramine is: **Cannabidiol (with clobazam)** The cost effectiveness of fenfluramine as an alternative 2L+ add-on treatment option (alongside stiripentol and cannabidiol (with clobazam)) at the same points in pathway), is inferred from the relative cost effectiveness of fenfluramine vs cannabidiol (with clobazam). Additional analyses, based on the robust and internally consistent fenfluramine RCT data versus SoC AEDs, support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. The established clinical management of patients is typically formed of an individually tailored background of combinations of SoC AEDs, diet and devices, which may include: • SoC AEDs (e.g.): o Sodium valproate o Stiripentol o Clobazam o Topiramate	Clobazam, stiripentol and cannabidiol (with clobazam) are recommended as add-on therapies in existing NICE guidance[13, 14]; however, as cannabidiol (with clobazam) is the only add-on therapy to have been formally appraised by NICE, and is accepted as a clinically and cost effective option (alongside stiripentol) in the existing add-on therapy pathway, and is also the only therapy with sufficient trial data to permit a robust comparison, **a primary clinical and economic comparison of fenfluramine against cannabidiol (with clobazam) is the most appropriate, relevant and robust comparison to address the decision problem in this appraisal.** The available clinical data for stiripentol (and clobazam) precludes a robust comparison of fenfluramine against other NICE-recommended add-on therapies, as accepted in the NICE appraisal of cannabidiol.[14] **In a 2L+ add-on therapy setting:** Cannabidiol (with clobazam) is accepted as a cost effective option alongside stiripentol. Conclusions on the cost effectiveness of fenfluramine as an add-on option at the same points in the add-on therapy pathway as cannabidiol (with clobazam) and stiripentol are recommended may therefore be inferred from the cost effectiveness of fenfluramine vs cannabidiol (with clobazam). **In a 1L add-on therapy setting:** We propose that fenfluramine would not be used as a direct alternative to clobazam but would be used where clobazam is not desirable or is not tolerated. The appropriate comparison would therefore be fenfluramine vs Soc AEDs, in a population of patients not receiving clobazam. However, most patients

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	○ Levetiracetam • Ketogenic diet • Vagus nerve stimulation	would receive fenfluramine as proposed in the 2L+ add-on therapy setting Comparative analyses of fenfluramine as an add-on therapy to background Soc AEDs that include or exclude stiripentol, or in patients not taking concomitant clobazam; support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. Ketogenic diet and Vagus nerve stimulation are excluded from the economic model on the basis they are used in a minority of patients and would be used equally in both the fenfluramine and comparator arms of the model. Their exclusion will therefore not impact the estimated incremental cost effectiveness of fenfluramine and is consistent with the approach taken in the NICE appraisal of cannabidiol (TA614).[14]
Based on Table 1 of the CS[1] 1L = first-line; 2L = second-line; 2L+ = second- and subsequent lines; AED = antiepileptic drug; CS = company submission; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; SoC = standard of care; TA = technology appraisal; UK = United Kingdom		

ERG comment: The company was asked what proportion of patients might receive fenfluramine as a first-line add-on therapy in patients where clobazam or a clobazam-based regimen is undesired. The company stated this would be a small proportion. They added that *"as clobazam is well established in the clinical pathway and clinicians managing people with Dravet syndrome are well experienced in the use of clobazam, we anticipate that clobazam would be considered as a first-line add-on in the vast majority of patients and assume it would be clinically suitable for the vast majority of patients. In our budget impact model, based on a number of simplifying assumptions (see details in Appendix O), we have estimated that clobazam would not be a clinically desirable first-line add-on therapy in* [redacted] *of patients, of which possibly* [redacted] *of all Dravet patients in need of add-on therapy) would receive fenfluramine in the year 2024 onwards".*[21]

The company was asked to clarify why stiripentol, a potential comparator to fenfluramine, was not included in the network meta-analysis. They replied that *"due to substantial differences in the assessment of convulsive seizure reduction endpoints in the stiripentol trials, and also the unclear risk of bias that limits the quality of the stiripentol trial evidence, we determined it is not feasible to conduct an ITC comparing add-on fenfluramine vs add-on stiripentol".*[21] This issue is discussed further in this report.

3.4 Outcomes

All outcomes defined in the final NICE scope were addressed in the CS, see Table 3.4.[1, 4] In addition to patient quality of life, caregiver/family quality of life was assessed in the main trials and was considered in the economic model. The primary outcome of the randomised trials, and hence that used in the economic model, was reduction in convulsive seizures. The company presented additional outcomes including seizure-free intervals (days).[1]

Table 3.4: The decision problem – Outcomes

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
The outcome measures to be considered include: • Seizure frequency (overall & by type) • Response rate (overall & by type) • Seizure severity • Incidence of status epilepticus • Mortality • Adverse effects of treatment	The outcome measures included are: • Seizure frequency (overall & by type): o Convulsive seizures o Non-convulsive seizures • Response rate (overall & by type) • Seizure severity* • Seizure-free intervals (days), over a defined period of time o Cumulative convulsive seizure-free days o Average longest convulsive seizure-free period	The primary and key secondary endpoints in the registration trials for fenfluramine measured measure reductions in convulsive seizure frequency. Whilst fulfilling standard regulatory requirements and providing a single metric of effect, these metrics alone have some limitations. For example, a 50% reduction from baseline seizures per month, would have different clinical, economic and QoL implications, if patients had experienced 2 or 60 seizures per month at baseline. Additional endpoints e.g. seizure-free intervals, provide metrics more closely aligned with the goals of treatment and in having a meaningful impact on patient quality of life. As widely reported by patient groups, Dravet syndrome is associated with a significant caregiver burden.[25] Therefore, data on HRQoL from the caregiver perspective in addition to the patient's was formally collected in the Phase 3 fenfluramine clinical studies.

Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
• Health-related quality of life.	o Convulsive seizure-freedom and near seizure freedom • Time to convulsive seizure event (relative between treatments) • Incidence of status epilepticus • Mortality • Adverse effects of treatment • Health-related quality of life: • Patient: • PedsQL • QOLCE • CGI-I • Caregiver/family: • EQ-5D-5L • PedsQL (family impact module).	Use of rescue medication and inpatient admission have been included, as valuable objective measures of the impact of seizure severity*, beyond patient/clinical experience alone.
Based on Table 1 of the CS[1] * Footnote included in Table 1 of the CS, however, no explanation was provided. CGI-I =Clinical Global Impression of Improvement; CS = company submission; EQ-5D-5L =EuroQOL 5 Dimension, 5 Level Instrument; HRQoL = health-related quality of life; NICE = National Institute for Health and Care Excellence; PedsQL =Paediatric Quality of Life Inventory; QoL = quality of life; QOLCE =Quality of Life in Childhood Epilepsy Questionnaire; SoC = Standard of Care		

ERG comment:

- The inclusion of caregiver quality of life outcomes in addition to patient quality of life outcomes is appropriate given the nature of Dravet syndrome. It is also consistent with the previous NICE assessment of cannabidiol.[14] However, the ERG had some concerns about how caregiver quality of life was implemented in the economic model, see section 5.2.8.
- The inclusion of additional outcomes including convulsive seizure-free days appears to be appropriate. However, the ERG had some concerns about how these outcomes were implemented in the economic model, see section 5.2.5.
- The main randomised trials, as previously stated, have a treatment maintenance period of just 12 weeks so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two randomised trials. In addition, it should be noted that in TA614 (considering cannabidiol for DS), the committee argued that *"there is insufficient evidence to prove that cannabidiol prolongs life"*.[14]

3.5 Other relevant factors

The company proposed a 'simple discount' patient access scheme (PAS) price (excluding value-added tax (VAT)). This is detailed below.[1]

[redacted]

Based on the above assumptions, the annual maintenance treatment cost, based on the proposed PAS price (Ex-VAT) of FINTEPLA, is estimated as: [redacted] *per patient not receiving concomitant stiripentol and* [redacted] *for patients concomitantly receiving stiripentol.*

The average annual per 30 kg patient price would therefore be estimated as [redacted] *per patient."*

ERG comment: The company included information in the equity section of Table 1 of the CS, but the ERG did not consider it to be relevant to the appraisal of this technology.[1]

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify and evaluate evidence on the efficacy and safety of fenfluramine as an add-on therapy for the treatment of seizures in patients with DS. Section 4.1 critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.

4.1.1 Searches

Appendix D.1.1 of the CS details a systematic literature review (SLR) conducted to identify and evaluate existing clinical data from both published and grey literature on the efficacy and safety of fenfluramine as an add-on therapy for the treatment of seizures in patients with DS.[24] It states that the SLR sought primarily to identify all comparative clinical evidence for fenfluramine. In addition, the SLR aimed to identify relevant clinical trial data for NICE-recommended add-on therapies, in order to explore the possibility of conducting an indirect treatment comparison (ITC) between fenfluramine and relevant comparators, where appropriate.

Searches were conducted on 28 June 2020 and were limited to English language publications. Databases were searched from date of inception. A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date ranges	Dates searched
Electronic databases	Embase/MEDLINE	Embase.com	Inception - 28/06/2020	28/06/2020
	Cochrane CDSR	Cochrane Library	Inception - 28/06/2020	28/06/2020
	Cochrane CENTRAL			
	PubMed	PubMed	Inception - 28/06/2020	28/06/2020
Conference proceedings	AES Annual Meetings	Hand search of online proceedings	2017-2019	28/06/2020
	BPNA meetings	via Embase.com (EPNSC 2019 hand-searched)		
	ECE meetings			
	EPNS meetings			
	IEC meetings			

AES = American Epilepsy Society; BPNA = British Paediatric Neurology Association; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Central Register of Controlled Trials; CS = company submission; ECE = European Congress on Epileptology; EPNS = European Paediatric Neurology Society; IEC = International Epilepsy Congress

ERG comment:

- A single set of searches was undertaken to identify clinical effectiveness and adverse events (AEs) data. The CS provided sufficient details for the ERG to appraise the literature searches. Several databases and a good range of conference proceedings were searched, and reference checking was conducted. Searches were generally well documented, making them transparent and reproducible.

- No date limits were applied to the database searches. The date limit applied to conference searches was considered justifiable.
- The ERG was concerned that limiting the searches to English language may have introduced potential language bias. Current best practice states that that *"whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"* and that *"research related to language bias supports the inclusion of non-English studies in systematic reviews"*.[26-28] In the response to request for clarification, the company stated that the decision to limit the inclusion criteria to English language publications was made for pragmatic reasons and based on previous precedent established by a recent NICE appraisal in Dravet syndrome [TA614], and that the Cochrane Library searches conducted did not include a language limit.[14, 21] The company subsequently re-ran the Embase.com and PubMed searches without a language limit, and assessed the additional publications retrieved.[29] No additional references were found that were of relevance for inclusion in the present review
- Study design filters were appropriately used and were based on Cochrane RCT filters.
- Separate AE searches were not performed. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to RCTs. Guidance by the Centre for Reviews and Dissemination (CRD) recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[30] The ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits used.
- For the SLR, the company searched Embase and MEDLINE simultaneously using a single database provider (Embase.com) and search strategy. This approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE medical subject heading (MeSH) terms, it is not clear if this is the case for all MeSH terms. Given the potential limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy in order to ensure that potentially relevant records were not missed by the search.
- The use of the Emtree subject heading 'myoclonus epilepsy'/exp is queried by the ERG, as according to the Emtree scope notes, this subject heading does not cover Dravet syndrome. The appropriate EMTREE heading would have been *"severe myoclonic epilepsy in infancy/"*, which is not included. It is unclear what relevant records may have been missed by this incorrect subject heading.
- The recall of the searches could have been increased by additional free-text synonyms such as 'severe polymorphic epilepsy of infancy', the use of truncation, for example 'myoclon* epileps*' and the use of acronyms, such as ICEGTCS (intractable childhood epilepsy with generalised tonic clonic seizures). The search of CENTRAL and CDSR via the Cochrane Library could have benefited from additional search terms, as this strategy did not include all the synonyms used in the MEDLINE/Embase or PubMed searches.
- The CS stated that a number of conference proceedings were searched via the Embase.com search. However, one of the conferences (EPNS 2019) is not currently indexed on Embase.com. In response to the request for clarification, the company acknowledged this oversight and conducted a search of the EPNS 2019 proceedings.[21] No additional relevant

references were found that would influence the conclusions on the efficacy, safety or cost effectiveness of fenfluramine or its relevant comparators.

- Discrepancies were noted by the ERG between the search result numbers provided for the CENTRAL searches and the PRISMA flow diagram. In response to request for clarification, the company acknowledged the error, and confirmed that the PRISMA diagram was correct.[21]

4.1.2 Inclusion criteria

As stated above, the company conducted a SLR of the evidence on the efficacy and safety of fenfluramine as an add-on therapy for the treatment of seizures in patients with Dravet syndrome. The company stated that the main aim of the review was to identify all comparative clinical effectiveness for fenfluramine.[24] Furthermore, the company stated that the review also aimed to identify relevant clinical trial data for NICE-recommended add-on therapies in order to explore whether an ITC between fenfluramine and relevant comparators could be conducted. The eligibility criteria for the SLR are given in Table 4.2.

Table 4.2: Eligibility criteria used in the systematic review of clinical evidence

Eligibility criteria	
Inclusion criteria	
Population	All patients with a defined clinical diagnosis of Dravet syndrome (with or without confirmed SCN1A mutation), irrespective of age. If studies include mixed populations of patients, only those reporting results separately for Dravet syndrome patients will be included
Interventions	Fenfluramine (synonym: ZX008) at a dose of 0.2 mg/kg per day, or 0.7 mg/kg/day, 0.4 mg/kg/day if co-administered with stiripentol, given as an add-on therapy to standard of care AEDs. This will include fenfluramine as the hydrochloride salt at doses of 0.2 mg/kg/day, or 0.8 mg/kg/day, or 0.5 mg/kg/day if co-administered with stiripentol. In addition, add-on therapies to standard of care AEDs recommended by NICE: • Clobazam • Stiripentol at doses up to 50 mg/kg/day • Cannabidiol (synonym: GWP42003-P) in the form of the highly purified cannabidiol used in the Epidyolex/Epidiolex formulation, at doses of up to 10 mg/kg/day or 20 mg/kg/day
Comparator(s)	• Any active pharmacological comparator used as add-on therapy to standard of care AEDs • Placebo/standard of care AEDs
Outcomes	Any outcome measure that aligns to the following measurements of clinical effectiveness or adverse events/tolerability of AEDs in the management of seizures in DS: • Convulsive seizure frequency • Change in convulsive seizure frequency from baseline • Responder rate (>25%, >50%, >75% reduction in convulsive seizure frequency • Seizure freedom • Seizure duration • Change in other impairments (e.g., cognitive, motor, speech/language)

Eligibility criteria	
	• QoL • Adverse effects & tolerability
Study design	Open-label or blinded RCTs – including re-analyses of RCTs Open-label extension (OLE) studies of RCTs Systematic literature reviews – for background information and reference checking only
Geographic coverage	Any geographic location
Exclusion criteria	
(Systematic reviews and meta-analyses will be used for background information and reference checking only) (Articles only available as abstracts will be used for background information, will be listed as associated publications but will not be fully extracted unless the abstract is the only available publication of an RCT)	
Based on Table 3 of Appendix D of the CS[24] AED = anti-epileptic drug; CS = company submission; DS = Dravet syndrome; NICE = National Institute for Health and Care Excellence; OLE = open-label extension; QoL = quality of life; RCT = randomised controlled trial; SCN1A = Sodium Voltage-Gated Channel Alpha Subunit 1	

ERG comment: The company was asked why ketogenic diet as well as vagus nerve stimulation were not included as comparators in the systematic review. The company stated that these treatments *"may be components of the SoC to which fenfluramine may be added, but would not be a clinically relevant alternative to fenfluramine"* and furthermore that *"their exclusion has no meaningful implications in presenting the evidence base for this STA"*.[21]

The ERG noted that Table 3 of the CS (reproduced in Table 4.3 above) did not list severity of seizures, non-convulsive seizures, incidence of status epilepticus, and mortality as outcomes of interest. The company provided a rationale for this decision and stated that *"in summary, whilst efforts have been made to provide evidence in line with the scope, the exclusion of these outcomes from the eligibility criteria of the clinical SLR is highly unlikely to have resulted in the inappropriate exclusion of relevant evidence, and would not influence the conclusions that could be drawn on the efficacy of fenfluramine in its clinical trials or its efficacy relative to relevant add-on therapy comparators"*.[21] The ERG is satisfied with this response.

The ERG noted that the systematic review was limited to studies published in English only. At least one study appeared to have been excluded on the basis of language. The company was asked if any relevant studies were omitted due to this language restriction. They replied that *"no relevant studies were omitted from the SLR as a result of limiting the publications to English language"*.[21]

The ERG queried how the observational studies included in the CS were identified as they would not meet the inclusion criteria for the systematic review. The ERG asked if there were any relevant further observational studies available which had been excluded from the submission. The company replied that *"the clinical SLR focused on identifying relevant RCTs of fenfluramine, and also identifying RCTs of relevant comparator add-on therapies to determine the possibility of conducting an ITC (…) We did not aim to compare observational data for fenfluramine against observational data for other possible comparators (not least because of the inherent methodological limitations in doing so) and therefore we did not employ a specific search filter for observational studies. The observational, long-term studies*

included in the submission (i.e. the two Belgian RWE studies) were included in the clinical development program and regulatory evidence package submitted to the EMA and FDA and provided the foundational data and supporting scientific basis of fenfluramine for the treatment of seizures in patients with Dravet syndrome".[21]

The ERG is satisfied that relevant studies did not appear to have been excluded from the systematic review.

4.1.3 Critique of data extraction

The company stated that data extraction was performed by one reviewer and the data extractions were validated by a second reviewer.

ERG comment: This approach does not represent best practice, e.g. the Cochrane Handbook recommends *"that more than one person extract data from every report to minimize errors and reduce introduction of potential biases by review authors"*.[31]

4.1.4 Quality assessment

The company assessed the quality of the two main trials Study 1 and Study 1504 cohort 2, concluding that both had an overall low risk of bias.[1] The open label trial, Study 1503, was not quality assessed, nor were the real world evidence studies.[32-34] The company used CRD's guidance for undertaking reviews in health care.[30] Elements assessed were randomisation, allocation concealment, baseline comparability, care provider, participant and outcome assessor blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis. No information was provided on the number of reviewers who assessed the quality of included studies.

ERG comment: It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.[31] Results of the company's quality assessment and the ERG's assessment are presented in section 4.2.

4.1.5 Evidence synthesis

The company stated that *"integrated efficacy analyses have been conducted for regulatory purposes but meta-analysis of the fenfluramine RCTs has not been undertaken"*.[1]

The company conducted a Bayesian network meta-analysis (NMA) to inform the comparative clinical and cost effectiveness of fenfluramine as an add-on therapy option alongside existing add-on therapies. This analysis is described in section 4.3.

ERG comment: In response to question B21 of the request for clarification, the company stated that meta-analyses across the two, phase III studies were not conducted. Both studies were included in the NMA.[21] The ERG considers that as the two studies a) evaluated different doses of fenfluramine and b) had different background medications they should not have been pooled in a meta-analysis, i.e. the ERG agrees with the company to not pool these studies in a meta-analysis.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS identified two RCTs of fenfluramine (Study 1 and Study 1504 (cohort 2)) as relevant to the submission.[18, 20] Study 1503, an open-label extension study, and two Belgian real world evidence studies were also included, see Table 4.3.[32-35] Both RCTs are complete whilst the open label extension Study 1503 is ongoing. Doses of fenfluramine varied across the studies. Although all studies supported

the marketing authorisation, only the RCTs informed the economic model in this submission with supporting evidence from the open label studies. Fenfluramine was compared to placebo in both RCTs. Participants were required to take at least one concomitant AED in Study 1. In Study 1504, all participants were required to take at a minimum stiripentol plus clobazam and/or valproate. The main focus of the RCTs was the reduction of convulsive seizures.

Table 4.3: Overview of the clinical effectiveness evidence for fenfluramine

Study	Study 1 (NCT02826863)[18, 36]	Study 1504 (cohort 2) (NCT02926898)[20, 37]	Study 1503 Open-label extension study (NCT02823145)[35]	Belgian RWE studies: Prospective and retrospective analyses[32-34]
Study design	Phase 3, randomised, double-blind, parallel group, multicentre, placebo-controlled trial (completed)	Phase 3, randomised, double-blind, multicentre, placebo-controlled trial (completed)	Open-label, multicentre, long-term safety study (ongoing)	Open-label safety and effectiveness study (ongoing)
Population	Children and young adults aged 2 to 18 years with Dravet syndrome (n=119)	Children and young adults aged 2 to 18 years with Dravet syndrome (n=87)	Children and young adults with Dravet syndrome who have successfully completed 14 weeks of treatment in Study 1 or Study 1504 (n=330 at last analysis)	Children and adults with Dravet syndrome (n=9) Children and adolescents (n=12)
Intervention/ comparator (doses as free FFA)	• FFA 0.2 mg/kg/day (max 26 mg/day) + concomitant AEDs (n=40) • FFA 0.7 mg/kg/day (max 26 mg/day) + concomitant AEDs (n=39) • Placebo + concomitant AEDs (n=40) • Most commonly used concomitant AEDs: VPA^, CLB, TPM, LVT	• FFA 0.4 mg/kg/day (max 17 mg/day) + STP + concomitant AEDs (n=43) • Placebo + STP + concomitant AEDs (n=44) • Most commonly used concomitant AEDs: VPA^, CLB, TPM, LVT	• FFA 0.2–0.7 mg/kg/day (max 26 mg/day) + concomitant AEDs • FFA 0.2–0.4 mg/kg/day (max 17 mg/day + STP + concomitant AEDs • Most commonly used concomitant AEDs: VPA^, CLB, STP, TPM, LVT, ZNS, ergenyl chrono	• FFA doses approx. 0.2–0.7 mg/kg/day (max 17 mg/day) + concomitant AEDs • Most commonly used concomitant AEDs: VPA^, CLB, TPM
Supports marketing authorisation	Yes	Yes	Yes	Yes
Used in economic model	Yes	Yes	Supportive[$]	Supportive[$]

Study	Study 1 (NCT02826863)[18, 36]	Study 1504 (cohort 2) (NCT02926898)[20, 37]	Study 1503 Open-label extension study (NCT02823145)[35]	Belgian RWE studies: Prospective and retrospective analyses[32-34]
Rationale for use/non-use in the model	Pivotal phase 3 study in children and young adults with Dravet syndrome treated with the investigational product. Provides individual patient-level data		Extension of the pivotal phase 3 studies in children and young adults with Dravet syndrome treated with the investigational product. Used to support extrapolation assumptions beyond trial periods	Provides external evidence to support long-term extrapolations in patients with Dravet syndrome treated with FFA
Key outcomes (bold = outcomes incorporated in the economic model)	**Convulsive seizure frequency** Response rate **Convulsive seizure-free days** HRQoL • Patient (**PedsQL**, QOLCE, and CGI-I) • Caregiver/family (EQ-5D-5L, and PedsQL family impact module) AEs of treatment		Seizure frequency (convulsive) Response rate **Discontinuations** AEs of treatment Incidence of rescue medication usage HRQoL • Patient (CGI-I)	Change in frequency of major motor seizures Response rate AEs of treatment

Based on Table 3 of the CS[1]

^ Includes valproate semisodium, valproate sodium, and valproic acid; $ Data from this study were not used explicitly in the economic model. Instead, results were used to support a number of model assumptions (see section B.3.3 of CS for further information); □ Dosing based on fenfluramine base equivalent doses, by request of the EMA and FDA. CSRs and early publications included doses based on fenfluramine hydrochloride salt e.g. 0.8 mg/kg/day fenfluramine hydrochloride, which when converted [redacted] is equivalent to 0.7 mg/kg/day fenfluramine. To assist with interpretation and consistency in the reported doses of fenfluramine, this conversion has been used in some places (e.g. Belgian RWE).

AE = adverse event; AED = anti-epileptic drug; CGI-I = Clinical Global Impression of Improvement; CLB = clobazam; CS = company submission; CSR = clinical study report; DS = Dravet syndrome; EMA = European Medicines Agency; EQ-5D-5L = European Quality of Life-5 Dimensions 5-level scale; FDA = Food and Drug Administration; FFA = fenfluramine; HRQoL = health-related quality of life; LVT = levetiracetam; NCT = National Clinical Trial; PedsQL = Paediatric Quality of Life Inventory; QOLCE = Quality of Life in Childhood Epilepsy; RWE = real-world evidence; SE = status epilepticus; STP = stiripentol; TPM = topiramate; VPA = valproate; ZNS = zonisamide

ERG comment:

- The main RCTs are discussed in more detail throughout Section 4.2. Study 1503 and the Belgian RWE studies are discussed in Section 4.2.7.
- Although the studies were reported to include adults, there were very few adults across the clinical trial programme. This issue is discussed further in this report.

4.2.1 Details of included fenfluramine RCTs

Both randomised controlled trials (RCTs; Study 1 and Study 1504) were conducted in children and adolescents with DS in secondary care across several countries, see Table 4.4. Study 1 had a two-week titration phase and Study 1504 a three-week titration. Study 1 had a fenfluramine treatment group receiving 0.2 mg/kg/d and a group who received 0.7 mg/kg/d. In Study 1504 patients received 0.4 mg/kg/d. The maximum dose in Study 1 was up to 26 mg/d and in Study 1504 up to 17 mg/d. Patients received this dose (or placebo) in a maintenance phase of 12 weeks. A transition/taper period of two weeks followed, after which participants could enter the OLE study (Study 1503) or exit the randomised trial. Participants were required to take at least one concomitant AED during study participation in Study 1. In Study 1504, all participants were required to take at a minimum stiripentol plus clobazam and/or valproate during the study. The primary endpoint of both RCTs was the change in convulsive seizure frequency (CSF; mean number of convulsive seizures per 28 days) from baseline to the treatment and maintenance (T+M) period (14 weeks).

Table 4.4: Summary of study methodology for included RCTs

	Study 1	**Study 1504 (cohort 2)**
Location	USA, Canada, Belgium, Denmark, Germany, Italy, Spain, United Kingdom, Australia	USA, Canada, France, Germany, Netherlands, Spain, United Kingdom
Trial design	Phase 3, double blind, RCT (completed)	
Eligibility criteria for participants	Children and adolescents with DS Groups stratified by age: <6 years and >6 years	
Setting	Secondary care	
Trial drugs	Fenfluramine (FFA) administered as an oral aqueous solution, divided into two equal daily doses with food. Matching placebo was supplied as an oral solution.	
Administration, dosing, and schedule	**Max dose**: up to 26 mg/d **Titration** (2 wk) Participants randomised (1:1:1) in a double-blind manner to receive: • FFA 0.2 mg/kg/d (n=39) • FFA 0.7 mg/kg/d (n=40)placebo (n=40). 0.7 mg/kg/day group received 0.2 mg/kg/day for 4 days, 0.4 mg/kg/day for 4 days and then 0.7 mg/kg/d dose. Other groups received dummy titrations.	**Max dose**: up to 17 mg/d **Titration** (3 wk) Participants randomised (1:1) in a double-blind manner to receive: • FFA 0.4 mg/kg/d + STP + concomitant therapies (n=43) • Placebo + STP + concomitant therapies (n=44). 0.4 mg/kg/day group received 0.2 mg/kg/day starting dose, titrated gradually to 0.4 mg/kg/day

	Study 1	Study 1504 (cohort 2)
	Maintenance (12 wk) Randomised dose of FFA or placebo BID in the morning and in the evening. **Transition/taper period** (2 wk) Participants entering OLE study (Study 1503) or exiting study. Intermediate dose of 0.4 mg/kg/d used for 0.7 mg/kg/d dose.	**Maintenance** (12 wk) Randomised dose of FFA or placebo BID in the morning and in the evening. **Transition/taper period** (2 wk) Participants entering OLE study (Study 1503) or exiting study.
Concomitant therapies	Participants were required to take at least one concomitant AED during study participation.	All participants were required to take at a minimum STP plus CLB and/or VPA during the study.
Disallowed concomitant medication	• AEDs that block sodium channels, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine, phenobarbital, or had taken any of these within the past 30 days, as maintenance therapy • Felbamate was prohibited as a concomitant medication unless the participant had been on felbamate for at least 18 months prior to screening, had stable liver function and haematology laboratory tests, and the dose was expected to remain constant throughout the study • Centrally-acting anorectic agents • Monoamine-oxidase inhibitors • Any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition • Any centrally-acting noradrenergic agonist such as atomoxetine • Cyproheptadine • Any form of marijuana, THC and THC derivatives, and cannabidiol products **Study 1 only**: Participants must have been off STP for a minimum of 21 days prior to the screening visit	
Primary outcomes	Change between baseline and combined T+M period (14 weeks) in the mean CSF per 28 days for FFA 0.7 mg/kg/d vs placebo	Change between baseline and combined T+M period (15 weeks) in the mean CSF per 28 days for FFA 0.4 mg/kg/d vs placebo
Exploratory subgroup analyses	Age strata: <6 years, ≥6 years. Exploratory subgroup analyses from pooled Study 1 and Study 1504 included: • baseline convulsive frequency as a categorical variable, • use of concomitant valproate and/or clobazam • CSF in Stiripentol naïve vs stiripentol experienced patients (Study 1 only) • Age <12 and >12 years	

Based on Table 4 of the CS[1]
AED = anti-epileptic drug; BID = twice a day; CLB = clobazam; CS = company submission; CSF = convulsive seizure frequency; d = day; DS = Dravet syndrome; FFA = fenfluramine; OLE = open-label extension; RCT = randomised controlled trial; STP = stiripentol; THC = tetrahydrocannabinol; T+M = treatment and maintenance; USA = United States of America; VPA = valproate; wk = week

ERG comment:

- The ERG notes that the evidence for fenfluramine is based on international RCTs investigating patient-relevant outcomes.
- The company was asked why the trials were stratified at age <6 years and ≥ 6 years and whether there was any expectation of differential effectiveness.[38] The company replied that *"at the request of the regulatory agencies, the populations were stratified by age to ensure an appropriate balance of younger patients (<6 years of age) and older patients (>6 years of age) in the trials (the studies targeted 25% of the trial population to be <6 years of age). There was no expectation of differential effectiveness by age"*.[21]
- The ERG draws to the attention of the committee that, as per the company's dosage instructions, fenfluramine is given at a lower dosage when combined with STP and the trials reflect this.
- The ERG queried how the fixed dosing of fenfluramine in the randomised trials would relate to use in clinical practice. The company stated that *"in clinical practice, patients will initiate fenfluramine at the 0.2mg/kg/day and will be titrated up to these maximum doses; however, dose adjustment will, of course, be permitted to optimise efficacy and adverse events. The fact that patients were maintained on a stable dose in the trials does not imply that the relative efficacy and safety will be systematically different in clinical practice as a result of dose optimisation. The same approach was adopted in the cannabidiol RCTs"*.[21] They also referred to how dosing was incorporated into the economic model. This issue is discussed in section 5.2.9.
- It should be noted that both of the key studies included in the CS (Study 1 and Study 1504) had a double-blind, treatment maintenance phase of just 12 weeks, which may not be considered adequate, given that the primary endpoint was change in 28-day convulsive seizure frequency. The ERG, therefore, considers that it is particularly important to establish whether any reductions in seizure frequency, observed in short-term trials of fenfluramine are sustained in the longer-term. Longer-term evidence is available from Study 1503, the open-label extension study which, using the latest data cut up to three years (14 October 2019) has outcomes relating to 330 patients. This suggests that positive outcomes relating to convulsive seizures are maintained up to this point.

4.2.2 Statistical analysis of the included fenfluramine RCTs

The company stated that their primary hypothesis was that the mean convulsive seizure frequency per 28 days for the fenfluramine group was statistically significantly different from the placebo group. Details of the trial hypotheses, endpoints, sample size calculation and statistical analysis methods are provided in Table 4.5. The company reported a serial hypothesis testing strategy to control for type I error (avoiding false positive findings).

All efficacy analyses were performed on the modified intention-to-treat population (mITT) which was defined as all patients who received at least one dose of randomised treatment and had at least one week of diary data. The ITT population was all patients who were randomised to study treatment, but the ITT and mITT populations contained the same numbers of patients. Analyses were repeated in the per-protocol population. All safety analyses used the safety population which was defined as all patients who had received at least one dose of fenfluramine or placebo.

The primary endpoint of CSF per 28 days during the treatment and maintenance period was analysed using an analysis of covariance (ANCOVA) model with treatment group and age group (<6 years and ≥6 years) as factors and baseline CSF as a covariate. The key secondary endpoint of proportion of

subjects who achieved a ≥50% reduction from baseline in convulsive seizure frequency was analysed using a logistic regression model incorporating the same factors as in the primary analysis. The longest interval in days between convulsive seizures was compared between groups using a Wilcoxon rank sum test.

Table 4.5: Summary of statistical analyses for included RCTs

	Study 1	Study 1504 cohort 2
Hypothesis	The primary hypothesis was that the mean convulsive seizure frequency per 28-days for the fenfluramine 0.7 mg/kg/day group was statistically significantly different from the placebo group.	The primary hypothesis was that the mean convulsive seizure frequency per 28-days for the fenfluramine 0.4 mg/kg/day group was statistically significantly different from the placebo group.
Sample size	The power analysis assumed that the SD of the percentage change in monthly seizure frequency was 55%, based on results from previous RCTs of stiripentol and cannabidiol for the treatment of seizures in patients with Dravet syndrome. Based on this assumption, a sample size of 40 patients per arm was determined to provide 90% power to detect a difference in mean change in monthly seizure frequency from baseline of 40%, using a two-sided t test at 0·05 significance.	
Missing data	There was no imputation of missing data for efficacy endpoints.	
Statistical tests	Primary endpoint: comparison of mean CSF per 28 days in the combined titration and maintenance periods in patients given fenfluramine 0.7 mg/kg/day (Study 1) or 0.4 mg/kg/day (Study 1504) compared with placebo, analysed using an analysis of covariance (ANCOVA) model with treatment group and age group (<6 years and ≥6 years) as factors and baseline CSF as a covariate. Percentage change from baseline in CSF frequency was a supplementary analysis using an ANCOVA model adjusting for the same covariates as the primary endpoint model.	
	Key secondary endpoints: proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, analysed using a logistic regression model that incorporates the same factors and covariate as the analysis of covariance in the primary analysis. Longest interval between convulsive seizures during the treatment and maintenance period, compared using a Wilcoxon rank sum test.	
	Other secondary endpoints: Responder analyses (proportion of patients who achieved ≥25%, ≥75%, or 100% reduction in mean convulsive seizure frequency per 28 days): assessed in the same way as the proportion of subjects who achieve a ≥50% reduction from baseline. Clinical Global Impression of Improvement: proportion of patients who were rated as very much improved or much improved in each fenfluramine dose group was compared with placebo using the Cochran-Mantel-Haenszel test stratified by age group. Quality-of-life assessments: comparisons made using Wilcoxon rank sum tests.	
Statistical analysis procedure	A serial gatekeeping strategy was developed to control the type I error rate for pairwise comparisons between active and placebo groups, among the primary and key secondary efficacy parameters. This started with the primary endpoint and if this comparison was statistically significant at the α=0.05 (2-sided) level, hypothesis testing proceeded to the secondary endpoints in order. Additional secondary endpoints were analysed without correction for multiplicity.	

Based on Table 8 of the CS[1]

	Study 1	Study 1504 cohort 2
ANCOVA = analysis of covariance; CSF = convulsive seizure frequency; RCT = randomised controlled trial; SD = standard deviation		

ERG comment:

- The statistical analyses appeared to have been conducted appropriately and model assumptions were checked. The analysis of the primary endpoint used logged values of CSF as this outcome was not normally distributed. The ANCOVA model results were then anti-logged to provide results on the original scale which gave results as the ratio between fenfluramine and placebo in CSF rates, this was reported as the percentage difference for fenfluramine compared to placebo.
- The ITT and mITT populations contained the same numbers of patients so the choice of the mITT population for the efficacy analysis did not raise any concerns as all randomised patients were included in the analysis.

4.2.3 Trial participant characteristics

Table 4.6 shows the main inclusion and exclusion criteria for the randomised trials. Briefly, participants needed to be aged between two and 18 years of age with DS with convulsive seizures not completely controlled by current AEDs. In terms of convulsive seizures, eligibility criteria were four or more convulsive seizures per four-week period for 12 weeks prior to screening. Participants needed to have a stable baseline with six or more convulsive seizures during the six weeks baseline period, with a minimum of two in the first three weeks and two in the second three weeks. All interventions for epilepsy had to be stable for at least four weeks prior to screening and expected to remain stable.

Participants had to be free of cardiovascular or cardiopulmonary abnormality based on screening echocardiogram (ECHO) and electrocardiogram (ECG) or physical examination and approved for entry by the central cardiac reader. Additionally, the patient's parent/caregiver had to be assessed as compliant with diary completion, visit schedule, and study drug accountability. Further exclusion criteria were specified, including current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for more than one month.

Table 4.6: Key inclusion and exclusion criteria for included RCTs

Study 1	Study 1504 (cohort 2)
Key Inclusion criteria	
	Current use of STP
Age ≥2 to ≤18 years with DS with documented medical history with convulsive seizures not completely controlled by current AEDs	
No cardiovascular or cardiopulmonary abnormality based on screening ECHO and ECG or physical examination and approved for entry by the central cardiac reader	
Parent/caregiver willing and able to be compliant with diary completion, visit schedule, and study drug accountability	
All the following 5 criteria: • Seizure onset in the first year of life in an otherwise healthy infant • Seizure history of either generalised tonic-clonic or unilateral clonic or bilateral clonic and prolonged • Normal initial development	

Study 1	Study 1504 (cohort 2)
• Normal brain MRI history without cortical brain malformation • Lacking alternative diagnosis	
At least one of the following 3 criteria: • Emergence of another seizure type, including myoclonic, generalised tonic-clonic, tonic, atonic, absence and/or focal developed after the first seizure type • Seizures induced by prolonged exposure to warm temperatures and/or associated with fevers due to illness or vaccines, hot baths, high levels of activity, and sudden temperature changes, and/or seizures induced by strong natural and/or florescent lighting, as well as certain visual patterns • Genetic tests consistent with DS diagnosis	
≥4 convulsive seizures per 4-week period for 12 weeks prior to screening	
Stable baseline with ≥6 convulsive seizures during the 6-week baseline period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks	
All interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulator /stimulation [VNS]) stable for at least 4 weeks prior to screening and expected to remain stable	
Buccal swab for CYP2D6 genotype/phenotype agreed to be provided throughout the study	
Key Exclusion criteria	
Current or had received STP in past 21 days prior to screening	
• Pulmonary arterial hypertension • Current or past history of cardiovascular or cerebrovascular disease • Current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for >1 month • Imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses in Columbia-suicide severity rating scale (C-SSRS). • Current or past history of glaucoma • Moderate or severe hepatic impairment • A clinically significant condition or had had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the screening visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.	
Based on Table 4 of the CS[1] and Table 6 of the CS appendix[24] C-SSRS = Columbia-suicide severity rating scale; CS = company submission; DS = Dravet syndrome; ECG = electrocardiogram; ECHO = echocardiogram; KD = ketogenic diet; MRI = magnetic resonance imaging; RCT = randomised controlled trial; STP = stiripentol; VNS = vagal nerve stimulation	

ERG comment:

- The ERG noted that the inclusion criteria for Study 1, Study 1504 (cohort 2), and Study 1503 suggested that patients with cardiovascular or cardiopulmonary abnormality be excluded. The company was asked to confirm that fenfluramine should not be prescribed to patients who are at risk of cardiovascular or cardiopulmonary events.[38] The company replied that *"although the label and SmPC for fenfluramine in Dravet syndrome is to be finalised by the EMA, it is anticipated that it will exclude the use of fenfluramine in patients with known cardiovascular or cardiopulmonary abnormalities, as per the RCT protocols and as reflected by the contraindications listed in the draft SmPC provided with our submission. The exclusion of patients with cardiovascular or cardiopulmonary abnormalities from the clinical trials is therefore aligned with the anticipated use of fenfluramine in clinical practice".*[21]

Table 4.7 shows the characteristics of the participants in Study 1 and Study 1504.

Study 1 had a total of 119 participants and Study 1504 had 87. The mean age across both trials was approximately nine years. Female and male participants were represented in the trials. The overall percentage of females in Study 1 was 46% and in Study 1504 43%. Both trials had predominantly participants who identified as white (Study 1: 82%, Study 1504: 60%). Around 60% of the participants in Study 1 were from the USA. The average number of concurrent treatments was under three in Study 1 but over three in Study 1504 where all participants needed to take stiripentol. In Study 1 approximately 59% took clobazam, 22% levetiracetam, 25% topiramate and 22% valproate (all forms). In Study 1504 the corresponding percentages were: 94% clobazam, 12% levetiracetam, 100% stiripentol, 24% topiramate and 19% valproate (all forms).

Table 4.7: Baseline characteristics of the RCTs

Baseline characteristics	Study 1			Study 1504 (cohort 2)	
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)
Female, n (%)	19 (47.5)	17 (43.6)	19 (47.5)	17 (38.6)	20 (46.5)
Age (years), mean (SD)	9.2 (5.1)	9.0 (4.5)	8.8 (4.4)	9.4 (5.1)	8.8 (4.6)
Age group <6 years, n (%)	11 (27.5)	9.0 (23.1)	11 (27.5)	12 (27.3)	12 (27.9)
SCN1A mutation, n (%)	31 (77.5)	31 (79.5)	33 (82.5)	39 (88.6)	37 (86.0)
Race, White, n (%)	31 (77.5)	33 (84.6)	34 (85.0)	29 (65.9)	23 (53.5)
Region/country, n (%) North America	24 (60)	24 (61.5)	24 (60.0)	14 (31.8)	15 (34.9)
Region/country, n (%) Europe / Australia	16 (40.0)	15 (38.5)	16 (40.0)	30 (68.2)	28 (65.1)
Baseline CSF per 28 days, mean (SD)	44.2 (40.2)	45.5 (99.8)	31.4 (30.6)	21.6 (27.7)	27.9 (36.9)
Baseline CSF per 28 days, median (min, max)	27.3 (3.3 to 147.3)	17.5 (4.7 to 623.5)	20.7 (4.8 to 124.0)	10.7 (2.7 to 162.7)	14.0 (2.7 to 213.3)
Number of concomitant AEDs, Mean (SD)	2.5 (0.9)	2.6 (1.1)	2.3 (0.9)	3.4 (0.6)	3.6 (0.8)
Clobazam	22 (55.0)	24 (61.5)	24 (60.0)	42 (95.5)	40 (93.0)
Levetiracetam	11 (27.5)	11 (28.2)	4 (10.0)	5 (11.4)	6 (14.0)
Stiripentol	-	-	-	44 (100.0)	43 (100.0)
Topiramate	9 (22.5)	10 (25.6)	11 (27.5)	7 (15.9)	14 (32.6)
Valproate (all forms)	8 (20.0)	7 (17.9)	11 (27.5)	9 (20.5)	8 (18.6)
Prior AED use*	NR	NR	NR	NR	NR

Based on Table 5 of the CS[1]

* This was requested at clarification and the company replied *"that the mean (SD) number of AEDs received by patients prior to enrolment in each of the trials requires reanalysis of the data and will be provided as soon as practicably possible"*.[21]

AED = anti-epileptic drug; CS = company submission; CSF = convulsive seizure frequency; FFA = fenfluramine; RCT = randomised controlled trial; SCN1A = Sodium Voltage-Gated Channel Alpha Subunit 1; SD = standard deviation

ERG comment:

- The trials reflect a younger population with Dravet syndrome (mean age of nine years and all participants under 18 years as per the trials' inclusion criteria)
- The company was asked to provide details of prior AEDs received by patients (mean, standard deviation (SD) and broken down by type). They replied that *"the mean (SD) number of AEDs received by patients prior to enrolment in each of the trials requires reanalysis of the data and will be provided as soon as practicably possible"*.[21] However, at the time of writing the report, this did not appear to have been provided. The company did, however, give an indication of the most commonly used prior AEDs, i.e. *"Study 1 - Overall, the most commonly used prior AEDs (≥25% overall), were clobazam (83.2%), levetiracetam (79.0%), topiramate (68.9%), valproate semisodium/ sodium (68.1%), stiripentol (48.7%), zonisamide (43.7%), phenobarbital (40.3%), lamotrigine (27.7%), cannabidiol (26.9%), clonazepam (26.9%), and valproic acid (31 subjects, 26.1%). Study 1504 - Overall, the most commonly used prior AEDs (≥25% overall), were clobazam (94.3%), valproate semisodium/sodium (57.4%), and topiramate (25.3%)"*.[21]
  In the model, cohorts of Study 1 and Study 1504 cohorts were modelled separately and afterwards merged together. For the Study 1504 cohort, the 94.3% clobazam use was incorporated.
- Due to the design of the trials, no participants in Study 1, and all participants in Study 1504 received stiripentol. The company was asked to provide evidence that the mix of concomitant AEDs was representative of UK clinical practice.[38] In response to the request for clarification, they concluded that "*both clinical expert opinion and available survey data from a significant proportion of UK patients indicate that the concomitant AEDs in the phase 3 trials are reflective of the AEDs received in clinical practice*".[21]

4.2.4 Risk of bias assessment for included fenfluramine RCTs

The company assessed the quality of the two main trials and concluded that both had an overall low risk of bias, see Table 4.8. The company used CRD's guidance for undertaking reviews in health care.[30] Elements assessed were randomisation, allocation concealment, baseline comparability, care provider, participant and outcome assessor blinding, dropout imbalances, selective outcome reporting and use of intention to treat analysis. No information was provided on the number of reviewers who assessed the quality of included studies.

Table 4.8: Company quality assessment of the fenfluramine RCTs

	Study 1	Study 1504 (cohort 2)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes: Baseline demographics, medical history and previous/concomitant therapies were generally balanced between the FFA and placebo study groups. There was variation in baseline CSF between groups. However,	Yes: Baseline demographics, medical history and previous/concomitant therapies were generally balanced between the FFA and placebo study groups.

	Study 1	Study 1504 (cohort 2)
	the mean baseline CSF was consistently high (>30 convulsive seizures per month) in all treatment groups. This reflects heterogeneity in patients in clinical practice	Both treatment groups generally had comparable baseline CSF
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.	Yes: neither the patients nor the caregivers recording seizures, nor the investigator had knowledge of what treatment was being administered.
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Based on Table 9 of the CS[1] CS = company submission; CSF = convulsive seizure frequency; FFA = fenfluramine; RCT = randomised controlled trial		

ERG comment:

- It is normally recommended that two reviewers are involved in the assessment of study quality to avoid bias and error.[31]
- The ERG examined the clinical study reports (CSRs) for the two trials and assessed the trials against the above criteria. Randomisation and allocation concealment procedures appeared to be appropriate. Methods to ensure blinding of care providers, participants and outcome assessors also appeared to be appropriate. All outcomes appeared to be reported. Although the studies used a modified intention to treat analysis, this included all trial participants. Therefore, the ERG agrees that the two trials were well conducted.

4.2.5 Efficacy results

In Study 1 the addition of fenfluramine 0.7 mg/kg/day to standard care resulted in a 62.3% (95% confidence interval [CI] 47.7 to 72.8%) reduction in CSF per 28 days compared with placebo and standard care which was an estimated ratio of 0.38 (95% CI 0.27 to 0.52). The addition of fenfluramine 0.2 mg/kg/day resulted in a 32.4% (95% CI 6.2 to 51.3%) reduction compared to placebo (estimated ratio 0.62 (95% CI 0.49 to 0.94)). In Study 1504 the addition of fenfluramine 0.4 mg/kg/day to stiripentol and concomitant medication resulted in a 54.0% (67.2% to 35.6%) reduction compared to

placebo with stiripentol and concomitant medication (estimated ratio 0.46 (95% CI 0.33 to 0.64)). A summary of efficacy results is presented in Table 4.9.

Patients in fenfluramine groups across the two trials were more likely to have 25%, 50% and 75% reductions in convulsive seizures than patients in placebo groups. For Study 1 participants were nearly five times as likely to have a 50% reduction in the fenfluramine 0.2 mg/kg/day group with an odds ratio (OR) of 4.8 (95% CI 1.5 to 15.0) and in the fenfluramine 0.7 mg/kg a day group fifteen times as likely (OR 15.0, 95% CI 4.5 to 50.0). In Study 1504 the corresponding OR was 26.0 (95% CI 5.5 to 123.2). Patients in fenfluramine groups had longer convulsive seizure-free intervals. In terms of total seizures, Study 1 showed an improvement of fenfluramine over placebo in % change from baseline: -61.1 (34.0) in the fenfluramine 0.7 mg/kg a day group and +18.6 (136.1) in the placebo group. In Study 1504 an improvement of fenfluramine over placebo for this outcome was not noted. There was no difference between fenfluramine and placebo in the [redacted][1]

Table 4.10 shows parent/caregiver ratings of their child's condition and quality of life. In terms of Clinical Global Impression of Change-Improvement (CGI-I) in Study 1 more parents/caregivers in fenfluramine groups rated their condition very much or much improved when compared to those in placebo groups (55% and 41% vs. 10%). In Study 1504, 33% vs. 21% reported this improvement but the difference was not statistically significant. Investigator ratings also showed improvements over placebo. Improvements in quality of life ratings were inconsistent, with Study 1 finding improvements in Paediatric Quality of Life Inventory (PedsQL) over placebo but Study 1504 did not. Using the Quality of Life in Childhood Epilepsy (QOLCE) measure, differences between groups were not observed. [redacted][1]

Table 4.9: Efficacy results of the fenfluramine RCTs

Endpoints	Study 1			Study 1504 (cohort 2)	
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)
Median baseline CSF (range)	27.3 (3.3 to 147.3)	17.5 (4.7 to 623.5)	20.7 (4.8 to 124)	10.7 (3 to163)	14.0 (3 to 213)
Median T+M CSF (range)	22.0 (3 to 164.0)	12.6 (0 to 200.0)	4.7 (0 to 169.9)	11.4 (2.2 to 170.1)	5.2 (0 to 458.6)
Primary endpoint					
% difference from placebo in baseline-adjusted CSF per 28 days, (95%CI); P-value vs placebo*	-	32.4 (6.2 to 51.3); P=0.0209	62.3 (47.7 to 72.8); P<0.001	-	54.0 (35.6 to 67.2); P<0.001
% change from baseline in CSF, median (range); P-value vs placebo	-19.2 (-76.0 to 51.8)	-42.3 (-100.0 to 197.6); P=0.2035	-74.9 (-100.0 to 196.4); P<0.0001	-1.1 (-82.8 to 435.1)	-63.1 (-100.0 to 115.0); P<0.001
Key secondary endpoints					
50% reduction in convulsive seizure frequency, n (%); P-value vs placebo; Odds ratio (95% CI)	5 (12.5)	15 (38.5); P=0.0091; 4.8 (1.5 to 15.5)	27 (67.5); P<0.0001; 15.0 (4.5 to 49.9)	2 (4.5)	23 (53.5); P<0.001; 26.0 (5.5 to 123.2)
Longest convulsive seizure-free interval, days Mean (SD); Median (range); Median treatment difference (95% CI); P-value vs placebo	10.6 (6.0) 9.5 (2 to 23)	26.0 (31.7) 15.0 (3 to 106); Diff: 4.5 (0 to 9); P=0.0352	32.9 (27.5) 25.0 (2 to 97); Diff: 15.5 (6 to 25); P<0.0001	13.4 (7.5) 13.0 (1.0-40.0)	29.7 (27.3) 22.0 (3.0 to 105.0); -; P=0.004
Other secondary endpoints					
Convulsive seizure-free days, mean (SD); Difference from placebo in convulsive seizure-free days, % (95% CI); P-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥25% reduction in convulsive seizure frequency, n (%); P-value vs placebo; Odds ratio (95% CI)	14 (35)	26 (67); P=0.0041; 4.1 (2 to 11)	36 (90); P<0.0001; 22.3 (6 to 84)	12 (27)	30 (70); P<0.001; 6.4 (2.5 to 16.5)
≥75% reduction in convulsive seizure frequency, n (%); P-value vs placebo; Odds ratio (95% CI)	1 (2)	9 (23); P=0.0229; 12.0 (1.4 to 102)	20 (50); P=0.0005; 55.1 (6 to 526)	1 (2)	15 (35); P=0.003; 23.7 (2.9 to 191.8)

Endpoints	Study 1			Study 1504 (cohort 2)	
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)
Convulsive seizure freedom (0 convulsive seizures), n (%):	0	3 (8)	3 (8)	0	1 (2)
Near seizure freedom (<1 convulsive seizure)[**], n (%):	0	5 (13)	10 (25)	0	5 (12)
Non-convulsive seizure[¶], % change from baseline, Mean (SD); Median (range); P-value	22.2 (211.3); -55.6 (-100 to 723.6)	-8.9 (151.2); -50.6 (-100.0 to 534.0); P=0.758	-60.5 (38.5); -76.0 (-100.0 to 69.2); P=0.046	1.68 (153.6); -49.67 (-100.0 to 529.4)	36.7 (176.7)[§]-0.47 (-100.0 to 611.2); P=0.182
Total seizures, Mean % change from baseline (SD) Median (range); P-value vs placebo	18.6 (136.1); -16.2 (-77.6 to 600.7)	-25.5 (77.1); -41.07 (-100 to 292.4); P=0.020	-61.1 (34.0); -68.3 (-100.0 to 35.6); P<0.001	12.7 (76.7); -5.9 (-73.8 to 375.6)	-27.0 (60.4); -41.1 (-100.0 to 133.2); P=0.137
Incidence of status epilepticus+, n (%); P-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Days of rescue medication use per 28 days, mean (SD); median (range); P-value vs placebo	3.1 (4.6); 1.7 (0 to 24)	1.7 (2.9); 0.3 (0 to 16.0); P=0.082	0.9 (1.9); 0 (0 to 8); P<0.0001	1.2 (2.6); 0.3 (0 to 15)	1.4 (2.2); 0.3 (0 to 9.0); P=0.248
Incidence of hospitalisations to treat seizures during treatment phase, n (%); P-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 10 of the CS[1, 36, 37]

[*] ANCOVA of log CSF during T+ M period adjusted for age and log baseline CSF rate (results were back-transformed to the original scale); [**] Post hoc analysis; [¶] Not all patients had non-convulsive seizures: Study 1 data based on n=21/40, 23/39 and 24/40 in the placebo, FFA 0.2mg/kg/day group and FFA 0.7 mg/kg/day group, respectively; Study 1504 data based on n= 22/44 and 17/43 in the placebo and FFA 0.4mg/kg/day group, respectively; [§] Data skewed for Study 1504; both placebo and FFA experienced a decrease from baseline in median number of non-convulsive seizures: Placebo from 4.33 at baseline to 3.79 at end of treatment period, and FFA from 13.33 to 8.88; [+] Status epilepticus incidence defined by seizures last >10mins, or requiring hospital treatment, or multiple episodes lasting >10 minutes in 24 hours and considered adverse events. The use of rescue medication may also provide a proxy indication of the emergence of SE events that were averted.

CI = confidence interval; CS = company submission; CSF = convulsive seizure frequency; FFA = fenfluramine; RCT = randomised controlled trial; SD = standard deviation; T + M = treatment and maintenance

Table 4.10: Condition ratings and quality of life results of the fenfluramine RCTs

Endpoints	Study 1			Study 1504 (cohort 2)	
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)
Patient condition rating and quality of life					
CGI-I rating very much/much improved by parent/caregiver, n (%); P-value vs placebo	4 (10)	16 (41); P=0.0036	22 (55); P<0.0001	9 (21)	14 (33)
CGI-I rating very much/much improved by investigator, n (%); P-value vs placebo	4 (10)	16 (41); P=0.0032	25 (62); P<0.0001	7 (16)	19 (44); P=0.008
QOLCE – overall quality of life Change from baseline, mean (SD); P-value vs placebo	1.5 (8.7)	0.8 (11.8); P=0.3683	5.8 (11.7); P=0.2807	0.1 (8.5)	-3.5 (10.3); P=0.191
PedsQL – total score Change from baseline, mean (SD); P-value vs placebo	-1.6 (10.4)	6.8 (11.2); P=0.0029	5.9 (15.1); P=0.0198	-0.3 (12.4)	-0.9 (11.8); P=0.618
Caregiver condition rating and quality of life					
EQ-5D-5L at end of study*					
Mobility – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Self-care – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain/discomfort – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety/depression – Problems (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L – overall health status based on VAS, change from baseline; Mean (SD); Median (range); P-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HADS – Total score , change from baseline, Mean (SD); Median (range); P-value vs placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Endpoints	Study 1			Study 1504 (cohort 2)	
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)
Based on Table 11 of the CS, Table 14.2.13.2 of study 1 CSR, and Table 34 of studies 1504 CSR[1, 36, 37] [redacted]					

CGI-I = Clinical Global Impression of Improvement; CS = company submission; CSF = convulsive seizure frequency; CSR = clinical study report; EQ-5D-5L = EuroQOL – 5 Dimensions – 5 Levels scale produced by the European Quality of Life group; FFA = fenfluramine; HADS = hospital anxiety and depression scale; NA = not assessed; PedsQL = Paediatric Quality of Life Inventory (increases in total score indicates improvement); QOLCE = Quality of Life in Childhood Epilepsy (increases in total score indicates improvement); SD = standard deviation; VAS = visual analogue scale (ranges 0-100, negative score indicates worsening, positive score indicates improvement in self-assessed overall health status)

ERG comment: It should be noted that both of the key studies included in the CS (Study 1 and Study 1504) had a double-blind, maintenance phase of just 12 weeks. However longer-term evidence is available from Study 1503, the open-label extension study which has results up to three years' follow-up.

In both trials, participants receiving fenfluramine had greater reductions in convulsive seizure frequency per 28 days compared to placebo. Patients were also more likely to have 25%, 50% and 75% reductions in convulsive seizures. Furthermore, participants in fenfluramine groups had longer convulsive seizure-free intervals. In terms of the percentage reduction in total seizures from baseline, an improvement with fenfluramine compared to placebo was observed in both, Study 1 as well as Study 1504.

There was no difference between fenfluramine and placebo in the [redacted][1] [redacted]

The ERG noted that results relating to quality of life varied according to the measure used and were not entirely consistent between the trials. For example, Study 1 found improvements in Paediatric Quality of Life Inventory (PedsQL) over placebo, but Study 1504 did not. In addition, [redacted][1]

4.2.6 Safety results

This section considers the information about adverse events provided in the CS. Safety data were available from the two RCTs, Study 1 and Study 1504, and from the ongoing open-label extension (OLE) Study 1503 in addition to a real-world study.[18, 20, 32-37] The overall safety profile of fenfluramine in the two RCTs and in the OLE and RWE studies is shown in Table 4.11. Adverse events by class are shown in Table 4.12 and adverse events occurring in ≥ 10% of participants in any study group are in Table 4.13. Discussion will focus on the RCTs and the OLE study as the data from the RWE studies were sparse and based on a very small of patients. The RCTs provide 16-week safety data including a treatment maintenance phase of 12 weeks. The OLE provides safety data up to three years. Cardiovascular safety assessments including an ECG and ECHO were conducted before starting the extension study, throughout the study and at follow-up (three to six months following the last dose of study medication).

In addition to this information, the company stated that *"given the mode of action and known adverse event profile of fenfluramine when used at much higher doses than used in Dravet syndrome, a comprehensive risk management plan is expected to specifically address the potential risks of weight loss, valvular heart disease, and pulmonary hypertension. Details are to be confirmed and will be provided if they become available during the appraisal process"*.[1]

[redacted]

The company noted that the most common adverse events (of any severity) with fenfluramine in the RCTs were decreased appetite, diarrhoea, and weight loss > 7%. The company observed that "*weight loss was often regained with continued treatment, and decreased appetite and weight loss are listed as common/very common adverse events with stiripentol and cannabidiol in their respective SmPCs*".[1] [redacted]

The company noted that fenfluramine was previously marketed at significantly higher doses of 60-120 mg/day as an appetite suppressant for the treatment of obesity but was withdrawn from the market over 20 years ago due to its reported association with valvular heart disease. Therefore, based on its known adverse event profile and mode of action, the incidence of adverse events of special interest (AESI) was collected for the RCTs Study 1 and Study 1504 and the OLE Study 1503. The company stated that *"whilst there were numerical differences between fenfluramine and placebo in the incidence of some AESIs in RCTs, none were found to be serious or led to study discontinuation"*.[1] The company further noted that that *"where differences in the incidence of AESIs existed between fenfluramine and placebo these are primarily due small differences in the numbers of patients experiencing* [redacted]*"*.[1] In the OLE, [redacted] of patients had an abnormal echocardiogram (all with normal physiological findings). The company further confirmed that there were no cases of mitral valve incompetence, valvular heart disease or pulmonary arterial hypertension (adverse events of special interest) in the RCTs, or in the open-label extension study.[1]

Table 4.11: Safety results of the fenfluramine studies

Number (%) of participants with safety event	Study 1			Study 1504 (cohort 2)		Study 1503	Belgian cohort
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)	FFA OLE 0.2-0.7 mg/kg/day (n=330)	FFA ≤17 mg/day (n=9)
Participants with any TEAE occurring in ≥5%	26 (65.0)	37 (94.9)	38 (95.0)	42 (95.5)	42 (97.7)	[redacted]	9 (100)
Treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Severe TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3 (33.3)
Serious TEAE	4 (10.0)	4 (10.3)	5 (12.5)	7 (15.9)	6 (14.0)	[redacted]	NR
Serious TEAE leading to death	0	0	0	0	0	[redacted]	0
Treatment-related serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Participants with any AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Serious AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
AESI leading to death	0	0	0	0	0	[redacted]	0
Treatment-related AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Treatment-related serious AESI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR
Adverse events leading to discontinuation	0	0	5 (12.5)	1 (2.3)	2 (4.7)	[redacted]	0
AESI leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0

Based on Table 19 of CS[1]
AESI = adverse events of special interest; CS = company submission; FFA = fenfluramine; OLE = open-label extension; TEAE = treatment emergent adverse event

Table 4.12: Adverse events in the fenfluramine studies by class

Adverse event class[a,b,c]	Study 1			Study 1504 (cohort 2)		Study 1503	Belgian cohort
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)	FFA OLE 0.2-0.7 mg/kg/day (n=232)	FFA ≤17 mg/day (n=9)
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 of CS Appendix F[24]

[a] A participant with more than one TEAE under a system organ class is counted once for that class; [b] Percentages are calculated based on the number of participants in the safety population; [c] AEs are classified as treatment-emergent if they started on or after the date of first dose of study treatment. AEs with partial or missing start dates are classified as treatment-emergent, unless the non-missing components of the start date confirm otherwise.

CS = company submission; FFA = fenfluramine; NR = not reported; OLE = open-label extension

Table 4.13: Adverse events in the fenfluramine studies occurring in ≥ 10% of participants in any study group

TEAE, n (%)[a,b,c]	Study 1			Study 1504 (cohort 2)		Study 1503	Belgian cohort
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)	FFA OLE 0.2-0.7 mg/kg/day (n=232)	FFA ≤17 mg/day (n=9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	2 (5.0)	8 (20.5)	15 (37.5)	5 (11.4)	19 (44.2)	37 (15.9)	[redacted]
Diarrhoea	3 (7.5)	12 (30.8)	7 (17.5)	3 (6.8)	10 (23.3)	25 (10.8)	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fall	2 (5.0)	4 (10.3)	0	NR	NR	[redacted]	[redacted]
Fatigue	1 (2.5)	4 (10.3)	4 (10.0)	2 (4.5)	11 (25.6)	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27 (11.6)	[redacted]
Lethargy	2 (5.0)	4 (10.3)	7 (17.5)	2 (4.5)	6 (14.0)	[redacted]	[redacted]
Nasopharyngitis	5 (12.5)	4 (10.3)	7 (17.5)	15 (34.1)	7 (16.3)	45 (19.4)	[redacted]
Pyrexia	8 (20.0)	7 (17.9)	2 (5.0)	4 (9.1)	11 (25.6)	50 (21.6)	[redacted]
Seizure	5 (12.5)	4 (10.3)	3 (7.5)	7 (15.9)	2 (4.7)	26 (11.2)	[redacted]
Somnolence	3 (7.5)	6 (15.4)	4 (10.0)	3 (6.8)	3 (7.0)	[redacted]	[redacted]
URTI/Bronchitis	5 (12.5)	8 (20.5)	0	3 (6.8)	4 (9.3)	24 (10.3)	[redacted]
Vomiting	4 (10.0)	4 (10.3)	3 (7.5)	3 (6.8)	2 (4.7)	[redacted]	[redacted]
Weight loss >7%	1 (2.5)	5 (13)	8 (20)	2 (4.5)	9 (20.9)	[redacted]	[redacted]

Based on Table 7 of CS Appendix F[24] and Table 20 of the CS[1]

[a] A participant with more than one TEAE with the same preferred term is counted once for that term; [b] Percentages are calculated based on the number of participants in the safety population; c AEs are classified as treatment-emergent if they started on or after the date of first dose of study treatment; [d] [redacted]

CS = company submission; FFA = fenfluramine; NR = not reported; OLE = open-label extension; TEAE = treatment-emergent adverse event

ERG comment:

- It should be noted that both of the key studies included in the CS (Study 1 and Study 1504 had a double-blind, treatment maintenance phase of just 12 weeks. However longer-term evidence is available from Study 1503, the open-label extension study which, using the latest data cut has up to three years' follow-up.
- The ERG draws the attention of the committee to the risk management plan to be supplied by the company if it becomes available during the appraisal process.
- Although additional treatment-related adverse events occurred with fenfluramine these were mainly not rated as serious. However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients.
- Although cardiac adverse events did not appear to be in the main serious, the committee should note the importance of ongoing cardiac monitoring.
- Decreased appetite and weight loss shown by fenfluramine also carry a burden for monitoring.

4.2.7 Supporting efficacy evidence from Study 1503 and the RWE studies

4.2.7.1 Study 1503

Study 1503 is an ongoing, open-label, multinational long-term safety study of fenfluramine for DS in children and young adults who have successfully completed 14 weeks of treatment in Study 1 or Study 1504. Safety results of this study have already been presented in section 4.2.6. As this is not a randomised trial and is it is not directly used in the company's economic model, only brief mention of the efficacy results is made here.

Regarding the study methodology, if patients previously received placebo in their feeder trial, they were given fenfluramine or if randomised to fenfluramine they continued. All participants received 0.2 mg/kg/d fenfluramine for one month to assess effectiveness, safety, and tolerability. This was escalated to 0.7 mg/kg/d in participants not receiving stiripentol (up to a maximum of 26 mg/d) or to 0.4 mg/kg/d (up to a maximum of 17 mg/d) in participants receiving concomitant stiripentol. The company noted that as of 13 March 2018 (n=232) the mean daily dose of fenfluramine across all patients in the OLE was [redacted]

Participants were required to take at least one concomitant AED during study participation. Approximately 72% took clobazam, 71.2% valproate (all forms), 29.1% stiripentol and 24.2% levetiracetam.

A similar proportion of female patients continued into Study 1503 as had been on the feeder trials (45.5%). Patient age was also similar to the feeder trials (an average of nine years old). Other characteristics appeared similar. However, mean baseline CSF was similar to Study 1 and higher than Study 1504 (46.4 per 28 days).

The main outcome was change in CSF per 28 days between the originating study pre-treatments baseline and the OLE treatment period (up to three years). An interim analysis was conducted on 13 March 2018 (n=232). At the time of the last data-cut (14 October 2019) 330 participants had been enrolled with data available for up to three years of treatment.

In the interim analysis (13 March 2018, n=232), CSF was reduced by 63.6% from a baseline median of 20 per 28 days to six per 28 days. The company noted these reductions in monthly CSF were irrespective of originating study treatment assignment (all changes were statistically significant). Using the latest

data-cut up to three years (14 October 2019, n=330) median percentage reduction from baseline in CSF was 64.48% (P < 0.001). [redacted] achieved a >25% reduction, [redacted] achieved a >50% (i.e. clinically meaningful) reduction and [redacted] achieved a >75% (i.e. profound) reduction in convulsive seizure frequency from their originating study baseline during the open-label treatment period. The latest data-cut (14 October 2019, n=330) gave corresponding reductions of [redacted] respectively. The median interval for time between convulsive seizures was one month (25 to 33 days).

Twenty-two (9.5%) of patients discontinued the OLE, most of whom discontinued due to lack of efficacy (16, 6.9%).[35]

ERG comment:

- The ERG noted that patients could progress to the OLE study on 'satisfactory completion' of Study 1 or Study 1504. The ERG asked how satisfactory completion was defined. The company responded "*At the end of the maintenance phase of treatment, patients from Study 1 or Study 1504 who remained eligible for treatment; willing to remain on treatment under trial conditions; and for whom the investigator, patients and/or caregiver determined continued treatment may provide continued benefit, were offered enrolment in the Study 1503 open-label extension study. Patients who discontinued study medication before completion of the 12-week maintenance phase of their core trial by definition did not complete the core study. Those who did not complete the 12-week maintenance period of the core study could have been, on a case-by-case basis, eligible for entrance into the OLE study after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a fenfluramine trial*." This should be borne in mind when interpreting the results of this open label study.
- The ERG noted that Study 1503 is ongoing. In the CS, two different data-cuts were mentioned (13 March 2018 and 14 October 2019). Results were reported for both. The ERG asked for the end date of the trial and wished to confirm that the latest data-cut had been provided.[38] The company replied that *"Study 1503 is due to complete December 2020 (www.clinicaltrials.gov); but could be subject to changes with EMA market authorisation timelines"*.[21] They stated that the latest publicly available data-cut for efficacy was 14 October 2019 and that results were presented in the CS for this data-cut.[21]
- The OLE suggests that reductions in convulsive seizures are maintained for those who respond to fenfluramine treatment.
- There is more long-term evidence for patients not taking stiripentol as a concomitant medication. The ERG noted that just 69 people (29.1%) took stiripentol in the OLE.
- As in the randomised trials, the number of patients taking concomitant clobazam was high (72.4%).
- As this is an extension study it still reflected a child rather than adult population (an average of nine years old).

4.2.7.2 RWE studies

The company presented two 'real-world' evidence studies reported in three papers.[32-34] As these are not randomised trials and are not directly used in the economic model, only brief mention of the efficacy results is made here. Both studies were conducted in Belgium and were open-label.

One prospective study included nine children and adults (aged 1.2 to 29.8 years) treated with fenfluramine for a median duration of 1.5 years.[33] Three of nine participants were female and all had SCN1A mutation. Those with cardiovascular pathology, hypertension treated with medication or

glaucoma were excluded. Patients underwent a three-month observation period taking their current AEDs before being given fenfluramine. The daily dose of fenfluramine could be adjusted according to efficacy or tolerability, with a maximum of 20 mg/day. Participants were required to take all current concomitant AEDs during study participation. All participants were taking valproate as a concomitant AED, three were taking clobazam and two were receiving STP. The study then assessed the overall change in frequency of all major motor seizures during fenfluramine treatment compared with the three-month baseline period. A reduction in the median frequency of major motor seizures was observed from baseline (15.0/month) to three months (2.0/month), six months (1.1/month), nine months (1.1/month) and 12 months (1.6/month). All patients demonstrated a reduction in seizure frequency during the treatment period with a median reduction of 75% (range, 28 to 100%). Seven patients (78%) experienced a ≥50% reduction in major motor seizure frequency. The most common adverse events were somnolence (n=5) and anorexia (n=4). Three of nine patients had fatigue, two had sleep difficulties and three had non-convulsive status epilepticus. No evidence of cardiac valvulopathy or pulmonary hypertension was observed.

A retrospective study reported in two papers included 12 participants aged three to 35 years.[32, 34] The mean follow-up duration was 11 years and four months, with a range of one to 22 years. Seven of 12 participants were female. Fenfluramine was prescribed at a mean of 0.34 (range 0.12–0.90) mg/kg/day. In all patients, fenfluramine was combined with valproate. Nine participants received at least triple combination therapy. Seven of the 10 participants who were still receiving fenfluramine at the time of the last visit had been seizure-free for at least a year. Two participants did not experience a positive effect on seizure frequency or severity. In one patient tonic–clonic seizures were reduced from approximately once per week to once per month. Pulmonary hypertension was not observed in any of the participants. Two participants had a mild thickening of one or two cardiac valves without clinical significance.

ERG comment:

- The prospective real-world evidence study was small (just nine participants) but showed some evidence of positive outcomes up to 1.5 years.
- The retrospective study is further limited by design and is also small (12 patients) but has long-term follow-up (over 11 years) and demonstrates generally positive outcomes.
- Although these small studies give longer-term evidence than the RCTs, they might not pick up on rarer adverse events. The lack of a control group means that findings may not be fully attributable to the intervention.
- The evidence in relation to adults remains sparse.

4.2.8 Ongoing trials

In addition to Study 1503, the company cited two further ongoing studies:

- Study 2: The second cohort from the ongoing double-blind 1501 and 1502 studies, with final study results expected in 2H 2020.[1]
- Study 1601: An international, multicentre, open-label, long-term safety study of fenfluramine in patients with epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Patients with Dravet syndrome currently enrolled in Study 1503, or in any other company-sponsored study by invitation, are eligible to participate. The study began in April 2019 and will provide safety and efficacy data for up to a further three years of treatment. Primary completion is expected in 2023.[39]

ERG comment:

- The ERG asked the company when data from Study 2 (the remaining participants from Studies 1501 and 1502) would be available. They stated that top line results had been presented in a press release and that further details of this study and analyses would be provided when the CSR was made available to the company.[21]
- The ERG also asked the company if any data were available as yet from Study 1601 listed as ongoing.[38] The company replied *"please note that this study should be Study 1900 (NCT03936777, EudraCT Number: 2019-001331-31), rather than Study 1601. Apologies for this confusion. No data are available from Study 1900 at this time"*.[21]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company performed a feasibility assessment evaluating the possibility of performing indirect treatment comparisons (ITCs) between fenfluramine and clobazam, stiripentol or cannabidiol with clobazam.[1] The SLR did not identify any trials evaluating clobazam in the treatment of Dravet syndrome. There were two trials comparing stiripentol with placebo in patients aged three to 18 years with Dravet syndrome and three trials comparing cannabidiol with placebo. The feasibility assessment compared the study designs, eligibility criteria, outcomes, and baseline patient characteristics between the trials to judge whether they were sufficiently similar to be included in an indirect comparison.

The designs and eligibility of the fenfluramine, stiripentol and cannabidiol trials were judged to be similar and all were placebo-controlled trials evaluating the intervention as an add-on to standard of care antiepileptic drugs. They all included patients experiencing four or more convulsive seizures per months during the baseline assessment period. An ITC with stiripentol was not considered appropriate as the stiripentol trials were conducted 15 to 20 years earlier than the fenfluramine and cannabidiol trials and so may not reflect current clinical management of patients with Dravet syndrome. There were also differences in the measurement of CSF. The CS stated that these trials reported percentage change after the first and after the second month of treatment and not during the whole treatment period so the measurement of the primary endpoint was not comparable to the fenfluramine trials.[1] The two stiripentol trials were also judged to be at an unclear risk of bias, one was published as a full paper but did not provide details on allocation concealment and patient withdrawal.[40, 41] However, it did appear to report percentage change in CSF for the whole double-blind period (8 weeks) and not after each month as reported in the CS, however this was a shorter treatment period compared to the fenfluramine trials. The other trial was published as an abstract and did not provide details of methods, nor did it report standard deviations for the percentage change from baseline in convulsive seizures so it would not have been possible to include it in an ITC. The company concluded that the limitations in the stiripentol evidence precluded a robust ITC comparing fenfluramine with stiripentol.

Three trials were identified for cannabidiol, one of which did not report convulsive seizure frequency and so could not be included in an ITC (GWPCARE1 Part A).[42] The two other trials (GWPCARE1 Part B and GWPCARE2) did report on CSF and were considered suitable for an ITC.[43, 44] These trials included patients taking cannabidiol with or without concomitant clobazam but as cannabidiol has been licensed for use in combination with clobazam the ITC used the subgroup of patients also receiving clobazam. However, relevant baseline data for this subgroup was not reported so the feasibility assessment used the baseline characteristics of the whole trial populations. The cannabidiol and fenfluramine trials were completed during a similar time period (between two and five years ago), the fenfluramine trials were judged to be at low risk of bias and the cannabidiol trials at a generally low risk of bias. These trials were also comparable in the timing of the assessment of seizure frequency over

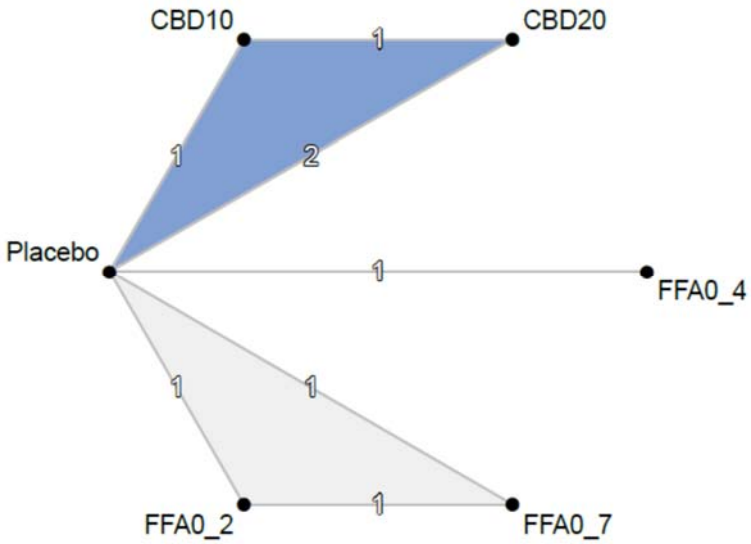
the 14 to 15 weeks treatment period, but the definition of convulsive seizures was different. The fenfluramine trials included focal seizures in the definition of convulsive seizures which means that *"any indirect comparison of fenfluramine against stiripentol or cannabidiol, whose trials exclude focal seizures from the definitions of convulsive seizures, will be conservative"*.[1] The company considered that an ITC comparing fenfluramine with cannabidiol was feasible.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The ITC was performed using NMA rather than the simpler Bucher ITC method. Both frequentist and Bayesian analysis methods were considered but after consulting an expert statistician the company decided to use a Bayesian NMA. The analysis was conducted using the gemtc package in R version 3.5.1. The model used four chains with 20,000 iterations per chain. As there were only four trials included in the NMA fixed effect models were used.

The outcomes analysed in the NMA were percentage change from baseline in CSF per 28 days (used in the economic model) and the number of patients achieving ≥ 50% reduction in CSF frequency from baseline (not used in the economic model). For the fenfluramine trials the NMA used the data for all patients regardless of concomitant treatments so in Study 1 59% were also taking clobazam and nearly all (95%) patients in Study 1504. The cannabidiol data was for the licensed subgroup receiving clobazam which was taken from the Epidyolex Summary of Product Characteristics.[45] The trial network for both outcomes is shown in Figure 4.1.

Figure 4.1: Network diagram



Based on Figure 17 of the CS[1]
CBD10 = cannabidiol 10 mg/kg/day with clobazam; CBD20 = cannabidiol 20 mg/kg/day with clobazam; CS = company submission; FFA0_2 = fenfluramine 0.2 mg/kg/day; FFA0_4 = fenfluramine 0.4 mg/kg/day; FFA0_7 = fenfluramine 0.7 mg/kg/day

Results from the NMA of percentage change from baseline in CSF for each treatment compared with placebo are shown in Table 4.14. This shows that while all doses of cannabidiol and fenfluramine were superior to placebo, with fenfluramine 0.4 and 0.7 mg/kg/day having the greatest reduction, there were no differences between cannabidiol and fenfluramine.

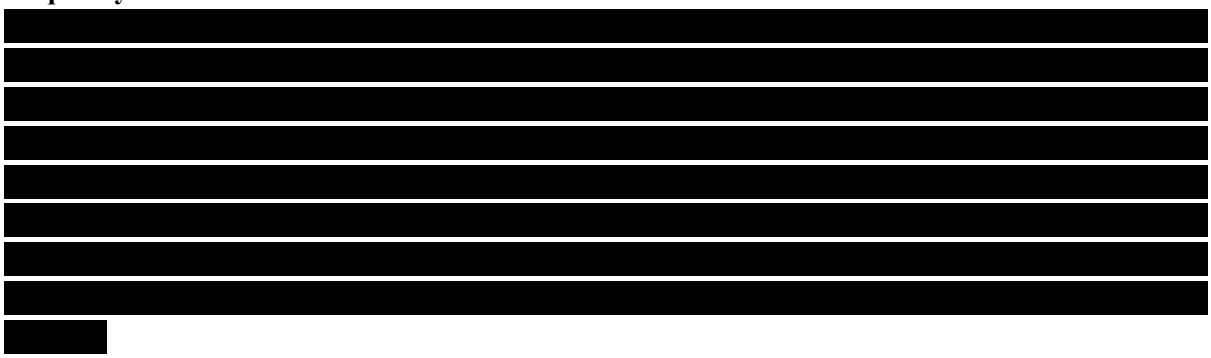
Table 4.14: NMA results for mean percentage change from baseline in CSF compared with placebo (back transformed to original scale)

Treatment	Mean (95%CrI) % change from baseline in CSF vs placebo*
Cannabidiol 10 mg/kg/day	[redacted]
Cannabidiol 20 mg/kg/day	[redacted]
Fenfluramine 0.2 mg/kg/day	[redacted]
Fenfluramine 0.4 mg/kg/day	[redacted]
Fenfluramine 0.7mg/kg/day	[redacted]

Based on Table 18 of the CS[1]
* Back transformed from logged relative rates as -100*(1-EXP(LogRR))
Note, small variations in probabilistic calculations with different runs of the MCMC generates small variations in estimates, compounded by back transformation of rounded results . Results here are the values used in the economic model
CrI = credible interval; CS = company submission; CSF = convulsive seizure frequency; MCMC = Markov chain Monte Carlo; NMA = network meta-analysis

Results from the NMA of the numbers of patients achieving ≥ 50% reduction in CSF frequency from baseline are shown in Figure 4.2. This shows that all doses of fenfluramine increased the odds of having a 50% reduction in CSF compared to cannabidiol with clobazam at both licensed doses.

Figure 4.2: NMA results for the number of patients achieving ≥ 50% reduction in CSF frequency



Based on Figure 19 of the CS[1]

The ERG checked the NMA programs and input data and could reproduce the results. However, it should be noted that the results reported for the percentage change from baseline in CSF per 28 days are actually the percentage difference compared to placebo and not the percentage change from baseline. The NMA used the results from the primary analysis which was the rate of CSF per 28 days during the T+M phase. The analysis used the log of the rate ratio which was back-transformed to provide results as the percentage difference compared with placebo, for example, a mean difference of -31.63% for fenfluramine 0.2 mg/kg/day is the same as a rate ratio of 0.6837 compared to placebo. In addition, the ERG is concerned about the similarity of the trials regarding concomitant treatments. The cannabidiol data used in the NMA were for those patients also receiving clobazam but this was not the case for the fenfluramine data from Study 1 as only around 59% were also on clobazam. There were also differences regarding stiripentol use as all patients in Study 1504 were also taking stiripentol, between 36 and 40% of patients in the cannabidiol trials but none of the patients in Study 1. The company stated that as the baseline CSF frequencies were similar across trials and the fact that each trials is measuring relative

treatment effects versus standard of care then *"the numerical differences observed in the baseline characteristics of the trials do not preclude the use of these data in an ITC"*.[1]

4.5 Conclusions of the clinical effectiveness section

The CS included a systematic review of the evidence for fenfluramine. From this review the company identified and presented evidence from two randomised trials (Study 1 and Study 1504), an open-label extension study (Study 1503) and 'real world evidence' from a prospective and retrospective study, see sections 4.2.1 and 4.2.7. Both randomised trials were conducted in patients up to 18 years with Dravet syndrome, whose seizures were incompletely controlled with previous AEDs. Although the decision problem in the NICE scope did not specify any age restriction and the expected licenced indication includes children and adults, neither of the key trials used in the submission (Study 1 and Study 1504) included adult patients (over the age of 18 years).[1, 4] Therefore, adults with DS are not fully represented in the CS. The numbers of adults in the non-RCT studies was small and this evidence is at greater risk of bias. The committee will need to decide if is satisfied that fenfluramine will be equally suitable for adults with Dravet syndrome. Of note, the clinical experts consulted by the ERG agree with the company, i.e. that results are applicable to adult patients with DS.

Unlike cannabidiol, fenfluramine can be given with or without concomitant clobazam. The company stated that a small proportion of patients would receive fenfluramine as a first-line add-on therapy in patients where clobazam or a clobazam-based regimen is undesired.[1] They stated that most patients would receive fenfluramine after clobazam as proposed in the second-line + add-on therapy setting. In this setting comparators are continuation of standard of care AEDs reflecting AEDs and add-on therapies continued from previous line, cannabidiol + SoC AEDs or stiripentol + SoC AEDs. However, the main trials in the CS compared fenfluramine to placebo (alongside concomitant AEDs) and the NMA focused on cannabidiol as a comparator. The committee will need to decide if the evidence is sufficient to place fenfluramine at both places in the pathway and that greater or at least equal efficacy against all comparators can be assumed.

The key RCTs (Study 1 and Study 1504) were well-conducted, multinational trials including a number of UK patients. However, they only included a 12-week treatment maintenance period so cannot provide long-term data on SUDEP and other deaths. The exact link between reduction in convulsive seizures and any associated reductions in mortality cannot be determined from the two randomised trials. The extension study suggested that improvements in convulsive seizures could be maintained for up to three years. The two 'real world' observational studies in the CS were small and the lack of a control group is a major limitation.

In Study 1504 all patients received stiripentol as concomitant treatment whereas in Study 1 stiripentol was not permitted. The ERG draws to the attention of the committee that, as per the company's dosage instructions, fenfluramine is given at a lower dosage when combined with stiripentol and the randomised trials reflect this.

Focusing on the results of the key trials, participants receiving fenfluramine had greater reductions in convulsive seizure frequency per 28 days compared to placebo. Patients were also more likely to have 25%, 50% and 75% reductions in convulsive seizures. Furthermore, participants in fenfluramine groups had longer convulsive seizure-free intervals. However, there was no difference between fenfluramine and placebo in the [redacted] The ERG noted that results relating to quality of life varied according to the measure used and were not entirely consistent between the trials.

Although additional treatment-related adverse events occurred with fenfluramine these were mainly not rated as serious. However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients. Although cardiac adverse events did not appear to be in the main serious, the committee should note the importance of ongoing cardiac monitoring. Decreased appetite and weight loss shown by fenfluramine also suggest a burden for monitoring.

A Bayesian NMA was performed to compare fenfluramine with cannabidiol plus clobazam. This used data from Study 1 and Study 1504 and two cannabidiol trials (GWPCARE1 part B and GWPCARE2). There was no evidence of a difference between any doses of fenfluramine and cannabidiol in the mean CSF rate during treatment. However, fenfluramine increased the number of patients achieving ≥50% reduction in CSF frequency from baseline compared to cannabidiol. The ERG is concerned about the clinical heterogeneity of studies in the NMA regarding concomitant AEDs as the use of clobazam and stiripentol varied between studies.

5 Cost effectiveness

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement, and evaluation of health effects as well as for cost and healthcare resource identification, measurement, and valuation.

5.1.1 Searches performed for cost effectiveness section

Appendix G.1.1 of the CS details an SLR which was conducted to identify and evaluate existing cost effectiveness analyses or other economic evaluations of fenfluramine or other pharmacological therapies used as add-on therapies to standard of care anti-epileptic drugs in Dravet syndrome.[24]

Searches were conducted on 29 June 2020. and were limited to English language publications. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness systematic review (as reported in CS)

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase/MEDLINE	Embase.com	Inception - 29/6/20	29/6/20
PubMed	PubMed	Inception - 29/6/20	29/6/20
HTA Database	CRD website	Inception - 29/6/20	29/6/20
NHS EED		Inception - 29/6/20	
Conference proceedings			
AES Annual Meetings	Hand search of online proceedings	2017-2019	29/6/20
BPNA meetings	via Embase.com (EPNSC 2019 hand-searched)		
ECE meetings			
EPNS meetings			
IEC meetings			
ISPOR			
Additional resources			
NICE	Web search	Not stated	29/6/20
AWMSG			
SMC			
CADTH			

AES = American Epilepsy Society; AWMSG = All Wales Medicines Strategy Group; BPNA = British Paediatric Neurology Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CRD = Centre for Reviews and Dissemination; CS = company submission; ECE = European Congress on Epileptology; EED = Economic Evaluation Database; EPNS = European Paediatric Neurology Society; HTA = health technology assessment; IEC = International Epilepsy Congress; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

Appendix H.1.1 details an SLR conducted to identify and evaluate published quality of life studies and health state utility values in patients with Dravet syndrome, or their caregivers.[24]

Searches were conducted on 3 July 2020. and were limited to English language publications. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.2.

Table 5.2: Data sources for the quality of life/health state utility values systematic review (as reported in CS)

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase/MEDLINE	Embase.com	Inception - 3/7/20	3/7/20
PubMed	PubMed	Inception - 3/7/20	3/7/20
ScHARRHUD Health State Utilities Database	Web searches	Inception - 3/7/20	3/7/20
HERC Database of mapping studies		Inception - 3/7/20	
Conference proceedings			
AES Annual Meetings	Hand search of online proceedings	2017-2019	3/7/20
BPNA meetings	via Embase.com (EPNSC 2019 hand-searched)		
ECE meetings			
EPNS meetings			
IEC meetings			
ISPOR			
Additional resources			
NICE	Web search	Not stated	3/7/20
AWMSG			
SMC			
CADTH			

AES = American Epilepsy Society; AWMSG = All Wales Medicines Strategy Group; BPNA = British Paediatric Neurology Association; CADTH = Canadian Agency for Drugs and Technologies in Health; CRD = Centre for Reviews and Dissemination; CS = company submission; ECE = European Congress on Epileptology; EPNS = European Paediatric Neurology Society; HERC = Health Economics Research Centre; IEC = International Epilepsy Congress; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; ScHARRHUD = School of Health and Related Research Health Utilities Database; SMC = Scottish Medicines Consortium

Appendix I.1.1 details an SLR conducted to identify and evaluate existing studies reporting on healthcare resource use and costs in Dravet syndrome.[24]

Searches were conducted on 29 June 2020. and were limited to English language publications. Databases were searched from date of inception. A summary of the sources searched is provided in Table 5.3.

Table 5.3: Data sources for the healthcare resource use and costs systematic review (as reported in CS)

Resource	Host/source	Date range	Date searched
Electronic databases			
Embase/MEDLINE	Embase.com	Inception - 29/6/20	29/6/20
PubMed	PubMed	Inception - 29/6/20	29/6/20
HTA Database	CRD website	Inception - 29/6/20	29/6/20
NHS EED		Inception - 29/6/20	
Conference proceedings			
AES Annual Meetings	Hand search of online proceedings	2017-2019	29/6/20
BPNA meetings	via Embase.com (EPNSC 2019 hand-searched)		
ECE meetings			
EPNS meetings			
IEC meetings			
ISPOR			
Additional resources			
NICE	Web search	Not stated	29/6/20
AWMSG			
SMC			
CADTH			

AES = American Epilepsy Society; AWMSG = All Wales Medicines Strategy Group; BPNA = British Paediatric Neurology Association; CADTH = CADTH = Canadian Agency for Drugs and Technologies in Health; CRD = Centre for Reviews and Dissemination; CS = company submission; ECE = European Congress on Epileptology; EED = Economic Evaluation Database; EPNS = European Paediatric Neurology Society; HTA = health technology assessment; IEC = International Epilepsy Congress; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

ERG comment:

- A single set of searches appears to have been undertaken for economic evaluations and healthcare resource use and cost studies, although the literature searches are recorded separately in Appendices G and I.[24] Separate searches were conducted for quality of life and health state utility value studies, and recorded in Appendix H.[24] As similar searches were conducted across all cost effectiveness sections, and the same comments apply to both, they are discussed together in this section.
- Several databases and a good range of conference proceedings and health technology assessment organisation websites were searched, and reference checking was conducted. Searches were well documented, making them transparent and reproducible.
- No date limits were applied to the database searches. The date limit applied to conference searches was considered justifiable.

- The ERG was concerned that limiting the searches to English language may have introduced potential language bias. Current best practice states that that "*Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"*[26] and that "*research related to language bias supports the inclusion of non-English studies in systematic reviews*".[27, 28] In the Clarification Response[21] the Company states that the decision to limit the inclusion criteria to English language publications was made for pragmatic reasons as the focus was specifically on UK clinical practice. Searches of other sources such as HTA organisation websites were intended to supplement the database searches and would be sufficiently comprehensive to find any relevant non-English publications. The Company subsequently re-ran the Embase.com and PubMed searches without a language limit, and assessed the additional publications retrieved[29]. No additional references were found that were of relevance for inclusion in the present review
- Study design filters were appropriately used and were based on CADTH filters.
- For all SLRs, the company searched Embase and MEDLINE simultaneously using a single database provider (Embase.com) and search strategy. This approach has limitations when using subject heading terms which could affect recall of results. Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE subject heading terms (MeSH), it is not clear if this is the case for all MeSH terms. Given the potential limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy in order to ensure that potentially relevant records were not missed.
- The use of the Emtree subject heading 'myoclonus epilepsy'/exp is queried by the ERG, as according to the Emtree scope notes, this subject heading does not cover Dravet syndrome. The appropriate EMTREE heading would have been 'severe myoclonic epilepsy in infancy'/, which is not included. It is unclear what relevant records may have been missed by this incorrect subject heading.
- Searches of the NHS EED and HTA databases include an apostrophe, which does not work on this interface, and could result in missed relevant records. In addition, the rationale behind not including the MeSH term 'Epilepsies, Myoclonic' in the searches of these databases is not clear. In the CS (Table 10; Appendix G and Table 24; Appendix I), 'use of the MeSH search for Epilepsies, Myoclonic yielded fewer hits' is given as justification for not including the term, however this could still have retrieved additional relevant records. In the Clarification Response[21] the Company acknowledged errors in the documentation of these searches and clarified the search terms used. Database searches were subsequently re-run, however no additional references were found that were of relevance for inclusion in the present review.
- The recall of all the searches could have been increased by additional free-text synonyms such as 'severe polymorphic epilepsy of infancy', the use of truncation, for example 'myoclon* epileps*' and the use of acronyms, such as ICEGTCS (intractable childhood epilepsy with generalised tonic clonic seizures). The searches of NHS EED, the HTA database, ScHARRHUD and the HERC mapping database could have benefited from additional search terms, as these strategies did not include all the synonyms used in the MEDLINE/Embase or PubMed searches.
- The CS stated that a number of conference proceedings were searched via the Embase.com search. However, one of the conferences (EPNS 2019) is not currently indexed on Embase.com. In the Clarification Response[21] the Company acknowledged this oversight, and conducted a search of the EPNS 2019 proceedings. No additional relevant references were found that would influence the conclusions on the efficacy, safety, or cost effectiveness of fenfluramine or its relevant comparators.

- Discrepancies were noted by the ERG between the search result numbers provided for the NHS EED/HTA searches and the PRISMA flow diagram in the cost effectiveness/healthcare resource use searches. In the response to the request for clarification, the company acknowledged the error, confirming that the search results were correct and the error was in the PRISMA flow diagram.[21] Updated PRISMA flow diagrams were provided.[29]

5.1.2 Inclusion/exclusion criteria used in the study selection

In- and exclusion criteria for the review on cost effectiveness studies, utilities and costs and resource use are presented in Table 5.4.

Table 5.4: Eligibility criteria for the systematic literature reviews

PICOS	Inclusion criteria	Exclusion criteria
Patient population	All patients with a defined clinical diagnosis of Dravet syndrome (with or without confirmed SCN1A mutation), irrespective of age. If studies include mixed populations of patients, only those reporting results separately for Dravet syndrome patients will be included.	No data reported on relevant population
Intervention	• Fenfluramine (synonym: ZX008) at a dose of 0.2 mg/kg per day, or 0.7 mg/kg/day, 0.4 mg/kg/day if co-administered with stiripentol, given as an add-on therapy to standard of care AEDs. This will include fenfluramine hydrochloride at dose equivalents of 0.2 mg/kg/day, or 0.8 mg/kg/day, or 0.5 mg/kg/day if co-administered with stiripentol. In addition, add-on therapies to standard of care AEDs recommended by NICE: • Clobazam • Stiripentol at doses up to 50 mg/kg/day • Cannabidiol (synonym: GWP42003-P) in the form of the highly purified cannabidiol used in the Epidyolex/Epidiolex formulation, at doses of up to 10 mg/kg/day or 20 mg/kg/day	No data reported on relevant intervention
Comparator	• Any active pharmacological comparator used as add-on therapy to standard of care AEDs • Placebo/standard of care AEDs	No data reported on relevant comparator
Outcomes(s) 1 (Published economic evaluations)	• Cost per QALY gained • Cost per DALY • Cost per life year gained • Net monetary benefit • Costs	No data reported on a relevant outcome
Outcomes(s) 2 (Utility studies)	• QoL measured with epilepsy-specific tools (e.g. QOLCE, PedsQL) • QoL measured using generic tools (e.g. EQ-5D, SF-36) • Utility values reported in cost utility analyses	No data reported on a relevant outcome; qualitative study reporting views

PICOS	Inclusion criteria	Exclusion criteria
Outcomes(s) 3 (Cost/resource use studies)	• Direct costs (drug costs, healthcare resource use costs) • Indirect costs (out of pocket, loss of productivity) • Health care resources (healthcare appointments, emergency ambulance, hospitalisations, rescue medication) • Loss of productivity/employed time	No data reported on a relevant outcome
Study design 1 (Cost effectiveness analysis studies)	• Cost utility analyses • Cost effectiveness analyses • Cost benefit analyses • Cost minimisation analyses • Cost consequence analyses • Cost analyses • Budget impact analyses • HTAs reporting any of the above study methods • Systematic review of the above type of studies – for background information and reference checking only	Other study design
Study design 2 (Utility studies)	• RCTs, or any other comparative studies reporting QoL • Quality of life studies • Cost utility analyses • HTAs reporting cost utility analyses • Surveys of parents or caregivers or siblings • Systematic reviews of quality of life studies	Other study design
Study design 3 (Cost/resource use studies)	• Observational studies (longitudinal or cross-sectional studies, including registry studies) • Patient/caregiver surveys • Cost of illness/burden of disease studies • (HTA reports including cost effectiveness results identified in Economic SLR) • (Cost effectiveness studies identified in Economic SLR) • (Budget impact studies identified in Economic SLR) Any geographic location, but only studies with UK patients will be extracted	Other study design

Based on Appendices G, H and I of the CS[24]

AED = antiepileptic drug; CS = company submission; DALY = disability-adjusted life year; EQ-5D-5L = EuroQOL–5 Dimensions; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; PICOS = Population, Intervention, Comparator(s), Outcome(s), and Study design; PedsQL = Paediatric Quality of Life Inventory; QALY = quality-adjusted life year; QoL = quality of life; QOLCE = Quality of Life in Childhood Epilepsy; SCN1A = Sodium Voltage-Gated Channel Alpha Subunit 1; SF-36 = short form 36; SLR = systematic literature review; 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.

5.1.3 Included/excluded studies in the cost effectiveness review

The company identified 483 records in the SLR, of which nine met the inclusion criteria (Table 14 of Appendix G of the CS).[24] The SLR identified no published economic evaluations of fenfluramine.

ERG comment: The rationales for excluding cost effectiveness studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

5.1.4 Conclusions of the cost effectiveness review

The CS provided an overview of the included cost effectiveness, utility and resource use and costs studies. It concluded that none of the identified studies evaluated the cost effectiveness of fenfluramine in patients with DS and therefore were not directly generalisable to the NICE decision problem.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.5: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Individual-patient state-transition model	NICE TA614[14]; to capture the benefits of different numbers of seizure-free days	B.3.2.2.2
States and events	The state-transition model consisted of three health states: 1) alive, on treatment, 2) alive, treatment discontinued and 3) death.		B.3.2.2.3
Comparators	Cannabidiol with a dose of 12 mg/kg/day	Cannabidiol (with clobazam) is the only NICE-recommended add-on therapy to have been formally appraised by NICE.	B.3.2
Population	People with Dravet syndrome whose seizures are inadequately controlled by established clinical management.	Consistent with the therapeutic indication proposed to the European Medicines Agency.	B.3.2.1
Treatment effectiveness	Treatment effectiveness was estimated based on the frequency of convulsive seizures, number of days without convulsive seizures and discontinuation rates.	Primary data sources for the model are the individual patient-level data from the two fenfluramine registration studies (Study 1 and Study 1504 cohort 2) to construct convulsive seizure-free profiles. Relative treatment effectiveness with fenfluramine and cannabidiol relative to placebo was assessed by performing an indirect treatment comparison (ITC) using the fenfluramine registration studies (Study 1 and Study 1504 cohort 2) and	B.3.2.2.1

	Approach	Source/Justification	Signpost (location in CS)
		subgroup analyses (patients taking concomitant clobazam) of the cannabidiol registration studies (GWPCARE1 and GWPCARE2).[42, 44]	
Adverse events	Adverse events were excluded from the model.	Data on the placebo and treatment arms of the fenfluramine registration studies indicated that there was an increase in TEAEs of all grades in the fenfluramine arms. However, the incidence of serious TEAEs was low and similar across the fenfluramine and placebo arms, and there was little difference in the number experiencing serious treatment-related adverse events between fenfluramine and placebo in either Study 1 (2 vs 0) or Study 1504 cohort 2 (1 vs 1).	B.3.3.4
Health related QoL	PedsQL data from the registration studies was mapped to EQ-5D-Y using the Khan et al. 2014 algorithm.[46] In addition, carer utilities were included in the base-case. To this extent, EQ-5D-5L data was collected directly from the carers in the registration studies.	In line with the approach adopted in the NICE appraisal of cannabidiol (TA614).[14]	B.3.4.2.1 & B.3.4.2.2
Resource utilisation and costs	The cost categories included in the model were treatment acquisition costs, monitoring costs and health state costs (ongoing and emergency resource use costs).	Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU). Estimates of resource use were elicited from physicians and nurses involved in the management and treatment of paediatric and adult patients with Dravet syndrome as reported in the UK Pathway research study.	B.3.5
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case.	Table 25

	Approach	Source/Justification	Signpost (location in CS)
Subgroups	No subgroups were explored.	Two populations of patients are run through the model; one in which the patient receives fenfluramine + SoC (referred to throughout as the intervention strategy) and one in which the patient receives cannabidiol + SoC (referred to throughout as the comparator strategy). However, to determine the ICER, the costs and QALYs were combined for the simulated patients by assuming population receiving the intervention is comprised of patients on concomitant stiripentol (58%) or not (42%), representing the use of stiripentol observed in UK patients in clinical practice in the DISCUSS study.	B.3.2.2.3.2
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses.		B.3.9

BNF = British National Formulary; CS = company submission; DSA = deterministic sensitivity analysis; EQ-5D-L = EuroQOL–5 Dimensions–5 Levels scale produced by the European Quality of Life Group; EQ-5D-Y = EuroQOL–5 Dimensions–Youth scale produced by the European Quality of Life Group; ICER = incremental cost effectiveness ratio; ITC = indirect treatment comparison; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PedsQL = Paediatric Quality of Life Inventory; PSA = probabilistic sensitivity analysis; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year; QoL = quality of life; SoC = standard of care; TA = technology appraisal; TEAE = treatment-emergent adverse event; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.6: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Yes	
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	Partly	Different (combinations of) AEDs were not considered as separate comparators.
Type of economic evaluation	Cost effectiveness analysis	Yes	

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Perspective on costs	NHS and Personal Social Services (PSS)	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	
Synthesis of evidence in outcomes	Systematic review (SLR)	Yes	
Measure of health effects	Quality adjusted life years (QALYs)	Yes	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Partly	Patients' utilities were mapped to EQ-5D-Y from PedsQL
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Partly	PedsQL was used but mapped to EQ-5D-3L
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic modelling	Yes	

AED = antiepileptic drug; EQ-5D-5L = EuroQOL–5 Dimensions–5 Levels scale produced by the European Quality of Life Group; EQ-5D-Y = EuroQOL–5 Dimensions–Youth scale produced by the European Quality of Life Group; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PedsQL = Paediatric Quality of Life Inventory; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

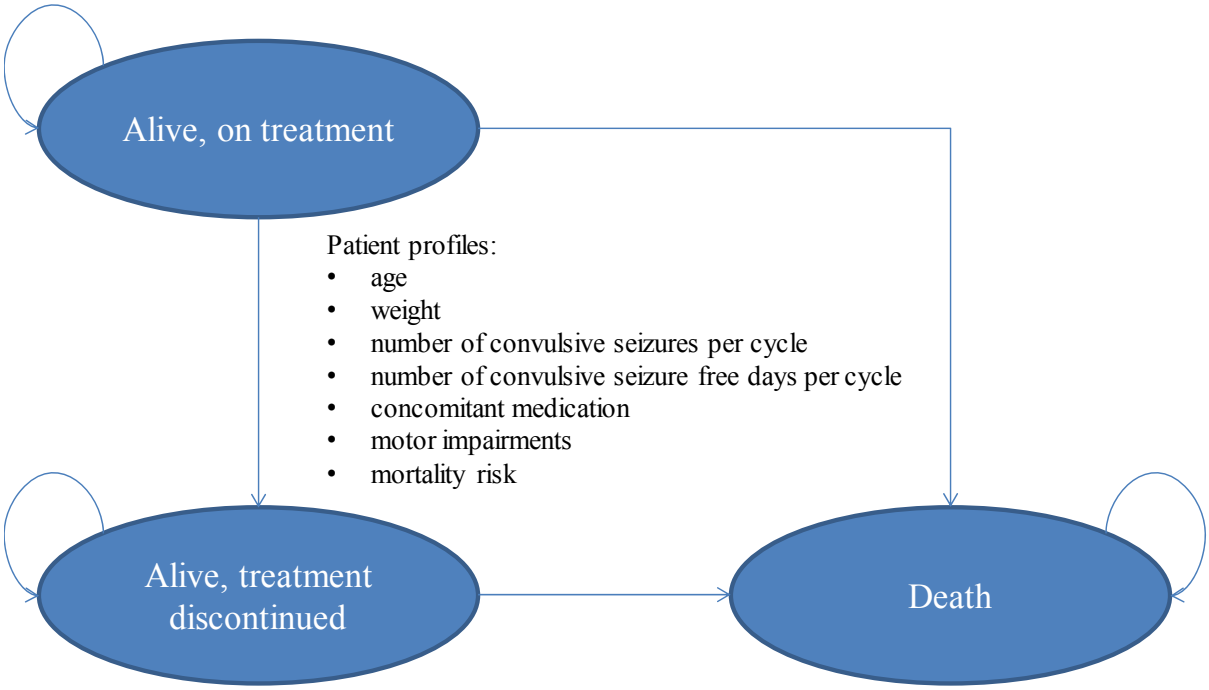
The company's modelling approach consisted of an individual-patient state-transition model (implemented in R version 3.5.2). The individual patient approach was justified by the company to more appropriately account for patient heterogeneity as well as by referring to the committee discussion of TA614, where it was stated that *"other approaches to modelling, such as discrete event simulation, may have been more appropriate to capture the benefits of different numbers of seizure-free days"*.[14]

The state-transition model consisted of three health states: 1) alive, on treatment, 2) alive, treatment discontinued and 3) death (see Figure 5.1). Due to insufficient data and to simplify the modelling approach, only the primary intervention in each strategy was considered, i.e. if patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC. Patient profiles were assigned to individual patients consisting of the following attributes: age, weight, number of convulsive seizures per cycle,

number of convulsive seizure-free days per cycle, concomitant medication (receiving stiripentol or not), motor impairments (none, ataxia, or severe) and mortality risk.

The company assumed based on the DISCUSS study, that 58% and 42% of the population would and would not receive concomitant stiripentol. The company calculated the cost effectiveness of fenfluramine separately for these two subpopulations and subsequently used these proportions to calculate a weighted average representing the cost effectiveness of the "merged" population.

Figure 5.1: Model structure



ERG comment: The main concerns of the ERG relate to: a) patients revert to baseline not placebo seizure frequency; b) patients might improve after discontinuation; c) if patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC.

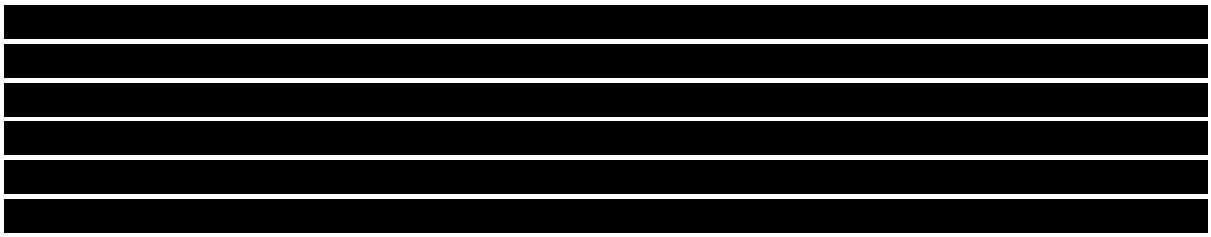
a) Once patients discontinue treatment, they are assumed to revert to baseline seizure frequency (as observed during the observational period of the trial) and not to the placebo 'on-treatment' seizure frequency (as observed during the maintenance period of the trial). In response to clarification question B16j, the company indicated that this was done to prevent that discontinued patients still experience the benefit of the placebo effect.[21] The ERG does not agree with this approach as this placebo effect may also be present in the fenfluramine and cannabidiol treated patients who are still on treatment (and hence is part of the demonstrated effects). Removing the presumed placebo effect (which could include other factors such as natural progress or regress of disease) for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment. Therefore, the ERG preferred to assume that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial. Although this scenario was requested from the company (clarification question C16), it was not provided. The ERG could not easily change this in the model as this change also impacted the placebo effect (which is added to the treatment effect) and therefore is likely to have impact on other assumptions in the

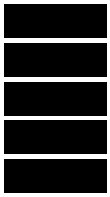
model (e.g. such as the stopping rule). However, the ERG did perform an exploratory scenario analysis in which the placebo 'on-treatment' seizure frequency (as observed during the maintenance period of the trial) was set equal to the baseline seizure frequency.[38]

b) In the committee discussion for TA614, it was mentioned that *"the model generates more favourable results for patients that stop cannabidiol than would be expected"*.[14] Specifically, some patients that discontinued treatment may have been reassigned to a health state with a lower frequency of seizures than they were in before treatment discontinuation, i.e. patients' health status improves after treatment discontinuation. Although in response to clarification question C16h, the company indicates that the current model does not have this limitation, the ERG believes that this statement is incorrect.[21] As highlighted in Figure 5.2, it is possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation. This model limitation was removed in the ERG analyses (by adjusting the post discontinuation convulsive seizure frequency and convulsive seizure-free days).

c) If patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC. This is a simplifying assumption. It is unclear what the impact would be of this assumption.

Figure 5.2: Density plots of convulsive seizures before versus after treatment discontinuation





5.2.3 Population

Consistent with the NICE scope, the population considered in the CS (CS Table 1) was people with DS whose seizures are inadequately controlled by established clinical management.[1, 4] The anticipated licensed indication of fenfluramine is: for the treatment of seizures associated with DS as an add on therapy to other AEDs in children aged two years to 17 years and adults. Thus, in contrast with cannabidiol, fenfluramine is anticipated to be licensed for use both with and without concomitant clobazam.

The phase III trial evidence for fenfluramine (includes Study 1 and Study 1504; two double-blind, randomised, placebo-controlled studies, and Study 1503; one long-term open label extension study) focused on DS patients aged ≥2 to ≤18 years, with convulsive seizures not completely controlled by current AEDs (≥4 convulsive seizures per 4-week period for 12 weeks prior to screening).

The key baseline patient characteristics in the economic model are listed in Table 5.7 below.

Table 5.7: Key baseline patient characteristics in the economic model

		Mean (SD) (%)	Min < med < max	IQR	Source	Comment
Age	**years**	12.7 (8.6)	2 < 11 < 34	12	DISCUSS UK dataset	Increases every cycle
Weight	**kg**	41.1 (21.8)	12 < 37.8 < 78	34.4	RCPCH and the NHS Health survey for England	Increases with age (12 kg at age 2 linearly increasing to a maximum of 78 kg at age 25)
Gender	**male**	53.8%	N/A			
	female	46.2%	N/A			
Motor impairments	**none**	50.2%	N/A		Study 1 and Study 1504 cohort 2	Assumed constant (static) over time
	ataxia	31.5%	N/A			
	severe physical issues	18.3%	N/A			
Concomitant medication	**stiripentol**	58%	N/A		DISCUSS UK dataset	Assumed constant (static) over time
	no stiripentol	42%	N/A			
Baseline convulsive seizure[a] (observational period of the trial, placebo)	**frequency**	[redacted]	[redacted]	[redacted]	Study 1504[b]	Bootstrapped data (assumed independent on age[c], weight, gender, and motor impairments). The baseline data was used after discontinuation while the trial period data was used for patients on treatment.
		[redacted]	[redacted]	[redacted]	Study 1[b]	
	free days	[redacted]	[redacted]	[redacted]	Study 1504[b]	
		[redacted]	[redacted]	[redacted]	Study 1[b]	
On-treatment convulsive seizure[a] (maintenance period of the trial, placebo)	**frequency**	[redacted]	[redacted]	[redacted]	Study 1504[b]	
		[redacted]	[redacted]	[redacted]	Study 1[b]	

	Mean (SD) (%)	Min < med < max	IQR	Source	Comment
free days	[redacted]	[redacted]	[redacted]	Study 1504[b]	
	[redacted]	[redacted]	[redacted]	Study 1[b]	

Based on the economic model and Table 27 of the CS[1]
[a] Calculated by the ERG based on the bootstrapped data (column 131 is removed as it was considered to have values that were unlikely to be plausible given the other data); [b] Clarified in response to clarification question C12, this was based on placebo patients that continued into the maintenance arm of the trial[21]; [c] The only age dependency included was the assumption that for patients beyond 18 years of age, the frequency of convulsive seizures was halved, and convulsive seizure-free days was doubled.
CS = company submission; ERG = Evidence Review Group; IQR = interquartile range; N/A = not applicable; NHS = National Health Service; RCPCH = Royal College of Paediatrics and Child Health; SD = standard deviation; UK = United Kingdom

ERG comment: The main concerns of the ERG relate to: a) the scope of the population, whether it is both with and without concomitant clobazam; b) considering the populations receiving treatment with and without concomitant stiripentol separately; c) assumption that fenfluramine is similarly effective and well tolerated in adult patients; d) the methods to construct patient profiles result in seemingly implausible patients profiles and e) do not capture all relevant correlations.

a) The license is anticipated to include fenfluramine for use both with and without concomitant clobazam (in contrast with cannabidiol). Nevertheless, in the CS base-case cannabidiol is used as the only comparator, implying that the cost effectiveness analyses are restricted to people receiving clobazam (i.e. the population for which cannabidiol is recommended). However, in response to clarification question C3, the company indicated that the submission covers the full anticipated marketing authorisation, i.e. fenfluramine with and without concomitant clobazam. The ERG believes that, in case the company focusses on the full anticipated marketing authorisation, the comparators should not be restricted to cannabidiol as cannabidiol is not a recommended comparator for the full anticipated marketing authorisation.[21] Moreover, given that cannabidiol is only relevant for a subgroup of the population considered, the cost effectiveness of the populations treated with and without concomitant clobazam should be considered separately. The company did provide a scenario for the subpopulation with concomitant clobazam (Table 9 of the response to request for clarification response), increasing the costs of clobazam for the patients receiving fenfluramine (i.e. given that in this scenario all patients receive clobazam) and thus assuming that the relative effectiveness (from the NMA) is unaffected by concomitant clobazam.[21] This scenario was implemented in the ERG analyses to reflect the concomitant clobazam population.
b) In response to clarification question C4, the company indicated that concomitant treatment with stiripentol is a treatment effect modifier due to a pharmacokinetic interaction or prior AEDs is a modifier of relative treatment effectiveness for fenfluramine.[21] Given this interaction, the (cost) effectiveness of fenfluramine likely differs for patients with and without concomitant stiripentol. Therefore, the ERG would prefer to report the results for these populations (based on concomitant stiripentol) separately. In combination with the preceding comment, this would result in three subpopulations that should be considered: 1) without concomitant clobazam and stiripentol; 2) with concomitant clobazam but without stiripentol and 3) with concomitant clobazam and stiripentol. Concomitant stiripentol without clobazam was not considered as this is not in line with the stiripentol licensed population.
c) The phase III fenfluramine trials targeted children or adolescents ≤18 years old. Nevertheless, the population considered in the CS base-case included children or adolescents that aged in adulthood as well as patients that initiated fenfluramine in adulthood (see Table 5.7 for the baseline age summary statistics). The company assumes that fenfluramine is similarly effective and well tolerated in adult patients. In response to clarification question C5, the company argues that this assumption is justified based on clinical evidence.[21] However, this clinical evidence was non-comparative, based on small samples and partly retrospective. Therefore, the assumption that fenfluramine is similarly effective and well tolerated in adult patients is subject to major uncertainty and can be questioned.
d) The output (.RDATA) files from the bootstrap code differed from the files that were used in the microsimulation, making it unclear whether the bootstrap code provided by the company did contain all calculations/data manipulation steps required to obtain the patients profiles. This is particularly worrying as the patient profiles generated did contain seemingly inconsistent/ implausible patient profiles that could not be explored by the ERG. This is illustrated in Figure 5.3 (mean of columns, in this data frame each column represents a cycle in the economic model)

indicating that column 131, i.e. the last model cycle, seems implausible as well as Figure 5.4 (scatterplot of convulsive seizure frequency and convulsive seizure-free days removing column 131), indicating for study 1504 an seemingly implausible peak for patient with 0 convulsive seizure-free days that seems to represent a cluster of 'outlier' patients in terms of convulsive seizure frequency. These inconsistencies/ seemingly implausible values undermine the validity of the patient profiles used. The column 131 inconsistency was removed in the ERG base-case by replacing it by values from the preceding column. Unfortunately, other inconsistencies could not be repaired by the ERG (given the lack of access to the original data as well as limited explanation of the bootstrap procedure).

e) Related to the preceding comments, the correlations between patient characteristics incorporated in the bootstrapped patient profiles were limited. The company did indicate (response to clarification question C8) that it could be clinically plausible that motor impairments and concomitant medication would be correlated with age, however the trial data shows that there is no correlation.[21] Additionally, the company did not elaborate on correlations between motor impairments and concomitant medication neither on the correlation between motor impairments and convulsive seizure frequency/ free days. In response to clarification question 12f, it is stated that clinicians believed that greater seizure frequency may be related to worse motor impairment, indicating that there are potential correlations that are not reflected in the patient profiles.[21] This might result in implausible combinations of patient characteristics and thus patient profiles.

Figure 5.3: Mean convulsive seizure frequency and convulsive seizure-free days over time

Figure 5.4: Scatterplots and histograms of convulsive seizure-free days and convulsive seizure frequency

[redacted]

5.2.4 Interventions and comparators

The intervention considered in the CS was fenfluramine with the anticipated licensed indication: for treatment of seizures associated with DS as an add-on therapy to other antiepileptic medicine in children aged two to 17 years and adults.[1] The doses which were used for fenfluramine with a dose of 0.7 mg/kg/day (with a maximum of 26 mg/day) when used without stiripentol and 0.4 mg/kg/day (with a maximum of 17 mg/day) when used with stiripentol. The comparator used in the model was cannabidiol with a dose of 12 mg/kg/day as preferred by the appraisal committee NICE TA614.[14] The company argued that this comparator was used because it is the only existing add-on therapy which has been appraised and accepted as clinically and cost effective in combination with clobazam.[1] The percentage of individuals using concomitant AEDs was retrieved from the fenfluramine registration studies (Table 5.8), except for stiripentol and clobazam.[18] The effects observed in Study 1504 (with 94% of patients receiving stiripentol) and Study 1 (with no patient receiving stiripentol) were applied to the frequencies of stiripentol use observed in the DISCUSS study.[47] To this extent, given that the population receiving fenfluramine was comprised of patients on concomitant stiripentol (58%) or not (42%), total costs and QALYs were merged by calculating weighted incremental costs and QALYs for the merged population by assuming these proportions of stiripentol.[47] The use of concomitant clobazam was applied to the comparator group as per the licensed indication for cannabidiol. Concomitant AEDs that were not listed in the final NICE scope were excluded from the analysis. Comparators which are mentioned in the final scope issued by NICE, but which were not included in the model are a ketogenic diet and vagus nerve stimulation.[4] These were excluded because according to the company they are used in a minority of patients and used equally in patients who would receive cannabidiol (CBD) and patients who would receive fenfluramine.

The company assumed that clinicians would stop treatment if there was insufficient improvement and hence introduced a stopping rule in the model. An insufficient improvement was defined in the model as any reduction in the number of convulsive seizures which was < 30% after six months after the start of the treatment and compared to the number of convulsive seizures at the beginning of the treatment.

Table 5.8: Concomitant AEDs used in the fenfluramine registration studies at baseline (total study populations)

Concomitant AEDs	Fenfluramine double-blind studies	
	Number of patients on each AED (percentage applied in the model)	
	Study 1 (N=119)	Study 1504 cohort 2 (N=87)
Clobazam†	71 (60%)	82 (94%)
Levetiracetam	29 (24%)	11 (13%)
Topiramate	30 25%)	21 (24%)
Valproate (semisodium & sodium)	57 (48%	50 (57%)
Valproic acid	18 (15%)	16 (18%)

Based on Table 26 of the CS[1]
† Applied in the intervention strategy only. All patients in the comparator strategy were assumed to be on concomitant clobazam as per the cannabidiol licensed indication.
AED = anti-epileptic drug; CS = company submission

ERG comment: The main concerns of the ERG relate to: a) the exclusion of comparators mentioned in the scope provided by NICE; b) the effect of the use of clobazam on the ICER; c) the introduction of a treatment stopping rule which is inconsistent with what has been proposed by the European Medicines

Agency (EMA) and by NICE; d) a scenario analysis in which stiripentol was varied in the frequency of its use.

a) According to Figure 2 in the company submission, the anticipated authorisation fenfluramine would not only allow it to be used instead of clobazam and cannabidiol but may also be used besides stiripentol and be used in combination with SoC AEDs.[1] Contrary to the final scope issued by NICE, which asked for the use of established clinical management without fenfluramine as comparators, several AEDs were not considered as comparators and subgroup analysis was not completed for combinations for comparators. Comparators which were not included were ketogenic diet and vagus nerve stimulation. When asked to clarify this issue in clarification question C10, the company argued that such a comparison was not feasible or clinically appropriate.[21] In response to question C10 asking why the company had not included a comparison to stiripentol, it stated that the clinical data were insufficient to do so.[21] The lack of comparison to both stiripentol and SoC AEDs hampers the informative value of the cost effectiveness analysis. To assess the effect of only SoC the ERG removed the CBD effect and cost from the analysis in the ERG base-case so that a comparison between SoC and fenfluramine would be possible.
b) The anticipated authorisation includes the use with and without clobazam. The model assumed that part of the population did not take clobazam. Therefore, a request was made in clarification question C3 for a separate analysis for individuals for patients who would receive clobazam with fenfluramine compared to individuals who would receive clobazam in addition to cannabidiol.[38] The company stated that for this subgroup the ICER would increase from £31,773 per QALY to £37,577 per QALY.[21]
c) In the CS a stopping rule was implemented for all patients whose seizure frequency did not reduce by at least 30%.[1] This stopping rule was based on NICE TA614 for cannabidiol and had not been proposed by the EMA and was not found in the scope provided by NICE.[14] Further analysis showed that not implementing this treatment stopping rule in the fenfluramine arm, while implementing it in the cannabidiol arm (in line with NICE TA614) led to an increase of the ICER from £31,773 per QALY to £63,268 per QALY. Although, this issue was adequately explored by the company at clarification, the ERG would have liked to examine its influence in an ERG scenario. However, given transparency issues and time constraint, the ERG was unable to explore this issue.
d) In clarification question C6 the ERG requested a scenario analysis in which stiripentol was varied in the frequency of its use.[38] The company responded with a sensitivity analysis in which the use of stiripentol was varied by 30% from the 58% at baseline.[21] In the case that 78% of patients received stiripentol, the ICER decreased to £26,973. In the case in which 41% of patients received stiripentol, the ICER increased to £34,788.

5.2.5 Perspective, time horizon and discounting

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was four weeks with a lifetime time horizon.

ERG comment: The approach is in concordance with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

The (relative) treatment effect was estimated based on convulsive seizure frequency assuming that a reduction in convulsive seizure frequency leads to more convulsive seizure-free days, reduces the risk of status epilepticus, reduces the risk of mortality and improves patients' and carers' quality of life.

5.2.6.1 Estimation of convulsive seizure frequency and convulsive seizure-free days

The convulsive seizure frequency and convulsive seizure-free days (both per 28-day cycle) were estimated using patient-level data from the placebo arm of the fenfluramine registration studies. Subsequently, a treatment effect of either fenfluramine or cannabidiol was applied. For extrapolating seizure frequency and convulsive seizure-free days, the number of convulsive seizures was simulated in each cycle by bootstrapping the placebo arm of the fenfluramine registration studies (to reflect patient heterogeneity over time). Notably, the company assumed that for patients beyond 18 years of age, the frequency of convulsive seizures was halved, and the number of convulsive seizure-free days was doubled. This was justified by company by stating that this reflects the decrease in seizures reported by clinicians in adults as reported in the UK Pathways research study.

An indirect treatment comparison (ITC) was conducted, see also section 4.3 of this report and section B.2.9 of the CS), using the fenfluramine registration studies and subgroup analyses (patients taking concomitant clobazam) of the cannabidiol registration studies.[1] The outcome considered in the ITC was percentage change in convulsive seizure frequency from baseline compared to placebo. The treatment effect derived from the ITC was then applied to the percent change (reduction) in convulsive seizures per 28-day cycle from baseline for each individual (Table 5.9). Notably, the company assumed that the percentage reduction was the same for convulsive seizure days as for convulsive seizure frequency. This was justified by a lack of available data on reduction in convulsive seizure days in the cannabidiol studies. The estimated reductions were applied to the seizure frequencies of patients in the placebo arm (in both strategies).

The company assumed that the relative treatment effect is constant and maintained over time while patients are on treatment, i.e. assuming no waning of the treatment effect (while on treatment) for both the fenfluramine and the cannabidiol (with clobazam) strategy. This was justified by stating that the OLE (Study 1503) trial data with up to 24 months of treatment and data from the Belgian RWE study (observational cohort) with up to five years of treatment do not show any indication that the treatment effect of fenfluramine wanes over time.

Table 5.9: Convulsive seizure frequency percentage change from baseline (ITC results)

Treatment	Convulsive seizure frequency percentage change (reduction) from baseline vs placebo	Credible intervals (95%)
Cannabidiol 10 mg/kg	[redacted]	[redacted]
Cannabidiol 20 mg/kg	[redacted]	[redacted]
Cannabidiol 12 mg/kg/day (weighted)	[redacted]	[redacted]
Fenfluramine 0.4 mg/kg	[redacted]	[redacted]
Fenfluramine 0.7 mg/kg	[redacted]	[redacted]

Based on Table 28 of the CS[1]
CS = company submission; ITC = indirect treatment comparison

5.2.6.2 Non convulsive seizures

The company did not incorporate non convulsive seizures in the model due to measuring difficulties (i.e. non convulsive seizures are often short and are in general less noticeable, so harder to record; as seizures are harder to record there will be variability of recording between patients) and consistency with the approach taken in the TA614.[1, 14]

5.2.6.3 Status epilepticus

Based on published literature, the company assumed that status epilepticus is driven by convulsive seizures through estimating status epilepticus events as a proportion of convulsive seizures (0.17%) based on the fenfluramine registration studies.[1]

5.2.6.4 Mortality

Total mortality for each cycle is composed of epilepsy related SUDEP, status epilepticus and accidental mortality and non-epilepsy related mortality (background mortality). Mortality estimates were retrieved from the published literature.[1]

5.2.6.4.1 Sudden Unexpected Death in Epilepsy

A study by Cooper et al. 2016 retrospectively studied mortality rates in a cohort of 100 DS patients over 14 years (this study was also used to estimate mortality in TA614).[23] The estimated SUDEP mortality rate was 9.32 per 1,000 person-years. However, no information was available in the Cooper study regarding the association between SUDEP and convulsive seizure frequency. Therefore, a study by Nilsson et al. 1999 in general epilepsy was used to inform the risk of SUDEP based on seizure frequency (not specifically convulsive seizures).[7] Nilsson et al. conducted a study based on 57 SUDEP cases to determine the risk factors for SUDEP in general epilepsy and calculated the relative risk (RR) of SUDEP by seizure frequency (see Table 29 of the CS).[1] Due to the differences between general epilepsy and DS in terms of seizure frequency, the company linearly extrapolated the RR of SUDEP by seizure frequency (assuming a plateau for ≥ 780 seizures annually which correspondents to 60 seizures per 28 days) to be applicable to the seizure frequencies observed in DS.

The extrapolated RR of SUDEP by seizure frequency was applied in the model to the background general population mortality. Subsequently, the calculated SUDEP mortality was calibrated to match the SUDEP mortality specific for DS as reported by Cooper et al. (see above).[23] This calibration indicated that a multiplier of 8.38 was needed to be applied to the extrapolated RR, which was implemented in the economic model. The resulting RR (versus general population mortality) of SUDEP by seizure frequency for convulsive seizure frequencies such as 20, 25, 30 and 35 per cycle were 206, 244, 282 and 319 respectively (retrieved/calculated from the economic model by the ERG).

5.2.6.4.2 Status epilepticus

Status epilepticus (SE) mortality was retrieved from Cooper et al. (0.029% per cycle) and applied to patients in the model experiencing a status epilepticus episode, as this was the only available data for patients with DS.[23]

5.2.6.4.3 Accidental mortality

Published evidence on the risk of accidental death by seizure frequency is lacking. Clinical experts in the UK Pathway research study (CS section B.3.11) noted that they presumed that seizure frequency (particularly generalised tonic-clonic seizures) would be a driver of accidental mortality, although there were no data to substantiate this.[1] Due to a lack of data on this, accidental death was applied as 24% of SUDEP and SE deaths as reported in Cooper et al. (indicating that 59% (10/17) of deaths were probable or definite SUDEP, 24% (4/17) were SE and 18% (3/17) were accidental).[23] Consequently, an indirect effect of treatment on accidental mortality was modelled via the effect on SUDEP and SE.

5.2.6.4.4 Background mortality

The background mortality for a normal population by gender and age was taken from the Office of National Statistics (ONS).

5.2.6.5 Treatment discontinuation

Three types of treatment discontinuation (lack of efficacy, other discontinuation, and ongoing discontinuation, see Table 5.10) as well as a stopping rule (at six months after treatment initiation) were applied. After discontinuation patients reverted to their baseline convulsive seizure frequency.

Although the EMA has not proposed a "stopping rule" for fenfluramine on the basis of efficacy, the company argued that it is expected that clinicians would stop fenfluramine and cannabidiol treatment if there was insufficient improvement in seizure frequency at six months.[1] Therefore, a treatment stopping rule was applied in the base-case for fenfluramine and cannabidiol in patients not achieving at least a 30% reduction in convulsive seizure frequency at six months after treatment initiation (compared with the patient's baseline seizure frequency prior to starting treatment). This was in line with the NICE recommendation for cannabidiol in TA614.[14]

Table 5.10: Treatment discontinuation

Treatment	Discontinuation type	Probability per cycle	Source
Titration (cycle 1)			
Fenfluramine + SoC	Lack of efficacy	[redacted]	Fenfluramine registration studies
Cannabidiol + SoC	Lack of efficacy	[redacted]	Assumed equal to fenfluramine + SoC
Fenfluramine + SoC	Other	[redacted]	Fenfluramine registration studies
Cannabidiol + SoC	Other	[redacted]	Assumed equal to fenfluramine + SoC
Maintenance (cycles 2-4)			
Fenfluramine + SoC	Lack of efficacy	[redacted]	Fenfluramine registration studies
Cannabidiol + SoC	Lack of efficacy	[redacted]	Assumed equal to fenfluramine + SoC
Fenfluramine + SoC	Other	[redacted]	Fenfluramine registration studies
Cannabidiol + SoC	Other	[redacted]	Assumed equal to fenfluramine + SoC
Post maintenance (cycles >4)			
Fenfluramine + SoC	Ongoing	[redacted]	Study 1503
Cannabidiol + SoC	Ongoing	[redacted]	GWPCARE5

Based on Table 30 of the CS[1]
Note: the discontinuation of patients due to lack of efficacy was relatively applied to the lowest performing patients; other discontinuation and ongoing discontinuation were randomly applied across the population
CS = company submission; SoC = standard of care

ERG comment: The main concerns of the ERG relate to: a) assumption that the relative treatment effect is constant and maintained over time while patients are on treatment; b) assuming the same percentage reduction for convulsive seizure days as was estimated for convulsive seizure frequency; c) excluding non-convulsive seizures in the economic model not necessarily a conservative assumption; d) concerns regarding the assumptions made to estimate mortality and the link to convulsive seizure frequency; e) SE mortality probability is not conditional on having SE; f) assumption that the frequency of convulsive seizures in patients aged 18 years and over were halved, and convulsive seizure-free days doubled lacks evidence and; g) the bootstrap procedure to extrapolate the estimated convulsive seizures frequency/free days is unclear.

a) The company assumed that the relative treatment effect is constant and maintained over time while patients are on treatment. This assumption was mainly based on OLE (Study 1503) trial data as well as data from the Belgian RWE study (observational cohort). However, these are non-comparative studies and it is therefore difficult to infer from these sources that the relative treatment effectiveness does not wane over time (while on treatment). For example, please note that, as mentioned in section 4.2.7, patients could progress to the OLE study on 'satisfactory completion' of Study 1 or Study 1504. Particularly given that for TA614 (cannabidiol for DS), the committee concluded that effectiveness of cannabidiol was likely to diminish over time (as with other AEDs).[14] Therefore, the ERG requested that the company include a scenario analysis incorporating treatment waning (clarification question C13b).[38] Unfortunately, the company did not provide this scenario analysis and thus did not explore the impact of treatment waning on the estimated cost effectiveness as was preferred by the committee for TA614.
b) The company assumed the same percentage reduction for convulsive seizure days as was estimated (based on the NMA) for convulsive seizure frequency, i.e. assumed these two outcomes are proportional. Although it is evident that there is an association between these two outcomes, it is unclear whether it is plausible to assume proportionality. In response to clarification response C15a, the company stated that this was assumed as there are no data on seizure-free days for cannabidiol.[21] Therefore, the company aimed to *"ensure that neither arm of the trials is having an incremental benefit due to this lack of data"*.[21] The ERG would in principle agree with this aim, however, not with its implementation. Given the convulsive seizure frequency percentage change (reduction) from baseline vs placebo was [redacted] for fenfluramine than for cannabidiol (see Table 5.9), the proportionality assumption is resulting in a [redacted] reduction in convulsive seizure days for fenfluramine than for cannabidiol. Moreover, the estimated reduction in convulsive seizure days is inconsistent with the reduction reported in Table 10 of the CS.[1] Based on that table, it can be derived that assuming the same reduction for both convulsive seizure frequency and convulsive seizure-free days is not plausible, rather the reduction in convulsive seizure days ≈ reduction in convulsive seizure frequency × 0.4. Therefore, in the ERG base-case reduction in convulsive seizure frequency × 0.4 is used to estimate the reduction in convulsive seizure days. This assumption is likely (still) favouring fenfluramine when compared with cannabidiol as a larger reduction in convulsive seizure days for fenfluramine is assumed than for cannabidiol while this might be questioned. Particularly given that the cannabidiol SmPC indicates that compared with placebo cannabidiol (10 mg) increased the convulsive seizure-free days by 2.7 days while fenfluramine co-administered with stiripentol increased convulsive seizure-free days by two days (CS section B2.6.1.3).[45] Given convulsive seizure-free days is the main driver of difference in health state utility values between the treatments (see section 5.2.8), the current assumptions might result in an overly optimistic utility benefit for fenfluramine (even with the ERG adjustment).

c) The company did not incorporate non-convulsive seizures in the economic model and stated that this is conservative (both in the CS and in response to clarification question C18).[1, 21] This claim is however highly questionable. Primarily because this is based on a comparison with the placebo arm, while in the CS base-case fenfluramine is compared with cannabidiol. The company did not provide any evidence that neglecting non-convulsive seizures in the economic model is a conservative approach when compared to cannabidiol. Moreover, in the FAD for TA614 it is stated that *"the clinical trials showed that cannabidiol also reduced non-convulsive seizures"* (next to a reduction in convulsive seizures).[14] Therefore, excluding non-convulsive seizures in the economic model may well be non-conservative.

d) In the company base-case it is assumed that mortality is linked to convulsive seizure frequency. This linking required multiple major assumptions: 1) The study by Nilsson et al. 1999 in general epilepsy was used to inform the risk of SUDEP based on seizure frequency, here it is assumed that this can be generalised from seizures in general to convulsive seizure as well as general epilepsy to DS,[7] 2) It is assumed that the RR from Nilsson et al. can be extrapolated linearly to be applicable to the seizure frequencies observed in DS. In Nilsson et al. the majority of patients had <4 seizures per four weeks while the median was [redacted] per four weeks in the placebo arms of Study 1504 and Study 1 (see Table 5.7); 3) The company assumed that the resulting RR can be applied to the general population background mortality. This implicitly assumes that patients with no convulsive seizures (but that have DS) have a SUDEP mortality that is equal to the general population background mortality; and 4) A multiplier of 8.38 can be applied to the calculated RR to calibrate the estimated mortality (to be consistent to the mortality reported by Cooper et al.[23] It should be noted that this resulted in seemingly implausible estimates of RR (e.g. for convulsive seizure frequencies such as 20, 25, 30 and 35 per cycle were 206, 244, 282 and 319 respectively). In response to clarification question C14, the company stated that there are significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency.[21] Moreover for TA614 (considering cannabidiol for DS), the committee argued that *"there is insufficient evidence to prove that cannabidiol prolongs life"*.[14] The company did provide a scenario analysis in which general epilepsy mortality risk were partially calibrated to DS, leading to an increased ICER of £40,865 per QALY gained. Given the strong assumptions the company was required to make (leading to seemingly implausible estimates of RR), the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the committee's preferences for TA614, the ERG preferred to remove the link between convulsive seizures and mortality.[14]

e) The ERG recalculated the SE mortality probability of 0.029% per cycle ((1-EXP(-15.84 × (4/17) × (28/365250)) = 0.00029)) and considered that this is not a conditional probability (conditional on having SE) and thus should not be applied to SE patient only (rather the whole DS population). This was adjusted in the ERG base-case. Multiple issues related to the implementation of mortality are highlighted in this and the preceding comment, hence, the ERG did adjust the approach to incorporate mortality in the economic model. Particularly, DS mortality was directly estimated based on reported SUDEP and non-SUDEP mortality (independent on convulsive seizures and not specifically incorporating SE mortality) as reported by Cooper et al.[23] This resulted in SUDEP and non-SUDEP mortality of 0.07142% and 0.04997% respectively per cycle. This approach is consistent with TA614 (considering cannabidiol for DS), i.e. the approach used by the ERG (except for the convulsive seizure-free health state) as well as the committee statement that *"there is insufficient evidence to prove that cannabidiol prolongs life"* indicating that the assumed link between convulsive seizures and mortality risk should be removed.[14] Given that the SE mortality probability could not easily be

amended in such a way that it would be treatment-independent (i.e. not related to seizure frequency), the ERG assumed this probability to be 0, which will result in an underestimation of mortality for both cannabidiol and fenfluramine.

f) The company assumed that the frequency of convulsive seizures in patients aged 18 years and over were halved, and convulsive seizure-free days doubled (compared with patients aged <18 years). In response to clarification question C1, the company justified this assumption by providing quotes from UK clinicians that were interviewed in the Pathway Mapping study.[21] However, it was also indicated that there is little data to inform/quantify this improvement when patients become older. Therefore, the company highlighted that a scenario assuming no change when patients age, would only result in a limited increase of the ICER (£32,468 per QALY gained compared with the base-case ICER of £31,773 per QALY gained). Nevertheless, given the limited evidence to support and quantify this improvement in frequency of seizures and seizure-free days and as the change is expected to be gradual (instead of an instant improvement at age 18 years) the ERG assumed no change when patients age.

g) Related to the ERG comments regarding patient profiles in section 5.2.3, the bootstrap procedure to extrapolate the estimated convulsive seizures frequency/ free days is unclear.

5.2.7 Adverse events

Treatment emergent adverse events (TEAEs) were considered for inclusion into the economic model. However, the company judged that *"the incidence of serious TEAEs was low and similar across the fenfluramine and placebo arms"*.[1] Therefore, the company adopted a pragmatic assumption that the same would be true for cannabidiol (with clobazam), and AEs were excluded from the model. However, Study 1 reported 12.5% of patients with AEs leading to discontinuation.

ERG comment: The main concern of the ERG relates to not including AEs into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation. Although additional treatment-related AEs that occurred with fenfluramine were mainly not rated as serious, AEs such as diarrhoea and fatigue can be bothersome to patients. Furthermore, cardiac events and decreased appetite and weight loss carry a burden for monitoring. The ERG acknowledges that the company incorporated discontinuation related to other causes into the model, which likely also covers AE-related discontinuation. However, the ERG would also have liked to see the impact of AEs on events costs and corresponding disutilities. The ERG therefore requested to include the effects of (at least) the most frequently occurring AEs on costs and QALYs (disutilities) in the model in question C20 of the clarification letter.[38] Despite this request and an additional request after having received the clarification response, the company was unable to provide these.

5.2.8 Health-related quality of life

PedsQL data from the registration studies were mapped to EQ-5D-Y using the Khan et al. 2014 algorithm to obtain patient utilities for the economic model.[46] In the registration studies, PedsQL data were available for visit 3 (randomisation), visit 8 (end of titration period) and visit 12 (end of maintenance period or discontinuation). A linear mixed effects regression model, including age group, 28-day frequency of number of seizure-free days, motor impairment and study ID as covariates, was used to predict a utility score in each 28-day cycle of the model.

Regression coefficients, standard errors, and P-values for all fixed effects covariates in the patient regression model are provided in Table 5.11.

The company argued that, as the severe needs of patients with DS have a major impact on the personal life of parents and carers, carer utilities were included in the base-case. EQ-5D-5L data were collected

from the carers in the registration studies at visit 3 (randomisation) and visit 12 (end of the maintenance period) and mapped onto EQ-5D-3L using the UK value set by van Hout et al. 2012.[48] A linear panel regression model with fixed effects, including the 28-day frequency of number of seizure-free days of their child as a covariate, was used to predict the carer utility score in each 28-day cycle of the model.

Regression coefficients, standard errors, and P-values for all fixed covariates in the patient regression model were provided in Table 32 of the CS.[1]

The cost effectiveness model considers the utilities of 1.8 carers per patient in the base-case as accepted in TA614; the carers' utility values are removed from the model when the patient dies.[14]

Table 5.11: Regression coefficients, standard errors and p-values for all fixed effects covariates in the patient regression model

Covariate	Coefficient†	Std. Error	P-value
28-day frequency of seizure-free days	[redacted]	0.1517	<0.001
Study 1	[redacted]	2.869	0.70
Age 6-11 years	[redacted]	3.504	0.06
Age >12 years	[redacted]	3.810	0.11
Motor impairments: Ataxia	[redacted]	2.920	<0.05
Motor impairments: Severe	[redacted]	7.821	0.07

Based on Table 31 of the CS[1]
† Coefficients refer to a 0-100 scale. All utility values predicted using these coefficients were divided by 100 before being used in the model.
CS = company submission

5.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified 16 published studies that reported data on HRQoL in DS, and an additional four HTAs (AWMSG; CADTH; SMC and NICE) and a published cost utility analysis of DS therapies that make reference to health state utility values.[1] However, no studies specifically reporting health state utility values for DS patients as a function of seizure-free days were identified through the SLR.

5.2.8.2 Health state utility values

The patient and carer utility scores in each 28-day cycle of the model were calculated through regression analyses and depended on several patient characteristics. To illustrate, this is also graphically depicted for in Figures 5.5 and 5.6 below. For example, a patient in Study 1 with 10 seizure-free days in a cycle, aged <6 years without motor impairments, has a corresponding utility value of 0.63. To calculate carer utilities per 28-cycle of the model, the company also used a regression analysis with the 28-day frequency of number of seizure-free days as covariate (Figure 26 of the CS).[1] Patient and carer utilities in the model ranged from respectively [redacted] to [redacted] and [redacted] to [redacted].

Figure 5.5: EQ-5D marginal means for patients not on concomitant stiripentol (Study 1)

[redacted]

Figure 5.6: EQ-5D marginal means for carers (Study 1 and Study 1504 cohort 2)

[redacted]

5.2.8.3 Adverse event related disutility values

AEs were not included in the model, so no specific AE utility values are assumed.

ERG comment: The main concerns of the ERG relate to: a) methodological issues underlying the mapping approach by Khan et al.; b) the application of carer utilities in the economic model; c) the absence of adverse event related disutilities; d) the role of convulsive seizures in the QALY estimation; and e) the application of carer utilities after a patient dies.

a) To generate utility values in the model, the company used the mapping study of Khan et al. 2014 to map PedsQL to EQ-5D-Y.[46] The authors of this mapping approach stated that it has some methodological weaknesses in that the algorithm performs worse as the quality of life of the population under consideration becomes worse. The ERG therefore requested the company in

question C21 of the clarification letter to comment on the likely impact of using this mapping approach on utility and cost effectiveness estimates as an alternative to direct utility measurement.[38] In their response, the company stated that *"the authors reported that there were overpredictions for the lower end of the EQ-5D range suggesting that the mapping tool may perform better when evaluating data for sicker individuals in comparison to more healthy ones. Therefore, this may suggest that the mapping algorithm may perform better (and more accurately capture the true PedSQL* [sic!] *data) when used to map to a population with lower utility scores such as ours in this population"*.[21] The ERG does not agree on this, given that the population in which the mapping study was performed largely comprised healthy children with a mean EQ-5D-Y utility score of 0.89 and that the performance of the estimated models in populations of less healthy children was not tested. Moreover, Khan et al. demonstrated that the lowest mapped utilities were higher compared to the observed data, which could indicate an overestimation of utility in worse health states.[46] Given that utilities for both treatments were incorporated in the same way, but on average the patients' health state is lower in the cannabidiol arm (given the lower effects), this could result in a slight overestimation of the ICER and thus favours cannabidiol. Nevertheless, the ERG agrees with the company that, although its limitations, the mapping approach by Khan et al. is currently the only suitable mapping algorithm to convert PedsQL to EQ-5D-Y.[46]

b) In line with TA614, carer utilities were included in the company's base-case using a regression function based on carers of children and adolescents in the registration studies.[14] However, contrary to TA614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month). Furthermore, the ERG questions whether the regression function based on carers of children and adolescents is also applicable to carers of adults and considers the assumption of 1.8 carer per patient over a whole lifespan to be high. Moreover, as mentioned in section 4.2.5, in the two clinical trials, [redacted]. In response to question C22 of the request for clarification, the company provided a scenario analysis assuming 0 carer utilities for individuals who had >20 seizure-free days a month, resulting in an ICER of £44,042 per QALY.[21] However, this approach is also not in line with TA614 given that the current appraisal focuses on carer utilities rather than disutilities.[14] The approach assuming 0 care utilities for individuals who have >20 seizure-free days per month is not conservative for the better health states (i.e. health states with higher numbers of seizure-free days) as these are performing worse because the higher caregiver utilities are not incorporated in the model. Hence, instead of assuming 0 carer utilities in for individuals who had >20 seizure-free days a month, the ERG assumed a utility of [redacted] (highest estimated utility by the company) for individuals with >20 seizure-free days a month. Furthermore, the ERG questions the applicability of the regression function for carers of adult patients and considers the assumption of 1.8 carers per patient over the whole patient's lifetime to be high. The latter two arguments cannot be easily overcome by the ERG in the model. Hence, in its base-case analysis, the ERG only amended the care utilities for individuals who had >20 seizure-free days a month.

c) As mentioned in section 5.2.7, the company did not include AEs in the economic model for both fenfluramine and CBD, and as a result did not include AE disutilities in the QALY calculation. The impact on the ICER is unknown.

d) The primary endpoint in the registration studies was the change in mean monthly convulsive seizure frequency. However, the company based the QALY estimates in the economic model

only on convulsive seizure-free days, assuming proportionality between these two outcomes. Although, as was already described in section 5.2.6, there is an association between convulsive seizure days and the convulsive seizure frequency, assuming proportionality between these outcomes is likely implausible. Therefore, although the ERG was unable to explore the impact in its base-case analysis, it preferred the use of monthly convulsive seizure frequency to estimate QALYs in the model.

e) When a patient in the economic model died, the corresponding carer utility was also set to zero. This overestimates the impact of mortality, given that the caregiver does not die together with the patient and its assumed utility value of 0 is therefore a (relatively large) underestimation of reality. Alternatively, this issue could have been tackled by using a different approach to incorporate carer utilities into the model. In TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility [redacted] for >8 to ≤25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died.[14] Although there is no clear guidance as to how best to incorporate carer utilities, the ERG considers this approach to be more appropriate than the applied approach in the current STA. Hence, the ERG explored the impact of using carer disutilities from TA614 in a scenario analysis.[14]

5.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs, monitoring costs and health state costs (ongoing and emergency resource use costs).

Unit prices were based on the National Health Service (NHS) reference prices, British National Formulary (BNF), and Personal Social Services Research Unit (PSSRU).[49-51]

5.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified nine studies reporting UK relevant resource use and cost information. Out of these, several reported on the use and associated costs of drugs, routine, and emergency care in the UK, but none of them did so at the level of detail needed for the patient-level simulation model.

5.2.9.2 Treatment costs (with PAS)

The dose of fenfluramine and other AEDs were weight dependent (as a function of age) and thus changed over the patient's lifetime (see Table 33 of the CS).[1] Average daily doses and costs were calculated for each cycle using the recommended BNF dose.[50] Total concomitant SoC AEDs costs were calculated by weighting the daily cost of each AED by the percentage of patients receiving each concomitant AED in the fenfluramine trials.

The general population average weight by age data was used to model patient weight in the model, as clinical opinion suggested that there are no big weight differences between DS patients and the general population of the same age.

To account for changes in a patient's weight over time, the model assumed a linear increase of average patient weight from 12 kg at age two years until a maximum weight of 78 kg at age 25 years was reached.

The assumed doses for SoC AEDs and rescue medications were based on the individual product doses from the BNF (March 2020), the draft SmPC for fenfluramine and the preferred appraisal committee dosing assumption for cannabidiol in NICE TA614.[14, 50]

Drug costs were taken from the drug tariff price as reported in the March BNF, the Prescription Cost Analysis (PCA) by Pharmacy and Appliance Contractors in England (November 2019) and expert opinion.[50, 52]

Table 5.12: Treatment acquisition costs with PAS

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
Intervention								
Fenfluramine	OS	60 ml	2.2 mg/ml	132	[redacted]	[redacted]	NA	NA
		120 ml		264	[redacted]			
		250 ml		550	[redacted]			
		360 ml		792	[redacted]			
Comparators								
Cannabidiol (list price)	OS	100 ml	100 mg/1 ml	10000	£850.29	£0.0850	NA	NA
Concomitant AEDs								
Clobazam	OS	150 ml	1 mg/ml	150	£90.00	£0.6000	30.6%	£0.2537
			2 mg/ml	300	£95.00	£0.3167	20.1%	
	Tablet	30	10 mg	300	£3.82	£0.0127	49.3%	
Levetiracetam	Tablet	60	250 mg	15000	£3.35	£0.0002	19.2%	£0.0003
			500 mg	30000	£7.21	£0.0002	27.9%	
			750 mg	45000	£6.34	£0.0001	5.3%	
			1000 mg	60000	£8.90	£0.0001	9.9%	
	Granules	60	250 mg	15000	£22.41	£0.0015	0.2%	
			500 mg	30000	£39.46	£0.0013	0.2%	
			1000 mg	60000	£76.27	£0.0013	0.1%	
	OS	300 ml	100 mg/ml	30000	£7.69	£0.0003	37.2%	
Stiripentol	Capsules	60	250 mg	15000	£284.00	£0.0189	19.4%	£0.0180
			500 mg	30000	£493.00	£0.0164	15.0%	
	Powder	60	250 mg	15000	£284.00	£0.0189	41.4%	
			500 mg	30000	£493.00	£0.0164	24.2%	

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
Topiramate	Tablet	60	25 mg	1500	£5.69	£0.0038	39.2%	£0.0063
			50 mg	3000	£11.59	£0.0039	27.7%	
			100 mg	6000	£19.72	£0.0033	17.6%	
			200 mg	12000	£44.67	£0.0037	2.9%	
	Capsules	60	15 mg	900	£14.79	£0.0164	1.9%	
			25 mg	1500	£16.02	£0.0107	4.3%	
			50 mg	3000	£36.45	£0.0122	3.6%	
	OS	150 ml	10 mg/ml	1500	£129.00	£0.0860	1.7%	
		280 ml	20 mg/ml	5600	£195.69	£0.0349	0.9%	
	MR tablet	100	200 mg	20000	£11.65	£0.0006	16.8%	
			300 mg	30000	£17.47	£0.0006	7.7%	
			500 mg	50000	£29.10	£0.0006	16.9%	
	MR capsule	100	150 mg	15000	£7.00	£0.0005	0.2%	
			300 mg	30000	£13.00	£0.0004	1.2%	
			100 mg	100000	£41.00	£0.0004	0.3%	
			250 mg	100000	£41.00	£0.0004	0.1%	
			500mg	100000	£41.00	£0.0004	0.3%	
			750 mg	100000	£41.00	£0.0004	0.1%	
			1000 mg	100000	£41.00	£0.0004	0.1%	
	OS	300 ml	40 mg/ml	12000	£9.77	£0.0008	53.3%	
Valproic Acid	GR capsule	100	150 mg	15000	£3.68	£0.0002	11.1%	£0.0002
			300 mg	30000	£7.35	£0.0002	27.3%	
			500 mg	50000	£12.25	£0.0002	61.6%	

Drug	Formulation	Pack size	Unit size	Units/pack (mg)	Cost/ pack	Cost/mg	PCA share	Avg cost/mg
Rescue medications								
Diazepam	Enema	5	5 mg	25	£5.90	£0.2360	44.9%	£0.1875
			10 mg	50	£7.40	£0.1480	55.1%	
Midazolam (hydrochloride)	Oromucosal solution	4	5 mg/1 ml	20	£85.50	£4.2750	17.4%	£2.9851
			7.5 mg/1.5 ml	30	£89.00	£2.9667	14.4%	
			10 mg/2 ml	40	£91.50	£2.2875	57.1%	
Midazolam (maleate)	Oromucosal solution	1	10 mg/1 ml	10	£45.76	£4.5760	11.1%	

Based on Table 34 of the CS[1]

Avg = average; CS = company submission; GR = gastro-resistant; MR = modified-release; NA = not applicable; OS = oral suspension

5.2.9.3 Monitoring costs

The use of echocardiograms was included in the model at the start of treatment, every six months from then on and annually thereafter, and finally upon discontinuation of treatment. In accordance with the NHS Reference Costs 2018/2019, the age categories of ≤ 5, 6-18 and 19+ were used to differentiate between echocardiogram cost (Table 35 of the CS).[49]

5.2.9.4 Health state costs

In the model, health state costs were divided into cost for the routine management of DS patients (ongoing resource use) and for emergency care in case of severe seizures. Estimates of the resource use were elicited from physicians and nurses involved in the management and treatment of paediatric and adult patients with DS as reported in the UK Pathway research study.[53] For the frequency of ongoing resource use, individuals in the model were categorized by age group (seven groups between age two and 25+) and the average monthly number of convulsive seizures, which were grouped in a "low", "medium" and "high" frequency of seizures group (see Table 36 of the CS).[1] The difference in frequency of visits by age group and seizure frequency group (low, medium, high) for paediatrics was given in Tables 37 to 39 of the CS. The percentage of adults visiting different healthcare settings is given in the UK Pathways Study reference provided with the CS.[1] A further differentiation between the adults and children was made in the percentage of individuals accessing a certain type of care at all, which was not reflected in the table. Equal intervals of annual resource use were assumed and therefore annual resource use was divided by the number of cycles a year to determine the resource use per 28-day cycle. The emergency resource use was calculated based on the occurrence of SE events which was calculated as a proportion of total seizures. The use of rescue medication was assumed for every SE event. With decreasing probability, individuals were then assumed to require ambulance call outs, transport to the A&E ward of a hospital and requirement of medical attention or require care in the general ward or the ICU. These probabilities change per age group, see Table 5.13.

Table 5.13: Annual emergency resource use by age group (following rescue medication)

Patient age (years)	% call ambulance	% attend A&E (of those that call an ambulance)	From A&E % admitted on general ward or ICU		Length of stay (days)	% discharged same day
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient age (years)	% call ambulance	% attend A&E (of those that call an ambulance)	From A&E % admitted on general ward or ICU		Length of stay (days)	% discharged same day
			[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 40 of the CS[1] A&E = accident and emergency; CS = company submission; ICU =intensive care unit						

5.2.9.5 Adverse event related costs

No costs related to adverse events were included in the model.

ERG comment: The main concerns of the ERG relate to: a) AE costs are not included with the exception of monitoring cost for abnormal cardiac valvular morphology, b) even though monitoring costs for abnormal cardiac valvular morphology was added, the incidence of abnormal morphology was assumed to be 0, and c) a difference in the patient body weight used for the model for cannabidiol reviewed in TA614 and used for the evaluation of fenfluramine.

a) In line with not including AE effects, the company did not include any other AE event costs in their economic model even though this was requested by the ERG. For further information we refer back to the ERG comment in section 5.2.7. However, as adverse events were also not included for cannabidiol, the effect on the ICER is unknown.
b) The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is however not further reflected in the model in cost or utilities. The ERG questioned (C23) the absence of additional cost caused by the association between the use of fenfluramine and unusual valvular morphology.[38] When asked to provide a scenario in which monitoring results lead to additional cost and disutility (C23b), the company provided a scenario in which all individuals who discontinue treatment receive one more echocardiogram, which increased the ICER marginally to £31,822 per QALY gained (c.f. base-case: £31,773 per QALY gained).[21] This response was not satisfactory, as it did not reflect additional cost or disutility as a result of the abnormal cardiac valvular morphology which was suggested in earlier studies. Moreover, this does not include the costs of weight monitoring.
c) The patient body weight which was applied in the cannabidiol submission (reviewed in TA614) used the median patient weight per age group which was found in its registration studies GWPCARE1 and GWPCARE2.[14] The patient body weight, which was applied in the model built for fenfluramine, was based on the median body weight of children to the average body weight of adults with a linear progression based on the age of the patient. As the fenfluramine dose increase is capped at 26 mg/day when patients are not taking concomitant stiripentol and 17 mg/day when patients are taking concomitant stiripentol and the cannabidiol dose is not, according to TA614, the lower weight applied in the submission for TA614 may lead to a lower price for the cannabidiol treatment in the cannabidiol treatment arm in the CS for TA614 than in the treatment arm for the fenfluramine submission.[14] As cannabidiol is more expensive relative to fenfluramine, when a higher weight is assumed, the use of higher patient weight in this submission therefore benefitted the cost effectiveness of fenfluramine.

6. Cost effectiveness results

6.1 Company's cost effectiveness results

In the deterministic base-case analysis, total LYs and QALYs gained were larger in the fenfluramine + SoC arm compared to the cannabidiol + clobazam + SoC arm. Incremental QALYs ([redacted]) were mainly driven by QALY gains resulting from carer utilities. Total costs were also higher for fenfluramine + SoC than for cannabidiol + clobazam + SoC. The incremental costs ([redacted]) mainly resulted from higher treatment costs. The deterministic ICER amounted to £31,773 per QALY gained (Table 6.1). The ICERs of the two separate models (model based on Study 1 and the model based on Study 1504) vary greatly (i.e. £38,874 per QALY gained for Study 1 and £10,770 per QALY gained for Study 1504).

Table 6.1: Company's base-case results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,773
Cannabidiol + clobazam + SoC	255,759	17.02	20.54				
Based on the base-case results in the economic model ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year; SoC = standard of care							

6.2 Company's sensitivity analyses

The company performed and presented a probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) in examine the uncertainty surrounding the initial CS base-case results.

Compared with the initial deterministic results, the PSA with 1,000 iterations showed similar incremental QALYs and incremental costs, which resulted in an ICER of £31,877 per QALY gained (Table 5.11).[redacted]

The company conducted DSAs by varying key model parameters between upper and lower values. The ICER was most sensitive to the carer utilities and the patient's weight. The ICER exceeded the WTP threshold of £35,000 (Figure 6.1) in two of these DSA analyses.

Table 6.2: Company's probabilistic base-case results

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,887
Cannabidiol + clobazam + SoC	257,530	16.99	20.55				
Based on the probabilistic base-case results in the economic model ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality adjusted life year; SoC = standard of care							

Figure 6.1: Tornado diagram presenting the results of the deterministic sensitivity analysis

Based on Figure 31 of the CS[1]
A&E = accident & emergency visits; AED = anti-epileptic drugs; CM = clinical management; CS = company submission; HRCU = Health care resource units; ICU = intensive care unit; RM = rescue medication; SE = status epilepticus

6.3 Scenario analyses

The company conducted several scenario analyses. Apart from the scenario in which fenfluramine was dominant (no ICER reported) when the CBD dosage was increased to 20 mg/kg/day, the results showed ICERs ranging between £8,532 and £104,835 per QALY gained. The three most influential scenarios that increased the ICER were excluding carer utilities (£104,835), assuming the disease-specific mortality risk to be the same as 'general epilepsy' (£57,990), and the general epilepsy mortality risk partially calibrated to DS (£40,865). The three most influential scenarios that decreased the ICER were assuming a cannabidiol dose of 20 mg/kg/day (cannabidiol dominated), including adults only (£8,532) and assuming a cannabidiol dose of 15 mg/kg/day (£14,355). In response to question C10 of the request for clarification, the company presented a fully incremental analysis of SoC AEDs, add-on CBD and add-on fenfluramine in a scenario, which showed that add-on fenfluramine extendedly dominated add-on CBD.[21]

In addition, the company explored the impact of several discount prices for cannabidiol and conducted several scenarios for the positioning of fenfluramine at various points in the add-on therapy pathway. The ICERs for cannabidiol discount prices ranged from approximately £32,000 (0% discount; CS base-case) to £66,000 (50% discount) per QALY gained. The scenarios in which fenfluramine was given 2L + add-on in addition to stiripentol with SoC (including stiripentol) as comparator (£51,365) and 2L

add-on before stiripentol use with SoC (without stiripentol) as comparator (£50,947), had the biggest impact on the ICER.

ERG comment: The main concerns of the ERG relate to a) the runtime of the DSA and PSA; b) not all requested scenarios were performed by the company and some scenario analyses were missing from the code.

a) In response to clarification question C25c, the company stated that one iteration of the DSA and PSA takes approximately 1 hour and 20 minutes.[21] To run a PSA of 1,000 iterations would require >55 days and it was therefore not feasible for the ERG to run these analyses.
b) In response to CQ25, the company provided the R-code which was used to run most of the scenario analyses. However, the scenario assuming that individuals who had >20 seizure-free days a month would be given 0 carer utilities was missing from the R-code and the ERG was not able to replicate the ICER mention by the company in response to CQ22b (i.e. £44,042 per QALY gained).[21] In addition, the company did not provide the following adjustments to their base-case or scenario analyses that were requested by the ERG in the clarification letter (either because they disagreed with the nature of the request, argued to lack evidence or did not provide a response at all):[38]
    a. CQ C1b: Seizure frequency reduction with a smaller percentage (e.g. only 50% of the reduction observed in seizure frequency) to provide a range of plausible incremental cost effectiveness ratios (ICERs).
    b. CQ C6b: All base-case results and scenario analyses for the two cohorts/models separately. The company only presented this data for their base-case only.
    c. CQ C10: A full incremental analysis of SoC and include the AEDs as separate comparators.
    d. CQ C13b: A scenario in which the efficacy of fenfluramine is assumed to decrease over time.
    e. CQ C14f: A scenario analysis assuming fenfluramine does not prolong life (i.e. does not result in positive incremental life years) through assuming mortality is independent of frequency and days without convulsive seizures
    f. CQ C16g: A scenario in which treatment discontinuation was assumed to depend on seizure frequency (similar to the assumption used in TA614).
    g. CQ C16j: A scenario assuming that after discontinuation patients revert to the placebo arm (instead of baseline) seizure frequency in a scenario analysis.
    h. CQ C20: Include the effects of (at least) the most frequently occurring adverse event in the model
    i. CQ C23b: A scenario in which monitoring results lead to additional cost and disutility. The company did however provide a scenario exploring some of this uncertainty.

6.4 Model validation and face validity check

6.4.1 Face validity

The company performed a qualitative and quantitative UK Pathway research study to gain further understanding of DS treatment pathways and disease concepts (e.g. seizure-free days), to inform modelling, and to estimate resource use for the economic analysis.

6.4.2 Internal validity

The company stated that model methodology, input parameters and assumptions were explored and agreed in an internal modelling workshop with the project team including internationally-respected,

senior academic experts in modelling and health economics. Moreover, the final economic model and regression models were quality checked by a modeller and statistician not involved in the development, to ensure the models were reliable, including: 1) audit of all the code in the models (line by line); 2) quality check of all input parameters; 3) validation of the base-case results against the predicted results (e.g. comparison of mortality to mortality observed in fenfluramine registration trials, comparison of mortality to published literature); and 4) internal consistency and plausibility of all results.

6.4.3 Cross validity

No cross-validation to other technology appraisals (e.g. NICE TA614) was performed in terms of outcome parameters (e.g. mortality rates, QALYs, or costs per cycle and over the full-time horizon).[14]

6.4.4 External validity

The company stated that the model methods, e.g. bootstrapping, were tested and validated against the seizure characteristics recorded in the fenfluramine registration studies and the OLE study (Study 1503) as a predictor of accuracy. To validate the mortality assumptions in the model, the mortality seen in the placebo arms of the fenfluramine registration trials was compared with an equivalent time period in the model. The first four cycles of the model were taken in which 0.43% of the population died compared to 0.49% of the trial population. Based on this result, the company argued this indicated that the mortality assumptions in the model reflects the mortality seen in the fenfluramine studies.

ERG comment: The main concerns of the ERG relate to: a) the stability of the model given the number of simulated patients used; b) lack of validation to external data and lack of information on validation by (clinical) experts; c) difference between discontinuation probabilities mention in the CS and the model; d) lack of cross-validation to NICE TA614 and discrepancy between TA614 and results in the current appraisal for cannabidiol; e) concerns regarding internal validity of the model.

a) In the model, 480 patients are simulated. However, it is not clearly stated in the CS why 480 patients were chosen. In response to clarification question 26a, the company argued that this number of patients in the model cohort reflects a similar total to the population of patients with DS in the UK.[21] However, the ERG believes that the number of simulated patients should be dependent on diagnostics such as a figure demonstrating mean outcomes (costs, QALYs, and ICER) vs. the number of patients (i.e. visual inspection of stochastic uncertainty) rather than the estimated total population in the UK. The ISPOR-SMDM Modelling Good Research Practices Task Force recommends that *"analysts should test the stability of outputs generated by similarly specified model runs and that they should identify the number of entities, replication duration, or number of replications (using the same inputs) required to ensure that the distribution of outputs is stable"*.[54] In response to CQ26c, the company did however present the ICER when assuming simulating 2,000 patients, which resulted in an ICER of £32,511 per QALY gained.[21] The ERG is concerned that the lack of diagnostic plots examining a range of the number of simulated patients leaves room for cherry picking. Moreover, it is unclear to the ERG how these 2,000 profiles were simulated.
b) Due to a lack of external data, mortality in the model was only compared to mortality observed in fenfluramine registration trials, which only had a limited time horizon. Furthermore, as mention by the company in response to CQ32, *"there are currently no externally available data on discontinuation rates for patients on fenfluramine"*.[21] While the ERG acknowledges this knowledge gap, the ERG believes the company could have performed, for example, face validity checks on the implemented mortality rates, i.e. given the high RR that are being used

in the model. Given these issues, the ERG would like to emphasise the lack of external validation on mortality and discontinuation assumptions implemented in the model. In the CS it is stated that *"model methodology, input parameters and assumptions were explored and agreed in an internal modelling workshop with the project team including internationally-respected, senior academic experts in modelling and health economics"*.[1] However, the company was not able to present any results of these workshops. In response to CQ8, the company mentions that *"given confidentiality agreements in place with participants, further details and minutes cannot be shared"*.[21] Although the ERG understands that given the confidentially agreement the company is not able to share further details or minutes, the insights of these meetings would have been useful to provide insights into the views of relevant stakeholders on the input parameters and assumptions in the model.

c) The discontinuation probabilities which are mention in CS Table 30, are not in line with the probabilities used in the model (file "Inputs_micro_4SF.R"). The ERG corrected this in their ERG base-case (i.e. probabilities were set equal to the ones reported in the CS).

d) Although the company referred to NICE TA614 for several methodological assumptions, the CS lacks cross-validation to that appraisal when looking at estimated outcomes of both models.[14] When comparing total costs of cannabidiol in NICE TA614 to the total costs for cannabidiol as estimated in the current appraisal a large discrepancy can be observed, i.e. total costs of £393,521per patient compared to £255,759 in the current appraisal.[1, 14] Moreover, the estimated QALYs gains for cannabidiol compared to SoC (or current clinical management as it is referred to in TA614) are notably larger in TA614 compared to the current appraisal, i.e. incremental QALY gain of 1.18 QALY in TA614 compared to 0.97 in the current appraisal.[14] Both the difference in total costs and QALY gains in the TA614 appraisal result in a substantially lower ICER for cannabidiol compared to SoC as what is shown in Table 8 of the company's response to clarification, with an ICER of £29,268 per QALY gained in TA614 (company base-case after appraisal consultation) and £69,478 per QALY gained in the current appraisal.[14, 21] Given different underlying assumptions in for example the methods to included patients' and carer' QALYs it is not straightforward to pin-point the exact origin of these differences, the ERG wants to stress that it cannot be certain that the costs and QALY gains associated with cannabidiol are in line with TA614.

e) The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model. First, although during the model walkthrough with the company it was mentioned that the "Inputs_micro_4SF.R"-file could be used to modify certain assumptions within the model, adjustment made to this file did not always work. For example, the switch "STOPPING.RULE == TRUE/FALSE" did not work and the ERG noted that the company also overruled this switch in their own scenario (by adjusting "Microsim function.R"). Moreover, the input-file can only be used for a limited number of changes. Second, when determining events in the model (e.g. death), random draws form probability distribution were used, which is generally done in patient-level simulation. However, these random draws were not similar for both cohorts (e.g. identical patients in both cohorts had different mortality rates), causing a difference in for example overall survival solely related to different random draws unrelated to any efficacy estimates in the model. Given time constraint, the ERG was not able to adjust the model in such a way that the same "random seed" was used for each cohort. Third, the R-code to run the code and all corresponding scenario analyses lacked important annotations and contained a lot of redundant code. Fourth, the adjustments to the model did not always lead to the anticipated (difference in) results, i.e. the model is not behaving as it is expected to behave (see for example ERG scenario 2).

7. Evidence Review Group's additional analyses

7.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 7.1 summarises the main issues highlighted by the ERG in section 5.2 of this report, indicates the expected direction of bias introduced by these issues and whether these are examined in ERG analysis either in the base-case or as a scenario conditional on the base-case.

Based on all considerations in section 5.2 (summarised in Table 7.1), 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 et al. 2016):[55]

- 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)

7.1.1 ERG new base-case

7.1.1.1 Fixing errors

1. Removal of the last cycle of bootstrapped patient data with convulsive seizure days and convulsive seizure frequency (cycle 131 of both data frames) as these data, seemed implausible to the ERG (section 5.2.3 - population).
2. Minor fixes:
    a. the ERG recalculated the SE mortality probability of 0.029% per cycle and considered that this is not a conditional probability (conditional on having SE) and thus should not be applied to SE patient only (rather the whole population, see section 5.2.6). This could not be easily adjusted in the model, but in order to incorporate treatment-independent mortality rates, this probability was set to 0 in the ERG base-case.
    b. the discontinuation probabilities used in the model were not in line with the probabilities mentioned in the CS. Based on Table 30 of the CS, identical discontinuation probabilities should have been implemented in the model for "Other discontinuation" in the titration and maintenance trial periods. Hence, the discontinuation probabilities were adjusted to be equal between both treatments, and
    c. in the CS, it was possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation. The ERG adjusted the post discontinuation convulsive seizure frequency and convulsive seizure-free days.

7.1.1.2 Fixing violations

3. The ERG added SoC as separate comparator in the model by incorporating results from the placebo arm of the trials by running the model twice (one in which a 0% reduction of cannabidiol was assumed, which essentially means that only the effectiveness of the placebo was included and the costs of cannabidiol were removed) and one with cannabidiol as per the CS base-case (section 5.2.4 – intervention and comparators).

7.1.1.3 Matters of judgment

4. The ERG decided to present their base-case for three subpopulations (section 5.2.3)
    d. No co-administered clobazam or stiripentol (including SoC and SoC + fenfluramine). For this population clobazam and stiripentol costs were set to 0 (and only the Study 1 cohort was considered).
    e. Co-administered clobazam without stiripentol, which includes SoC, SoC + cannabidiol, SoC + fenfluramine. For this population, clobazam costs were added to the fenfluramine arm and only the Study 1 cohort was considered.
    f. Co-administered clobazam with stiripentol, which includes SoC, SoC + cannabidiol, SoC + fenfluramine. For this population, clobazam costs were added to the fenfluramine arm and only the Study 1504 cohort (fenfluramine + stiripentol) was considered.
5. In the subpopulation that receives co-administered clobazam with or without stiripentol, clobazam was also added to the fenfluramine arm (to reflect the concomitant clobazam population). It should be noted that, similar to what was done in the company's scenarios, only costs were added assuming the effectiveness of the treatments remained similar.
6. The ERG preferred to remove the link between convulsive seizures and mortality (consistent with committee preferences for TA614). The ERG implemented DS mortality as reported by Cooper et al. for DS (section 5.2.6).
7. The ERG assumed no change when patients age (section 5.2.6).
8. The ERG assumed a carer utility of [redacted] (highest estimated utility by the company) for individuals with >20 seizure-free days a month (section 5.2.8).
9. In the ERG base-case reduction in convulsive seizure frequency × 0.4 was used to estimate the reduction in convulsive seizure days (section 5.2.6).

7.1.2 ERG scenarios

1. In TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility [redacted] for >8 - ≤ 25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died. Hence, the ERG explored the impact of using carer disutilities from TA614.
2. The ERG assumed that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial instead of the observational trial period (section 5.2.2 Model structure).
3. The accidental mortality was increased to reflect all non-SUDEP mortality as reported by Cooper et al., for DS.
4. In response to the factual accuracy check, the ERG implemented a scenario in which discontinuation probabilities for lack of efficacy and other discontinuation for both the titration as well as the maintenance period were similar between CBD and fenfluramine (in line with table 30 of the CS).

Table 7.1: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
Model structure (section 5.2.2)			
Patients should revert to placebo seizure frequency instead of baseline seizure frequency.	+/-	Scenario	-
Some patients that discontinued treatment may have been reassigned to a health state with a lower frequency of seizures than they were in before treatment discontinuation (i.e. patients' health status improves after treatment discontinuation).	+/-	BC	-
If patients discontinued treatment, they do not switch to a subsequent treatment	+/-	-	-
Population, interventions and comparators, perspective, and time horizon (sections 5.2.3 to 5.2.5)			
The use of cannabidiol with concomitant clobazam as only comparator.	+	BC	-
Results for the subpopulations with and without concomitant stiripentol should be presented separately. In combination with the preceding comment, this would result in three subpopulations that should be considered: 1) without concomitant clobazam and stiripentol; 2) with concomitant clobazam but without stiripentol and 3) with concomitant clobazam and stiripentol.	+/-	BC	-
Assumption that fenfluramine is similarly effective and well tolerated in adult patients (given that phase 3 fenfluramine trials targeted children or adolescents ≤18 years old).	+	-	-
The model contains seemingly inconsistent/ implausible patient profiles. Moreover, correlations between patient characteristics incorporated in the bootstrapped patient profiles were limited.	+/-	-	-
The exclusion of comparators mentioned in the scope provided by NICE.[4]	+	-	-
Introduction of a treatment stopping rule which is inconsistent with what has been proposed by the EMA and by NICE.	+/-	-	Scenario

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
Treatment effectiveness and extrapolation (section 5.2.6)			
Assumption that the relative treatment effect is constant and maintained over time while patients are on treatment.	+/-	-	-
Concerns regarding the assumptions made to estimate mortality and the link to convulsive seizure frequency.	+/-	BC	Scenario
The same percentage reduction for convulsive seizure days as was estimated for convulsive seizure frequency (i.e. assumed these two outcomes are proportional) without (trial) evidence to support this assumption.	+	BC	Scenario
Excluding non-convulsive seizures in the economic model not necessarily a conservative assumption	+/-	-	-
Assumption that the frequency of convulsive seizures in patients aged 18 years and over were halved, and convulsive seizure-free days doubled (compared with patients aged <18 years) lacks evidence	+/-	BC	Scenario
Adverse events (section 5.2.7)			
No adverse events were included in the model	+/-	-	-
Health-related quality of life (section 5.2.8)			
Methodological issues underlying the mapping approach by Khan et al.	+/-	-	-
Various remarks on the way carer utilities are incorporated in the economic model. Moreover, contrary to TA614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency).[14]	+	BC and scenario	Scenario
Resources and costs (section 5.2.9)			
The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is however not further reflected in the model in cost or utilities.	+	-	Scenario
Use of lower patient body weight in the current model compared to TA614. As the fenfluramine dose increase is capitated at 26 mg and the cannabidiol dose	+	-	-

Issue	Likely direction of bias introduced in ICER[a]	ERG analyses (BC or scenario)	Addressed in company analysis?
is not, a higher weight may lead to a higher price for cannabidiol compared to TA614.[14]			
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Various adjustments or scenario analyses requested by the ERG were not performed by the company.	+/-	-	-
Validation (section 5.2.12)			
Stability of the model given the number of simulated patients used	+/-	-	-
Lack of validation to external data and lack of information on validation by (clinical) experts	+/-	-	-
Cross-validation of modelled outcomes for cannabidiol in the current appraisal and NICE TA614 is not performed and there is a large discrepancy between both appraisals in terms of incremental costs and QALYs.[14]	+/-	-	-
Assumptions regarding the bootstrap procedure are unclear and the resulting individual seizure frequency profiles lack face validity in a small proportion of the sampled cycles.	+/-	BC (fixed last cycle)	-
Discontinuation probabilities which are mention in CS Table 30, are not in line with the probabilities used in the model	+	BC	-

[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.
BC = base-case; ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; ICER = incremental cost effectiveness ratio; MJ = matters of judgement;

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In section 7.1 the ERG base-case was presented, which was based on various changes compared to the company base-case. Tables 7.2 to 7.11 show how individual changes impact the results. Tables 7.11 to 7.17 present the combined effect of all changes simultaneously for the three populations a) no co-administered clobazam or stiripentol; b) co-administered clobazam without stiripentol; and c) co-administered clobazam with stiripentol. The exploratory scenario analyses are presented in Tables 7.18 to 7.33. These are all conditional on the ERG base-case. The submitted model file (in R; "Base_case_ERG.R" and "Microsim function_ERG.R" contains technical details on the analyses performed by the ERG (e.g. at the beginning of the R-code in "Base_case_ERG.R" an overview is presented of the lines of code that were altered for each adjustment (please note that this can be in "Base_case_ERG.R" and/or "Microsim function_ERG.R").

Please note that adjustment 3 and 4a are related to a comparison without cannabidiol, and hence in those analyses, fenfluramine is compared to the placebo arm of the fenfluramine trials (henceforth referred to as SoC). Furthermore, as the model does not allow to simultaneously include SoC, cannabidiol, and fenfluramine, the "merged population" always refers to the Study 1 (without stiripentol) and Study 1504 (with stiripentol) cohorts.

7.2.1. Individual ERG adjustments

Table 7.2: Deterministic ERG base-case – adjustment 1&2 - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
Cannabidiol	£259,294	20.000			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£40,438
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.3: Deterministic ERG base-case – adjustment 1&2&3 (removal of effects of cannabidiol to mimic fenfluramine placebo arm) - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
SoC	£186,353	19.464			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£79,986
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 7.4: Deterministic ERG base-case –adjustment 1&2&3&4a (removal of effects of cannabidiol to mimic fenfluramine placebo arm; without clobazam or stiripentol)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
SoC	£31,388	17.671			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£ 69,893

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 7.5: Deterministic ERG base-case – adjustment 1&2&3&4b (removal of effects of cannabidiol to mimic fenfluramine placebo arm with co-administered clobazam without stiripentol)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
SoC (+clobazam)	£56,321	17.671			
Fenfluramine (+clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£70,585
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 7.6: Deterministic ERG base-case – adjustment 1&2&3&4c (removal of effects of cannabidiol to mimic fenfluramine placebo arm; with co-administered clobazam and stiripentol)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
SoC (+clobazam + stiripentol)	£289,408	20.763			
Fenfluramine (+clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£99,800
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 7.7: Deterministic ERG base-case – adjustment 1&2&6 (treatment-independent mortality risks) - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
Cannabidiol	£420,075	34.491			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£162,886
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.8: Deterministic ERG base-case – adjustment 1&2&7 (no change in convulsive seizure-free days when patients age) - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
Cannabidiol	£263,701	21.354			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£19,863
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.9: Deterministic ERG analyses – adjustment 1&2&8 (alternative carer utilities) - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
Cannabidiol	£259,294	20.717			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£41,694
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.10: Deterministic ERG analyses – adjustment 1&2&9 (assuming the reduction in convulsive seizure days ≈ reduction in convulsive seizure frequency × 0.4) - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG analysis					
Cannabidiol	£259,294	19.697			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£50,067
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

7.2.1. Complete ERG base-case

Table 7.11: Deterministic ERG base-case – All changes – removal of effects of cannabidiol to mimic fenfluramine placebo arm – population without clobazam or stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
SoC	£50,973	31.041			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£77,440
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; SoC = standard of care					

Table 7.12: Deterministic ERG base-case – All changes - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Cannabidiol (+ clobazam)	£190,430	32.355			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£82,865
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.13: Deterministic ERG base-case – All changes - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
SoC (+clobazam	£96,576	31.041			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£77,437
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.14: Deterministic ERG base-case – All changes - Population with co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Cannabidiol (+ clobazam + stiripentol)	£597,995	35.184			
Fenfluramine (+ clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£121,216
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.15: Deterministic ERG base-case – All changes - Population with co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Soc (+ clobazam + stiripentol)	£524,276	34.521			
Fenfluramine (+ clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£121,651
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.16: Deterministic ERG base-case – All changes – Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
Cannabidiol	£426,818	33.996			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£83,426
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.17: Deterministic ERG base-case – All changes – Merged population – SoC only vs fenfluramine

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base-case					
SoC	£298,557	33.059			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£90,095
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

7.3 ERG scenarios

As mentioned above, the ERG explored two alternative scenarios, which include all ERG base-case changes in addition to 1) in TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility [redacted] for >8 to ≤25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died which were taken from TA614[14]; 2) the ERG assumed that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial instead of the observational trial period (section 5.2.2 Model structure); and 3) the accidental mortality was increased to reflect all non-SUDEP mortality as reported by Cooper et al. for DS,[23] and 4) in response to the factual accuracy check, the ERG implemented a scenario in which discontinuation probabilities for lack of efficacy and other discontinuation for both the titration as well as the maintenance period were similar between CBD and fenfluramine (in line with Table 30 of the CS).

Table 7.18: Deterministic ERG - Scenario 1 - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 1					
Cannabidiol (+ clobazam)	£190,430	6.46			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£91,155
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.19: Deterministic ERG - Scenario 1 - Population co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 1					
Cannabidiol (+ clobazam (+ stiripentol)	£597,995	8.293			
Fenfluramine (+ clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£3,910
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.20: Deterministic ERG - Scenario 1 - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 1					
Cannabidiol	£426,818	7.523			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£61,837
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.21: Deterministic ERG - Scenario 1 - Merged population – SoC only vs fenfluramine

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 1					
SoC	£298,557	6.756			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£88,183
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.22: Deterministic ERG - Scenario 2 - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ER|G – Scenario 2					
Cannabidiol (+ clobazam)	£230,142	32.882			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£206,749
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.23: Deterministic ERG - Scenario 2 - Population co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 2					
Cannabidiol (+ clobazam (+ stiripentol)	£644,430	35.003			
Fenfluramine (+ clobazam (+ stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.24: Deterministic ERG - Scenario 2 - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 2					
Cannabidiol	£470,429	34.112			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£49,574
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.25: Deterministic ERG - Scenario 2 - Merged population – SoC only vs fenfluramine

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 2					
SoC	£54,575	31.153			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£158,354
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.26: Deterministic ERG - Scenario 3 - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 3					
Cannabidiol (+ clobazam)	£180,606	30.932			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£84,637
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.27: Deterministic ERG - Scenario 3 - Population co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 3					
Cannabidiol (+ clobazam + stiripentol)	£558,546	33.232			
Fenfluramine (+ clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£20,727
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.28: Deterministic ERG - Scenario 3 - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 3					
Cannabidiol	£399,811	32.266			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£74,789
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.29: Deterministic ERG - Scenario 3 - Merged population – SoC only vs fenfluramine

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case – Scenario 3					
SoC	£280,800	30.463			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£100,117
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.30: Deterministic ERG - Scenario 4 - Population with co-administered clobazam without stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 4					
Cannabidiol (+ clobazam)	£187,081	32.32			
Fenfluramine (+ clobazam)	[redacted]	[redacted]	[redacted]	[redacted]	£75,236
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.31: Deterministic ERG - Scenario 4 - Population co-administered clobazam with stiripentol

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 4					
Cannabidiol (+ clobazam + stiripentol)	£592,242	35.163			
Fenfluramine (+ clobazam + stiripentol)	[redacted]	[redacted]	[redacted]	[redacted]	£14,014
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.32: Deterministic ERG - Scenario 4 - Merged population

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 4					
Cannabidiol	£422,075	33.969			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£75,828
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 7.33: Deterministic ERG - Scenario 4 - Merged population – SoC only vs fenfluramine

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG – Scenario 4					
SoC	£298,841	32.052			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£96,664
CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

7.4 Conclusions of the cost effectiveness section

The company's modelling approach consisted of an individual-patient state-transition model. Although the anticipated license for fenfluramine likely allows fenfluramine to be used both with and without concomitant clobazam (in contrast with cannabidiol), in the CS base-case cannabidiol is used as the only comparator, implying that the cost effectiveness analyses are restricted to people receiving clobazam (i.e. the population for which cannabidiol is recommended). If patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC. Hence, contrary to the final scope issued by NICE, several AEDs or treatments were not considered as comparators.[4] The exclusion of SoC and the choice for cannabidiol as sole comparator severely hampers the interpretation of the cost effectiveness results.

Moreover, the phase III fenfluramine trials only targeted children or adolescents ≤18 years old. Nevertheless, the population considered in the CS base-case included children or adolescents that aged in adulthood as well as patients that initiated fenfluramine in adulthood.

Although the company referred to NICE TA614 for several methodological assumptions, the CS lacks cross-validation to that appraisal when looking at estimated outcomes of both models.[14] For example, both the difference in total costs and QALY gains in the TA614 appraisal result in a substantially lower ICER for cannabidiol compared to SoC as what is shown in the CS. Furthermore, the ERG would like to emphasise that the company did not provide all R-files and/or annotated guidance to the ERG in order to reproduce or check specific analyses.

According to the ERG, there are fundamental problems with the economic model that potentially result in unstable/unexpected outcomes when conducting ERG base-case or scenario analyses. Consequently, the cost effectiveness results, calculated using the economic model submitted by the company, lack credibility. Due to the complexity and limited transparency of the model, the ERG was unable to satisfactory resolve these validation issues within the available timeframe. Key uncertainties in this cost effectiveness assessment are, according to the ERG, the methods to construct patient profiles, the lack of treatment waning in the model, assumptions related to the impact of cannabidiol and fenfluramine on the reduction in convulsive seizure-free days, the way carer utilities were incorporated, assumptions related to mortality, concerns regarding treatment discontinuation and concerns regarding the internal validity as well as transparency of the model.

- First, the methods to construct patient profiles are unclear and the correlations between patient characteristics incorporated in the bootstrapped patient profiles were limited. For example, the company did not elaborate on correlations between motor impairments and concomitant medication neither on the correlation between motor impairments and convulsive seizure frequency/ free days. Moreover, amongst other things, the resulting patient profiles demonstrated a seemingly implausible peak for patient with 0 convulsive seizure-free days.
- Second, the company assumed that the relative treatment effect is constant and maintained over time while patients are on treatment. This assumption was mainly based on OLE (Study 1503) trial data as well as data from the Belgian RWE study (observational cohort). However, these are non-comparative studies, and it is therefore difficult to infer from these sources that the relative treatment effectiveness does not wane over time (while on treatment). Particularly given that for TA614 (cannabidiol for DS), the committee concluded that effectiveness of cannabidiol was likely to diminish over time (as with other AEDs).
- Third, the company assumed the same percentage reduction for convulsive seizure days as was estimated (based on the NMA) for convulsive seizure frequency, i.e. assumed these two outcomes are proportional. However, based on the CS it can be derived that assuming the same reduction for both convulsive seizure frequency and convulsive seizure-free days is not plausible. Particularly given that the cannabidiol SmPC indicates that compared with placebo cannabidiol (10 mg) increased the convulsive seizure-free days by 2.7 days while fenfluramine co-administered with stiripentol increased convulsive seizure-free days by two days.[45]
- Fourth, the ERG is concerned regarding the methods of incorporating carer QALYs. Contrary to TA614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 - ≤ 25 and >25 convulsive seizures a month). Moreover, the use of carer utilities rather than disutilities (which was used in TA614), comes with additional methodological concerns (e.g. carer utilities were set to 0 when a patient died).
- Fifth, the link between convulsive seizures and mortality is topic of uncertainty. Given the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the committee's preferences for TA614, the ERG believes this link should

not be part of the base-case.[14] The resulting RRs (versus general population mortality) of SUDEP by seizure frequency for convulsive seizure frequencies, as used by the company were seemingly implausible. To illustrate this, for convulsive seizure frequencies of for instance, 20, 25, 30 and 35 per cycle RRs of 206, 244, 282 and 319 were used respectively.

- Sixth, once patients discontinue treatment, they are assumed revert to baseline seizure frequency (as observed during the observational period of the trial) and not to the placebo 'on-treatment' seizure frequency (as observed during the maintenance period of the trial). However, this placebo effect may also be present in the fenfluramine and cannabidiol treated patients who are still on treatment (and hence is part of the demonstrated effects). Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.
- Lastly, some issues related to the internal validity were shown in addition to the generation of patient profiles mentioned above. For example, the discontinuation rates used in the model did not match the ones reported in the CS and the model did not behave as expected when changing input parameters/ adopting alternative assumptions.

In the company base-case (probabilistic), the ICER amounted to £31,887 per QALY gained. However, the ICERs of the two separate models (model based on Study 1 and the model based on Study 1504, vary greatly (i.e. £38,874 per QALY gained for Study 1 and £10,770 per QALY gained for Study 1504). The ERG has incorporated various adjustments to the CS base-case (using the revised economic model with input parameters from the original CS as starting point). However, the ERG considers that there remains substantial uncertainty about the presented cost effectiveness results.

The individual ERG adjustments had large impact on the ICER, ranging from £19,863 per QALY gained to £162,886 per QALY gained in the merged population (population representing both with and without co-administered stiripentol and/ or clobazam population Study 1 and Study 1504). It should be noted however that results between the three considered subpopulations vary greatly, with the ICER in the ERG base-case including all changes for the no co-administered clobazam or stiripentol population being £77,440 per QALY gained, for the co-administered clobazam without stiripentol population £82,865 per QALY gained and for the co-administered clobazam with stiripentol population fenfluramine was £121,216 per QALY gained compared with cannabidiol. The ERG base-case ICER for the merged population was £83,426 per QALY gained compared to cannabidiol and £90,095 per QALY gained when comparing fenfluramine to SoC. Moreover, the ERG scenario using carer disutilities in line with TA614, resulted in lower ICERs for the three populations as well as the merged population, with an ICER of £61,837 per QALY gained for the merged population compared to cannabidiol and £88,183 per QALY gained when comparing fenfluramine to SoC. Additionally, the scenario with increased accidental mortality to reflect all non-SUDEP mortality resulted in an ICER of £74,789 per QALY gained compared to cannabidiol in the merged population and £100,117 per QALY gained when comparing fenfluramine to SoC. Lastly, the ERG scenario in which it was assumed that once patients discontinue treatment, these patients would revert to the placebo seizure frequency as observed during the maintenance period of the trial instead of the observational trial period resulted in an ICER of £49,574 per QALY gained compared to cannabidiol in the merged population and £158,354 per QALY gained when comparing fenfluramine to SoC. It should be noted however, that this scenario should be interpreted with extreme caution as this scenario could not be easily implemented in the model as this change also impacted the placebo effect (which is added to the treatment effect) and therefore is likely to have impact on other assumptions in the model (e.g. such as the stopping rule). This resulted in implausible survival estimates (survival benefit of fenfluramine compared to

cannabidiol, whereas all mortality in the ERG should be treatment-independent). This underscores the validity issues related to the economic model that remain unresolved, even though multiple errors were fixed by the ERG.

It should be reiterated that some of the abovementioned potential biases (see for instance the model structure and validity sections) could not be explored by the ERG. Consequently, the ICERs reported are subject to great uncertainty.

8. End of life

In the CS, the company did not include any statement regarding fenfluramine meeting the end of life criteria defined by NICE.[1, 24]

9. References

[1] Zogenix International Ltd. *Fenfluramine for treating Dravet syndrome [ID1109]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission*: Zogenix International Ltd., 2020. 182p.

[2] Wyers L, Van de Walle P, Hoornweg A, Tepes Bobescu I, Verheyen K, Ceulemans B, et al. Gait deviations in patients with Dravet syndrome: a systematic review. *Eur J Paediatr Neurol* 2019;23(3):357-367.

[3] Connolly MB. Dravet syndrome: diagnosis and long-term course. *Can J Neurol Sci* 2016;43:S3-S8.

[4] National Institute for Health and Care Excellence. *Fenfluramine for treating Dravet syndrome [ID1109]. Final scope [Internet]*. London: National Institute for Health and Clinical Excellence, 2020 [accessed 11.8.20]. 4p. Available from: https://www.nice.org.uk/guidance/gid-ta10373/documents/final-scope-2

[5] Nabbout R, Auvin S, Chiron C, Irwin J, Mistry A, Bonner N, et al. Development and content validation of a preliminary core set of patient- and caregiver-relevant outcomes for inclusion in a potential composite endpoint for Dravet syndrome. *Epilepsy Behav* 2018;78:232-242.

[6] Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. *Epilepsy Behav* 2016;64(Pt A):69-74.

[7] Nilsson L, Farahmand B, Persson P-G, et al. Risk factors for sudden unexpected death in epilepsy: a case control study. *Lancet* 1999;353(9156):888-893.

[8] Donner EJ, Camfield P, Brooks L. Understanding death in children with epilepsy. *Pediatr Neurol* 2017;20:7-15.

[9] Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. *Neurology* 2017;88(17):1674-1680.

[10] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55(4):475-82.

[11] Wilson G. *Patient organisation submission: Dravet Syndrome UK. Fenfluramine for treating Dravet syndrome [ID1109]*. London: NICE, 2020. 9p.

[12] Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain* 2019;142(8):2303-2318.

[13] National Institute for Health and Care Excellence. *Epilepsies: diagnosis and management. Clinical Guideline 137 [Internet]*. London: NICE, 2012; updated 2020 Available from: https://www.nice.org.uk/guidance/cg137

[14] National Institute for Health and Care Excellence. *Cannabidiol with clobazam for treating seizures associated with Dravet syndrome. Technology appraisal guidance [TA614]. Final Appraisal Determination [Internet]*. London: NICE, 2019 Available from: https://www.nice.org.uk/guidance/ta614

[15] Caraballo RH, Cersósimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with Dravet syndrome. *Epilepsia* 2005;46(9):1539-44.

[16] Dibué-Adjei M, Fischer I, Steiger HJ, Kamp MA. Efficacy of adjunctive vagus nerve stimulation in patients with Dravet syndrome: a meta-analysis of 68 patients. *Seizure* 2017;50:147-152.

[17] Sisodiya S. *Professional organisation submission: Association of British Neurologists. Fenfluramine for treating Dravet syndrome [ID1109]*. London: NICE, 2020. 12p.

[18] Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. *Lancet* 2019;394(10216):2243-2254.

[19] Zogenix International Ltd. *Integrated summary of efficacy: fenfluramine. CONFIDENTIAL [Data on file]*, 2020

[20] Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. *JAMA Neurol* 2020;77(3):300-308.

[21] Zogenix International Ltd. *Fenfluramine for treating Dravet syndrome [ID1109]: Response to request for clarification from the ERG*: Zogenix International Ltd., 2020. 97p.

[22] Dravet Syndrome UK. About Dravet syndrome: treatments and outcomes [Internet]. [accessed 7.10.20]. Available from: https://www.dravet.org.uk/about-dravet-syndrome/treatments-and-outcomes/

[23] Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. *Epilepsy Res* 2016;128:43-47.

[24] Zogenix International Ltd. *Fenfluramine for treating Dravet syndrome [ID1109]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Appendices C-N*: Zogenix International Ltd., 2020. 98p.

[25] Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. *Dev Med Child Neurol* 2018;60(1):63-72.

[26] Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28(2):138-44.

[27] Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;350(9074):326-9.

[28] Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf MI, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*: Cochrane, 2019. Available from: http://www.training.cochrane.org/handbook

[29] Zogenix International Ltd. *Fenfluramine for treating Dravet syndrome [ID1109]: Response to request for clarification from the ERG: Appendix O*: Zogenix International Ltd., 2020. 17p.

[30] Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]*. York: University of York, 2009 [accessed 23.3.11] Available from: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm

[31] Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. *Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019) [Internet]*: Cochrane, 2019 [accessed 6.7.20] Available from: https://training.cochrane.org/handbook

[32] Ceulemans B, Schoonjans A-S, Marchau F, et al. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. *Epilepsia* 2016;57(7):129-134.

[33] Schoonjans A, Paelinck BP, Marchau F, Gunning B, Gammaitoni A, Galer BS, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. *Eur J Neurol* 2017;24(2):309-314.

[34] Ceulemans B, Boel M, Leyssens K, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. *Epilepsia* 2012;53(7):1131-1139.

[35] Zogenix International Ltd. *Study 1503 Interim CSR; 21 December 2018 CONFIDENTIAL*, 2018

[36] Zogenix International Ltd. *Study 1 CSR; August 2019 CONFIDENTIAL*, 2019

[37] Zogenix International Ltd. *Study 1504 CSR; December 2018 CONFIDENTIAL*, 2018

[38] National Institute for Health and Care Excellence. *Fenfluramine for treating Dravet syndrome [ID1109]: Clarification letter*. London: NICE, 2020

[39] Zogenix Inc. A study to investigate the long-term safety of ZX008 (fenfluramine hydrochloride) oral solution in children and adults with epileptic encephalopathy including Dravet syndrome and Lennox-Gastaut syndrome (NCT03936777) [Internet]. 2019 [accessed 4.8.20]. Available from: https://clinicaltrials.gov/ct2/show/NCT03936777

[40] Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO Study Group. *Lancet* 2000;356(9242):1638-42.

[41] Guerrini R, Tonnelier S, d'Athis P, et al. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial (P496). *Epilepsia* 2002;43(Suppl 8).

[42] Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, Harden CL, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* 2018;90(14):e1204-e1211.

[43] Devinsky O, Cross JH, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;377(7):699-700.

[44] Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. *JAMA Neurol* 2020;77(5):613-621.

[45] GW Pharma Ltd. *Epidyolex 100 mg/ml oral solution. Summary of product characteristics*. Cambridge: GW Pharma Ltd, 2019. 14p.

[46] Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. *PharmacoEcon* 2014;32(7):693-706.

[47] Pagano K, Irwin J, Lagae L, Wynne T. The clinical and socioeconomic impact of Dravet syndrome in the UK. *Dev Med Child Neurol* 2019;61(Suppl 1):61 (abstract 111).

[48] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-15.

[49] NHS Improvement. *National Cost Collection for the NHS - National schedule of NHS costs 2018/19 [Internet]*. London: Department of Health, 2020 Available from: https://improvement.nhs.uk/resources/national-cost-collection/#ncc1819

[50] Joint Formulary Committee. *British National Formulary. July 2020*. London: BMJ Group and Pharmaceutical Press, 2020. Available from: https://bnf.nice.org.uk/

[51] Curtis LA, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury: PSSRU, University of Kent, 2019. 176p. Available from: https://kar.kent.ac.uk/79286/11/UCFinalFeb20.pdf

[52] NHS Business Services Authority. Prescription cost analysis (PCA); November 2019 [Internet]. NHS Business Services Authority, 2019. Available from: https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data

[53] Aquarius Population Health. *Dravet syndrome: UK patient pathways, and how syndrome features influence care and quality of life*. London: Aquarius Population Health, July 2020, 2020. 27p.

[54] Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-4. *Med Decis Making* 2012;32(5):701-11.

[55] Kaltenthaler E, Carroll C, Hill-McManus D, Scope A, Holmes M, Rice S, et al. The use of exploratory analyses within the National Institute for Health and Care Excellence single technology appraisal process: an evaluation and qualitative analysis. *Health Technol Assess* 2016;20(26):1-48.

National Institute for Health and Care Excellence

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ERG report – factual accuracy check and confidential information check

Fenfluramine for treating Dravet syndrome [[ID1109]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 30 October** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Summary of Company Issues regarding the factual accuracy of the ERG Report

Many of the factual accuracy Issues we wish to raise relate to the ERG's key issues. We have therefore mapped a summary of these to the ERG's Summary of 16 key issues in Table 1. However, it should be noted that there are several additional factual accuracy Issues that we believe also need to be addressed by the ERG. These are summarised at the end of Table 1. All factual accuracy Issues are detailed further in the sections that follow the table.

Table 1. Summary of Company factual accuracy Issues, mapped to the ERGs summary of Issue

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
1	Lack of evidence on adult patients with Dravet Syndrome	**Executive summary**: □ Table 1.2 **Main report**: □ Section 3.1 □ Section 4.2.1 □ Section 4.2.7 □ Section 4.6	Clinical data adequately reflect adults. The ERG is incorrect to suggest they do not. We agree there is a lack of evidence in adults from the RCTs; however, there are data in adults from the OLE, and the RWE studies, and the CHMP and clinical experts consulted by the ERG agree that the results of the RCTs are applicable to adults	**Issue 2**
2	Not all relevant comparators have been fully investigated	**Executive summary**: □ Table 1.3 **Main report**: □ Section 3.3 □ Section 4.1.2 Section 4.6	All relevant comparators have been fully investigated and considered. The ERG is incorrect to state they have not been fully investigated	**Issue 10**
3	Short-term nature of the included randomised trials	**Executive summary:** □ Table 1.4 **Main repor**t: □ Section 4.2.1 □ Section 4.6	The fenfluramine trials were appropriately designed, with study durations ethically aligned to ensure patients with a rare disease, limited therapy options and a high unmet need for new treatments were not unnecessarily prevented from receiving an effective new medicine at the earliest opportunity. The ERG's suggestion that they may not be of adequate duration is not consistent with the acceptance of	**Issue 3**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
			other therapies with the same or shorter trial durations for this vulnerable group of patients.	
4	Adverse events and need for monitoring	**Executive summary**: □ Table 1.5 **Main report**: □ Section 4.2.6 Section 4.6	Adverse events and need for monitoring are appropriately considered and reflected in our submission and model. The ERG has overstated the influence and need for monitoring of adverse events and is incorrect to suggest they are not appropriately considered.	**Issue 9**
5	Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**Executive summary**: □ Table 1.6 **Main report**: Section 5.2.2	Treatment discontinuation is modelled appropriately. The ERG's suggestion that convulsive seizure frequency should revert to the placebo rate is not supported, nor evidenced and irrationally biases the model towards proposing that a less effective treatment option (where patients in need of a new treatment option are rewarded by reverting to SoC) is more desired over an effective treatment option	**Issue 14**
6	In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**Executive summary**: □ Table 1.7 **Main report**: □ Section 5.2.3 Section 5.2.4	The submission and evidence reflect the full licensed indication for fenfluramine. Cost-effectiveness analyses are not restricted to people receiving clobazam. The ERG is incorrect to state that they are. All relevant comparators (not just cannabidiol with clobazam) have been fully investigated and considered. The ERG is incorrect to state they have not been fully considered	**Issue 11** **Issue 10**
7	The company implemented a treatment stopping rule for all patients whose seizure frequency	**Executive summary**: □ Table 1.8	Implementation of the stopping rule we have proposed is appropriate.	**Issue 16**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
	was not reduced by at least 30% at 6 months.	**Main report**: Section 5.2.4		
8	The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**Executive summary**: □ Table 1.9 **Main report**: Section 5.2.6	Our use and estimation of convulsive seizure-free days is appropriate. The ERG's alternative estimation of convulsive seizure-free days is unclear but appears to be incorrect. There is a correlation between seizure frequency and number of seizure free days, and therefore it is appropriate to use a proportional reduction in which fenfluramine creates a greater absolute increase in seizure free days (due to a greater absolute decrease in seizure frequency).	**Issue 12**
9	In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**Executive summary**: □ Table 1.9 **Main report**: Section 5.2.6	Mortality is linked to convulsive seizure frequency. Mortality modelling is justified. The ERG's exclusion of mortality from the model irrationally biases its analyses against fenfluramine	**Issue 15**
10	Adverse events (AEs) were not included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**Executive summary**: □ Table 1.10 **Main report**: Section 5.2.7	Adverse events and need for monitoring are appropriately considered and reflected in our submission and model. The ERG has overstated the influence and need for monitoring of adverse events and is incorrect to suggest they are not appropriately considered.	**Issue 9**
11	Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the	**Executive summary**: □ Table 1.11 **Main report**: Section 5.2.8	Carer utilities were estimated and implemented appropriately based on carer-level data from the trials. The ERG's suggested approach in line with TA614 is not supported by the available data and is not applicable to our patient-level modelling approach	**Issue 20**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
	two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).			
12	When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**Executive summary**: Table 1.11 **Main report**: Section 5.2.8	Carer utilities were estimated and implemented appropriately based on carer-level data from the trials. The ERG acknowledges elsewhere there is currently no clear guidance on the best way to incorporate carer utilities following the patient's death. The ERG's suggested approach in line with TA614 is not supported by the available data and is not applicable to our patient-level modelling approach.	**Issue 20**
13	The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology This association is, however, not further reflected in the model in cost or utilities.	**Executive summary**: Table 1.12 **Main report**: Section 5.2.9	Adverse events and need for monitoring are appropriately considered and reflected in our submission and model. The ERG's reference to an association of fenfluramine with abnormal cardiac valvular morphology refers to an association observed in obese patients taking doses many times greater than would ever be used in Dravet syndrome. There is no evidence of an increase in clinically meaningful cardiac adverse events with fenfluramine in any Dravet syndrome studies, and therefore there is no cost or utility impact to include in the model.	**Issue 9**
14	Due to a lack of external data, mortality in the model was only compared to mortality observed in	**Executive summary**: Table 1.13 **Main report**: Section 6.3	Mortality is linked to convulsive seizure frequency. Mortality modelling is justified.	**Issue 15**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
	the fenfluramine registration trials, which had a limited time horizon.		The resulting mortality curves are informed by and aligned with what would be expected based on the Dravet specific mortality in the wider literature.	
15	There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**Executive summary**: Table 1.13 **Main report**: Section 6.3	ERG's comparisons of the results from our patient-level simulation model with those of the cohort model in TA614 are flawed and inappropriate. In addition to fundamentally different modelling approaches, the source of efficacy data is different between the two models, the results from TA614 are based on the PAS price of cannabidiol rather than the list price appropriately used in our model, and the maximum patient weight in TA614 is lower than the evidence-based weight adopted in our model. Comparison of these results is therefore flawed. The ERG has provided no reason or rationale for why the model in TA614 is the benchmark against which our model should be judged and there is no basis for assuming that the TA614 model is more accurate in determining the cost effectiveness of cannabidiol (or any other therapy).	**Issue 1**
16	The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model.	**Executive summary**: Table 1.13 **Main report**: Section 6.3	At a walk-through of the model meeting, the run time of our patient-level simulation model was explained to the ERG, and whilst the PSA run time was protracted as would be expected, the run time for deterministic analyses was not prohibitive. There are significant issues and uncertainties in the analyses that have been run by the ERG.	**Issue 21**
-	-	**-**	Both convulsive and total seizure frequencies are significantly reduced by fenfluramine	**Issue 4**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
-	-	-	The trials were not powered for status epilepticus events	**Issue 5**
-	-	-	There is no evidence of waning of effect with fenfluramine. The ERG is incorrect to assume a waning of effect for fenfluramine based on the fact there is evidence of a waning effect with cannabidiol	**Issue 6**
-	-	-	Fenfluramine is clearly superior to cannabidiol (and continued SoC) for convulsive seizure reduction based on the ITC. It is incorrect for the ERG to suggest there is no evidence of a difference in efficacy	**Issue 7**
-	-	-	Stiripentol trials were limited and appropriately excluded from the ITC. The ERG report should clarify this.	**Issue 8**
-	-	-	Exclusion of Non-convulsive seizures from the economic analyses is appropriate and conservative	**Issue 13**
-	-	-	Dosing and patient weight were appropriately implemented in the model. The ERG's reference to patient weight assumed in the TA614 model is not supported by evidence	**Issue 17**
-	-	-	Resource use was fully provided	**Issue 18**
-	-	-	Patient utilities were estimated and implemented appropriately	**Issue 19**

ID	ERG Summary of issues	ERG Report sections	Summary of Company Issue	Issue number
-	-	-	Dravet syndrome and its management are appropriately described in our submission. The ERG is incorrect to state we did not discuss key aspects of this in our submission	**Issue 22**
-	-	-	The SLRs were appropriate and are unlikely to have missed any relevant evidence	**Issue 23**
-	-	-	Key evidence has been omitted from the ERG report	**Issue 24**
-	-	-	Range of other inaccuracies	**Issue 25**

Issue 1 The ERG's comparisons of results from the fenfluramine patient-level simulation model with those of the cohort model in TA614 are flawed and inappropriate

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ID 15, Table 1.1, page 15: states:" *There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal*." and Section 1.2, page 15 states:"…*Moreover, when comparing the incremental costs and QALYs of cannabidiol in NICE TA614 to the incremental costs and QALYs for cannabidiol as estimated in the current appraisal a large discrepancy can be observed resulting in a substantially lower ICER for cannabidiol compared to SoC than what is shown in the current appraisal, with an ICER of £29,268 per QALY gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal*"	**All direct comparisons of the outputs of the cohort model in TA614 and our patient-level simulation should be removed.**	The ERG makes reference to the differences in outputs of the fenfluramine model vs TA614. It should be noted that we have a fundamentally different patient-level simulation model, aligned with the suggestions of the committee in TA614 given the inability of the cohort model in TA614 to adequately account for patient heterogeneity and other aspects of the disease such as quality of life. The ERG refers throughout the report to the results of our analyses of cannabidiol vs SoC as being different to those observed in TA614. However, when doing so, the ERG makes no reference to the fact that, in addition to being fundamentally different modelling approaches (i.e. a patient-level simulation Vs cohort model), our model uses different data to that in TA614 because it employs a robust network meta-analysis (NMA); as well as clinical	Not a factual inaccuracy. Although the outcomes are expected to be different between both models given the highlighted differences in model structure and modelling approach, both models are expected to examine the impact of the same intervention (i.e. cannabidiol), in the same patient population. Hence, the magnitude of incremental differences could be expected to be similar irrespective of the underlying model structure/ approach. The ERG believes it is important to draw these parallels to provide a comparison to the previous STA on cannabidiol (TA614).

Section 6.4.3 and ERG comment d) on page 119/120 states: "*Although the company referred to NICE TA614 for several methodological assumptions, the CS lacks cross-validation to that appraisal when looking at estimated outcomes of both models*" Throughout the ERG report: makes similar comparisons of the model in TA614 to our model. This comparison is incorrect, inappropriate and has potential to mislead the decision-making committee and other readers regarding the uncertainty in our model.		and quality of life metrics directly taken and applied, on a patient-level basis, from the patients in the RCTs. This was carefully and appropriately developed to ensure the diversity in seizures that patients experience on an individual basis and the spectrum of the syndrome across patients, is appropriately captured in the modelling approach. Furthermore, the ICER form TA614 the ERG refers to throughout is based on the confidentially agreed and discounted PAS price of cannabidiol (with cannabidiol dosing capped at a weight for 18 years old patients) whereas in our model the price of cannabidiol (and clobazam) is appropriately based on the list price (with cannabidiol dosing more appropriately capped based on the weight of adults). It is therefore fully expected that our model would generate costs and QALYs and ICER estimates that differ to those in the TA614 model. The ERG has provided no reason or rationale for why the model in TA614 is the benchmark against which our model should be judged and there is no basis	

		for assuming that the TA614 model is more accurate in determining the cost effectiveness of cannabidiol, or the component costs and QALYs, particularly given the list of limitations of the TA614 model identified by the same ERG and presented in the FAD for TA614. All negative references to the fact that our model generates different results to the TA614 model should therefore be removed. As our SLR of cost effectiveness analyses did not identify any other patient simulation models, and only identified cohort models in Dravet syndrome, it is therefore to be expected that our model outputs will similarly not be aligned with any other HTA model outputs. The implicit suggestion that there is some uncertainty arising in our evidence submission because we have not presented what could only ever be a flawed comparison against other technology appraisals is therefore factually unwarranted.	

Issue 2 Clinical data, as agreed by the EMA and the clinical experts consulted by the ERG, are adequate to support the use of fenfluramine in adults. The ERG is incorrect to suggest they do not.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 1 states: "*Lack of evidence on adult patients with Dravet Syndrome*" " Section 1.3, page 15 states: "…*there is a lack of evidence on adult patients*... ". And the Title of Table 1.2 states: "*Key Issue 1 - Lack of evidence on adult patients*". This is a hanging statement that implies there is no evidence presented in the submission supporting the use of fenfluramine in adults. This is incorrect.	Table 1.1 should be amended to more correctly state:" ***There is a lack of evidence in adults from the RCTs; however, there are data in adults from the OLE, and the RWE studies. These clinical data were considered sufficiently robust for the EMA to grant fenfluramine a positive CHMP opinion for use in adults. Furthermore, clinical experts consulted by the ERG agree that the results of the RCTs are applicable to adults*"** Text should be amended to: Table 1.1 ID 1:"…**the RCTs excluded adult patients**.."; "*Table 1.2: Key issue 1 -* ***there is limited evidence from*** *adult patients*", with inclusion in Table 1.2 that **data from RWE studies and OLE studies included adults**	The RCTs excluded adult patients; however, our submission includes data from adult patients in RWE studies and the OLE. The CHMP has issued a positive recommendation for the granting of a market authorisation in DS patients aged 2 years and older, without restriction on use in adults, based on the RCTs and the RWE evidence similarly provided to NICE and the ERG. Furthermore, in Table 1.2 of the ERG report it states that clinical experts consulted by the ERG agree that the results of the RCTs are applicable to adults. Importantly, Table 1.2 does not make any reference to the fact that data in adults from the RWE studies was provided in our submission. This statement alone is therefore a hanging statement that is open to misinterpretation and should be clarified to avoid misleading the readers, who may only read the summary statements.	Not a factual inaccuracy The ERG report, e.g. Table 1.2, specifies that the lack of evidence on adults relates to the "key trials used in the submission", discusses evidence from non-randomised studies, and summarises the views of clinical experts consulted on this issue.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.2, page 16 states: "*Robust evidence in adult patients with DS is needed. Unresolvable uncertainty with the current evidence*." It is incorrect to state that there is unresolvable uncertainty with the current evidence.	This statement should be amended to state: **"Further evidence in adults with DS would be beneficial"**	Whilst the RCTs excluded adults, the ERG has consulted clinical experts who have confirmed that the results are applicable to adults. This expert opinion is a valuable source of evidence that resolves the uncertainty in whether the results of the RCTs are applicable to adults; as was determine by the EMA in granting a positive CHMP opinion for fenfluramine in adults (see point above).	Not a factual inaccuracy
Table 1.2, page 16 states: *"If convulsive seizure frequency and convulsive seizure days decrease in adults (as argued in the CS), the absolute decrease in seizures achieved by using fenfluramine (compared to children) would be smaller in adults and hence the incremental cost effectiveness ratio would increase."* This statement is oversimplistic, is incorrect and is irrelevant to whether or not there is clinical data available supporting the use of fenfluramine in adults.	The **text should be removed** from this table.	Firstly, this statement is incorrect – the ICER is influenced by both costs and effects. The maximum daily dose limit for fenfluramine means that the costs of fenfluramine are capped as patients increase in weight. This is in contrast to the uncapped dosing and costs of cannabidiol (the key comparator), that will incur increasing cost with increasing patient weight (age) . In patients of heavier weight (i.e. adults) the cost difference between fenfluramine relative to cannabidiol actually decreases. Furthermore, specifically related to the incremental cost effectiveness ratio	Not a factual inaccuracy. If seizure-free days / seizure frequency is halved in adults, the maximum absolute improvement in seizure-free days / seizure frequency is also halved. Hence, incremental effects are potentially smaller, resulting in an increased ICER.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		(applied as a ratio of the differences between treatment costs to their differences between treatment effects), a reduction in seizure frequency in adulthood applies to patients treated with both fenfluramine and the comparator – however, the superior effectiveness of fenfluramine when compared with cannabidiol remains. Therefore, the combined effect in adults of an increasing cost of cannabidiol and lower relative efficacy compared to fenfluramine means there is a reduction in the ICER, as would be expected given the above, and as demonstrated in the results previously presented in our submission. Secondly, this statement relates to the assumption that seizure frequency decreases in adulthood and is irrelevant to the issue of whether or not clinical data are available to support the use of fenfluramine in adults. (It is also of note that we provided a scenario analysis in our original submission that showed the assumption of seizure frequency (as a constant or reduced) when patients	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		enter into adulthood had minimal impact on the ICER). On the basis of being both incorrect and irrelevant this text should be removed.	
Section 5.2.3, ERG comment c) page 92 states: "*The company assumes that fenfluramine is similarly effective and well tolerated in adult patients. In response to clarification question C5, the company argues that this assumption is justified based on clinical evidence.22 However, this clinical evidence was non-comparative, based on small samples and partly retrospective. Therefore, the assumption that fenfluramine is similarly effective and well tolerated in adult patients is subject to major uncertainty and can be questioned*". This statement is not aligned with the clinical expert opinion included elsewhere in the ERG report and lacks the context of that clinical expert opinion. It should be amended to avoid misleading the committee and other readers.	The statement should be qualified with the **expert opinion received by the ERG, which confirmed that the trial results are applicable to adults.**	This comment neglects the clinical expert opinion sought by the ERG and presented in the ERG report on page 32: "*Of note, the clinical experts consulted by the ERG agree with the company, i.e. that results are applicable to adult patients with D*S". The uncertainty implied by the ERG regarding the applicability if the trial data to adults therefore does not seem to be supported by expert clinicians, nor the opinion of the CHMP, and it is incorrect to imply this uncertainty without providing this context. It should be amended to avoid misleading the committee and other readers.	Not a factual inaccuracy

Issue 3 The fenfluramine trials were appropriately designed, with study durations ethically aligned to ensure patients with a rare disease, limited therapy options and a high unmet need for new treatments were not unnecessarily prevented from receiving an effective new medicine at the earliest opportunity. The ERG's suggestion that they may not be of adequate duration is not consistent with the acceptance of other therapies with the same or shorter trial durations for this vulnerable group of patients.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.1, text on page 49 and table 4.4 states the trials were conducted in "*children"*. For accuracy this should be children and adolescents.	Amend to clarify **children and adolescents aged 2-18 years were eligible**	Study protocol inclusion/exclusion criteria.	Changed accordingly
Table 1.1, ID 3 states:" *Short-term nature of the included randomised trials*" and Section 4.2.1, text on page 51 states: "*It should be noted that both of the key studies included in the CS (Study 1 and Study 1504) had a double-blind, treatment maintenance phase of just 12 weeks, which may not be considered adequate, given that the primary endpoint was change in 28-day convulsive seizure frequency.* " It is incorrect to say that the trial duration may be inadequate when other therapies that are recommended by NICE have the same or shorter trial durations.	Amend to **provide context and clarification that this is aligned with the duration of the cannabidiol trials and is longer than the stiripentol trials, and both are recommended by NICE**.	The trial design was adequate to demonstrate the efficacy and safety of fenfluramine as a regulatory approved therapy for this rare disease. The trial durations are the same as the cannabidiol trials and are longer than those for stiripentol, both of which are recommended as therapy options by NICE. The endpoints of CSF per 28 days are also aligned with the CBD trial endpoints. It is therefore incorrect to state that trials durations may be inadequate, when other therapies with similar or shorter trial durations have been recommended by NICE.	Not a factual inaccuracy

Issue 4 Both convulsive and total seizure frequencies are significantly reduced by fenfluramine

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.5, ERG comment, page 64 states: "*In both trials, participants receiving fenfluramine had greater reductions in convulsive seizure frequency per 28 days compared to placebo. Patients were also more likely to have 25%, 50% and 75% reductions in convulsive seizures. Furthermore, participants in fenfluramine groups had longer convulsive seizure-free intervals. In terms of the percentage reduction in total seizures from baseline, an improvement with fenfluramine compared to placebo was in Study 1 but not in Study 1504*.". Apologies for an error in our reporting of the p-value for total seizures - this should have read p=0.003 indicating a significant difference in favour of fenfluramine for both convulsive and total seizures. Please amend accordingly.	Please amend text to read: "*In both trials, participants receiving fenfluramine had greater reductions in convulsive seizure frequency per 28 days compared to placebo. Patients were also more likely to have 25%, 50% and 75% reductions in convulsive seizures. Furthermore, participants in fenfluramine groups had longer convulsive seizure-free intervals. In terms of the percentage reduction in total seizures from baseline, an improvement with fenfluramine compared to placebo was observed **in both Study 1 and Study 1504***."	Table 10 of the CS (replicated in Table 4.9 of the ERG report) indicates that the Median total seizure frequency was -5.9 for placebo vs -41.1 for fenfluramine, with p=0.137; however, this is p-value was reported by us in error. The p-value should read p=0.003 as reported in Nabbout 2019. There was a statistically significant difference in total seizure frequency in favour of fenfluramine. Please amend this text accordingly. (ref: Nabbout et al. JAMA Neurol. 2020;77(3):300-308.)	Changed accordingly The ERG checked the cited paper and made the change to rectify the error in the CS.

Issue 5 The trials were not powered for status epilepticus events

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.5, page 75 states: "[redacted]." Text should be amended to reflect the fact the trials were not powered for this endpoint	Text should be amended to reflect the fact **the trials were not powered to show differences in SE events**.	The trials were not powered for SE endpoint. Without this context this is a hanging statement and is potentially misleading. Given the frequency of this event and the practicalities of undertaking a trial in this rare disease population, the number of patients required for such a trial, and/or the substantially extended study duration, would not be feasible.	Changed accordingly

Issue 6 There is no evidence of waning of effect with fenfluramine. The ERG is incorrect to assume a waning of effect for fenfluramine based on the fact there is evidence of a waning effect with cannabidiol

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.9, page 20 states: "*The company assumed that the relative treatment effect was constant and maintained over time while patients were on treatment. This assumption was mainly based on the open-label extension (OLE, study 1503) trial data as well as data from the Belgian real-world evidence (RWE) study (observational cohort). It should be noted that these are non-comparative studies*	These comments should be clarified to fully explain the rationale for excluding a waning of effect from the model, and for not providing the requested scenario analysis, with reference to: - The use of the OLE trial data and the Belgian RWE data	The implications of these ERG's comments are that waning of treatment effect of an unspecified amount for fenfluramine must be included in the model because cannabidiol may have a waning of effect, and could only be excluded from the model if comparative data of an unspecified duration of follow-up categorically proves that waning of effect is not evident. We believe this is a flawed argument as it is	Not a factual inaccuracy. The ERG believes there is insufficient evidence to support the absence of treatment waning so the impact should have been explored.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
and it is therefore difficult to infer from these sources that the relative treatment effectiveness does not wane over time (while on treatment)." Section 5.2.6. ERG comment a) states: *This assumption was mainly based on OLE (Study 1503) trial data as well as data from the Belgian RWE study (observational cohort). However, these are non-comparative studies and it is therefore difficult to infer from these sources that the relative treatment effectiveness does not wane over time (while on treatment). For example, please note that, as mentioned in section 4.2.7, patients could progress to the OLE study on 'satisfactory completion' of Study 1 or Study 1504. Particularly given that for TA614 (cannabidiol for DS), the committee concluded that effectiveness of cannabidiol was likely to diminish over time (as with other AEDs).15 Therefore, the ERG requested that the company include a scenario analysis incorporating treatment waning (clarification question C13b).39 Unfortunately, the company did not provide this scenario analysis and thus*	- The comparison of fenfluramine and cannabidiol long term efficacy and **- removal of the suggestion that because cannabidiol shows a well demonstrated treatment waning that fenfluramine must also show treatment waning, given the compelling evidence for fenfluramine (as well as other AEDs in Dravet syndrome, such as stiripentol) to the contrary**	unreasonable to expect that a comparative trial would maintain patients on a clearly inferior comparator for a prolonged duration having already demonstrated that the intervention (i.e. fenfluramine) offers early, profound clinical benefit in this severe, life threatening and rare disease. Although the fenfluramine OLE and RWE studies are not comparative, they demonstrate that the clinical effects observed in the RCTs are sustained. Indeed, the ERG in section 4.2.1 of the report acknowledges the sustained efficacy of fenfluramine over 3 years, where it specifically states: "*Longer-term evidence is available from Study 1503, the open-label extension study which, using the latest data cut up to three years (14 October 2019) has outcomes relating to 330 patients. This suggests that positive outcomes relating to convulsive seizures are maintained up to this point*." It should be noted that this is in stark contrast to the GWPCARE5 OLE study data for cannabidiol presented in the Epidyolex SmPC, which reports the median percentage reduction from baseline in convulsive seizure frequency was 60% during Week 1-12, and was 45% through to	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
did not explore the impact of treatment waning on the estimated cost effectiveness as was preferred by the committee for TA614. The ERG comment focusses solely on why treatment waning should be included but gives no consideration to the reasons provided in the CS and our response to clarification questions that explain why it should not be included. It is incorrect to assume that because there is a waning of effect with cannabidiol there must also be a waning of effect with fenfluramine, particularly when we provided the ERG with evidence to the contrary. The comment does not give full consideration to the justification we provided for not including a scenario for waning of fenfluramine efficacy. The comment should be amended to avoid misleading the committee and other readers.		Week 37-48, i.e. a 25% reduction in convulsive seizure frequency over less than 1 year of treatment. This difference in sustained efficacy was well documented in the CS in section B2.9 and in the response to clarification question C13a. We also provided the ERG with data indicating that the efficacy of stiripentol does not appear to wane over time (see Chiron et al 2018), supporting the fact that just because cannabidiol efficacy may wane over time does not mean that fenfluramine efficacy must wane over time. It is therefore incorrect to simply assume that because there is a waning of effect with cannabidiol that there must therefore be a waning of effect with fenfluramine. However, these facts appear to have been largely ignored by the ERG when discussing the economic model. The facts remain that there is positive evidence of a waning of effect with cannabidiol over less than 1 year of use, and a lack of evidence of a waning effect with fenfluramine over 3 years of use, supported by prospective RWE data showing sustained efficacy for fenfluramine over 5 years of use and retrospective RWE indicating sustained benefit over many more years of use. Given	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		the weight of this evidence, and the fact that it is unrealistic to expect long-term comparative data that categorically proves no waning of treatment effect, we do not believe it is difficult to infer that the relative treatment effect with fenfluramine does not wane over time. Cannabidiol was approved by NICE based on a model that did not specifically include waning of treatment effect and was later adapted via a modification to the discontinuation rate to provide an indication of the implications of waning in the model. In our model, we have adopted a base case approach that clinically favours cannabidiol in not modelling a waning of cannabidiol treatment effect over time. It should be noted that the model does include treatment discontinuations due to lack of efficacy, and also includes a stopping rule that discontinues treatment in patients not achieving a 30% reduction in convulsive seizure frequency by 6 months. This is the rationale for not providing a scenario analysis incorporating an unspecified and unsupported degree of waning of effect, which the ERG has	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		neglected to include in its report. This and the other issues we outline above should be included in the report and the comment clarified to avoid misleading the committee and other readers.	

Issue 7 Fenfluramine is clearly superior to cannabidiol (and continued SoC) for convulsive seizure reduction based on the ITC. It is incorrect for the ERG to suggest there is no evidence of a difference in efficacy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.4, page 73 states: "*...This shows that while all doses of cannabidiol and fenfluramine were superior to placebo, with fenfluramine 0.4 and 0.7 mg/kg/day having the greatest reduction, there were no differences between cannabidiol and fenfluramine*." And section 4.5, page 76 states: "*There was no evidence of a difference between any doses of fenfluramine and cannabidiol in the mean CSF rate during treatment*". There were clear numerical differences in favour of	Text should be amended to:"*...This shows that all doses of cannabidiol and fenfluramine were superior to placebo, with fenfluramine 0.4 and 0.7 mg/kg/day* ***clearly having the greatest reduction. Due to wide credible intervals, there were no statistically significant differences between cannabidiol and fenfluramine for mean reduction from baseline in convulsive seizure frequency*** ."	It is not correct to imply there were no differences between fenfluramine and cannabidiol - the magnitude of the numerical differences in reduction from baseline in convulsive seizure frequency compared with placebo is obvious, but the wide credible intervals (often observed in Bayesian NMAs and particularly with relatively small trial populations) preclude a claim of statistical significance. These data are also supported by the clear, significantly greater odds of achieving a $\geq$50% reduction from baseline in convulsive seizure frequency for both	Not a factual inaccuracy Text refers to Table 4.14 which presents detailed results. The NMA results favoured fenfluramine but the wide credible intervals for the difference showed that there were differences (in Bayesian terms) between fenfluramine and

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
fenfluramine. Amend text to reflect no statistically significant difference based on the wide confidence intervals		fenfluramine 0.7mg/kg/day without concomitant stiripentol and fenfluramine 0.4mg/kg/day with concomitant stiripentol when compared to cannabidiol at doses of either 10mg/kg/day or 20mg/kg/day.	cannabidiol in mean CSF rate. Of note, the ERG report already stated that the 50% reduction results showed that fenfluramine increased the odds compared with cannabidiol.
Section 4.5, page 75 states: "*The committee will need to decide if the evidence is sufficient to place fenfluramine at both places in the pathway and that greater or at least equal efficacy against all comparators can be assumed.*"	This **text should be amended to fairly reflect the evidence presented in our submission.**	The ERG has agreed that the fenfluramine RCTs are of good quality and low risk of bias. These robust trial data demonstrate that fenfluramine is clearly superior to SoC AEDs. We provided in the CS, data demonstrating the superior efficacy of fenfluramine irrespective of clobazam use, which indicated that clobazam is not a significant treatment effect modifier (this important data is not provided in the ERG report). The NMA clearly demonstrates that fenfluramine is superior to cannabidiol. It is not possible to compare against stiripentol due to limitations in the trial data supporting stiripentol. The clinical evidence in support of fenfluramine is more complete and robust than any of the comparators that have been	Not a factual inaccuracy The cited sentence concludes a paragraph discussing clobazam.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		recommended by NICE. It is incorrect to suggest that there is doubt in whether fenfluramine is superior to SoC AEDs or cannabidiol, or to suggest that fenfluramine and SoC AEDs, or fenfluramine and cannabidiol may or may not even be of equal efficacy. This text should be amended to fairly reflect the evidence presented in our submission.	
Section 4.4 of page 74 states:" *the ERG is concerned about the similarity of the trials regarding concomitant treatments. The cannabidiol data used in the NMA were for those patients also receiving clobazam but this was not the case for the fenfluramine data from Study 1 as only around 55% were also on clobazam. There were also differences regarding stiripentol use as all patients in Study 1504 were also taking stiripentol, between 36 and 40% of patients in the cannabidiol trials but none of the patients in Study 1*." And	This text should clarify that, **although there are differences noted in the use of concomitant clobazam and stiripentol, the results of the ITC are likely to be sound.** **The percentage use of clobazam in Study 1 should be corrected to 59%.** **The percentage use of stiripentol in the cannabidiol trials should be amended to that observed in the subgroup of patients taking cannabidiol with concomitant clobazam (38-51%).**	The ERG report omits the published data we provided in our submission demonstrating that clobazam is not a significant treatment effect modifier of fenfluramine. This is also supported by the fact that the label for fenfluramine does not specify a requirement for concomitant use of clobazam (in contrast to the labels for cannabidiol and stiripentol). The fact that only 59% (Note the 55% stated by the ERG is incorrect) of patients in Study 1 were taking clobazam therefore would not invalidate its comparison with the cannabidiol data. This should be clarified.	Changed "approximately 55%" to "59%" For the other points: Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.5 on page 76 states: "*The ERG is concerned about the clinical heterogeneity of studies in the NMA regarding concomitant AEDs as the use of clobazam and stiripentol varied between studies*."		The ERG is correct in noting that stiripentol use differed between the trials. However, the ERG should clarify that: a) there are no efficacy data from the cannabidiol RCTs broken down by stiripentol use, and so a comparison of fenfluramine Vs. cannabidiol based on concomitant stiripentol use is not possible, and b) the cannabidiol SmPC notes that exposure to stiripentol is increased by cannabidiol, and so the fact that stiripentol was taken by 38-51% of patients taking cannabidiol plus clobazam (see Gunning et al 2020 – the 36-40% quoted by the ERG was for the whole cannabidiol trial populations and not the relevant subgroup) may actually increase its efficacy in any comparisons with fenfluramine in Study 1 (without concomitant stiripentol), and c) fenfluramine is clearly numerically superior to cannabidiol 10 and 20mg/kg/day in its reduction of convulsive seizure frequency vs placebo and is statistically superior to cannabidiol 10 and	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		20mg/kg/day for ≥50% reduction in convulsive seizure frequency at doses of both 0.7mg/kg/day (without concomitant stiripentol) and 0.4mg/kg/day (with stiripentol) (see Table 4.14 and Figure 4.2 in the ERG report). Therefore, despite the differences (heterogeneity) noted in the concomitant use of clobazam and stiripentol amongst the trials included in the ITC, the results of the ITC appear to be sound. Without this context these statements in the ERG report are open to misinterpretation. The ERG report should therefore be clarified with this context. (Refs: Epidyolex SmPC Gunning et al. Acta Neurol Scand. 2020 Sep 24. doi: 10.1111/ane.13351. Online ahead of print.)	

Issue 8 Stiripentol trials were limited and appropriately excluded from the ITC. The ERG report should clarify this.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.3, page 72 states: "*The two stiripentol trials were also judged to be at an unclear risk of bias, one was published as a full paper but did not provide details on allocation concealment and patient withdrawal.41, 42 However, it did appear to report percentage change in CSF for the whole double-blind period (8 weeks) and not after each month as reported in the CS, however this was a shorter treatment period compared to the fenfluramine trials.*" The time point of the endpoint assessment was one feature that precluded the inclusion of the STP trials; but there were other features that precluded their assessment from the ITC. This statement should be amended to reflect this and remove any suggestion that our exclusion of the stiripentol trials from the ITC was not appropriate.	Text should be amended to: *"The two stiripentol trials were also judged to be at an unclear risk of bias, one was published as a full paper but did not provide details on allocation concealment and patient withdrawal.41, 42* ***It is unclear whether the trial reported the percentage change in CSF for the whole double-blind period (8 weeks) or for only the last month of the double-blind period,*** *however this was a shorter treatment period compared to the fenfluramine trials.* ***Furthermore, the trial did not report an adjusted percentage change from baseline compared with placebo, as was reported for both fenfluramine and cannabidiol and as was used in the ITC to provide the data for the economic model."***	The Chiron et al 2000 paper (STICLO-FR) in the methods sections states: "*Primary outcome was the percentage of responders on stiripentol and on placebo, defined as having experienced at least a 50% reduction of clonic (or tonic-clonic) seizure frequency* ***during the second month of the double-blind period compared with baseline****. ……. Secondary outcomes were the absolute count of clonic (or tonic-clonic) seizures* ***during the second month of the double-blind period*** *(normalised to 30 days, by dividing the raw count by the exact number of days of observation and multiplying by 30) and the percentage of change from baseline."* We interpreted this to mean that the change from baseline in seizure frequency was the change observed between the 2nd month of the double blind phase and the frequency at baseline. It should also be noted that the paper does not report an adjusted percentage change from baseline compared with placebo, as was reported for both fenfluramine and cannabidiol and	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		as was used in the ITC to provide the data for the economic model. The 50% responder rate , which was also an endpoint explored in our ITC also appears to have been reported only for the second month of the trial rather than across the trial treatment period.	
Section 4.5, page 75 states: "*However, the main trials in the CS compared fenfluramine to placebo (alongside concomitant AEDs) and the NMA focused on cannabidiol as a comparator.*" Clarify the NMA compared fenfluramine to cannabidiol and to SoC. Stiripentol was excluded by necessity.	This should be amended to state: **"*However, the main trials in the CS compared fenfluramine to placebo (alongside concomitant AEDs) and the NMA focused on cannabidiol and SoC (placebo) as comparators. Stiripentol was excluded as the trial data supporting stiripentol were insufficient to permit a comparison against fenfluramine*".**	This does not reflect the fact that it was not possible to conduct an ITC against stiripentol due to limitations in the STP data. It also neglects to mention placebo in the NMA which reflects SoC.	Not a factual inaccuracy

Issue 9 Adverse events and need for monitoring are appropriately considered and reflected in our submission and model. The ERG has overstated the influence and need for monitoring of adverse events and is incorrect to suggest they are not appropriately considered.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 4 states:"*Adverse events and need for monitoring*", and Table 1.1, ID 10 states:" *Adverse events (AEs) were not included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation*.", and Table 1.1 ID 13 states:" *The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is, however, not further reflected in the model in cost or utilities."* Table 1.5, page 17 (and also in section 5.2.7, page 104) states: "*Although additional treatment-related adverse events occurred with fenfluramine these were mainly not rated as serious. However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients. Although cardiac adverse events did not appear to be serious, the committee should*	**The exclusion of adverse events from the model should be clarified as being appropriate.** **Reference to increased diarrhoea fatigue, decreased appetite and weight loss, and monitoring for these should be removed in all areas.** **The statements regarding cardiac adverse events should be removed or amended to reflect the lack of evidence of cardiac adverse events of any clinical significant with fenfluramine use in the treatment of Dravet syndrome.**	There are several reasons why the ERG is incorrect in raising issues about adverse events and how they were considered in the model. First, there was no meaningful difference between fenfluramine and placebo in the fenfluramine RCTs in the incidence of serious TEAEs (see the CS, with data from Lagae 2019 and Nabbout 2020). A paper (Gunning et al 2020) has recently been published detailing the adverse events observed with cannabidiol plus clobazam in the GWPCARE 1 and 2 trials. These and the fenfluramine trials are of limited size, meaning a small difference in events due to chance can have a seemingly large impact on incidence rates. However, data from Gunning et al 2020 and the fenfluramine RCTs suggest there is little difference in the incidence of these and other TEAEs between fenfluramine and cannabidiol with clobazam, with the	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
note the importance of ongoing cardiac monitoring. Decreased appetite and weight loss shown by fenfluramine also suggest a burden for monitoring". The ERG comment in section 3.2, page 35 also states: "*The committee should consider the implications of the need for increased cardiac monitoring and weight monitoring. It should be noted that only costs for echocardiograms (ECGs) but not for weight monitoring were included in the model.*" The ERG comment in section 4.2.6, page 69 also states: "•*Although additional treatment-related adverse events occurred with fenfluramine these were mainly not rated as serious. However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients.* •*Although cardiac adverse events did not appear to be in the main serious, the committee should note the importance of ongoing cardiac monitoring.* •*Decreased appetite and weight loss shown by*		exception of somnolence, which based on these data appears to occur at a notably greater frequency with cannabidiol plus clobazam (34-35%) than with fenfluramine (up to 10%) over the same treatment durations (see Table 2 provided for reference at the bottom of this section). The incidence of serious TEAEs was also higher for cannabidiol than for fenfluramine. We invite the ERG and appraisal committee to review these data and also the SmPCs of cannabidiol and other AEDs, which list similar AEs for these therapies. Second, it is usual and appropriate to concentrate comparisons of adverse events in HTA analyses on those that are serious enough to attract costs and impact quality of life. Table 1.5 lists diarrhoea and fatigue, decreased appetite and weight loss as specific adverse events. However, these were not graded as serious adverse events. There is therefore little evidence to suggest a greater incidence of these adverse events with fenfluramine treatment compared with other relevant comparators.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
fenfluramine also carry a burden for monitoring." And Section 4.5, page 75 states: "*However, it is important to note that adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients. Although cardiac adverse events did not appear to be in the main serious, the committee should note the importance of ongoing cardiac monitoring. Decreased appetite and weight loss shown by fenfluramine also suggest a burden for monitoring.*" Reference to diarrhoea, fatigue, decreased appetite and weight loss and monitoring for these should be removed from these sections - monitoring of weight loss and cardiac events are already appropriately captured in the model as part of routine/ongoing care and it is incorrect to say it is not included. The statement that "*Although cardiac adverse events did not appear to be serious, the committee should note the importance of ongoing cardiac monitoring"* is misleading and should be removed or amended to reflect the		Third, there is no reason to highlight or suggest that monitoring or management of these adverse events within typical routine visits (e.g. decreased appetite and weight loss) should be any more burdensome than would be the case for any other SoC therapy. Moreover, routine monitoring for these minor adverse events has already been appropriately accounted for, as patients would be assessed for these at all routine/ongoing healthcare visits; as stated in the "UK Pathways study" by clinicians. Hence, any costs of monitoring and their typical clinical management within routine / ongoing healthcare visits are already included in the ongoing management costs for all patients currently captured in the model. We have therefore made the assumption in the model that monitoring for adverse events would typically occur for fenfluramine within routine healthcare visits and data suggests that the adverse events occurring would not be different in terms of frequency, monitoring or typical treatment management to other SoC AEDs received. The SmPC for cannabidiol specifically states: "*Cannabidiol can cause weight loss. In LGS and DS patients, the*	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
lack of evidence of cardiac adverse events of any severity.		*decrease in weight appeared to be dose-related, with 19% of patients on cannabidiol 20 mg/kg/day experiencing a decrease in weight ≥ 5%, compared to 8% in patients on cannabidiol 10 mg/kg/day. In some cases, the decreased weight was reported as an adverse event (see the table above). Decreased appetite and weight loss may result in slightly reduced height gain. Continuous weight loss/absence of weight gain should be periodically checked to evaluate if cannabidiol treatment should be continued."* The SmPC for stiripentol also notes that weight loss is very common. On this basis it is not warranted or appropriate to list these adverse events or the burden of additional monitoring for adverse events as being a particular issue for fenfluramine, and monitoring for adverse events is already included in the model. Therefore, these statements by the ERG should be removed. Fourth, regarding cardiac adverse events, cardiac monitoring is a precaution, based on observations of increased risks of cardiac and cardiopulmonary adverse events in obese patients taking	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		fenfluramine at doses many times greater than those that will be used for patients with Dravet syndrome. As per the trials, fenfluramine will not be used in patients with pre-existing cardiovascular or valvular disease, and an ECHO should be used to rule out patients with cardiac abnormalities who should not be given fenfluramine. As such, there is no evidence of an increase in cardiac or cardiopulmonary adverse events of any clinical significance in the Dravet syndrome trials, which is supported by the RWE studies that followed Dravet syndrome patients using fenfluramine on a daily basis over several years. The cardiac monitoring required by the regulator will be stated in the SmPC. We included cardiac monitoring in our base case model and in response to the ERG's clarification questions we included the costs of monitoring for the proportion of patients who tested positive before initiation of fenfluramine in the trials and so could not go on to receive fenfluramine. This increased the total costs by 0.01% and so had minimal impact on the ICER. Collectively, the requirement for cardiac monitoring does not, on a	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		qualitative or quantitative basis, influence the conclusions that can be drawn on the clinical and cost effectiveness of fenfluramine compared with the relevant comparators. Indeed, we note that clinical experts including those consulted by the ERG have stated that fenfluramine would be simpler to use than stiripentol and cannabidiol (ERG report page 32). The inclusion by the ERG of adverse events and monitoring as a key issue that could influence the committee's decision-making is therefore not factually justified, the manner in which they are presented is open to misinterpretation, and they should therefore be removed. (refs: Gunning et al. Acta Neurol Scand. 2020 Sep 24. doi: 10.1111/ane.13351. Online ahead of print. Lagae et al. Lancet 2019 Dec 17. https://doi.org/10.1016/ S0140-6736(19)31239-5 Nabbout et al. JAMA Neurol. 2020;77(3):300-308)	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
4	Table 2. Comparison of TEAEs for fenfluramine vs cannabidiol plus clobazam		
Table 1.5, page 17 states: " *Adverse events were not considered in the model for both cannabidiol and fenfluramine. Hence, the impact on the ICER is unclear. The need for monitoring (which was only partially included in the model), does lead to higher costs for fenfluramine and would therefore increase the*	This is incorrect and should be changed to: **"Adverse events were considered and appropriately excluded from the model for both cannabidiol and fenfluramine. The need for additional monitoring with an ECHO for heart**	It is incorrect to say that AEs were not considered; indeed the cost of monitoring and managing AEs were considered and appropriately included in the model. Routine/ongoing monitoring visits (including both face to face clinical appointments and phone calls with nurse	Not a factual inaccuracy. [redacted]

	Study 1 (Lagae 2019)			Study 1504 (Nabbout 2019)		Pooled DS CBD studies (on CLB) (Gunning 2020		
	Placebo (n=40)	FFA 0.2 mg/kg/day (n=39)	FFA 0.7 mg/kg/day (n=40)	Placebo (n=44)	FFA 0.4 mg/kg/day (n=43)	Pooled Placebo in CBD trials (on CLB) (n=84)	CBD 10 (on CLB) (n=50)	Pooled CBD 20 (on CLB) (n=88)
At least 1 TEAE	26 (65)	37 (95)	**38 (95)**	42 (96)	**42 (98)**	73 (87)	**44 (88)**	**93 (94)**
Serious TEAE	4 (10.0)	4 (10.3)	**5 (12.5)**	7 (15.9)	**6 (14.0)**	9 (11)	**11 (22)**	**20 (23)**
Serious TEAE leading to death	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	**0 (0.0)**	**0 (0.0**	**0 (0.0**	**0 (0.0**
Adverse events leading to discontinuation	0 (0.0)	0 (0.0)	**5 (12.5)**	1 (2.3)	**2 (4.7)**	1 (1)	**0 (0.0)**	**10 (11)**
TEAE, n (%) in >10% patients								
Decreased appetite	2 (5)	8 (20)	**15 (38)**	5 (11)	**19 (44)**	8 (10)	**9 (18)**	**30 (34)**
Diarrhoea	3 (8)	12 (31)	**7 (18)**	3 (7)	**10 (23)**	9 (11)	**7 (14)**	**22 (25)**
Fatigue	1 (2)	4 (10)	**4 (10)**	2 (5)	**11 (26)**	7 (8)	**4 (8)**	**24 (27)**
Lethargy	2 (5)	4 (10)	**7 (18)**	2 (5)	**6 (14)**	5 (6)	**1 (2)**	**9 (10)**
Nasopharyngitis	5 (12)	4 (10)	**7 (18)**	15 (34)	**7 (16)**	5 (6)	**5 (10)**	**8 (9)**
Pyrexia	8 (20)	7 (18)	**2 (5)**	4(9)	**11 (26)**	13 (16)	**11 (22)**	**17 (19)**
Seizure	5 (12)	4 (10)	**3 (8)**	7 (16)	**2 (5)**			
Somnolence	3 (8)	6 (15)	**4 (10)**	0	**0**	13 (16)	**17 (34)**	**31 (35)**
URTI/Bronchitis	5 (12)	8 (21)	**0**	2 (5)	**5 (12)**	4 (5)	**3 (6)**	**9 (10)**
Vomiting	4 (10)	4 (10)	**3 (8)**	0	**0**	5 (6)	**3 (6)**	**14 (16)**
Weight decreased	1 (3)	5 (13)	**2 (5)**			1 (1)	**0**	**5 (6)**

Abbreviations: FFA, fenfluramine; TEAE, treatment emergent adverse event; URTI, upper respiratory tract infection

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ICER." This should be removed and in fact directly contradicts the text on page 104 (Section 5.2.7) which states, "*Treatment emergent adverse events (TEAEs) were considered for inclusion into the economic model.*" Table 1.5, page 18 states: "*More data will become available, however, for now monitoring of the issues described above might be warranted*." This is incorrect. Page 104, section 5.2.7: The ERG state, "*However, the ERG would also have liked to see the impact of AEs on events costs and corresponding disutilities. The ERG therefore requested to include the effects of (at least) the most frequently occurring AEs on costs and QALYs (disutilities) in the model in question C20 of the clarification letter. Despite this request and an additional request after having received the clarification response, the company was unable to provide these*." These statements are not correct and should be changed to that suggested. Page 107, section 5.2.8.3.c - the ERG state: "*As mentioned in section 5.2.7, the company did not*	**irregularities was incorporated into the model, and had a very small and non-significant impact on the ICER."** As the second quote is factually incorrect, it should be replaced with "**Monitoring for AEs has been appropriately incorporated in the model."** The statement on p104 should be changed to "**However, the ERG acknowledge that the costs of most AEs would have been included in the costs of routine/ongoing healthcare visits, and would be minor so do not attract a disutility."** The statement on p107 should be changed to "***The impact on the ICER is unknown but is likely to be small and not change decision-making."*** *The last sentence is incorrect and should be changed."* **ERG comments a) on page 114**	specialists) are included for all patients. Based on the UK Pathways Study and clinician feedback, they stated that any AEs would be detected at these visits, rather than at separate visits, hence what we assumed in the model. It would have led to double counting if the cost of adverse events were included in addition to routine monitoring visits. It is incorrect that the need for monitoring is only partially included in the model - it is fully included for the reason above, and therefore this cost is already included in the total costs and the impact on the ICER. Additionally, there are no observed differential rates of adverse events with fenfluramine compared with cannabidiol (see above) with the exception of somnolence, which was more frequent with cannabidiol. There was a higher incidence of serious TEAEs with cannabidiol (see Table 1) and therefore our exclusion of any specific AEs from the model is actually likely to be conservative. There were no meaningful differences in serious TEAEs between fenfluramine and placebo. There would therefore be no incremental	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
include AEs in the economic model for both fenfluramine and CBD, and as a result did not include AE disutilities in the QALY calculation. The impact on the ICER is unknown." The last sentence is incorrect and should be changed. Section 5.2.9.5, ERG comments a) on page 114 states: "*...the company did not include any other AE event costs in their economic model even though this was requested by the ERG. For further information we refer back to the ERG comment in section 5.2.7. However, as adverse events were also not included for cannabidiol, the effect on the ICER is unknown*". This statement is misleading and should be clarified. Section 5.2.9.5, ERG comments b) on page 114 states: "*The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is however not further reflected in the model in cost or utilities. The ERG questioned (C23) the absence of additional cost caused by the association between the use of fenfluramine and unusual valvular morphology....this response was not satisfactory , as it did not reflect additional cost or disutility as a results of abnormal cardiac valvular*	**should be clarified - no analysis was provided as there is no evidence to suggest a difference between fenfluramine and cannabidiol. The impact on the ICER of exclusion of adverse events would be minimal (and the exclusion is actually conservative given there appears to be an increased incidence of somnolence and serious TEAEs with cannabidiol - see Table** 2) **ERG comments b) on page 114 should be removed - there is no evidence of an increase in clinically meaningful cardiac adverse events with fenfluramine at the licensed doses used in Dravet syndrome.** **ERG comments c) on page 114 should be removed.**	cost or disutility that would impact on the ICER to be included. This was stated in the CS and clarified to the ERG in the response to clarification questions. Monitoring for weight loss is stated in the SmPC for fenfluramine, but is also suggested in the SmPC for cannabidiol and weight loss is noted to be very common AE with stiripentol. There is therefore no rationale for suggesting that weight monitoring is a differential requirement for fenfluramine. There is no evidence of an increase in clinically meaningful cardiac AEs with fenfluramine in any Dravet syndrome studies, and the ERG's reference to abnormal cardiac valvular morphology suggested in earlier studies presumably refers to the association observed in obese patients taking doses many times greater than would ever be used in Dravet syndrome. This statement therefore requires clarification or removal to avoid misleading the committee or other readers.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
morphology which was suggested in earlier studies. Moreover, this does not include the costs of weight monitoring." The whole of point b) requires significant edits and clarification to avoid misleading the committee and other readers. It is factually inaccurate to suggest that costs and disutilities associated with abnormal cardiac valvular morphology should be included, when there is no evidence of an increase in cardiac AEs with fenfluramine at doses used in Dravet syndrome. Section 5.2.9.5, ERG comments c) on page 114 states: "...*The percentage for adults is not reflected in the table so it is unclear to the ERG how these estimates were derived*". These data were provided to the ERG in response to clarifications - Supplemental Appendix, p14, fig 7. It is therefore incorrect to imply that the ERG has not had access to these data. This comment should be removed.		An additional scenario analysis was conducted and detailed in response to clarification questions, and showed the impact on the ICER of including monitoring for heart defects with an ECHO before initiation of fenfluramine for all potential patients. This demonstrated an increase in costs of 0.01% which has no meaningful influence on the ICER. Adverse events and monitoring for these are therefore not a key issue that would influence the conclusions that can be drawn regarding the clinical and costs effectiveness of fenfluramine. These statements in the ERG report must therefore be removed or extensively clarified.	
Table 1.10, page 21 states: "*Adverse events (AEs) were not included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation*." and also: "*Could potentially have a substantial*	**This entire table should be removed from the list of issues.** The text in section 5.2.7 should be amended to say "***The ERG***	We have demonstrated that there were no meaningful differences in individual serious AEs that may have an impact on costs and utilities for fenfluramine compared with placebo. The discontinuations due to AEs	The ERG acknowledges that adverse events were partially included in the

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
impact on the cost effectiveness." The first statement is factually incorrect as discontinuation due to AEs is indeed appropriately included in the model as part of the discontinuation rate estimate. The second statement is incorrect a hanging statement that lacks context and is open to misinterpretation. This is also given in Section 5.2.7: "*The ERG acknowledges that the company incorporated discontinuation related to other causes into the model, which may also cover AE-related discontinuation*." This is factually incorrect as above, as discontinuation due to AEs is included in the discontinuation rate. Section 5.2.9.8.a states: "*In line with not including AE effects, the company did not include any other AE event costs in their economic model even though this was requested by the ERG. For further information we refer back to the ERG comment in section 5.2.7. However, as adverse events were also not included for cannabidiol, the effect on the ICER is unknown*."	***acknowledges that the company incorporated discontinuation related to all causes including AE-related discontinuation.*"** The text in section 5.2.9.8.a should be amended to say "***Although AEs were not explicitly modelled and disutilities were not included in the model, the company included the monitoring and management costs of AEs as part of routine/ongoing healthcare visits.*"**	are already captured in the discontinuations modelled, as AEs are one of the explicit reasons for discontinuation; hence this statement is incorrect. We assumed the same for cannabidiol, although at the time of our submission there were no AE data available specific to the licensed use of cannabidiol that requires concomitant clobazam. We refer the ERG to the recently published paper by Gunning et al 2020, which now provides these data for cannabidiol. These data indicate that there are no meaningful differences in individual TEAEs, with the exception of somnolence which appears to occur more frequently with cannabidiol than with fenfluramine over the same treatment periods. Of note, the overall rates of serious TEAEs were higher with cannabidiol (22-23%) than with fenfluramine (12.5%-14%). Furthermore, discontinuations due to adverse events occurred in 11% of patients taking cannabidiol 20mg/kg/day, which is very similar to the rate for fenfluramine referred to by the ERG, and is actually already captured in the discontinuations that have been modelled. Our pragmatic	model. Hence, the wording "not included" was changed to "only partially included".

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		assumption that adverse events are similar and so can be ignored therefore is supported by the available data, and is unlikely to have the potentially substantial impact on the cost effectiveness claimed by the ERG. We believe that, now the ERG has access to these data for cannabidiol, it would be appropriate to remove this table to avoid placing an undue emphasis on what is unlikely to be a key issue.	
Table 1.12. page 22 states: "*The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is, however, not further reflected in the model in cost or utilities*." and also: "*The ERG would suggest that monitoring costs should be adequately reflected in the model* " and also: "*Could potentially have a substantial impact on the cost effectiveness*." It is incorrect to suggest that monitoring is not adequately reflected in the model and we have demonstrated that including the costs of monitoring for patients both before fenfluramine initiation who subsequently are excluded from using fenfluramine is minimal and has no significant impact on the ICER, as well as the ongoing	**These statements should be removed.**	Cardiac monitoring is a precaution, based on observations of increased risks of cardiac and cardiopulmonary AEs in obese patients taking fenfluramine at doses many times greater than those that will be used in Dravet syndrome. As per the trials, fenfluramine will not be used in patients with pre-existing cardiovascular or valvular disease. The cardiac monitoring required by the regulator will be stated in the SmPC. We appropriately included routine cardiac monitoring for all patients on fenfluramine in our base case model and in response to the ERG's clarification questions we included the costs of monitoring for the proportion of patients who tested positive	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
monitoring of cardiac irregularities during routine and ongoing healthcare visits is accounted for already in the ICERs reported. Therefore, these statements should be removed.		before initiation of fenfluramine in the trials and so could not go on to receive fenfluramine. This increased the total costs by 0.01% and so had minimal impact on the ICER. Collectively, the requirement for cardiac monitoring does not on a qualitative or quantitative basis influence the conclusions that can be drawn on the clinical and cost effectiveness of fenfluramine compared with the relevant comparators. There is also no evidence of an increase in cardiac or cardiopulmonary AEs of any severity in the Dravet syndrome trials, which is supported by the RWE studies that followed Dravet syndrome patients using fenfluramine on a daily basis over several years. There is therefore no additional cost or disutility associated with cardiac AEs to be included in the model. The suggestion by the ERG that cardiac adverse events and monitoring is a key issue that could potentially have a substantial impact on cost effectiveness is therefore not justified, nor factually evidenced and the manner in which they are presented is open to misinterpretation and they should therefore be removed.	

Issue 10 All relevant comparators have been fully investigated and considered. The ERG is incorrect to state they have not been fully considered

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 2 states: "*Not all relevant comparators have been fully investigated*" and Table 1, ID 6 states: "*In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended*." And Section 1.3, page 15 states: "*…there is a lack of evidence….on certain comparators*" and the heading of Table 1.3 states: "*Table 1.3 - Not all relevant comparators have been fully investigated*". The description of the issue in Table 1.3 refers to SoC, cannabidiol and stiripentol. These are the most relevant comparators and it is incorrect to state that these	**Remove the text string that cannabidiol was the only comparator.** **The ERG should remove the statement or amend to state that:" *there is a lack of evidence FOR certain comparators that precludes a comparison with fenfluramine*".** **The Title of Table 1.3 requires amendment to remove the incorrect suggestion that not all relevant comparators have been investigated.**	The final scope of this appraisal indicates the comparator as "established clinical management without fenfluramine", which may include combinations of 8 different listed therapies. Putting aside the fact that it is not feasible, nor reasonable to expect us to provide comparisons of fenfluramine against every possible permutation of these therapies, as fenfluramine is licensed for use as an add-on to SoC AEDs, we appropriately focused our comparisons of add-on fenfluramine against other add-on therapies that are licensed as add-on therapies and/or are recommended as add-on therapies in existing NICE guidance (CG137 and TA614) and so could plausibly be expected to be replaced by 'add-on fenfluramine'. These therapies are **the only relevant comparators to add-on fenfluramine and are: continued SoC AEDs, add-on clobazam, add-on stiripentol, and add-on cannabidiol, as was clearly explained in our submission**. We fully investigated the possibility of providing comparison against all of these therapies and we specifically demonstrated in our SLRs that there are no trials of clobazam in Dravet syndrome and that the trials of stiripentol preclude a robust comparison with fenfluramine. We provided clinical and economic analyses of add-on fenfluramine vs the remaining relevant therapies, i.e. add-on cannabidiol	Not a factual inaccuracy As detailed in section 3.3 of the ERG report, not all comparators of the final NICE scope were fully investigated.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
comparators were not fully investigated.		and SoC in both our original submission and in our response to clarification questions. We have therefore fully investigated all relevant comparators and we have provided comparative clinical and economic analyses against those NICE recommended therapies that have sufficient data available to permit such comparisons. **It is therefore incorrect to state that we have not fully investigated all relevant comparators , and it is not a fair reflection of the evidence base to suggest or imply that the lack of evidence for other therapies is a reflection of uncertainty in the evidence base for fenfluramine.**	
Table 1.3, page 16 states: "*The comparison against cannabidiol + clobazam does not provide information regarding the cost effectiveness of fenfluramine against SoC. Although the ERG acknowledges the lack of evidence, the company could have incorporated the placebo + concomitant AEDs arm of the trial in their base-case model in order to produce a comparison with SoC.*" It is incorrect to suggest that we have not provided	**Comparison of fenfluramine +SoC vs SoC has been presented. This statement should be removed.**	Our original submission compared fenfluramine vs cannabidiol, both added to SoC AEDs, and also provided scenario analyses against SoC. In response to clarification questions we provided a fully incremental analysis incorporating SoC, cannabidiol and fenfluramine in both the same population as the base case (with and without concomitant clobazam) and in patients taking clobazam. It is therefore incorrect to suggest that we have not provided comparisons against SoC in the base case or otherwise.	Not a factual inaccuracy. The company only presents a comparison of cannabidiol versus fenfluramine in their base case. It is true that a scenario analysis was conducted upon request.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
comparisons against SoC in the base case.			
Table 1.3, page 16 states: "*Robust evidence on all comparators is needed. Unresolvable uncertainty with the current evidence*."	This statement should be amended to state: "*There is a lack of evidence for some relevant comparators.* ***Without evidence for comparators it not possible for the company to provide more comparative clinical and economic evidence than has been provided in the CS***"	The scope for this appraisal states that the comparator is established clinical management that may include combinations of a list of 8 different therapies. It is not feasible or reasonable to expect us to provide comparisons against all possible comparator combinations listed in the NICE scope. We provided comparisons against the relevant comparators where the data for those relevant comparators allowed. The collective clinical and economic evidence base for fenfluramine is arguably more robust and complete than for any other NICE recommended therapy for Dravet syndrome. See other comments above. (ref: https://www.nice.org.uk/guidance/gid-ta10373/documents/final-scope-2)	Not a factual inaccuracy
Section 5.2, Table 5.5, page 83 states that the comparator is cannabidiol with the justification for the comparator: "*Cannabidiol (with clobazam) is the only NICE-recommended add-on therapy to*	Amend to include SoC AEDs in the comparators. Amend the justification to: **"*It is not possible to provide comparisons against stiripentol due to limitations in the stiripentol trial data. Cannabidiol (with clobazam) is the only NICE-recommended***	This statement omits the fact that it is not possible to provide comparisons against stiripentol, due to limitations in the stiripentol trial data. **It also omits that we provided analyses against SoC AEDs in both the CS and in the response to clarification questions**.	Not a factual inaccuracy. SoC was not presented in the base case results.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
have been formally appraised by NICE."	***add-on therapy to have been formally appraised by NICE and provides a relevant comparator that is deemed to be a cost effective add on therapy in the add-on therapy pathway. SoC AEDs is the relevant comparator when clobazam-based treatment is not desirable*."**		
Table 5.6, p.85 row 2 (excluding header row) states *Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice* are "*Partly"* included in the submission	*"Partly"* should be **amended to "*Yes"***	Therapies routinely used in the NHS were considered as comparators in both the base case (cannabidiol) and in scenarios (when compared to background AEDs, i.e. SoC), and in the fully incremental analyses provided in response to clarification questions (Soc vs cannabidiol vs fenfluramine). Stiripentol was fully considered but could not be included due to limitations in the stiripentol trial data. The DISCUSS study provides evidence that these background AEDs are routinely used in the NHS. As we fully considered the relevant comparators in our submission and these are routine NHS therapies, it is incorrect to state that this is "*Partly"* considered.	Not a factual inaccuracy See above.
Section 5.2.4 ERG comment a) p. 98 states: "*Contrary to the final scope issued by NICE, which asked for the use of established clinical management without*	**ERG comment a) should be removed, as these are not issues, or should at least be significantly amended to fairly reflect the evidence we provided**	The scope stated that the comparator should be established clinical management without fenfluramine which may include combinations of a list of 8 different therapies. It is neither feasible nor appropriate to expect comparisons against each and every possible	Not a factual inaccuracy See above.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
fenfluramine as comparators, several AEDs were not considered as comparators and subgroup analysis was not completed for combinations for comparators. Comparators which were not included were ketogenic diet and vagus nerve stimulation. When asked to clarify this issue in clarification question C10, the company argued that such a comparison was not feasible or clinically appropriate.22 In response to question C10 asking why the company had not included a comparison to stiripentol, it stated that the clinical data were insufficient to do so.22 The lack of comparison to both stiripentol and SoC AEDs hampers the informative value of the cost effectiveness analysis". This statement by the ERG implies that the submission did not compare fenfluramine to established clinical management as SoC, and that comparisons against stiripentol would be	**and remove the errors contained therein. e.g. Deletion of the first sentence and clarification that VNS and ketogenic diet are inherently captured when comparing to SoC.** **Clarification that the CS and our response to clarification questions did include both a comparison with SoC (without the effect/cost of cannabidiol), in addition to subgroup analysis with and without the use of stiripentol and clobazam.** Furthermore, the sentence **T*he lack of comparison to both stiripentol and SoC AEDs hampers the informative value of the cost effectiveness analysis*** **should be amended to reflect that although these direct comparisons would provide informative information, these analyses are not possible, as was accepted in NICE TA614**.	combination of these therapies. Fenfluramine is an add-on pharmacological therapy to SoC, and that SoC may include KD or VNS. It is not expected that the clinical decision faced by patients and clinicians will be to use either fenfluramine or VND/KD. We therefore justified clearly in the CS why we didn't make specific comparisons against VNS and KD. This is in line with the approach taken and accepted in the appraisal of cannabidiol in TA614. We provided comparisons against the most relevant comparators where the data for those comparators allowed, which were add-on cannabidiol or continued SoC AEDs. We provided analyses against SoC in both the CS and in response to the ERG's clarification questions. We explained clearly why the data limitations for stiripentol precluded a comparison of fenfluramine against stiripentol. The challenges of providing those analyses are the same as those acknowledged and accepted in the appraisal of cannabidiol in TA614, in which cannabidiol was accepted as a cost effective add-on therapy alongside stiripentol despite not being compared against stiripentol. Our comparison against cannabidiol is therefore a comparison against an add-on therapy that has been accepted as cost effective alongside stiripentol. It is therefore incorrect to state "the lack of comparison to both stiripentol and SoC AEDs hampers the informative value of the cost effectiveness analysis", when the comparisons against SoC have been provided and we have provided the most relevant and	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
possible. This is incorrect. *To assess the effect of only SoC the ERG removed the CBD effect and cost from the analysis in the ERG base-case so that a comparison between SoC and fenfluramine would be possible.* This statement implies that we did not provide an analysis of fenfluramine and SoC, which is incorrect.	The comparison of fenfluramine against cannabidiol is highly relevant to the decision problem given that cannabidiol has been accepted as cost effective alongside stiripentol, despite also not being compared against stiripentol, in the add-on therapy pathway recommended by NICE. **The inability to make comparisons of either cannabidiol or fenfluramine against stiripentol should therefore not impact on the ability of our analyses to appropriately address the decision problem**.	robust analyses possible against cannabidiol, which is accepted as a cost effective therapy alongside stiripentol. The scenario that the ERG describes running for fenfluramine vs SoC was provided by us in the CS (with subgroup analysis), and fully incremental analyses including SoC vs cannabidiol vs fenfluramine were specifically provided in response to the ERG's clarification requests (question C10). Despite this, the ERG has made little mention of the analyses of fenfluramine against SoC provided in the CS and has neglected to include our fully incremental analyses in the ERG report. It is therefore incorrect to suggest these comparisons have not been provided and to suggest that the ERG has provide analyses that are above or beyond those that we had provided. The issues presented in ERG comment a) are therefore not the issue the ERG suggests they are. ERG comment a) should therefore be removed or at least significantly amended to address several errors and avoid misleading the committee and other readers.	

Issue 11 The submission and evidence reflect the full licensed indication. Cost effectiveness analyses are not restricted to people receiving clobazam. The ERG is incorrect to state that they are

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 6 states:" *In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.*" and Table 1.7, page 18-19 states: "*The license is anticipated to include fenfluramine for use both with and without concomitant clobazam (in contrast with cannabidiol). Nevertheless, in the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended)*....". The base case cost effectiveness analyses are not restricted to people receiving clobazam. This statement is incorrect and should be amended or removed	The statements should be amended to **remove the suggestion our analyses are limited to people receiving clobazam and to acknowledge that we provided fully incremental analyses in the base case population of patients irrespective of clobazam use, or alternatively, as this is a non-issue, should be removed.**	The cost effectiveness analyses were not restricted to patients taking clobazam. Fenfluramine is an add-on therapy to SoC and therefore other add-on therapy to SoC is the most relevant comparison to make. In our submission we provided a primary analysis of fenfluramine in its licensed indication vs cannabidiol in its licensed indication. This was a primary analysis because it was not possible to provide analyses against any other relevant add-on therapies that have a license and/or a NICE recommendation for use in Dravet syndrome. This provides an analysis of cost effectiveness of fenfluramine against the only add-on therapy that has been formally appraised by NICE and has been deemed to be cost effective in the existing add-on therapy pathway. It should be noted that stiripentol is recommended by NICE (CG137) as an add-on therapy although it has not been formally appraised by NICE. Due to a lack of comparable data for stiripentol we were unable to make a clinical or cost effectiveness comparison of fenfluramine against stiripentol, but as	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		stiripentol is only licensed for use in combination with both valproate and clobazam and its trials were conducted in combination with clobazam, any hypothetical comparison of fenfluramine vs stiripentol would also have been against stiripentol in patients taking clobazam. Our comparison of fenfluramine vs cannabidiol therefore provides an assessment of the cost effectiveness of fenfluramine against a relevant comparator that is accepted to be cost effective at the same point in the add-on therapy pathway as stiripentol. We acknowledged in our submission that the majority of use will be following clobazam and our primary analysis reflected that use but we provided in our original submission specific positioning scenario analyses (See Table 52 of CS) that compared add-on fenfluramine against SoC irrespective of clobazam use. In our response to clarification questions we provided fully incremental analyses of SoC vs cannabidiol vs fenfluramine, both in the base case population of patients irrespective of clobazam use and in a population of patients taking clobazam. We demonstrated in our clinical evidence that clobazam is not a significant treatment	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		effect modifier of fenfluramine (supported by the fact that the licensed indication for fenfluramine - in contrast to cannabidiol and stiripentol - does not limit it to use only in combination with clobazam). It is therefore incorrect to state that the cost effectiveness analyses are restricted to people receiving clobazam. The implication of the ERG's statement is that scenario analyses and the additional analyses provided in response to clarification questions do not inform the decision-making process. We believe this is incorrect.	
Table 1.7, page 18 states: "*.....In combination with the preceding comment, this resulted in three subpopulations that should be considered:* • *Patients without concomitant clobazam and stiripentol,* • *Patients with concomitant clobazam but without stiripentol, and* • *Patients with concomitant clobazam and stiripentol.*" and further states in relation to the alternative approach that the ERG suggests: "*Include all comparators listed in the scope, provide results for the three subpopulations listed above (including all*	This statement should be amended to acknowledge that **these populations were explored.** **The suggestion that these do not consider the relevant comparators should be removed** **The suggestion to focus on children or adolescents (which would ignore the adult population meeting the licensed indication) should be removed.**	We have discussed in responses above that the relevant comparators were considered in our submission and analyses as far as the available data for those relevant comparators allows. Regarding the three populations suggested by the ERG: 1) Patients without concomitant clobazam and stiripentol - this population is already reflected in our analyses of fenfluramine vs SoC. Clobazam is not a modifier of fenfluramine treatment effect and we provided analyses of fenfluramine against SoC based on Study 1, which excluded	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
relevant comparators per population), ensure the constructed patient profiles are plausible and focus on children or adolescents."		stiripentol use (see positioning analyses, Table 52 in the CS). 2) Patients with concomitant clobazam but without stiripentol - it is not possible to provide this specific analysis versus cannabidiol because there are no public data for cannabidiol in patients only taking / not taking stiripentol. We noted this in our submission (Table 52) and made the pragmatic assumption that the base case analysis would reflect this analysis. For a comparison against SoC in patients taking clobazam but without stiripentol, we provided analyses in patients who were stiripentol naive and stiripentol experienced but not currently taking stiripentol in Table 52 of the CS (note that **clobazam is not a treatment effect modifier for fenfluramine**). 3) Patients with concomitant clobazam and stiripentol - this population is already reflected in our analyses in our submission. This is provided in our positioning analyses vs cannabidiol and vs SoC in Table 52 of the CS. As already explained, these analyses in these populations already use the most	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		relevant comparators. It is therefore incorrect to suggest that these populations are not considered in our submission, or that they should consider different comparators. It is also incorrect to suggest that these analyses should focus on children or adolescents given that the fenfluramine label will include adults and the clinical experts consulted by the ERG have confirmed that the results of the clinical trials are applicable to adults.	
Section 5.2.3, ERG comment a) page 92 states:"*...in response to clarification question C3, the company indicated that the submission covers the full anticipated marketing authorisation, i.e. fenfluramine with and without concomitant clobazam. The ERG believes that, in case the company focusses on the full anticipated marketing authorisation, the comparators should not be restricted to cannabidiol as cannabidiol is not a recommended comparator for the full anticipated marketing authorisation*". This does not adequately reflect the response we provided to C3 and incorrectly implies we have not provided analyses against SoC	**ERG comment a) should be removed, or at the very least significantly amended to reflect the evidence and analyses that were provided but have been neglected by the ERG in its report.** This includes the evidence we provided that clobazam is not a treatment effect modifier, and cost effectiveness analyses of fenfluramine vs SoC in the CS and the fully incremental analyses we provided in our response to the ERG's priority clarification question C10.	We provided several scenario analyses in the CS (see Table 52 of the CS) comparing fenfluramine against SoC AEDs, which is the only other relevant comparator it is possible to provide analyses against. In response to the ERG clarification question C10 (which was labelled as a priority question by the ERG) we provided fully incremental analyses of SoC vs cannabidiol vs fenfluramine, which demonstrated fenfluramine extendedly dominates cannabidiol. This fact has been completely omitted from the ERG report, although we note that the ERG has taken the results of the comparison of cannabidiol vs SoC from these analyses to state that the results of our model differ from those reported for	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
AEDs. This should be amended to avoid misleading the committee and other readers.		cannabidiol vs SoC using the completely different model in TA614. It is therefore incorrect of the ERG to imply that our analyses were either restricted to cannabidiol or did not consider other relevant comparators. This factual inaccuracy should be amended to avoid misleading the committee and other readers of the ERG report.	
Section 5.2.3, ERG comment a) page 92 goes on to state: "*Moreover, given that cannabidiol is only relevant for a subgroup of the population considered, the cost effectiveness of the populations treated with and without concomitant clobazam should be considered separately. The company did provide a scenario for the subpopulation with concomitant clobazam (Table 9 of the response to request for clarification response), increasing the costs of clobazam for the patients receiving fenfluramine (i.e. given that in this scenario all patients receive clobazam) and thus assuming that the relative effectiveness (from the NMA) is unaffected by concomitant clobazam*." This does not reflect the evidence we provided	**ERG comment a) should be removed, or at the very least significantly amended to reflect the evidence and analyses that were provided but have been neglected by the ERG in its report.** This includes the evidence we provided that clobazam is not a treatment effect modifier, and cost effectiveness analyses of fenfluramine vs SoC in the CS and the fully incremental analyses we provided in our response to the ERG's priority clarification question C10.	In the CS we provided analyses demonstrating that fenfluramine is similarly effective irrespective of clobazam use, indicating that clobazam is not a treatment effect modifier for fenfluramine (CS section B.2.6.1.1.1) – this is supported by the fact that the label for fenfluramine does not require concomitant clobazam, which is in direct contrast to the label for cannabidiol. The ERG completely omits these data. As clobazam is not a treatment effect modifier for fenfluramine then it is reasonable to expect that the relative effectiveness of fenfluramine in the NMA would be largely unaffected by clobazam use - our analyses are therefore reasonable reflections of the use of fenfluramine	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		either with or without concomitant clobazam . **We reiterated these data in our response to the ERG's clarification question C3b. Despite this, the ERG report neglects to include this and instead implies that we have simply assumed no difference in efficacy based on clobazam use. This is incorrect and should be amended to avoid misleading the committee and other readers of the ERG report.**	
Section 5.2.3, ERG comment b) page 92 states: "*In combination with the preceding comment, this would result in three subpopulations that should be considered: 1) without concomitant clobazam and stiripentol; 2) with concomitant clobazam but without stiripentol and 3) with concomitant clobazam and stiripentol.*" In line with our response to the preceding comments, these populations are already reflected in the analyses we provided in our CS.	**Clarify that these analyses were already provided in the CS given that clobazam is not a treatment effect modifier for fenfluramine**.	In line with our response to the preceding comments, these populations are already reflected in the analyses we provided in our CS.	Not a factual inaccuracy. Base case results were not presented for these sub–populations.

Issue 12 Our use and estimation of convulsive seizure-free days is appropriate. The ERG's alternative estimation of convulsive seizure-free days is unclear but appears to be incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 8 states: "*The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional*." Section 5.2.6.5 ERG comment b) p102 states: *"Given the convulsive seizure frequency percentage*	These statements **should be amended to reflect that a larger reduction in convulsive seizure days would be expected given a larger reduction in seizure frequency, and therefore it is appropriate to calculate percentage change and a larger reduction would be expected to be seen in the fenfluramine arm compared to cannabidiol** **Clarification is required of the calculations used by the ERG in its estimates that the seizure free day increase is 40% that of seizure frequency decrease. If the calculations are as they appear to be, this assumption should be disregarded and the ERG's estimates of cost effectiveness based on this calculation of estimated seizure free days should be removed.**	Figure 5.4 of the ERG report shows that there is a correlation between seizure frequency and number of seizure free days, and therefore it is appropriate to use a proportional reduction in which fenfluramine creates a greater absolute increase in seizure free days (due to a greater absolute decrease in seizure frequency) The calculation that the ERG has conducted to estimate convulsive seizure days is not clear, but it appears to be using the data shown in Table 3 (taken from Table 10 in the CS). If this is the case, it is inappropriate to compare the seizure frequency and seizure free day frequency reported in this table, as they use different measures (**median vs mean**) and relate to different outcome assessment (i.e. reductions from baseline in convulsive seizure frequency vs reduction from baseline in convulsive seizure days *compared with placebo*). Given the large range of seizures experienced by patients it is inappropriate	Not a factual inaccuracy. The company does not present evidence that the reduction is proportional. Based on table 10 of the CS, it can be concluded that the % decrease in CSF compared to placebo is -62.3% and -54.0% for Study 1 and Study 1504, respectively. The corresponding % decrease in

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
change (reduction) from baseline vs placebo was larger for fenfluramine than for cannabidiol (see Table 5.9), the proportionality assumption is resulting in a larger reduction in convulsive seizure days for fenfluramine than for cannabidiol." This statement implies that it is not likely that a larger reduction in seizures would result in a larger increase in seizure free days, which we believe is incorrect		to compare these two different measures in this way, and the ERG's estimates of cost effectiveness based on this assumption would be flawed and should be removed to avoid misleading the committee and other readers. Further information on the calculation is required to determine whether there are other issues with this assumption.	convulsive seizure-free days is -27% and -21.9%.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.9, page 20 states: "*The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the NMA, for convulsive seizure frequency, i.e. assumed these two outcomes are proportional. Although it is evident that there is an association between these two outcomes, it is unclear whether it is plausible to assume proportionality*" and *Section 5.2.6.5*			

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ERG comment b) p102 states "Moreover, the estimated reduction in convulsive seizure days is inconsistent with the reduction reported in Table 10 of the CS.1 Based on that table, it can be derived that assuming the same reduction for both convulsive seizure frequency and convulsive seizure-free days is not plausible, rather the reduction in convulsive seizure days ≈ reduction in convulsive seizure frequency × 0.4 . Therefore,			

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
in the ERG base-case reduction in convulsive seizure frequency × 0.4 is used to estimate the reduction in convulsive seizure days." The calculations used in this assumption are unclear, however as the ERG stated that data from Table 10 of the CS are used, then the calculations are based on two different measures that are not comparable and therefore this calculation and the associated assumptions			

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG comment</th></tr>
<tr><td>would be incorrect.</td><td></td><td></td><td></td></tr>
<tr><td></td><td>Table 3. Data possibly used by ERG to estimate proportionality between convulsive seizure frequency and convulsive seizure free days.<table><tr><td></td><td>Fenfluramine 0.7mg/kg/day</td><td>Fenfluramine 0.4mg/kg/day</td></tr><tr><td>Change from baseline in CSF, median (range); p-value vs placebo</td><td>-74.9 (-100.0 to 196.4) p<0.0001</td><td>-63.1 (-100.0 to 115.0) p<0.001</td></tr><tr><td>Convulsive seizure-free days, mean (SD); Difference from placebo in convulsive seizure free days, % (95%CI); p-value vs placebo</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td></td><td>The ERG looked at the difference from placebo in CSF per 28 days and difference from placebo in convulsive seizure free days as presented in table 10 of the CS.</td></tr>
<tr><td>Table 1.9, page 20 states: "Moreover, particularly given that the cannabidiol Summary of Product Characteristics (SmPC) indicated that, compared</td><td>The statements comparing seizure free days with cannabidiol vs fenfluramine should be removed, or at least clarified with the reporting of all data for cannabidiol and fenfluramine and an acknowledgement that it is unclear whether these data are based on comparable measures.</td><td>The basis of the estimate of 2.7 additional seizure-free days with cannabidiol 10mg/kg/day vs placebo reported in the Epidyolex SmPC and reported here by the ERG is unclear. The additional 2 days with fenfluramine 0.4mg/kg/day in study 1504 is based on the mean estimate, and was actually 2.6 days that we conservatively rounded down (see Table 10 of the CS). It would be inappropriate to compare these</td><td>Not a factual inaccuracy.</td></tr>
</table>

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
with placebo, cannabidiol 10mg increased the convulsive seizure-free by 2.7 days while fenfluramine co-administered with stiripentol increased convulsive seizure-free days by two days. Given convulsive seizure-free days is the main driver of the incremental QALYs between the treatments, the current assumptions might result in an overly optimistic utility benefit for fenfluramine." and Section 5.2.6.5		data if the cannabidiol data are based on median data. There is no indication of the variance or range in these cannabidiol data. Furthermore, the ERG is selectively reporting these data, ignoring the fact that for cannabidiol 20mg/kg/day there was a gain in seizure-free days compared with placebo of only 1.3 to 2.2 days, whereas for fenfluramine 0.7mg/kg/day in study 1 there was a gain of 5.6 days. This statement in the ERG report should be removed or at least clarified. (ref Epidyolex SmPC; Table 10 of CS)	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ERG comment b) page 102 states: "*This assumption is likely (still) favouring fenfluramine when compared with cannabidiol as a larger reduction in convulsive seizure days for fenfluramine is assumed than for cannabidiol while this might be questioned. Particularly given that the cannabidiol SmPC indicates that compared with placebo cannabidiol (10 mg) increased the convulsive seizure-free days by 2.7 days while*			

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
fenfluramine co-administered with stiripentol increased convulsive seizure-free days by two days (CS section B2.6.1.3)." This is selective reporting based on incomplete data and should be clarified to avoid misleading the committee and other readers.			

Issue 13 Exclusion of Non-convulsive seizures from the economic analyses is appropriate and conservative

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.9, page 20 states:" *The company did not incorporate non-convulsive seizures in the economic model and stated that this is conservative (both in the CS and in response to clarification question C18). This claim is, however,*	The ERG's comments **should clarify that our model is conservative in comparing fenfluramine vs SoC, and is likely to be conservative in**	The ERG's comments do not take into account that SoC is a comparator, with results for fenfluramine vs SoC provided in both the CS and our response clarification questions. Our model is therefore conservative for fenfluramine vs SoC.	Not a factual inaccuracy.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
highly questionable, especially as this is based on a comparison with the placebo arm, while in the company's base-case fenfluramine is compared with cannabidiol." and Section 5.2.6. ERG comment c) p. 103 states:"... *Primarily because this is based on a comparison with the placebo arm, while in the CS base-case fenfluramine is compared with cannabidiol. The company did not provide any evidence that neglecting non-convulsive seizures in the economic model is a conservative approach when compared to cannabidiol. Moreover, in the FAD for TA614 it is stated that "the clinical trials showed that cannabidiol also reduced non-convulsive seizures" (next to a reduction in convulsive seizures).15 Therefore, excluding non-convulsive seizures in the economic model may well be non-conservative .*" The ERG's comments do not take into account that SoC is a comparator. Available data also suggest reduction in total seizure frequency (which includes both convulsive and non-convulsive seizure frequency) appears to favour fenfluramine vs cannabidiol. It is therefore likely that the exclusion of non-convulsive seizures is	**comparing fenfluramine vs cannabidiol.**	The ERG comment correctly points out that cannabidiol also has a treatment effect on non-convulsive seizures (NCS); however, there are issues in the recording of NCS (as detailed in our submission) and data specifically on NCS for cannabidiol in combination with clobazam are lacking. Nonetheless, recently published analyses of trial data for cannabidiol in combination with clobazam (Gunning et al 2020) provide data on reductions from baseline in total seizure frequency (which includes both convulsive and non-convulsive seizure frequency), and these data would suggest that the median reductions in total seizure with cannabidiol (plus clobazam) vs placebo are less than the median reductions in total seizures for fenfluramine vs placebo (compare median reductions from baseline in total seizure for cannabidiol (plus clobazam) vs placebo in Table S4 in the supplementary material to Gunning et al 2020 vs median reduction from baseline in total seizure frequency for fenfluramine 0.7mg/kg/day vs placebo in Table 2 of Lagae et al 2019 and for fenfluramine 0.4mg/kg/day vs placebo in Table 2 of Nabbout et al 2019). Fenfluramine is therefore superior to cannabidiol (plus clobazam) for reductions in convulsive seizure frequency and is likely to be superior to cannabidiol (plus clobazam)	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
conservative. The ERG's comments therefore need to be clarified.		for reduction in total seizures, which include NCS. The exclusion of NCS from the model is conservative for both fenfluramine and cannabidiol and is likely to be more conservative for fenfluramine based on the limited available evidence. The ERG's comments should be amended to reflect that the model is conservative for fenfluramine vs SoC and is likely to be conservative for fenfluramine vs cannabidiol.	

Issue 14 Treatment discontinuation is modelled appropriately. The ERG's suggestion that convulsive seizure frequency should revert to the placebo rate is not supported and biases the model against effective treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 5 states:" *Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment*." And 5.2.2. ERG comment a) p.87 states: "*Once patients discontinue treatment, they are*	Acknowledge that **the ERG's approach would be biased against effective therapy that maintains patients on treatment for longer.** Acknowledge that **there is no evidence to suggest that fenfluramine effects observed in the RCTs are driven by a substantial placebo effect, and therefore the ERG's suggested approach is not**	The ERG's suggested approach would maintain a benefit for therapy that is discontinued whilst reducing costs. This would be biased against the more effective therapy that maintains patients on treatment for longer. The placebo response in the fenfluramine RCTs was low, and as acknowledged by the ERG elsewhere in its report the OLE study data indicate that the effects of	Not a factual inaccuracy. This is a point that has come up for many appraisals. The ERG justified this approach in ERG comment "a" of section 5.2.2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
*assumed to revert to baseline seizure frequency (as observed during the observational period of the trial) and not to the placebo 'on-treatment' seizure frequency (as observed during the maintenance period of the trial). In response to clarification question B16j, the company indicated that this was done to prevent that discontinued patients still experience the benefit of the placebo effect.22 The ERG does not agree with this approach as this placebo effect may also be present in the fenfluramine and cannabidiol treated patients who are still on treatment (and hence is part of the demonstrated effects).Removing the presumed placebo effect (**which could include other factors such as natural progress or regress of disease**) for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment. Therefore, the ERG preferred to assume that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial.* " It should	**more robust.** Acknowledge that **the requested scenario analysis would therefore be biased and not clinically rational and this is the reason why it was not provided.** Acknowledge that **exploratory scenario analyses conducted by the ERG using this assumption are therefore unreasonably biased and not clinically rationale against fenfluramine as the most effective therapy.** **Amend brackets to: (*which could include natural variation in seizure frequency experienced by patients*)**	fenfluramine observed in the RCTs is sustained for up to 3 years. It is therefore unlikely that the effects of fenfluramine observed in the RCTs is driven by a substantial placebo effect. In the absence of evidence to suggest that the placebo effect should be maintained over the lifetime of patients who have discontinued therapy, the ERG's approach is not justified nor more robust than the approach used in the CS. A placebo effect is however already included in the model when fenfluramine is being compared to SoC (excluding cannabidiol), which is detrimental for fenfluramine and therefore a conservative assumption we have already taken, particularly as the placebo group would not see a placebo effect in the long term. Importantly this already applied assumption suggests that a patient maintained on their existing SoC, receives a "placebo benefit", that is unlikely to occur in practice, especially for such a comparative patient that is in need of a new treatment option but doesn't actually receive a change in their SoC	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
be clarified that to maintain the placebo effect as suggested by the ERG would benefit early discontinuation, with the less effective therapy that leads to earlier discontinuation accruing benefits but not additional costs. **This approach is therefore biased against more effective therapy – and essentially favours those therapies that are less effective as a treatment strategy**. **It should be clarified that there is no evidence to suggest that fenfluramine effects in the RCTs are driven by a substantial placebo effect.** It also states: "*Although this scenario was requested from the company (clarification question C16), it was not provided*". Clarify that we provided the justification for not providing this biased scenario analysis. It also states: *"Removing the presumed placebo effect (which could include other factors such as natural progress or regress of disease)".* ***T*****his should be amended.**		therapy. Other factors such as natural progress / regress of the disease would not be apparent in the time frame the trial took place in (40 day observational period, followed by a 14-15 week treatment and maintenance period)	
5.2.2 ERG comment b) p.88 states: "*In the committee discussion for TA614, it was mentioned that "the model generates more favourable results for patients that*	**Remove the statement that suggests this is a limitation of our model and acknowledge that as a patient-level simulation model driven by actual**	A limitation of the cohort model in TA614 was that patients were moving from a higher seizure frequency to a lower seizure frequency upon	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
stop cannabidiol than would be expected".15 Specifically, some patients that discontinued treatment may have been reassigned to a health state with a lower frequency of seizures than they were in before treatment discontinuation, i.e. patients' health status improves after treatment discontinuation. Although in response to clarification question C16h, the company indicates that the current model does not have this limitation, the ERG believes that this statement is incorrect.22 As highlighted in Figure 5.2, it is possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation. This model limitation was removed in the ERG analyses (by adjusting the post discontinuation convulsive seizure frequency and convulsive seizure-free days)." It is incorrect to state this is a limitation of our model and to assume that all patients experience both an improvement in seizure control whilst on treatment and a worsening of seizure control when treatment is discontinued.	**patient-level data, the model appropriately accounts for the heterogeneity in that patient-level data.** **Acknowledge that the ERG's approach and its analyses assuming an improvement in seizure control while on treatment and a worsening of seizure control when treatment is discontinued for all patients is not necessarily correct and is not supported by the patient-level data. All ERG analyses based on this assumption and are subject to limitations that have been imposed by the ERG and do not reflect the data.**	discontinuation, with no evidence to show that this happens on an individual level. In our patient-level simulation model, although it is possible for a few individuals to move from a higher on treatment seizure frequency to a lower discontinued frequency, as the seizure frequency is taken directly from patient level data in the trial this directly reflects the seizures that patients experienced. It is therefore incorrect to state this as a limitation of our model. It is also incorrect to assume that all patients experience a decrease in seizures during the maintenance period (for both placebo and treatment arms), and impose this ERG's assumption on the data, when those clinical data show this is not always the case. In addition to this not being a limitation of our model, it should be noted that our data driven approach is actually more robust and more conservative compared with the ERG's suggested approach. As patients on cannabidiol discontinue sooner, in those rare cases where the data show seizure frequency is reduced following discontinuation, the	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		cannabidiol arm will see an increase in quality of life sooner and for longer than the fenfluramine arm. The modifications imposed on the data by the ERG would preclude this. The ERG's statement that our approach reflects a limitation of the model should be removed and the analyses conducted by the ERG based on its imposition of this limit to the data should be removed.	
Section 5.2.7 ERG comment, page 104 states: "*The ERG acknowledges that the company incorporated discontinuation related to other causes into the model, which may also cover AE-related discontinuation*" The use of the word 'may' implies that the AE-related discontinuation also may not be included, which is incorrect	This text should be changed to: "The ERG acknowledges that the company incorporated discontinuation related to other causes into the model**, which cover AE-related discontinuation"**	The discontinuation probabilities for the model were calculated from the discontinuation seen in the trial. As stated in the CS, the discontinuation being discussed here does include any discontinuation that occurred due to an adverse event, and it would be wrong to suggest this is in any way in doubt. The text should be amended accordingly.	Changed accordingly

Issue 15 As highlighted in the NICE scope, mortality is a recognised risk associated with Dravet syndrome, and is linked to convulsive seizure frequency. Modelling mortality is therefore justified. The ERG's exclusion

of mortality is inconsistent with a fair clinical representation of the disease and irrationally biases the model analyses against fenfluramine

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 14 states:" *Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon*." and Table 1.9, page 20 states: "*In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency. Given the strong assumptions the company was required to make leading to seemingly implausible estimates of relative risk, the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the preference of the committee working on TA614, the ERG preferred to remove the link between convulsive seizures and mortality*." and Section 5.2.6 ERG comment d) page 103 states: " d) *In the company base-case it is assumed that mortality is linked to convulsive seizure frequency. This linking required multiple major assumptions:….*". And also states: "*In response to clarification question C14, the company stated that*	**These statements should be clarified to convey the fact we didn't simply assume there is a link between convulsive seizures and mortality - the assumption is based on and supported by the literature, and based on this literature there is a logical expectation that therapy that reduces convulsive seizures will reduce the risks of seizure-related deaths**. Given the significant challenges in providing empirical evidence to quantify the link between mortality and convulsive seizure frequency, the approach taken, using Dravet specific mortality data, was justified, and although relative risks may appear high, **the resulting mortality curves are aligned with what would be expected. The statement that the relative risks are implausibly high should therefore be removed.** **The ERG should also clarify that removal of a mortality benefit in its analyses leads to ICERs that are overestimated and biases the model against**	It should be noted we have not simply assumed there is a link between convulsive seizure frequency and mortality - the assumption is based on the literature that indicates the link between convulsive seizures and SUDEP generally and that demonstrate SUDEP is the leading cause of death in DS as explained in CS section B.1.3.1.3. It is therefore a logical expectation that therapy that reduces convulsive seizures will reduce seizure-related deaths. The ERG notes we explained in our response to clarification questions that there are significant challenges to provide empirical evidence to link mortality to convulsive seizure frequency, but by simply saying we stated this doesn't acknowledge that we showed this robustly with reference to general epilepsy literature and doesn't acknowledged that this would be even more challenging to quantify in a rare disease like Dravet syndrome. The literature-supported link between	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
there are significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency". And also states: "*Given the strong assumptions the company was required to make (leading to seemingly implausible estimates of RR), the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the committee's preferences for TA614, the ERG preferred to remove the link between convulsive seizures and mortality*". These statements should be clarified to ensure the committee and other readers understand that the assumption was supported by the literature, and given the challenges to providing empirical evidence in Dravet syndrome, the approach taken was justified. It should be clarified that the ERG's removal of any mortality benefit from reducing seizure frequency is therefore not aligned with the logical expectation of a reduction in seizure-related death with effective treatment, and would lead to ICER estimates that are overestimated through their failure to capture a logically expected benefit with therapy. As fenfluramine provides superior reduction in convulsive	**fenfluramine as this is the most effective therapy that is modelled.**	convulsive seizures and death should be acknowledged, as should the challenge to quantifying the link empirically in Dravet syndrome. The ERG reports relative risks and claims these are seemingly implausible but neglects to comment on the resulting mortality when implemented in the model. When implemented in the model, the resulting mortality aligns with the mortality seen in the trial, and the mortality reported in published literature on Dravet Syndrome mortality. It is therefore incorrect to state that the RR are seemingly implausible. This should be amended to state the RRs may appear to be high but when implemented in the model, the resulting mortality aligns with the mortality seen in the trial, and the mortality reported in published literature on Dravet Syndrome mortality. The approach taken to quantify the link between convulsive seizure frequency and mortality is therefore justified. It should also be clarified that the ERG's removal of any mortality benefit from reducing seizure frequency is therefore	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
seizure frequency compared to cannabidiol, this assumption of the ERG particularly biases the model against fenfluramine. This must be clarified to avoid misleading the committee and other readers.		not aligned with the logical expectation of a reduction in seizure-related death with effective treatment, and would lead to ICER estimates that are overestimated through their failure to capture a logically expected benefit with therapy. As fenfluramine provides superior reduction in convulsive seizure frequency compared to cannabidiol, this assumption of the ERG particularly biases the model against fenfluramine. This must be clarified to ensure the committee and other readers are fully aware of the consequences of simply assuming no mortality benefit from the significant and often profound reductions in convulsive seizures observed with fenfluramine.	
Section 5.2.6. ERG comment e) p.103 states: "…*Particularly, DS mortality was directly estimated based on reported SUDEP and non-SUDEP mortality (independent on convulsive seizures and not specifically incorporating SE mortality) as reported by Cooper et al.24 This resulted in SUDEP and non-SUDEP mortality of 0.07142% and 0.04997 % respectively per cycle".* These calculations do not take into account	**The mortality for non-SUDEP should be adjusted to 0.05000 (0.0499986)**	When the raw data in Cooper is used, the probability of non-SUDEP mortality per cycle should be 0.05000. This is more accurate than 0.04997 which is calculated using the rates that have already been rounded in Cooper. This is unlikely to make any difference given the small discrepancy, however best	Not a factual inaccuracy. While the best approach can be discussed, the ERG used the rates reported by Cooper et al.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
the raw data from Cooper, but rather use reported rates and rounded		practice suggests that the raw data should be used.	

Issue 16 Implementation of the stopping rule(s) we have proposed is appropriate

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.8, page 19 states: [in reference to 30% stopping rule] "*Explore the impact of this stopping rule in more detail, e.g. conditional on the ERG or committee preferences. This could not be done by the ERG in the current model."*	**Clarify that we provided in response to clarification questions analyses including 3 alternative stopping rules (based on different requirements of achieving a % reduction in seizures from baseline after 6 months of treatment), as well as the removal of the stopping rule altogether.**	We provided in response to clarification questions analyses including 3 alternative stopping rules, and the removal of the stopping rule.	Not a factual inaccuracy
Table 1.1, ID 7 states: "*The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months*." And Section 5.2.4 ERG comments c) page 98 states: "c) *In the CS a stopping rule was implemented for all patients whose seizure frequency did not reduce by at least 30%.1 This stopping rule was based on NICE TA614 for cannabidiol and had not been proposed by*	**Remove ERG comment c) or clarify that this supports the stopping rule proposed by the company and also note that if the stopping rule is removed for both fenfluramine and cannabidiol the ICER for fenfluramine vs cannabidiol reduces to less than £20,000/QALY**	We are proposing that a stopping rule is applied in line with that adopted for cannabidiol in TA614 in order to ensure the appropriate clinical and cost effective use of fenfluramine. The ERG's reporting of the ICER if the stopping rule for fenfluramine is removed serves only to demonstrate that our inclusion of the stopping rule is supported, but the ERG appears to have presented this in a negative light rather than the positive light in which it should be viewed. **As we are proposing the**	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
the EMA and was not found in the scope provided by NICE.15 Further analysis showed that not implementing this treatment stopping rule in the fenfluramine arm, while implementing it in the cannabidiol arm (in line with NICE TA614) led to an increase of the ICER from £31,773 per QALY to £63,268 per QALY."		**stopping rule and this is appropriate and aligned with that accepted for cannabidiol it is not a key issue as presented by the ERG.** One could also argue that if the ICER with removal of the stopping rule for fenfluramine is informative for decision-making , then so also is **the ICER for removal of the stopping rule for both fenfluramine and cannabidiol, in which the ICER is less than £20,000/QALY**. This ERG comment should therefore be removed or clarified as suggested.	

Issue 17 Dosing and patient weight were appropriately implemented in the model. The ERG's reference to patient weight assumed in the TA614 model is not supported by evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.2.9.5 ERG comment p114 states: "*As the fenfluramine dose increase is capped at 26 mg and the cannabidiol dose is not, according to TA614, the lower weight applied in the submission for TA614 may lead to a lower price for*	**The maximum dose should take into account the use of stiripentol and the units for the dosage (i.e. 26mg/day when patients are not taking concomitant stiripentol and 17mg/day when patients are taking concomitant stiripentol).**	The maximum dose should be quoted correctly to avoid confusion. By leaving the statement that a lower weight 'may' lead to a lower price for cannabidiol ambiguous, the reader is led to believe this might not be the case. In	The maximum dose has been changed (section 5.2.9.5). The rest of the company's remarks

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
the cannabidiol treatment in the cannabidiol treatment arm in the CS for TA614 than in the treatment arm for the fenfluramine submission.15 As cannabidiol is more expensive relative to fenfluramine, when a higher weight is assumed, the use of higher patient weight in this submission therefore benefitted the cost effectiveness of fenfluramine" . The maximum dose for fenfluramine is incorrectly quoted The use of the word *'may'* in regards to the lower weight in TA614 leading to a lower CBD price is misleading The observation that the higher weight used in this submission benefits the cost effectiveness of fenfluramine is misleading as presented, and it should be clarified that our approach is supported by evidence.	The comment should clarify that **the lower weight would definitely lead to a lower price of cannabidiol per patient/day than a higher weight, and this is entirely to be expected given that the costs of fenfluramine and cannabidiol are determined by patient weight.** The last sentence should include some **commentary on which approach is more fitting for an English adult population, and should clarify that rather than benefitting the cost effectiveness of fenfluramine the data we have used is justified and appropriately reflects the fact that the costs of fenfluramine and cannabidiol are determined by patient weight.**	reality, as the price of cannabidiol is directly associated to the weight of a patient, a lower weight would definitely lead to a lower price per patient/day. The last sentence correctly points out that a higher patient weight benefits the cost effectiveness of fenfluramine, however this is phrased as a weakness of the model, whereas it is likely that the higher weight assumed in the CS is more representative of an English adult population. There is no evidence to show that the average weight of the English population plateaus at age 18 (as assumed in TA614), whereas there is evidence, provided in the CS, to show that weight continues increasing up to the age of 25. As the licensed indications of both fenfluramine and cannabidiol include adults, there is no justification to limit the weight of patients to 18 years old when there is clear evidence that weight does not plateau at age 18. It is also possible that weight continues to increase after the age of 25, however this was not included in the CS to ensure that the model was conservative.	are not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		It is inaccurate for the ERG report to comment on the impact of the assumption without commenting on the validity of the assumption, and the validity of the assumption that it is being compared to. Our approach is justified and based on data, in contrast to the approach noted by the ERG based on TA614. These statements should be clarified to avoid creating a false impression that the costs we have adopted for fenfluramine and cannabidiol are somehow not correct.	

Issue 18 Resource use was fully provided in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.12. page 22 states: "*A differentiation between adults and children requiring access to a specific type of care was applied in the model. The percentage for adults is not reflected in the CS so it is unclear to the ERG how these estimates were derived*." and "*that it is made clear how resource use among adults was established.*" This table	Table 1.12 of the ERG report - This table should be removed as it is not correct. See the proposed amended text which clarifies the source of the data within the CS. On page 113 of the ERG report this should be changed to: "***The difference in frequency of visits by age group and***	The proportion of adults and children requiring access to a specific type of care was incorporated into the model, and these proportions differed for adults and children. In Tables 37-39 of the CS, the values were only for children, the Supplemental file "UK Pathways Study" which was submitted along with the Document B, included the different	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
should be removed. Page 113, section 5.2.9.4: the ERG states: "*The difference in frequency of visits per age group was made clear in Tables 37 to 39 of the CS*." This is partially correct but should be amended to reflect the data that was implemented in the model.	***seizure frequency group (low, medium, high) for paediatrics was given in Tables 37 to 39 of the CS. The percentage of adults visiting different healthcare settings is given in the UK Pathways Study reference provided with the CS.***"	values for adults and children used in the model (page 14, Fig 7). Therefore, while it may have been unclear in Document B to the ERG, the data were provided at the initial CS for review and can be checked for accuracy. Therefore Table 1.12 and statements should be removed as it is not accurate.	

Issue 19 Patient utilities were estimated and implemented appropriately

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.11. page 21/22 states: "*Estimating health state utilities conditional on convulsive seizure frequency (not convulsive seizure-free days*) and Page 106/107 - point d) states: "*The primary endpoint in the registration studies was the change in mean monthly convulsive seizure frequency. However, the company based the QALY estimates in the economic model only on convulsive seizure-free days, assuming proportionality between these two outcomes. Although, as was already described in section 5.2.6, there is an association between convulsive seizure*	**Clarify that these metrics are related to one another.** **In addition to being more clinically meaningful, seizure-free days was also used in the model in TA614.** **Remove the statement that assuming proportionality between**	Data from clinical interviews (provided in the Supplemental file "UK Pathways Study") supports the concept of seizure freedom and seizure-free days as clinically important. It was considered by clinicians that seizure frequency and seizure freedom days are both important for patients. If a patient has 5 or 10 seizures in a day it is still a seizure day, however if they have no seizures in a day this would be seen as important and of value to the patient. Furthermore, in the FAD for TA614 – in section 3.2, page 4 it is noted that "*an increase in the number of convulsive seizure-free days would also benefit people with Dravet*	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
days and the convulsive seizure frequency, assuming proportionality between these outcomes is likely implausible." There is no assumption of proportionality between these outcomes. ERG should clarify the approach taken and remove the incorrect statement.	**these outcomes is likely implausible.**	*syndrome. This is because it would mean having fewer nights with seizures, where there is a higher risk of unexpected adult death in epilepsy*", further highlighting the importance of seizure free days for patients. Therefore, there is evidence to suggest that the concept of seizure-free days is clinically relevant to the Dravet patient population. Furthermore, seizure-free days have been calculated directly from the data and the relationship between seizure free days and utility values was estimated using a regression framework while adjusting for confounders. As such, **no assumptions were made about proportionality as all values were estimated directly from the trial data and the strength of evidence (in terms of statistical significance) directly inferred from the data.** The ERG should therefore clarify the approach that was taken and remove the incorrect statement on assuming proportionality	

Issue 20 Carer utilities were estimated and implemented appropriately based on carer-level data from the trials. The ERG's suggested approach in line with TA614 is not supported by the available data and is not applicable to our patient-level modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1, ID 11 states:" *Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month)."* and Table 1.11. page 21/22 states: "*In line with TA614, carer utilities were included in the company's base-case using a regression function based on carers of children and adolescents in the registration studies. However, contrary to TA614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month)*." The ERG has suggested an "*Alternative approach related to the*	Clarify that **we have used specific data from patients and carers in the trial and thus the estimated utilities are rooted in data and specifically reflect the impact of fenfluramine on patients and carer.** **Remove the suggested alternative approach on the basis there is no clear scientific reason to aggregate the utility data as done in TA614 when we have higher resolution data available.**	In this submission carer utilities have been calculated directly from the available trial data for fenfluramine with insights on the relationship between the number of convulsive seizure free days a patient has and the resulting impact on the carers QoL score. From this data it is clear that incremental improvements in the number of seizure free days a patient experienced also impact on the carers QoL. Therefore, to only model the impact of treatment on two health states defined by higher seizure frequencies observed in different trials, as was done in TA614, is not aligned with the patient simulation modelling approach we have appropriately taken. Furthermore, this approach would disadvantage a product that has high efficacy in reducing seizure frequency to below these artificial, arbitrary thresholds. This would also result in the implementation of stepped changes in utility benefits, which do not reflect the continuous nature of the data. If the approach from TA614 were to be used it would assume that if individuals had	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
implementation of carer utilities, consistent with TA614." This require clarification		up to 7 days of seizures per month this would have no impact on carers, which is not supported by the actual data that we have from the trial population and seems unrealistic given the consistently acknowledged substantial burden that Dravet syndrome places on carers. Additionally, in TA614 a sub categorization of seizure freedom within the health state groups was used in order to determine patient utilities. Page 53 of TA614 committee papers notes "*Compared to patients with a high number of seizures, patients with a low number of convulsive seizures are more likely to experience a high number of seizure-free days. These sub-categories help in assigning different utility scores for patients in a specific seizure group based on the number of seizure-free days they experience*.". Furthermore, it is not clear how the health states and categorisations were defined in TA614. On page 52 of the TA614 committee papers it is stated: "*seizure categories were determined to ensure that that patients enrolled in the Phase 3 trials were split into three equal groups and the analyses could be based on sufficient statistical power*". This appears to be a decision made out of statistical convenience	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		and not clinical relevance, and thus arguably is not an appliable assumption for our trial data or methodological approach. Our estimates of the impact on carer QoL with changes in a patients' numbers of seizure-free days has been estimated directly from data gathered in the trial and is therefore most relevant for our patient level continuous time model. Equally it is appropriate to assume carer utilities for all patients as we are estimating carer utilities as a function of seizure free days directly from the trial data so they should be considered for all patients.	
Table 1.11. page 21/22 states: "*Furthermore, the ERG questions whether the regression function based on carers of children and adolescents is also applicable to carers of adults and considers the assumption of 1.8 carer per patient over a whole lifespan to be high.*"	Clarify that **we acknowledged this as a potential limitation, but the approach is appropriate in the absence of any other data or better approach.**	We considered that the application of the regression function to estimate utilities in carers looking after adult patients based on data from carers looking after patients aged up to 18 years is appropriate in the absence of detailed patient-level data on how seizure-free days in adult patients impact a carers QoL. We used the full age range of data available from the trials (carers of patients up to age 18). Given the immense burden that this progressive condition places on carers, it was deemed important to capture the ongoing impact that Dravet syndrome has on the QoL of carers of older patients. Estimates of EQ-5D	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		index values showed that patient QoL continues to decline with age (Lagae 2018 and Irwin 2017). The study from which our carer QoL life data was obtained captures at least some of the diversity in carer burden within the Dravet syndrome patient population over time and as patients enter into adulthood. The burden of caring for Dravet syndrome patients is by no means limited to immediate seizure management; there will be ongoing psychological stress associated with dealing with such patients, ongoing anxiety about their health, managing other co-morbidities and dealing with the progressive long-term implications of seizures that occurred when patients were much younger. These can still place a considerable burden on carers as a patient's condition evolves. The accidents and injuries that accumulate before adulthood are likely to carry on into later life and means that patients are highly dependent on carers, and the burden remains high even if the condition can be managed better by carers following initial diagnosis. As patients age they may need to move to a care home, which may reduce the burden on a carer at home as they may be more likely to move into professional care. However, the parents and family of	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		Dravet syndrome patients will still experience some level of burden through the stress, anxiety and care even if a patient moves into professional care. As such, even if patients move into professional care there is still a relevant impact and a requirement for an assignment of utilities, as they will still have suffered irreversible damage as a result of living with and caring for a Dravet patient and are unlikely to return to a normal QoL. It is likely that patients will need a variable number of carers throughout different periods of their life, however given the longitudinal follow-up data that would be needed in order to understand the true burden is unavailable, an assumption in line with that presented in TA614 around the average number of 1.8 carers over a whole patient lifespan was used in the model.	
Table 1.1, ID 12 states: "*When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality*" and Table 1.11. page 21/22 states: "*When a patient in the economic model died, the corresponding carer utility was also set to zero. This clearly*	Clarify that **the ERG acknowledges there is no best way to model carer utility following the death of patients.** Acknowledge **that the alternative approach suggested by the ERG and attempted in its scenario analysis is also open to challenge, being based**	The ERG acknowledges there is currently no clear guidance on the best way to incorporate carer utilities. If the patient dies it is unrealistic to assume that this does not have an impact on the carers themselves. Providing a utility benefit to the carer when a patient dies would seem perverse in the context of caring for patients and assuming that if the	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
overestimates the impact of mortality, given that the caregiver does not die together with the patient and its assumed utility value of 0 is therefore an implausible underestimation of the reality" and Section 5.2.8, ERG comment e), page 107 states: "*Alternatively, this issue could have been tackled by using a different approach to incorporate carer utilities into the model. In TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility (-0.201 for >8 to ≤25 convulsive seizure per month and -0.244 for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died. Although there is no clear guidance as to how best to incorporate carer utilities, the ERG considers this approach to be more appropriate than the applied approach in the current STA. Hence, the ERG explored the impact of using carer disutilities from TA614 in a scenario analysis.15* " This alternative approach is not appropriate.	**on artificial, arbitrary seizure thresholds** and **irrationally penalising fenfluramine based on its greater efficacy in reducing seizure frequency.**	patient dies a burden no longer exists on the carer is also not realistic. There are currently insufficient data to suggest the best approach on how to model carer utility when a patient dies. Whilst it is possible that setting carer utilities to zero after the patient's death risks over-stating the incremental survival effects, as the ERG highlights there is no standardised and straightforward solution for this. If you include carer benefits in any model where there is a survival impact you need to consider carer utilities post the patient's death. Setting them to zero may overstate the impact of the patient's death. However, setting them to a level higher than that seen before death would reduce the benefit of reducing survival benefits. The approach used in TA614 is a reasonable compromise if you have a responder / non-responder model, where an incremental benefit of being in the responder state can be included and by definition this will be zero after death. This would be equivalent to using absolute utilities and setting the post-death utility equal to the non-responder utility. However, this is not possible in our model as we are modelling seizure frequencies / seizure free intervals, which is a superior approach.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		It should be noted that to implement the ERG's suggested alternative approach a carer disutility regression framework would need to be developed. From the information presented it is currently unclear where the disutility values referenced in the response are from, therefore we cannot check this for factual accuracy or appropriateness. Furthermore, as previously described it seems that the main health state categories (<8, 8-25 and >25 seizures per month) have been established for statistical convenience based on the cannabidiol trial data and not clinical relevance. Therefore, **there appears to be no rational basis for adopting their use in our patient simulation model that uses patient profiles based on the fenfluramine trial data.** The assignment of disutility only to carers whose patients have >8 seizures per month implies that there is no impact on carer quality of life for those patients experiencing up to 7 days with seizures every month, which is unlikely to be the case and also has the perverse effect of penalising treatments that reduce seizures more effectively. The ERG's suggestion that this is a more appropriate	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		approach is therefore open to challenge on several fronts.	
Section 5.2.8, ERG comment b), page 107 states:" *Moreover, as mentioned in section 4.2.5, in the two clinical trials, there were no differences between groups in change from baseline in caregiver quality of life as measured by the EQ-5D-5L – overall health status.*" This statement should be removed as it is irrelevant.	**This statement should be removed.**	Data presented in section 4.2.5. reports changes in all carers EQ-5D-5L scores for all patients in the trial, however the individual level trial data indicates that patient response to treatment was heterogenous. Therefore, within this aggregate carer 5Q-5D-5L data we have a mixture of data from carers whose patients responded well to treatment and those who did not. From the aggregate values presented in section 4.2.5 it is not possible to disentangle the changes in carer EQ-5D-5L. Thus, given we assume changes in carers QoL based on changes in the patients' number of seizure free days impact on carers QoL we only model an impact on carer QoL if the patient is responding well and a reduction in the number of seizure free days is reported. Looking only at the aggregate data presented in 4.2.5 in isolation it is not possible to adjust for potential confounders such as age, comorbidities or disease severity. The regression framework we adopted is therefore appropriate to estimate both patient and carer utilities, and it is not appropriate to compare the regression model outputs with	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		the aggregate summary measure across the whole population. This statement should be removed to avoid misleading the committee and other readers.	
Section 5.2.8 ERG comment b), p.107 states: "*Hence, instead of assuming 0 carer utilities in for individuals who had >20 seizure-free days a month, the ERG assumed a utility of 0.74 (highest estimated utility by the company) for individuals with >20 seizure-free days a month"* The ERG has described this adjustment as assuming a utility of 0.74 (highest estimated utility by the company) for individuals with >20 seizure-free days a month	**This assumption is factually inaccurate and contradicts available evidence, and should be removed from the ERG's proposed base case**	This assumption is inaccurate for multiple reasons: - The use of >20 seizure free days as the cut off for 'maximum' carer utility is completely arbitrary, it seems to be loosely based on the seizure bandings used in TA614, where <8 seizures a month is the best health state. However, this would assume that each seizure occurs on different days, which goes against evidence seen in all trials. Furthermore, the seizure bandings used in TA614, are based solely on the distribution of seizures seen in the cannabidiol trials, which do not necessarily represent the fenfluramine trials. There is no evidence that those with 20 seizure-free days have the same carer quality of life as those that have 28 seizure-free days, and furthermore, the fenfluramine trial data shows that each incremental seizure-free day does in fact affect carer quality of life. The assumption therefore contradicts the available evidence, and it is not factually correct to discard the relevant data we have from the	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		trial population and use the arbitrary assumed health state groupings from a different trial population. - Furthermore, this assumption is inherently biased in favour of a treatment that ensures patients are having just over 20 seizure free days, and punishes treatments that ensure patients have substantially more seizure-free days (or seizure freedom), as the jump in carer QoL from 20 seizure free days to the maximum (as used in the suggested new base case) is more than 0.1, whereas the jump from 27 seizure-free days to the maximum is less than 0.02. This assumption therefore favours treatments that are less effective. Given that the aim of treatment is to reduce seizure frequency and increase seizure-free days, this assumption would seem to reflect a perverse incentive.	

Issue 21 ERG analyses: significant issues and uncertainties in the model modifications made by the ERG that informs their report

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
NOTE: Due to delayed receipt of the R code files containing the modifications the ERG made for these analyses to inform its report, as well as labelling errors in the ERG report received, Zogenix had limited time to check the ERG's analyses as thoroughly as we would have liked. The below Issues are those we have identified in the limited time we have had to check and run the ERG's analyses.			The ERG wants to clarify that all documents were uploaded to NICE in time.
Section 7.1.1.1 adjustment 2b p.121 The changing of discontinuation rates has not been implemented correctly in the file Microsim_ERG	**Correct the code and clarify it wasn't all the discontinuation rates** **Lines 172 177 in the Microsim function_ERG file should be adjusted to:** **if(Trt == 0){** **#Change the titration discontinuation rates base on whether they are on trt or not** **titr.discon < -if(ERG_BC2 == 1) {titr.discon.trt} else {titr.discon.plc}** **trial.discon <- if(ERG_BC2 == 1) {trial.discon.trt} else {trial.discon.plc}** **} else {**	The rates used in the ERG code (at least as outlined by the ERG in the report) are not those presented in the CS, instead they use the placebo rates, and changed the fenfluramine arm rates to match the placebo rates. The ongoing probabilities were correctly implemented, the short term ones for CBD were set to mirror the placebo arm discontinuation in the trial.	The description of ERG analyses was subject to discussion. Based on table 30 of the CS, identical discontinuation probabilities should have been implemented in the model for "Other discontinuation" in the titration and maintenance trial periods, which is what was done in the ERG analyses. However, the ERG indeed used the placebo probabilities instead of the discontinuation probabilities in the trial. The description of the ERG analysis (section7.1.1.1 adjustment 2b) has now been changed accordingly. To assess the impact of using the fenfluramine arm rates instead of the placebo rates, the ERG re-run

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
	titr.discon <- titr.discon.trt **trial.discon <- trial.discon.trt** **}**		the ERG base case using the rates mentioned in table 30 of the CS (in line with the proposed amendment by the company). However, the ERG noticed that also the lack of efficacy discontinuation rates were unequal between both treatment arms. These have also been amended in this revised analysis. This resulted in an ICER of £75,828 per QALY gained for fenfluramine compared to cannabidiol. This analysis has been added as Scenario 4 in the ERG report.
Section 7.1.1.1 2c. ERG new base case p.121 states: "*in the CS, it was possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation. The ERG adjusted the post discontinuation convulsive seizure frequency and convulsive seizure-free days.*" This is not an unequivocal error and	Clarify that **this is a subjective adjustment and move out of the "Fixing errors" section and into the "Matters of judgment" section.** **Clarify where this has been implemented in the code – we have not been able to verify the results**	Regardless of the ERGs comments on the appropriateness of this assumption, this is not unequivocally wrong and therefore should be included as a "matter of judgement", rather than in the "fixing errors section". As described above in the response to section 5.2.2.2, there is strong justification for this assumption, and to remove it means that other assumptions are inherently included in the model,	Not a factual inaccuracy. This has been adjusted in the ERG base case.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
therefore should not be included in this section. We have been unable to verify the results as it is unclear where/how this has been implemented in the code.		particularly regarding the efficacy of treatment. Furthermore, it is unclear where this has been implemented in the code; we could not find any adjustments to reflect this (the only adjustments found when searching for ERG_BC2_1/ERG_BC2 in the base case_ERG and Microsim_function_ERG files were reflecting to 6a and 6b), and therefore cannot verify the results.	
Section 7.1.1.2 p.121 adjustment 3 and 7.1.1.3 adjustments 4a,b and c p121/122 (labelled as 8 on p.121/122) refer to: *"The ERG added SoC as separate comparator in the model by incorporating results from the placebo arm of the trials by running the model twice"* These scenarios are already included in the CS	**Clarification that these scenarios have already been included in the CS, and these are not new scenarios incorporated by the ERG**		Not a factual inaccuracy
Section 7.1.1.3 adjustment 5, p.122	**Remove adjustment 5**	This adjustment is already incorporated in adjustment 4, and no results are presented	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
This is repetition of the change made in adjustment 4. b and c		for it. The inclusion of this adjustment implies that the ERG made more changes than they did. This should be removed	
Section 7.1.1.3 adjustment 9 p.122 and 7.2.1 Table 7.10 refer to: As outlined in the response to Section 5.2.6.5 p102 the calculation used work out that the seizure days reduction is 40% of the seizure reduction is likely incorrect as the data used is not comparable	**The ICER presented in Tables 7.10 should be adjusted to take into account the inaccuracies in section 5.2.6.5** **The ICERs in tables 7.11-7.25 will also be impacted by this change and should be adjusted accordingly** **As the calculations used by the ERG in Section 5.2.6.5 are unclear, it is not possible to say what the ICER should be changed to.**	Factual inaccuracies highlighted in the rest of this document should be incorporated into the modelling conducted by the ERG.	Not a factual inaccuracy
Section 7.2.1 Individual ERG adjustments Given the errors in the implementation of section 7.1.1 (outlined above), the ICERs	**Recalculation of all the ICERs presented in section 7.2.1 to take into account the implemented errors in section 7.1.1 (particularly incorrect adjustment of discontinuation rates and**	The ICERs presented in this section should show the correct implementation of the ERG comments, and should not include adjustments that are subjective (i.e. the removal of some of the treatment effect as described in the reply to section 7.1.1.1 6c)	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
presented in tables 7.2-7.25 are not correct.	**inappropriate removal of placebo effect in the new base case).**		
Section 7.1.2 ERG Scenarios (p.122) Section 7.3 Scenario results (p.130) The three scenarios outlined in this section do not match the 2 scenarios described in the results section 7.3, and it is unclear whether they match the 3 scenario results presented in section 7.3 The two scenarios described and implemented in the code do not reflect the scenarios outlined in sections 7.1.2. and 7.3 Section 7.1.2 describes 3 scenarios (labelled 3,4 and 5,): 3. Use of carer disutilities 4. Discontinued patients reverting to maintenance frequency 5. Changing accidental mortality Section 7.3 outlines 2 scenarios: 1. Exclusion of stopping rule	**Clarification of the scenarios presented in the report, and how they were incorporated into the model code files is required**		Changed accordingly. In the model file; by accident scenario 3 was missing in the submitted model. The model file has been resubmitted to NICE

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
2. Use of carer disutilities Section 7.3 also presents results from 3 scenarios, labelled 1-3 (it is unclear what these refer to, presumably the same mislabeled scenarios outlined in section 7.1.2 above) The model R files outline 2 scenarios, labelled 1 and 2 and described as: 1.Discontinued patients reverting to maintenance frequency 2. Carer disutilities			
Section 7.1.2 ERG Scenarios (p.122) states: "*In TA614, as opposed to adding the carer utility to the patient's utility as was done in the current STA, a carer disutility ([redacted] for >8 - ≤ 25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month) was applied to the two worst health states in the model until a patient died. Hence, the ERG explored the impact of using carer disutilities from TA614.*"	**A clear description of methods and how this scenario was incorporated, and the associated assumptions and justifications is required.** **We are unable to verify the results without this clarification.**	This scenario assumes that patients with 4-20 seizure free days per cycle have a disutility of [redacted], those with 0-3 seizure free days a months have a disutility of [redacted] and those with 21-28 seizure free days a cycle have no disutility. There is no evidence presented to show that these seizure-free day bands align with seizure bands used in TA614 ([redacted] for >8 - ≤ 25 convulsive seizure per month and [redacted] for >25 convulsive seizures per month), and therefore there is no	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG does not describe the method for how this scenario was implemented in the model, and implies that it was implemented in the same way as in TA614. However, this appears not to be the case and therefore this is misleading.		justification for these disutilities. Banding in TA 614 is arbitrarily based on dividing the cannabidiol trial population into three subgroups. If patients in the fenfluramine trials were arbitrarily divided in to three subgroups they may not have the same banding profile. There is also no evidence to confirm that these bandings are representative of the general DS population. This approach is therefore highly questionable and without further information on methods and assumptions invoked by the ERG, it is not possible to verify the ERG's approach or results.	

Issue 22 Dravet syndrome and its management are appropriately described in our submission. The ERG is incorrect to state we did not discuss key aspects of this in our submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 2.1, page 28 ERG comment states: "*...However, the CS did not explicitly discuss cognitive impairment and motor disorders associated with the disease*". This is incorrect.	**This statement should be removed.**	This is incorrect – A whole section of the submission (B.1.3.1.4) specifically discussed cognitive and other developmental comorbidities, and these are mentioned appropriately in other sections of the	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		submission in relation to impact on patient and carer quality of life and carer burden.	
Section 2.1, page 28 ERG comment states: "...*Furthermore, the company did not explicitly mention the stages of Dravet syndrome described as "(1) the febrile or diagnostic stage in the first year; (2) the worsening (preferred to 'catastrophic') stage between one and five years: period with frequent seizures and statuses, behavioural deterioration, and neurologic signs; and (3) the stabilisation stage after five years: convulsive seizures decrease and occur mainly in sleep, myoclonic and absence seizures can disappear, focal seizures persist or decrease; mental development and behaviour tend to improve but cognitive impairment persists, although of variable degree*". This is incorrect	**This statement should be removed**	This is incorrect – the stages of Dravet syndrome are specifically included in the submission. Section B.1.3.1.1 states: "*Dravet syndrome was only recognised as a distinct epileptic syndrome around 40 years ago [2]. It typically presents in the first year of life with recurrent, prolonged convulsive seizures, often triggered by heat such as a mild fever or hot bath, in an otherwise healthy child. From around 1 to 5 years of age, patients experience a progressive worsening in their seizures, including more frequent seizures and prolonged convulsive seizures that may lead to status epilepticus (i.e., a state of continuous seizure that can cause permanent neurological damage, SE). Many patients experience several seizures per day. Additional seizure types, including non-conclusive seizures may also emerge, and everyday occurrences such as physical exertion, emotion, eating, bathing and flashing light may act as seizure triggers. During this worsening phase, developmental delay also becomes evident, together with a spectrum of comorbidities, including ataxia, which affects balance, co-ordination and*	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		speech, and learning difficulties. Patients may also begin to exhibit behavioural disorders, including autism and attention deficit hyperactivity disorder (ADHD), and experience sleep disturbances. In later childhood and adolescence, seizures may stabilise; however, seizure frequency and severity remain high and persist into adulthood, as do the associated developmental impacts and comorbidities". This statement should therefore be removed.	
Section 2.2, page 32, ERG comment states: "*The company's overview of the current pathway is appropriate....However, even though NICE CG 137 highlights that "the ideal treatment strategy is personalised and considers a range of factors including the change in typical seizure patterns over time, seizure types, co-medications, comorbidities, adverse effects, lifestyles, and the personal preferences of patients, families and carers" that personalised component is missing in the CS*". This is incorrect. The ERG goes on to say: "*For instance, the company insists that the ketogenic diet is rarely used and not considered in the appraisal (e.g. see footnote of Figure 2.1). However, research shows that one year after starting the ketogenic diet, 77% of children had*	**Remove the statement claiming the personalised component is missing from the CS, and amend text to make clear that the rationale for excluding KD and VNS was provided, is reasonable, and is aligned with the approach taken in TA614.**	This is incorrect. The submission specifically states in section B1.3.2.2: "*The NICE scope for this current appraisal of fenfluramine references a specific combination of sodium valproate, stiripentol and clobazam [11], and UK data from the DISCUSS study indicates valproate is used by 68% of patients, with clobazam and stiripentol used in 74% and 58% of patients, respectively [16]. However, as noted in NICE CG 137, the ideal treatment strategy is personalised and considers a range of factors including the change in typical seizure patterns over time, seizure types, co-medications, comorbidities, adverse effects, lifestyles, and the personal preferences of patients, families and carers [9]. As different patients may respond to different therapies in*	Not a factual inaccuracy. However, slight wording change to increase clarity.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
achieved a >75% decrease in their seizures.16 Similarly, positioning of vagus nerve stimulation (VNS) in the current treatment pathway is also unclear or missing in the CS, however, research shows that VNS appears to reduce seizure frequency in patients with Dravet syndrome.17 " At no point have we claimed that KD or VNS are ineffective - the rationale for excluding them was clearly provided in Table 1 of the CS as well as the footnote to Figure 2.1. It is misleading to suggest the position of VNS is missing from the CS.		*different ways, it is important that a range of therapy options are available in order to tailor therapy to patients' individual needs.* " It is therefore incorrect to suggest we have not considered the personalised component. The ERG's inclusion of data supporting the efficacy of KD and VNS does not provide any information on the extent to which they are/are not used in practice, and does not negate the fact that if they are used they form part of the background therapy and we do not expect the decision a clinician and patient/carers would face would be between using either fenfluramine or VNS and/ or KD. We expect the relevant decision would be between adding in to background therapy either fenfluramine or one of the other pharmacological add-on therapies recommended by NICE. The large DISCUSS cross-sectional study, which surveyed around 15% of all Dravet patients across Europe, indicates that VNS and KD were currently being used in less than 10% of patients (See Lagae et al 2018), and in 72 UK patients included in the DISCUSS Study, KD was currently being used in <6% of patients (see Pagano et al 2019). Our assumption that KD and VNS are used in a minority of patients and	

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		would form part of background therapy if used, which is also aligned with the approach taken in TA614, is therefore supported. The ERG should therefore clarify its statement to remove any suggestion that this is a source of uncertainty in the clinical and cost effectiveness of fenfluramine.	

Issue 23 The SLRs were appropriate and are unlikely to have missed any relevant evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.11, ERG comment page 42 and Section 5.1.1, ERG comments page 80 states: : "*Embase subject heading terms (Emtree) were used in the search strategy, and although simultaneous searching of Embase.com should automatically identify and search for equivalent MEDLINE medical subject heading (MeSH) terms, it is not clear if this is the case for all MeSH terms. Given the potential limitations of this approach, the ERG considered it preferable to search each database separately, or at least to ensure inclusion of both Emtree and MeSH terms in the search strategy in order to ensure that potentially relevant records were not missed by the search".*	**Clarify that it is unlikely that the collective searches of MEDLINE using both the Embase.com and PubMed platforms missed any relevant evidence.**	The ERG statement omits the fact that MEDLINE was also searched in the PubMed searches and so it is highly unlikely that the collective MEDLINE searches missed any important evidence.	Not a factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.12, ERG comments page 44 and Section 5.1.1, ERG comments page 80 states: "*The ERG noted that the systematic review was limited to studies published in English only. At least one study appeared to have been excluded on the basis of language. The company was asked if any relevant studies were omitted due to this language restriction. They replied that "no relevant studies were omitted from the SLR as a result of limiting the publications to English language"*". This omits the fact we demonstrated this was the case.	**Clarify that we re-ran the searches to demonstrate that no relevant evidence was missed by the English language limit.**	We replied with this because we actually demonstrated by re-running the searches with English language limit removed that the English language limit had no impact on the identification of relevant evidence.	Not a factual inaccuracy Details on re-running searches are presented in sections 4.1.1 and 5.1.1, respectively

Issue 24 Key evidence has been omitted from the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ERG report omits key evidence we provided in our submission that demonstrates clobazam is not a treatment effect modifier of fenfluramine	**Include evidence demonstrating that clobazam is not a treatment effect modifier of fenfluramine (which is supported by the fact the label does not require concomitant use of clobazam)**	We note that the ERG has omitted any reference to the analyses that were provided in the CS that indicate clobazam is not a significant treatment effect modifier of fenfluramine (supported by the fact the label does not require concomitant use of clobazam, which is in contrast to cannabidiol and stiripentol). As the ERG raises the concomitant use of clobazam as a key issue in several places throughout the report, this omission is concerning and should be rectified to ensure	Not a factual inaccuracy. All relevant information has been presented in the ERG report, e.g. several times the expected label population is referred to.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
		the committee and other readers are provided with key data / to avoid misleading the committee and other readers.	
ERG report omits the fully incremental analyses of SoC vs cannabidiol vs fenfluramine, which demonstrate that fenfluramine extendedly dominates cannabidiol.	**Include the results of the fully incremental analyses demonstrating that fenfluramine extendedly dominates cannabidiol.**	The ERG has completely omitted and failed to acknowledge the fully incremental analyses we provided in the response to clarification questions that demonstrate fenfluramine extendedly dominates cannabidiol. As the ERG has included the results of the comparison of cannabidiol vs SoC from these analyses in order to further a flawed comparison of the outputs of our model and those of the TA614 model, we are concerned that the ERG has neglected to provide the full results of this fully incremental analysis. This should be rectified in order to provide the committee and other readers with the opportunity to consider the evidence we provided.	Changed accordingly. We have now added the results of this analysis to section 6.3 of the report: "In response to question C10 of the clarification letter, the company presented a fully incremental analysis of SoC AEDs, add-on CBD and add-on fenfluramine in a scenario, which showed that add-on fenfluramine extendedly dominated add-on CBD".

Issue 25 Range of other inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.2 on page 51, incomplete first sentence: "*The company stated that their primary hypothesis was that the mean convulsive seizure frequency per 28 days*." This sentence appears to be incomplete, as doesn't say what the hypothesis was regarding mean CSF per 28 days	**Complete the sentence.**		Incomplete sentence amended
Section 4.4, page 73 states: "*...in Study 1 approximately 55% were also taking clobazam …*", and on page 74 states: "*The cannabidiol data used in the NMA were for those patients also receiving clobazam but this was not the case for the fenfluramine data from Study 1 as only around 55% were also on clobazam.*". This should be 59%.	Text should be amended to: **...in Study 1 approximately 59% were also taking clobazam …"**	As per the Lagae 2019 publication of Study 1.	Changed accordingly
Table 5.7 p.90: The min/max for concomitant stiripentol use have been left blank	**The min/max for concomitant stiripentol use and motor impairments should read: N/A**	Leaving these values blank implies that the min and max have been omitted but as categorical variables, these columns are not applicable.	Changed accordingly
Figure 5.3 p.94	**Clarification of title and x axis label**	It is unclear what these graphs are displaying- it is assumed they are showing the mean seizure frequency/seizure free day frequency in a specific group per cycle(?) using the bootstrapped data.	Changed accordingly
Section 5.2.6.4.1 on page 100 states: "*Due to the differences between general epilepsy and DS in terms of*	**Replace 'cycles' with 'seizures'**	Language correction to ensure accuracy.	Changed accordingly

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
seizure frequency, the company linearly extrapolated the RR of SUDEP by seizure frequency (assuming a plateau for ≥ 780 seizures annually which correspondents to 60 cycles per 28 days) to be applicable to the seizure frequencies observed in DS". The 780 annual seizures corresponds to 60 seizures per 28 days (not cycles).			
Section 6.2 p.115 states: "*The ICER exceeded the WTP threshold of £30,000 (Figure 6.1) in these DSA analyses*." This is incorrect as 2 of the analyses in the DSA resulted in an ICER below £30,000	**This sentence should be changed to reflect that not all the analyses in the DSA were above the £30,000 WTP threshold.**	The ICER for the minimum value for carer utilities, and the maximum value for weight utilities were both below £30,000 therefore the statement included in the report is incorrect	Changed accordingly
Section 6.3 p.117 *The results showed ICERs ranging between £8,532 and £104,835 per QALY gained.* The minimum ICER calculated in scenario analyses is incorrect.	**This statement should be corrected to reflect that fenfluramine was dominant in one of the scenarios.**	The lowest ICER calculated in scenario analyses was when the cannabidiol dosage was increased to 20mg/kg/day, in which fenfluramine is dominant. This should be reflected in the range quoted in the text.	Changed accordingly
Section 7.2.1 Tables all include a row containing *"CS base-case".* This should be removed	**Remove the row that states "*CS base-case*" from all tables reporting the ERG's analyses.**	The results presented in the tables in this section are not the CS base case and this row should be removed to avoid confusing or misleading the committee and any other readers.	Changed accordingly

NICE National Institute for Health and Care Excellence

Technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Thursday 17 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the issues below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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.

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.

About you

Your name	**Dr Toby Toward** Head of Market Access, Europe. Zogenix International Ltd
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Zogenix International Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Company: Research, development and manufacturer of fenfluramine (Fintepla)**

Key issues for engagement

- **We welcome the opportunity to respond to the ERG Report as part of the Technical Engagement phase of the appraisal process.**
- **We do, however, believe it is important to highlight that we have previously provided extensive comments in our: 'Responses to Clarification Questions'; in the 'Factual Accuracy Checks' document on the draft ERG report; and at 'Technical Engagement Meeting(s)', which had addressed and clearly refuted many of the items that have been again re-listed in the latest ERG report as "Key Issues".**
- **As a consequence, we are deeply concerned that the ERG Report has not taken these extensive comments, the evidence-base and compelling arguments into consideration.**
- **We are therefore in the position that we need to restate that we do not agree that the ERG Report provides an objective, balanced or fair view of our submission, the model or the evidence provided:**
    - **Several of the items listed as "Key issues" are not actually issues that would have a meaningful impact on the decision-making process.**
    - **There is a lack of context and qualification of several issues listed in the report, which precludes a fair interpretation.**
    - **There are repeated listings of the same point as separate "Key issues", which has the potential to create a false impression of the extent of uncertainties and their interpretation in the evidence we have provided.**
    - **The language and tone adopted in the ERG Report substantially overstates incorrect assumptions, that are unnecessarily alarmist and is also not conducive to an objective understanding.**

- **We understand that this appraisal is one of the first to go through the revised Technical Engagement process, which no longer provides a Technical Engagement Report. As a consequence, an important part of the moderating influence from the NICE Technical Team has been excluded from the process. This in turn means that there is now no insight into NICE's perspective on the appraisal going into the Appraisal Committee meeting (scheduled for the 4th Feb 2021).**
- **Given the concerns we have highlighted with the ERG Report, we trust that the materials produced by NICE for the Appraisal Committee meeting will give full consideration to the full range of evidence and the extensive comments provided in our submission, the Responses to Clarification Questions, and the Factual Accuracy Checks document, as well as this document.**
- **As the revised Technical Engagement process has removed an early view of NICE's perspective on the issues raised in the ERG Report, we respectfully request that the consolidated slides are provided to us in a timely manner so that we may attend the Appraisal Committee meeting with knowledge of any truly outstanding issues and a shared understanding of NICE's perspective on this important and much needed new treatment for Dravet Syndrome patients and their families in the UK.**

Please use the table below to comment on key issues raised in the ERG report. You may also provide additional comments on any key issues that you would like to raise but which are not covered by the existing issues.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	**YES**	**There is no reason to believe that the effects of fenfluramine observed in the RCTs will differ in adults. This is supported by open label extension and real-world evidence studies, the view of the EMA in licensing fenfluramine in this population, and by the clinical experts consulted by the ERG. We therefore do not believe this is a Key issue that should influence decision-making, as outlined in the Factual accuracy check response document (pages 10-13). Given there are no clinical reasons to doubt the efficacy and safety of fenfluramine in adults, nor its cost effectiveness, any differentiation in access by age would be unwarranted.** In summary: • We agree there is a lack of evidence in adults from the RCTs. There was also a lack of evidence in adults in the RCTs of cannabidiol; however, cannabidiol was recommended for use in its full licensed population (including adults) in NICE TA614. • In our submission, data from the OLE and the RWE studies have been provided that support the use of fenfluramine in adults. • Furthermore, the CHMP has issued a positive recommendation for the granting of a market authorisation in DS patients aged 2 years and older, without restriction on use in adults, based on the same RCTs and the RWE data provided to NICE and the ERG • The clinical experts consulted by the ERG agreed that the results of the RCTs are applicable to adults.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• These data are further supported by a recently presented paper from the US Early Access programme (Perry et al.,2020), highlighting that the benefits of fenfluramine in adults is considered comparable to that demonstrated in children [new evidence]. • Based on the above, the clinical data are adequate to support the use of fenfluramine in adults. • The Association of British Neurologists as a stakeholder in the process states: "Both adults and children should be able to benefit from the option of having fenfluramine" (page 337 of technical engagement papers). • The question of whether seizure frequency reduces at age 18, as implemented in the model, is irrelevant to the question of whether there is evidence to support the use of fenfluramine in adults. We however demonstrated that the assumption of a reduction in seizure frequency at age 18 has minimal impact on the ICER (Table 51 of the CS). • Given there are no clinical reasons to doubt the efficacy and safety of fenfluramine in adults, nor its cost effectiveness (as shown in the CS), compared with younger patients, any differentiation by age would be unwarranted, and would potentially introduce equality issues. • Collectively, the limited data in adults should not be viewed as a Key issue for decision-making. **Reference to previously provided documents** • CS Table 51 • CS section B.2.13.3.2 • Factual accuracy check response document, pages 10-13 **New evidence provided** • Perry et al. Fenfluramine (FINTEPLA) provides comparable clinical benefit in adults and children with Dravet syndrome: Real-world experience from the US Early Access

Key issue	Does this response contain new evidence, data or analyses?	Response
		Program. Virtual American Epilepsy Society (AES) Annual Meeting, December 4-8, 2020
Key issue 2: Not all relevant comparators have been fully investigated	**NO**	**This claim is factually incorrect. We fully investigated all relevant comparators in the CS and provided a detailed explanation on why this claim is incorrect in the Factual accuracy check response document (pages 34-39). We therefore do not believe this is a Key issue.** In summary: • The final scope of this appraisal indicates the comparator as "established clinical management without fenfluramine", which *may* include combinations of 8 different listed therapies. • It is neither feasible nor reasonable to expect comparisons against all possible combinations of these different therapies. • VNS and KD were included in the list of 8 different therapies but are considered as part of standard background therapy – we do not believe the clinical decision will be a choice between fenfluramine (or indeed any other drug therapy) versus KD or VNS, i.e. KD and VNS are not relevant comparators for fenfluramine. • This was explained in the CS (Table 1 and Figure 2), and was explained again in the Response to Clarification Questions B5a. • This also is the same principle of approach implicitly accepted in the TA614 appraisal of cannabidiol. • We appropriately focused our comparisons of add-on fenfluramine against other add-on therapies that are licensed and/or are recommended as add-on therapies in existing

Key issue	Does this response contain new evidence, data or analyses?	Response
		NICE guidance (CG137 and TA614). The only relevant comparators are therefore add-on clobazam, add-on stiripentol and add-on cannabidiol, or continued SoC AEDs. This is fully explained in the CS section B1.3.4. • It is not possible to provide analyses of fenfluramine vs clobazam as there are no RCTs of clobazam in Dravet syndrome, as clearly demonstrated by the SLR results presented in the CS (section B2.9 and Appendix D). • It is not possible to provide analyses vs stiripentol as the endpoints of the stiripentol RCTs are limited and incompatible with the endpoints of the fenfluramine trials. A Cochrane review concluded that the stiripentol RCTs are associated with uncertainty and provide moderate to low quality evidence. For the same reasons no comparisons vs stiripentol were considered in the TA614 appraisal of cannabidiol. This is clearly explained in the CS section B2.9 and was explained again in the Response to Clarification Questions B3a and B3b. • We provided analyses vs cannabidiol as a primary base case because cannabidiol was appraised by NICE [TA614] and is accepted as an option in the add-on therapy pathway, alongside stiripentol. • We have provided analyses of add-on fenfluramine vs SoC AEDs alone, in scenario analyses in the CS (Table 52), noting that this scenario is less reflective of a true clinical decision a physician/patient would likely make if a patient was in need of a new therapy, as it infers that a patient would be retained on an inadequate SoC, if cannabidiol could be offered. • We have also provided a scenario whereby patients that are unable to receive clobazam ('clobazam undesirable'), and thereby could also not receive stiripentol or cannabidiol (both requiring clobazam, per licensed indication), could alternatively receive add on fenfluramine to their SoC without clobazam.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• We have also provided additional, fully incremental analyses in the Response to Clarification Questions C10, which showed that fenfluramine extendedly dominates cannabidiol with clobazam. • It is therefore incorrect to state that we have not fully investigated all relevant comparators, or (as suggested in the ERG report) that we have not provided analyses against SoC AEDs. The ERG report has not been amended accordingly and so does not provide a fair reflection of the evidence base we have presented. • See also related response to Issue 6 (base case comparators) **Reference to previously provided documents** • CS section B1.3.4, section 2.9, Table 1, Figure 2, Table 52, Appendix D • Response to Clarification Questions B3a, B3b, B5a, C10
Key issue 3: Short-term nature of the included randomised trials	**NO**	**We have previously provided a detailed response explaining why we do not believe this is a key issue in the Factual accuracy check response document (pages 13-14).** In summary: • The trial design was adequate to demonstrate the efficacy and safety of fenfluramine as a regulatory approved therapy for a rare disease such as Dravet syndrome. • The fenfluramine trial durations were the same as the cannabidiol trials and were somewhat longer than those for stiripentol; both of which are recommended as add-on therapy options by NICE. The convulsive seizure endpoints are also aligned with the cannabidiol trial endpoints. • It is therefore incorrect to state that trial durations may be inadequate, when other therapies with the same or shorter trial durations have been recommended by NICE.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• We also provided data from the OLE study, which the ERG report (Table 1.4) acknowledges indicates efficacy could be maintained for at least 3 years. • We also provided published prospective RWE data demonstrating efficacy over 5 years, and further observational data relating to its use (and sustained efficacy and maintained safety profile) for up to 27 years. • The suggestion in the ERG report that the RCTs may not be adequate appears to ignore this additional supportive and compelling evidence of the sustained efficacy and safety of fenfluramine with long-term treatment. • The trials were not powered for mortality (or for status epilepticus or SUDEP) and it is unreasonable to expect that they ever could be. This was fully explained in the Response to Clarification Questions (C14). The modelling of survival was therefore appropriately informed by Dravet syndrome specific mortality data from the literature (Cooper et al and Schmuely et al), which observed that SUDEP and status epilepticus were the primary causes of premature death. • The Association of British Neurologists as a stakeholder in this process states in its responses that the main aim of treatment “is to improve seizure control”, which “in turn can”…”reduce the risk of status epilepticus and SUDEP”. and further that they expect fenfluramine to increase length of life more than current care “if seizure freedom or improved control of seizures, especially convulsive seizures, is achieved”. • As there is no doubt that fenfluramine improves convulsive seizure control compared with SoC AEDs and cannabidiol (the relevant comparators against which it is possible to compare fenfluramine) there is little reason to doubt there would also be a mortality benefit with fenfluramine. • In contrast to the fenfluramine OLE study data, which the ERG acknowledges supports sustained efficacy for up to 3 years, the OLE study data for cannabidiol presented in

Key issue	Does this response contain new evidence, data or analyses?	Response
		the Epidyolex® SmPC, suggests a loss of efficacy of approximately 25% over 48 weeks of treatment. • The collective evidence on the short and long-term efficacy and safety of fenfluramine is arguably more complete than that for any other therapy that has been recommended by NICE for the testament of seizures in DS. • The ERG's claim that this is a key issue is therefore not reflective of the evidence that has been provided in support of fenfluramine. • See also related response to Issue 9 and issue 14 (mortality) **Reference to previously provided documents** • CS section B2.13.1.2, section B3.3.3 • Response to Clarification Questions C13, C14 • Factual accuracy check document, pages 13 to 14
Key issue 4: Adverse events and need for monitoring	**NO**	**We have provided a detailed response in the Factual accuracy check response document (pages 23-34), reiterating what we had demonstrated in the CS and Response to Clarification Questions document; that the model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. The suggestion by the ERG that adverse events and monitoring are "Key issues" does not fairly reflect the available data on adverse events; nor does it fairly reflect the evidence and analyses we have provided and is therefore open to misinterpretation. The ERG report should clarify that our approach to modelling adverse events and monitoring are not Key issues that could impact decision-making.** In summary:

Key issue	Does this response contain new evidence, data or analyses?	Response
		• Adverse events (AEs) and the need for monitoring were appropriately considered for inclusion in the model. • There was no meaningful difference in AEs between fenfluramine and placebo (i.e. SoC AEDs) in the fenfluramine RCTs in the incidence of serious TEAEs, as explained in the CS (section B2.10). • At the time of our submission, adverse event data for cannabidiol specifically in the licensed subgroup (taking concomitant clobazam) were not available. However, these data became available in a published review (Gunning et al, 2020) shortly after our submission. The data in Gunning et al (2020) indicate there is little difference in the incidence of TEAEs between fenfluramine and cannabidiol (with clobazam), but the incidence of serious TEAEs and incidence of somnolence was notably higher for cannabidiol (with clobazam) than for fenfluramine. • Gunning et al (2020) also reported discontinuation rates due to AEs with cannabidiol (with clobazam). Comparison of discontinuations due to adverse events were not meaningfully different between cannabidiol (with clobazam) and fenfluramine. • In our model, the overall discontinuation rates include discontinuation due to AEs that would have been observed in the trials (including any serious AEs). • Minor adverse events (e.g. diarrhoea, fatigue, etc) occurred in both the fenfluramine and cannabidiol arms, and these were generally not severe and so would not have a significant additional impact on resource use, costs or utilities other than that already included (e.g. monitoring during routine healthcare visits). Not explicitly modelling any specific additional impact of an AE(s) in the model is therefore justified on the basis of both: no differential rates of AEs are reported; and the expected minor impact of the actual AE types reported for fenfluramine and cannabidiol vs placebo.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• The need for monitoring for weight loss is common to cannabidiol, stiripentol and fenfluramine, and so there is no differential burden. Weight would be routinely monitored and managed as part of the routine/ongoing healthcare visits which are already accounted for (including their associated cost) in the model. • The need for cardiac monitoring with fenfluramine is precautionary based on a historical association with valvular heart disease and pulmonary hypertension when fenfluramine was used at far higher doses for the treatment of obesity in adults. This routine monitoring is fully accounted for in the model. We note that in "Key issue 13" the ERG have acknowledged that the model does include these costs associated with routine cardiac monitoring. • There is no evidence of any cases of valvular heart disease or pulmonary hypertension with fenfluramine at the doses used in Dravet syndrome. There have been no cases reported in the RCTs, the OLE study or in RWE studies including use for up to 27 years. It is therefore entirely appropriate that the model does not include any resource use, costs or disutilities for such (hypothetical) adverse events. • Therefore, as has been explained in the CS, in the Response to Clarification Questions B10, C16b, C20, and in great detail in the Factual accuracy check response document (pages 23-34), the capturing of adverse events in the model is appropriate, and the need for routine cardiac monitoring has also been appropriately reflected in the model. • We note that the ERG report (Table 1.5) states that an alternative approach is not suggested, and the ERG simply wanted to highlight the "issue". The ERG also confirmed during the Technical Engagement meeting of 10th December 2020 that the approach to modelling adverse events and monitoring were not major issues. • Given the above, there is no factual justification for the ERG to highlight 'an incorrect capturing of adverse events' or 'cardiac monitoring' as Key issues that could impact on

Key issue	Does this response contain new evidence, data or analyses?	Response
		decision-making; the model accounts for adverse events and cardiac monitoring to the full extent that it is appropriate to do so. • The repeated presentation of adverse events and monitoring as three separate Key issues in the ERG report (Key issues 4, 10 and 13) is therefore particularly unwarranted, it unnecessarily overstates a relatively minor point, and as mentioned above is an example of distortion that has the potential to create an erroneous impression that there are multiple serious issues with the evidence we have provided. • We refer to the ERG and NICE committee to the comments of stakeholders in the process, that further support the safety profile of fenfluramine and the approach we have taken to adverse events and monitoring in our model: o **Dravet Syndrome UK** ▪ P313. "*There was some initial apprehension around fenfluramine due to the history of the drug as a diet pill (children/adults with Dravet Syndrome often have problems with eating) and its withdrawal for this use due to cardiac side effects. However, among families who have trialled fenfluramine these soon dissipated."* ▪ P313. "*Generally, fenfluramine appears well-tolerated and, anecdotally, side effects do not seem to have been an issue to date among our community of families. If cardiac monitoring is required, this does pose an additional burden, however, because parents/ carers are in desperate need of treatments that improve Dravet-related seizures and other comorbidities, they will adhere to monitoring. It's also important to note that if fenfluramine does not have a noticeable benefit, parents/carers will not want to continue with an additional treatment*

Key issue	Does this response contain new evidence, data or analyses?	Response
		given that their child/adult with Dravet Syndrome will already be on multiple medications." o **Association of British Neurologists** ▪ P333. "*The main adverse effect of concern is of cardiac valve structural change, which arose from previous use of the agent in combination with another drug for the treatment of obesity. However, available data suggest this is not an important issue for use of fenfluramine alone, at the doses currently recommended. The adverse effect profile of fenfluramine does not otherwise raise specific concerns in comparison to other available treatments."* ▪ P335. Q: Are there any adverse effects that were not apparent in clinical trials? A: *Not currently*. ▪ See also related response to Issue 10 and 13 (monitoring and adverse events) **Reference to previously provided documents** • CS section B2.10 • Factual accuracy check document, page 23 to 34
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment	**YES**	**The approach we have taken in the model in the CS reverts patients who discontinue treatment back to their individual baseline seizure frequency before randomisation in the trials. As there is no evidence of the effectiveness of fenfluramine being driven by a significant placebo effect component in the trials, we believe our approach is justified. The ERG's suggested approach of reverting patients back to seizure frequency they experienced whilst receiving placebo treatment in the trials would artificially elevate the effectiveness of discontinued treatment in the long term, which would bias the model**

Key issue	Does this response contain new evidence, data or analyses?	Response
versus patients that discontinued treatment. **Subsequent treatment post-discontinuation** (included as an issue in the Technical Engagement meeting 10th December 2020): Only the primary intervention in each strategy was considered, i.e. if patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC		**against the most effective therapy that maintains patients on treatment for longer. Following the Technical Engagement Meeting we have further explored the impact of these assumptions by removing the placebo effect from the model entirely. The resulting ICER is lower than our base case ICER in the CS, indicating, in contrast to the ERG's suggestion, that our approach in the CS does not overestimate the treatment effect.** In summary: • Our model in the CS reverts patients back to baseline seizure frequency. This baseline is measured after patients have been screened but before being selected for inclusion in the trial and receiving a treatment intervention. Therefore, it is less likely that there would be significant regression to the mean between the baseline and post-randomisation period influencing the observed treatment effects of fenfluramine vs placebo, compared with trials where baseline is estimated based on screening measurements or in achieving a defined treatment success criteria. • The ERG's suggested approach of reverting patients back to a placebo-level of seizure frequency (rather than to their baseline) would maintain the comparator arm efficacy at an artificially elevated level for the patients' lifetime despite the discontinuation of the comparator treatment. This might be an appropriate approach if the observed treatment effect included a substantial placebo effect component, and the difference in efficacy between the intervention and the placebo arm of the RCTs was due to regression to the mean. However, the placebo response in the fenfluramine RCTs was low, and as acknowledged by the ERG elsewhere in its report, the OLE study data indicate that the effects of fenfluramine observed in the RCTs is sustained for up to 3 years. It is therefore unlikely that the treatment effect of fenfluramine observed in the

Key issue	Does this response contain new evidence, data or analyses?	Response
		RCTs is driven by a substantial placebo effect, that would likely wane over time. In the absence of evidence to suggest that the placebo effect should be maintained over the lifetime of patients who have discontinued therapy, the ERG's approach is therefore considered not justified by the evidence nor more robust than the approach used in the CS. • It should be noted that in the CS base case, a placebo effect is already included in the model when fenfluramine is being compared to SoC (excluding cannabidiol), which is detrimental for fenfluramine and therefore is considered a conservative assumption we have already taken. This assumes that a patient currently receiving their existing SoC, who stays on that SoC, receives a 'placebo effect' treatment benefit at the point of alternatively receiving a fenfluramine intervention. Furthermore, it would be unlikely that this 'placebo effect' benefit would persist in the long term, particularly for a refectory patient that discontinues therapy for a lack of therapeutic effect, and when there are limited follow-on therapeutic options available for patients. Critically, this approach to return patients to their placebo, rather than to their baseline assumes all of the placebo effect is due to regression to the mean. • Following the Technical Engagement Meeting we have further explored the possible impacts of the assumption of reverting patients back to a placebo-level rather than their baseline level of seizure frequency after treatment discontinuation. • In looking to support the ERG's request, we have undertaken analyses whereby the placebo contribution of seizures has been removed from the model entirely. Therefore, the treatment effect is applied to patients' baseline seizure frequencies to model patients on treatment, and upon discontinuation patients have the treatment effect removed so that they experience their baseline seizure frequency. Compared with cannabidiol, our primary base case ICER reduced from £31,773/QALY to

Key issue	Does this response contain new evidence, data or analyses?	Response
		£21,255/QALY. This indicates the base case we provided in the CS was not overestimating treatment effects for remaining on therapy compared with the discontinued comparator as was suggested by the ERG. Further details, including results of the fully incremental analysis are provided in the table Summary of changes to the company's cost-effectiveness estimate(s) below. • Regarding the lack of subsequent treatments following discontinuation, it should be noted that this is not applicable across all positionings of fenfluramine in the add on therapy pathway, and it is unreasonable to expect there are data to support all possible combinations of sequential therapy. The reversion of patients to SoC AEDs following discontinuation of fenfluramine and cannabidiol is a pragmatic approach that may actually be conservative: o When used as a first-line add-on therapy in patients unable to use clobazam, by definition there are no other follow-on therapies beyond SoC AEDs (as stiripentol and cannabidiol are both only licensed for use in combination with clobazam). Reversion to SoC AEDs is therefore entirely justified. o When used in patients who are already taking stiripentol, the addition of fenfluramine is likely to represent an end of line use. If fenfluramine was discontinued then it is theoretically possible that cannabidiol could subsequently be added, and vice versa; however, there are no specific data to support the use of fenfluramine following failure of cannabidiol or vice versa. As these patients are at the end of line having "failed" with several previous lines of therapy including fenfluramine, their capacity to benefit beyond SoC AEDs is likely to be low. Reversion to SoC AEDs includes reversion of both the effects and costs to those of SoC AEDs. As fenfluramine is more effective than

Key issue	Does this response contain new evidence, data or analyses?	Response
		cannabidiol, patients on cannabidiol are likely to revert to the lower costs of SoC AEDs at a greater rate than with fenfluramine, which reduces their accrued costs more quickly than with fenfluramine. o When used in patients who are not taking stiripentol, the same issues of data availability apply o It appears that the model in the TA614 appraisal followed the same approach. **Reference to previously provided documents** • ERG report p.87/88 • Factual accuracy check p50-54
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**NO**	**The ERG report includes this statement and fails to report the extensive additional analyses provided to compare fenfluramine against SoC AEDs (as mentioned previously in "Key issue2"); we provided a full range of cost effectiveness analyses in the CS and in the Response to Clarification questions, which reflect the full licensed indication for fenfluramine against all relevant comparators for which data are available. It is incorrect to suggest our cost effectiveness analyses are restricted to people receiving clobazam. This was fully explained in the 'Factual accuracy check' response document (pages 39-44), but has not been adequately addressed in the ERG report.** In summary: • We have provided a primary economic analysis of add-on fenfluramine against add-on cannabidiol (with clobazam) for the fully justified reasons stated in Document B (Table 1); with a secondary/scenario analyses against continued SoC AEDs with or without

Key issue	Does this response contain new evidence, data or analyses?	Response
		clobazam, to support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. • This was explained in CS section B1.1 and section B1.3.4, with results of the secondary analyses provided in CS (Table 52). • This point was also reiterated in the Response to Clarification Questions C3, but ignored. • We also provided fully incremental analyses (SoC AEDs vs cannabidiol vs fenfluramine) in populations taking clobazam and also irrespective of clobazam use in Response to Clarification Question C10, which showed that **fenfluramine extendedly dominates cannabidiol plus clobazam (see Table 1)**. • The implications of the ERG including this (primary economic analysis against cannabidiol plus clobazam) as a "Key issue", is that the scenario analyses provided in the CS and the fully incremental analyses provided in the Response to Clarification Questions are not presented in the ERG report to inform committee decision-making (see below). We believe this is wrong. In the context of having provided a full range of cost effectiveness analyses, the fact we had a primary analysis against cannabidiol plus clobazam in the CS should not be considered a key issue. • By listing this as a key issue, whilst also neglecting to fully report the analyses we have provided against SoC AEDs, the ERG report has great potential to mislead the committee and other readers who understandably may not have the opportunity to read through the entirety of the CS in order to realise these were clearly provided. As a consequence, the committee are therefore not in a position to have reasonably been able to consider the full range of presented cost effectiveness analyses and fully incremental analyses provided. • The ERG report is therefore incorrect to suggest our cost effectiveness analyses are restricted to people receiving clobazam in whom cannabidiol is recommended, when we have provided a full range of cost effectiveness analyses across the full licensed

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
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indication for fenfluramine, including analyses irrespective of the use of concomitant clobazam.
• We note that this issue is very similar to the stated Key issue 2. In addition to not actually being a key issue when considered in the context of the full range of analyses that have been provided (but which have been omitted from the ERG report), the presentation of this as a separate Key issue has the potential to create an erroneous impression that there were many serious issues with the evidence we have provided. This is not factually justified.

Table 1. Fully incremental analysis – assuming the proportional use and costs of clobazam as per the base case analysis
<table>
<tr><th>Treatment</th><th>ICER compared to next most effective AED</th><th>ICER compared to underlying SoC AEDs</th></tr>
<tr><td>SoC AED (trial data)</td><td>-</td><td>-</td></tr>
<tr><td>Cannabidiol (with clobazam) + SoC AED</td><td>£69,478/QALY</td><td>£69,478/QALY

(Extendedly dominated by fenfluramine + SoC AED)</td></tr>
<tr><td>Fenfluramine + SoC AED</td><td>£31,638/QALY</td><td>£50,968/QALY</td></tr>
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</td></tr>
</table>

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>
Fully incremental analysis – assuming all patients receiving clobazam amongst their SoC AEDs.
<table>
<tr><th>Treatment</th><th>ICER compared to next most effective AED</th><th>ICER compared to underlying SoC AEDs</th></tr>
<tr><td>SoC AED (trial data) including clobazam</td><td>-</td><td>-</td></tr>
<tr><td>Cannabidiol (with clobazam) + SoC AED</td><td>£64,271/QALY</td><td>£64,271/QALY

(Extendedly dominated by fenfluramine + SoC AED)</td></tr>
<tr><td>Fenfluramine + SoC AED including clobazam</td><td>£37,577/QALY</td><td>£51,205/QALY</td></tr>
</table>
See also related response to Issue 2 (base case comparators).

Reference to previously provided documents

CS Table 1 and 52
Response to Clarification Questions C3, C10
Factual accuracy checks document pages 39 to 44

</td></tr>
<tr><td>Key issue 7: The company implemented a treatment stopping rule for all patients</td><td>NO</td><td>We proposed a 30% stopping rule for fenfluramine in our base case in line with that adopted for cannabidiol in TA614. This ensures the appropriate ongoing clinical and cost-effective use of fenfluramine. We do not believe this is a controversial proposal</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
whose seizure frequency was not reduced by at least 30% at 6 months.		**and we do not believe this constitutes a Key issue in the way presented in the ERG report, as explained in our response to the Factual accuracy check (pages 57 to 58).** In summary: • We are proposing that a stopping rule is applied in line with that adopted for cannabidiol in TA614. This will ensure fenfluramine is continued only in those in whom it is clinically and cost effective. • We explored the impact of 3 alternative stopping rules, and for completeness the removal of a stopping rule, in the Response to Clarification Questions C9. However, if the impact on the ICER from removal of the stopping rule for fenfluramine is informative for decision-making then one could argue so is the removal of the stopping rule for both fenfluramine and cannabidiol, for which the ICER reduces to <£20,000/QALY. • We note that the responses of the Association of British Neurologists, on page 328 of the Technical engagement papers, states that "*achieving a 30% reduction in convulsive seizure frequency is an important outcome for patients*", and on page 332 notes that "*it is likely that rules similar to those for cannabidiol, which has established a precedent, should be applied when starting or stopping fenfluramine*" (which would include the 30% stopping rule). • As the model already accounts for discontinuations, and appropriately does not include a waning of treatment effect for fenfluramine, the implementation of further stopping rules every 6 months is not warranted – the stopping rule after the first 6 months would remove those patients who do not achieve the required 30% reduction in convulsive seizure frequency. • As we are proposing this stopping rule for fenfluramine, and this is aligned with that accepted for cannabidiol in TA614 (and the views of the Association of British

Key issue	Does this response contain new evidence, data or analyses?	Response
		Neurologists), we do not believe our proposal of a stopping rule is a Key issue as presented by the ERG. **Reference to previously provided documents** • CS section B3.3.5.2 • Response to Clarification Questions C9 • Factual accuracy checks document pages 57 to 58
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**YES**	**The fenfluramine clinical trial data demonstrate that the reduction in convulsive seizure days and convulsive seizure frequency are proportional on a near 1:1 basis, validating our approach. The ERG's estimate that the reduction in convulsive seizure days is only 0.4x the reduction in convulsive seizure frequency is flawed, and as a result all ERG ICER estimates based on this assumption are incorrect.** In summary: • As patients with Dravet syndrome may experience high seizure frequencies, with sometimes multiple seizures per day, we considered that **convulsive seizure-free days** (i.e. days with no seizures) would be a more appropriate determinant of quality of life than **convulsive seizure frequency** (i.e. the number of seizures over a 28 day period). This view was also supported by the physicians and patient advocacy groups, in the development of UK patient pathways research report (provided as supplementary information to the CS). • It was therefore necessary to derive convulsive seizure free days as the inverse of assessing convulsive seizure days observed in the trial. • Sufficient data on convulsive seizure days in the subgroup of patients in the cannabidiol trials taking clobazam were not available to us

Key issue	Does this response contain new evidence, data or analyses?	Response
		• Given the close relationship between convulsive seizure frequency and convulsive seizure days we applied the same proportional reduction in convulsive seizure frequency (taken from the NMA) to estimate convulsive seizure days. • The ERG, based on an observation that treatment effects in terms of a percentage change in 'seizure free days' were approximately 40% of the treatment effect seen on the 'percent change from baseline in convulsive seizure frequency', decided to reduce the estimated treatment effects in seizure days by 40% in the model. • However, **it is not valid to directly transfer a percentage reduction in the 'percent change in the convulsive seizure frequency' and apply it directly as a percent change in 'seizure free days per 28 day period'**: o **A percentage change in seizure free days** per 28-day period will in general not be the same as the **negative change in days with seizure** per 28-day period. o e.g. If a patient goes from 1 convulsive seizure to 0 per cycle, this is 100% reduction in convulsive seizures. However, this same patient would go from 1 seizure day per cycle to 0 seizure days per cycle, this a 100% reduction in seizure days (1/1). Conversely, in terms of seizure free days, this equates to 27 seizure free days per cycle going to 28 seizure free days per cycle, an increase of 3.7% (1/27). • Therefore, it is not possible to make inferences about the relationship between a percentage change in the 'percent change in the convulsive **seizure frequency'** being similarly proportionate to a percentage change in '**days with seizure** per 28 days' based on an observed 'percent change in the convulsive **seizure frequency**' to a change in **seizure free days** per 28 day period. • To further support the ERG, we have examined the fenfluramine trial data for percent change from baseline in convulsive seizure days per 28 days and the percentage change in 'percent change in the convulsive seizure frequency per 28 day period'.

<table>
<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th></tr>
<tr><td></td><td></td><td>These data (provided as new evidence following the Technical Engagement meeting) demonstrate a near 1:1 relationship, validating our approach and providing further evidence to refute the ERG's assumption.
• The ERG's assumption in the model is therefore not justified, and ICER estimates based on this assumption are therefore incorrect.
• Table 2 showing the proportionality of percentage change in seizure frequency to percentage change in days with seizures:

New evidence provided

Table 2. Proportionality between percentage change (per 28 days) in seizure frequency and percentage change in days with seizures
<table>
<tr><th>Arm</th><th>Mean percentage change in days with seizure per 28 days from baseline over the trial period</th><th>Mean percentage change in seizure frequency per 28 days from baseline over the trial period</th><th>Change in seizure days vs change in seizures</th></tr>
<tr><td>0.4 FFA dose</td><td>-0.42</td><td>-0.44</td><td><u>97%</u></td></tr>
<tr><td>0.7 FFA dose</td><td>-0.56</td><td>-0.61</td><td><u>92%</u></td></tr>
</table>
•

Reference to previously provided documents
• Factual accuracy check document, page 44-48</td></tr>
<tr><td>Key issue 9: In the company's base-case, it was assumed</td><td>YES</td><td>Patients with Dravet syndrome are at a high risk of premature seizure-related mortality (as highlighted in the NICE scoping document for this appraisal). We provided a detailed response in the 'Factual accuracy check' response document (pages 54-57), demonstrating the clear link between convulsive seizure frequency and mortality. The</td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response
that mortality was linked to convulsive seizure frequency.		**ERG's exclusion of mortality from its analyses is inconsistent with a fair clinical representation of the impact of Dravet syndrome on patients and carers, and irrationally biases the model towards less effective therapy. As fenfluramine is more effective than the comparators, this approach particularly biases the model against fenfluramine.** In summary: • The model does not simply assume there is a link between convulsive seizure frequency and mortality – this approach is based on the clear evidence from the literature that indicates the link between convulsive seizures and SUDEP and that demonstrates SUDEP is the leading cause of death in Dravet syndrome, as explained in CS section B.1.3.1.3. • It is not possible to provide empirical evidence of a reduction in mortality with fenfluramine or any other therapy in Dravet syndrome; RCTs in such a rare disease cannot realistically be powered for mortality events. This was fully explained in the Response to Clarification Questions C14. • To further demonstrate this, we have performed a power calculation based around the mortality rate reported in the most comprehensive review of mortality in Dravet syndrome available in the literature (Cooper et al 2016): o Assuming a power of 0.8 and a 5% decrease in mortality as a significant change from the 15% seen in Cooper et al 2016 (i.e. a mortality of 10% in the intervention arm), this would require a trial involving 1,400 patients followed up for 10 years, i.e. 14,000 patient years of follow-up. This is clearly not possible. • The modelling of survival was therefore appropriately informed by Dravet syndrome specific mortality data from the literature (Cooper et al 2016 and Shmuely et al 2016). • We refer the ERG and NICE committee to the comments of the Association of British Neurologists, as stakeholders in the process, which state "*Currently, the main aim [of treatment] is to improve seizure control. This in turn can lead to slowing, arrest or*

Key issue	Does this response contain new evidence, data or analyses?	Response
		reversal of cognitive, motor and behavioural decline, and reduce the risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP)", and further in response to the question of whether they expect the technology (fenfluramine) to increase length of life more than current care: "*Yes, if seizure freedom or improved control of seizures, especially convulsive seizures, is achieved*". (Technical Engagement Papers p.327 and p.330). • It is therefore a logical expectation that therapy that reduces convulsive seizures will reduce seizure-related deaths. As there is no doubt that fenfluramine improves convulsive seizure control compared with SoC AEDs and cannabidiol (the relevant comparators against which it is possible to compare fenfluramine) there is little reason to doubt there would be a mortality benefit with fenfluramine. • The ERG claims that the implied relative risks when deriving Dravet-related mortality from general epilepsy mortality are seemingly implausible. However, the ERG neglects to comment on the resulting mortality when implemented in the model, which is aligned with the mortality event rate observed in the RCTs, and the mortality rate reported in published literature on Dravet syndrome. • Furthermore, when assessing relative risks, it is important to consider the relative risks of natural background mortality (or even general epilepsy) are substantially lower in healthy children, compared to children with Dravet syndrome, whereby patients are typically diagnosed in early infancy and experience one of the highest mortality rates of all epileptic encephalopathies. • It is therefore incorrect and potentially misleading to suggest that the relative risks are implausible when the resulting modelled mortality is in line with expectations. • The existence of a link between convulsive seizure frequency and mortality is clear based on the literature and expert opinion. This is further supported by new data recently presented examining the overall and SUDEP mortality rates associated with

Key issue	Does this response contain new evidence, data or analyses?	Response
		patients with Dravet syndrome; and a potential reduction in estimated event rate in patients receiving fenfluramine when adjusted for time on treatment (Cross et al 2020) • Therefore, the approach we have taken to quantify the link between convulsive seizure frequency and mortality is reasonable and justified, particularly as it is impossible to provide direct empirical evidence of the impact of add-on treatment in Dravet syndrome, and as the resulting mortality in our model is aligned with expectations. • Despite this, the ERG has adapted our model to remove any mortality benefit arising from a reduction in convulsive seizure frequency on the basis that there is no empirical evidence of a survival benefit with fenfluramine. This was the same approach the appraisal committee took in TA614, which excluded a mortality benefit for cannabidiol for the same reason. Given that it is impossible to provide such empirical data, it is inappropriate to remove the logically expected survival benefit with treatment from the model: o In adopting this approach, the ERG is effectively rejecting the well documented risk of premature mortality experienced by patients with Dravet syndrome due largely to their high seizure burden. o As it is impossible to provide empirical evidence of a survival benefit with therapy in Dravet syndrome, this approach will effectively exclude consideration in the model of a key benefit of treatment. • Therefore, the ERG's analyses do not provide a fair clinical representation of Dravet syndrome nor a fair consideration of the aims and benefits of treatment. • This means that the ERG's analyses clearly underestimate the cost effectiveness of fenfluramine, as they overestimate the ICERs for fenfluramine vs the comparators. The ERG report does not explain this when presenting these ICER estimates. • As fenfluramine provides superior reduction in convulsive seizure frequency compared to cannabidiol and SoC AEDs, this assumption of the ERG particularly biases its analyses against fenfluramine.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• See also related response to Issue 3 and issue 14 (mortality) **New evidence provided** Power calculation informing the estimated sample size required to demonstrate treatment effect on mortality Publication: Cross et al., Impact of FINTEPLA (fenfluramine) on the expected incidence rate of SUDEP in patients with Dravet syndrome. American Epilepsy Society (AES) Annual Meeting, December 4-8, **Reference to previously provided documents** • CS section B.1.3.1.3 • Factual accuracy response pages 54-57
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**NO**	**As detailed above in response to Key issue 4, adverse events were fully considered and, based on the RCT evidence that showed no increase in the rate of serious TEAEs that would attract resource use and costs or impact on quality of life, there were no resource use, costs or utility decrements due to adverse events to include in the model. The model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. This was explained in detail in the Factual accuracy check response document (pages 23-34).** In addition to the points detailed in response to Key issue 4, we also refer the ERG and NICE committee to the following: • The model appropriately accounts for the 12.5% of patients discontinuing fenfluramine due to adverse events in one of the two fenfluramine RCTs and these are fully

Key issue	Does this response contain new evidence, data or analyses?	Response
		reflected in the overall discontinuations applied in the model. It should be noted that data on adverse events with cannabidiol in the subgroup taking clobazam have been published recently (Gunning et al 2020) and demonstrate that there is no meaningful difference in the rates of discontinuations with cannabidiol plus clobazam vs fenfluramine (maximum incidences reported in the RCTs 11.0% vs 12.5%, respectively). This was explained in the Factual accuracy check response document (pages 23-34). • The only notable differences in adverse events were a greater incidence of serious TEAEs and greater incidence of somnolence with cannabidiol plus clobazam compared with the incidences reported in the fenfluramine RCTs. This was explained in the Factual accuracy check response document (pages 23-34). • The exclusion of resource utilisation and costs of specific adverse events from the model is therefore unlikely to bias the model in favour of fenfluramine in any comparisons vs cannabidiol. As there were no meaningful differences in rates of serious adverse events between fenfluramine and the placebo group of the RCTs, the exclusion of adverse events from the model is also unlikely to bias the model in favour of fenfluramine in any comparisons against SoC AEDs. • Taken collectively with the points detailed in response to Key issue 4, the ERG has overstated the influence and need for monitoring of adverse events and is incorrect to suggest adverse events are only partially included in the economic model; the model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. ▪ See also related response to Issue 4 and 13 (monitoring and adverse events) **Reference to previously provided documents**

Key issue	Does this response contain new evidence, data or analyses?	Response
		• CS section B.3.3.4 • Factual accuracy response pages 23–34
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	**NO**	**We have previously provided a detailed response in the 'Factual accuracy check' response document (pages 62-69) explaining that carer utilities were estimated and implemented appropriately based on individual carer-level data collected directly from the fenfluramine RCTs. The ERG's suggested approach, in line with TA614, is not supported by the carer-level data in our RCTs; is not applicable to our patient-level modelling approach; and would irrationally penalise a therapy for being highly effective in reducing seizure frequency and demonstrated in the trials to have had a significant and meaningful benefit to carers**. In summary: • We have calculated carer utilities directly from the available trial data for fenfluramine using the relationship between the number of convulsive seizure-free days a patient has and the resulting impact on the carers QoL score; these data demonstrated that incremental improvements in the number of seizure-free days a patient experienced also impacts carer QoL. Our approach is therefore most relevant for our patient-level continuous time model, and is based on superior data than the vignette study-based data used in the TA614 model. • The model in TA614 and the ERG's scenario analyses using our model assume that if individuals had up to 7 days of seizures per month this would have no impact on carer quality of life, which is not supported by the carer-level data from our RCTs and seems unrealistic given the known substantial burden that Dravet syndrome places on patients and carers. • There is no evidence that the grouping of seizure frequency used in TA614 have any clinical relevance. TA614 committee papers stated: "*seizure categories were determined to ensure that that patients enrolled in the Phase 3 trials were split into*

Key issue	Does this response contain new evidence, data or analyses?	Response
		three equal groups and the analyses could be based on sufficient statistical power". Thus, the grouping appears to be a decision made out of statistical convenience rather than clinical relevance, and is not a relevant assumption for either our trial data or the individual patient-level modelling approach. • Adoption of the approach in TA614 would also result in the implementation of artificial stepped changes in utility benefits, which do not reflect the continuous nature of the data and is not aligned with the patient simulation modelling approach we have appropriately taken. • The approach in TA614 would therefore appear to irrationally penalise a product that has high efficacy in reducing seizure frequency to below these artificial, arbitrary thresholds. • We therefore consider the method used in TA614 and in the ERG's analyses is inferior to the approach we have adopted as it dichotomises patients into 2 seizure severity groups through an arbitrary classification based purely on cannabidiol trial data. . • Regarding the ERG's concerns on whether QOL of carers of children or adolescents applies to QoL in adults, and the suggestion that 1.8 carers may be too high over a lifespan, we feel these ignore the context of the disease course, with seizures contributing to the development of a range of co-morbidities and developmental issues, with few patients able to live independently. This was described in detail in the CS and is clearly reflected in the patient group stakeholder comments provided in the Technical Engagement Papers that convey the extensive, lifelong impact of Dravet syndrome on quality of life of patients, carers and the wider family: o **Dravet Syndrome UK** ▪ p309. "*Living with the constant threat that your child might die, either from a seizure or SUDEP is terrifying and often the first thing a parent will do in the morning upon waking is to check that their child is still breathing. Living in a heightened state of emergency and never being*

Key issue	Does this response contain new evidence, data or analyses?	Response
		able to switch off in case a seizure occurs, never knowing if it will be short, prolonged or fatal is something that no one will ever get used to." ▪ p311: *Very few children/adults experience a seizure-free existence with the currently available treatments (see answer to question 7, above). In addition, the combination of treatment-resistant seizures, debilitating comorbidities and the requirement for 24-hour monitoring cause DS to have a catastrophic impact, not only on health-related quality of life but overall quality of life*. ▪ *Another important unmet need in DS is to reduce the burden of status epilepticus, leading to emergency admissions and rescue medication. A European survey among 584 parents/carers of children/adults with DS found that half of these individuals required at least one emergency admission, and 46% needed at least one ambulance call within a 12-month period (see Lagae et al, 2018). Improved treatment of seizures will reduce the likelihood of status epilepticus and consequently reduce the time patients spend at hospital, with less need of emergency rescue medication. This improves quality of life for the whole family, including siblings (who frequently need to accompany their brother or sister to the hospital with their parents, as there is no one else who can look after them) as well as reducing the burden on in-hospital NHS resources.* o **Dravet Syndrome UK** ▪ p314. *Improved seizure control affects the whole aspect of looking after a child/adult with this catastrophic condition, leading to significant improvements not only for the individual with Dravet Syndrome, but also the wider family, including siblings. Living with a brother or sister with Dravet Syndrome can have a huge impact on the well-being of siblings. Their routines are disrupted (e.g. via emergency hospital visits); they*

Key issue	Does this response contain new evidence, data or analyses?	Response
		worry and wonder what is happening and if their sibling will be all right. Often their own time with parents/carers is limited by the complex needs of the child/adult with Dravet Syndrome, who needs 24/7 care. o **Epilepsy Action** ▪ p319. *The severe needs of many people with Dravet syndrome can have a major impact of the personal life of parents, carers and other family members. These include financial pressures, strain on relationships and an impact of the health of parents and carers.* ▪ p319. One parent carer noted that '*the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially*.' It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and family life noting that '*it has been a real toll on our health and family life*'. This was echoed by other respondents, '*we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up*.' The same parent carer went on to note that the burden of caring for their son has made them suicidal. • The **ERG's suggested approach, in line with TA614, is therefore not supported by the carer-level data in our RCTs; is not applicable to our patient-level modelling approach; and would irrationally penalise a therapy for being highly effective in reducing seizure frequency and demonstrated in the trials to have had a significant and meaningful benefit to carers** • See also related response to Issue 12 (carer utility) **Reference to previously provided documents** • Company submission B.1.3.1

Key issue	Does this response contain new evidence, data or analyses?	Response
		• Factual accuracy response pages 62–69
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**NO**	**The ERG report (page 108) acknowledges there is currently no clear guidance on the best way to incorporate carer utilities. As noted in our response in the Factual accuracy check document (pages 65-66), the alternative approach suggested by the ERG and used in its scenario analysis is also open to challenge, being based on artificial, arbitrary seizure thresholds and irrationally penalising the most effective therapy.** In summary: • There is currently no clear guidance on the best way to incorporate carer utilities, and our approach is reasonable and justifiable by the directly collected evidence from RCTs. • Given the aims of treatment are to reduce the incidence of seizures which in turn reduces the risk of seizure-related mortality, the ERG's approach would seem to perversely reward therapies that are less effective in reducing the incidence of seizures, and penalise the most effective therapy. • Whilst it is possible that setting carer utilities to zero after the patient's death may overstate the incremental survival effects, the ERG's suggested approach of setting them to a level higher than that seen before death would understate the benefit of improved survival by penalising effective therapy that reduces mortality. It also appears to perversely incentivise a patient's death by awarding a utility benefit, which we doubt the ERG is advocating for in their approach and which we do not feel is appropriate or defensible. • The ERG's suggestion, based on the approach taken in the cohort model for TA614, would apply a carer disutility in the health states defined by categories of seizure frequencies (8 to 25, and >25 convulsive seizures per month) until a patient dies. This approach may be reasonable in a responder / non-responder model, where an

Key issue	Does this response contain new evidence, data or analyses?	Response
		incremental benefit of being in the responder state can be included and will be zero after death. However, this is not appropriate in our simulation model as we are modelling seizure frequencies / seizure free intervals on a continuous time basis. • As previously described (relating to key issue 11), it seems that the main health state categories (<8, 8-25 and >25 seizures per month) in the cohort model in TA614 have been established for statistical convenience based on the cannabidiol trial data and not clinical relevance. Therefore, there appears to be no rational basis for adopting their use in our patient simulation model that uses patient profiles based on the fenfluramine trial data. The assignment of disutility only to carers whose patients have >8 seizures per month implies that there is no impact on carer quality of life for those patients experiencing up to 7 days with seizures every month, which is unlikely to be the case and also has the perverse effect of penalising treatments that reduce seizures more effectively. Similarly, it would assume the same carer impact for a patient experiencing 2 seizures a week (8 out of 28 days), to that of a patient that experienced seizures almost daily (25 out of 28 days). The ERG's suggestion that this is a more appropriate approach is therefore open to challenge on several fronts. • See also related response to Issue 11 (carer utility) **Reference to previously provided documents** • Factual accuracy response pages 65–66
Key issue 13: The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular	**NO**	**The ERG acknowledges that the model reflects monitoring costs. As explained for Issue 4 and Issue 10, and in the 'Factual accuracy check' document (pages 23-34) and in the CS and in the Response to Clarification Questions, there is no evidence of valvular heart disease or pulmonary hypertension with fenfluramine at the doses used in Dravet syndrome. This includes in the RCTs, in the open-label extension study with up to 3 years of follow-up, and in real-world evidence studies that include use for up to 27**

Key issue	Does this response contain new evidence, data or analyses?	Response
morphology This association is, however, not further reflected in the model in cost or utilities.		**years. There are therefore no costs or utilities to be included in the model associated with unusual cardiac valvular disease morphology. This is not a Key issue that would influence decision-making, and the ERG's listing of this as a Key issue does not fairly reflect the available data on adverse events; is fundamental without evidence (i.e. speculation) as does not fairly reflect the analyses we provided, and is therefore open to misinterpretation.** ▪ See also related response to Issue 4 and 10 (monitoring and adverse events) **Reference to previously provided documents** • Factual accuracy response pages 23–34
Key issue 14: Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	**NO**	**As noted in our response to Issue 9, the resulting mortality in our model was aligned with the mortality observed in the RCTs and also the mortality observed in Cooper et al 2016, which is the most comprehensive source of Dravet syndrome specific mortality data available in the literature. As it is impossible for RCTs in this disease area to demonstrate mortality benefit (see the power calculation and publication Cross et al 2020, presented in response to Issue 9), our use of the mortality data from Cooper et al 2016 is a reasonable approach, and fact that the resulting mortality in our model is aligned with these data would suggest that our modelled survival is reasonable. We therefore do not believe this is a Key issue as presented by the ERG.** • See also related response to Issue 3 and issue 9 (mortality) **Reference to previously provided documents** • CS section B.1.3.1.3. • Factual accuracy response p.54-57

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**NO**	**The ERG's comparisons of the results from our patient-level simulation model with those of the cohort model in TA614 are fundamentally flawed, and the comparisons are unable to provide meaningful information on the merits of each modelling approach or reliability of their outputs. This was fully explained in the Factual accuracy check response document (pages 9-10), but the ERG report retains this flawed comparison without any qualification or context. To avoid misleading the committee and other readers of the ERG report, these flawed comparisons should be removed**. In summary: • We have developed a fundamentally different, superior, patient-level simulation model with a substantial effort on the manufacture's side to address the short-comings in the cohort modelling approach taken in TA614 o The manufacturer of cannabidiol developed a cohort model for TA614. This required the subgrouping of clinical trial data to accommodate arbitrarily defined health states, and used utility data derived from simple rating of vignettes to weight these arbitrary health states. The appraisal committee for TA614 suggested that a discrete event simulation-type model would better account for the heterogeneity in the modelled population. o We have developed a patient-level simulation model, which accounts for the heterogeneity in the Dravet syndrome population, explicitly models absolute seizure frequencies and employs higher resolution, continuous patient-level data rather than relative seizure frequencies and arbitrary categorical data cut offs used in the TA614 model. This is a superior modelling approach for this disease, aligned with the suggestions of the appraisal committee in TA614. o Given the differences in modelling approach it is fully expected that the results of the models will differ in terms of both costs and outcomes.

Key issue	Does this response contain new evidence, data or analyses?	Response

		• Our model also uses superior clinical and quality of life data within this modelling approach.
		  o Whilst the RCTs informing the efficacy of cannabidiol are the same, the population is appropriately defined in our model based on the robust patient-level data from the fenfluramine studies.
		  o A robust network meta-analysis of the RCTs provides adjusted comparative data, and the utility estimates are directly linked to clinical outcomes, being based on regression analyses of quality of life data against seizure metrics observed directly in the patient-level and carer-level trial data.
		• The ICER and costs for cannabidiol vs SoC AEDs from TA614 and from our model are based on completely different prices.
		  o The ICER and costs quoted by the ERG from TA614 are based on the confidential discounted PAS price of cannabidiol (with cannabidiol dosing capped at a weight for 18 year old patients); we did not have access to these prices and therefore are unable to test them in our base case or scenario analyses.
		  o The treatment costs and resulting ICER quoted by the ERG from our model are appropriately based on the list price of cannabidiol as this is what is publicly available. In addition, in our model cannabidiol dosing is more appropriately capped based on the weight of adults.
		• Therefore, the cost, QALYs and ICER estimates from our model and from the model in TA614 are clearly not comparable. The ERG's direct comparison of our model outputs with those from the cohort model in TA614 is therefore fundamentally flawed.
		• The ERG report does not include any of this context or other qualification of the comparisons that have been presented. There is no basis for assuming that the TA614 model is more accurate in determining the cost effectiveness of cannabidiol, or the component costs and QALYs, particularly given the list of limitations of the TA614

Key issue	Does this response contain new evidence, data or analyses?	Response
		model identified by the same ERG and presented in the FAD for TA614, and the views of the committee in TA614 that a different modelling approach (aligned with our modelling approach) may be more appropriate. Therefore, there is no sound reason to assume the model in TA614 as the benchmark against which our model should be judged. • **Importantly, the data presented by the ERG do not reflect all the comparators in the same model. Only partial results are provided from the fenfluramine model. These are SoC Vs cannabidiol; however this omits the results for fenfluramine Vs SoC and fenfluramine Vs cannabidiol (with clobazam) from the fully incremental analysis (key issue 6, Table 2).** • **As highlighted in the above (Table 2), if these missing data were presented (rather than the abstract results of SoC Vs Cannabidiol from the TA614 appraisal); it would show within the same (fenfluramine) model, that fenfluramine demonstrated extended dominance over cannabidiol (with clobazam). We believe this is important information for the Committee to be able to make an informed decision on fenfluramine in the context of a previous NICE decision (TA614) in recommending use of cannabidiol (with clobazam)**. • During the Technical Engagement meeting (10th December 2020) the ERG explained that this comparison was included in the ERG report as a cross-validation of our model with TA614 because we had not included such a cross-validation in the CS. Given the fundamental differences in modelling approach, data quality and handling, and the fact that costs are (appropriately) completely different, we do not believe this comparison of the outputs of our superior model against the outputs of an inferior model can provide a meaningful validation of our model. Indeed, the differences noted in the outputs of our model and the TA614 model reflect this very point rather than providing meaningful information on the merits of each modelling approach or reliability of their outputs.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• This unqualified and unjustified comparison of model outputs provided in the ERG report has the potential to mislead the committee and other readers. We therefore believe this flawed comparison should be removed. **Reference to previously provided documents** • Factual accuracy response pages 9-10
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	**NO**	**We forewarned the ERG of the long run-time of the model, we provided all code for the model and answered all points of clarification. We therefore question the suggested issues of "transparency" and strongly reject the suggestion that any issues that has been listed under Key Issue 16 could possibly "threaten the internal validity of the model".** In summary: • During the Technical Engagement meeting (10th December 2020) the ERG clarified in the agenda that this Issue relates to the long run time of the model particularly for the probabilistic sensitivity analyses (PSA), the omission of the R code for one of the scenario analyses that the ERG had requested (provided shortly after), and the basis of the number of simulated patients used in the base case. • We forewarned the ERG of the long run time of the model during the telephone call to discuss the Clarification requests. We explained we had optimised the R code as far as possible; however, it is well recognised that conducting PSA within a patient-level simulation model is a lengthy process. • We trust that the ERG was able to replicate our base case and other scenario analyses that have a very manageable run time, and that this provides confidence that the analyses we have reported are true reflections of the model outputs.

Key issue	Does this response contain new evidence, data or analyses?	Response
		• We provided all the code requested to run the model and the bootstrapping of seizures, and answered all points of clarification, including the basis for the number of simulated patients and demonstration that the model results were stable to that number of simulated patients. We therefore question why the ERG feels there are potential transparency issues. • We reject the suggestion of the ERG that any of the issues it has raised under Key Issue 16 “threaten the internal validity of the model” and, given the above, firmly believe this is inappropriate and misleading. • We are of course willing to provide any further clarifications or explanations, and resend the R code, for any and all analyses we have provided in the CS and clarification responses.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 ICER
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**Our base** case model in the CS reverts patients back to baseline seizure frequency upon treatment discontinuation. The placebo component of treatment effect was incorporated for both fenfluramine and the comparator arms.	The placebo contribution of seizures has been removed from the model entirely. Therefore, the treatment effect is applied to patients' baseline seizure frequencies to model patients on treatment, and upon discontinuation patients have the treatment effect removed so that they experience their baseline seizure frequency.	The ICER reduced compared with base case in CS

Company's preferred base case following technical engagement	Fenfluramine vs Cannabidiol Incremental QALYs: 0.522	Fenfluramine vs Cannabidiol Incremental costs: £11,722	The ICER reduced from £31,773/QALY to £21,255/QALY
Fully incremental analysis	Cannabidiol vs SoC AEDs Incremental QALYs: 1.172 Fenfluramine vs SoC AEDs Incremental QALYs: 1.724	Cannabidiol vs SoC AEDs Incremental costs: £109,556 Fenfluramine vs SoC AEDs Incremental costs: £121,728	Fenfluramine extendedly dominates cannabidiol as observed in base case analyses provided in CS and Response to Clarifications

Additional issues identified during the technical engagement meetings and prior clarifications responses.

Additional Issues	Does this response contain new evidence, data or analyses?	Details
All of the ERG's base case ICERs and scenario analyses presented in the ERG Report are overestimated, and should be amended	**NO**	• All of the ERG's base case and scenario analyses erroneously assume that the reduction in convulsive seizure days ~ 0.4 x reduction in convulsive seizure frequency: o We demonstrate in our response to Key Issue 8 that this is a flawed assumption and that our approach using a 1:1 relationship is essentially valid. o The ERG's analyses therefore overestimate the ICERs and should be amended in line with this evidence. • The ERG's base case and sensitivity analyses irrationally exclude the impact of convulsive seizure reduction on mortality. As explained in our response to Key Issue 9: o This is inconsistent with a fair clinical representation of the impact of Dravet syndrome on patients and carers, and the views of clinical experts who confirmed that the aim of therapy is to reduce convulsive seizures and in turn reduce the risk of mortality.

		o It is impossible to demonstrate empirically that any therapy would have a mortality benefit in in Dravet syndrome. o Excluding mortality irrationally biases the model against effective therapy. o As fenfluramine is more effective than the comparators, this approach particularly biases the model against fenfluramine.
The ERG Report omits the full results of our fully incremental analyses	**NO**	• The ERG Report includes details of the comparison of cannabidiol vs SoC AEDs, taken from our fully incremental analyses, but not the full details of the comparison of FFA vs Cannabidiol vs SoC AEDs the show how fenfluramine extendedly dominates cannabidiol
The ERG has not presented fully incremental analyses for its analyses	**NO**	• Once corrected for the above erroneous assumptions, the ERG's base case and scenario analyses should be presented as fully incremental analyses comparing SoC AEDs vs cannabidiol vs fenfluramine to facilitate interpretation.

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your 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. The ERG report and stakeholder 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:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- 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. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 17 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.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.

PART 1 – Treating a patient with Dravet syndrome and current treatment options	
About you	
1. Your name	**Professor J Helen Cross**
2. Name of organisation	**UCL Great Ormond Street Institute of Child Health & Great Ormond Street Hospital for Children**
3. Job title or position	**The Prince of Wales's Chair of Childhood Epilepsy & Head of Developmental Neurosciences**
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):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Dravet syndrome is an early onset complex developmental and epileptic encephalopathy. Children present in the first year of life with prolonged often lateralised febrile or afebrile seizures requiring hospital admission. In the second year they develop other seizure types and are likely to slow in developmental progress, with a drop in IQ over time. In the longer term there is a high seizure burden, and significant cognitive and behavioural impairment, and impairment of mobility The primary aim of treatment is to reduce seizure burden; secondary aims for families would be improvement in social interaction and cognitive performance. In the longer term reduction of risk of SUDEP; as well as maintained mobility
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	In the short term a significant clinical response would be an overall reduction in seizures by >50%; reduced utilisation of emergency rescue medication and hospital admission would also be seen as a response

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a high unmet need for patients and health care professionals. In a study surveying families of individuals with Dravet syndrome, children and adults, only 6.3% had been seizure free in the last 3 months (Lagae et al Dev Med Child Neurol 2018; 60(1):63−72). Continued high burden of seizures is associated with higher rates of comorbidities and lower quality of life. There is also a high rate of mortality.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	Currently children presenting with prolonged seizures in the first year of life will be reviewed by a paediatrician with an expertise in epilepsy, and likely seen or at least discussed with a tertiary paediatric neurologist. Once a diagnosis is made initial treatment would now be expected to be sodium valproate, with the addition subsequently of stiripentol and later clobazam. Subsequently if seizure continue, cannabidiol would likely be the next medication. Patients will be reviewed regularly by a paediatrician with an expertise in epilepsy as well as a tertiary paediatric neurologist. These individuals have a continued high seizure burded, specifically the tendency to prolonged seizures requiring rescue emergency medication and hospital admission. This is particularly seen in the young, although the tendency remains throughout life. Patients should have individualised protocols with regard to the treatment of prolonged seizures and when to attend hospital.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidelines 137 (currently in the process of update) –clearly states that child should be discussed with or referred to a tertiary paediatric neurologist Suggest Sodium Valproate or Topiramate first line, clobazam +/-stiripentol as add on therapy. NICE HTA on cannabidiol (https://www.nice.org.uk/guidance/ta614) – can be prescribed with Clobazam in the treatment of Dravet syndrome >2 years Other international protocols

	Wirrell EC, Laux L, Donner E, et al Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatr Neurol. 2017;68:18-34.e3. Cross JH, Caraballo R, Nabbout R, Vigevano F, Guerrini R, Lieven L. Dravet syndrome: Treatment Options & Management of Prolonged Seizures Epilepsia. 2019 Dec;60 Suppl 3:S39-S48. doi: 10.1111/epi.16334.
• 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.)	The pathway for Dravet syndrome is clearly defined with regard to treatment. The main variance would be when to diagnose the syndrome after initial presentation- after two prolonged seizures, or after the emergence of other seizure types. And when to undertake the genetic evaluation (for an SCN1A mutation). Previously there could be variance as to first line medication (topiramate vs valproate) but this is less now. There may be some variance as to the frequency patients are seen by tertiary care
• What impact would the technology have on the current pathway of care?	Fenfluramine appears to have given a definitive overall reduced seizure burden in clinical trials; we have seen this in clinical practice. In the clinical trials, although blinded it was clear clinically which patietns had been initiated on active therapy. With the impact seen on individuals the discussion will need to be where in the line of medication fenfluramine is utilised ie earlier in the natural history rather than wait for resistance to current therapies. By alleviating the burden of seizures early, there would be reduced hospital admissions, reduced carer burden and possibly improved neurodevelopmental outcome
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Referral pathways and diagnosis would remain the same. Any further discussion would be when in the treatment pathway this medication would be utilised
• How does healthcare resource use differ between the technology and current care?	There is the real possibility that admission to hospital and/or use of rescue medication would be reduced in this population with use of fenfluramine, particularly the young (<6years) However regular cardiac monitoring would be required, which is in excess of current standard of care

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary care, with access to cardiology review. There is a need with this medication for regular cardiology review
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	If utilised in a tertiary environment no additional training would be required. However cardiologist would need instruction on the abnormalities they would be looking for (minimal training)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	On the basis of the response noted in clinical trials, and open label data, I would expect a clinical meaningful impact in most children trialled on this medication with reduction of seizure burden and improved quality of life
• Do you expect the technology to increase length of life more than current care?	There is some evidence that there is a reduced risk of SUDEP in the Dravet population treated with fenfluramine, compared to those not (American Epilepsy Society meeting abstract 2020) In children with Dravet syndrome there is overall a higher mortality rate than in other epilepsies; the mortality rate in the epilepsies is higher than the general population
• Do you expect the technology to increase health-related quality of life more than current care?	With the markedly reduced seizure burden I would expect to see improved quality of life over current care. This I have already seen in children trialled on the medication

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The population to be addressed is specifically those with epilepsy as part of Dravet syndrome. There is currently no evidence for use outside this group The question would be whether the technology would be applicable to individuals with other types of epilepsy; this said there are some mechanistic proposals suggesting a possible greater benefit in Dravet syndrome
The use of the technology	
15. 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.)	There will be required a greater degree of monitoring than current standard of care, specifically the need for regular echocardiogram. Although routine monitoring visits to hospital would not be more frequent.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology?	I would suggest that a minimum reduction in seizures after 6m be taken as a marker for continuation – as with previous technologies in this area would suggest

Do these include any additional testing?	Should cardiac valvular change be noted, this could be another marker for discontinuation
17. 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?	I do – through reduced seizure burden and improved quality of life
18. 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 improve the way that current need is met?	With the reduced seizure burden - it is presumed that with fewer convulsive seizures there would be impact on interaction and mobility
• Is the technology a 'step-change' in the management of the condition?	Yes – the reduced seizure burden in those treated is unprecedented – no other treatment has led to such a significant reduction in seizures in any population where used as add on therapy
• Does the use of the technology address any particular unmet need of the patient population?	Continuing convulsive epileptic seizures in Dravet syndrome

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In view of the previous history of the medication, regular cardiac monitoring is required. However doses currently ustilised are much lower than originally used when the medication was used in the treatment of obesity.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Two randomised clinical trials are available – one of use of fenfluramine vs placebo where individuals were not receiving stiripentol, and a second where fenfluramine is added to stiripentol as one of the AEDs. There the trials do reflect current clinical practice. The open label data also reflect current UK practice.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduced seizure burden remains the most important outcome, and this was measured. However QoL was also assessed. In a short term trial it is difficult to assess any change in cognition – they attempted to review attention, and succeeded to some degree reviewing subtests of the BRIEF.
• If surrogate outcome measures were used, do they adequately predict	These are reflected in the open label continuation studies

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA614?	Miller et al Dose ranging effect of an adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome JAMA Neurology 2020;77(5):613-621 Laux LC, et al Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. Epilepsy Res. 2019 Aug;154:13-20.
23. How do data on real-world experience compare with the trial data?	Reviewing previous Belgian experience, data are comparable
Equality	

24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Making sure availability across all geographical areas, and regardless of socioeconomic status
24b. Consider whether these issues are different from issues with current care and why.	No

PART 2 – Technical engagement issues for clinical experts	
Issues arising from technical engagement	
We welcome your comments on the issues below described in full within the ERG report, but you do not have to comment on every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	There is no reason to think that seizures the result of Dravet syndrome, would be different in response to treatment in adults compared to children. Not considering adults with the same syndrome would be discriminatory. There have been problems in the past when only children have been considered for a beneficial treatment, particularly during transition form childhood to adult care There could be differences in tolerability expected that would need to be monitored although data from the open label study, EAP and historical cohorts suggest to the contrary, it is well tolerated in adults
Key issue 2: Not all relevant comparators have been fully investigated	The data for stiripentol by which to compare are limited. Further, stiripentol is in general used with valproate and/or clobazam – it is not considered an independent antiseizure medication. Therefore any comparison would also include one or both of these medications, acknowledging fenfluramine would be added regardless of the concomitant medications

Key issue 3: Short-term nature of the included randomised trials	This is an ongoing problem with regulatory comparator trials; one would presume ongoing open label data will be available, although data put forward suggest sustainability of response and no emergence of different AEs
Key issue 4: Adverse events and need for monitoring	Acknowledged that the need for cardiac monitoring would need to be included in cost analysis. Appetite and weight loss would be accounted for in routine (standard) monitoring of the condition
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	Although acknowledging a placebo effect may be seen on introducing a treatment, in this group of patients removing a treatment is likely to be because of no improvement or adverse events. One could expect a reverse – an assumption of return to baseline of seizures when removing a treatment considering the natural history of this condition with knowledge of the natural history.
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e.	The position of fenfluramine is likely to be at a similar add on level to cannabidiol (with clobazam) so in the short term this as a comparator would appear appropriate. Standard therapy currently would likely be first line sodium valproate or topiramate with subsequent addition of stiripentol or clobazam respectively. If fenfluramine was to be considered sooner in the protocol, then comparison with stiripentol would seem appropriate.

the population for which cannabidiol is recommended.	
Key issue 7: The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	In monitoring antiseizure medication, a reduction <30% at 6m would seem appropriate to consider an alternative, and whether the medication should continue It is commented that those that discontinued for this reason in the model were all individuals who saw <15% or no reduction in convulsive seizures
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	These two outcomes are related, ; increasing seizure free days provide a significant benefit for patients and families.
Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	A risk factor for SUDEP is ongoing convulsive seizures, this is therefore not an unreasonable assumption although does not infer causality SUDEP is a real fear for families – the rate amongst individuals with Dravet syndrome is higher than other types of epilepsy, presumed to be related to the frequency of ongoing convulsive seizures

Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	Cardiac monitoring would be the only additional monitoring required over standard of care, despite the relatively high report of AEs in study 1. This is not unusual in paediatric studies. Standard of care for Individuals with Dravet syndrome would include regular clinical monitoring.
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	Owing to the high comorbidity burden in addition to seizures, it would be more correct to assume 1.8 carers/patient, although for comparison it would be presumed that similar inclusion would be seen to be appropriate Also, few, if any, individuals with Dravet syndrome achieve independence, and all continue to have seizures. There is therefore no evidence for a reduced need for carers per patient in adulthood.
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an	If a patient dies then there is no continuing carer requirement for that individual? I think it unlikely there is an overestimation of the impact of mortality

overestimation of the impact of mortality	
Key issue 13: The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is, however, not further reflected in the model in cost or utilities.	There is no evidence to date that the proposed dose and usage of fenfluramine is associated with the cardiac toxicity previously reported (with higher doses than used in the trials) The cardiac monitoring is required in view of the historical concern. Acknowledging a model perhaps should consider cost/utilities if such cardiac toxicity should occur, it would be very difficult to estimate any real risk at present.
Key issue 14: Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	This is likely to give an underestimate rather than overestimate?
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental	

cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	
Are there any important issues that have been missed in ERG report?	The overall reduction in seizures seen with fenfluramine in this complex population demonstrated real benefits in quality of life. The percent reduction seen in this group of particularly complex patients, with no prospect of seizure remission with current standard therapies, was unprecedented compared to other previous trials of anti seizure medication.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- Dravet syndrome is a complex early onset developmental and epileptic encephalopathy
- Prognosis for seizure control and neurodevelopmental outcome remains poor despite recent introduction of newer antiseizure medicines
- Fenfluramine provides a step change in the treatment of convulsive seizures in Dravet syndrome
- Fenfluramine achieves reduced seizure burden at a greater level seen in previous studies
- Ongoing cardiac monitoring provides the only change to standard of care in these patients if fenfluramine utilised.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your 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. The ERG report and stakeholder 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:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- 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. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Thursday 17 December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.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.

PART 1 – Treating a patient with Dravet syndrome and current treatment options	
About you	
1. Your name	**Amanda Hirst**
2. Name of organisation	**ESNA**
3. Job title or position	**Paediatric Epilepsy Specialist Nurse**
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):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
The aim of treatment for this condition	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Adjunctive treatment for people with a diagnosis of Dravet Syndrome. Epilepsy within Dravet is particularly hard to control and this new treatment may offer reduction in seizure burden
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	Reduction in frequency or severity of seizures Potential positive impact on Quality of Life

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines Epilepsies Cannabidiol
• 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.)	Clear pathway regarding investigations and initial treatments but when these are unsuccessful it can differ due to professional preferences.
• What impact would the technology have on the current pathway of care?	Adjunctive medication options

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist epilepsy clinics Need to consider prescribing restrictions – would GP be able to continue prescriptions or would it need to be hospital prescription?
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	If ECHO is required then potential for investigations that aren't normally required and potential cost implications to undertake.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase	If it helps reduce incidence of Status Epilepticus in patients then length of life could also be increased. Also potential to reduce incidence of SUDEP.

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes it has the potential to increase QoL outcomes
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
The use of the technology	
15. 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	Prescriber needs to be aware of dosing differences +/- Stiripentol

ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. 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?	
18. 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 improve the way that current need is met?	

• Is the technology a 'step-change' in the management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	All epilepsy medications have the potential to cause unacceptable side effects. When initiating medications it is important to keep a close eye on this with the family & child.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes,	

and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA614?	

23. How do data on real-world experience compare with the trial data?	
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	
24b. Consider whether these issues are different from issues with current care and why.	

PART 2 – Technical engagement issues for clinical experts	
Issues arising from technical engagement	
We welcome your comments on the issues below described in full within the ERG report, but you do not have to comment on every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	
Key issue 2: Not all relevant comparators have been fully investigated	
Key issue 3: Short-term nature of the included randomised trials	

Key issue 4: Adverse events and need for monitoring	
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	
Key issue 7: The company implemented a treatment stopping	

rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	
Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of	

patients with AEs leading to discontinuation.	
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	
Key issue 13: The model reflects the monitoring costs, made	

necessary through an association of the drug with unusual cardiac valvular morphology. This association is, however, not further reflected in the model in cost or utilities.	
Key issue 14: Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of	

£29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	
Are there any important issues that have been missed in ERG report?	
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement: • •	

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-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

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Technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Thursday 17 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the issues below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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.

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.

About you

Your name	**Sanjay Sisodiya**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to comment on key issues raised in the ERG report. You may also provide additional comments on any key issues that you would like to raise but which are not covered by the existing issues.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	**NO**	It is vital that adult patients are not disadvantaged by the inappropriate exclusion of adults from the clinical trials. Adults with DS have the same fundamental biology. In most cases of DS, there is a genetic cause, and this does not change at age 18. Moreover, gene expression studies show that *SCN1A* expression continues into adulthood. The prevailing view is that seizures become less frequent in adulthood in DS. However, this is based on biased data, and lack of follow up into adulthood. Our own clinical service sees many adults with continuing frequent convulsive seizures. Adults therefore must not be excluded from consideration. Data are being generated on seizure occurrence in adulthood.
Key issue 2: Not all relevant comparators have been fully investigated	**NO**	I agree with the ERG evaluation. Redactions make full evaluation difficult (throughout this response).

Key issue 3: Short-term nature of the included randomised trials	**YES**	4.2.1 alludes to additional information on longer-term follow up. It is important that fenfluramine is subject to the same evaluation criteria as cannabidiol was: cannabidiol benefitted from significant pressure outside the formal evaluation processes, which other drugs do not have or have not had. Fenfluramine represents a realistic alternative that may prove more effective than cannabidiol, and the opportunity for patients to benefit from its use should not depend on, or be harmed by, arbitrary external factors. It is not realistic for longer term trials to be undertaken in order for licensing to be considered. Similar criteria were not used to evaluate other drugs that are already licensed for DS.
Key issue 4: Adverse events and need for monitoring	**NO**	The adverse effects and monitoring required are well known. Redactions again make it impossible to judge this fully. There is no section 4.6 referred to within the ERG report
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**NO**	I agree with the ERG evaluation summarised in Table 1.6.
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**YES**	It would seem information was provided, but has been redacted. I agree mainly with the ERG report, but I disagree that the suggested analyses be restricted to children and adolescents.

Key issue 7: The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	**NO**	No comments beyond those of ERG
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**NO**	I agree with ERG comments. It is also important to note that we know little about premature mortality in adults with DS. We do not know SUDEP rates, nor rates of premature mortality from other causes. Convulsive and other seizures may cluster in DS (and some patients may in practice have rescue protocols that account for this), so that a proportional relationship between seizure frequency and seizure days cannot necessarily be assumed.
Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**NO**	Convulsive seizure frequency has a well-established and strong link to some forms of premature mortality in epilepsy in general. There is no reason to consider this observation would specifically not apply to DS. There may be additional causes of premature mortality in DS, as comorbidities are often seen, some of which may lead to other routes to premature mortality. Convulsive seizures remain the main risk for SUDEP.
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**NO**	I agree with the ERG report on this.
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	**NO**	I agree with the ERG to the extent I am able to comment on the methods. However, I would note that it is not unreasonable to consider that adults with DS require 1.8 carers over the lifespan. It is my clinical experience that this

		is in fact typical – most adult patients with DS require 2 carers
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**NO**	I agree with ERG.
Key issue 13: - This question has been removed as it has commercially in confidential information so will only be viewed by the company and appointed experts.	-	-
Key issue 14: Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	**NO**	I agree with ERG.
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**NO**	I am not qualified to address this issue.
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	**NO**	I agree with the ERG position. Redactions to the documents do not help.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 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
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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Technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Thursday 17 December 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the issues below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Dravet Syndrome UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to comment on key issues raised in the ERG report. You may also provide additional comments on any key issues that you would like to raise but which are not covered by the existing issues.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	**YES - data & caregiver testimony from DSEF survey**	We are pleased to be able to submit additional data on adult experience with fenfluramine, recently gathered by the Dravet Syndrome European Federation (DSEF), an organisation representing patient and family groups with Dravet Syndrome (DS) from across Europe. DSUK is also a member of DSEF. Between 31st July to 14th August 2020, DSEF conducted a survey among 118 patient caregivers in 8 European countries (including the UK). Patient ages were 1 to 40 years old, with 29 patients being adult (18 years old and older) at the time of the survey. A summary of survey results was submitted to the Public and Stakeholders Engagement department from the EMA and is attached to this response. We also attach findings specifically related to adults as a subset of the overall data. (Note: the survey wording was reviewed by Public and Stakeholders Engagement department from the EMA to identify and modify potential leading questions that might compromise the quality of the results). The survey did not attempt to capture quantitative data on efficacy or safety of fenfluramine in this population, which are already documented in the evaluation package by the company. Instead, the focus remained on the patient experience. It contained 13 questions, with the last one being open text. We will refer to this dataset throughout our response. With regard to this particular issue proposed by the ERG, 'lack of evidence on adult patients', we refer also to the adult subset data (representing 29 adult patients with DS aged 18 to 40 years old). Of these adult patients, 20 (69%) had been receiving fenfluramine for more than a year. A further 4 (14%) were receiving fenfluramine for between 6 months to one year. All survey respondents were asked to score on a 6-point CGI-like scale the impact of all previous medications before

		fenfluramine on the patient's Quality of Life and the impact of fenfluramine. While most caregivers of DS patients younger than 18 years old report "minimally improved" as the impact for all previous (i.e. not fenfluramine) treatments, caregivers of adult patients report notably *less* positive experiences, including a large group (around 50%) reporting "no change" or "negative change" with prior treatments. In contrast, more than 80% of caregivers of adult patients reported a "very much" or "much improved" impact after receiving fenfluramine (see tables on page 2 of the attached adult subset report). This is somewhat higher even than the group representing patients younger than 18 years old, where around 70% of caregivers reported a "very much" or "much improved" impact following treatment with fenfluramine. Asked to score on a -5 to +5 numerical scale the impact of fenfluramine in the overall state of the patient, including both seizure and non-seizure disease aspects, both age groups reported positive impact for fenfluramine in the overall state of the patients, with most scores in the +3 to +5 range. To put these survey results in context, we would like to share some background regarding the unmet needs of adults with DS. DS is a life-long condition. However, until recently it was seen primarily as a childhood syndrome. This misperception has led to many disadvantages for adult patients with DS, including: • There is much less data/published literature about the adult experience compared to paediatric • Adults are often not diagnosed until later in life and are likely to have spent many years trialling medications that do not control seizures or potentially make them worse (e.g. sodium channel blockers are contraindicated in DS). • Due to many years of uncontrolled seizures, they are likely to have poorer outcomes with regards to the comorbidities of DS. So while the best available evidence indicates that seizures tend to decrease in adults, as the ERG report highlights, it is *not* correct to take from this that seizures uniformly or consistently "settle" in adults or that the need for effective and well-tolerated treatment is any

		less for adults than for children. It is also not correct to assume that because seizures are fewer, there are fewer benefits associated with treating adults. Around 92% of adults still experience frequent seizures ('Caregivers of Adults with Dravet Syndrome', Dravet Syndrome Foundation, 2018). For these patients, finally achieving some improvement in seizure control can be just as transformative as for younger patients, in ways that cannot be measured by simply counting seizures. In addition to the data summarised in the adult subset, the DSEF survey summary includes the free-text caregiver testimonies in their entirety, including those from the 29 adult care-givers. Most testimonies are positive, and many describe significant improvements across quality of life, including rediscovering the ability to speak, becoming more active, and being more "present" or engaged in family life. For some, it has even lead to greater autonomy and independence. Below are some examples, including a proportional balance of positive and negative experiences, as shared in the survey results. We do also urge the committee to read the attached reports in full. • *"Fewer seizures at night mean more sleep for caregivers. The patient is more aware of his environment and his surroundings and can use this better according to his abilities. He can also express better without language how he feels or how he is doing."* • *"We all sleep at night. When we leave we are more serene. We travel. More social life for the family. The patient is more present, less tired and therefore more involved in the context."* • *"We don't do more or less like with / without fenfluramine, it is more important for us that our son appears happier, not so apathetic, follows things in our everyday life and in the facility. Furthermore, we are no longer plagued by the everyday fears of falls and its consequences. -Sleeping rhythm has improved significantly -improved gait security -shows emotions -motorically more active / not hyperactive -less aggressive because less trapped in his body"* • *"Our family was able to lower the level of anxiety compared to the danger of seizures and was able to live and plan daily activities and extraordinary activities such as travel and*

		entertainment with greater serenity. We have also begun to plan the possibility of an independent life for our daughter. Too bad that the crisis control lasted only 12 months and then they reappeared, thus eliminating the benefit obtained because the anxiety returned and, again, we cannot plan anything for fear of seizures and we went back to living for the day". • *"Speaks more, talks much more intensely, looks clearly and she "is there", takes part in life much more, more attentively, perceives her surroundings a lot more, is no longer so spaced out. Can e.g. unlocking the mobile phone yourself with a simple combination of numbers was not possible before."* • *"The patient is more independent, less aggressive. And in general more cheerful and lively."* • *"The difference between a few epileptic attacks per day or a few epileptic attacks per month / year makes a big difference in quality of life for the person and the home environment !!!"* • *"No change"* • *"Visiting relatives is now a lot easier because the fear of seizures has been greatly reduced. Even a very modest outing to a café is possible. Our son blinks much less with his eyes and his epilepsy is clearly much less. We now see that he is still making progress, albeit very small, in his development, such as, for example, a small expansion of his vocabulary. He also has an increasing tendency to 'talk'."* In summary, this is a patient population which has been under-recognised for many years. The need for better treatments for adults is urgent. Historically, there is little data on adults living with DS, compared to the paediatric population. • Because adults are under-diagnosed, it is often a lot harder to gather data on adults living with DS. This situation should not lead to adults being disadvantaged. We welcome recent efforts by researchers, companies and regulators towards better inclusion of adults with DS in clinical trials, and urge the committee not to exclude adults living in the UK from the opportunity for better seizure control and better quality of life.

Key issue 2: Not all relevant comparators have been fully investigated	**YES - data & caregiver testimony from DSEF survey**	In response to whether the patient is taking or has taken the only two EMA-approved treatments for Dravet syndrome, stiripentol and cannabidiol (117 responses) 30,7% of participants reported not having tried these treatments while 69,3% had tried one or both (49,6% only stiripentol, 9,4% only cannabidiol, and 10,3% both). Note: survey participants were *not* asked to give information about other commonly prescribed medicines (e.g. sodium valproate or clobazam) because the survey aimed to compare patient experience with AEDs that already have an indication for DS, rather than all possible medicines. Asked to score on a 6-point scale the collective impact of these prior treatments (cannabidiol and stiripentol) on the patient quality of life (117 responses), a majority (64,1%) of responders selected “no improvement or change” or “minimal improvement”, followed by 12,8% indicating a “negative impact”, and only 15,4% reporting much improved or very much improved (see figure below). Of note, the question specified that “quality of life means not only seizure reduction but overall improvement in the life of the patient” so responders impact statements refer to global impact and not only to seizure changes. Asked to score on the same 6-point scale that was used to capture the collective efficacy of all these prior treatments the impact of fenfluramine, 71,8% of 117 responders reported much improvement (29,9%) or very much improvement (41,9%). 12,8% reported minimal improvement, 8,6% reported no change or don’t know, and 6,8% reported negative impact (see figure below). Again, responders were asked to report on global impact, and not only on seizure changes. In conclusion, we understand the ERG’s concern that the company’s submission should reflect the treatment pathway. We also ask the committee to bear in mind that seizure control is extremely rare in this patient population and there remains an urgent need for new, more effective treatment options to improve the likelihood of seizure control in this rare and catastrophic disorder, regardless of the comparator. We’re concerned that setting a benchmark for new treatments for DS to be compared against all possible AED combinations sets an unnecessarily high barrier that will delay and prevent new treatments from becoming available, both in terms of the time it will take to

		conduct these trials and the investment costs to developers. This would be an absolutely devastating blow to families living with this catastrophic condition. Fenfluramine may not work for all individuals with DS, this is to be expected due to the spectrum nature of the condition (described above). However, we have heard from many families in the UK and Europe for whom fenfluramine has been transformative. As one caregiver puts it: *"The drug [fenfluramine] has honestly been life changing for not only [my son who has Dravet Syndrome] but for us as a family. Our biggest achievement was taking him on a summer holiday abroad in the height of summer last year (seizure free). Before the drug we couldn't even take him from the house to the car without seizures. This was HUGE and very overwhelming. Instead of counting seizures now, we count sunsets. We feel very lucky."*
Key issue 3: Short-term nature of the included randomised trials	**YES - data & caregiver testimony from DSEF survey**	The length of the randomised clinical trials seems appropriate for patients with DS, given that this is a rare disease with limited treatment options. Other treatments approved for use in DS, e.g. cannabidiol, were of a similar duration. Trial duration is also broadly aligned with real-life experience in terms of how long it might take to see benefits associated with a new treatment, and make a decision whether to stop or continue that treatment. DS is a spectrum disorder, meaning that children/adults respond differently to different treatments. Most of the current treatments/treatment combinations are given on a trial and error basis to see which work best. If a treatment does not have a noticeable benefit, parents/carers will not want to continue with an additional treatment given that their child/adult will already be on multiple medications and no parent/carer wants their child/adult to be on more medications than absolutely necessary. Regarding evidence of sustained improvement with fenfluramine (beyond the term of the RCTs), data gathered by DSEF in July/August 2020 from 118 caregivers in 8 European countries (including the UK) includes many examples of sustained improvement with fenfluramine. Out of 118 responses, 90,7% of the participants were currently taking fenfluramine (9,3% took fenfluramine in the past but not currently), and 62,7% of the patients had taken fenfluramine for more than a year with only 5,9% of participants having taken it for less than 3 months. While fenfluramine did not work for all, 71,8% of 117 responders reported much

		improvement (29,9%) or very much improvement (41,9%). In many cases, improvements are in overall quality of life, rather than seizure control alone. The caregiver testimonies from the survey are included in their entirety in the attached report. Below are some examples, including a proportional balance of positive and negative experiences: • *"Our son has been seizure free for over 1 year now, ever since he's been taking fenfluramine. Before that, every 4-7 days, an attack with various fractures and hospital stays".* • *"After 3 months we have saw much improvement, even with eating. Today we have been almost 365 days without seizures. Before, the average was at least 3 seizures a week."* • *"The [adult] patient has been seizure-free for 3 years thanks to fenfluramine. Surely having no seizures you live in a "more free" way, and without the constant fear that a seizure can be triggered by a negative event. From having 17 daily generalized seizures to having zero, to improvements in cognitive aspects, stability and better mood".* • *"Fenfluramine has had a positive effect on my daughter's behavior, attention to motor skills and all that is the psychomotor aspect. Her seizures remained almost unchanged (tonic-clonic). As for myoclonia, we can say with extreme certainty that fenfluramine did not bring any benefit. So a big improvement only on a behavioral and physical level."* • *"Certainly at the level of epileptic seizures it had a very positive influence, in the sense that they reduced for a couple of years and then came back and we suspended, but at the behavioral level it worsened, more oppositional, uncontrollable crying fits and in certain situations more indistinct"* In addition to the DSEF survey, we have several anecdotal reports of the sustained improvements with fenfluramine from families registered with DSUK, for example: • *"In 13 years we have tried many treatments, nothing has worked for us… Within 2 weeks of starting Fenfluramine her seizures were much reduced and even then they were mild mainly myoclonic, she regained her balance, her mobility and the drooling disappeared. She wanted to feed herself and eat a varied diet. It was as if she was suddenly awake and*

		alert and had a sparkle in her eyes we hadn't seen in a long time. She is happy all the time, full of life and learning new words and skills every day. In addition to all this we have not experienced any adverse side effects which usually come with treatments. • *Having been on the drug for 2 years now I can honestly say it has transformed his quality of life tremendously…we were housebound and unable to leave due to <redacted> being so photosensitive to any kind of daylight. He had to wear sunglasses and a patch daily 24/7 even indoors, all blinds and curtains were drawn and some days switching on some lights was difficult….Since the first dose of fenfluramine his photosensitivity has disappeared. He is no longer affected by sunlight and can go outdoors and enjoy life again… before the drug we couldn't even take him into the garden."* Regarding concerns about "treatment waning", raised by the ERG. Whilst it is true that all medicines are likely to have a 'honeymoon' period, it is not correct to assume that 'waning' seen with one type of AED (e.g. cannabidiol) will be seen in all other medications. Because DS is a spectrum disorder, it is very difficult to predict how individuals will respond to treatments and for how long. In summary, real world experience from families living with DS in the UK and Europe shows that fenfluramine has the potential to offer sustained improvement for some, if not many, leading to substantial improvements in quality of life for families who previously struggled with seizure control and other Dravet comorbidities.
Key issue 4: Adverse events and need for monitoring	**YES - data & caregiver testimony from DSEF survey**	The ERG report states that "adverse events such as increased diarrhoea and fatigue observed in the study programme, even when not classed as serious, can be bothersome to patients". While this is certainly true within a general population, we ask the ERG to consider more fully the context of DS. All approved AEDs come with side effects that are more than bothersome, such as such as suppression of appetite, aggression, insomnia, somnolence, etc. Side effects from treatments can also increase some of the symptoms associated with comorbidities. The caregiver survey conducted by DSEF in July/August 2020 among 118 caregivers in 8 European countries (including the UK) supports this real world experience. When asked to consider in a scale of -5 to +5 the change in the overall state of the patient with DS while taking fenfluramine, including seizure and non-seizure improvements, 70,1% of 107 participants selected +3 to +5 which are significant positive improvements. 8,4% (9 patients)

		reported -3 to -5, and therefore a worsened patient state as a response to fenfluramine (see attached report). If fenfluramine does not have a noticeable benefit or if side effects become overly burdensome, parents/carers will not continue with it, given that their child/adult will already be on multiple medications. Equally, if seizure control can be achieved, families living with DS are willing to manage bothersome side effects, as the benefits of seizure control outweigh the risks of these, as improved seizure control affects the whole aspect of looking after a child/adult with this catastrophic condition. Good seizure control means fewer emergency medications and hospitalisations; it can also lead to better cognitive outcomes and improvements in quality of life. As one caregiver of an adult son with DS, reported in the DSEF survey: • *"Our son has been seizure free for over 1 year now, ever since he's been taking fenfluramine. Before that, every 4-7 days, an attack with various fractures and hospital stays. Our fear is almost gone and we can sleep more peacefully. Our son is VERY proud himself that he has no seizures and now goes shopping independently, to the hairdresser. Food etc. really great! 2 negative side effects are insomnia and loss of appetite. But none of us would do without fenfluramine because of that".* If cardiac monitoring is required, this does pose an additional burden, however, because most patients with DS anyway need to see a neurologist at least every six months, adhering to this should not be too much of an imposition on families' time and if the outcome is better seizure control, this is something most parents/carers would be happy to do.
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**YES - data & caregiver testimony from DSEF survey**	Real world experience, as documented in the caregiver survey conducted by DSEF in July/August 2020 among 118 caregivers in 8 European countries (including the UK), shows that fenfluramine has the potential to offer sustained improvement for some, if not many, leading to substantial improvements in quality of life for families who previously struggled with seizure control. It is also worth noting that 59% of 117 participants in the DSEF survey had reduced the number or the dose of other anti-epileptic treatments as a result of adding fenfluramine. Of these, 57 provided more information about the reasons for these adjustments. Most of these cases were as a result of better seizure control, leading to needing less drugs or dose

		(61,4% of those who reduced number of dose), but in some cases these changes reflect the need to adjust levels following pharmacokinetic interactions (26,3%). See response to key issue 3 for more detail.
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**YES - data & caregiver testimony from DSEF survey**	No comment on specifics of the chosen comparator. See our response to key issue 2 for additional context regarding currently available treatments and unmet need in DS, including survey data compiled by by the Dravet Syndrome European Federation (DSEF).
Key issue 7: The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	**YES - data & caregiver testimony from DSEF survey**	The stopping rule seems appropriate for patients with DS, given that this is a rare disease with limited treatment options. It also reflects real world clinical practice. If a treatment does not have a noticeable benefit, parents/carers will not want to continue with an additional treatment given that their child/adult will already be on multiple medications and no parent/carer wants their child/adult to be on more medications than absolutely necessary. Most of the current treatments/treatment combinations for DS are given on a trial and error basis to see which work best (this is clearly shown in the DSEF survey where 56 patients out of 117 had tried more than 6 treatments before fenfluramine). The DSEF survey (undertaken with 118 caregivers in 8 European countries) also asked about experience with fenfluramine. 55 participants reported taking fenfluramine as part of a clinical trial, 41 under compassionate use, and 27 as part of open label studies. These numbers add up to 123 because some patients took fenfluramine first as part of a double-blind clinical trial and then as part of the open-label extension and recorded both options. From these (118 responders), 90,7% of the participants were currently taking fenfluramine (9,3% took fenfluramine in the past but are not currently taking it), and 62,7% of the patients had taken fenfluramine for more than a year with only 5,9% of participants having taken it for less than 3 months.

		Asked to score on the same 6-point scale that was used to capture the collective efficacy of all these prior treatments the impact of fenfluramine, 71,8% of 117 responders reported much improvement (29,9%) or very much improvement (41,9%). 12,8% reported minimal improvement, 8,6% reported no change or don't know, and 6,8% reported negative impact Note: responders were asked to report on global impact, and not only on seizure changes.
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**YES - data & caregiver testimony from DSEF survey**	While we have no comment on the specifics of modelling data raised here, we would like to highlight that from the anecdotal experience shared by families with DS, fenfluramine does seem to have a positive impact on quality of life for many (although not for all). While better seizure control and seizure-freedom undoubtedly have a transformative impact on the lives of those affected by DS, changes to Dravet comorbidities can also have a big impact on quality of life. Given the spectrum nature of DS, and its unpredictability, simply counting seizures and/or seizure free days may not fully capture the range of quality of life improvements. One of the main aspirations of Dravet Syndrome families is to have the ability to live "a normal life", beyond simply having a child or adult family member without seizures. The survey conducted by DSEF in July/August 2020, among 118 caregivers in 8 European countries (including the UK), asked caregivers if the patient had experienced improvements while taking fenfluramine in symptoms other than seizures, and to select from a list of potential non-seizure improvements those that their loved ones had experienced. 87 responders reported some non-seizure improvement. The most common improvements reported by caregivers were improved behavior, cognition and social interaction, followed by life quality-related aspects such as ability to do activities that they could not do before. When asked to consider in a scale of -5 to +5 the change in the overall state of the patient, including seizure and non-seizure improvements, 70,1% of 107 participants selected +3 to +5 which are significant positive improvements. 8,4% (9 patients) reported -3 to -5, and therefore worse patient state as a response to fenfluramine. In addition, the final survey question asked caregivers to provide a short testimony of how fenfluramine has impacted the quality of life of the patient and their family. These testimonies help us understand what the patients and caregivers perceive as valuable improvements in quality of life. All testimonies received have been translated into English and are included in the attached report. Most were very positive, although as is to be expected in DS, some

		indicate no change or a worsening of symptoms. Below are some examples, including a proportional balance of positive and negative experiences: • *"The improvements are minimal, a little less seizures but it's no miracle. She looks more calm, less agitated. She is more sociable with others and can concentrate a little more. However, she is far behind in relation to her age group."* • *"Our daughter is more alert and receptive, which means more understanding for us in everyday life"* • *"Fenfluramine made our daughter much more sociable, present, attentive and stable in balance. Unfortunately, nothing or almost nothing has changed from the point of view of the seizures: they have slightly decreased in number."* • *"My son's quality of life has majorly improved in every way. He is eating orally, more stable in walking and running. He is able to enjoy activities and this drug has given him the chance to explore the world around him."* • *"Due to the significantly higher resilience and the currently reduced seizure situation, we can experience an almost normal everyday life. The temperature sensitivity has fallen sharply, so that even exertions with a rise in body temperature are finally possible. Examples: Our child can now manage a bike ride with us on their own, they can take much longer walks, they can jump on the trampoline, go swimming, and move outside at temperatures above 25 °. In addition, they have made great progress cognitively, for example: learning to read, vocabulary, language comprehension. Fenfluramine is currently the best thing that could have happened to us!"* • *"Significantly improved behavior – increase in independence - much fewer unusable days for him and for us - emotions are again present in a wider range - he has always been very depressed / wretched in series of seizures, he now has much less reason for it - motor skills become slow better - the development is finally slowly progressing again (language, cognition and motor skills) - previously 80 now 12 seizures / month. Seizures remained nocturnal and were even shorter than before - recovery after the seizures faster, that is, 2-3 bad days before the series (2-3 days duration), 2-3 recovery days afterwards, 1-2 good days, then came the preliminary phase of the next series. Now 1 day a little less satisfied before the series, then 2-3 nights with only 2-5 attacks, then 1 day of recovery and then many good days until the next series!"*

		• *"The use of fenfluramine has completely changed our lives for the better. Since we started to use it, [our son] has had only 2 tonic-clonic seizures (due to severe fever 40+), and these attacks were over very quickly. Before using fenfluramine, our son had many seizures and as a family we were often in the hospital as a precaution. In addition, his tonic-clonic seizures almost always lead to a status epilepticus. Since the use of fenfluramine he has not had a status epilepticus and his (measured) epileptic activity has decreased from 5 to 10% of the day to not measurable or very minimal. In addition, our son has started to talk and walk better since using fenfluramine. Too many positive developments to mention".*
Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**NO**	The ERG report has raised concerns about various assumptions regarding mortality (e.g. SUDEP and non-SUDEP related). In our understanding, based both on real world experience and peer review literature, there is absolutely no doubt of the link between premature mortality and the frequency of convulsive seizures (particularly generalised tonic-clonic seizures). We highlight some key statistics below but above all wish to convey that for families living with DS, the threat of premature mortality is real and ever-present. As one UK-based parent says: • "*Living with the constant threat that your child might die, either from a seizure or SUDEP is terrifying and often the first thing a parent will do in the morning upon waking is to check that their child is still breathing. Living in a heightened state of emergency and never being able to switch off in case a seizure occurs, never knowing if it will be short, prolonged or fatal is something that no one will ever get used to."* The ERG report states that around 85% of children with DS survive into adulthood. This is correct, but shouldn't diminish the fact that 15% do not survive. DS occurs in around one in every 15,000 live births in the UK (Symons et al, 2019). These means there are still far, far too many young lives cut tragically short. For every parent/carer living with DS, keeping their son or daughter alive is the foremost concern of every day. Never knowing when a fatal seizure could occur means that children/adults with DS need 24/7 care and supervision, even throughout the night (when many seizures take place, especially in older children and adults), and being prepared to administer emergency medication or to rush to hospital at any moment. This situation places a huge emotional and financial burden on families. According to a recent, 10-year longitudinal study, in over 90% of families, at least one parent had to quit their job or cut back on hours due to the burden of

		looking after a very unwell child (Brunklaus et al; publication ending). We provide approximately £15,000 of funding every year to provide families with seizure monitors to help with monitoring night-time seizures, while one of the most heart-breaking aspects of our work is supporting families who lose a child or adult to SUDEP (we also provide a Bereavement Fund for these families). We would not expect fenfluramine studies to be powered for mortality (for ethical reasons). At the same time, the risk of premature death due to convulsive seizures is a fact of everyday life with DS and cannot be dismissed. A reminder of some of the key statistics on this topic from published literature: SUDEP is responsible for around half of all premature deaths in DS, with status epilepticus responsible for around one-third of these; the risk of SUDEP is up to 15 times higher in DS than other childhood-onset epilepsies and tends to occur at a younger age - 73% of SUDEP deaths occur before the age of 11 (see Cooper et al, 2016 & Shmuely et al, 2016). Mouse studies by Kalume et al, 2013 & Cheah et al, 2013 shed further light on the association between SUDEP and convulsive seizures, we would highlight. Finally, Akiyama et al, 2010 is a useful summary of status epilepticus and mortality risk (e.g. “Prevention of the occurrence of convulsive status epilepticus was indicated to be critically important for the improvement of seizure prognosis in DS.”).
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**NO**	See response to key issue 4.
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure	**YES/NO**	While we have no comment on the specifics of modelling data raised here, we can offer insights into realistic expectations of care required to look after children and adults with DS. A critical point to bear in mind here is that DS is more than epilepsy. DS is a neurological condition, caused by a genetic variation in the sodium ion channel, which causes not only seizures but also intellectual disability and a spectrum of comorbidities, which may include

frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).		autism, ADHD, behaviours that challenge and difficulties with speech, mobility, eating and sleep. All individuals with DS have complex needs. Most children and adults require 24-hour supervision, but this is only partly due to the high seizure burden (and related high risk of premature mortality). Intellectual disability is moderate or severe in 70.5% of adolescents and in 80% of adults (see Darra et al, 2019). Autistic features and challenging behaviour is also very common, occurring in more than half of all individuals with DS. Very few adults with DS will ever be able to live independently. Given this situation, care requirements or carer utilities in DS cannot be calculated by simply looking at changes in seizures. In particular, it does not follow that a reduction in seizure activity (at any age) will lead to a reduction in care requirements. In fact, care requirements are more likely to *increase* than decrease in adulthood. Two-to-one care is not unusual, whether in the family home or residential care. Therefore, from our experience, 1.8 carers per patient for all individuals, irrespective of seizure frequency, is the minimum required and is unlikely to be affected by a reduction in seizure activity.
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**YES/NO**	No comment.
Key issue 13: - This question has been removed as it has commercially in confidential information so will only be viewed by the company and appointed experts.	-	No comment.
Key issue 14: Due to a lack of external data, mortality in the	**YES/NO**	See response to key issue 9.

model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.		
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**YES/NO**	No comment.
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	**YES/NO**	No comment.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 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
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

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Technical engagement response form

Fenfluramine for treating Dravet syndrome [ID1109]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. 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.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments **Thursday 17 December 2020**

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Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- 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.

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About you

Geoffrey Wyatt	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**GW Pharmaceuticals Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to comment on key issues raised in the ERG report. You may also provide additional comments on any key issues that you would like to raise but which are not covered by the existing issues.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	**NO**	<u>Use of general population average weight by age</u> The company submission uses a general population weight assuming that it is representative of an English adult population. However, it is our understanding from clinical consultation and the evidence gathered in GWPCARE 1 and 2 that patients with Dravet syndrome are usually lighter than the general population. It is therefore likely that using a general population weight is an overestimate, and it would be more representative of this patient population to use the patient weight per age group from the fenfluramine registration studies rather than general population weight. Data from LGS could be used as more representative for adults. This use of trial weights would also be in line with TA614.
Key issue 2: Not all relevant comparators have been fully investigated	**NO**	Based on the proposed treatment positioning for fenfluramine, restricting the cost-effectiveness analysis to one comparator only, cannabidiol and clobazam, does not provide relevant information on the cost-effectiveness of fenfluramine compared to other treatment options in these settings. We suggest that the analysis incorporate a

		comparison to the appropriate standard of care in each setting.
Key issue 3: Short-term nature of the included randomised trials	**YES/NO**	No comments
Key issue 4: Adverse events and need for monitoring	**NO**	Given the potential safety impact of fenfluramine on cardiac events, we suggest that costs associated with cardiac adverse events monitoring are fully incorporated within the cost-effectiveness model.
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**YES/NO**	No comments
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**YES/NO**	No comments
Key issue 7: The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	**NO**	The stopping rule in the company submission is applied at one time point only (6 months). This does not align with the stopping rule time points applied in TA614 (stopping rule applied at 6 months, 1 year and 2 years). We suggest that the stopping rule time points applied in the model for cannabidiol should be representative of those used in TA614 to allow consistency of comparison
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**YES**	<u>The relevant dose</u> As per the SmPC for cannabidiol and as discussed at length in TA614 the majority of patients receive a maintenance dose of 10mg/kg/day. Patients are only titrated above this dose "based on individual clinical response and tolerability". If patients are titrated up "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/day twice daily (20 mg/kg/day).” We would therefore consider data from the 10mg/kg/day arm from GWPCARE2 to be the relevant data for use in the NMA as the relevant dataset also considered by the Committee in TA614. <u>Seizure free days</u> The company were unable to include the secondary endpoint, convulsive seizure free days, within the NMA as they were unable to access this data for cannabidiol and clobazam. To enable a relevant comparison, we have provided data on the seizure free days endpoint for the 10mg/kg/day arm from the GWPCARE2 study at the end of this response. The current assumption of proportionality between seizure frequency and seizure free days is not supported. [redacted] The relevant data to use for comparison is provided at the end of this document. <u>Non-convulsive seizures</u> The NMA does not include a comparison of non-convulsive seizure outcomes. We believe that lack of consideration of non-convulsive seizures in the comparison to cannabidiol (rather than standard of care) may not be conservative. To enable a relevant comparison within the NMA, we have provided data on this endpoint for the 10mg/kg/day arm from the GWPCARE2 study.

Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**YES/NO**	No comments
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**YES/NO**	No comments
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25 convulsive seizures a month).	**YES/NO**	No comments
Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**YES/NO**	No comments
Key issue 13: - This question has been removed as it has commercially in confidential information so will only be viewed by the company and appointed experts.	-	-
Key issue 14: Due to a lack of external data, mortality in the model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.	**YES/NO**	No comments

Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.	**YES**	The discrepancy in results may be due in part to the issues raised above. These issues include: • Unjustified assumption of proportionality of seizure frequency and seizure free days outcomes • Application of stopping rules is not comparable to TA614 • Patient weights are based on a general population which may not be representative of a population with Dravet syndrome We welcome the ERG's efforts to investigate the large discrepancy which is currently leading to implausible results in the comparison of cannabidiol versus standard of care. In addition, in the company submission, it is noted in Section B.2.9.5 that cannabidiol dosing towards the top end recommended in the SmPC may be plausible in practice. The company based this assumption on a published interim analysis of the GWPCARE5 OLE study, in which patients titrated to cannabidiol 20mg/kg/day, with a mean modal dose of cannabidiol over 48 weeks of treatment of 21.2mg/kg/day. However, this is a misinterpretation of the GWPCARE5 OLE study. The protocol of this trial required investigators to titrate patients to tolerability limits within doses of up to 30 mg/kg/day. The GWPCARE2 and GWPCARE3 studies clearly demonstrated that there was no dose response on efficacy endpoints with cannabidiol above 10mg/kg/day, even though adverse events worsened considerably. A dose-based subgroup analysis of GWPCARE5 also

		showed that patients on doses of ≤15 mg/kg/day had numerically and statistically indistinguishable seizure outcomes from baseline relative to patients on higher doses. For this reason, the CHMP defined 10mg/kg/day as the recommended maintenance dose. In clinical practice, doses at or abut 10mg/kg/day predominate, and few patients are maintained on doses at or close to 20mg/kg/day. This is acknowledged in TA614 by NICE, who assumed an average dose of 12 mg/kg/day following advice from clinical experts in their preferred base case. A study of patients in the French nATU programme for Epidyolex (n=103) also reported a mean dose of 12mg/kg/day [Chemaly 2020]. An assumption of 20mg/kg/day for cannabidiol considerably overestimates the average costs of this drug in clinical practice; a dose of 12mg/kg/day is more appropriate. *Chemaly N, et al. Abstract C003 presented at the 30eme Congrès de la Société Française de Neurologie Pédiatrique, Toulouse, January 2020.*
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	**YES/NO**	No comments

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[redacted]	[redacted]	

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Technical engagement response form
Fenfluramine for treating Dravet syndrome [ID1109]

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About you

Your name	**Dr Toby Toward** Head of Market Access, Europe. Zogenix International Ltd
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Zogenix International Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Company: Research, development and manufacturer of fenfluramine (Fintepla)**

Key issues for engagement

- **We welcome the opportunity to respond to the ERG Report as part of the Technical Engagement phase of the appraisal process.**
- **We do, however, believe it is important to highlight that we have previously provided extensive comments in our: 'Responses to Clarification Questions'; in the 'Factual Accuracy Checks' document on the draft ERG report; and at 'Technical Engagement Meeting(s)', which had addressed and clearly refuted many of the items that have been again re-listed in the latest ERG report as "Key Issues".**
- **As a consequence, we are deeply concerned that the ERG Report has not taken these extensive comments, the evidence-base and compelling arguments into consideration.**
- **We are therefore in the position that we need to restate that we do not agree that the ERG Report provides an objective, balanced or fair view of our submission, the model or the evidence provided:**
    - **Several of the items listed as "Key issues" are not actually issues that would have a meaningful impact on the decision-making process.**
    - **There is a lack of context and qualification of several issues listed in the report, which precludes a fair interpretation.**
    - **There are repeated listings of the same point as separate "Key issues", which has the potential to create a false impression of the extent of uncertainties and their interpretation in the evidence we have provided.**
    - **The language and tone adopted in the ERG Report substantially overstates incorrect assumptions, that are unnecessarily alarmist and is also not conducive to an objective understanding.**

- **We understand that this appraisal is one of the first to go through the revised Technical Engagement process, which no longer provides a Technical Engagement Report. As a consequence, an important part of the moderating influence from the NICE Technical Team has been excluded from the process. This in turn means that there is now no insight into NICE's perspective on the appraisal going into the Appraisal Committee meeting (scheduled for the 4th Feb 2021).**
- **Given the concerns we have highlighted with the ERG Report, we trust that the materials produced by NICE for the Appraisal Committee meeting will give full consideration to the full range of evidence and the extensive comments provided in our submission, the Responses to Clarification Questions, and the Factual Accuracy Checks document, as well as this document.**
- **As the revised Technical Engagement process has removed an early view of NICE's perspective on the issues raised in the ERG Report, we respectfully request that the consolidated slides are provided to us in a timely manner so that we may attend the Appraisal Committee meeting with knowledge of any truly outstanding issues and a shared understanding of NICE's perspective on this important and much needed new treatment for Dravet Syndrome patients and their families in the UK.**

Please use the table below to comment on key issues raised in the ERG report. You may also provide additional comments on any key issues that you would like to raise but which are not covered by the existing issues.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
Key issue 1: Lack of evidence on adult patients with Dravet Syndrome	**YES**	There is no reason to believe that the effects of fenfluramine observed in the RCTs will differ in adults. This is supported by open label extension and real-world evidence studies, the view of the EMA in licensing fenfluramine in this population, and by the clinical experts consulted by the ERG. We therefore do not believe this is a Key issue that should influence decision-making, as outlined in the Factual accuracy check response document (pages 10-13). Given there are no clinical reasons to doubt the efficacy and safety of fenfluramine in adults, nor its cost effectiveness, any differentiation in access by age would be unwarranted. In summary: • We agree there is a lack of evidence in adults from the RCTs. There was also a lack of evidence in adults in the RCTs of cannabidiol; however, cannabidiol was recommended for use in its full licensed population (including adults) in NICE TA614. • In our submission, data from the OLE and the RWE studies have been provided that support the use of fenfluramine in adults. • Furthermore, the CHMP has issued a positive recommendation for the granting of a market authorisation in DS patients aged 2 years and older, without restriction on use in adults, based on the same RCTs and the RWE data provided to NICE and the ERG • The clinical experts consulted by the ERG agreed that the results of the RCTs are applicable to adults. • These data are further supported by a recently presented paper from the US Early Access programme (Perry et al.,2020), highlighting that the	No change to the ERG report. The company and the ERG agree that the RCT evidence in adults is lacking. However, the ERG report, e.g. Table 1.2, gives a fair summary of this issue, i.e. acknowledges evidence from non-randomised studies while highlighting that these are smaller and at higher risk of bias compared to the RCTs. It also states that the ERG clinical expert agreed that the RCT evidence can be applied to adults which aligns with stakeholder comments received by other clinical experts.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		benefits of fenfluramine in adults is considered comparable to that demonstrated in children [new evidence]. • Based on the above, the clinical data are adequate to support the use of fenfluramine in adults. • The Association of British Neurologists as a stakeholder in the process states: "Both adults and children should be able to benefit from the option of having fenfluramine" (page 337 of technical engagement papers). • The question of whether seizure frequency reduces at age 18, as implemented in the model, is irrelevant to the question of whether there is evidence to support the use of fenfluramine in adults. We however demonstrated that the assumption of a reduction in seizure frequency at age 18 has minimal impact on the ICER (Table 51 of the CS). • Given there are no clinical reasons to doubt the efficacy and safety of fenfluramine in adults, nor its cost effectiveness (as shown in the CS), compared with younger patients, any differentiation by age would be unwarranted, and would potentially introduce equality issues. • Collectively, the limited data in adults should not be viewed as a Key issue for decision-making. **Reference to previously provided documents** • CS Table 51 • CS section B.2.13.3.2 • Factual accuracy check response document, pages 10-13 **New evidence provided** • Perry et al. Fenfluramine (FINTEPLA) provides comparable clinical benefit in adults and children with Dravet syndrome: Real-world experience from the	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		US Early Access Program. Virtual American Epilepsy Society (AES) Annual Meeting, December 4-8, 2020	
Key issue 2: Not all relevant comparators have been fully investigated	**NO**	This claim is factually incorrect. We fully investigated all relevant comparators in the CS and provided a detailed explanation on why this claim is incorrect in the Factual accuracy check response document (pages 34-39). We therefore do not believe this is a Key issue. In summary: • The final scope of this appraisal indicates the comparator as "established clinical management without fenfluramine", which *may* include combinations of 8 different listed therapies. • It is neither feasible nor reasonable to expect comparisons against all possible combinations of these different therapies. • VNS and KD were included in the list of 8 different therapies but are considered as part of standard background therapy – we do not believe the clinical decision will be a choice between fenfluramine (or indeed any other drug therapy) versus KD or VNS, i.e. KD and VNS are not relevant comparators for fenfluramine. • This was explained in the CS (Table 1 and Figure 2), and was explained again in the Response to Clarification Questions B5a. • This also is the same principle of approach implicitly accepted in the TA614 appraisal of cannabidiol. • We appropriately focused our comparisons of add-on fenfluramine against other add-on therapies that are licensed and/or are recommended as add-on therapies in existing NICE guidance (CG137 and TA614). The only	No change to the ERG report. The ERG agrees with the company that "it is neither feasible nor reasonable to expect comparisons against all possible combinations of these different therapies". However, the ERG report, e.g. in section 3.3, highlights that not all comparators listed in the NICE final scope were fully investigated, i.e. results were not available for all of these, which might limit decision-making. This assessment appears to be in line with a stakeholder comment by Sanjay Sisodiya, representing the Association of British Neurologists. Although alternative comparators have been examined in the CS, the ERG emphasizes that the results of the CS base case only include

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		relevant comparators are therefore add-on clobazam, add-on stiripentol and add-on cannabidiol, or continued SoC AEDs. This is fully explained in the CS section B1.3.4. • It is not possible to provide analyses of fenfluramine vs clobazam as there are no RCTs of clobazam in Dravet syndrome, as clearly demonstrated by the SLR results presented in the CS (section B2.9 and Appendix D). • It is not possible to provide analyses vs stiripentol as the endpoints of the stiripentol RCTs are limited and incompatible with the endpoints of the fenfluramine trials. A Cochrane review concluded that the stiripentol RCTs are associated with uncertainty and provide moderate to low quality evidence. For the same reasons no comparisons vs stiripentol were considered in the TA614 appraisal of cannabidiol. This is clearly explained in the CS section B2.9 and was explained again in the Response to Clarification Questions B3a and B3b. • We provided analyses vs cannabidiol as a primary base case because cannabidiol was appraised by NICE [TA614] and is accepted as an option in the add-on therapy pathway, alongside stiripentol. • We have provided analyses of add-on fenfluramine vs SoC AEDs alone, in scenario analyses in the CS (Table 52), noting that this scenario is less reflective of a true clinical decision a physician/patient would likely make if a patient was in need of a new therapy, as it infers that a patient would be retained on an inadequate SoC, if cannabidiol could be offered. • We have also provided a scenario whereby patients that are unable to receive clobazam ('clobazam undesirable'), and thereby could also not receive stiripentol or cannabidiol (both requiring clobazam, per licensed	cannabidiol as a comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam (i.e. the population for which cannabidiol is recommended).

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		indication), could alternatively receive add on fenfluramine to their SoC without clobazam. • We have also provided additional, fully incremental analyses in the Response to Clarification Questions C10, which showed that fenfluramine extendedly dominates cannabidiol with clobazam. • It is therefore incorrect to state that we have not fully investigated all relevant comparators, or (as suggested in the ERG report) that we have not provided analyses against SoC AEDs. The ERG report has not been amended accordingly and so does not provide a fair reflection of the evidence base we have presented. • See also related response to Issue 6 (base case comparators) **Reference to previously provided documents** • CS section B1.3.4, section 2.9, Table 1, Figure 2, Table 52, Appendix D • Response to Clarification Questions B3a, B3b, B5a, C10	
Key issue 3: Short-term nature of the included randomised trials	**NO**	**We have previously provided a detailed response explaining why we do not believe this is a key issue in the Factual accuracy check response document (pages 13-14).** In summary: • The trial design was adequate to demonstrate the efficacy and safety of fenfluramine as a regulatory approved therapy for a rare disease such as Dravet syndrome.	No change to the ERG report. As discussed, e.g. in Table 1.4 of the ERG report, the short-term nature of the included randomised trials "adds to the overall uncertainty of the results" and as such should be considered to be relevant to the decision-making of the committee.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		• The fenfluramine trial durations were the same as the cannabidiol trials and were somewhat longer than those for stiripentol; both of which are recommended as add-on therapy options by NICE. The convulsive seizure endpoints are also aligned with the cannabidiol trial endpoints. • It is therefore incorrect to state that trial durations may be inadequate, when other therapies with the same or shorter trial durations have been recommended by NICE. • We also provided data from the OLE study, which the ERG report (Table 1.4) acknowledges indicates efficacy could be maintained for at least 3 years. • We also provided published prospective RWE data demonstrating efficacy over 5 years, and further observational data relating to its use (and sustained efficacy and maintained safety profile) for up to 27 years. • The suggestion in the ERG report that the RCTs may not be adequate appears to ignore this additional supportive and compelling evidence of the sustained efficacy and safety of fenfluramine with long-term treatment. • The trials were not powered for mortality (or for status epilepticus or SUDEP) and it is unreasonable to expect that they ever could be. This was fully explained in the Response to Clarification Questions (C14). The modelling of survival was therefore appropriately informed by Dravet syndrome specific mortality data from the literature (Cooper et al and Schmuely et al), which observed that SUDEP and status epilepticus were the primary causes of premature death. • The Association of British Neurologists as a stakeholder in this process states in its responses that the main aim of treatment "is to improve seizure control", which "in turn can"…"reduce the risk of status epilepticus and	In her statement, Prof J Helen Cross, representing UCL Great Ormond Street Institute of Child Health & Great Ormond Street Hospital for Children, described this as "an ongoing problem with regulatory comparator trials".

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		SUDEP". and further that they expect fenfluramine to increase length of life more than current care "if seizure freedom or improved control of seizures, especially convulsive seizures, is achieved". • As there is no doubt that fenfluramine improves convulsive seizure control compared with SoC AEDs and cannabidiol (the relevant comparators against which it is possible to compare fenfluramine) there is little reason to doubt there would also be a mortality benefit with fenfluramine. • In contrast to the fenfluramine OLE study data, which the ERG acknowledges supports sustained efficacy for up to 3 years, the OLE study data for cannabidiol presented in the Epidyolex® SmPC, suggests a loss of efficacy of approximately 25% over 48 weeks of treatment. • The collective evidence on the short and long-term efficacy and safety of fenfluramine is arguably more complete than that for any other therapy that has been recommended by NICE for the testament of seizures in DS. • The ERG's claim that this is a key issue is therefore not reflective of the evidence that has been provided in support of fenfluramine. • See also related response to Issue 9 and issue 14 (mortality) **Reference to previously provided documents** • CS section B2.13.1.2, section B3.3.3 • Response to Clarification Questions C13, C14 • Factual accuracy check document, pages 13 to 14	
Key issue 4: Adverse events	**NO**	**We have provided a detailed response in the Factual accuracy check response document (pages 23-34), reiterating what we had demonstrated in the CS and**	Although the ERG still considers this to be a possible issue of

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
and need for monitoring		**Response to Clarification Questions document; that the model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. The suggestion by the ERG that adverse events and monitoring are "Key issues" does not fairly reflect the available data on adverse events; nor does it fairly reflect the evidence and analyses we have provided and is therefore open to misinterpretation. The ERG report should clarify that our approach to modelling adverse events and monitoring are not Key issues that could impact decision-making.** In summary: • Adverse events (AEs) and the need for monitoring were appropriately considered for inclusion in the model. • There was no meaningful difference in AEs between fenfluramine and placebo (i.e. SoC AEDs) in the fenfluramine RCTs in the incidence of serious TEAEs, as explained in the CS (section B2.10). • At the time of our submission, adverse event data for cannabidiol specifically in the licensed subgroup (taking concomitant clobazam) were not available. However, these data became available in a published review (Gunning et al, 2020) shortly after our submission. The data in Gunning et al (2020) indicate there is little difference in the incidence of TEAEs between fenfluramine and cannabidiol (with clobazam), but the incidence of serious TEAEs and incidence of somnolence was notably higher for cannabidiol (with clobazam) than for fenfluramine. • Gunning et al (2020) also reported discontinuation rates due to AEs with cannabidiol (with clobazam). Comparison of discontinuations due to	interest, it acknowledges that the issue may have been over–represented in the key issues presented in the executive summary. Hence, key issues 10 & 13 have been removed from the executive summary.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		adverse events were not meaningfully different between cannabidiol (with clobazam) and fenfluramine. • In our model, the overall discontinuation rates include discontinuation due to AEs that would have been observed in the trials (including any serious AEs). • Minor adverse events (e.g. diarrhoea, fatigue, etc) occurred in both the fenfluramine and cannabidiol arms, and these were generally not severe and so would not have a significant additional impact on resource use, costs or utilities other than that already included (e.g. monitoring during routine healthcare visits). Not explicitly modelling any specific additional impact of an AE(s) in the model is therefore justified on the basis of both: no differential rates of AEs are reported; and the expected minor impact of the actual AE types reported for fenfluramine and cannabidiol vs placebo. • The need for monitoring for weight loss is common to cannabidiol, stiripentol and fenfluramine, and so there is no differential burden. Weight would be routinely monitored and managed as part of the routine/ongoing healthcare visits which are already accounted for (including their associated cost) in the model. • The need for cardiac monitoring with fenfluramine is precautionary based on a historical association with valvular heart disease and pulmonary hypertension when fenfluramine was used at far higher doses for the treatment of obesity in adults. This routine monitoring is fully accounted for in the model. We note that in "Key issue 13" the ERG have acknowledged that the model does include these costs associated with routine cardiac monitoring.	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		• There is no evidence of any cases of valvular heart disease or pulmonary hypertension with fenfluramine at the doses used in Dravet syndrome. There have been no cases reported in the RCTs, the OLE study or in RWE studies including use for up to 27 years. It is therefore entirely appropriate that the model does not include any resource use, costs or disutilities for such (hypothetical) adverse events. • Therefore, as has been explained in the CS, in the Response to Clarification Questions B10, C16b, C20, and in great detail in the Factual accuracy check response document (pages 23-34), the capturing of adverse events in the model is appropriate, and the need for routine cardiac monitoring has also been appropriately reflected in the model. • We note that the ERG report (Table 1.5) states that an alternative approach is not suggested, and the ERG simply wanted to highlight the "issue". The ERG also confirmed during the Technical Engagement meeting of 10th December 2020 that the approach to modelling adverse events and monitoring were not major issues. • Given the above, there is no factual justification for the ERG to highlight 'an incorrect capturing of adverse events' or 'cardiac monitoring' as Key issues that could impact on decision-making; the model accounts for adverse events and cardiac monitoring to the full extent that it is appropriate to do so. • The repeated presentation of adverse events and monitoring as three separate Key issues in the ERG report (Key issues 4, 10 and 13) is therefore particularly unwarranted, it unnecessarily overstates a relatively minor point, and as mentioned above is an example of distortion that has the	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		potential to create an erroneous impression that there are multiple serious issues with the evidence we have provided. • We refer to the ERG and NICE committee to the comments of stakeholders in the process, that further support the safety profile of fenfluramine and the approach we have taken to adverse events and monitoring in our model: o **Dravet Syndrome UK** ▪ P313. "*There was some initial apprehension around fenfluramine due to the history of the drug as a diet pill (children/adults with Dravet Syndrome often have problems with eating) and its withdrawal for this use due to cardiac side effects. However, among families who have trialled fenfluramine these soon dissipated."* ▪ P313. "*Generally, fenfluramine appears well-tolerated and, anecdotally, side effects do not seem to have been an issue to date among our community of families. If cardiac monitoring is required, this does pose an additional burden, however, because parents/ carers are in desperate need of treatments that improve Dravet-related seizures and other comorbidities, they will adhere to monitoring. It's also important to note that if fenfluramine does not have a noticeable benefit, parents/carers will not want to continue with an additional treatment given that their child/adult with Dravet Syndrome will already be on multiple medications."*	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		o **Association of British Neurologists** ▪ P333. "*The main adverse effect of concern is of cardiac valve structural change, which arose from previous use of the agent in combination with another drug for the treatment of obesity. However, available data suggest this is not an important issue for use of fenfluramine alone, at the doses currently recommended. The adverse effect profile of fenfluramine does not otherwise raise specific concerns in comparison to other available treatments."* ▪ P335. Q: Are there any adverse effects that were not apparent in clinical trials? A: *Not currently*. ▪ See also related response to Issue 10 and 13 (monitoring and adverse events) **Reference to previously provided documents** • CS section B2.10 • Factual accuracy check document, page 23 to 34	
Key issue 5: Removing the presumed placebo effect for discontinued patients while	**YES**	**The approach we have taken in the model in the CS reverts patients who discontinue treatment back to their individual baseline seizure frequency before randomisation in the trials. As there is no evidence of the effectiveness of fenfluramine being driven by a significant placebo effect component in the trials, we believe our approach is justified. The ERG's suggested approach of reverting patients back to seizure frequency they experienced whilst receiving placebo**	No change to the ERG report. See section 5.2.2 of the ERG report for the ERG rationale for removing the presumed placebo effect. Additionally, the ERG has some concerns regarding the

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment. **Subsequent treatment post-discontinuation** (included as an issue in the Technical Engagement meeting 10th December 2020): Only the primary intervention in		**treatment in the trials would artificially elevate the effectiveness of discontinued treatment in the long term, which would bias the model against the most effective therapy that maintains patients on treatment for longer. Following the Technical Engagement Meeting we have further explored the impact of these assumptions by removing the placebo effect from the model entirely. The resulting ICER is lower than our base case ICER in the CS, indicating, in contrast to the ERG's suggestion, that our approach in the CS does not overestimate the treatment effect.** In summary: • Our model in the CS reverts patients back to baseline seizure frequency. This baseline is measured after patients have been screened but before being selected for inclusion in the trial and receiving a treatment intervention. Therefore, it is less likely that there would be significant regression to the mean between the baseline and post-randomisation period influencing the observed treatment effects of fenfluramine vs placebo, compared with trials where baseline is estimated based on screening measurements or in achieving a defined treatment success criteria. • The ERG's suggested approach of reverting patients back to a placebo-level of seizure frequency (rather than to their baseline) would maintain the comparator arm efficacy at an artificially elevated level for the patients' lifetime despite the discontinuation of the comparator treatment. This might be an appropriate approach if the observed treatment effect included a substantial placebo effect component, and the difference in efficacy	updated model. First, the ERG was not able to reproduce the reported ICER. When running the updated model provided by the company (without placebo effect), the merged ICER appears to be £32,519 per QALY gained instead of £21,255 per QALY gained. Second, the removal of the placebo effects seems to have impact on the responder rates. When comparing the % of people on treatment over time between the old and the new model, it appears as if a substantial higher proportion remains on treatment. It is not clear to the ERG why this is the case. Lastly, the ERG would have appreciated a detailed list with all changes to the original model (e.g. what were any adjustments made to the implementation of the stopping rule given that the

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
each strategy was considered, i.e. if patients discontinued treatment, they did not switch to a subsequent different intervention (e.g. from fenfluramine to cannabidiol), but instead returned to their baseline SoC		between the intervention and the placebo arm of the RCTs was due to regression to the mean. However, the placebo response in the fenfluramine RCTs was low, and as acknowledged by the ERG elsewhere in its report, the OLE study data indicate that the effects of fenfluramine observed in the RCTs is sustained for up to 3 years. It is therefore unlikely that the treatment effect of fenfluramine observed in the RCTs is driven by a substantial placebo effect, that would likely wane over time. In the absence of evidence to suggest that the placebo effect should be maintained over the lifetime of patients who have discontinued therapy, the ERG's approach is therefore considered not justified by the evidence nor more robust than the approach used in the CS. • It should be noted that in the CS base case, a placebo effect is already included in the model when fenfluramine is being compared to SoC (excluding cannabidiol), which is detrimental for fenfluramine and therefore is considered a conservative assumption we have already taken. This assumes that a patient currently receiving their existing SoC, who stays on that SoC, receives a 'placebo effect' treatment benefit at the point of alternatively receiving a fenfluramine intervention. Furthermore, it would be unlikely that this 'placebo effect' benefit would persist in the long term, particularly for a refectory patient that discontinues therapy for a lack of therapeutic effect, and when there are limited follow-on therapeutic options available for patients. Critically, this approach to return patients to their placebo, rather than to their baseline assumes all of the placebo effect is due to regression to the mean.	placebo effect has now been removed?). Although the ERG welcomes the additional scenario analysis examining the removal of the placebo effect, it should be noted that this was not explicitly requested by the ERG. The ERG requested "...to assume that once patients discontinue treatment, these patients will revert to the placebo seizure frequency as observed during the maintenance period of the trial", which is not the same as removing the placebo effect.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		• Following the Technical Engagement Meeting we have further explored the possible impacts of the assumption of reverting patients back to a placebo-level rather than their baseline level of seizure frequency after treatment discontinuation. • In looking to support the ERG's request, we have undertaken analyses whereby the placebo contribution of seizures has been removed from the model entirely. Therefore, the treatment effect is applied to patients' baseline seizure frequencies to model patients on treatment, and upon discontinuation patients have the treatment effect removed so that they experience their baseline seizure frequency. Compared with cannabidiol, our primary base case ICER reduced from £31,773/QALY to £21,255/QALY. This indicates the base case we provided in the CS was not overestimating treatment effects for remaining on therapy compared with the discontinued comparator as was suggested by the ERG. Further details, including results of the fully incremental analysis are provided in the table Summary of changes to the company's cost-effectiveness estimate(s) below. • Regarding the lack of subsequent treatments following discontinuation, it should be noted that this is not applicable across all positionings of fenfluramine in the add on therapy pathway, and it is unreasonable to expect there are data to support all possible combinations of sequential therapy. The reversion of patients to SoC AEDs following discontinuation of fenfluramine and cannabidiol is a pragmatic approach that may actually be conservative:	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		o When used as a first-line add-on therapy in patients unable to use clobazam, by definition there are no other follow-on therapies beyond SoC AEDs (as stiripentol and cannabidiol are both only licensed for use in combination with clobazam). Reversion to SoC AEDs is therefore entirely justified. o When used in patients who are already taking stiripentol, the addition of fenfluramine is likely to represent an end of line use. If fenfluramine was discontinued then it is theoretically possible that cannabidiol could subsequently be added, and vice versa; however, there are no specific data to support the use of fenfluramine following failure of cannabidiol or vice versa. As these patients are at the end of line having "failed" with several previous lines of therapy including fenfluramine, their capacity to benefit beyond SoC AEDs is likely to be low. Reversion to SoC AEDs includes reversion of both the effects and costs to those of SoC AEDs. As fenfluramine is more effective than cannabidiol, patients on cannabidiol are likely to revert to the lower costs of SoC AEDs at a greater rate than with fenfluramine, which reduces their accrued costs more quickly than with fenfluramine. o When used in patients who are not taking stiripentol, the same issues of data availability apply o It appears that the model in the TA614 appraisal followed the same approach. **Reference to previously provided documents**	

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		• ERG report p.87/88 • Factual accuracy check p50-54	
Key issue 6: In the company's base-case, cannabidiol was used as the only comparator, implying that the cost effectiveness analyses were restricted to people receiving clobazam, i.e. the population for which cannabidiol is recommended.	**NO**	The ERG report includes this statement and fails to report the extensive additional analyses provided to compare fenfluramine against SoC AEDs (as mentioned previously in "Key issue2"); we provided a full range of cost effectiveness analyses in the CS and in the Response to Clarification questions, which reflect the full licensed indication for fenfluramine against all relevant comparators for which data are available. It is incorrect to suggest our cost effectiveness analyses are restricted to people receiving clobazam. This was fully explained in the 'Factual accuracy check' response document (pages 39-44), but has not been adequately addressed in the ERG report. In summary: • We have provided a primary economic analysis of add-on fenfluramine against add-on cannabidiol (with clobazam) for the fully justified reasons stated in Document B (Table 1); with a secondary/scenario analyses against continued SoC AEDs with or without clobazam, to support the clinical and cost effectiveness of fenfluramine across the add-on therapy pathway. • This was explained in CS section B1.1 and section B1.3.4, with results of the secondary analyses provided in CS (Table 52). • This point was also reiterated in the Response to Clarification Questions C3, but ignored. • We also provided fully incremental analyses (SoC AEDs vs cannabidiol vs fenfluramine) in populations taking clobazam and also irrespective of clobazam use in Response to Clarification Question C10, which showed that	No change to the ERG report. This issue is solely related to the CS base case (as is clearly mentioned). Similarly, the ERG report summaries reflect the CS base-case as reported in the CS. The clarification response is referred to in the ERG comments. Moreover, this is only one aspect of key issue 6 that consists of multiple components.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		fenfluramine extendedly dominates cannabidiol plus clobazam (see Table 1). • The implications of the ERG including this (primary economic analysis against cannabidiol plus clobazam) as a "Key issue", is that the scenario analyses provided in the CS and the fully incremental analyses provided in the Response to Clarification Questions are not presented in the ERG report to inform committee decision-making (see below). We believe this is wrong. In the context of having provided a full range of cost effectiveness analyses, the fact we had a primary analysis against cannabidiol plus clobazam in the CS should not be considered a key issue. • By listing this as a key issue, whilst also neglecting to fully report the analyses we have provided against SoC AEDs, the ERG report has great potential to mislead the committee and other readers who understandably may not have the opportunity to read through the entirety of the CS in order to realise these were clearly provided. As a consequence, the committee are therefore not in a position to have reasonably been able to consider the full range of presented cost effectiveness analyses and fully incremental analyses provided. • The ERG report is therefore incorrect to suggest our cost effectiveness analyses are restricted to people receiving clobazam in whom cannabidiol is recommended, when we have provided a full range of cost effectiveness analyses across the full licensed indication for fenfluramine, including analyses irrespective of the use of concomitant clobazam. • We note that this issue is very similar to the stated Key issue 2. In addition to not actually being a key issue when considered in the context of the full	

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<tr><th>Key issue</th><th>Does this response contain new evidence, data or analyses?</th><th>Response</th><th>ERG Comments</th></tr>
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range of analyses that have been provided (but which have been omitted from the ERG report), the presentation of this as a separate Key issue has the potential to create an erroneous impression that there were many serious issues with the evidence we have provided. This is not factually justified.

Table 1. Fully incremental analysis – assuming the proportional use and costs of clobazam as per the base case analysis
<table>
<tr><th>Treatment</th><th>ICER compared to next most effective AED</th><th>ICER compared to underlying SoC AEDs</th></tr>
<tr><td>SoC AED (trial data)</td><td>-</td><td>-</td></tr>
<tr><td>Cannabidiol (with clobazam) + SoC AED</td><td>£69,478/QALY</td><td>£69,478/QALY (Extendedly dominated by fenfluramine + SoC AED)</td></tr>
<tr><td>Fenfluramine + SoC AED</td><td>£31,638/QALY</td><td>£50,968/QALY</td></tr>
</table>
Fully incremental analysis – assuming all patients receiving clobazam amongst their SoC AEDs.
<table>
<tr><th>Treatment</th><th>ICER compared to next most effective AED</th><th>ICER compared to underlyi SoC AEDs</th></tr>
<tr><td>SoC AED (trial data) including clobazam</td><td>-</td><td>-</td></tr>
<tr><td>Cannabidiol (with clobazam) + SoC AED</td><td>£64,271/QALY</td><td>£64,271/QALY (Extendedly dominated by fenfluramine + SoC AED)</td></tr>
</table>
</td><td></td></tr>
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Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		Fenfluramine + SoC AED including clobazam | £37,577/QALY | £51,205/QALY See also related response to Issue 2 (base case comparators). **Reference to previously provided documents** • CS Table 1 and 52 • Response to Clarification Questions C3, C10 • Factual accuracy checks document pages 39 to 44	
Key issue 7: The company implemented a treatment stopping rule for all patients whose seizure frequency was not reduced by at least 30% at 6 months.	**NO**	**We proposed a 30% stopping rule for fenfluramine in our base case in line with that adopted for cannabidiol in TA614. This ensures the appropriate ongoing clinical and cost-effective use of fenfluramine. We do not believe this is a controversial proposal and we do not believe this constitutes a Key issue in the way presented in the ERG report, as explained in our response to the Factual accuracy check (pages 57 to 58).** In summary: • We are proposing that a stopping rule is applied in line with that adopted for cannabidiol in TA614. This will ensure fenfluramine is continued only in those in whom it is clinically and cost effective. • We explored the impact of 3 alternative stopping rules, and for completeness the removal of a stopping rule, in the Response to Clarification Questions C9. However, if the impact on the ICER from removal of the stopping rule for fenfluramine is informative for decision-making	The ERG now acknowledges in the ERG report (section 5.2.4) that the company explored this issue adequately at clarification: "*Although, this issue was adequately explored by the company at clarification, the ERG would have liked to examine its influence in an ERG scenario. However, given transparency issues and time constraint, the ERG was unable to explore this issue*". The company and ERG seem to differ in their view on what

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		then one could argue so is the removal of the stopping rule for both fenfluramine and cannabidiol, for which the ICER reduces to <£20,000/QALY. • We note that the responses of the Association of British Neurologists, on page 328 of the Technical engagement papers, states that "*achieving a 30% reduction in convulsive seizure frequency is an important outcome for patients*", and on page 332 notes that "*it is likely that rules similar to those for cannabidiol, which has established a precedent, should be applied when starting or stopping fenfluramine*" (which would include the 30% stopping rule). • As the model already accounts for discontinuations, and appropriately does not include a waning of treatment effect for fenfluramine, the implementation of further stopping rules every 6 months is not warranted – the stopping rule after the first 6 months would remove those patients who do not achieve the required 30% reduction in convulsive seizure frequency. • As we are proposing this stopping rule for fenfluramine, and this is aligned with that accepted for cannabidiol in TA614 (and the views of the Association of British Neurologists), we do not believe our proposal of a stopping rule is a Key issue as presented by the ERG. **Reference to previously provided documents** • CS section B3.3.5.2 • Response to Clarification Questions C9 • Factual accuracy checks document pages 57 to 58	constitutes as a key issue. However, the ERG acknowledges that the stopping rule is not an unprecedented proposal. It is notable that the stopping rule was not proposed by the European Medicines Agency (EMA) nor was it found in the scope provided by NICE. Consequently further exploring this issue seems warranted.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
Key issue 8: The company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the network meta-analysis (NMA), for convulsive seizure frequency, i.e. assumed these two outcomes are proportional.	**YES**	**The fenfluramine clinical trial data demonstrate that the reduction in convulsive seizure days and convulsive seizure frequency are proportional on a near 1:1 basis, validating our approach. The ERG's estimate that the reduction in convulsive seizure days is only 0.4x the reduction in convulsive seizure frequency is flawed, and as a result all ERG ICER estimates based on this assumption are incorrect.** In summary: • As patients with Dravet syndrome may experience high seizure frequencies, with sometimes multiple seizures per day, we considered that **convulsive seizure-free days** (i.e. days with no seizures) would be a more appropriate determinant of quality of life than **convulsive seizure frequency** (i.e. the number of seizures over a 28 day period). This view was also supported by the physicians and patient advocacy groups, in the development of UK patient pathways research report (provided as supplementary information to the CS). • It was therefore necessary to derive convulsive seizure free days as the inverse of assessing convulsive seizure days observed in the trial. • Sufficient data on convulsive seizure days in the subgroup of patients in the cannabidiol trials taking clobazam were not available to us • Given the close relationship between convulsive seizure frequency and convulsive seizure days we applied the same proportional reduction in convulsive seizure frequency (taken from the NMA) to estimate convulsive seizure days.	No change to the ERG report. It is unclear to the ERG why the calculations used in the ERG report are flawed. In their response, the company seems to indicate that the ERG mixed relative reductions with absolute reductions. However, this is not the case. From table 10 of the CS, the following information was used: "Difference from placebo in CSF per 28 days in %" and "Difference from placebo in convulsive seizure free days in %", more specifically -27.0%/ -62.3% as well as -21.9%/ -54.0% which both correspond to approximately 40% reduction). The ERG welcomes the addition of new data on the proportionality assumption. However, it is unclear to the ERG how the new evidence relates to the data presented in the CS (e.g. CS Table 10).

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
		• The ERG, based on an observation that treatment effects in terms of a percentage change in 'seizure free days' were approximately 40% of the treatment effect seen on the 'percent change from baseline in convulsive seizure frequency', decided to reduce the estimated treatment effects in seizure days by 40% in the model. • However, **it is not valid to directly transfer a percentage reduction in the 'percent change in the convulsive seizure frequency' and apply it directly as a percent change in 'seizure free days per 28 day period'**: o **A percentage change in seizure free days** per 28-day period will in general not be the same as the **negative change in days with seizure** per 28-day period. o e.g. If a patient goes from 1 convulsive seizure to 0 per cycle, this is 100% reduction in convulsive seizures. However, this same patient would go from 1 seizure day per cycle to 0 seizure days per cycle, this a 100% reduction in seizure days (1/1). Conversely, in terms of seizure free days, this equates to 27 seizure free days per cycle going to 28 seizure free days per cycle, an increase of 3.7% (1/27). • Therefore, it is not possible to make inferences about the relationship between a percentage change in the 'percent change in the convulsive **seizure frequency'** being similarly proportionate to a percentage change in '**days with seizure** per 28 days' based on an observed 'percent change in the convulsive **seizure frequency**' to a change in **seizure free days** per 28 day period. • To further support the ERG, we have examined the fenfluramine trial data for percent change from baseline in convulsive seizure days per 28 days and	In addition, it should be noted that, based on the technical engagement response from GW Pharma, for the GWPCARE2 study, the assumption of proportionality between seizure frequency and seizure free days is not supported.

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the percentage change in ‘percent change in the convulsive seizure frequency per 28 day period’. These data (provided as new evidence following the Technical Engagement meeting) demonstrate a near 1:1 relationship, validating our approach and providing further evidence to refute the ERG’s assumption.
• The ERG’s assumption in the model is therefore not justified, and ICER estimates based on this assumption are therefore incorrect.
• Table 2 showing the proportionality of percentage change in seizure frequency to percentage change in days with seizures:

New evidence provided

Table 2. Proportionality between percentage change (per 28 days) in seizure frequency and percentage change in days with seizures
<table>
<tr><th>Arm</th><th>Mean percentage change in days with seizure per 28 days from baseline over the trial period</th><th>Mean percentage change in seizure frequency per 28 days from baseline over the trial period</th><th>(
sei
(</th></tr>
<tr><td>0.4 FFA dose</td><td>-0.42</td><td>-0.44</td><td></td></tr>
<tr><td>0.7 FFA dose</td><td>-0.56</td><td>-0.61</td><td></td></tr>
</table>
•

Reference to previously provided documents
• Factual accuracy check document, page 44-48
</td><td></td></tr>
</table>

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG Comments
Key issue 9: In the company's base-case, it was assumed that mortality was linked to convulsive seizure frequency.	**YES**	**Patients with Dravet syndrome are at a high risk of premature seizure-related mortality (as highlighted in the NICE scoping document for this appraisal). We provided a detailed response in the 'Factual accuracy check' response document (pages 54-57), demonstrating the clear link between convulsive seizure frequency and mortality. The ERG's exclusion of mortality from its analyses is inconsistent with a fair clinical representation of the impact of Dravet syndrome on patients and carers, and irrationally biases the model towards less effective therapy. As fenfluramine is more effective than the comparators, this approach particularly biases the model against fenfluramine.** In summary: • The model does not simply assume there is a link between convulsive seizure frequency and mortality – this approach is based on the clear evidence from the literature that indicates the link between convulsive seizures and SUDEP and that demonstrates SUDEP is the leading cause of death in Dravet syndrome, as explained in CS section B.1.3.1.3. • It is not possible to provide empirical evidence of a reduction in mortality with fenfluramine or any other therapy in Dravet syndrome; RCTs in such a rare disease cannot realistically be powered for mortality events. This was fully explained in the Response to Clarification Questions C14. • To further demonstrate this, we have performed a power calculation based around the mortality rate reported in the most comprehensive review of mortality in Dravet syndrome available in the literature (Cooper et al 2016): o Assuming a power of 0.8 and a 5% decrease in mortality as a significant change from the 15% seen in Cooper et al 2016 (i.e. a	No change to the ERG report. See ERG report section 5.2.6 for the ERG's justification for this assumption. In short, given the strong assumptions the company was required to make (leading to seemingly implausible estimates of RR), the significant challenges in providing empirical evidence to link mortality to convulsive seizure frequency as well as the committee's preferences for TA614, the ERG preferred to remove the link between convulsive seizures and mortality. Patients with Dravet are indeed at an elevated risk of SUDEP, however, the ERG is uncertain about the link between SUDEP and seizure frequency. Given that empirical evidence is lacking, the ERG prefers to keep the mortality assumptions consistent with TA614.

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		mortality of 10% in the intervention arm), this would require a trial involving 1,400 patients followed up for 10 years, i.e. 14,000 patient years of follow-up. This is clearly not possible. • The modelling of survival was therefore appropriately informed by Dravet syndrome specific mortality data from the literature (Cooper et al 2016 and Shmuely et al 2016). • We refer the ERG and NICE committee to the comments of the Association of British Neurologists, as stakeholders in the process, which state "*Currently, the main aim [of treatment] is to improve seizure control. This in turn can lead to slowing, arrest or reversal of cognitive, motor and behavioural decline, and reduce the risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP)"*, and further in response to the question of whether they expect the technology (fenfluramine) to increase length of life more than current care: "*Yes, if seizure freedom or improved control of seizures, especially convulsive seizures, is achieved*". (Technical Engagement Papers p.327 and p.330). • It is therefore a logical expectation that therapy that reduces convulsive seizures will reduce seizure-related deaths. As there is no doubt that fenfluramine improves convulsive seizure control compared with SoC AEDs and cannabidiol (the relevant comparators against which it is possible to compare fenfluramine) there is little reason to doubt there would be a mortality benefit with fenfluramine. • The ERG claims that the implied relative risks when deriving Dravet-related mortality from general epilepsy mortality are seemingly implausible. However, the ERG neglects to comment on the resulting mortality when	

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		implemented in the model, which is aligned with the mortality event rate observed in the RCTs, and the mortality rate reported in published literature on Dravet syndrome. • Furthermore, when assessing relative risks, it is important to consider the relative risks of natural background mortality (or even general epilepsy) are substantially lower in healthy children, compared to children with Dravet syndrome, whereby patients are typically diagnosed in early infancy and experience one of the highest mortality rates of all epileptic encephalopathies. • It is therefore incorrect and potentially misleading to suggest that the relative risks are implausible when the resulting modelled mortality is in line with expectations. • The existence of a link between convulsive seizure frequency and mortality is clear based on the literature and expert opinion. This is further supported by new data recently presented examining the overall and SUDEP mortality rates associated with patients with Dravet syndrome; and a potential reduction in estimated event rate in patients receiving fenfluramine when adjusted for time on treatment (Cross et al 2020) • Therefore, the approach we have taken to quantify the link between convulsive seizure frequency and mortality is reasonable and justified, particularly as it is impossible to provide direct empirical evidence of the impact of add-on treatment in Dravet syndrome, and as the resulting mortality in our model is aligned with expectations. • Despite this, the ERG has adapted our model to remove any mortality benefit arising from a reduction in convulsive seizure frequency on the basis	

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		that there is no empirical evidence of a survival benefit with fenfluramine. This was the same approach the appraisal committee took in TA614, which excluded a mortality benefit for cannabidiol for the same reason. Given that it is impossible to provide such empirical data, it is inappropriate to remove the logically expected survival benefit with treatment from the model: o In adopting this approach, the ERG is effectively rejecting the well documented risk of premature mortality experienced by patients with Dravet syndrome due largely to their high seizure burden. o As it is impossible to provide empirical evidence of a survival benefit with therapy in Dravet syndrome, this approach will effectively exclude consideration in the model of a key benefit of treatment. • Therefore, the ERG's analyses do not provide a fair clinical representation of Dravet syndrome nor a fair consideration of the aims and benefits of treatment. • This means that the ERG's analyses clearly underestimate the cost effectiveness of fenfluramine, as they overestimate the ICERs for fenfluramine vs the comparators. The ERG report does not explain this when presenting these ICER estimates. • As fenfluramine provides superior reduction in convulsive seizure frequency compared to cannabidiol and SoC AEDs, this assumption of the ERG particularly biases its analyses against fenfluramine. • See also related response to Issue 3 and issue 14 (mortality) **New evidence provided**	

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		Power calculation informing the estimated sample size required to demonstrate treatment effect on mortality Publication: Cross et al., Impact of FINTEPLA (fenfluramine) on the expected incidence rate of SUDEP in patients with Dravet syndrome. American Epilepsy Society (AES) Annual Meeting, December 4-8, **Reference to previously provided documents** • CS section B.1.3.1.3 • Factual accuracy response pages 54-57	
Key issue 10: Adverse events (AEs) were only partially included into the economic model, despite Study 1 reporting 12.5% of patients with AEs leading to discontinuation.	**NO**	**As detailed above in response to Key issue 4, adverse events were fully considered and, based on the RCT evidence that showed no increase in the rate of serious TEAEs that would attract resource use and costs or impact on quality of life, there were no resource use, costs or utility decrements due to adverse events to include in the model. The model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. This was explained in detail in the Factual accuracy check response document (pages 23-34).** In addition to the points detailed in response to Key issue 4, we also refer the ERG and NICE committee to the following: • The model appropriately accounts for the 12.5% of patients discontinuing fenfluramine due to adverse events in one of the two fenfluramine RCTs and these are fully reflected in the overall discontinuations applied in the model. It should be noted that data on adverse events with cannabidiol in the subgroup taking clobazam have been published recently (Gunning et al 2020) and demonstrate that there is no meaningful difference in the rates	This issue is now removed from the executive summary. The ERG still believes that some aspects of adverse events have not been included in the model (see ERG report section 5.2.7). However, it also acknowledges that the implications of this are likely to be small (see section 5.2.5. in the CS).

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		of discontinuations with cannabidiol plus clobazam vs fenfluramine (maximum incidences reported in the RCTs 11.0% vs 12.5%, respectively). This was explained in the Factual accuracy check response document (pages 23-34). • The only notable differences in adverse events were a greater incidence of serious TEAEs and greater incidence of somnolence with cannabidiol plus clobazam compared with the incidences reported in the fenfluramine RCTs. This was explained in the Factual accuracy check response document (pages 23-34). • The exclusion of resource utilisation and costs of specific adverse events from the model is therefore unlikely to bias the model in favour of fenfluramine in any comparisons vs cannabidiol. As there were no meaningful differences in rates of serious adverse events between fenfluramine and the placebo group of the RCTs, the exclusion of adverse events from the model is also unlikely to bias the model in favour of fenfluramine in any comparisons against SoC AEDs. • Taken collectively with the points detailed in response to Key issue 4, the ERG has overstated the influence and need for monitoring of adverse events and is incorrect to suggest adverse events are only partially included in the economic model; the model accounts for adverse events and monitoring to the full extent that it is appropriate to do so. ▪ See also related response to Issue 4 and 13 (monitoring and adverse events) **Reference to previously provided documents**	

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		• CS section B.3.3.4 • Factual accuracy response pages 23–34	
Key issue 11: Contrary to NICE technology appraisal (TA) 614, carer utilities of 1.8 carers per patient were included for all patients (i.e. irrespective of seizure frequency) whereas in TA614 they were only included for patients with the two health states reflecting the highest frequency of seizures (>8 to ≤25 and >25	**NO**	**We have previously provided a detailed response in the 'Factual accuracy check' response document (pages 62-69) explaining that carer utilities were estimated and implemented appropriately based on individual carer-level data collected directly from the fenfluramine RCTs. The ERG's suggested approach, in line with TA614, is not supported by the carer-level data in our RCTs; is not applicable to our patient-level modelling approach; and would irrationally penalise a therapy for being highly effective in reducing seizure frequency and demonstrated in the trials to have had a significant and meaningful benefit to carers**. In summary: • We have calculated carer utilities directly from the available trial data for fenfluramine using the relationship between the number of convulsive seizure-free days a patient has and the resulting impact on the carers QoL score; these data demonstrated that incremental improvements in the number of seizure-free days a patient experienced also impacts carer QoL. Our approach is therefore most relevant for our patient-level continuous time model, and is based on superior data than the vignette study-based data used in the TA614 model. • The model in TA614 and the ERG's scenario analyses using our model assume that if individuals had up to 7 days of seizures per month this would have no impact on carer quality of life, which is not supported by the carer-level data from our RCTs and seems unrealistic given the known substantial burden that Dravet syndrome places on patients and carers.	No changes to the ERG report. The ERG is not convinced that carer utilities are adequately incorporated in the model, i.e. that carer utilities of 1.8 carers per patient should be included for all patients (i.e. irrespective of seizure frequency). (see section 5.2.8 of the ERG report).

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convulsive seizures a month).		• There is no evidence that the grouping of seizure frequency used in TA614 have any clinical relevance. TA614 committee papers stated: "*seizure categories were determined to ensure that that patients enrolled in the Phase 3 trials were split into three equal groups and the analyses could be based on sufficient statistical power*". Thus, the grouping appears to be a decision made out of statistical convenience rather than clinical relevance, and is not a relevant assumption for either our trial data or the individual patient-level modelling approach. • Adoption of the approach in TA614 would also result in the implementation of artificial stepped changes in utility benefits, which do not reflect the continuous nature of the data and is not aligned with the patient simulation modelling approach we have appropriately taken. • The approach in TA614 would therefore appear to irrationally penalise a product that has high efficacy in reducing seizure frequency to below these artificial, arbitrary thresholds. • We therefore consider the method used in TA614 and in the ERG's analyses is inferior to the approach we have adopted as it dichotomises patients into 2 seizure severity groups through an arbitrary classification based purely on cannabidiol trial data. . • Regarding the ERG's concerns on whether QOL of carers of children or adolescents applies to QoL in adults, and the suggestion that 1.8 carers may be too high over a lifespan, we feel these ignore the context of the disease course, with seizures contributing to the development of a range of co-morbidities and developmental issues, with few patients able to live independently. This was described in detail in the CS and is clearly reflected	

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		in the patient group stakeholder comments provided in the Technical Engagement Papers that convey the extensive, lifelong impact of Dravet syndrome on quality of life of patients, carers and the wider family: o **Dravet Syndrome UK** ▪ p309. "*Living with the constant threat that your child might die, either from a seizure or SUDEP is terrifying and often the first thing a parent will do in the morning upon waking is to check that their child is still breathing. Living in a heightened state of emergency and never being able to switch off in case a seizure occurs, never knowing if it will be short, prolonged or fatal is something that no one will ever get used to."* ▪ p311: *Very few children/adults experience a seizure-free existence with the currently available treatments (see answer to question 7, above). In addition, the combination of treatment-resistant seizures, debilitating comorbidities and the requirement for 24-hour monitoring cause DS to have a catastrophic impact, not only on health-related quality of life but overall quality of life*. ▪ *Another important unmet need in DS is to reduce the burden of status epilepticus, leading to emergency admissions and rescue medication. A European survey among 584 parents/carers of children/adults with DS found that half of these individuals required at least one emergency admission, and 46% needed at least one ambulance call*	

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		within a 12-month period (see Lagae et al, 2018). Improved treatment of seizures will reduce the likelihood of status epilepticus and consequently reduce the time patients spend at hospital, with less need of emergency rescue medication. This improves quality of life for the whole family, including siblings (who frequently need to accompany their brother or sister to the hospital with their parents, as there is no one else who can look after them) as well as reducing the burden on in-hospital NHS resources. o **Dravet Syndrome UK** ▪ p314. *Improved seizure control affects the whole aspect of looking after a child/adult with this catastrophic condition, leading to significant improvements not only for the individual with Dravet Syndrome, but also the wider family, including siblings. Living with a brother or sister with Dravet Syndrome can have a huge impact on the well-being of siblings. Their routines are disrupted (e.g. via emergency hospital visits); they worry and wonder what is happening and if their sibling will be all right. Often their own time with parents/carers is limited by the complex needs of the child/adult with Dravet Syndrome, who needs 24/7 care.* o **Epilepsy Action** ▪ p319. *The severe needs of many people with Dravet syndrome can have a major impact of the personal life of parents, carers and other family members. These include*	

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		financial pressures, strain on relationships and an impact of the health of parents and carers. ▪ p319. One parent carer noted that '*the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially*.' It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and family life noting that '*it has been a real toll on our health and family life*'. This was echoed by other respondents, '*we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up*.' The same parent carer went on to note that the burden of caring for their son has made them suicidal. • The **ERG's suggested approach, in line with TA614, is therefore not supported by the carer-level data in our RCTs; is not applicable to our patient-level modelling approach; and would irrationally penalise a therapy for being highly effective in reducing seizure frequency and demonstrated in the trials to have had a significant and meaningful benefit to carers** • See also related response to Issue 12 (carer utility) **Reference to previously provided documents** • Company submission B.1.3.1 • Factual accuracy response pages 62–69	

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Key issue 12: When a patient in the economic model died, the corresponding carer utility was also set to zero, causing an overestimation of the impact of mortality	**NO**	**The ERG report (page 108) acknowledges there is currently no clear guidance on the best way to incorporate carer utilities. As noted in our response in the Factual accuracy check document (pages 65-66), the alternative approach suggested by the ERG and used in its scenario analysis is also open to challenge, being based on artificial, arbitrary seizure thresholds and irrationally penalising the most effective therapy.** In summary: • There is currently no clear guidance on the best way to incorporate carer utilities, and our approach is reasonable and justifiable by the directly collected evidence from RCTs. • Given the aims of treatment are to reduce the incidence of seizures which in turn reduces the risk of seizure-related mortality, the ERG's approach would seem to perversely reward therapies that are less effective in reducing the incidence of seizures, and penalise the most effective therapy. • Whilst it is possible that setting carer utilities to zero after the patient's death may overstate the incremental survival effects, the ERG's suggested approach of setting them to a level higher than that seen before death would understate the benefit of improved survival by penalising effective therapy that reduces mortality. It also appears to perversely incentivise a patient's death by awarding a utility benefit, which we doubt the ERG is advocating for in their approach and which we do not feel is appropriate or defensible.	No change to the ERG report. The ERG is not convinced that carer utilities are adequately incorporated in the model and still favours the use of disutilities over utilities which were used in the current model (see section 5.2.8 of the ERG report). In particular, the assumption that when a patient in the economic model died, the corresponding carer utility is set to zero. This overestimates the impact of mortality, given that the caregiver does not die together with the patient and its assumed utility value of 0 is therefore a relatively large underestimation of reality.

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		• The ERG's suggestion, based on the approach taken in the cohort model for TA614, would apply a carer disutility in the health states defined by categories of seizure frequencies (8 to 25, and >25 convulsive seizures per month) until a patient dies. This approach may be reasonable in a responder / non-responder model, where an incremental benefit of being in the responder state can be included and will be zero after death. However, this is not appropriate in our simulation model as we are modelling seizure frequencies / seizure free intervals on a continuous time basis. • As previously described (relating to key issue 11), it seems that the main health state categories (<8, 8-25 and >25 seizures per month) in the cohort model in TA614 have been established for statistical convenience based on the cannabidiol trial data and not clinical relevance. Therefore, there appears to be no rational basis for adopting their use in our patient simulation model that uses patient profiles based on the fenfluramine trial data. The assignment of disutility only to carers whose patients have >8 seizures per month implies that there is no impact on carer quality of life for those patients experiencing up to 7 days with seizures every month, which is unlikely to be the case and also has the perverse effect of penalising treatments that reduce seizures more effectively. Similarly, it would assume the same carer impact for a patient experiencing 2 seizures a week (8 out of 28 days), to that of a patient that experienced seizures almost daily (25 out of 28 days). The ERG's suggestion that this is a more appropriate approach is therefore open to challenge on several fronts. • See also related response to Issue 11 (carer utility)	

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		Reference to previously provided documents • Factual accuracy response pages 65–66	
Key issue 13: The model reflects the monitoring costs, made necessary through an association of the drug with unusual cardiac valvular morphology. This association is, however, not further reflected in the model in cost or utilities.	**NO**	**The ERG acknowledges that the model reflects monitoring costs. As explained for Issue 4 and Issue 10, and in the 'Factual accuracy check' document (pages 23-34) and in the CS and in the Response to Clarification Questions, there is no evidence of valvular heart disease or pulmonary hypertension with fenfluramine at the doses used in Dravet syndrome. This includes in the RCTs, in the open-label extension study with up to 3 years of follow-up, and in real-world evidence studies that include use for up to 27 years. There are therefore no costs or utilities to be included in the model associated with unusual cardiac valvular disease morphology. This is not a Key issue that would influence decision-making, and the ERG's listing of this as a Key issue does not fairly reflect the available data on adverse events; is fundamental without evidence (i.e. speculation) as does not fairly reflect the analyses we provided, and is therefore open to misinterpretation.** ▪ See also related response to Issue 4 and 10 (monitoring and adverse events) **Reference to previously provided documents** • Factual accuracy response pages 23–34	This issue has now been removed from the executive summary as key issue. The ERG still believes that some aspects of adverse events have not been included in the model. However, it also acknowledges that the implications of this are likely to be small (see section 5.2.5. in the CS).
Key issue 14: Due to a lack of external data, mortality in the	**NO**	**As noted in our response to Issue 9, the resulting mortality in our model was aligned with the mortality observed in the RCTs and also the mortality observed in Cooper et al 2016, which is the most comprehensive source of Dravet syndrome specific mortality data available in the literature. As it is impossible for RCTs in this**	No changes to the ERG report. The ERG believes this to be a key issue, especially given the strong assumptions made by the

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model was only compared to mortality observed in the fenfluramine registration trials, which had a limited time horizon.		**disease area to demonstrate mortality benefit (see the power calculation and publication Cross et al 2020, presented in response to Issue 9), our use of the mortality data from Cooper et al 2016 is a reasonable approach, and fact that the resulting mortality in our model is aligned with these data would suggest that our modelled survival is reasonable. We therefore do not believe this is a Key issue as presented by the ERG.** • See also related response to Issue 3 and issue 9 (mortality) **Reference to previously provided documents** • CS section B.1.3.1.3. • Factual accuracy response p.54-57	company in linking seizure frequency to mortality.
Key issue 15: There is a large discrepancy between results in TA614 and the current appraisal. TA614 appraisal demonstrated a substantially lower incremental cost effectiveness	**NO**	**The ERG's comparisons of the results from our patient-level simulation model with those of the cohort model in TA614 are fundamentally flawed, and the comparisons are unable to provide meaningful information on the merits of each modelling approach or reliability of their outputs. This was fully explained in the Factual accuracy check response document (pages 9-10), but the ERG report retains this flawed comparison without any qualification or context. To avoid misleading the committee and other readers of the ERG report, these flawed comparisons should be removed**. In summary: • We have developed a fundamentally different, superior, patient-level simulation model with a substantial effort on the manufacture's side to address the short-comings in the cohort modelling approach taken in TA614	No changes to the ERG report. Given that TA614 considers the same population and treatment (cannabidiol) as in the current appraisal, the ERG believes it is relevant to present a cross-validation between the two appraisals. The ERG acknowledges the differences in modelling approach and model structure but does not agree the comparison is fundamentally flawed.

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ratio (ICER) for cannabidiol compared to standard of care (SoC) than that presented in the CS, with an ICER of £29,268 per quality-adjusted life year (QALY) gained in TA614 (company base-case after ACD) and £69,478 per QALY gained in the current appraisal.		○ The manufacturer of cannabidiol developed a cohort model for TA614. This required the subgrouping of clinical trial data to accommodate arbitrarily defined health states, and used utility data derived from simple rating of vignettes to weight these arbitrary health states. The appraisal committee for TA614 suggested that a discrete event simulation-type model would better account for the heterogeneity in the modelled population. ○ We have developed a patient-level simulation model, which accounts for the heterogeneity in the Dravet syndrome population, explicitly models absolute seizure frequencies and employs higher resolution, continuous patient-level data rather than relative seizure frequencies and arbitrary categorical data cut offs used in the TA614 model. This is a superior modelling approach for this disease, aligned with the suggestions of the appraisal committee in TA614. ○ Given the differences in modelling approach it is fully expected that the results of the models will differ in terms of both costs and outcomes. • Our model also uses superior clinical and quality of life data within this modelling approach. ○ Whilst the RCTs informing the efficacy of cannabidiol are the same, the population is appropriately defined in our model based on the robust patient-level data from the fenfluramine studies. ○ A robust network meta-analysis of the RCTs provides adjusted comparative data, and the utility estimates are directly linked to	

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		clinical outcomes, being based on regression analyses of quality of life data against seizure metrics observed directly in the patient-level and carer-level trial data. • The ICER and costs for cannabidiol vs SoC AEDs from TA614 and from our model are based on completely different prices. o The ICER and costs quoted by the ERG from TA614 are based on the confidential discounted PAS price of cannabidiol (with cannabidiol dosing capped at a weight for 18 year old patients); we did not have access to these prices and therefore are unable to test them in our base case or scenario analyses. o The treatment costs and resulting ICER quoted by the ERG from our model are appropriately based on the list price of cannabidiol as this is what is publicly available. In addition, in our model cannabidiol dosing is more appropriately capped based on the weight of adults. • Therefore, the cost, QALYs and ICER estimates from our model and from the model in TA614 are clearly not comparable. The ERG's direct comparison of our model outputs with those from the cohort model in TA614 is therefore fundamentally flawed. • The ERG report does not include any of this context or other qualification of the comparisons that have been presented. There is no basis for assuming that the TA614 model is more accurate in determining the cost effectiveness of cannabidiol, or the component costs and QALYs, particularly given the list of limitations of the TA614 model identified by the same ERG and presented in the FAD for TA614, and the views of the	

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		committee in TA614 that a different modelling approach (aligned with our modelling approach) may be more appropriate. Therefore, there is no sound reason to assume the model in TA614 as the benchmark against which our model should be judged. • **Importantly, the data presented by the ERG do not reflect all the comparators in the same model. Only partial results are provided from the fenfluramine model. These are SoC Vs cannabidiol; however this omits the results for fenfluramine Vs SoC and fenfluramine Vs cannabidiol (with clobazam) from the fully incremental analysis (key issue 6, Table 2).** • **As highlighted in the above (Table 2), if these missing data were presented (rather than the abstract results of SoC Vs Cannabidiol from the TA614 appraisal); it would show within the same (fenfluramine) model, that fenfluramine demonstrated extended dominance over cannabidiol (with clobazam). We believe this is important information for the Committee to be able to make an informed decision on fenfluramine in the context of a previous NICE decision (TA614) in recommending use of cannabidiol (with clobazam)**. • During the Technical Engagement meeting (10th December 2020) the ERG explained that this comparison was included in the ERG report as a cross-validation of our model with TA614 because we had not included such a cross-validation in the CS. Given the fundamental differences in modelling approach, data quality and handling, and the fact that costs are (appropriately) completely different, we do not believe this comparison of the outputs of our superior model against the outputs of an inferior model can provide a meaningful validation of our model. Indeed, the differences	

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		noted in the outputs of our model and the TA614 model reflect this very point rather than providing meaningful information on the merits of each modelling approach or reliability of their outputs. • This unqualified and unjustified comparison of model outputs provided in the ERG report has the potential to mislead the committee and other readers. We therefore believe this flawed comparison should be removed. **Reference to previously provided documents** • Factual accuracy response pages 9-10	
Key issue 16: The ERG encountered several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model	**NO**	**We forewarned the ERG of the long run-time of the model, we provided all code for the model and answered all points of clarification. We therefore question the suggested issues of "transparency" and strongly reject the suggestion that any issues that has been listed under Key Issue 16 could possibly "threaten the internal validity of the model".** In summary: • During the Technical Engagement meeting (10th December 2020) the ERG clarified in the agenda that this Issue relates to the long run time of the model particularly for the probabilistic sensitivity analyses (PSA), the omission of the R code for one of the scenario analyses that the ERG had requested (provided shortly after), and the basis of the number of simulated patients used in the base case. • We forewarned the ERG of the long run time of the model during the telephone call to discuss the Clarification requests. We explained we had	No changes to the ERG report. The ERG strongly disagrees with the responses made by the company. The ERG did not receive the required code to re-run scenario analyses (e.g. the scenario with alternative carer utilities). Moreover, some "switches" in the "Input parameters" sheet did not seem to work, the model contained redundant code, there were some issues with the generated patient profiles and when determining events in the model (e.g. death),

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		optimised the R code as far as possible; however, it is well recognised that conducting PSA within a patient-level simulation model is a lengthy process. • We trust that the ERG was able to replicate our base case and other scenario analyses that have a very manageable run time, and that this provides confidence that the analyses we have reported are true reflections of the model outputs. • We provided all the code requested to run the model and the bootstrapping of seizures, and answered all points of clarification, including the basis for the number of simulated patients and demonstration that the model results were stable to that number of simulated patients. We therefore question why the ERG feels there are potential transparency issues. • We reject the suggestion of the ERG that any of the issues it has raised under Key Issue 16 "threaten the internal validity of the model" and, given the above, firmly believe this is inappropriate and misleading. • We are of course willing to provide any further clarifications or explanations, and resend the R code, for any and all analyses we have provided in the CS and clarification responses.	random draws form probability distribution were used, which is generally done in patient-level simulation. However, these random draws were not similar for both cohorts (e.g. identical patients in both cohorts had different mortality rates), causing a difference in for example overall survival solely related to different random draws unrelated to any efficacy estimates in the model (see section 6.4.4 of the ERG report).

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

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 ICER	ERG response
Key issue 5: Removing the presumed placebo effect for discontinued patients while not removing it for patients on treatment would likely result in an overestimated treatment effect for being on treatment versus patients that discontinued treatment.	**Our base** case model in the CS reverts patients back to baseline seizure frequency upon treatment discontinuation. The placebo component of treatment effect was incorporated for both fenfluramine and the comparator arms.	The placebo contribution of seizures has been removed from the model entirely. Therefore, the treatment effect is applied to patients' baseline seizure frequencies to model patients on treatment, and upon discontinuation patients have the treatment effect removed so that they experience their baseline seizure frequency.	The ICER reduced compared with base case in CS	As mentioned above, the ERG has some concerns regarding the updated model. Most importantly, the ERG was not able to reproduce the reported ICER. When running the updated model provided by the company (without placebo effect), the merged ICER appears to be £32,519 per QALY gained instead of £21,255 per QALY gained.

Company's preferred base case following technical engagement	Fenfluramine vs Cannabidiol Incremental QALYs: [redacted]	Fenfluramine vs Cannabidiol Incremental costs: [redacted]	The ICER reduced from £31,773/QALY to £21,255/QALY	
Fully incremental analysis	Cannabidiol vs SoC AEDs Incremental QALYs: [redacted] Fenfluramine vs SoC AEDs Incremental QALYs: [redacted]	Cannabidiol vs SoC AEDs Incremental costs: [redacted] Fenfluramine vs SoC AEDs Incremental costs: [redacted]	Fenfluramine extendedly dominates cannabidiol as observed in base case analyses provided in CS and Response to Clarifications	

Additional issues identified during the technical engagement meetings and prior clarifications responses.

Additional Issues	Does this response contain new evidence, data or analyses?	Details	ERG response
All of the ERG's base case ICERs and scenario analyses presented in the ERG Report are overestimated, and should be amended	**NO**	• All of the ERG's base case and scenario analyses erroneously assume that the reduction in convulsive seizure days ~ 0.4 x reduction in convulsive seizure frequency: o We demonstrate in our response to Key Issue 8 that this is a flawed assumption and that our approach using a 1:1 relationship is essentially valid. o The ERG's analyses therefore overestimate the ICERs and should be amended in line with this evidence. • The ERG's base case and sensitivity analyses irrationally exclude the impact of convulsive seizure reduction on mortality. As explained in our response to Key Issue 9: o This is inconsistent with a fair clinical representation of the impact of Dravet syndrome on patients and carers, and the views of	As mentioned above, it is unclear to the ERG why the calculations used in the ERG report are flawed. In their response, the company seems to indicate that the ERG mixed relative reductions with absolute reductions. However, this is not the case. From table 10 of the CS, the following information was used: "Difference from placebo in CSF per 28 days in %" and "Difference from placebo in convulsive

		clinical experts who confirmed that the aim of therapy is to reduce convulsive seizures and in turn reduce the risk of mortality. o It is impossible to demonstrate empirically that any therapy would have a mortality benefit in in Dravet syndrome. o Excluding mortality irrationally biases the model against effective therapy. o As fenfluramine is more effective than the comparators, this approach particularly biases the model against fenfluramine.	seizure free days in %" (more specifically -27.0%/ -62.3% as well as -21.9%/ -54.0% which both correspond to approximately 40% reduction).
The ERG Report omits the full results of our fully incremental analyses	**NO**	• The ERG Report includes details of the comparison of cannabidiol vs SoC AEDs, taken from our fully incremental analyses, but not the full details of the comparison of FFA vs Cannabidiol vs SoC AEDs the show how fenfluramine extendedly dominates cannabidiol	Results of the fully incremental analyses are mentioned in the ERG report in section 6.3
The ERG has not presented fully incremental analyses for its analyses	**NO**	• Once corrected for the above erroneous assumptions, the ERG's base case and scenario analyses should be presented as fully incremental analyses comparing SoC AEDs vs cannabidiol vs fenfluramine to facilitate interpretation.	Given that the model was only able to run two treatments (i.e. SoC/CBD or fenfluramine) at the same time and that results differed due to different random seeds (e.g. results in the fenfluramine arm when compared to SoC were different to the results in the fenfluramine arm when compared to cannabidiol), the model is not optimally suited to present fully incremental analyses. Therefore, the incremental analyses were only presented as scenario analysis in the ERG report (section 6.3 of the ERG report).