NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Contents:

The following documents are made available to consultees and commentators:

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

Appraisal title

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Professional group	Association of British Neurologists	We are concerned that this recommendation will lead to a potentially very effective drug not being available for this highly treatment refractory group of patients.	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.
2	Professional group	Association of British Neurologists	Regarding the committee's concern about long-term efficacy of treatment, data suggests that treatment effect can be maintained over at least a 3-year period. We appreciate that patients continuing in the open label studies are those who have had a benefit, but this is going to be the case for any drug and as clinicians, we regularly discontinue drugs if there is no benefit, or a beneficial effect is lost. Further, even if effects were to wear off after three years, we do not consider that a valid reason to withhold an effective treatment or not to use the treatment to reduce seizure and carer burden during this time and discontinue it once it is no longer effective. Additionally, 3 years of improvement would count as a long time for most in this patient group.	Thanks for your comment. The committee considered evidence from the company that the treatment effect on percentage change in convulsive seizure frequency per 28 days relative to baseline was largely maintained at 3-year follow up in Study 1503. The committee concluded that it was appropriate for waning to be excluded from in the model (FAD section 3.11). The final guidance also notes that clinicians would not continue treatment if there was no benefit. Taking into consideration the consultation comments along with the company's updated models and the updated discount, fenfluramine is now recommended for Dravet syndrome.
3	Professional group	Association of British Neurologists	We note the committee's concern regarding where QALY gains come from and what factors contribute to them. We also note that the committee has previously appraised and approved CBD for the same indication and it is not clear to us why the committee is not using the same factors as taken into account for that treatment. Reviewing the modelling in the TA for CBD, that appears to be different to the current modelling and the committee seems to have used Markov multistate model to compare fenfluramine to CBD, when the original CBD approval was not actually based on this level of modelling. Similarly, seizure free days were not included in the CBD modelling and the criteria for continuing prescription is 30% reduction of seizure frequency. Overall, we are concerned that the level of scrutiny of data and modelling appears to be different for fenfluramine compared with that for CBD.	Thank you for your comment. The model submitted in this case was developed by the company. NICE and the ERG can only scrutinise the model that it submitted to it.
4	Professional group	Association of British Neurologists	We are concerned that the committee is putting so much emphasis on whether treatment should be used with or without Stiripentol or if Stiripentol is a treatment modifier. Data supports benefit for Fenfluramine with and without concomitant use of Stiripentol and there are interactions between the drugs (resulting in higher serum levels of Fenfluramine if used with Stiripentol), is the likely reason lower	Thanks for your comment. The final guidance notes that several issues were resolved during consultation on the first appraisal consultation document, and the committee agreed that stiripentol's impact on fenfluramine's effectiveness reflects an underlying

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			dose of Fenfluramine can be used when taken in combination with Stiripentol.	pharmacokinetic interaction, not a modified treatment effect.
5	Professional group	Association of British Neurologists	We strongly disagree with the statement that "it is unclear if fenfluramine meets the criteria for an innovative treatment". The mode of action is different to previously used drugs and it is clear from clinical experience and trials that the same benefits have not been seen in other drugs.	NICE considers "the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). Upon review of the consultation comments, the committee now consider that there are likely to be additional benefits of fenfluramine which are not captured in the model. Fenfluramine is recommended for Dravet syndrome.
6	Professional group	Association of British Neurologists	We are concerned about the reports of valvopathies when the drug was uses in higher doses for other indications previously and would therefore recommend that cardiac monitoring (cost of echocardiogram) is included in the economic modelling.	Thanks for your comment. Section 2.22 of the guidance explains how this was captured in the model and also notes the minor impact on the cost-effectiveness estimate.
7	Clinical expert	n/a	I am concerned that this recommendation may deny individuals with Dravet syndrome a step change state of the art treatment, for which there is evidence for significant clinical efficacy, in a condition where current treatments offer little prospect for seizure control	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.
8	Clinical expert	n/a	Section 3.3 Stiripentol is usually added to valproate and then ultimately a small dose of clobazam added, as if stiripentol is added to maximal doses of valproate and clobazam there will be drowsiness. The dose of clobazam needs to be individually titrated	Thanks for your comment. This has been captured in section 3.3 and 3.4 of the guidance.
9	Clinical expert	n/a	Section 3.8 There is comment about a significant benefit in Quality of Life being seen with fenfluramine over placebo in study 1, but the difference not reaching significance in study 1504, albeit over 14 weeks. The company submission (B1.4.2) highlights the need for weighting of Quality of Life to prevent underestimation of the true impact of convulsive seizures	Thanks for your comment. Section 3.27 notes that there are likely benefits not included in the model and these may include the benefit of fenfluramine on reducing the duration of seizures or, as the company note, the benefit on quality of life for people with Dravet syndrome.
10	Clinical expert	n/a	Section 3.9 I challenge that although usual for efficacy to be quoted vs placebo, rather than as a difference from placebo and therefore has led to concern about interpretation of the inclusion of placebo effect, the difference in effect relative to placebo is still very significant, a degree of effect not seen in any other clinical trials of anti seizure medication	Thanks for your comment. The final guidance notes that 'fenfluramine may be more effective than cannabidiol plus clobazam in reducing convulsive seizure frequencies'. During consultation, the committee considered a new indirect treatment comparison submitted by the company, which compared fenfluramine, cannabidiol, and placebo on the outcome of percentage change from baseline in convulsive seizure frequency (FAD section 3.9). This led to the committee changing their position.
11	Clinical expert	n/a	Section 3.10 The document states that it is unclear as to whether stiripentol is an effect modifier of fenfluramine. Previous pharmacokinetic studies suggested the	Thanks for your comment. The final guidance notes that several issues were resolved during consultation

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			need for a lower dose of fenfluramine in view of the interaction with stiripentol (due to inhibition of the CYP 450 system in the liver), and consequent effect on fenfluramine metabolism. I would challenge there is any evidence of a modifier effect; the dose in combination with stiripentol was lower, but still showed significant benefit.	on the first appraisal consultation document, and the committee agreed that stiripentol's impact on fenfluramine's effectiveness reflects an underlying pharmacokinetic interaction, not a modified treatment effect.
12	Clinical expert	n/a	Section 3.11 I would suggest that any 'honeymoon' effect with a waning of effect of fenfluramine over time would be seen sooner than 3 years – at less than a year. I acknowledge the concern about lack of data on long term effect, but minimal drop out was seen over a 3 year period suggesting good retention and maintenance of benefit	Thanks for your comment. The committee considered evidence from the company that the treatment effect on percentage change in convulsive seizure frequency per 28 days relative to baseline was largely maintained at 3-year follow up in Study 1503. The committee concluded that it was appropriate for waning to be excluded from in the model (FAD section 3.11). Taking into consideration the consultation comments along with the company's updated models and the updated discount, fenfluramine is now recommended for Dravet syndrome.
13	Clinical expert	n/a	Section 3.18 It is stated that it is incorrect to assume that patients stopping treatment will return to the baseline seizure frequency rather than that seen on placebo, the placebo effect not taken into consideration. Where individuals are taken off the treatment it would be presumed in the majority to be lack of effect- in only a very small number this was due to poor tolerability.	Thanks for your comment. The final guidance notes that several issues were resolved during consultation on the first appraisal consultation document, and the committee agreed that people in the model who stop treatment revert to the seizure frequency in the placebo arm during the trial maintenance period. During consultation, the committee submitted a revise base case model where it followed the approach recommended by the committee in the appraisal consultation document.
14	Clinical expert	n/a	Section 3.24 Non convulsive seizures; there is no question that these remain difficult to count securely and therefore numbers are less reliable. However on the data submission there is a reduction in nonconvulsive seizures (and total seizures) compared to placebo. It is less certain it would be detrimental rather than supportive to include the data in comparison with that of cannabidiol.	Thanks for your comment. The committee acknowledged the difficulties with measuring non-convulsive seizures and considered it an existing uncertainty. However, fenfluramine is now recommended.
15	Clinical expert	n/a	There is a concern about the high level of uncertainty in the relationship between convulsive seizure frequency and mortality and the assumption that reducing the frequency of seizures prolongs life. The mortality rate and rate of Sudden Unexpected Death in Epilepsy (SUDEP) in Dravet syndrome is high; the highest association is with ongoing convulsive seizures, so an assumption that reduction of convulsive seizures will reduce the risk of SUDEP is not inappropriate. [redacted]. This said another marker of success of treatment would be reduction of hospital admissions (for	Thanks for your comment. The committee took these comments into consideration along with the additional analyses provided by the company, the company's updated models and the updated discount. As noted in section 3.17 and 3.18, the committee agreed there may be a relationship between seizure frequency and mortality but concluded the strength of that relationship is unclear. However, fenfluramine has now been recommended for Dravet syndrome.

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			prolonged seizures or exacerbation of seizure frequency).	
16	Clinical expert	n/a	It appears that the main concern within this report is one of uncertainties about the modelling put forward for cost effectiveness of the use of fenfluramine. I hope that the data required to amend this can be reviewed. There appears little question about the efficacy of fenfluramine in Dravet syndrome. I would like to emphasise that lack of access to fenfluramine for the Dravet population in the UK may be seen as discriminatory against this population when considering standard of care now acknowledged worldwide.	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.
17	Patient organisation	Dravet Syndrome UK	We feel the NICE committee hasn't fully taken into account the testimony previously submitted by DSUK in December 2020, which describes Dravet Syndrome as a spectrum disorder that is highly unpredictable (see our response to key issue 2). Not all children/adults with Dravet Syndrome respond in the same way to treatments. While fenfluramine may not work for all individuals with Dravet Syndrome, and their response to the treatment may change over time, it is important to recognise that this is to be expected due to the spectrum nature of the condition and its intractability. However, as stated in our previous submission, we have heard from many families in the UK and Europe for whom fenfluramine has worked, and some for whom it has been transformative. It is clear from the lived experience of our patient community that even small improvements in seizure control can lead to a dramatic improvement in quality of life for families. We submitted evidence to support this statement as an appendix to our submission - a survey conducted by the Dravet Syndrome European Federation (DSEF) among 118 patient caregivers in 8 European countries (including the UK). We are providing a summary of this research, which includes verbatim caregiver testimonies, as an appendix and ask that the NICE Committee read this document again in full.	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.
18	Patient organisation	Dravet Syndrome UK	Regarding the statement in the ACD that there is uncertainty about fenfluramine's treatment effect in adults. We feel that given expert clinician testimony and data now available from several real-world/open label studies, any exclusion of adults would be discriminatory. We refer the NICE committee to the evidence DSUK previously submitted in December 2020 (see our response to key issue 1) which describes how the adult Dravet population which has been under-recognised for many years. Historically, there is little data on adults living with Dravet Syndrome, compared to the paediatric population. Because adults are under-diagnosed, it is often a lot harder to gather data on adults. This situation should not lead to adults being disadvantaged. We urge the committee not to exclude adults living in the UK from the opportunity for better seizure control and better quality of life.	Thanks for your comment. The committee considered a lack of evidence to be an uncertainty and concluded that the evidence in children and young people with Dravet syndrome is generalisable to adults in absolute terms, and the relative treatment effect is likely to be similar. It acknowledged the difficulties noted with including adults in studies. Fenfluramine is recommended for all people with Dravet syndrome, regardless of age.
19	Patient organisation	Dravet Syndrome UK	Numerous other statements in the ACD (e.g., 'It is unclear if fenfluramine meets the criteria for an innovative treatment', 'The relationship between convulsive seizure frequency and mortality is not clear') are surprising to read because they do not correspond with the experience of our patient community or with what we have read and heard to date from the medical community. We are concerned that the experience and views of clinical experts have not be represented and taken	NICE considers "the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). Upon

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			into account as fully as they might be in the submissions and consultation. The anticipation for fenfluramine in the Dravet community has not been driven by the manufacturers but by grassroots experience and the excitement we have heard from the medical community involved in trials to date. We understand it is the company's responsibility to make the submission for approval of fenfluramine, but we also urge the NICE committee to take into account evidence from independent clinicians who have consistently expressed their view that fenfluramine represents a significant step change for a significant number of patients, who have not responded to currently available treatments. These patients, and their families, are desperately in need of new, effective and well-tolerated treatments for this absolutely devastating condition.	review of the consultation comments, the committee now consider that there are likely to be additional benefits of fenfluramine which are not captured in the model. Fenfluramine is recommended for Dravet syndrome.
20	Patient organisation	Epilepsy Action	Epilepsy Action is concerned that this recommendation may imply that fenfluramine is not an effective add-on therapy for treating seizures associated with Dravet syndrome despite available clinical evidence and lived experience to the contrary. Concerns raised in the appraisal consultation document (ACD) around economic modelling are valid and need to be addressed. However, these technicalities should be assessed against the clinical benefits of the proposed treatment and the severe impact of this severe condition. It is our view that the impact of uncertainties and limitations in both the company modelling and that of the ERG on cost-effective considerations should not prevent an effective and much needed additional add-on treatment option for seizures associated with Dravet from being recommended. We would encourage the company and NICE to work together at pace to address the issues highlighted in the ACD for an informed decision to be taken on the basis of rigorous data and evidence.	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.
21	Patient organisation	Epilepsy Action	While due consideration should be given to whether treatment effect will stay the same in the long term it is not uncommon for antiepileptic drugs to reduce in effectiveness over time for some patients. There is some evidence that currently recommended add-on treatments for seizures associated with Dravet syndrome such as cannabidiol can reduce in effectiveness in the long term. Uncertainties around longer-term treatment effect should be compared against the severe and often life limiting nature of Dravet syndrome. If a treatment option can provide a reduction in frequency of convulsive seizures even for a short time the associated quality of life benefits for the patient and others involved with their care are likely to be significant.	Thanks for your comment. The committee considered evidence from the company that the treatment effect on percentage change in convulsive seizure frequency per 28 days relative to baseline was largely maintained at 3-year follow up in Study 1503. The committee concluded that it was appropriate for waning to be excluded from in the model (FAD section 3.11). Taking into consideration the consultation comments along with the company's updated models and the updated discount, fenfluramine is now recommended for Dravet syndrome.

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22	Patient organisation	Epilepsy Action	Epilepsy Action is concerned about the proposed date for review of the treatment and would recommend a process of iterative review as and when modelling issues have been addressed or more high-quality data is made available. Given that the decision not to recommend at this stage is largely based on economic modelling considerations rather than concerns around safety and efficacy the proposed three-year review period is overly restrictive. We would encourage NICE to engage with the company and other experts to address the issues identified in the ACD as a matter of urgency and seek a review of the appraisal as soon as possible.	Thanks for your comment. The recommendation has changed and fenfluramine is recommended for Dravet syndrome.
23	Patient organisation	Epilepsy Action	Given the intractable nature of Dravet syndrome, a treatment such as fenfluramine that offers significant benefits for some in terms of reductions in convulsive seizures and associated improvements in quality of life should be recognised as an innovative treatment. Epilepsy Action would echo the comments of the clinical expert in the ACD and encourage NICE to appraise fenfluramine as an “innovative treatment” offering a potential step change in the treatment of Dravet syndrome.	NICE considers “the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure” (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). Upon review of the consultation comments, the committee now consider that there are likely to be additional benefits of fenfluramine which are not captured in the model. Fenfluramine is recommended for Dravet syndrome.
24	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Preliminary recommendation (section 1, page 3)** • We are disappointed that the ACD currently determines a preliminary negative recommendation for the use of fenfluramine in the treatment of seizures associated with Dravet syndrome. • Often diagnosed in early infancy, Dravet syndrome is a very rare, genetic, and complex epileptic encephalopathy. Existing therapies are unable to control the daily and life-threatening convulsive seizures associated with Dravet syndrome and lamentably, 1 in 5 to 7 parents will not see their child reach adulthood; with the daily risks of seizure-related injuries and premature mortality continuing into adulthood (see references 2-4 of CS). Life-long seizures and a progressive deterioration in functional (e.g. walking, talking, washing), cognitive and behavioural development, affects every part of daily-living and the overall quality of life of patients, their immediate carer-givers providing around the clock care (Pagano et al 2018) and their broader family unit (Bailey et al, 2020: https://doi.org/10.1016/j.yebeh.2020.107377). There is a compelling clinical, economic and humanistic need for effective and tolerable treatment options that reduce the seizures associated with Dravet	Thanks for your comment. The committee took all consultation comments into consideration along with the company’s updated models and the updated discount. Fenfluramine is now recommended for Dravet syndrome.

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			syndrome to alleviate the daily burden on patients, their carer-givers and their families, as well as for the multi-disciplinary team of health care professionals that support them. • Fenfluramine is clearly a highly effective and well tolerated treatment that can address this unmet need. It is supported by the most compelling and comprehensive evidence package of any of the NICE-recommended Dravet syndrome therapies currently available, including robust indirect evidence that indicates fenfluramine provides superior seizure control compared with the most-recently recommended therapy, cannabidiol plus clobazam. During the appraisal process fenfluramine it was described by clinical experts as providing "unprecedented" improvements in seizure control, and by patient carers as "life changing"; however, this is not reflected in the ACD, nor was it reflected in the slides presented during the appraisal committee meeting. • We have carefully reviewed the ACD and have taken steps to explore and address the committee's views and preferences in our economic modelling as far as is reasonably possible. We have also identified and addressed areas in the ACD that we believe are incorrect and require clarification. • We remain committed to working with NICE and the ERG to resolve perceived outstanding issues so that patients, their carers and the NHS can benefit from the full potential of fenfluramine.	
25	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Effectiveness of fenfluramine compared to cannabidiol plus clobazam:** *It is incorrect to state that fenfluramine is not more effective than cannabidiol plus clobazam[1] for reducing convulsive seizure frequencies (section 3.9, page 10). This conclusion is inconsistent with: the clinical trial-based evidence showing the superiority of fenfluramine; with the opinions of experienced UK and internationally-respected Dravet syndrome clinical experts; and with the European regulatory authority:* • **The mean placebo-adjusted reductions from baseline in convulsive seizure frequency clearly favours fenfluramine:** In line with NICE guidance on technical methods, robust indirect treatment comparison methods were employed. In the provided Bayesian network meta-analyses (NMA), comparing between adding either placebo or fenfluramine (0.7mg/kg/day) to the existing standard of care (SoC) of	Thank you for your comment. The final guidance notes that 'fenfluramine may be more effective than cannabidiol plus clobazam in reducing convulsive seizure frequencies'. During consultation, the committee considered a new indirect treatment comparison submitted by the company, which compared fenfluramine, cannabidiol, and placebo on the outcome of percentage change from baseline in convulsive seizure frequency (FAD section 3.9). This led to the committee changing their position.

[1] The European license requires cannabidiol (Epidyolex) to be used in conjunction with clobazam

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			patients receiving anti-epileptic drugs (AEDS) that did not include stiripentol[2], the mean difference in monthly convulsive seizure frequency (MCSF) was [redacted]. Comparing between adding either placebo or fenfluramine (0.4mg/kg/day) to the regimen of patients already receiving stiripentol as part of their existing SoC, the mean difference in MCSF was [redacted]. [redacted]. [redacted]. This compares with a much lower mean difference in MCSF between adding either placebo or cannabidiol 10mg/kg/day(plus clobazam) [redacted]. [redacted]. and between placebo or cannabidiol 20mg/kg/day (plus clobazam) - [redacted]. [redacted]. [redacted]. in similar patients receiving their existing SoC AEDs (see section B.2.9.4.2 of the company submission). The magnitude of the differences clearly favours fenfluramine over cannabidiol with clobazam and indicates these cannot be judged to be of the same efficacy for convulsive seizure reduction – the conclusion of the ACD based on these analyses is incorrect. **Please note**: the 0.2 mg/kg/day dose group of fenfluramine in Study 1 was only of the purposes of evaluating a dose-response. It is not the intended dose of fenfluramine and was not included as a dosing group in the Study 1504. • **The marginal overlap of 95% credible intervals cannot be interpreted as no difference in efficacy:** We presume that the reason for this erroneous statement in the ACD is because of the marginal overlap of the wide credible intervals for these differences from placebo. The credible intervals are wide due to the small trial populations in this very rare disease. Whilst there was a marginal overlap in these wide credible intervals, this cannot be interpreted to mean there is no difference between fenfluramine and cannabidiol; Bayesian analyses do not rely on a categorical inference of "significant" or "non-significant" and interpretation of the marginal overlap in credible intervals as indicating "no difference" and therefore "fenfluramine is not more effective than cannabidiol plus clobazam" is flawed. Wide credible intervals are also often observed in NMAs, particularly when based on trials with relatively small trial populations, as is the case for trials in this rare disease. It should be noted that the modelled probabilistic sensitivity analyses which accounts for variance around the point estimate, resulted in a mean ICER result that was highly consistent with the deterministic base case results. • **There is >99% probability that fenfluramine is more effective than cannabidiol plus clobazam in reducing convulsive seizure**	

[2] It is important to note that stiripentol is not a requirement of the licensed indication for fenfluramine. Stiripentol may be an existing treatment within a patients SoC. A pharmacokinetic interaction of fenfluramine and stiripentol requires a dose adjustment. The European Medicines Agency has determined that in patients concomitantly receiving stiripentol, an adjusted 0.4mg/kg/day dose of fenfluramine is bioequivalent to the 0.7 mg/kg/day dose in patients not receiving stiripentol.
Please see related point 4 below.

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			frequency: Bayesian NMA allows for making intuitive probability statements of a relative effect size, and probabilistic ranking of treatments from most effective to least effective. Based on these analyses, there is a >99% probability that fenfluramine in its licensed dose regimens would be ranked as the most effective therapy, and <1% probability that cannabidiol plus cannabidiol in its licensed dose regimens would be ranked as the most effective therapy for mean reduction in convulsive seizure frequency (see the probability ranking tables provided in the Appendix, Figure 2). This further demonstrates that the conclusion of the ACD is incorrect. • **Fenfluramine is clearly superior to cannabidiol plus clobazam in achieving clinically meaningful reductions from baseline in convulsive seizure frequency:** In addition to the indirect treatment comparison of the difference between fenfluramine and cannabidiol plus cannabidiol in mean monthly convulsive seizure frequency, we also provided in our submission an indirect treatment comparison of fenfluramine against cannabidiol for the proportion of patients achieving at least a 50% reduction in monthly convulsive seizure frequency (see section B.2.9.4.3 of the company submission). This convulsive seizure frequency endpoint is commonly used in epilepsy disorder trials, and is recognised as an accepted threshold measure of a clinically meaningful reduction in seizure frequency. It is therefore considered as a key endpoint by the European regulatory authority (See: Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (europa.eu)). This endpoint was a key prespecified endpoint in both the fenfluramine and cannabidiol trials. These analyses show a clearly greater odds of achieving a ≥50% reduction from baseline in convulsive seizure frequency, with no overlap in 95% credible intervals, for both licensed doses of fenfluramine (0.7mg/kg/day without concomitant stiripentol and 0.4mg/kg/day with concomitant stiripentol) when compared to licensed doses of cannabidiol of either 10mg/kg/day or 20mg/kg/day with concomitant clobazam. This was acknowledged in the ERG report (section 4.4, page 73), which states: "*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*". Despite this, we are concerned to have observed that these analyses have been omitted from the ACD and were not included in the Lead presentation during the appraisal committee meeting. As these analyses clearly demonstrate that fenfluramine is superior to cannabidiol plus clobazam for this key convulsive seizure frequency reduction endpoint, the conclusion of the ACD that "fenfluramine is not more effective than	

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			cannabidiol plus clobazam for reducing convulsive seizure frequencies" is not supported by the available evidence and is incorrect. • **Fenfluramine has maintained its orphan status based on a demonstrated significant benefit in reducing convulsive seizure frequency compared with cannabidiol plus clobazam:** To qualify for European orphan designation, a medicine must be intended for the treatment of a rare, life threatening or chronically debilitating condition, and there must be either no satisfactory treatment for the condition, or where treatment(s) currently exists the new medicine must provide a significant benefit over that existing treatment(s) (see Orphan designation: Overview | European Medicines Agency (europa.eu)). Evidence provided to the EMA to demonstrate this benefit included indirect treatment comparisons of fenfluramine vs cannabidiol plus clobazam. As cannabidiol plus clobazam was fully licensed by the EMA at the time of its decision to maintain the orphan designation for fenfluramine, this indicates that the regulator accepts that fenfluramine provides a significant benefit compared with cannabidiol plus clobazam. It also highlights that given there are limited effective treatments for patients with Dravet syndrome, fenfluramine may provide a new effective alternative treatment option for patients that have been unable to gain sufficient seizure control from their existing therapies (include cannabidiol). These points were further supported by a consensus statement of 4 leading European clinical experts in Dravet syndrome, presented to the EMA, which noted that the relative effect sizes for fenfluramine in the indirect treatment comparisons were consistently greater than those for cannabidiol plus clobazam across multiple convulsive seizure reduction endpoints and supported a clear benefit of fenfluramine over cannabidiol in terms of both magnitude and consistency of effect (data on file, December 2019). • **UK Clinical expert opinion solicited by NICE further emphasises that fenfluramine is a step change in the management of Dravet syndrome, and that the reductions in seizure frequency with fenfluramine are unprecedented:** In addition to the clear, consistent clinical trial data-based evidence of the superiority of fenfluramine for convulsive seizure frequency reduction presented in our submission, clinical expert opinion obtained by NICE during the appraisal process states (page 666 of the committee papers), in response to the question of whether fenfluramine is a step-change in the management of Dravet syndrome: "*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.*" This view is also represented in the ACD in section 3.31, where it states: "*A clinical expert said that they considered fenfluramine to be a step*	

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			change in managing Dravet syndrome because the same benefits have not been seen in trials of other drugs." This further supports a conclusion of superior efficacy of fenfluramine compared with cannabidiol plus clobazam. **The conclusion of the ACD that fenfluramine is not more effective than cannabidiol plus clobazam for reducing convulsive seizure frequency is not justified based on the available evidence, and is inconsistent with the interpretation of that evidence and experience of several leading clinical experts and the regulatory authority. The ACD and FAD should remove this incorrect conclusion and reflect the clear superior efficacy of fenfluramine in reducing convulsive seizure frequency compared with cannabidiol plus clobazam.**	
26	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Indirect treatment comparison:** *We are unable to provide an additional indirect treatment comparison of fenfluramine and cannabidiol plus clobazam using absolute changes from baseline in convulsive seizure frequency due to insufficient data for cannabidiol plus clobazam (section 3.9, page 10). Our analyses using relative changes from baseline versus placebo remain valid and appropriate:* • **The standard errors for the absolute change from baseline in convulsive seizure frequency for cannabidiol plus clobazam are not publicly available. Without these data we cannot conduct the indirect treatment comparison.** We reported data for absolute change from baseline in convulsive seizure frequency for fenfluramine and cannabidiol plus clobazam in Table 17 of our submission. The point estimates for placebo and cannabidiol plus clobazam (the relevant population) from the cannabidiol trials were taken from the SmPC for Epidyolex because the cannabidiol trial publications did not report the results for this subgroup of patients. This excludes the standard errors for these point estimates. A subsequent publication by Gunning et al 2020 provides further data on the cannabidiol plus clobazam subgroup from the trials, but this also excludes the standard errors for these point estimates. As the indirect treatment comparison requires both the point estimates and the standard errors as inputs we are unable to conduct this analysis. • **The indirect treatment comparison we provided in our submission based on the percentage change from baseline in convulsive seizure frequency relative to placebo remains entirely appropriate and valid.** These data were required for the economic model. The use of treatment effects relative to placebo mitigates any natural and expected heterogeneity that may exist in baseline seizure frequencies between the different trials in this rare and heterogenous syndrome. As these data	Thanks for your comment. The final guidance notes that 'fenfluramine may be more effective than cannabidiol plus clobazam in reducing convulsive seizure frequencies'. During consultation, the committee considered a new indirect treatment comparison submitted by the company, which compared fenfluramine, cannabidiol, and placebo on the outcome of percentage change from baseline in convulsive seizure frequency (FAD section 3.9). This led to the committee changing their position.

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			were based on analyses that provided both the point estimates and the standard errors, they could be appropriately used to undertake the indirect treatment comparison, providing key information on the relative effects of fenfluramine and cannabidiol plus clobazam.	
27	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Clarification of the effect of stiripentol as a treatment modifier (section 3.10, page 10-11):** *Our approach to estimate relative treatment effects and to modelling fenfluramine vs cannabidiol plus clobazam is appropriate:* • **Fenfluramine is licensed by the European (and US) regulatory authority at a dose of 0.7mg/kg/day (maximum 26mg/day) without concomitant stiripentol and 0.4mg/kg/day (maximum 17mg/day) when used with concomitant stiripentol.** This was based on a pharmacokinetic study of the effect of stiripentol on fenfluramine exposure, and estimation of bioequivalence of dosing between the fenfluramine 0.7mg/kg/day dose (without concomitant stiripentol) and the fenfluramine 0.4mg/kg/day dose (with concomitant stiripentol). This was a regulatory consideration leading to the fenfluramine dose regimens used in the pivotal clinical trials, and the same dose regimens that were subsequently licensed by the regulatory authority. We did not include the pharmacokinetic study in our submission because these are the licensed dose regimens to be appraised by NICE; the pharmacokinetic study is therefore irrelevant to the NICE decision-making process. • **Treatment of seizures in Dravet syndrome is individualised (as noted in section 3.4 of the ACD).** Since in clinical practice, patients, whose seizures are usually refractory to treatment, have a dynamic spectrum of seizures with differing need for a treatment at a particular time, it would be entirely expected that the concomitant treatments forming their SoC (and that underpins the regimen basis for an add-on therapy) will also be heterogeneous . This regimen basis of SoC may or may not include stiripentol. In reflecting this intended population, the clinical trials also appropriately enrolled patients with a similar heterogenous mix of treatments underpinning SoC. Given the pharmacokinetic interaction between fenfluramine and stiripentol [2], as well as geographical differences in the commercial availability of stiripentol, the registration studies of fenfluramine as an add-on therapy included patients for whom SoC was included (Study 1504) and excluded (Study 1) stiripentol. • **When fenfluramine is used alongside stiripentol at the licensed dose of 0.4mg/kg/day, stiripentol is not a further treatment effect modifier.** A more likely explanation for the observed differences in the reduction from baseline in convulsive seizure frequency between fenfluramine 0.7mg/kg/day (without stiripentol) and fenfluramine	Thanks for your comment. The final guidance notes that several issues were resolved during consultation on the first appraisal consultation document, and the committee agreed that stiripentol's impact on fenfluramine's effectiveness reflects an underlying pharmacokinetic interaction, not a modified treatment effect.

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			0.4mg/kg/day (with concomitant stiripentol) is the fact that Dravet syndrome is a very rare and heterogenous disease and, consequently, the number of patients enrolled in the trials is small, which amplifies the effect of any heterogeneity arising from different treatment histories and baseline seizure frequencies. This is mitigated by using the same '% change from baseline in monthly convulsive seizure frequency' endpoint assessments from the fenfluramine and cannabidiol trials to inform the indirect treatment comparison, which estimate relative treatment effects for the interventions (fenfluramine and cannabidiol) and placebo, in terms of their respective changes from baseline in convulsive seizure frequency. • **It should be noted that the GWPCARE 1 and 2 clinical trials of cannabidiol included a mixed population of patients in terms of concomitant use of stiripentol.** However, there are no data available for cannabidiol plus clobazam by concomitant use of stiripentol. By necessity we assume that stiripentol is not an effect modifier of cannabidiol because we do not have access to trial data for cannabidiol with clobazam broken down by stiripentol use. This assumption is consistent with the implicit assumptions of both the regulatory authority and NICE, neither of which has differentiated the use of cannabidiol plus clobazam by concomitant use or not of stiripentol, based on the same clinical trial data. • **Clobazam is not a significant treatment effect modifier of fenfluramine [1].** We included in section B.2.6.1.1.1 of our submission a published analysis indicating that clobazam is not a significant treatment effect modifier of fenfluramine; however, this was omitted from the ERG report, despite our requests to include these data (see Response to factual accuracy check of ERG report, 04 Nov 2020). Although this analysis is limited by small sample size, the conclusion is supported by the European regulatory authority's licensing of fenfluramine, which does not differentiate the use of fenfluramine by concomitant clobazam use (in contrast to the licensing of cannabidiol and stiripentol, both of which are only licensed for use with concomitant clobazam). Our assumption that clobazam is not a significant treatment effect modifier of fenfluramine is therefore justified and should not be imposed on patients taking fenfluramine if their existing SoC does not already contain it. In the interests of treatment simplification, and in providing alternative options for patients where clobazam (and therefore stiripentol and cannabidiol) may be unsuitable, we provided an analysis for this (albeit small anticipated use) "clobazam undesirable" sub-population in our CS. • **Despite some expected heterogeneity in baseline seizure frequencies and concomitant treatments received, our approach to estimating the relative treatment effects of fenfluramine and**	

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			cannabidiol plus clobazam is justified. • **Our cost-effectiveness analyses appropriately represent the use of fenfluramine without stiripentol vs cannabidiol (plus clobazam), and the use of fenfluramine with stiripentol vs cannabidiol (plus clobazam).** • **These separate analyses are combined in the base case to represent the expected cost effectiveness of the use of fenfluramine across this rare, heterogeneous patient population in UK clinical practice.** We note that the committee concluded that a merging of these population results is acceptable in principle (ACD section 3.15, page 14). To provide further transparency in the proposed cost-effectiveness of fenfluramine in the UK setting, the merged and individual analyses of fenfluramine on top of a patient's existing SoC that includes (Study 1504) and excludes (excludes Study 1) stiripentol have been provided. The results from all three analyses have also been disaggregated (e.g. **Costs**: intervention costs, AED SoC costs, primary and out-patient costs, rescue medicines and emergency treatment costs; **effects**: QALYs by patient and carers, life years gained, seizures, status epilepticus, seizure days) in line with the Committee's request (see Appendix).	
28	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Long-term effectiveness data for fenfluramine:** *Long-term effectiveness data for fenfluramine in this rare disease, characterised by seizures that are typically refractory to therapy, show a sustained effect of fenfluramine over several years of use. There is little uncertainty in the long-term effectiveness of fenfluramine (section 3.11, page 11-12), and the long-term effectiveness of fenfluramine is not a key source of uncertainty in the model ("Why the committee made these recommendations", page 3; section 3.29, page 23):* • **The duration of our comparative clinical trials is entirely appropriate. It would be unethical to conduct longer comparative trials**. Our submission included comparative trial data with 14-15 weeks of on-treatment follow up, which is similar to that available for cannabidiol and substantially longer than the 8-week on-treatment trials of stiripentol, both of which are recommended as therapy options by NICE. As the addition of fenfluramine to standard of care therapy demonstrated a rapid and sustained, significantly superior treatment effect compared with standard of care therapy alone, it would be unethical to expect patients who were randomised to standard of care therapy alone to continue in the trials on that clearly inferior therapy. It is therefore unreasonable to expect that longer comparative trial data should be available in this disease area. • **Our submission included 3 year open-label extension data in patients who are representative of those in clinical practice.** Patients	Thanks for your comment. The committee considered evidence from the company that the treatment effect on percentage change in convulsive seizure frequency per 28 days relative to baseline was largely maintained at 3-year follow up in Study 1503. The committee concluded that it was appropriate for waning to be excluded from in the model (FAD section 3.11). Taking into consideration the consultation comments along with the company's updated models and the updated discount, fenfluramine is now recommended for Dravet syndrome.

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			enrolled in the comparative trials were reflective of patients in clinical practice, who are typically refractory to existing therapy. These patients were permitted to enrol in the open-label extension study if they were felt able to continue to benefit from therapy. The ERG suggests this was a highly select population; however, as noted by the clinical experts, fenfluramine (or any other therapy) would only be continued in practice in patients who continue to benefit. The open-label extension study therefore reflects the use of fenfluramine as would be anticipated in clinical practice. • **The data from the open-label extension study indicates that the effects of fenfluramine are sustained over 3 years**. This was acknowledged in the ACD, with the clinical experts noting there was no evidence of a waning of effect in practice. In the context of this rare disease, characterised by seizures that are typically refractory to therapy, this evidence of sustained effect of fenfluramine for up to 3 years is compelling. • **Our submission also included prospective real-world evidence studies providing evidence of sustained effects of fenfluramine over 5 years, and retrospective real-world evidence studies of up to 27 years of sustained use.** Whilst acknowledging their limitations, these data support the sustained efficacy of fenfluramine over very long periods of time in patients who are felt would continue to benefit from treatment in clinical practice. • **Collectively, the evidence of long-term effectiveness of fenfluramine is as comprehensive and compelling as it is possible to be in this rare disease. There is little uncertainty in the long-term effectiveness of fenfluramine.** • **Our economic model appropriately accounts for potential loss of effectiveness over time.** The implementation of the stopping rule, in which fenfluramine or cannabidiol treatment is discontinued at 6 months in those not achieving at least a 30% reduction from baseline in convulsive seizure frequency, ensures that these treatments are only continued in the longer term in patients achieving a sufficient response to treatment. In addition, the model implements treatment discontinuation rates observed in the open-label extension study, which includes discontinuations for all reasons, including loss of efficacy, over the model lifetime. This ensures only those with sustained clinical benefit are maintained on treatment in the long-term. • **There is little uncertainty in the long-term effectiveness of fenfluramine, and little risk that any residual uncertainty in the long-term effectiveness of fenfluramine biases the economic model**.	
29	Company	Zogenix	**Proposed discontinuation criteria (stopping rules) for fenfluramine:**	Thank you for your comments. Since this consultation

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		International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	*We agree it is appropriate to assess response to treatment every 6 months and stop fenfluramine if it is not effective (section 3.13, page 13). Our model accounts for this appropriately:* • **Our economic model includes a stopping rule at 6 months after initiating therapy.** This ensures treatment is only continued in patients achieving a sufficient response (at least 30% reduction from baseline in convulsive seizure frequency) with treatment, and it is noted in the ACD that was considered appropriate by the clinical experts (page 13). • **The model implements treatment discontinuation rates observed in the open-label extension study. This includes discontinuations for all reasons, including loss of efficacy, over the remaining model lifetime.** This ensures only those with sustained clinical benefit are maintained on treatment in the long-term; those who do not sustain a sufficient clinical benefit discontinue treatment at the rates observed in the open-label extension study. As the open-label extension study did not protocolise continued treatment, the discontinuation rates observed in this study are likely to reflect clinician and patient/carer decision to discontinue treatment as per routine clinical practice. • **Implementation of a waning of effect is not supported by the evidence for fenfluramine.** There is no evidence of a waning of effect (i.e. a loss of effect over time) with fenfluramine from the randomised clinical trials, open-label extension studies or in the real-world context of expanded access programmes and small-studies of patients receiving treatment for over 27 years (Section B.2.6.1 of the CS). This opinion is also consistent with the clinical expert opinion contained in the ACD (page 12). Therefore the model excludes waning of effect. To impose a waning of effect on top of the existing 30% stopping rule and discontinuation rates would not be evidence-based and would lead to double counting of any loss of effect. • **Clinically and economically perverse consequences from implementing a waning of effect for cannabidiol in the model**. Given a waning of effect has been clinically observed with cannabidiol within a 48 week trial period (www.medicines.org.uk/emc/product/10781#gref); it is rational on a clinical and general cost-effectiveness basis to implement a stopping rule to discontinue treatment in patients that are no longer maintaining a minimum threshold of efficacy benefit. However, as noted in the appraisal committee discussions of cannabidiol (TA614), a perverse consequence with modelling a waning of effect occurs in that although by returning discontinued patients to a worse state of seizures without the costs of cannabidiol, the overall cost of the strategy decreases and the overall cost-effectiveness of the strategy improves, to the point that the cannabidiol strategy becomes increasingly cost-	comment, the company have changed their approach and presented an updated model using a 50% stopping rule at 6 months in their base case (see company addendum dated 6 April 2022). As noted in section 3.12 of the final appraisal document, the committee preferred a 30% stopping rule. However, upon taking into consideration all consultation comments along with the company's updated models and the updated discount, fenfluramine is recommended for Dravet syndrome.

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			effective the more waning of effect is assumed. In practice however, given the limited number of available therapies for patients with Dravet syndrome, it is likely that patients will be titrated to a higher dose of cannabidiol before totally discontinuing treatment (and returning to the pre-treatment SoC therapies). The removal of a wanning of effect for both strategy arms in our model is therefore a clinically conservative decision that overstates the sustainability of cannabidiol therapy. The implications of comparing a treatment strategy of fenfluramine to plausible higher doses of cannabidiol (15mg/kg/day and 20mg/kg/day) have been shown in scenario analyses (Appendix Table 23 and 24) . • **Implementing additional stopping rules in the model is therefore futile.** Given the first stopping rule already removes treatment from those patients who did not achieve a sufficient response within 6 months of starting treatment, and there is no evidence of waning of effect with fenfluramine, implementing further stopping rules at subsequent 6-month periods in the model would not remove treatment from any further patients, because the only patients who continue treatment with fenfluramine beyond the initial 6 months are those who achieved at least a 30% reduction in seizures, and they do not experience a subsequent waning of effect. Technically, if one was to introduce a repeated 6-monthly stopping rule, a few additional patients may discontinue their index treatment, but this would be an unintended consequence for a few patients that by chance (arising from the random generation of patient seizures in the microsimulation approach) meet the stopping threshold of seizures within a cycle. The ongoing discontinuation rates from the open-label extension study account for the clinician and patient/carer decision to discontinue treatment beyond the initial 6-months of treatment as per routine clinical practice and are included separately in the model. • **It is incorrect to equate our exclusion of subsequent stopping rules every 6 months with the suggestion that we have excluded assessment of response to treatment every 6 months.** The fact that our model does not implement subsequent 6-month stopping rules does not mean that patients in our model are not routinely monitored and assessed for their response to treatment. We fully agree that patients would be routinely seen and assessed for their response to treatment at 3–6-month periods in clinical practice and we have included the full costs of this in the model. • **In summary, our implementation of the stopping rule and subsequent treatment discontinuation, and incorporation of the full costs associated with regular, routine management, appropriately captures the long-term effectiveness and costs of treatment with fenfluramine.** • **We have explored the impact of implementing alternative stopping**	

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			rules of at least a 40% (£25,852/QALY) or 50% (£21,956/QALY) reduction in seizure frequency required for continued treatment beyond 6 months in our revised base case (see Appendix).	
30	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Applicability of fenfluramine in all patients with Dravet syndrome:** *Evidence from children and young people is applicable to adults (section 3.12, page 12):* • **We are pleased that the committee agrees that the evidence from our trials is applicable to adults**. Although there is less evidence in adults than in younger patients, which may be perceived to lead to uncertainty, it should be noted that this is also the case for stiripentol and cannabidiol, which are both recommended for use by NICE. • **Fenfluramine should be available to all Dravet syndrome patients, irrespective of age.** Cannabidiol is licensed for use in children and adults and its NICE recommendation (TA614) does not impose limits on its use by age. As such, and in the interests of equality, there would be no reason to impose limits on the use of fenfluramine based on age. • **The issue of whether adults experience a lower convulsive seizure frequency than children is a minor consideration (section 3.20, page17).** In our original base case, we included a halving of convulsive seizure frequency in patients aged 18+ years as the literature indicated that seizure frequency may be reduced in older patients compared with younger patients. This assumption was applied to both arms of the model and we demonstrated in a scenario analysis (reported in Table 51 of the company submission) that removal of this assumption had very little impact on the ICER. We have provided a revised base case analysis in response to the ACD in which the convulsive seizure frequency is assumed to remain constant irrespective of age (see Revised base case analysis in the Appendix).	Thanks for your comment. The committee considered a lack of evidence to be an uncertainty and concluded that the evidence in children and young people with Dravet syndrome is generalisable to adults in absolute terms, and the relative treatment effect is likely to be similar. It acknowledged the difficulties noted with including adults in studies. The committee took these comments into consideration along with the company's updated models and the updated discount. Fenfluramine is recommended for all people with Dravet syndrome, regardless of age.
31	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Model validity issues:** *We believe our economic model works as it should (section 3.14-3.15, page 13-14). We are unclear why the ERG was unable to run or replicate certain analyses (section 3.21, page 18; section 3.28, page 22-23). We had offered to directly address these concerns with the ERG before the AC meeting (4th March 2021) but this was possible . An opportunity was provided to discuss these issues on the 7May 2021. Unfortunately, this has left us with little time to have fully investigated the issues before submitting this response to meet the deadline.* We would welcome the opportunity in continuing to collaborate with the ERG to resolve any outstanding issues, or in assisting them with making any proposed modifications to the model.	These issues were resolved during consultation. The ERG considered the overall the model results were valid.
32	Company	Zogenix	**Adjusting for placebo effects:**	Thanks for your comment. The final guidance notes

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		International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	*Reversion to placebo-level of convulsive seizure frequencies, rather than baseline, upon treatment discontinuation (section 3.16, page 16):* • **To accommodate the committee's preferences we have revised our base case model to return patients to the placebo convulsive seizure frequencies upon discontinuation, rather than their baseline convulsive seizure frequencies.** This change marginally reduces the base case ICER from our original base case analysis. The ICER for this and the fully revised base case ICER are provided in the Appendix). • **It should be noted that returning patients to placebo seizure frequencies upon treatment discontinuation may overestimate the lifetime effectiveness of the inferior comparator therapies whilst minimising their costs. We have therefore provided a scenario analysis using an alternative approach that removes this bias.** In this analysis the placebo component of efficacy for each arm in the model is removed entirely and patients return to their baseline level of seizure frequencies (equivalent to the placebo efficacy). Since the placebo effect has been removed and forms the new baseline (to eliminate the potential effects caused from a regression to the mean), it is assumed that this is the true baseline level of convulsive seizures at the time of starting the index intervention (e.g. fenfluramine, cannabidiol or SoC). In this analysis, and in line with the NICE recommendations for cannabidiol in TA614, patients discontinue treatment in all arms, if their seizures are not reduced by more than 30% from their starting baseline. • **A less biased modelling approach to entirely remove the placebo effect on convulsive seizures experienced at baseline, during the index intervention, and following discontinuation of the index intervention, yielded an ICER of £21,842/QALY, which is significantly lower than in the base case. Potentially, this analysis also demonstrates that our currently revised base case analysis (which inflates a placebo-level of effectiveness in discontinuing patients as per the committee's preferences in the ACD) is conservative.** Full results are provided in the Appendix. As the ERG reported difficulties in running this analysis previously (no specific details provided), we have provided full instructions and annotated model code to help the ERG to verify the technical operation of the model and all other analyses and results.	that several issues were resolved during consultation on the first appraisal consultation document, and the committee agreed that people in the model who stop treatment revert to the seizure frequency in the placebo arm during the trial maintenance period. During consultation, the committee submitted a revise base case model where it followed the approach recommended by the committee in the appraisal consultation document.
33	Company	Zogenix International Ltd Research, development and manufacturer of	**Proportionality between convulsive seizure frequency and convulsive seizure days:** *Clarification of the use and calculation of convulsive seizure-free days in the model (section 3.19-3.21, page 17-18). It is important to model convulsive seizure free days to adequately capture the impact of Dravet syndrome and therapies on*	Thanks for your comment. The committee took these comments into consideration along with the additional explanations provided by the company (see company addendum dated 6 April 2022), the company's updated models and the updated discount. As noted in section

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		fenfluramine (Fintepla)	*patients and carer quality of life:* • **Patients with Dravet syndrome may experience high seizure frequencies, often with multiple seizures per day. In addition to reductions in convulsive seizure frequency, patient carers and clinicians have explained that increases in convulsive seizure-free days are of particular value to patients and their families.** 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 (TA614 FAD, section 3.2). Clinicians consulted as part of our UK Pathway study reported that seizure-free days is a meaningful concept, associated with significant respite for patients and carers, and increased activities of daily living (Data on file, 2020). From the perspective of patients and their families, increases in seizure-free days can 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 o (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. o Berg, A., et al., *Seizure burden in severe early-life epilepsy: Perspectives from parents.* Epilepsia open 2019. **4**(2): p. 293-301.). • **Initial regression analyses of patient- and carer-level data from our trials indicate that seizure-free days had a greater impact on quality of life than did seizure frequency.** • **To capture the impact of seizures and the value of therapies that reduce seizure frequency in Dravet syndrome it is therefore important that the model considers the impact of seizure frequency reduction on seizure-free days.** To model seizure reduction without considering seizure-free days will not adequately reflect the burden of convulsive seizure frequency and the quality-of-life benefits of treatment in reducing convulsive seizure frequency. • **There is a logical relationship between convulsive seizure frequency and days with seizures (seizure days) and seizure-free days**. **Due to lack of published convulsive seizure-free days data for cannabidiol plus clobazam it was necessary to estimate convulsive seizure-free days based on this logical relationship.** Given the median baseline	3.16, the committee agreed basing the model on seizure-free days was reasonable, but concluded this is an existing uncertainty. However, fenfluramine has now been recommended for Dravet syndrome.

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			number of convulsive seizures per 28-day period in the fenfluramine and cannabidiol trials ranged from 9 to 27, with wide ranges (see Table 15 of the CS), a reduction in convulsive seizure frequencies in a given 28-day period would logically lead to a reduction in the number of days upon which seizures may occur. It therefore follows that a reduction in the number of days upon which seizures may occur in a given 28-day period would lead to an increase in the number of days without seizures (i.e., an increase in seizure-free days) in that given 28-day period.
			• **The ERG estimates that the reduction in seizure days is 0.4 times the reduction in convulsive seizure frequency; however, these calculations are flawed.** The ERG has attempted to estimate a direct relationship between a 'percentage reduction in convulsive seizure frequency' and a 'percentage reduction in days with convulsive seizure' based on the ratio of a 'percentage reduction in seizure frequency' : [to] 'percentage increase in seizure-free days'. As explained in our written responses to technical engagement (17th December 2020) and subsequently ahead of the appraisal committee (25th February 2021), it is not valid to directly transfer this relationship to the 'percentage change in convulsive seizure **frequency** and 'percentage change in **seizure days**.
			  • A 'percentage change in seizure-free days per 28-day period' will in general not be the same as the inverse 'percentage change in seizure days per 28-day period'. E.g.: If a patient goes from having 1 convulsive seizure to 0 per 28-day period, this is 100% decrease in convulsive seizures. Alongside this, the same patient would go from 1 seizure day to 0 seizure days per 28-day period, which is a 100% decrease in seizure days. This also equates to the same patient going from 27 seizure-free days per 28-day period to 28 seizure-free days per 28-day period, which is an increase in seizure-free days of 3.7% (i.e. 1/27).
			  • Therefore, it is not possible to make inferences about the relationship between the 'percent reduction in the convulsive **seizure frequency**' and the '**percentage reduction in seizure days** per 28 days' based on the ratio of an observed 'percent reduction in the convulsive seizure frequency' :[to] 'percentage increase in seizure-free days per 28 days' – in the above example, the ERG's approach would be the equivalent of assuming the 3.7% increase in seizure-free days results in a 3.7% decrease in seizure days, when in fact the decrease in seizure days was 100%.
			The ERG's approach is therefore flawed.
			• **In our base case analysis, due to the absence of published data for cannabidiol plus clobazam, we have assumed that the percentage reduction in seizure days would be the same as the percentage reduction in seizure frequency based on the logical relationship**	

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			between these parameters. We have applied this assumption to both the fenfluramine and the cannabidiol plus clobazam arms of the model in order to ensure consistency. • **We have further explored the relationship between percentage change in seizure frequency vs the percentage change in seizure days based on patient-level data from our trials. Regression analysis of these data supports a near 1:1 relationship and counters the ERG's estimate**. We acknowledge that the exact relationship between reduction in convulsive seizure frequency and reduction in convulsive seizure days may be more complex due to the fact that seizure frequency is theoretically unbounded, but seizure days and seizure free-days are bounded by the range 0-28. However, using regression analysis of individual patient level data the percentage change in seizure days is [redacted] times the reduction in convulsive seizure frequency. This supports our assumption of a near 1:1 relationship in our base case analysis and further demonstrates that the ERG's estimate of the relationship is not appropriate (see Appendix). • **We have included this evidence-based estimate of the relationship in our revised model**	
34	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Relationship between convulsive seizures and mortality applied in the model:** *Assuming the existence of a relationship between convulsive seizure frequency and mortality, the model is reasonable and justified (section 3.22-3.23, page 18-19). Our model generates estimates of Dravet syndrome mortality that are aligned with expectations based on the most comprehensive sources of Dravet syndrome mortality available in the literature:* • **Patients with Dravet syndrome are at a high risk of premature seizure-related mortality. Improvement in convulsive seizure control is expected to reduce the risk of sudden unexpected death in epilepsy (SUDEP) and status epilepticus, which are the leading causes of Dravet-syndrome mortality.** The Association of British Neurologists, as stakeholders in the process, 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). The Lead presentation to the appraisal committee also noted clinical expert views: "*Convulsive seizure*	Thanks for your comment. The committee took these comments into consideration along with the additional analyses provided by the company (see company addendum dated 6 April 2022), the company's updated models and the updated discount. As noted in section 3.17 and 3.18, the committee agreed there may be a relationship between seizure frequency and mortality but concluded the strength of that relationship is unclear. However, fenfluramine has now been recommended for Dravet syndrome.

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			frequency has strong, well-established link to some forms of premature mortality in epilepsy and that this is likely to apply to Dravet syndrome, with high frequency and ongoing seizures, high sudden unexpected death in epilepsy (SUDEP) rates, other comorbidities that may result in premature mortality." There is therefore a clinical expectation that improving convulsive seizure control will reduce the risk of mortality. • **It is not possible to power a trial for mortality events in a rare disease such as Dravet syndrome.** As we explained in the Response to Clarification Questions C14, and further demonstrated in our response to the Technical engagement (17 December 2020), where we provided a sample size calculation: 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. • **It is therefore unreasonable to expect empirical evidence of a mortality benefit with fenfluramine (or any other therapy in Dravet syndrome). Given the clear reasons to expect an effect on mortality through improved convulsive seizure control, we believe it is unreasonable to exclude the possibility of a mortality benefit on the basis of a lack of evidence that is impossible to collect**. Removal of a mortality effect in the model would not reflect the reality of the risk of premature death faced by Dravet syndrome patients and their families every day and would irrationally bias the model in favour of less effective therapy. A mortality benefit should therefore be reflected in the model based on convulsive seizure reduction. **Our approach to modelling mortality generates estimates of Dravet syndrome mortality that are aligned with expectations based on the most comprehensive sources of Dravet syndrome mortality available in the literature; and are consistent with those indicated in the NICE scoping document for this appraisal.** The ACD notes that the Cooper et al study used to estimate Dravet syndrome mortality acknowledged that the rates they reported may overestimate the true mortality rates because the participants had been referred for tertiary specialist care. However, given the refractory nature of their seizures, patients with Dravet syndrome are unlikely not be referred at some point for highly specialist care for diagnosis and management. It therefore seems reasonable to adopt these rates of mortality as reflective of those in Dravet syndrome patients in practice. The ERG also claims that our approach to estimating Dravet syndrome mortality based on convulsive seizure frequencies leads to implausibly high relative risks of SUDEP compared with the general population, but neglects to note that the risk of SUDEP in the general population is very low relative to that in Dravet	

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			syndrome and our resulting survival curve (Figure 23 of the company submission) has been confirmed by UK clinicians to be aligned with mortality expectations in Dravet syndrome. Nilssen et al 1998 (used to inform the calibration of the modelled mortality curve) highlights that deaths in general epilepsy are correlated with seizure frequency. There is no reason to doubt that seizure frequency and deaths in Dravet syndrome are also correlated. • **It is important to note that our mortality estimates in the model are not based only on SUDEP - they include status epilepticus and accidental deaths:** o SUDEP (50% of all deaths) was calculated from Cooper et al 2016 - the most comprehensive source of Dravet syndrome-specific mortality data available in the literature. o A flat rate of SE from Cooper was applied for those that experienced a seizure episode. o Accidental death was assumed as 24% of SUDEP+SE deaths (as inferred from Cooper et al). A treatment effect (as a reduction in seizure frequency) is applied to all 3 causes of death. • **As requested, we have provided analyses exploring alternative relationships between convulsive seizure frequency and mortality. But given that our base case mortality is based on and aligned with real-world evidence and clinical expectations, we believe these analyses are biased against fenfluramine given its superior efficacy vs comparators in improving convulsive seizure control.** The ACD notes the committee's preferences to see scenario analyses testing different strengths of the relationship between convulsive seizure frequency and SUDEP. We provided two alternative scenarios exploring the relationship between convulsive seizure frequency and mortality in our original submission (Table 51 in the company submission), but these were omitted from the Lead presentation during the appraisal committee meeting. We have re-provided these for our revised base case. The committee also requested an analysis removing the possibility that treatment prolongs life. , ; however, our model is built on the foundation that differences in seizure frequency drive differences in mortality, quality of life and health care resource use and costs. It is technically challenging to completely remove the link between seizure differences arising from treatment (which drives mortality, quality of life and costs) and seizure differences leading to mortality differences, whilst also retaining the background Dravet syndrome mortality. We have therefore implemented an alternative analysis demonstrating the contribution of mortality to the QALY estimates. It should be noted that these analyses would bias the model against fenfluramine given its superior efficacy in improving	

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			convulsive seizure control compared with both cannabidiol plus clobazam and standard of care therapy.	
35	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Non-convulsive seizures:** *Exclusion of non-convulsive seizures from the model is justified (section 3.24, page 19-20):* • **We excluded non-convulsive seizures from the model because of the risk of introducing spurious inputs arising from the difficulties in recording these events in practice.** Clinical experts acknowledged the difficulties in measuring these events (ACD page 20). Fenfluramine reduced the incidence of non-convulsive seizures in the pivotal trials; however, neither our trials nor those of cannabidiol were designed to assess non-convulsive seizures as a key endpoint, and these data are less reliable than convulsive seizure data. This precludes a robust comparison between therapies for non-convulsive seizure reduction, and precludes a robust assessment of the impact of non-convulsive seizures on quality of life and mortality. • **Our exclusion of non-convulsive seizures from the model is in line with the approach taken by the manufacturer of cannabidiol in NICE TA614.** The manufacturer of cannabidiol did not include non-convulsive seizures in its original model for NICE TA614. Upon request, the manufacturer of cannabidiol provided a scenario analysis to reflect a hypothetical impact of non-convulsive seizures on quality of life in its model; however, we note this did not employ its actual non-convulsive seizure data in the model and was ultimately not accepted with confidence by the appraisal committee. • **We acknowledged in our submission and subsequent responses that our exclusion of non-convulsive seizures from the model is conservative for both fenfluramine and cannabidiol plus clobazam when compared with standard of care.** We also explained in our response to the Factual Accuracy Check (FAC) of the ERG report (30 October 2020) that it is possible that the exclusion of non-convulsive seizures may be conservative for our comparison of fenfluramine vs cannabidiol plus clobazam based on total seizures data (convulsive and non-convulsive seizures) (see page 49-50 of that response). • Although the manufacturer of cannabidiol provided NICE with some non-convulsive seizure data, as academic in confidence, in its response as a stakeholder to this appraisal, we note that this only relates to cannabidiol 10mg/kg/day vs placebo, and ignores the data for cannabidiol 20mg/kg/day that make up two-thirds of the phase 3 randomised controlled trial evidence available in support of cannabidiol in Dravet syndrome. Notwithstanding this issue, the data for non-convulsive seizure	Thanks for your comment. The committee acknowledged the difficulties with measuring non-convulsive seizures and considered it an existing uncertainty. However, fenfluramine is now recommended.

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			frequency from all trials remains unsuitable for making a robust comparison between therapies for the reasons described above.	
36	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Adverse events applied in the model** *The model reflects adverse events and monitoring to the full extent that it is appropriate to do so. It is incorrect to suggest that additional monitoring is not appropriately reflected in the model (section 3.25, page 20-21):* • **Our model excludes adverse events because there is no evidence of a differential effect of serious adverse events between SoC, fenfluramine or cannabidiol treatments that would accrue more than negligible differences in costs or would exert a measurable influence on patient quality of life. The ERG agreed that the impact of this pragmatic approach is likely to be small.** • **Monitoring for adverse events is fully captured in the routine management of patients.** As routine management of patients will be the same irrespective of therapy received, there are no additional or differential costs or quality of life impacts to be included for routine monitoring. • **The additional costs of echocardiography before, during and after fenfluramine treatment, as a regulatory obligation specified in the SmPC due to a historical association with cardiopulmonary adverse events when of fenfluramine was used at far higher doses in the management of obesity, are appropriately captured in the model.** There is no reason to believe that the conduct of an echocardiogram will have a meaningful and measurable influence on patient quality of life that could influence the accrual of QALYs in the model. • **Given the above we believe the ACD is incorrect to state that additional monitoring is not appropriately reflected.** This was explained in several of our previous responses and we are unclear why this has been presented as an issue in the ACD. • **It should be noted that to date there has been no evidence of an increase in clinically meaningful valvulopathy or any other cardiopulmonary adverse events with fenfluramine at doses used in the treatment of Dravet syndrome, in neither the clinical trials, the long-term extension study, nor in the longer-term real-world evidence studies.** There are therefore no costs or quality of life impacts to be reflected in the model for this. • **Our model therefore reflects adverse events and monitoring to the full extent that it is appropriate to do so.**	Thanks for your comment. The committee took these comments into consideration. This section (now section 3.22) has been changed.
37	Company	Zogenix International Ltd Research,	**Carer utility applied in the model:** *In the absence of an agreed method of incorporating carer utilities into the model, we believe our approach is reasonable and possibly less biased than the*	Thank you for your comment. Since this consultation comment, the company have changed their approach and presented an updated model using carer disutiltiies

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		development and manufacturer of fenfluramine (Fintepla)	*alternative suggested by the ERG (section 3.26, page 21). We have conducted a scenario analysis exploring an alternative approach to applying carer utility when the patient dies, which highlights the challenges of retaining a contribution of the carer QoL beyond the patient's survival:* • **We are pleased the committee has agreed that incorporation of carer utilities in the model is appropriate.** Dravet syndrome is a lifelong condition that exerts a heavy, lifelong toll on the quality of life of patients, their immediate full-time caregivers and the whole family unit. Seizures in Dravet syndrome contribute to the development of a range of co-morbidities and developmental issues, with few patients able to live independently and most requiring around-the-clock care. It is therefore appropriate to capture the lifelong impact of the disease and treatment on quality of life of carers, in addition to the patient. We have not incorporated the quality-of-life impact of Dravet syndrome on patients' siblings, which as noted by the committee in NICE TA614 underestimates the impact of the disease (TA614 FAD, section 3.21). • **Utility values in our model are based on individual patient- and carer-level quality of life data collected directly from the fenfluramine trials. Our approach is therefore evidence based and is aligned with our individual patients/carer level simulation modelling approach.** We have previously provided a detailed explanation of how our approach, based on the empirical evidence of carer quality of life from the clinical trial data, demonstrates an impact on carer quality of life across all seizure frequencies (and seizure free days) and is therefore most relevant for our patient-level continuous time model.(see company response to the 'Factual accuracy check', page 62-69). • **The approach suggested by the ERG, to implement disutilities in line with the approach taken in NICE 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**. The ERG's suggestion would apply a carer disutility in health states defined by categories of seizure frequencies (8 to 25, and >25 convulsive seizures per month) until a patient dies. These are arbitrary categorisations of seizure frequency (based on convenience, but not clinical or statistical significance), at odds with the empirical evidence from out trial, and are not appropriate in our simulation model where we are modelling seizure frequencies / seizure free intervals on a continuous time basis. Furthermore, applying a carer disutility to patient utility can lead to unintended consequences in which the application of a carer disutility actually penalises the most effective therapy more so than if	(see company addendum dated 6 April 2022). The committee took into consideration all consultation comments along with the company's updated models and the updated discount. Fenfluramine is recommended for Dravet syndrome.

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			carer utility was not incorporated in the model (see the Appendix to this response for an example demonstrating this). The ERG's suggested approach is therefore not appropriate to adopt in our model.
			• **We assume that carer utility is removed from the model when the patients dies, as this is aligned with usual modelling practices. In addition, to continue to include carer utility beyond the patient's death would introduce a number of undesirable consequences and arbitrary assumptions and uncertainties**
			  • Applying carer utilities in the model only until the patient dies is aligned with the general principle that when patients die in any other model, they do not continue to accrue any additional resource use, costs, or quality of life benefits, or impairments, and so patients who die in our model should not continue to accrue carer utility.
			  • By retaining carer utilities in the model after the patients die retains a benefit to the treatment strategy but none of the costs, which favours the least effective treatment in the model. As fenfluramine is superior in reducing convulsive seizure frequency (and so would plausibly reduce the risk of seizure associated mortality) compared with cannabidiol plus clobazam, or continued standard of care; this approach biases the model in favour of the comparators and against fenfluramine.
			  • It is unclear at what level the carers' quality of life should be retained at in the model once the patient dies; increasing the carer's quality of life in the model once the patient dies (e.g. towards population norms, as was suggested in a scenario by the ERG) would have the (unintended) effect in the model of rewarding the patient's death. A strong arbitrary assumption is therefore required.
			  • It is unclear how long the carer's quality of life should be retained in the model following the patient's death; imposing an ongoing carer utility beyond the patient's death is incompatible with a patient lifetime time-horizon, and requires a further arbitrary strong assumption.
			• **Given these issues, we believe our base case is appropriate and internally consistent with the available data and our simulation model. However, to address the committee's concerns with our approach we have undertaken a scenario analysis in which we retain a carer utility in the model once the patient dies.** As this approach is associated with the above-mentioned uncertainties and biases it is important to limit these as far as possible. For this scenario analysis we have therefore included a retained carer utility once the patient dies equal to the lowest quality of life that the carer experienced while the patient was alive, which it should be noted still favours the least	

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			effective therapies over a prolonged time-horizon. The results from this analyses are reported in the Appendix. • **For clarification, the ACD reports there was no significant difference in PedsQL score between fenfluramine and placebo in Study 1504 (section 3.8, page 9); however the results it reports are unadjusted.** As highlighted in section B.3.4.2 of the CS (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", as indicated in the footnote on Table 11 of the CS.	
38	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Clarification of QALY accrued and differences in cost-effectiveness estimates in the model** (section 3.27, page 22)**.** *For all analyses we have provided full disaggregation of the results.* This includes disaggregation by stiripentol use (analyses based on Study 1504 and by patients and carer QALY estimates. to show the contribution of carer utilities to the ICER. All results are as would be expected given the construct of the revised base case model in line with the committee's preferences.	Thank you for your comment and for the additional analyses. The committee took these analyses into consideration along with the other consultation comments, updated model, and the updated discount. Fenfluramine is recommended for Dravet syndrome.
39	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Innovation** *We believe fenfluramine should be considered an innovative treatment in this rare, treatment refractory disease, with high unmet needs (section 3.31 page 24):* • **There is no clear definition of an innovative therapy in NICE's methods or process guidance, but using other NHS criteria fenfluramine would clearly fulfil the definition of "innovative".** We note that for designation as a Promising Innovative Medicine under the Early Access to Medicines Scheme the medicine must be for the treatment of a life-threatening or seriously debilitating condition with high unmet needs, it must be likely to offer a significant advantage over current therapy, and its potential adverse effects must be likely to be outweighed by the benefits (see: PIM_designation_guidance.pdf (publishing.service.gov.uk)). Fenfluramine clearly fulfils all of these criteria. • **UK Clinical expert opinion solicited by NICE highlights that fenfluramine is a "step change" in the management of Dravet syndrome, and that the reductions in seizure frequency with fenfluramine are "unprecedented":** In addition to the clear trial data-	NICE considers "the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). Upon review of the consultation comments, the committee now consider that there are likely to be additional benefits of fenfluramine which are not captured in the model. Fenfluramine is recommended for Dravet syndrome.

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			based evidence of the superiority of fenfluramine for convulsive seizure frequency reduction presented in our submission, clinical expert opinion obtained by NICE during the appraisal process states (page 666 of the committee papers), in response to the question of whether fenfluramine is a step-change in the management of Dravet syndrome: "*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*." • **Patient caregiver survey data indicate that fenfluramine has for many families been transformative, with benefits that are unlikely to be fully captured in our economic model:** Patient advocacy group opinion obtained during the appraisal process noted that fenfluramine has been transformative for many families in the UK and across Europe (see page 700-703 of the committee papers). In addition to often dramatic seizure reduction, non-seizure improvements reported by caregivers in the survey included improved behaviour, cognition and social interaction, ability to speak, becoming more active, and being more "present" or engaged in family life, and greater autonomy and independence. These reported benefits of fenfluramine treatment are unlikely to be fully captured in our QALY estimates. • **Fenfluramine may be used at any point in the add-on therapy, in contrast to stiripentol and cannabidiol, which are licensed only for use in combination with 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. • **Collectively, we believe fenfluramine is an innovative therapy for patients with Dravet syndrome.**	
40	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Conservatism in our approach to modelling** *It should be noted that our analyses are plausibly conservative on several fronts, which if addressed and/or pragmatically considered would substantially reduce the reference base case ICER(s) for fenfluramine and reduce uncertainty for decision-makers:* 1) We assume maximum licensed doses of fenfluramine but only a 12 mg/kg/day dose of cannabidiol, which is towards the lower end of its 10-20mg/kg/day licensed dose range. Given evidence of a waning effect of cannabidiol within a 48 week duration of use (cannabidiol SmPC: www.medicines.org.uk/emc/product/10781#gref) and doses tending towards the upper end of its licensed dose range in the cannabidiol open-	NICE considers "the innovative nature of a technology… [when it] adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure" (section 6.3.3 of NICE guide to the methods of a technology appraisal 2013). Upon review of the consultation comments, the committee now consider that there are likely to be additional benefits of fenfluramine which are not captured in the model. Fenfluramine is recommended for Dravet syndrome.

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			label extension study (discussed in section **Error! Reference source not found.** of our submission), and mounting evidence of higher doses from real-world use (see: www.frontiersin.org/articles/10.3389/fneur.2020.00829/full), it is plausible that effective doses in practice could be towards the upper end of its recommended dose range. With increasing doses of cannabidiol, the ICER decreases sharply, such that at a maximum dose of cannabidiol, fenfluramine becomes economically dominant at the model-based drug costs (see appendix). 2) Clinical experts have indicated that they would aim to reduce or remove concomitant therapies where possible when patients have a good response to add-on therapy. Based on evidence from the DFES survey of patient carers provided in the committee papers, 59% of the 117 participants had reduced the number or the dose of other anti-epileptic treatments as a result of adding fenfluramine. It is of note that at the time of this survey, the duration for some patients being on fenfluramine outside of a trial setting was not long. It is therefore plausible that with the introduction of fenfluramine, these data underestimate the potential for simplification in a patient's AED therapies over a longer period of introduction. Although these data are not mature enough to robustly evaluate at this time, they do point to conservativism in the currently modelled approach and potential for cost-savings. As fenfluramine is superior to cannabidiol plus clobazam it would be expected to permit reduction or removal of add-on therapy to a greater extent. In our current model we assume the full costs of continued concomitant therapy throughout, which may favour cannabidiol plus clobazam. 3) The model excludes the influence of non-convulsive seizures on quality of life, which is conservative in our comparison against standard of care and may be conservative in our comparisons against cannabidiol plus clobazam. 4) We do not include the impact of Dravet syndrome across patient siblings (Baily et al., 2020 https://doi.org/10.1016/j.yebeh.2020.107377), which was recognised in NICE TA 614 as an omission that, if included, would further reduce the ICER. As fenfluramine is superior in achieving convulsive seizure control, this omission currently favours the comparators in our model. 5) Due to a lack of specific data and for pragmatic reasons we are unable to model any subsequent add-on strategies following treatment discontinuation. 6) As the superior efficacy of fenfluramine means that treatment discontinuations due to a lack of efficacy would occur more frequently with cannabidiol plus clobazam than with fenfluramine, in the model, this would return patients starting on the cannabidiol plus clobazam strategy	

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			to their less costly standard of care treatment more quickly, ultimately reducing the overall cost of the comparator strategy. As commented upon during the appraisal of cannabidiol (TA614), increasing the rate of discontinuing treatment improves the cost-effectiveness of a treatment, albeit counterintuitive and contradictory to a medical intent to reduce seizures. 7) We have implemented the committee's preference to return patients to placebo-based convulsive seizure frequencies upon treatment discontinuation; however, as the placebo-based convulsive seizure frequencies are lower than those observed at baseline, in returning patients to their placebo-based convulsive seizure frequencies the current model retains a benefit in continuing to reduce seizures (from baseline) for the discontinued therapy, whilst minimising its costs. As fenfluramine has a superior efficacy, discontinuations due to a lack of efficacy would occur more frequently with cannabidiol plus clobazam. This consequently returns patients in the cannabidiol plus clobazam arm of the model to an elevated placebo-based convulsive seizure frequency more quickly, over-estimating the strategy's lifetime effectiveness whilst also minimising its costs relative to ongoing treatment with fenfluramine. The scenario analysis in which the placebo effect is removed entirely removes this bias from the model and substantially reduces the ICER, demonstrating just how conservative the revised base case is. The ICER associated with this analysis is: £21,843/QALY (see Appendix). It is noteworthy that this analysis may also be considered as a conservative assumption, since patients that discontinue a treatment for lack of efficacy may be considered to be uncontrolled and as such have more seizures than experienced before treatment, or over time with the sequential loss of a limited number of therapeutic options available to them. 8) Currently in our comparisons of fenfluramine to SoC, patients not receiving fenfluramine are assumed to have a placebo effect in line with that observed in the trial. In clinical reality, these patients would continue to receive their existing SoC treatment and would not expect to have incurred any benefit of a reduction from their baseline level of seizures, but rather continue at their baseline level of seizures. The current model therefore potentially under-estimates the difference between fenfluramine and SoC effect sizes. 9) Consistent with the cannabidiol recommendation (TA614), a similar treatment discontinuation criteria (stopping rule) has been implemented for fenfluramine in the model for patients not achieving a greater than 30% reduction from baseline seizures at 6 months. If this rule were changed for fenfluramine to require a 40% or 50% reduction from baseline to continue therapy, the ICER would change from	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			£31,078/QALY to £25,852/QALY and £21,956/QALY, respectively.	
41	Company	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)	**Other issues and clarifications:** • Section 3.7, page 9 of ACD: Error - "*stiripentol 0.4 mg/kg/day*" should read "*fenfluramine 0.4 mg/kg/day*" • Section 3.7, page 9: Clarify that although fenfluramine 0.2mg/kg/day was included in the Study 1 trial, this is not a licensed dose of fenfluramine • Why the committee made these recommendations (page 3 of ACD): Bullet point stating "*removing the placebo effect*"– Our original base case model reverted patients to baseline upon treatment discontinuation. We provided an analysis in response to the ERG report in which we removed placebo entirely, which improved the ICER considerably, but the ERG claims it was unable to replicate. Without any qualification / context this statement in the ACD is meaningless and should be removed. • Emailed query from NICE regarding negative values for the difference from placebo in convulsive seizure-free days reported in Table 10 of the company submission: We have confirmed with company statisticians that the negative signs can be ignored; the magnitude of the estimates of convulsive seizure free days and associated confidence intervals reported in Table 10 are however correct. • Clarification: "The clinical and patient experts noted that comorbidities and learning disabilities require care, which was not a direct function of seizure frequency of accrual in the model" (section 3.26, page 21). It should be noted that the assigned quality of life for patients in the model have been adjusted for underlying age and comorbidities, as well seizure frequency. See section B.3.4.2.1. in the CS • Please note a minor correction to figure 2 of the CS that has not been possible to amend at any earlier point in the evaluation process. The correction clarifies that cannabidiol plus clobazam and fenfluramine may be added on therapies to SoC that may or may not include stiripentol. For convenience this revised Figure 2 has been provided the Appendix. It should be noted that our patient-level simulation modelling approach is fundamentally different to the approach taken for cannabidiol in NICE TA614, it uses more robust quality of life data, efficacy data from a robust indirect treatment comparison and appropriately uses different prices of cannabidiol given that we do not have access to the confidential discount on its list price. Given all of the reasons, it is not possible to make a meaningful comparison between the outputs of our model and those reported for cannabidiol in NICE TA614.	Thank you for your comments. - Stiripentol has been replaced with fenfluramine in the reference cited in section 3.7. - Section 2.2 already notes the licensed doses so section 3.7 has not been amended. - The issue related to the placebo effect has been resolved so is no longer referred to in the introduction section of the guidance. - Comments in all other bullets have been noted.
42	Web comment	Web comment	*Has all of the relevant evidence been taken into account?* See below for animal data	Thanks for your comment. The committee took these comments into consideration along with the company's updated models and the updated discount.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Are the summaries of clinical and resource savings reasonable interpretations of the evidence? See below for my view of this statement *Are the recommendations sound and a suitable basis for guidance to the NHS?* I would argue not, which I mention in my statement *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?* Not to my reading *Comments* NICE have determined that fenfluramine not be recommended for the management of Dravet syndrome: I disagree with this, and would urge NICE to review the information they have used. The most relevant line of evidence I would submit that the committee should review is from figure 2 in Brunklaus, et al 'Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome' Brain 2012: 135; 2329-2336 which depicts the inexorable progression of this disorder. No disease-modifying agents exist to manage this process, but it does seem, to me, that fenfluramine might be considered to be an useful agent in modifying this process. First, it does have a novel mechanism (and in this I disagree with section 3.31), as it works via agonism of 5-HT(1D) and 5-HT(2C) receptors, as well as its blockade of sigma1 receptors. I would argue that this is distinct from other anti-convulsant drug activities, and I would submit that this makes it an attractive agent to use in concert with other (more conventional) agents in the management of this disorder (Sourbron, et al 'Pharmacological Analysis of the Anti-epileptic Mechanisms of Fenfluramine in scn1a Mutant Zebrafish' Front Pharmacol 2017: 8; 191 1-13). Second, there is a suggestion that fenfluramine might contribute to a disease-modifying activity through the restoration of neuronal cytoarchitecture, which might alter the trajectory I mentioned earlier (Tiraboschi, et al 'New insights into the early mechanisms of epileptogenesis in a zebrafish model of Dravet syndrome' Epilepsia 2020: 61; 549-560) I would appreciate your considering these findings, and their potential, when reconsidering your decision (it has also rendered the children with Dravet	Fenfluramine is recommended for Dravet syndrome.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			syndrome whom I manage, significantly seizure-free in comparison to their seizure burden prior to starting fenfluramine).	

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Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Zogenix International Ltd Research, development and manufacturer of fenfluramine (Fintepla)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	Dr Toby Toward Head of Market Access and HE&OR. Zogenix International Ltd

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

Context of this ACD response:

- Immediately prior to and following the first Appraisal Committee meeting held on the 4th March 2021, Zogenix requested NICE to arrange a meeting with the ERG to collaboratively discuss the perceived outstanding issues and agree appropriate steps and approaches to resolve them to appropriately respond to the ACD.

- A meeting was arranged with the ERG on the 7th May 2021, i.e., 9 weeks after our initial and subsequent requests and 1 working day before Zogenix's response to the ACD was due. Following that meeting, Zogenix provided a response to the ACD on 12th May 2021 and notified NICE that it had been unable to address every perceived issue raised in the discussion with the ERG due to the limited available time, but agreed to follow up with an "Addendum to the ACD response" to address remaining issues raised by the ERG. Zogenix submitted this Addendum on the 24th May 2021.

- Unbeknown to Zogenix (until October 2021), the ERG had already completed its assessment of Zogenix's ACD response on 19th May 2021, and had not taken into consideration the Addendum Zogenix submitted to NICE on the 24th May 2021. The ERG's report therefore listed several perceived issues relating to the validity of the simulation model as not having been addressed, even though these were addressed in the Addendum.

- In consequence, the outstanding issues perceived in the ERG report appear to have resulted in NICE delaying the 2nd Appraisal Committee meeting that was scheduled for June 2021. NICE, acting as an intermediary between Zogenix and the ERG, suggested that the key issue causing the delay was that the ERG was unable to confirm the validity of the model due to the fact that Zogenix had provided separate models for each scenario analysis.

- On the 27th May 2021, having been informed that the 2nd Appraisal committee scheduled for June 2021 would not be going ahead, Zogenix proactively requested NICE to engage the NICE Decision Support Unit (DSU) to find a way to independently validate the model. NICE forwarded the DSU's review to Zogenix on the 19th July 2021. This was a superficial review and appeared to be mostly based on the ACD rather than the model itself. The DSU did not have capacity to undertake a validation of the model.

- On the 12th August 2021 NICE informed Zogenix that it had identified an internal reviewer to undertake a review of our model. After several weeks Zogenix received an email from NICE on 22nd September 2021 stating: "*his view is that the current model can be used for the appraisal, albeit will require longer than usual to perform the cross checks and so on because of the different model files*". This was followed by a further email on 5th October 2021 stating: "*Our colleague at NICE looked at the model and was able to run it/understand what is going on. But he didn't perform the validation tasks that the ERG feel they are required to undertake*".

- Zogenix requested an urgent meeting with NICE and the ERG to try to move the appraisal forward. A meeting was provided with the NICE project team on the 8th October 2021. During this meeting it was confirmed that the ERG had produced a report on Zogenix's ACD response (dated 19th May 2021). Zogenix requested a copy of this ERG report, which was provided on the 8th October 2021. A meeting with the ERG and NICE was subsequently held on the 14th October 2021. It was

only by Zogenix compiling a list of 'perceived outstanding issues' to be discussed at that meeting that Zogenix established that their Addendum had not been considered when the ERG prepared its report. This misalignment of information and responses was confirmed at the meeting on the 14th October 2021.

- At that meeting, the NICE project manager was keen to note that it is not a "usual procedure" for the company to be provided with the ERG's report on its response to the ACD until a couple of days before the next Appraisal Committee meeting. However, given that the Appraisal Committee meeting was postponed in June specifically due to the NICE project team's concerns based on the ERG's report and perceived outstanding issues, Zogenix believe that provision of the ERG report at the time of postponing the 2nd Appraisal Committee meeting would have been a logical step that would have avoided the misalignment of information and misunderstanding between key stakeholders in the process. This would have led to a more expedited resolution of the 'perceived issues', and avoided the significant and unnecessary 7-month delay in progressing this appraisal, which has been to the detriment of patients, their carer-givers and clinicians.
- As agreed between the ERG, NICE and Zogenix at the meeting on the 14th October, a 're-set' of the appraisal process was required from the point of the ACD being issued by NICE.
- On this basis, Zogenix are currently re-providing their response to the ACD as a consolidation of: the previous ACD response and Addendum, updated with a further understanding of the ERG's concerns following receipt (8th October 2021) of the ERG's report dated 19th May 2021, and taking into account the clarification of points raised at the meeting held with NICE, the ERG and Zogenix on the 14th October 2021.
- To facilitate an easier review of this current response by NICE and the ERG, Zogenix have highlighted revised or previously unseen text in blue, with the original text from our ACD response in black.

Consolidated ACD response – Summary:

- Zogenix welcomes the opportunity to respond to the issued ACD. In reviewing the document, Zogenix has taken note of the Committee's preferred assumptions and recommendations alongside those raised by the ERG. Zogenix has looked to address the perceived outstanding validity issues in the model where appropriate, and through providing clarifications (below) and with further supplementary evidence in an appendix.
- To accommodate the Appraisal Committee's preferred assumptions and the ERG's suggested corrections, Zogenix has revised the original base case model. The base case ICER has changed marginally from £31,772/QALY to **£31,841/QALY**.
- The incremental modifications for each change from the original base case have been described in terms of: the rationale for the change, the specific change to the model code, the impact of the change on the overall ICER result and the disaggregated (costs, QALYs, life years etc) results, by each contributing study and their merged output. These insights into analyses are also provided for the resultant 'revised base case' model that combined all the modifications, and all scenario analyses.

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- As agreed with the ERG, Zogenix have implemented switches to enable the ERG to move between the revised base case and the original base case model for each modification.

- We have also provided additional analyses incorporating these base case revisions, to update:
    - Previously presented scenarios that provide guidance on the cost-effectiveness of fenfluramine within different positions of use in the treatment pathway
    - Scenarios that provide insight into areas highlighted in the ACD where there appears to be a level of uncertainty in the model assumptions to be able inform decision-making.

  Full details of these analyses are provided in the accompanying Appendix to this document.

  In addition, a spreadsheet has been provided containing all the code to run each model and the model results. This contains:
    - A user guide explaining exactly how to download the files, and set them to run to generate the revised base case (1st Tab)
    - A summary of the runs completed. Each of these gives:
        - A scenario number and name for identification
        - The reason for the change, and a description of the model changes implemented
        - The intervention compared
        - A description of the specific changes to the model code
        - A description of what changes are observed and their interpretation
    - For each scenario analyses, 3 sheets with the fully disaggregated results (19 dimensions relating to costs, QALYs, life years, clinical measures) are separately presented for:
        - The merged result, Study 1 and Study 1504
- For transparency, all model variants (with accompanying files) have been individually provided as separate self-contained folders.

Based on our revised base case analyses, the fully incremental analyses is shown below:

Fully incremental analysis – merged population (Table 8, Appendix)

Intervention	**ICER**	
Cannabidiol plus clobazam Vs SoC	= £69,469/QALY*	**Fenfluramine extendedly dominates cannabidiol plus clobazam*
Fenfluramine Vs SoC	= £49,828/QALY	
Fenfluramine Vs. Cannabidiol plus clobazam	= £31,841/QALY	

For ease of review, specific responses to the ACD are summarised in the table below, with detailed responses in the text that follows. Zogenix have also highlighted the conservatism in their model that the Appraisal Committee should be made aware of, alongside some additional scenarios that could be pragmatically considered to reduce uncertainty.

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Issue #	Description of perceived issue	How addressed in ACD response	Resulting ICER (original ICER £31,772)
1	Preliminary recommendation	Company view on ACD recommendation	n/a
2	Revised base case amended in line with Appraisal Committee's preferences and ERG's perceived issues. Included switches in model so can revert between original base case and the revised base case for each amendment	Implemented amendments to original base case (ICER for each revision separately and then combined):	
		• Amendment for Committee preference – Revert to placebo convulsive seizure frequency upon treatment discontinuation	£29,093
		• Amendment for Committee preference– No change in seizure frequency in adulthood	£32,468
		• Correction – Minor coding corrections	£31,688
		• Amendment – Proportionality of reduction in seizure frequency : reduction in seizure days amended to 1:[redacted]	£33,464
		• Correction – Replaced cycle 131 with cycle 130	£31,555
		Revised base case (above combined)	**£31,841**
		Fully incremental analysis of SoC vs Cannabidiol + clobazam vs Fenfluramine	**Fenfluramine extendedly dominates cannabidiol**
3	Effectiveness of fenfluramine compared to cannabidiol plus clobazam - We believe the ACD is incorrect to state fenfluramine is not more effective than cannabidiol	Reiterated evidence provided in our submission that was not presented to the Appraisal Committee. Provided further evidence of fenfluramine's superior efficacy	n/a
4	Indirect treatment comparison – request for additional analysis using absolute change from baseline in seizure frequency	We are unable to provide this due to lack of necessary data for cannabidiol plus clobazam. Current ITC analyses remain appropriate.	n/a
5	Clarification of stiripentol as a 'treatment modifier' of fenfluramine	Clarified basis of fenfluramine dosing based on stiripentol use, further justifying our approach to modelling. Disaggregated model results by stiripentol use also provided for transparency (see response to Issue #16)	n/a

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6	Uncertainty in long-term effectiveness data for fenfluramine	Clarified the long-term data available in support of fenfluramine, explained why not ethically possible to provide longer term comparative data and how this is not a key source of uncertainty	n/a
7	Proposed discontinuation criteria (stopping rules) for fenfluramine and confusion in assessment of response	Clarified that our approach is reasonable and explained how the model fully accounts for monitoring of response to treatment. Provided scenario analyses of alternative stopping rules:	
		• 40% stopping rule	£26,436
		• 50% stopping rule	£22,474
8	Applicability of fenfluramine in all patients with Dravet syndrome	Agree with Appraisal Committee's conclusions that the data from the RCTs are applicable to adults. Revision to the base case now incorporates no change to the background seizure frequency in adulthood	See Revisions to base case above
9	Model validity issues:	Addressed all perceived validity issues outlined in ACD and Lead presentation slides presented at 1st AC meeting:	
	People who stop treatment [with fenfluramine or cannabidiol] can go on to have fewer convulsive seizures and more convulsive seizure-free days (ACD section 3.28, page 22)	Patients who stop treatment revert to their own range of bootstrapped placebo seizures. Clarified how natural variation in seizure frequency is to be expected in this stochastic model and this is not a validity issue.	n/a
	Generated patient profiles contain seemingly implausible/inconsistent profiles (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43, and ERG report, section 5.2.3, page 92-93)	Determined a minor artefact in bootstrapped profiles and corrected in line with ERG's suggestion (replaced cycle 131 with cycle 130). Had minimal impact on ICER. Demonstrated that the bootstrapped profiles match the trial data well, and there are no implausible or inconsistent profiles.	See Revisions to base case above
	Bootstrapping method was not clear (ACD section 3.28, page 22)	Provided further clarification of the methods used for bootstrapping and their implementation in the model.	n/a
	Possible correlations between patient characteristics (such as motor impairment and convulsive seizure frequency) were not explored (ACD section 3.28, page 22)	Provided further clarification on the rationale for why Zogenix would not anticipate such correlations	n/a
	"Random draws differed between both cohorts in the model causing a difference" e.g. in overall survival unrelated to treatment efficacy estimates (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43)	Demonstrated that survival, QALYs and Costs are identical for each strategy when the model treatment effect is removed, indicating this is not an issue.	n/a

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	ERG minor fixing issue: Application of the probability for status epilepticus (SE) mortality (0.029% per cycle) applied to whole population rather than being conditional on experiencing a SE event.	Demonstrated that our base case approach in applying the probability of SE mortality to actual SE events (rather than to whole population) is clinically appropriate and conservative (see response to Issue #12). Zogenix have therefore pragmatically retained this	See response to Issue #12
	ERG minor fixing issue: Equalisation of "other discontinuations" in the titration and maintenance periods	We have looked at the model and are unsure of the discrepancy referred to by the ERG in the model. We would welcome further clarification to address the ERG's concerns.	n/a
	Stability of the model based on 480 simulated patients (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43)	Demonstrated model is stable across a wide range of simulated patient population sizes. 480 stimulated patients provides a reasonable balance between run time efficiency and stability.	n/a
	External validity of the model: Mortality in model validated based on short trials; company does not provide information from its workshop exploring input parameters (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43)	Clarified we had validated mortality vs trials and clinicians' expectations and alignment with most comprehensive Dravet syndrome mortality data available in literature. Clarified workshop was a confidential meeting with health economic modelling experts, that should not influence ERG's independent assessment of model validity, nor be considered a validity issue	n/a
	Company does not validate results against cannabidiol appraisal (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43):	Reiterated detailed explanation of why results would be fully expected to differ between models, and that the model in the cannabidiol appraisal (TA614) cannot reasonably be used to infer the validity of our model	n/a
10	Adjusting for placebo effects (reversion to placebo rather than baseline seizure frequency upon treatment discontinuation)	Amended the model in line with the Appraisal Committee's request and clarified the method used in the revised base case. • Included additional scenario analysis of removing a placebo effect completely (i.e. a patient's baseline is determined as the placebo, to which patients return upon discontinuation).	See Revisions to base case above £22,973
11	Basing the model on convulsive seizure free days rather than convulsive seizure frequency alone	Demonstrated that clinicians and care-givers consider convulsive seizure-free days are important, and that improvement in convulsive seizure free days has greater impact on patient and carer quality of life than reduction in convulsive seizure frequency. Model should represent impact of Dravet syndrome and treatment on seizure free days.	n/a
	Proportionality between reduction in convulsive seizure frequency and reduction in convulsive seizure days	Demonstrated that ERG approach to estimating proportionality is not technically appropriate. Re-estimated strength of relationship based on regression analysis of individual-patient data from the fenfluramine trials	See Revisions to base case above

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12	Relationship between convulsive seizures and mortality is not clear	Justified approach, demonstrating alignment of resulting mortality with clinical expectations and data. Showed contribution of mortality to ICER estimates	n/a
		• Demonstrated SE mortality modelling in the current base case is conservative by increasing probability of SE mortality per SE event by 3-fold	£29,587
		Provided scenario analyses exploring *highly conservative* alternative relationships as requested by the Appraisal Committee:	
		• Assuming same mortality as general epilepsy • Assuming mortality midpoint between base case and general epilepsy population	£48,088 £40,656
13	Impact of excluding non-convulsive seizures from model is not clear	Justified exclusion from model on basis of measurement difficulties, in line with model in cannabidiol appraisal (TA614). Clarified potentially conservative for comparisons against standard of care.	n/a
14	Adverse events – additional monitoring is not reflected in costs or utilities	Justified exclusion of adverse events and clarified how the model already reflects both adverse events and the monitoring for adverse events to the full extent that it is appropriate to do so	n/a
15	Carer utility applied in the model are overestimated	Agreed with Committee that incorporation of carer utility is appropriate in DS (as confirmed in the directly captured data from the RCTs), but acknowledged there is currently no consensus or technical guidance on how best to incorporate within the model. Clarified and justified our evidence-based approach and discussed how the arbitrary approach suggested by the ERG based on the cannabidiol model in TA614 is not evidence-based and is not appropriate. Provided scenario analysis to explore retaining carer quality of life once the patient dies	
		• *Highly conservative* scenario analysis retaining lowest carer quality of life in the model beyond the patient dying	£45,247
16	Clarification of QALYs accrued and differences in cost-effectiveness estimates in the model	For all analyses we have provided a spreadsheet of fully disaggregated results, including by concomitant stiripentol use and patient and carer	n/a

		QALY estimates to ensure transparency. Provided explanations of results in Appendix and all individual models separately for full transparency	
17	Unclear if fenfluramine meets the criteria for an innovative treatment	Clarified why we believe fenfluramine should be considered an innovative treatment, with reference to patient and clinician views of its effectiveness, and benefits unlikely to be fully captured in our QALY estimates	n/a
18	Conservatism in our modelling approach	Detailed the many ways in which our modelling approach is conservative, and which we believe the Appraisal Committee should be made aware of to inform its decision-making. Included additional scenarios that could be pragmatically considered by the Committee to reduce uncertainty	n/a

Full consolidated ACD response:

1	**Preliminary recommendation (ACD section 1, page 3)** • We are disappointed that the ACD currently determines a preliminary negative recommendation for the use of fenfluramine in the treatment of seizures associated with Dravet syndrome. • Often diagnosed in early infancy, Dravet syndrome is a very rare, genetic, and complex epileptic encephalopathy. Existing therapies are unable to control the daily and life-threatening convulsive seizures associated with Dravet syndrome and lamentably, 1 in 5 to 7 parents will not see their child reach adulthood; with the daily risks of seizure-related injuries and premature mortality continuing into adulthood (see references 2-4 of CS). Life-long seizures and a progressive deterioration in functional (e.g. walking, talking, washing), cognitive and behavioural development, affects every part of daily-living and the overall quality of life of patients, their immediate carer-givers providing around the clock care (Pagano et al 2018) and their broader family unit (Bailey et al, 2020: https://doi.org/10.1016/j.yebeh.2020.107377). There is a compelling clinical, economic and humanistic need for effective and tolerable treatment options that reduce the seizures associated with Dravet syndrome to alleviate the daily burden on patients, their care-givers and their families, as well as for the multi-disciplinary team of health care professionals that support them. • Fenfluramine is clearly a highly effective and well tolerated treatment that can address this unmet need. It is supported by the most compelling and comprehensive evidence package of any of the NICE-recommended Dravet syndrome therapies currently available, including robust indirect evidence that indicates fenfluramine provides superior seizure control compared with the most-recently recommended therapy, cannabidiol plus clobazam. During the appraisal process fenfluramine was described by clinical experts as providing “unprecedented” improvements in seizure control, and by patient carers as “life changing”; however, this is not reflected in the ACD, nor was it reflected in the slides presented during the appraisal committee meeting. • We have carefully reviewed the ACD and have taken steps to explore and address the committee’s views and preferences in our economic modelling as far as is reasonably possible. We have also identified and addressed areas in the ACD that we believe are incorrect and require clarification.

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document - re-submission of Company response to ACD 28th October 2021

	• We remain committed to working with NICE and the ERG to progress this appraisal so that patients, their carers and the NHS can benefit from the full potential of fenfluramine.
2	**Revised base case:** *We have revised the original base case to accommodate the Committee's preferred assumptions and to address perceived validity issues and reduce uncertainty in our base analyses. The revised base case ICER across the patient populations is only marginally changed:* • We have revised our original base case to correct for a minor coding error and minor specification error relating to utilities • We have implemented a correction to address a minor anomaly in the simulated population • We have made revisions to accommodate appraisal committee preferences for: o Removal of a change in background seizure frequency when patients reach adulthood o Patients to return to a placebo level of seizure frequencies rather than baseline seizure frequency upon treatment discontinuation • We have implemented a revised, evidence-based estimation of the proportional strength of relationship between the reduction in convulsive seizure frequency and the reduction in seizure days. • Collectively these revisions led to a marginal change in the base case ICER estimate for fenfluramine vs cannabidiol plus clobazam from £31,772 to £31,840/QALY (see Appendix Table 2) • These revisions led to a marginal changed in the base case ICER estimate for fenfluramine vs continued standard of care AEDs from £48,460 to £49,828/QALY (see Appendix Table 5) • In fully incremental analyses fenfluramine extendedly dominated cannabidiol (see Appendix Table 8)
3	**Effectiveness of fenfluramine compared to cannabidiol plus clobazam:** *It is incorrect to state that fenfluramine is not more effective than cannabidiol plus clobazam[1] for reducing convulsive seizure frequencies (ACD section 3.9, page 10). This conclusion is inconsistent with: the clinical trial-based evidence showing the superiority of fenfluramine; with the opinions of experienced UK and internationally-respected Dravet syndrome clinical experts; and with the European regulatory authority:* • **The mean placebo-adjusted reductions from baseline in convulsive seizure frequency clearly favours fenfluramine:** In line with NICE guidance on technical methods, robust indirect treatment comparison methods were employed. In the provided Bayesian network meta-analyses (NMA), comparing between adding either placebo or fenfluramine (0.7mg/kg/day) to the existing standard of care (SoC) of patients receiving anti-

[1] The European license requires cannabidiol (Epidyolex) to be used in conjunction with clobazam

	epileptic drugs (AEDS) that did not include stiripentol[2], the mean difference in monthly convulsive seizure frequency (MCSF) was [redacted] Comparing between adding either placebo or fenfluramine (0.4mg/kg/day) to the regimen of patients already receiving stiripentol as part of their existing SoC, the mean difference in MCSF was [redacted]. This compares with a much lower mean difference in MCSF between adding either placebo or cannabidiol 10mg/kg/day(plus clobazam) [redacted] and between placebo or cannabidiol 20mg/kg/day (plus clobazam) - [redacted] in similar patients receiving their existing SoC AEDs (see section B.2.9.4.2 of the company submission). The magnitude of the differences clearly favours fenfluramine over cannabidiol with clobazam and indicates these cannot be judged to be of the same efficacy for convulsive seizure reduction – we note that the Lead presentation slides presented to the committee on 4th March 2021 stated: "*Fenfluramine more effective than cannabidiol + clobazam at reducing convulsive seizure frequency per 28 days (% change from placebo)*"; however, these slides were amended after the committee meeting to state: "*Both fenfluramine and cannabidiol superior to placebo, fenfluramine 0.4 and 0.7 mg/kg/day having the greatest reduction, but no difference between fenfluramine and cannabidiol".* The conclusion of the ACD based on these analyses is incorrect. **Please note**: the 0.2 mg/kg/day dose group of fenfluramine in Study 1 was only of the purposes of evaluating a dose-response. It is an initiation dose but is not the intended maintenance dose of fenfluramine in patients with DS and was not included as a dosing group in the Study 1504. • **The marginal overlap of 95% credible intervals cannot be interpreted as no difference in efficacy:** We presume that the reason for this erroneous statement in the ACD is because of the marginal overlap of the wide credible intervals for these differences from placebo. The credible intervals are wide due to the small trial populations in this very rare disease. Whilst there was a marginal overlap in these wide credible intervals, this cannot be interpreted to mean there is no difference between fenfluramine and cannabidiol; Bayesian analyses do not rely on a categorical inference of "significant" or "non-significant" and interpretation of the marginal overlap in credible intervals as indicating "no difference" and therefore "fenfluramine is not more effective than cannabidiol plus clobazam" is flawed. Wide credible intervals are also often observed in NMAs, particularly when based on trials with relatively small trial populations, as is the case for trials in this rare disease. It should be noted that the modelled probabilistic sensitivity analysis which accounts for variance around the point estimate, resulted in a mean ICER result that was highly consistent with the deterministic base case results. • **There is >99% probability that fenfluramine is more effective than cannabidiol plus clobazam in reducing convulsive seizure frequency:** Bayesian NMA allows for making intuitive probability statements of a relative effect size, and probabilistic ranking of treatments from most effective to least effective. Based on these analyses, there is a >99% probability that fenfluramine in its licensed dose regimens would be ranked as the most effective therapy, and <1% probability that cannabidiol plus cannabidiol in its licensed dose regimens would be ranked as the most effective therapy for mean reduction in convulsive seizure frequency (see the probability ranking tables provided in the Appendix, Figure 9). • **Fenfluramine is clearly superior to cannabidiol plus clobazam in achieving *clinically meaningful* reductions from baseline in convulsive seizure frequency:** We also provided in our submission a Bayesian NMA of fenfluramine against cannabidiol for the proportion of patients achieving at least a 50% reduction from baseline in monthly convulsive seizure frequency (see section B.2.9.4.3 of the company submission). This convulsive seizure frequency endpoint is commonly used in epilepsy disorder trials, and is recognised as an accepted threshold measure of a

[2] It is important to note that stiripentol is not a requirement of the licensed indication for fenfluramine. Stiripentol may be an existing treatment within a patients SoC. A pharmacokinetic interaction of fenfluramine and stiripentol requires a dose adjustment. The European Medicines Agency has determined that in patients concomitantly receiving stiripentol, an adjusted 0.4mg/kg/day dose of fenfluramine is bioequivalent to the 0.7 mg/kg/day dose in patients not receiving stiripentol.
Please see related point 4 below.

clinically meaningful reduction in seizure frequency. It is therefore considered as a key endpoint by the European regulatory authority (See: Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (europa.eu)). This endpoint was a key prespecified endpoint in both the fenfluramine and cannabidiol trials. These analyses show a clearly greater odds of achieving a ≥50% reduction from baseline in convulsive seizure frequency (with no overlap in 95% credible intervals) for both licensed doses of fenfluramine (0.7mg/kg/day without concomitant stiripentol and 0.4mg/kg/day with concomitant stiripentol) when compared to licensed doses of cannabidiol of either 10mg/kg/day or 20mg/kg/day with concomitant clobazam. This was acknowledged in the ERG report (section 4.4, page 73), which states: "*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*". Despite this, we are concerned to have observed that this evidence was omitted from the Lead presentation during the appraisal committee meeting and have been omitted from the ACD. As these analyses clearly demonstrate that fenfluramine is superior to cannabidiol plus clobazam for this key convulsive seizure frequency reduction endpoint, the conclusion of the ACD that "fenfluramine is not more effective than cannabidiol plus clobazam for reducing convulsive seizure frequencies" is not supported by the available evidence and is incorrect.

- **Supplemental Bucher pairwise indirect treatment comparisons support the superiority of fenfluramine for mean placebo-adjusted reductions from baseline in convulsive seizure frequency, and for clinically meaningful reductions in convulsive seizure frequency:** Indirect comparisons using the Bucher method consistently favour fenfluramine over cannabidiol across a range of convulsive seizure outcomes (Appendix Table 29). Fenfluramine 0.7mg/kg/day provided a statistically significant additional [redacted] reduction in monthly convulsive seizure frequency vs. cannabidiol 10mg (plus clobazam), and a statistically significant additional [redacted] reduction vs. cannabidiol 20mg (plus clobazam) based on the GWPCARE2 study. The odds ratio for achieving a 50% (clinically meaningful) reduction in monthly convulsive seizure frequency for fenfluramine 0.7mg.kg/day vs. cannabidiol 10mg/kg/day (plus clobazam) was [redacted], and vs. cannabidiol 20mg/kg/day (plus clobazam) was [redacted], and for fenfluramine 0.4mg/kg/day vs. cannabidiol 10mg/kg/day (plus clobazam) was [redacted] and vs. cannabidiol 20mg/kg/day (plus clobazam) was [redacted] These consistent statistically significant results in favour of fenfluramine further counter the conclusion of the ACD that there is no difference between fenfluramine and cannabidiol.
- **Fenfluramine has maintained its orphan status based on a demonstrated significant benefit in reducing convulsive seizure frequency compared with cannabidiol plus clobazam:** To qualify for European orphan designation, a medicine must be intended for the treatment of a rare, life threatening or chronically debilitating condition, and there must be either no satisfactory treatment for the condition, or where treatment(s) currently exists the new medicine must provide a significant benefit over that existing treatment(s) (see Orphan designation: Overview | European Medicines Agency (europa.eu)). Evidence provided to the EMA to demonstrate this benefit included indirect treatment comparisons of fenfluramine vs cannabidiol plus clobazam. As cannabidiol plus clobazam was fully licensed by the EMA at the time of its decision to maintain the orphan designation for fenfluramine, this indicates that the regulator accepts that fenfluramine provides a significant benefit compared with cannabidiol plus clobazam. It also highlights that given there are limited effective treatments for patients with Dravet syndrome, fenfluramine may provide a new effective alternative treatment option for patients that have been unable to gain sufficient seizure control from their existing therapies (include cannabidiol). These points were further supported by a consensus statement of 4 leading European clinical experts in Dravet syndrome, presented to the EMA, which noted that the relative effect sizes for fenfluramine in the indirect treatment comparisons were consistently greater than those for

	cannabidiol plus clobazam across multiple convulsive seizure reduction endpoints and supported a clear benefit of fenfluramine over cannabidiol in terms of both magnitude and consistency of effect (data on file, December 2019). • **UK Clinical expert opinion solicited by NICE further emphasises that fenfluramine is a step change in the management of Dravet syndrome, and that the reductions in , seizure frequency with fenfluramine are unprecedented:** In addition to the clear, consistent clinical trial data-based evidence of the superiority of fenfluramine for convulsive seizure frequency reduction presented in our submission, clinical expert opinion obtained by NICE during the appraisal process states (page 666 of the committee papers), in response to the question of whether fenfluramine is a step-change in the management of Dravet syndrome: "*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*." This view is also represented in the ACD in section 3.31, where it states: "*A clinical expert said that they considered fenfluramine to be a step change in managing Dravet syndrome because the same benefits have not been seen in trials of other drugs*." This further supports a conclusion of superior efficacy of fenfluramine compared with cannabidiol plus clobazam. **The conclusion of the ACD that fenfluramine is not more effective than cannabidiol plus clobazam for reducing convulsive seizure frequency is not justified based on the available evidence, and is inconsistent with the interpretation of that evidence and experience of several leading clinical experts and the regulatory authority. The ACD and FAD should remove this incorrect conclusion and reflect the clear superior efficacy of fenfluramine in reducing convulsive seizure frequency compared with cannabidiol plus clobazam.** • **It is important that the Appraisal Committee is made aware of this response and provided with the opportunity to review its conclusion.**
4	**Indirect treatment comparison:** *We are unable to provide an additional indirect treatment comparison of fenfluramine and cannabidiol plus clobazam using absolute changes from baseline in convulsive seizure frequency due to insufficient data for cannabidiol plus clobazam (ACD section 3.9, page 10). Our analyses using relative changes from baseline versus placebo remain valid and appropriate:* • **The standard errors for the absolute change from baseline in convulsive seizure frequency for cannabidiol plus clobazam are not publicly available. Without these data we cannot conduct the indirect treatment comparison.** We reported data for absolute change from baseline in convulsive seizure frequency for fenfluramine and cannabidiol plus clobazam in Table 17 of our submission. The point estimates for placebo and cannabidiol plus clobazam (the relevant population) from the cannabidiol trials were taken from the SmPC for Epidyolex because the cannabidiol trial publications did not report the results for this subgroup of patients. This excludes the standard errors for these point estimates. A subsequent publication by Gunning et al 2020 provides further data on the cannabidiol plus clobazam subgroup from the trials, but this also excludes the standard errors for these point estimates. As the indirect treatment comparison requires both the point estimates and the standard errors as inputs we are unable to conduct this analysis. • **The indirect treatment comparison we provided in our submission based on the percentage change from baseline in convulsive seizure frequency relative to placebo remains entirely appropriate and valid.** These data were required for the economic model. The use of treatment effects relative to placebo mitigates any natural and expected heterogeneity that may exist in baseline seizure frequencies between the different trials in this rare and heterogenous syndrome. As these data were based on analyses that provided both the point estimates and the standard

	errors, they could be appropriately used to undertake the indirect treatment comparison, providing key information on the relative effects of fenfluramine and cannabidiol plus clobazam. • **It is important that the Appraisal Committee is made aware that we have explored their request and were unable to undertake the analysis due to a lack of required data for cannabidiol.**
5	**Clarification of the effect of stiripentol as a treatment modifier (ACD section 3.10, page 10-11):** *Our approach to estimate relative treatment effects and to modelling the cost effectiveness of fenfluramine vs cannabidiol plus clobazam is appropriate:* • **Fenfluramine is licensed by the European (and US) regulatory authority at a dose of 0.7mg/kg/day (maximum 26mg/day) without concomitant stiripentol and 0.4mg/kg/day (maximum 17mg/day) when used with concomitant stiripentol.** This was based on a pharmacokinetic study of the effect of stiripentol on fenfluramine exposure, and estimation of bioequivalence of dosing between the fenfluramine 0.7mg/kg/day dose (without concomitant stiripentol) and the fenfluramine 0.4mg/kg/day dose (with concomitant stiripentol). This was a regulatory consideration leading to the fenfluramine dose regimens used in the pivotal clinical trials, and the same dose regimens that were subsequently licensed by the regulatory authority. We did not include the pharmacokinetic study in our submission because these are the licensed dose regimens to be appraised by NICE; the pharmacokinetic study is therefore irrelevant to the NICE decision-making process. • **Treatment of seizures in Dravet syndrome is individualised (as noted in section 3.4 of the ACD).** Since in clinical practice, patients, whose seizures are usually refractory to treatment, have a dynamic spectrum of seizures with differing need for a treatment at a particular time, it would be entirely expected that the concomitant treatments forming their SoC (and that underpins the regimen basis for an add-on therapy) will also be heterogeneous. This regimen basis of SoC may or may not include stiripentol. In reflecting this intended population, the clinical trials also appropriately enrolled patients with a similar heterogenous mix of treatments underpinning SoC. Given the pharmacokinetic interaction between fenfluramine and stiripentol [2], as well as geographical differences in the commercial availability of stiripentol, the registration studies of fenfluramine as an add-on therapy included patients for whom SoC was included (Study 1504) and excluded (Study 1) stiripentol. • **When fenfluramine is used alongside stiripentol at the licensed dose of 0.4mg/kg/day, stiripentol is not a further treatment effect modifier.** A more likely explanation for the observed differences in the reduction from baseline in convulsive seizure frequency between fenfluramine 0.7mg/kg/day (without stiripentol) and fenfluramine 0.4mg/kg/day (with concomitant stiripentol) is the fact that Dravet syndrome is a very rare and heterogenous disease and, consequently, the number of patients enrolled in the trials is small, which amplifies the effect of any heterogeneity arising from different treatment histories and baseline seizure frequencies. This is mitigated by using the same '% change from baseline in monthly convulsive seizure frequency' endpoint assessments from the fenfluramine and cannabidiol trials to inform the indirect treatment comparison, which estimates relative treatment effects for the interventions (fenfluramine and cannabidiol) and placebo, in terms of their respective changes from baseline in convulsive seizure frequency. • **It should be noted that the GWPCARE 1 and 2 clinical trials of cannabidiol included a mixed population of patients in terms of concomitant use of stiripentol.** However, there are no data available for cannabidiol plus clobazam by concomitant use of stiripentol. By necessity we assume that stiripentol is not an effect modifier of cannabidiol because we do not have access to trial data for cannabidiol with clobazam broken down by stiripentol use. This assumption is consistent with the implicit assumptions of both the regulatory authority and NICE, neither of which has differentiated the use of cannabidiol plus clobazam by concomitant use or not of stiripentol, based on the same clinical trial data.

	• **Clobazam is not a significant treatment effect modifier of fenfluramine [1].** We included in section B.2.6.1.1.1 of our submission a published analysis indicating that clobazam is not a significant treatment effect modifier of fenfluramine; however, this was omitted from the ERG report, despite our requests to include these data (see Response to factual accuracy check of ERG report, 04 Nov 2020). Although this analysis is limited by small sample size, the conclusion is supported by the European regulatory authority's licensing of fenfluramine, which does not differentiate the use of fenfluramine by concomitant clobazam use (in contrast to the licensing of cannabidiol and stiripentol, both of which are only licensed for use with concomitant clobazam). Our assumption that clobazam is not a significant treatment effect modifier of fenfluramine is therefore justified and should not be imposed on patients taking fenfluramine if their existing SoC does not already contain it. In the interests of treatment simplification, and in providing alternative options for patients where clobazam (and therefore stiripentol and cannabidiol) may be unsuitable, we provided an analysis for this (albeit small anticipated use) "clobazam undesirable" sub-population in our CS. • **Despite some expected heterogeneity in baseline seizure frequencies and concomitant treatments received, our approach to estimating the relative treatment effects of fenfluramine and cannabidiol plus clobazam is justified.** • **Our cost-effectiveness analyses appropriately represent the use of fenfluramine without stiripentol vs cannabidiol (plus clobazam), and the use of fenfluramine with stiripentol vs cannabidiol (plus clobazam).** • **These separate analyses are appropriately combined in the base case to represent the expected cost effectiveness of the use of fenfluramine across this rare, heterogeneous patient population in UK clinical practice, which was accepted in principle by the Appraisal Committee.** The committee concluded that a merging of these population results is acceptable in principle (ACD section 3.15, page 14). To provide further transparency in the proposed cost-effectiveness of fenfluramine in the UK setting, the merged and individual analyses of fenfluramine on top of a patient's existing SoC that includes (Study 1504) and excludes (excludes Study 1) stiripentol have been provided. The results from all three analyses have also been disaggregated (e.g. **Costs**: intervention costs, AED SoC costs, primary and out-patient costs, rescue medicines and emergency treatment costs; **effects**: QALYs by patient and carers, life years gained, seizures, status epilepticus, seizure days) in line with the Committee's request (see Appendix). • **As the ACD listed the effect of stiripentol on fenfluramine's treatment effect as a source of uncertainty, it is important that this response is given due consideration**
6	**Uncertainty in long-term effectiveness data for fenfluramine:** *Long-term effectiveness data for fenfluramine in this rare disease, characterised by seizures that are typically refractory to therapy, show a sustained effect of fenfluramine over several years of use. There is little uncertainty in the long-term effectiveness of fenfluramine (ACD section 3.11, page 11-12), and the long-term effectiveness of fenfluramine is not a key source of uncertainty in the model (ACD, "Why the committee made these recommendations", page 3; section 3.29, page 23):* • **The duration of our comparative clinical trials is entirely appropriate. It would be unethical to conduct longer comparative trials**. Our submission included comparative trial data with 14-15 weeks of on-treatment follow up, which is similar to that available for cannabidiol and substantially longer than the 8-week on-treatment trials of stiripentol, both of which are recommended as therapy options by NICE. As the addition of fenfluramine to standard of care therapy demonstrated a rapid and sustained, significantly superior treatment effect compared with standard of

	care therapy alone, it would be unethical to expect patients who were randomised to standard of care therapy alone to continue in the trials on that clearly inferior therapy. It is therefore unreasonable to expect that longer comparative trial data should be available in this disease area. • **Our submission included 3 year open-label extension data in patients who are representative of those in clinical practice.** Patients enrolled in the comparative trials were reflective of patients in clinical practice, who are typically refractory to existing therapy. These patients were permitted to enrol in the open-label extension study if they were felt able to continue to benefit from therapy. The ERG suggests this was a highly select population; however, as noted by the clinical experts, fenfluramine (or any other therapy) would only be continued in practice in patients who continue to benefit. The open-label extension study therefore reflects the use of fenfluramine as would be anticipated in clinical practice. • **The data from the open-label extension study indicates that the effects of fenfluramine are sustained over 3 years**. This was acknowledged in the ACD, with the clinical experts noting there was no evidence of a waning of effect in practice. In the context of this rare disease, characterised by seizures that are typically refractory to therapy, this evidence of sustained effect of fenfluramine for up to 3 years is compelling. • **Our submission also included prospective real-world evidence studies providing evidence of sustained effects of fenfluramine over 5 years, and retrospective real-world evidence studies of up to 27 years of sustained use.** Whilst acknowledging their limitations, these data support the sustained efficacy of fenfluramine over very long periods of time in patients who are felt would continue to benefit from treatment in clinical practice. These data were referenced in the Lead presentation to the Appraisal Committee, but only in relation to the use of fenfluramine in adults. The ACD is incorrect to state in section 3.11 that there are no data beyond 3 years. • **Collectively, the evidence of long-term effectiveness of fenfluramine is as comprehensive and compelling as it is possible to be in this rare disease. There is little uncertainty in the long-term effectiveness of fenfluramine.** • **Our economic model appropriately accounts for potential loss of effectiveness over time.** The implementation of the stopping rule, in which fenfluramine or cannabidiol treatment is discontinued at 6 months in those not achieving at least a 30% reduction from baseline in convulsive seizure frequency, ensures that these treatments are only continued in the longer term in patients achieving a sufficient response to treatment. In addition, the model implements treatment discontinuation rates observed in the open-label extension study, which includes discontinuations for all reasons, including loss of efficacy, over the model lifetime. This data driven approach, which is applied to both arms of the model, ensures only those with sustained clinical benefit are maintained on treatment in the long-term. Adoption of any other approach would require imposition of an unsubstantiated assumption that would not be aligned with the actual data available from the open-label extension studies, which indicate a 0.7% discontinuation probability per 28-day cycle with fenfluramine and a similar probability of 0.8% with cannabidiol. • **Collectively, there is little uncertainty in the long-term effectiveness of fenfluramine, and little risk that any residual uncertainty in the long-term effectiveness of fenfluramine biases the economic model**.
7	**Proposed discontinuation criteria (stopping rules) for fenfluramine and confusion in assessment of response:** *We agree it is appropriate to assess response to treatment every 6 months and stop fenfluramine if it is not effective (ACD section 3.13, page 13). Our model accounts for this appropriately:* • **Our economic model includes a stopping rule at 6 months after initiating therapy.** This ensures treatment is only continued in patients achieving a sufficient response (at least 30% reduction from baseline in convulsive seizure frequency) with treatment, and it is noted in the ACD that was considered appropriate by the clinical experts (page 13).

	• **The model implements treatment discontinuation rates observed in the open-label extension study. This includes discontinuations for all reasons, including loss of efficacy, over the remaining model lifetime.** This ensures only those with sustained clinical benefit are maintained on treatment in the long-term; those who do not sustain a sufficient clinical benefit discontinue treatment at the rates observed in the open-label extension study. As the open-label extension study did not protocolise continued treatment, the discontinuation rates observed in this study are likely to reflect clinician and patient/carer decision to discontinue treatment as per routine clinical practice. • **Implementation of a waning of effect is not supported by the evidence for fenfluramine.** There is no evidence of a waning of effect (i.e. a loss of effect over time) with fenfluramine from the randomised clinical trials, open-label extension studies or in the real-world context of expanded access programmes and small studies of patients receiving treatment for over 27 years (Section B.2.6.1 of the CS). This observation is also consistent with the clinical expert opinion contained in the ACD (page 12). Therefore the model excludes waning of effect. To impose a waning of effect on top of the existing 30% stopping rule and data driven discontinuation rates from the open-label extension studies would not be evidence-based and would lead to double counting of any loss of effect. • **There are clinically and economically perverse consequences from implementing a waning of effect for cannabidiol in the model**. In line with NICE TA614, it is rational on a clinical and general cost-effectiveness basis to implement a stopping rule to discontinue treatment in patients that are no longer maintaining a minimum threshold of efficacy benefit. However, as noted in the appraisal committee discussions of cannabidiol in NICE TA614, a perverse consequence with modelling a waning of effect occurs in that by returning discontinued patients to a worse state of seizures without the costs of cannabidiol, the overall cost of the strategy decreases and the overall cost-effectiveness of the strategy improves, to the point that the cannabidiol strategy becomes increasingly cost-effective the more waning of effect is assumed. In practice, however, given the limited number of available therapies for patients with Dravet syndrome, it is likely that patients who experience a waning of effect will be titrated to a higher dose of cannabidiol before totally discontinuing treatment (and returning to the pre-treatment SoC therapies). This appears to be supported by the stated mean modal dose of 21mg/kg/day in the Epidyolex open-label extension study (Devinsky, 2018) and reported experience in the nominative ATU programme in France, where a starting dose of 10 mg/kg/day is increased towards 15-20mg/kg/day within 6 months of treatment (D'Onofrio et al, 2021). As we already assume the maximum doses of fenfluramine in our base case analysis, but a dose of cannabidiol of 12mg/kg/day (significantly lower than the maximum permitted dose of 20mg/kg/day), the exclusion of a waning of effect for both strategy arms in our model is therefore a clinically conservative decision that potentially overstates the sustainability of cannabidiol therapy. The implications of comparing a treatment strategy of fenfluramine to plausible higher doses of cannabidiol (15mg/kg/day and 20mg/kg/day) have been shown in scenario analyses (Appendix Table 27 and 28) . • **Implementing additional stopping rules in the model is therefore futile.** Given the first stopping rule already removes treatment from those patients who did not achieve a sufficient response within 6 months of starting treatment, and there is no evidence of waning of effect with fenfluramine that is not already captured in the open-label extension study-based treatment discontinuations, implementing further stopping rules at subsequent 6-month periods in the model would not remove treatment from any further patients. Technically, if one was to introduce a repeated 6-monthly stopping rule, a few additional patients may discontinue their index treatment, but this would be an unintended consequence for a few patients that by chance (arising from the random generation of patient seizures in the microsimulation approach) meet the stopping threshold of seizures within a cycle. The ongoing discontinuation rates from the open-label extension study account for the clinician and patient/carer decision to discontinue treatment beyond the initial 6-months of treatment as per routine clinical practice and are included separately in the model.

	• **It is incorrect to equate our exclusion of subsequent stopping rules every 6 months with the suggestion that we have excluded assessment of response to treatment every 6 months.** The fact that our model does not implement subsequent 6-month stopping rules does not mean that patients in our model are not routinely monitored and assessed for their response to treatment. We fully agree that patients would be routinely seen and assessed for their response to treatment at 3–6-month periods in clinical practice and we have included the full costs of this in the model. • **In summary, our implementation of the stopping rule and subsequent treatment discontinuation, and incorporation of the full costs associated with regular, routine management, appropriately captures the long-term effectiveness and costs of treatment with fenfluramine.** • **We have explored the impact of implementing alternative stopping rules of at least a 40% (£26,436/QALY) or 50% (£22,474/QALY) reduction in seizure frequency required for continued treatment beyond 6 months in our revised base case (see Appendix, Table 27 and 28).**
8	**Applicability of fenfluramine in all patients with Dravet syndrome:** *Evidence from children and young people is applicable to adults (ACD section 3.12, page 12):* • **We are pleased that the committee agrees that the evidence from our trials is applicable to adults**. Although there is less evidence in adults than in younger patients, which may be perceived to lead to uncertainty, it should be noted that this is also the case for stiripentol and cannabidiol, which are both recommended for use by NICE. • **Fenfluramine should be available to all Dravet syndrome patients, irrespective of age.** Cannabidiol is licensed for use in children and adults and its NICE recommendation (TA614) does not impose limits on its use by age. As such, and in the interests of equality, there would be no reason to impose limits on the use of fenfluramine based on age. • **The issue of whether adults experience a lower convulsive seizure frequency than children is a minor consideration (ACD section 3.20, page17).** In our original base case, we included a halving of convulsive seizure frequency in patients aged 18+ years as the literature indicated that seizure frequency may be reduced in older patients compared with younger patients. This assumption was applied to both arms of the model and we demonstrated in a scenario analysis (reported in Table 51 of the company submission) that removal of this assumption had very little impact on the ICER. We have provided a revised base case analysis in response to the ACD in which the convulsive seizure frequency is assumed to remain constant irrespective of age (see response to Issue #2 above).
9	**Model validity issues:** *We are unclear why the ERG was unable to run or replicate certain analyses (ACD section 3.21, page 18; ACD section 3.28, page 22-23). We had offered to directly address these concerns with the ERG before the 1st AC meeting (4th March 2021) but this was not possible. We have since revisited the economic model and explored the ERG's concerns about the validity of the model (ACD section 3.28, page 22), as discussed below.*

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	People who stop treatment [with fenfluramine or cannabidiol] can go on to have fewer convulsive seizures and more convulsive seizure-free days (ACD section 3.28, page 22): • Variation in seizures frequency for patients who discontinue treatment is expected in a stochastic, patient-level simulation model and would be consistent with clinical practice. We do not believe this indicates a 'validity issue' with our model • For patients with Dravet syndrome, seizures arise spontaneously and their frequency, both within and between patients, is consequently heterogeneous; (see Appendix Figure 7 for plots of seizure frequencies by individual patients over time in Study 1 and Study 1504, clearly showing the heterogeneity in frequencies). • In line with the Appraisal Committee's suggestions in the TA614 FAD, we developed a stochastic model using patient-level data from the clinical trials to account for this natural intra- and inter-patient heterogeneity. • In contrast to a cohort model (as developed by the cannabidiol manufacturer for TA614), which reflects the average seizure frequencies across the cohort, our model simulates individual patients and their seizures. • As the individual patient-level seizure data from the trials is extrapolated using bootstrapping methods, we would expect some natural variation in convulsive seizures episodes (and therefore seizure-free days) for patients at 'baseline', 'on-treatment' and following 'treatment discontinuation'. Seizures are not expected to be exactly the same between given time frames (although less variation is likely observed over longer time frames), or between patients. • Patients who discontinue therapy are reverted (in our revised base case) to their individual range of bootstrapped placebo seizures. At the modelled patient-level, we would expect, albeit in a few patients only, to observe periods whereby a patient within a particular time frame, may have fewer seizures after discontinuing their 'treatment'. This is not unexpected given the stochastic nature of the data and model. We therefore do not believe this indicates a validity issue with our patient-level simulation model, and to impose a 'trimming' or constraint to the model so as to prevent this expected phenomenon would not be aligned with the patient-level data and the premise of the model.
	Generated patient profiles contain seemingly implausible/inconsistent profiles (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43, and ERG report, section 5.2.3, page 92-93): • The ERG report referred to a perceived anomaly in the number of seizures and seizure days in the 10-year bootstrapped data relating to the 131st 28-day cycle – the number of seizures in that last cycle was approximately half of the number observed in the previous 130 cycles. We have further explored this and have determined that the issue arises due to the fact that 10 years is equivalent to 3652 days, which is equivalent to 130.43 x 28-day cycles. The last cycle (cycle 131) is therefore a partial cycle and so accrues only a partial number of seizures (hence the anomaly vs other previous cycles). Replacing cycle 131 with cycle 130 and propagating the full 131 cycles over the model lifetime (which is the same approach adopted by the ERG in its analyses in the ERG report) results in a marginal reduction in the ICER (base case ICER of £31,772 changed to £31,155/QALY). We have adopted this minor correction into the revised base case, as agreed with the ERG at our meeting of the 8th October 2021. • The ERG report (Figure 5.4, page 92-93,) referred to a "*seemingly implausible peak for patients with zero convulsive seizure-free days that seems to represent a cluster of outlier patients in terms of convulsive seizures*" in Study 1504, which it implied "*undermined the validity of the patent profiles used*". We have further explored the individual patients-level data used in the bootstrapping and can confirm that the patient profiles match the underlying data. The peak in patients with zero convulsive seizure free days in Study 1504, referred to in Figure 5.4 of the ERG report, is actually due to just one patient who had a higher number of seizures at baseline and throughout the study compared with the other patients in the trial (see Appendix

	Figure 2). The "cluster" in zero seizure free days referred to in Figure 5.4 of the ERG report is entirely consistent with the trial data and does not represent any form of error in the bootstrapping and generation of patient profiles. Given the limited size of the trial in this rare disease, we do not consider this patient to be an "outlier"; rather, it is an accurate reflection of the heterogenous nature of seizures in Dravet syndrome amongst the participants recruited to the trial, who have been confirmed to reflect patients in need of add-on therapy in clinical practice. The generated patient profiles is therefore plausible and consistent with the trial data, and is valid.
	Bootstrapping method was not clear (ACD section 3.28, page 22): We provided details of the bootstrapping methodology in the CS and in Appendix L to the CS. We have re-provided the explanation from the CS Appendix L, with further clarifications, in the Appendix to this response.
	Possible correlations between patient characteristics (such as motor impairment and convulsive seizure frequency) were not explored (ACD section 3.28, page 22): A pragmatic approach to generate patient profiles was required due to data limitations in this very rare disease. As this applies to both arms of the model, we do not believe this is a significant challenge to the validity of the model: • In the model, patients are simulated (bootstrapping method) with a given seizure profile derived from the trial data. Once the profiles are created, each individual patient is then assigned further clinical characteristics for their gender and co-morbidities. Given that Dravet syndrome is a very rare disease, and the trials consequently contain a small sample of patients followed up for an appropriate but limited time, it was not possible using the trial data to take a different approach. • In our Response to Clarification questions, 16th September 2020, we agreed it could be plausible that motor impairments and number of concomitant medications would be correlated with age (given that motor impairments may deteriorate over time, and that seizures are typically intractable to existing therapy and so may require additional concomitant medications in an attempt to achieve better seizure control). However, upon examining our trial data we did not observe any evidence of such correlations (see response to the non-priority question C8c). • We did observe correlation in quality of life and seizure frequency, which is accounted for. We did not specifically account for a correlation in, for example, patient seizures and motor impairments, when undertaking the bootstrapping due to sample sizes from the trials included in the bootstrapping not being large enough. Given that we see no obvious evidence of correlation in the most obvious potential correlates (motor impairment and age) in the trial data, we do not anticipate that patient seizure frequency (which can be dynamic and heterogeneous) and motor impairments will be correlated to the extent that they require specific consideration in the bootstrapping of these same trial data. Our approach to the bootstrapping is therefore reasonable based on the available data.

	Random draws differed between both cohorts in the model causing a difference in e.g. overall survival unrelated to treatment efficacy estimates (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43): We have not experienced issues with random draws leading to differences in model outputs independent of treatment effects. We do not believe this is an issue with our model:
	• To explore this concern, we have run the model by removing any possible treatment effect from each arm of the model.
	• We used a population of all patients on clobazam, in which we assumed there is no placebo effect and no treatment effect for fenfluramine or cannabidiol, no difference in discontinuations and no costs for either drug. We also assumed the same concomitant drug profile. This resulted in perfectly identical results for both fenfluramine and cannabidiol (merged model, see accompanying spreadsheet "Merged_disaggregated results_basecase v.2_26_OCT", scenario 18):
	  • Life years: 14.13 vs 14.13
	  • Patient QALYs: 5.81 vs 5.81

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	• Carer QALYs: 11.14 vs 11.14 • Total Costs: £163, 491 vs £163,491 • This demonstrates there is no effect upon mortality or other effects in the absence of a data-driven treatment effect; random draws are not causing a difference in mortality or other outputs.
	Other minor "fixing" issues implemented by the ERG: **i) Application of probability of status epilepticus mortality (0.029% per cycle) to whole population rather than being conditional on experiencing status epilepticus:** We have revisited the data upon which the probability of SE mortality was based and agree with the ERG that this specific probability should theoretically be applied to the whole population; in effect, our application of the 0.029% probability of SE death to SE events in our base case model is underestimating the risk of death for each SE event. However, we have conducted scenario analyses that demonstrate our base case approach is actually conservative (see our response under Issue # 12). We have therefore pragmatically retained our approach in the revised base case. **ii) Equalisation of "other discontinuations" in the titration and maintenance periods:** We have looked at the model and are unsure of the discrepancy referred to by the ERG. We would welcome further clarification to address the ERG's concerns.
	Stability of the model based on 480 simulated patients (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43): The choice of 480 simulated patients provides stable results and also ensures the simulation model run-time is manageable: • We previously provided results from an analysis simulating 2000 patients, which showed that this generated very similar results to our base case model simulating 480 patients (see Addendum to the Response to clarification document, question C26; September 2020). • This indicated that the results of our base case model were stable and the choice of 480 patients (which was also similar to an estimate of the NHS patient population anticipated to be eligible for Dravet syndrome treatment) was appropriate and unlikely to bias the results compared with simulating a larger population. • To further demonstrate this, we generated a plot showing the ICER for simulated population sizes of 400, 480 (base case population), 600, 700, 800, 900 and 1000 based on the model presented to ERG in May 2021 (see Appendix **Error! Reference source not found.**). In the interests of time we have not re-run these analyses with the revised base case presented in this response; however, this confirms that the 480 simulated patients in the base case model is sufficient to provide stable results and supports the validity of our model. It also provides a reasonable balance considering the time constraints of running the model with larger populations. We therefore do not believe this is an issue.
	External validity of the model: Mortality in model validated based on short trials; company does not provide information from its workshop exploring input parameters (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43): Mortality in the model was validated based on the longest available trial data in this rare disease and was developed using, and is aligned with, the most comprehensive source of Dravet syndrome mortality data available in the literature. UK clinicians have confirmed the mortality estimates in the model are reasonable. We do not believe this challenges the validity of our model: • Dravet syndrome is a rare disease associated with seizure-related premature mortality.

	• It is not ethically possible to provide longer term comparative trial data, or trial data powered for mortality, as has been explained in detail previously. Therefore, there are no longer-term trial data against which to validate the modelled survival. • Nonetheless, we ensured that the modelled survival was validated against the FFA trials – the most robust, longest time-horizon comparative evidence available. We have shown that survival in the model was indeed aligned with these trial data (CS Appendix J). • It is important to note that validation of our modelled mortality for Dravet syndrome was not simply limited to a comparison with the available trial data. We modelled the Dravet syndrome mortality based on the most comprehensive mortality data available in the literature for this population of patients. The resulting mortality curve for Dravet syndrome in our model is also aligned with the expected mortality of these patients. • Furthermore, UK clinicians have confirmed the mortality in the model is reasonably aligned with their clinical expectations, and have confirmed there is no better data to have used, including any unpublished data. • This supports the validity of using the most appropriate data for our modelled mortality. The workshop exploring input parameters was not confined to a discussion of mortality and did not include clinician validation of mortality; it was a workshop involving health economic modelling experts discussing a range of modelling considerations in a confidential setting. It was and remains confidential, and does not negate the fact that we validated (with independent experts) the approach to implementing mortality in the model as robustly as possible, and later confirmed with UK clinical experts that mortality is reasonably aligned with expectations in this rare disease. We do not believe further details of this confidential workshop should influence the ERG's independent assessment of our model and external validity, and this should not be considered a validity issue.
	Company does not validate results against cannabidiol appraisal (per the Lead presentation slide presented to Appraisal committee 4th March 2021, slide 43): Differences in costs, QALYs and ICERs are fully expected given that we have developed a fundamentally different, and superior model that uses appropriately different costs and quality of life data. The fact that differences exist in the outputs of our model and those of the inferior cannabidiol model cannot be taken to indicate that there are issues with the validity of our model: • We have previously extensively detailed why it is not appropriate to draw direct comparisons between the modelled outputs of our model and those of the model submitted by the manufacturer of cannabidiol in NICE TA614 (see responses to Technical Engagement, December 2020). • There are significant differences in our modelling approach and that used in TA614, which are expected to lead to differences in modelled costs, QALYs and ICERs. We have summarised these again, and have indicated how these are expected to impact the model outputs, in **Error! Reference source not found.**. • Given the known issues with the cannabidiol model in TA614, there is no basis for assuming that inferior model is the benchmark against which our superior model should be "validated". • We therefore believe the ERG's comparisons of our model outputs vs. those in NICE TA614 (presented in the ERG report) are flawed and cannot be taken to indicate the validity of our model.

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10	**Adjusting for placebo effects (reversion to placebo rather than baseline seizure frequency upon treatment discontinuation):** *Reversion to placebo-level of convulsive seizure frequencies, rather than baseline, upon treatment discontinuation (ACD section 3.16, page 16):* • **To accommodate the committee's preferences we have revised our base case model to return patients to the placebo convulsive seizure frequencies upon discontinuation, rather than their baseline convulsive seizure frequencies.** This change marginally reduces the base case ICER from our original base case of £31,772/QALY to £29,093/QALY (see Appendix Table 1). • **It should be noted that returning patients to placebo seizure frequencies upon treatment discontinuation may overestimate the lifetime effectiveness of the inferior comparator therapies whilst minimising their costs. We have therefore provided a scenario analysis using an alternative approach that removes this bias.** In this analysis the placebo component of efficacy for each arm in the model is removed entirely and patients return to their baseline level of seizure frequencies (equivalent to the placebo efficacy). Since the placebo effect has been removed and forms the new baseline (to eliminate the potential effects caused from a regression to the mean), it is assumed that this is the true baseline level of convulsive seizures at the time of starting the index intervention (e.g. fenfluramine, cannabidiol or SoC). In this analysis, and in line with the NICE recommendations for cannabidiol in TA614, patients discontinue treatment in all arms, if their seizures are not reduced by more than 30% from their starting baseline. • **This less biased modelling approach to entirely remove the placebo effect on convulsive seizures experienced at baseline, during the index intervention, and following discontinuation of the index intervention, yielded an ICER of £22,973/QALY, which is significantly lower than in the base case (see Appendix Table 16). Potentially, this analysis also demonstrates that our currently revised base case analysis (which inflates a placebo-level of effectiveness in discontinuing patients as per the committee's preferences in the ACD) is conservative**. As the ERG reported difficulties in running this analysis previously (no specific details provided), we have provided full instructions and annotated model code in the accompanying spreadsheet to help the ERG to verify the technical operation of the model and all other analyses and results.
11	**Basing the model on convulsive seizure-free days rather than convulsive seizure frequency alone** *Clarification of the use of convulsive seizure-free days in the model (ACD section 3.19-3.21, page 17-18). It is important to model convulsive seizure free days to adequately capture the impact of Dravet syndrome and therapies on patients and carer quality of life:* • **Patients with Dravet syndrome may experience high seizure frequencies, often with multiple seizures per day. In addition to reductions in convulsive seizure frequency, patient carers and clinicians have explained that increases in convulsive seizure-free days are of particular value to patients and their families.** 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 important, as fewer days with seizures means fewer days in which patients are at risk of SUDEP (TA614 FAD, section 3.2). Clinicians consulted as part of our UK Pathway study also reported that seizure-free days is a meaningful concept, associated with significant respite for patients and carers, and increased activities of daily living (Data on file,

	2020). From the perspective of patients and their families, increases in seizure-free days can 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 o Berg, A., et al., *Seizure burden in severe early-life epilepsy: Perspectives from parents.* Epilepsia open 2019. **4**(2): p. 293-301.). • **Published quality of life studies conducted specifically in Dravet syndrome using different methods consistently indicate that seizure-free days have a larger impact on quality of life than does reduction in seizure frequency.** o Initial regression analyses of patient- and carer-level quality of life data collected in the fenfluramine trials using validated instruments indicate that seizure-free days had a greater impact on quality of life than did seizure frequency. *(Pinset A, et al. Determining the Relationship of Seizures, Seizure-Free Days and Other Predictors of Health-Related Quality of Life in Patients with Dravet Syndrome (DS) and Their Carers. Presented at the Virtual International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2021 Congress, May 17-20, 2021)* o Vignette studies in the UK and France conducted to elicit quality of life in Dravet syndrome patients and/or their carers indicate that seizure-free days have a significantly ($p<0.001$) greater impact on quality of life than reduction in seizure frequency (*Auvin S, et al. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy & Behavior 123 (2021) 108239*). • **Fenfluramine significantly increases the number of seizure free days and time between seizures in patients with Dravet syndrome.** Published time to event analyses of Study 1 indicate that fenfluramine 0.7mg/kg/day provided a median of 24.4 convulsive seizure-free days per 28 days compared with 15.1 days for placebo (from baselines of 17.6 and 13.3, respectively). In Study 1504 fenfluramine 0.4mg/kg/day provided a median of 24.4 seizure free days compared with 20.3 days with placebo (from baselines of 20.0 and 21.0, respectively) (*Sullivan et al 2021. Fenfluramine significantly reduces day-to-day seizure burden by increasing number of seizure-free days and time between seizures in patients with Dravet syndrome: A time-to-event analysis. Epilepsia.* 2021;00:1–9.). Across its licensed dose regimens, the mean number of convulsive seizure free days with fenfluramine increased by 2.6 to 5.6 days per 28 days (See table 10 of CS). For reference, licensed doses of cannabidiol plus clobazam increased the mean number of convulsive seizure free days by 1.3 to 2.7 days (Epidyolex SmPC). • **To capture the impact of seizures, and the value of therapies that reduce seizure frequency in Dravet syndrome, it is therefore important that the model considers the impact of seizure frequency reduction on seizure-free days.** The suggestion in the ACD to base the model on seizure reduction without modelling seizure-free days is not aligned with the consisting and growing evidence of the clinical and quality of life benefits of seizure free days for patients and carers. We therefore believe it is appropriate and justified to model the impact of Dravet syndrome seizures and seizure reduction using seizure free days.
	Proportionality between reduction in convulsive seizure frequency and reduction in convulsive seizure days: *Clarification of the estimation of relationship between reduction in convulsive seizure frequency and reduction in convulsive seizure days (ACD section 3.19, pages 17-18)* • **There is a logical relationship between convulsive seizure frequency and days with seizures (seizure days) and seizure-free days**. **Due to lack of published convulsive seizure-free days data for cannabidiol plus clobazam it was necessary to estimate convulsive seizure-free days based on this logical relationship.** Given the median baseline number of convulsive seizures per 28-day period in the fenfluramine and

cannabidiol trials ranged from 9 to 27 (see Table 15 of the CS), a reduction in convulsive seizure frequencies in a given 28-day period would logically lead to a reduction in the number of days upon which seizures may occur. It therefore follows that a reduction in the number of days upon which seizures may occur in a given 28-day period would lead to an increase in the number of days without seizures (i.e., an increase in seizure-free days) in that given 28-day period.

- **The ERG estimated that the reduction in seizure days was 0.4 times the reduction in convulsive seizure frequency, and later estimated it was 0.584; however, we believe the ERG's calculations are inappropriate.** The ERG has attempted to estimate a direct relationship between a 'percentage reduction in convulsive seizure frequency' and a 'percentage reduction in days with convulsive seizure' based on the ratio of a 'percentage reduction in seizure frequency' : [to] 'percentage increase in seizure-free days'. As explained in our written responses to Technical Engagement (17th December 2020) and subsequently ahead of the appraisal committee (25th February 2021), it is not valid to directly transfer this relationship to the 'percentage change in convulsive seizure **frequency** and 'percentage change in **seizure days**.
  - A 'percentage change in seizure-free days per 28-day period' will in general not be the same as the inverse 'percentage change in seizure days per 28-day period'. E.g.: If a patient goes from having 1 convulsive seizure to 0 per 28-day period, this is 100% decrease in convulsive seizures. Alongside this, the same patient would go from 1 seizure day to 0 seizure days per 28-day period, which is a 100% decrease in seizure days. This also equates to the same patient going from 27 seizure-free days per 28-day period to 28 seizure-free days per 28-day period, which is an increase in seizure-free days of 3.7% (i.e. 1/27).
  - Therefore, it is not possible to make inferences about the relationship between the 'percent reduction in the convulsive **seizure frequency**' and the '**percentage reduction in seizure days** per 28 days' based on the ratio of an observed 'percent reduction in the convulsive seizure frequency' :[to] 'percentage increase in seizure-free days per 28 days' – in the above example, the ERG's approach would be the equivalent of assuming the 3.7% increase in seizure-free days results in a 3.7% decrease in seizure days, when in fact the decrease in seizure days was 100%.

  We therefore feel that the ERG's approach is flawed.
- **In our base case analysis, due to the absence of published data for cannabidiol plus clobazam, we assumed that the percentage reduction in seizure days would be the same as the percentage reduction in seizure frequency based on the logical relationship between these parameters.** We applied this assumption to both the fenfluramine and the cannabidiol plus clobazam arms of the model in order to ensure consistency.
- **We have further explored the relationship between percentage change in seizure frequency vs the percentage change in seizure days based on patient-level data from our trials.** Regression analysis of individual patient level data from all arms of the Study 1 and Study 1504 trials has been conducted on the basis that we are interested in the general relationship between these two parameters, irrespective of treatment received (a necessary, pragmatic assumption given that patient level data are not available for cannabidiol plus clobazam, nor for any other therapies comprising the background standard of care to which fenfluramine or cannabidiol plus clobazam may be added, and there is no sound basis for assuming that, on average, the days upon which seizures may occur is determined by anything other than the effectiveness of the therapy in reducing the risk of those seizures). We have undertaken linear regression analysis on these data as visual inspection of the scatter plot of the change in seizure frequency vs the change in seizure days indicates a linear relationship in that portion of the plot where the clear majority of points sit, corresponding to a reduction in seizure frequency (see Appendix Figure 8). We acknowledge that the exact relationship between reduction in convulsive seizure frequency and reduction in convulsive seizure days may be more complex due to the fact that seizure frequency is theoretically

	unbounded but seizure days and seizure free-days are bounded in the range 0-28; however, based on these patient-level data, this approach appears to be reasonable. This regression analysis indicates that the percentage reduction in seizure days is [redacted] times the reduction in convulsive seizure frequency. We note this estimate is a reasonable midpoint between the 1:1 relationship assumed in our original base case and the 1:0.584 relationship erroneously estimated by the ERG. **We have therefore adopted this value of [redacted] in our revised base case, which resulted in a small change of the base case ICER from £31,772/QALY to £33,464/QALY** (see Appendix Table 1**).** • We note that the ERG report (section 5.2.6) implied that basing the reduction in convulsive seizure free days on the reduction in convulsive seizure frequency would favour fenfluramine due to the fact that the reduction in seizure frequency was larger with fenfluramine than with cannabidiol plus clobazam, and questioned this by reporting that cannabidiol 10mg/kg/day plus clobazam increased the number of convulsive seizure free days by 2.7 days per 28 days, compared with 2 days for fenfluramine 0.4mg/kg/day. As detailed in our response to the Factual Accuracy Check on the ERG report, whilst the ERG is correct to note that reduction in convulsive seizure frequency is greater with fenfluramine than with cannabidiol plus clobazam, this is selective and incorrect reporting regarding the gain in convulsive seizure free days; across licensed fenfluramine doses the mean gain in convulsive seizure free days per 28 days was 2.6 to 5.6 days (see Table 10 of the CS), and across licensed cannabidiol doses was 1.3 to 2.7 days (see Epidyolex SmPC). Based on these (fuller) data, it is plausible that the superior reduction in convulsive seizure frequency observed with fenfluramine (see our response to Issue #3 above) would translate into superior reduction in seizure days and a corresponding increase in seizure-free days compared with cannabidiol. We therefore believe the relationship we have modelled is plausible, appropriate and valid.
12	**Relationship between convulsive seizures and mortality is not clear:** *Our model generates estimates of Dravet syndrome mortality that are aligned with clinical expectations based on the most comprehensive sources of Dravet syndrome mortality available in the literature. Assuming the existence of a relationship between convulsive seizure frequency and mortality, the model is reasonable and justified (ACD section 3.22-3.23, page 18-19).:* • **Patients with Dravet syndrome are at a high risk of premature seizure-related mortality. Clinical expectations are that improvement in convulsive seizure control is expected to reduce the risk of sudden unexpected death in epilepsy (SUDEP) and status epilepticus, which are the leading causes of Dravet-syndrome mortality.** The Association of British Neurologists, as stakeholders in the process, 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). The Lead presentation to the appraisal committee also noted clinical expert views: "*Convulsive seizure frequency has strong, well-established link to some forms of premature mortality in epilepsy and that this is likely to apply to Dravet syndrome, with high frequency and ongoing seizures, high sudden unexpected death in epilepsy (SUDEP) rates, other comorbidities that may result in premature mortality*." There is therefore a clinical expectation that improving convulsive seizure control will reduce the risk of mortality. • **It is not possible to power a trial for mortality events in a rare disease such as Dravet syndrome.** As we explained in the Response to Clarification Questions C14, and further demonstrated in our response to the Technical engagement (17 December 2020), where we provided a sample size calculation: 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.
	• **It is therefore unreasonable to expect empirical evidence of a mortality benefit with fenfluramine (or any other therapy in Dravet syndrome). Given the clear reasons to expect an effect on mortality through improved convulsive seizure control, we believe it is unreasonable to exclude the possibility of a mortality benefit on the basis of a lack of evidence that is impossible to collect**. Removal of a mortality effect in the model would not reflect the reality of the risk of premature death faced by Dravet syndrome patients and their families every day and would irrationally bias the model in favour of less effective therapy. A mortality benefit should therefore be reflected in the model based on convulsive seizure reduction, in line with clinical expectations.
	• **Our approach to modelling mortality generates estimates of Dravet syndrome mortality that are aligned with expectations based on the most comprehensive sources of Dravet syndrome mortality available in the literature; and are consistent with those indicated in the NICE scoping document for this appraisal.** The ACD notes that the Cooper et al 2016 study used to estimate Dravet syndrome mortality acknowledged that the rates they reported may overestimate the true mortality rates because the participants had been referred for tertiary specialist care. However, given the refractory nature of their seizures, and the fact that fenfluramine (and cannabidiol) are to be used when standard of care therapies are not providing satisfactory response, patients with Dravet syndrome eligible for fenfluramine (or cannabidiol) are unlikely not to be referred at some point for highly specialist care for diagnosis and management. It therefore seems reasonable to adopt these rates of mortality as reflective of those in Dravet syndrome patients in practice for whom fenfluramine (or cannabidiol) may be used. The ERG also claims that our approach to estimating Dravet syndrome mortality based on convulsive seizure frequencies leads to implausibly high relative risks of SUDEP compared with the general population, but neglects to note that the risk of SUDEP in the general population is, by definition, very low relative to that in Dravet syndrome (which would substantiate a high relative risk) and, more importantly, neglects to note that irrespective of what the implied relative risk versus the general population is, our resulting survival curve (Figure 23 of the company submission) has been confirmed by UK clinicians to be aligned with mortality expectations in Dravet syndrome. Nilssen et al 1998 (used to inform the calibration of the modelled mortality curve) highlights that deaths in general epilepsy are correlated with seizure frequency, and there is no reason to doubt that seizure frequency and deaths in Dravet syndrome are also correlated. Of note, Cooper et al 2016 reported that sex, age of seizure onset, MRI abnormality, presence and type of SCN1A mutation, and severity of cognitive impairment were not associated with an increased risk of death or SUDEP in their cohort, which would appear to further support our proposition that seizure frequency is linked with mortality sufficiently to permit its use to estimate mortality in our model.
	• **Total mortality estimates in the model include SUDEP, status epilepticus deaths and accidental deaths, with probabilities of these deaths applied conservatively in our model:**
	  o The probabilities of SUDEP, SE and accidental deaths are derived from Cooper et al, 2016, the most comprehensive source of Dravet syndrome-specific mortality data available in the literature.
	  o The probability of SUDEP was calculated directly from Cooper et al 2016.
	  o The probability of SE mortality (0.029% per cycle) was calculated directly from Cooper et al 2016, and was conservatively applied to each SE event (see below).
	  o Accidental death was assumed as 24% of SUDEP+SE deaths (as inferred from Cooper et al 2016).

	A treatment effect is applied to SUDEP, SE mortality and accidental death via the plausible relationship between these events and convulsive seizure frequency. The ERG noted that the probability of SE mortality derived from Cooper et al 2016 is not conditional on the occurrence of an SE event and should be applied to the cohort as a whole (ERG report section 3.2.6.5, part e)); in effect, our application of the 0.029% probability of SE death to SE events in our base case model is underestimating the risk of death for each SE event. We have explored the impact of this on the ICER in a scenario analysis by increasing the probability of SE mortality applied to SE events by a factor of 3. This reduces the base case ICER from £32,841/QALY to £29,587/QALY (see Appendix Table 22). The blanket application of the probability of SE mortality increased the ICER marginally to £33,440/QALY (see Appendix Table 23); however, this removes the logical associations between SE mortality, SE events and the occurrence of seizures that may become SE events, and so would be overly conservative towards fenfluramine as the most effective therapy for reducing seizure frequency. Whilst acknowledging that our approach is theoretically incorrect, given that the impact is to make our model conservative we have pragmatically retained this approach in our revised base case. • **As requested by the Appraisal Committee, we have provided analyses exploring alternative relationships between convulsive seizure frequency and mortality. However, it should be noted that our base case mortality is based on and aligned with real-world evidence and clinical expectations specifically in Dravet syndrome, and we therefore believe these analyses are biased against fenfluramine given its superior efficacy vs comparators in improving convulsive seizure control.** The ACD notes the committee's preferences to see scenario analyses testing different strengths of the relationship between convulsive seizure frequency and SUDEP. We provided two alternative scenarios exploring the relationship between convulsive seizure frequency and mortality in our original submission (Table 51 in the company submission - i) assuming mortality in Dravet syndrome is the same as in the general epilepsy population; ii) calibration of mortality in Dravet syndrome to be midway between the base case estimates and general epilepsy mortality), but these were omitted from the Lead presentation during the Appraisal Committee meeting on 4th March 2021. We have re-provided these for our revised base case (see Appendix Table 19 and 20). The committee also requested an analysis removing the possibility that treatment prolongs life; however, our model is built on the foundation that differences in seizure frequency drive differences in mortality, quality of life and health care resource use and costs. It is technically challenging to completely remove the link between seizure differences arising from treatment (which drives mortality, quality of life and costs) and seizure differences leading to mortality differences, whilst also retaining the background Dravet syndrome mortality. We have therefore implemented an alternative exploratory analysis demonstrating the contribution of mortality to the QALY estimates (see Appendix Table 21). It should be noted that, whilst these analyses increase the ICER, they bias the model against fenfluramine given its superior efficacy in improving convulsive seizure control compared with both cannabidiol plus clobazam and standard of care therapy.
13	**Impact of excluding non-convulsive seizures from model is not clear:** *Exclusion of non-convulsive seizures from the model is justified (ACD section 3.24, page 19-20):* • **We excluded non-convulsive seizures from the model because of the risk of introducing spurious inputs arising from the difficulties in recording these events in practice.** Clinical experts acknowledged the difficulties in measuring these events (ACD page 20). Fenfluramine reduced the incidence of non-convulsive seizures in the pivotal trials; however, neither our trials nor those of cannabidiol were designed to assess non-convulsive seizures as a key endpoint, and these data are less reliable than convulsive seizure data. This precludes a robust comparison

	between therapies for non-convulsive seizure reduction, and precludes a robust assessment of the impact of non-convulsive seizures on quality of life and mortality. • **Our exclusion of non-convulsive seizures from the model is in line with the approach taken by the manufacturer of cannabidiol in NICE TA614.** The manufacturer of cannabidiol did not include non-convulsive seizures in its original model for NICE TA614. Upon request, the manufacturer of cannabidiol provided a scenario analysis to reflect a hypothetical impact of non-convulsive seizures on quality of life in its model; however, we note this did not employ its actual non-convulsive seizure data in the model and was ultimately not accepted with confidence by the appraisal committee. • **We acknowledged in our submission and subsequent responses that our exclusion of non-convulsive seizures from the model is conservative for both fenfluramine and cannabidiol plus clobazam when compared with standard of care.** We also explained in our response to the Factual Accuracy Check (FAC) of the ERG report (30 October 2020) that it is possible that the exclusion of non-convulsive seizures may be conservative for our comparison of fenfluramine vs cannabidiol plus clobazam based on total seizures data (convulsive and non-convulsive seizures) (see page 49-50 of that response). • Although the manufacturer of cannabidiol provided NICE with some non-convulsive seizure data, as academic in confidence, in its response as a stakeholder to this appraisal, we note that this only relates to cannabidiol 10mg/kg/day vs placebo, and ignores the data for cannabidiol 20mg/kg/day that make up two-thirds of the phase 3 randomised controlled trial evidence available in support of cannabidiol in Dravet syndrome. Notwithstanding this issue, the data for non-convulsive seizure frequency from all trials and trial arms remains unsuitable for making a robust comparison between therapies for the reasons described above.
14	**Adverse events** – a**dditional monitoring is not reflected in costs or utilities** *The model reflects adverse events and monitoring for adverse events to the full extent that it is appropriate to do so. It is incorrect to suggest that additional monitoring is not appropriately reflected in the model (ACD section 3.25, page 20-21):* • **Our model excludes adverse events because there is no evidence of a differential effect of serious adverse events between SoC, fenfluramine or cannabidiol treatments that would accrue more than negligible differences in costs or would exert a measurable influence on patient quality of life.** • **The ERG agreed that the impact of this pragmatic approach is unlikely to significantly impact cost effectiveness.** • **Monitoring for adverse events is fully captured in the model.** • The costs of routine monitoring are fully captured in the model in the costs of routine management. Routine management of patients will be the same irrespective of therapy received, and there are no additional or differential costs or quality of life impacts to be included for routine management. • **The additional costs of echocardiography before, during and after fenfluramine treatment, as a regulatory obligation specified in the SmPC due to a historical association with cardiopulmonary adverse events when of fenfluramine was used at far higher doses in the management of obesity, are fully captured in the model.** The model specifically includes the costs of echocardiography with fenfluramine. There is no reason to believe that the conduct of an echocardiogram will have a meaningful and measurable influence on patient quality of life that could influence the accrual of QALYs in the model. It is therefore entirely appropriate that only the costs of echocardiography are included.

	• **Given the above we believe the ACD is incorrect to state that additional monitoring is not appropriately reflected.** This was explained in several of our previous responses to the ERG. • **Our exclusion of the costs and quality of life impacts of adverse events are likely to be conservative.** The Lead presentation (slide 41) noted that Gunning et al 2020 indicates similar discontinuations due to adverse events with cannabidiol 20mg/kg/day as the 12.5% observed with fenfluramine 0.7mg/kg/day in Study 1; however, the slides exclude the fact that the rate of serious treatment-emergent adverse events (that may accrue costs and impact quality of life) was actually higher for cannabidiol (22-23%) than for fenfluramine (12.5-14%) across their licensed doses (see Gunning et al 2020; Lagae et al 2019; Nabbout et al 2020). Our exclusion of adverse event costs and quality of life decrements is therefore likely to be conservative in the primary comparison of fenfluramine against cannabidiol. • **It should be noted that to date there has been no evidence of an increase in clinically meaningful valvulopathy or any other cardiopulmonary adverse events with fenfluramine at doses used in the treatment of Dravet syndrome, in either the clinical trials, the long-term extension study, or in the longer-term real-world evidence studies.** There are therefore no costs or quality of life impacts to be reflected in the model for these. • **Our model therefore reflects both adverse events and the monitoring for adverse events to the full extent that it is appropriate to do so.** Applying any other assumptions on adverse events in our model would be arbitrary, not evidence-based and would be unlikely to be meaningful given that the ERG has already agreed that the exclusion of adverse events is unlikely to significantly impact on the estimates of cost effectiveness.
15	**Carer utility applied in the model are overestimated:** *In the absence of an agreed method of incorporating carer utilities into the model, we believe our approach is reasonable and possibly less biased than the alternative suggested by the ERG (ACD section 3.26, page 21). We have conducted a scenario analysis exploring an alternative approach to applying carer utility when the patient dies, which highlights the challenges of retaining a contribution of the carer QoL beyond the patient's survival:* • **We are pleased the committee has agreed that incorporation of carer utilities in the model is appropriate.** Dravet syndrome is a lifelong condition that exerts a heavy, lifelong toll on the quality of life of patients, their immediate full-time caregivers and the whole family unit. Seizures in Dravet syndrome contribute to the development of a range of co-morbidities and developmental issues, with few patients able to live independently and most requiring around-the-clock care. It is therefore appropriate to capture the lifelong impact of the disease and treatment on quality of life of carers, in addition to the patient. We have not incorporated the quality-of-life impact of Dravet syndrome on patients' siblings, which as noted by the committee in NICE TA614 underestimates the impact of the disease (TA614 FAD, section 3.21). • **There is no consensus or technical guidance on how best to incorporate carer utility into models.** As noted in the ACD, there is no agreed way to incorporate carer utility in the model (ACD section 3.2.6, page 21). • **Utility values in our model are based on individual patient- and carer-level quality of life data collected directly from the fenfluramine trials. Our approach is therefore evidence based and is aligned with our individual patients/carer level simulation modelling approach.** We have previously provided a detailed explanation of how our approach, based on the empirical evidence of carer quality of life from the clinical trial data, demonstrates an impact on carer quality of life across all seizure frequencies (and seizure free days) and is therefore most relevant for our patient-level continuous time model.(see company response to the 'Factual accuracy check', page 62-69).

	• **The approach suggested by the ERG, to implement disutilities in line with the approach taken in NICE 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**. The ERG's suggestion would apply a carer disutility in health states defined by categories of seizure frequencies (8 to 25, and >25 convulsive seizures per month) until a patient dies. These are arbitrary categorisations of seizure frequency (based on convenience, but not clinical or statistical significance), at odds with the empirical evidence from our trial, and are not appropriate in our simulation model where we are modelling seizure frequencies / seizure free intervals on a continuous time basis. The ERG's suggested approach is therefore not appropriate to adopt in our model.
	• **We assume in our base case that carer utility is removed from the model when the patients dies, as this is aligned with usual modelling practices. In addition, to continue to include carer utility beyond the patient's death would introduce a number of undesirable consequences and arbitrary assumptions and uncertainties**
	  • Applying carer utilities in the model only until the patient dies is aligned with the general principle that when patients die in any other model, they do not continue to accrue any additional resource use, costs, or quality of life benefits, or impairments, and so patients who die in our model should not continue to accrue carer utility.
	  • By retaining carer utilities in the model after the patients die retains a benefit to the treatment strategy but none of the costs, which favours the least effective treatment in the model. As fenfluramine is superior in reducing convulsive seizure frequency (and so would plausibly reduce the risk of seizure associated mortality) compared with cannabidiol plus clobazam or continued standard of care, this approach biases the model in favour of the comparators and against fenfluramine.
	  • It is unclear at what level the carers' quality of life should be retained at in the model once the patient dies; increasing the carer's quality of life in the model once the patient dies (e.g. towards population norms, as was suggested in a scenario by the ERG) would have the (unintended) effect in the model of rewarding the patient's death. A strong arbitrary assumption is therefore required.
	  • It is unclear how long the carer's quality of life should be retained in the model following the patient's death; imposing an ongoing carer utility beyond the patient's death is incompatible with a patient lifetime time-horizon, and requires a further arbitrary strong assumption.
	• **Given these issues, we believe our base case is appropriate and internally consistent with the available data and our simulation model. However, to address the committee's concerns with our approach we have undertaken a scenario analysis in which we retain a carer utility in the model once the patient dies.** As this approach is associated with the above-mentioned uncertainties and biases it is important to limit these as far as possible. For this scenario analysis we have therefore included a retained carer utility once the patient dies equal to the lowest quality of life that the carer experienced while the patient was alive. The results from this analyses are reported in the Appendix Table 24. It should be noted this still favours the least effective therapies over a prolonged time-horizon, and whilst hypothetical, it would also be entirely hypothetical to assume an alternative, higher level of carer utility in the model following the death of a carer's child.
	• **For clarification, the ACD reports there was no significant difference in PedsQL score between fenfluramine and placebo in Study 1504 (ACD section 3.8, page 9); however the results it reports are unadjusted.** As highlighted in section B.3.4.2 of the CS (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", as indicated in the footnote on Table 11 of the CS.

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16	**Clarification of QALYs accrued and differences in cost-effectiveness estimates in the model** (ACD section 3.27, page 22)**.** *For all analyses we have provided full disaggregation of the results.* This includes disaggregation by concomitant stiripentol use and by patients and carer QALY estimates to show the contribution of carer utilities to the ICER. All results are as would be expected given the construct of the revised base case model in line with the committee's preferences.
17	**Unclear if fenfluramine meets the criteria for an innovative treatment** *We believe fenfluramine should be considered an innovative treatment in this rare, treatment refractory disease, with high unmet needs (ACD section 3.31 page 24):* • **There is no clear definition of an innovative treatment in NICE's methods or process guidance, but using other NHS criteria fenfluramine would clearly fulfil the definition of "innovative".** We note that for designation as a Promising Innovative Medicine under the Early Access to Medicines Scheme the medicine must be for the treatment of a life-threatening or seriously debilitating condition with high unmet needs, it must be likely to offer a significant advantage over current therapy, and its potential adverse effects must be likely to be outweighed by the benefits (see: PIM_designation_guidance.pdf (publishing.service.gov.uk)). Fenfluramine clearly fulfils all of these criteria. • **UK Clinical expert opinion solicited by NICE highlights that fenfluramine is a "step change" in the management of Dravet syndrome, and that the reductions in seizure frequency with fenfluramine are "unprecedented":** In addition to the clear trial data-based evidence of the superiority of fenfluramine for convulsive seizure frequency reduction presented in our submission, clinical expert opinion obtained by NICE during the appraisal process states (page 666 of the committee papers), in response to the question of whether fenfluramine is a step-change in the management of Dravet syndrome: "*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*." • **Patient caregiver survey data indicate that fenfluramine has for many families been transformative, with benefits that are unlikely to be fully captured in our economic model:** Patient advocacy group opinion obtained by NICE during the appraisal process noted that fenfluramine has been transformative for many families in the UK and across Europe (see page 700-703 of the committee papers). In addition to often dramatic seizure reduction, non-seizure improvements reported by caregivers in the survey included improved behaviour, cognition and social interaction, ability to speak, becoming more active, and being more "present" or engaged in family life, and greater autonomy and independence. These reported benefits of fenfluramine treatment for patients, carers and the wider family unit are unlikely to be fully captured in our QALY estimates. • **Fenfluramine is licensed for and may be used at any point in the add-on therapy pathway, in contrast to stiripentol and cannabidiol, which are licensed only for use in combination with 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. • **Collectively, we believe fenfluramine is an innovative therapy for patients with Dravet syndrome.**

18	**Conservatism in our approach to modelling** *It should be noted that our analyses are plausibly conservative on several fronts, which if addressed and/or pragmatically considered would substantially reduce the base case ICER(s) for fenfluramine and reduce uncertainty for decision-makers. These should be made clear to the Appraisal Committee so they may be taken into account in its decision-making:* 1) We assume maximum licensed doses of fenfluramine but only a 12 mg/kg/day dose of cannabidiol, which is towards the lower end of its 10-20mg/kg/day licensed dose range. Given evidence of doses tending towards the upper end of its licensed dose range in the cannabidiol open-label extension study (discussed in section **Error! Reference source not found.** of our submission), and mounting evidence of higher doses from real-world use (see: www.frontiersin.org/articles/10.3389/fneur.2020.00829/full), it is plausible that effective doses in practice could be towards the upper end of its recommended dose range. With increasing doses of cannabidiol, the ICER decreases sharply, such that at a maximum dose of cannabidiol, fenfluramine becomes economically dominant at the model-based drug costs (see Appendix Table 25 and 26). 2) Clinical experts have indicated that they would aim to reduce or remove concomitant therapies where possible when patients have a good response to add-on therapy. Based on evidence from the DFES survey of patient carers provided in the committee papers, 59% of the 117 participants had reduced the number or the dose of other anti-epileptic treatments as a result of adding fenfluramine. It is of note that at the time of this survey, the duration for some patients being on fenfluramine outside of a trial setting was not long. It is therefore plausible that with the introduction of fenfluramine, these data underestimate the potential for simplification in a patient's AED therapies over a longer period of introduction. Although these data are not mature enough to robustly evaluate at this time, they do point to conservativism in the currently modelled approach and potential for cost-offsets. As fenfluramine is superior to cannabidiol plus clobazam for seizure control it would be expected to permit reduction or removal of add-on therapy to a greater extent. In our current model we assume the full costs of continued concomitant therapy throughout, which may favour cannabidiol plus clobazam. 3) The model excludes the influence of non-convulsive seizures on quality of life, which is conservative in our comparison against standard of care and may be conservative in our comparisons against cannabidiol plus clobazam. 4) We do not include the impact of Dravet syndrome across patient siblings (Baily et al., 2020 https://doi.org/10.1016/j.yebeh.2020.107377), which was recognised in NICE TA 614 as an omission that, if included, would further reduce the ICER. As fenfluramine is superior in achieving convulsive seizure control, this omission currently favours the comparators in our model. 5) Due to a lack of specific data and for pragmatic reasons we are unable to model any subsequent add-on strategies following treatment discontinuation. As the superior efficacy of fenfluramine means that treatment discontinuations due to a lack of efficacy would occur more frequently with cannabidiol plus clobazam than with fenfluramine, in the model, this would return patients starting on the cannabidiol plus clobazam strategy to their less costly standard of care treatment more quickly, ultimately reducing the overall cost of the comparator strategy. As commented upon during the appraisal of cannabidiol (TA614), increasing the rate of discontinuing treatment improves the cost-effectiveness of a treatment, albeit counterintuitive and contradictory to a medical intent to reduce seizures. 6) We have implemented the committee's preference to return patients to placebo-based convulsive seizure frequencies upon treatment discontinuation; however, as the placebo-based convulsive seizure frequencies are lower than those observed at baseline, in returning patients to

	their placebo-based convulsive seizure frequencies upon treatment discontinuation the current model retains a benefit for discontinued treatment in continuing to reduce seizures (from baseline), whilst minimising its costs. As fenfluramine has a superior efficacy, discontinuations due to a lack of efficacy would occur more frequently with cannabidiol plus clobazam. This consequently returns patients in the cannabidiol plus clobazam arm of the model to an elevated placebo-based convulsive seizure frequency more quickly, over-estimating the strategy's lifetime effectiveness whilst also minimising its costs relative to ongoing treatment with fenfluramine. The scenario analysis in which the placebo effect is removed entirely removes this bias from the model and substantially reduces the ICER, demonstrating just how conservative the revised base case is. The ICER associated with this analysis is: £22,973/QALY (see Appendix Table 16). It is noteworthy that this analysis may also be considered as a conservative assumption, since patients that discontinue a treatment for lack of efficacy may be considered to be uncontrolled and as such have more seizures than experienced before treatment, or over time with the sequential loss of a limited number of therapeutic options available to them. 7) Currently in our comparisons of fenfluramine to SoC, patients not receiving fenfluramine are assumed to have a placebo effect in line with that observed in the trial. In clinical reality, these patients would continue to receive their existing SoC treatment and would not expect to have gained any benefit of a reduction from their baseline level of seizures, but rather continue at their baseline level of seizures. The current model therefore potentially under-estimates the difference between fenfluramine and SoC effect sizes. 8) Our base case analysis underestimates the impact of treatment on SE mortality, which favours the comparators and results in conservative ICER estimates. 9) Consistent with the cannabidiol recommendation (TA614), a similar treatment discontinuation criterion (stopping rule) has been implemented for fenfluramine in the model for patients not achieving a greater than 30% reduction from baseline seizures at 6 months. If an alternative stopping rule for fenfluramine was employed, e.g. a 40% or 50% reduction from baseline required to continue therapy, the ICER would change from £31,841/QALY to £26,436/QALY and £22,474/QALY, respectively (see Appendix Table 27 and 28) .
19	**Other issues and clarifications:** • Section 3.7, page 9 of ACD: Error - "*stiripentol 0.4 mg/kg/day*" should read "*fenfluramine 0.4 mg/kg/day*" • Section 3.7, page 9: Clarify that although fenfluramine 0.2mg/kg/day was included in the Study 1 trial, this is not a licensed maintenance dose of fenfluramine • Why the committee made these recommendations (page 3 of ACD): Bullet point stating "*removing the placebo effect*"– Our original base case model reverted patients to their baseline upon treatment discontinuation. We provided an analysis in response to the ERG report in which we removed placebo entirely, which improved the ICER considerably, but the ERG claims it was unable to replicate. Without any qualification / context this statement in the ACD is meaningless and should be removed. • Emailed query from NICE regarding negative values for the difference from placebo in convulsive seizure-free days reported in Table 10 of the company submission: We have confirmed with company statisticians that the negative signs can be ignored; the magnitude of the estimates of convulsive seizure free days and associated confidence intervals reported in Table 10 remain correct. • Clarification: "The clinical and patient experts noted that comorbidities and learning disabilities require care, which was not a direct function of seizure frequency of accrual in the model" (ACD section 3.26, page 21). It should be noted that the assigned quality of life for patients in the model have been adjusted for underlying age and comorbidities, as well seizure frequency. See section B.3.4.2.1. in the CS

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document - re-submission of Company response to ACD 28th October 2021

	• Please note a minor correction to Figure 2 of the CS that has not been possible to amend at any earlier point in the evaluation process. The correction clarifies that cannabidiol plus clobazam and fenfluramine may be added on therapies to SoC that may or may not include stiripentol. For convenience this revised Figure 2 of the CS has been provided as Appendix Figure 10. • It should be noted that our patient-level simulation modelling approach is fundamentally different to the cohort modelling approach taken for cannabidiol in NICE TA614, it uses more robust quality of life data, efficacy data from a robust indirect treatment comparison and appropriately uses different prices of cannabidiol given that we do not have access to the confidential discount on its list price. Given all of the reasons, it is not possible to make a meaningful comparison between the outputs of our model and those reported for cannabidiol in NICE TA614.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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NICE National Institute for Health and Care Excellence

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document - re-submission of Company response to ACD 28th October 2021

Comments received during our consultations 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.

Appendix to ACD response for ID1109 – Fenfluramine for treating seizures associated with Dravet syndrome – 28th October 2021

Revised 01 Dec 2021 in line with ERG discussions on 26 November 2021 to include 1 extra scenario analysis (discontinuation rates) and an expanded description of differences in outputs between the current model and the model used in NICE TA614. The changes from the previous 28 October version of this document are contained to pages 35-41 and 52-53.

Contents

Revised base case and scenario analyses

Revised base case

1. Revisions to base case model

As detailed in the ACD response, we have revised our original base case to correct for a minor coding error and minor specification error relating to utilities. We have implemented a correction to address a minor anomaly in the simulated population. We have also made revisions to accommodate appraisal Committee preferences and to remove uncertainty in the relationship between reduction in convulsive seizure frequency and reduction in seizure days (see Table 1). Full details of the changes made to the code are provided in the accompanying excel workbook, along with full disaggregation of all results: “Merged_disaggregated results_basecase v2_26_OCT”.

Table 1. Revisions to base case model

Type of change	Scenario / Switch number	Scenario name	Description of the scenario	Comparison	ICER (Merged result)	ICER (Study 1 only result)	ICER (Study 1504 only result)
Original base case_31,772	0	Original base case_31,772	Original base case model (as per the CS; for reference)	FFA + SoC vs CANNABIDIOL +CLB +SoC	£31,772	£38,874	£10,770
Corrections							
Correction	1	Original base case - Corrected Outputs for FFA strategy	Updated outputs to correct for minor reporting errors in the FFA strategy, adjusted from the "old base case model" (submitted in the CS)	FFA + SoC vs CANNABIDIOL +CLB +SoC	£31,432	£38,638	£10,119
Correction	2	Corrected original base case ("Corrected Outputs for FFA strategy" [scenario B] and comorbidities)	Updated "original base case - corrected outputs for FFA strategy" with a minor correction to co-morbidities. This analyses is combined with scenario B.	FFA + SoC vs CANNABIDIOL +CLB +SoC	£31,688	£38,515	£10,955

Type of change	Scenario / Switch number	Scenario name	Description of the scenario	Comparison	ICER (Merged result)	ICER (Study 1 only result)	ICER (Study 1504 only result)
Correction	6	Original base case – cycle 131 correction	Original base case corrected for cycle 131 anomaly by replacing cycle 131 with cycle 130 (as done by ERG)	FFA + SoC vs CANNABIDIOL +CLB +SoC	£31,555	£38,628	£10,857
Revisions to base case assumptions							
Amendment based on NICE Committee's preferred approach	3	No change in seizures at adulthood (Folder name "Pts SF remains constant")	Original base case amended so patients' seizure frequency remains constant throughout life. Previously, in the "original" CS base case, patient's seizures were assumed to halve at aged 18 years onwards	FFA + SoC vs CANNABIDIOL +CLB +SoC	£32,468	£41,428	£14,367
Amendment based on NICE Committee's preferred approach	4	Revert to placebo at discontinuation	Original base case amended so upon discontinuing their index intervention (existing SoC [placebo effect], FFA or CBD), patients receive a seizure profile equivalent to their "placebo effect", rather than reverting patients back to their baseline seizure profile as previously implemented in the original CS base case	FFA + SoC vs CANNABIDIOL +CLB +SoC	£29,093	£37,326	£11,578
Amendment to proportionality between change in CSF and change in seizure days	5	Reduction in SF:SD change 1:[redacted] FFA vs CBD	The reduction in convulsive seizure days is [redacted] x the reduction in convulsive seizure frequency (based on regression model provided in Figure 1), rather than a 1:1 relationship used in the original base case.	FFA + SoC vs CANNABIDIOL +CLB +SoC	£33,464	£40,979	£11,313
Combined corrections and amendments	**7. Full revised base case**		Fully revised base case model: Combines **Scenario C to G** above	FFA + SoC vs CANNABIDIOL +CLB +SoC	**£31,841**	£41,531	£14,183

Explanation of analyses and results leading to the Revised Base Case:

- Implementing the minor coding corrections (Scenario 2) had a very minor impact on the resulting ICERs; the ICER for fenfluramine vs cannabidiol plus clobazam marginally reduced from the original base case.
- Implementing the correction of cycle 131 by replacement with cycle 130 (Scenario 6) had a minimal impact on the resulting ICER, leading to a small reduction compared with the original base case model.
- Implementing changes to accommodate appraisal Committee preferences had minor but mixed impacts on the results:
    - **No change in seizures at adulthood (Scenario 3):** Keeping the number of seizures constant throughout adulthood results in a higher frequency of seizures and more seizure days per 28 days over the life-time of the patient. This increases the risk of earlier / premature mortality (due to more seizures), reduces the overall life years of patients and reduces quality of life, leading to fewer

QALYs for patients and carers to be accumulated (as patients do not live as long). From a costs perspective, although this reduces the overall fixed costs and treatment costs for a strategy (as patients die sooner and consequently do not accrue ongoing costs of treatment), it also increases the more variable (emergency) costs due to patients experiencing more seizures over their life time that require more emergency care. The ICERs marginally increase.

- **Revert to placebo at discontinuation (Scenario 4):** Reverting to placebo rather than baseline seizure frequency means that when patients discontinue their index treatment their seizure frequency reverts to a common placebo frequency determined from the indirect treatment comparison. Due to natural heterogeneity in seizure frequencies and treatment experience that are to be expected in Dravet syndrome, when patients in the Study 1 population discontinue treatment, they revert to the new placebo-defined seizure frequency that is lower than their baseline seizure frequency. When patients in the Study 1504 population discontinue treatment, they revert to the new placebo-defined seizure frequency that is higher than their baseline seizure frequency. Patients in Study 1 therefore experience slightly fewer seizures when reverting to this new placebo compared with when they reverted to baseline in our original base case. This increases their time in the model (as they are less likely to die) during which they accrue more QALYs and additional costs of standard of care (SoC) therapy compared with in the original base case model; however, as the costs of SoC therapy in Study 1 are very low (they do not include stiripentol), the net result is a slight decrease in the ICER compared with the original base case. Conversely, patients in the Study 1504 population experience slightly more seizures when reverting to this new placebo compared with when they reverted to baseline in our original base case. These patients therefore spend less time in the model (as they are more likely to die) during which they accrue fewer QALYs and lower costs of SoC therapy compared with in the original base case model; however, as the costs of SoC in Study 1504 are very high (they include stiripentol), the net result is a slight increase in the ICER compared with the original base case. It should be noted that the actual changes in Costs and QALYs between the original and revised base case are generally small. The merged ICER is estimated on the basis of individual costs and QALYs arising in the Study 1 population (42%) and the Study 1504 population (58%), and not their individual ICERs. The merged base case results (which was accepted in principle as appropriate by the Appraisal Committee) represents the costs and QALYs of a mixed cohort of patients reflective of those we see in practice in the UK.

- **Implementing a revised, evidence-based relationship between reduction in convulsive seizure frequency and reduction in seizure days (Scenario 5) had a limited impact on the ICER in the expected direction**; the ICER for fenfluramine vs cannabidiol plus clobazam marginally increased from the original base case:
  - Our model appropriately captures quality of life associated with seizure-free days rather than seizure frequency (see the justification for this approach in the response to the ACD document, Issue #11). Due to a lack of published data on seizure-free days for cannabidiol plus clobazam we needed to estimate these data. To do this in our original base case we assumed that the reduction in seizure frequency would be the same as the reduction in the number of days with seizures, from which the increase in seizure-free days could be calculated. The ERG estimated that the reduction in days with seizures would be 0.4 x the observed reduction in seizure frequency, and later estimated this to be 0.584 based on calculations that we have demonstrated

are inappropriate (see the explanation in the response to the ACD document, Issue #11). To explore this issue further we have re-visited our trial data and conducted regression analysis on the patient-level data for all arms of the trials to estimate the relationship between the percentage change in convulsive seizure frequency vs the percentage change in seizure days. Based on this analysis we have determined that the average reduction in days with seizures would be [redacted]x the observed reduction in seizure frequency (see Figure 8 at the end of this document). We note this is a reasonable midway point between the 1:1 relationship adopted in our original base case model and the 1:0.584 relationship calculated (inappropriately) by the ERG.

    - To remove uncertainty in this element of modelling we have incorporated this evidence-based relationship between reduction in convulsive seizure frequency and reduction in convulsive seizure days in our base case model. This marginally increased the ICERs, due to the smaller resulting increase in seizure-free days for any given reduction in convulsive seizure frequency, leading to a smaller increase in patients and carer quality of life, compared with the original base case model.
- The resulting **Revised Base Case** implements minor corrections, accommodates the Committee's preferences and removes the uncertainty in modelling of seizure days. The net impact of the changes is a minimal increase in the individual ICERs for Study 1 and Study 1504 compared with the original base case. The collective impact of implementing indicating that the perceived issues with our original base case model collectively did not have a material impact on the resulting cost effectiveness estimates.the Appraisal Committee's preferences and corrections merged ICER is therefore minimally increased (from £31,772 to £31,841), and is estimated on the basis of individual costs and QALYs arising in the Study 1 population (42%) and the Study 1504 population (58%), and not their individual ICERs. The collective The merged base case represents the costs and QALYs of a mixed cohort of patients reflective of those we see in practice in the UK.
    - All subsequent analyses are based on this Revised Base Case model.

2. Revised base case results – fenfluramine vs cannabidiol + clobazam

Results of the revised base case analysis for fenfluramine vs cannabidiol + clobazam are provided below. As the appraisal Committee requested greater clarification of the results by stiripentol use, and by the contribution of carer utility, we have provided results for the merged population, reflecting 58% use of concomitant stiripentol in the population as per our original base case assumption (Table 2), and separately for patients without concomitant use of stiripentol (based on Study 1, Table 3) and with concomitant stiripentol (based on Study 1504, Table 4). Within this we have disaggregated the QALYs into those accrued by patients and those accrued by carers.

Table 2. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
1	Cannabidiol +clobazam	£227,384	14.71	6.08	11.84	17.92	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,841**

Table 3. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1 population (without concomitant stiripentol)

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
1	Cannabidiol +clobazam	£113,527	13.98	5.81	11.01	16.82	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,531**

Table 4. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1504 population (with concomitant stiripentol)

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
1	Cannabidiol +clobazam	£309,831	15.24	6.28	12.44	18.72	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,183**

Interpretation of the results: The merged base case ICER is £31,708/QALY, this is estimated from the individual costs and QALYs of Study 1 and Study 1504.

- Influence of stiripentol:
    - Costs: In Study 1, no patients are taking concomitant stiripentol in either arm of the model, whereas in Study 1504 all patients are taking concomitant stiripentol. When patients discontinue treatment, they revert back to standard of care (SoC) therapies, which in Study 1 is much less costly than in Study 1504, because of the difference in use of high cost stiripentol (SoC contains stiripentol in Study 1504). Consequently, the ongoing costs in Study 1 are significantly lower than in Study 1504, and as patients on cannabidiol plus clobazam revert to SoC therapy more quickly than patients on fenfluramine, the incremental costs in the Study 1 population are greater than in the Study 1504 population.
    - QALYs: The absolute QALYs accrued by fenfluramine and cannabidiol plus clobazam are greater in Study 1504 than in Study 1; however the incremental QALYs are greater in Study 1 (for the reasons explained when reverting patients to the new placebo seizure frequencies in the development of the revised base case).
    - The net effect of stiripentol is to reduce the ICER in the Study 1504 population compared with in the Study 1 population.
- Contribution of carer utility to total QALYs: Both patient and carer utilities are driven by seizure-free days in the model. We assume 1.8 carers in the base case model, in line with that accepted for cannabidiol in NICE TA614. This accounts for the carer's QALYs being almost double that of the patients. The quality-of-life impact for carers is estimated robustly based on the fenfluramine trial data. Given the heavy burden of Dravet syndrome faced by carers, it is plausible that the impact of Dravet syndrome on carers' quality of life is of a similar magnitude to the impact on patients.
- Further disaggregation of all results is provided in the accompanying excel workbook called "Merged_disaggregated results_basecase v2_26OCT".
- In the context of the Committee's preferred assumption to revert patients back to placebo-based seizure frequency, the above results are as would be expected. A scenario analysis in which the placebo effect is removed from the model entirely has been conducted to explore an alternative, potentially less biased approach to dealing with estimation of seizure frequencies upon treatment discontinuation (see Table 16).

3. Revised base case results – fenfluramine + SoC vs continued SoC

As the ACD noted that continued standard of care (SoC) may be a relevant comparator, we have provided results of the revised base case analysis for fenfluramine + SoC vs continued SoC. As above, the appraisal Committee requested greater clarification of the results by stiripentol use, and by the contribution of carer utility, we have provided results for the merged population, reflecting 58% use of stiripentol in the population as per our original base case assumption (Table 5), and separately for patients without concomitant use of stiripentol (based on Study 1, Table 6) and with concomitant stiripentol (based on Study 1504, Table 7). Within this we have disaggregated the QALYs into those accrued by patients and those accrued by carers.

Table 5. Revised base case – fenfluramine + SoC vs continued SoC – merged population

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
13	SoC	£164,915	14.29	5.83	11.20	17.02	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,828**

Table 6. Revised base case – fenfluramine + SoC vs continued SoC – Study 1 population (without concomitant stiripentol)

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
13	SoC	£45,712	13.36	5.50	10.20	15.71	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,625**

Table 7. Revised base case – fenfluramine + SoC vs continued SoC – Study 1504 population (with concomitant stiripentol)

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
13	SoC	£251,235	14.97	6.07	11.91	17.98	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£50,119**

Interpretation of the results: The ICER estimates for the merged and the individual Study 1 and Study 1504 populations are very similar; although the incremental costs and incremental QALYs are different. As the comparison is against SoC, the QALY accrual with fenfluramine is greater than when compared against cannabidiol plus clobazam; however, because there are no costs of cannabidiol plus clobazam in the model, the incremental costs of fenfluramine are greater. This has a more notable effect in the Study 1504 population, where the efficacy decrement arising from the Committee's preferred assumption to revert patients back to placebo is offset to a lesser extent due to the lower costs of the SoC arm when cannabidiol plus clobazam is not an option.

Further disaggregation of all results is provided in accompanying excel workbook called "Merged_disaggregated results_basecase v2_26OCT

4. Fully incremental analyses for revised base case

In addition to the pairwise comparisons, we have provided fully incremental analyses of SoC AEDs vs add-on cannabidiol + clobazam vs add-on fenfluramine, assuming the distribution of concomitant clobazam use (costs) as per our base case analysis. These are provided for the merged population, reflecting 58% use of stiripentol in the licensed population as per our original base case assumption (Table 8), and separately for patients without concomitant use of stiripentol (based on Study 1, Table 9) and with concomitant stiripentol (based on Study 1504, Table 10).

Table 8. Fully incremental analysis - merged population

Scenario #	Treatment	Total Cost (£)	Total LYG	Total QALYs	Incr. costs (£) vs next most effective treatment	Incr. LYG vs next most effective treatment	Incr. QALYs vs next most effective treatment	ICER compared to next most effective treatment	ICER compared to underlying SoC
1	SoC	£164,915	14.29	17.02		-	-	-	-
	Cannabidiol (with	£227,384	14.71	17.92	£62,469	0.42	0.90	**£69,469**	**£69,469 (Cannabidiol with clobazam**

	clobazam) + SoC								**extendedly dominated)**
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,841**	**£49,828**

Table 9. Fully incremental analysis - Study 1 population (without concomitant stiripentol)

Scenario #	**Treatment**	**Total Cost (£)**	**Total LYG**	**Total QALYs**	**Incr. costs (£) vs next most effective treatment**	**Incr. LYG vs next most effective treatment**	**Incr. QALYs vs next most effective treatment**	**ICER compared to next most effective treatment**	**ICER compared to underlying SoC**
1	SoC	£45,712	13.36	15.71	-	-	-	-	-
	Cannabidiol (with clobazam) + SoC	£113,527	13.98	16.82	£67,815	0.62	1.11	**£61,094**	**£61,094 (Cannabidiol with clobazam extendedly dominated)**
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,531**	**£49,625**

Table 10. Fully incremental analysis - Study 1504 population (with concomitant stiripentol)

Scenario #	Treatment	Total Cost (£)	Total LYG	Total QALYs	Incr. costs (£) vs next most effective treatment	Incr. LYG vs next most effective treatment	Incr. QALYs vs next most effective treatment	ICER compared to next most effective treatment	ICER compared to underlying SoC
1	SoC	£251,235	14.97	17.98	-	-	-	-	-
	Cannabidiol (with clobazam) + SoC	£309,831	15.24	18.72	£58,596	0.27	0.74	**£79,183**	**£79,183 (Cannabidiol with clobazam extendedly dominated)**
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£14,183**	**£50,119**

Interpretation:

- These analyses demonstrate that add-on cannabidiol + clobazam is significantly less cost effective than add-on fenfluramine when compared against continued SoC therapy; add-on cannabidiol + clobazam is extendedly dominated by add-on fenfluramine in all analyses.
- Results are as would be expected, given the above explanations of the results of the revised base case.
- As add-on cannabidiol + clobazam 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.

Scenario analyses

We have provided a range of scenarios around the base case analyses of fenfluramine vs cannabidiol + clobazam to address areas of uncertainty highlighted by the Committee in the ACD, and to provide alternative assumptions that will help the Committee to understand the influence of assumptions on the ICER. Positioning analyses are provided of fenfluramine vs cannabidiol + clobazam and fenfluramine vs continued standard of care therapy where relevant.

5. Positioning analyses

Our base case analyses demonstrate the cost effectiveness of fenfluramine across the licensed population. In our initial submission we provided further positioning analyses to demonstrate the cost effectiveness of fenfluramine at different points in the add-on treatment pathway. As it is accepted in the ACD that stiripentol forms a part of standard of care (see section 3.3, page 6-7), stiripentol itself may not be a direct comparator (and there are insufficient stiripentol data available to permit a robust comparison with fenfluramine). However, in addition to the possible use of fenfluramine on top of stiripentol (as per its use in Study 1504), it is possible that fenfluramine could be used as an add-on before stiripentol is used, or after stiripentol has been used but failed. In addition, as fenfluramine does not require the concomitant use of clobazam, it provides a treatment option where clobazam (and therefore cannabidiol and stiripentol) is not / is no longer a desirable option. We have therefore provided positioning analyses using the revised base case assumptions. In these analyses we assume that stiripentol is not a treatment effect modifier for CBD, and clobazam is not a treatment effect modifier of fenfluramine, as is explained and justified in the response to ACD document (Point 4).

i) Use of fenfluramine <u>before</u> stiripentol:

These analyses are based on data from the subgroup of patients in Study 1 who were stiripentol naïve (and are not currently taking stiripentol).

Table 11. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Before use of stiripentol

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
2	Cannabidiol +clobazam	£119,433	14.74	6.09	11.62	17.72	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,382**

Table 12. Revised base case – fenfluramine + SoC vs continued SoC –Before use of stiripentol

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
14	SoC	£46,328	14.06	5.78	10.80	16.57	-	-	-	-	-	-
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£53,157**

ii) Use of fenfluramine <u>on top</u> of stiripentol:

These analyses are based on data from patients in Study 1504.

See Table 4 for the comparison of fenfluramine vs cannabidiol + clobazam when used on top of stiripentol.

See Table 7 for the comparison of fenfluramine + standard of care vs continued standard of care.

iii) Use of fenfluramine <u>after</u> stiripentol:

These analyses are based on data from the subgroup of patients in Study 1 who were stiripentol experienced (and not currently taking stiripentol).

Table 13. Revised base case – fenfluramine vs Cannabidiol + clobazam (both + SoC) – After use of stiripentol

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
4	Cannabidiol +clobazam	£112,678	13.64	5.66	10.54	16.19	-	-	-	-	-	-

	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£42,377**

Table 14. Revised base case – fenfluramine + SoC vs continued SoC – After use of stiripentol

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
16	SoC	£44,835	12.36	5.12	9.37	14.49	-	-	-	-	-	-
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,919**

iv) Use of fenfluramine when clobazam is not / is no longer a desirable treatment option:

This analysis is based on data from the whole of Study 1, with the costs of clobazam removed from both the fenfluramine and SoC arms. As cannabidiol requires the concomitant use of clobazam, continued SoC is the only relevant comparator in this analysis.

Table 15. Revised base case – fenfluramine + SoC vs continued SoC – when clobazam is not/no longer desirable

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
17	SoC	£32,290	13.36	5.50	10.20	15.71	-	-	-	-	-	-
	Fenfluramine + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,025**

Interpretation of positioning analyses: Results of each analysis are consistent with the explanations provided for the behaviour of the model previously. Of note, the resulting ICERs are reasonably consistent across the different positionings. This consistency in cost effectiveness estimates suggests the base case estimates are indicative of the cost effectiveness of fenfluramine across the whole pathway, including in the small proportion of patients who are unable to take clobazam.

Further disaggregation of all results is provided in accompanying excel workbook called “Merged_disaggregated results_basecase v2_26OCT”

6. Seizure frequencies upon discontinuation - Removal of the placebo effect entirely from the model

In our original base case, we assumed that patients who discontinue their index therapy will revert back to standard of care treatment and have their individual baseline seizure frequencies. The ERG and Appraisal Committee expressed a preference for patients to instead revert back to placebo baseline seizure frequencies, which we have implemented in the revised base case model. As this may introduce bias into the model, we have provided an alternative scenario analysis in which we completely remove the placebo effect from the model, so that when patients discontinue their index therapy, they revert back to an unbiased baseline seizure frequency.

Table 16. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population - removal of placebo effect

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
19	Cannabidiol +clobazam	£274,153	15.01	6.16	11.99	18.16	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,973**

Table 17. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1 population - removal of placebo effect

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
19	Cannabidiol +clobazam	£138,011	13.31	5.53	10.30	15.83	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£52,679**

Table 18. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1504 population - removal of placebo effect

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
19	Cannabidiol +clobazam	£372,738	16.24	6.62	13.22	19.84	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**-£25,928**

Interpretation: Similar to when we developed the revised base case and introduced a common (adjusted) placebo effect, when we remove the common (adjusted) placebo effect for this analysis we see differential effects between study 1504 and Study 1 due to the same placebo adjustment in both arms in the context of the underlying natural heterogeneity in patients and treatment experience that characterises Dravet syndrome.

Removal of the placebo effect from the model entirely may help to remove potential bias created in the model by reverting patients to placebo upon treatment discontinuation. The ICER in the Study 1 population has increased and in the Study 1504 population fenfluramine dominates cannabidiol plus clobazam. The merged population ICER has reduced due to the greater contribution of the Study 1504 population (58%) vs the Study 1 population (42%). This merged ICER reflects a mixed cohort of patients in practice.

7. Alternative relationships between convulsive seizure frequency and mortality.

In our base case we model mortality based on seizure frequency using relative risks of death by seizure frequency obtained from the general epilepsy population (Nilsson et al 1999), calibrated to the most comprehensive Dravet syndrome-specific data mortality available in the literature (Cooper et al, 2016). The resulting survival curve was confirmed by clinicians to be representative of mortality in Dravet syndrome. However, the appraisal Committee requested exploration of alternative strengths of the relationship between seizure frequency and mortality. We have therefore provided 3 alternative scenarios.

In addition, the ERG noted that the probability of SE mortality derived from Cooper et al 2016 (0.029%) that we have applied to SE events is not conditional on the occurrence of an SE event and was actually estimated across the Cooper Dravet syndrome cohort as a whole (ERG

report section 3.2.6.5, part e)); in effect, our application of the 0.029% probability of SE death to SE events in our base case model is underestimating the risk of death for each SE event. We have conducted two further exploratory scenario analysis to explore the impact of this issue.

i) Assume the same mortality in Dravet syndrome as in the general epilepsy population

In this scenario we assume the same risk of mortality from seizures as observed in the general epilepsy population.

Table 19. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population - mortality assumed to be same as general epilepsy

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
6	Cannabidiol +clobazam	£389,616	33.52	10.59	20.44	31.03	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,088**

Interpretation: Results are as expected; reducing the risk of death associated with seizure frequencies reduces the impact of the seizure reduction with therapy on life years, which has a greater impact on the therapy that is most effective in reducing seizure frequency (i.e. fenfluramine). Given that the risk of death in Dravet syndrome is well recognised to be greater than in the general epilepsy population, this scenario is likely to significantly underestimate the risk of death in the model.

ii) Partial calibration of the Nilsson et al 1999 general epilepsy relative risks to Cooper et al 2016.

In this scenario we have calibrated the mortality curve to a point mid-way between that with the full calibration to Cooper et al 2016, and that with general epilepsy.

Table 20. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – mortality relationship - partial calibration of Nilsson 1999 to Cooper 2016

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
7	Cannabidiol +clobazam	£287,439	20.20	7.68	14.91	22.60	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,656**

Interpretation: Results are as would be expected from reducing the strength of the relationship between seizure frequency and mortality. Both, analyses are likely to underestimate the actual risk of death in the model, and as there are sound grounds for modelling mortality based on convulsive seizure frequency reduction (see response to ACD, Issue # 12), weakening the expected relationship would underestimate the expected mortality benefit of the reductions in convulsive seizure frequency. These analyses are therefore biased against fenfluramine given its superior convulsive seizure control compared with cannabidiol.

iii) Exploring the contribution of mortality to QALY gains

Based on appropriate assumptions, our model is built on the foundation that differences in seizure frequency drive differences in mortality, quality of life and health care resource use and costs. It is technically challenging to completely remove the link between seizure differences arising from treatment (which drives mortality, quality of life and costs) and seizure differences leading to mortality differences, whilst also retaining the background Dravet syndrome mortality. We have therefore provided a scenario analysis to explore the contribution of QALY gains that are due to survival differences only.

For the purposes of this scenario analysis, to remove the impact of seizure differences on quality of life and so isolate the contribution of mortality to QALY gains, we have assumed that there is no reduction in seizure days with any given reduction in seizure frequency. **Note: We believe this scenario is unrealistic and are providing this only as a means of exploring the contribution of survival to QALY gains; this analysis does not represent a company preferred scenario.**

Table 21. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population - exploring contribution of mortality to QALY gains

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
10	Cannabidiol +clobazam	£227,384	14.71	6.02	11.57	17.59	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,964**

Interpretation: In order to give the Committee insight into the different contributors to QALYs in the model an exploratory academic analysis is provided. In this analysis all QALY differences are due to differences in survival; no differences in quality of life arise from differences in seizures between strategies. As would expected, the ICER is increased compared with the base case.

iv) Exploring the impact of our underestimation of the risk of SE mortality

In these scenario analyses we have adopted two alternative approaches to explore the impact of our underestimation of SE mortality in our base case model. In the first (Table 22), we increased the probability of SE mortality applied to SE events by a factor of 3. Whilst this multiplier is not data driven, it provides a means of testing the direction and impact of our underestimation of SE mortality in the base case model.

Table 22. Exploratory scenario analysis - fenfluramine vs cannabidiol + clobazam (both + SoC) – merged population - exploring impact of a higher risk of SE mortality

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
24	Cannabidiol +clobazam	£200,932	12.74	5.41	10.53	15.94	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,587**

In the second (), we have applied the 0.029% probability to the whole population rather than this being conditioned on experiencing an SE event.

Table 23. Exploratory scenario analysis – fenfluramine vs cannabidiol + clobazam (both + SoC) – merged population – applying SE mortality probability across whole population

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
23	Cannabidiol +clobazam	£217,437	14.02	5.84	11.37	17.21	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,440**

Interpretation: The first exploratory scenario analysis (Table 22) demonstrates that our base case model, in underestimating the risk of SE mortality, is actually conservative; increasing the probability of SE mortality reduces the ICER. The second exploratory analysis (Table 23) in which the probability of SE mortality is applied across the whole population increases the base case ICER marginally; however, in our model this latter approach removes the logical associations between SE mortality, SE events and the occurrence of seizures that may become SE events, and so would be overly conservative towards fenfluramine as the most effective therapy for reducing seizure frequency.

Whilst acknowledging that our approach in our base case is theoretically incorrect, given that the impact of this is to make our model conservative we have pragmatically retained this approach in our revised base case.

8. Alternative assumption on carer utility when patients die

The appraisal Committee agreed that it is appropriate to include carer utilities in the model and acknowledged that there is no agreed way to do this. In our base case model, we assigned carer utilities using robust evidence of the relationship between carer quality of life and seizure-free days based on carer-level data from our trials. Our approach is therefore evidence-based and is aligned with our individual patients/carer level simulation modelling approach. The ERG's suggested alternative approach, using carer disutilities and only for those patients with >8 seizures per month in line with the approach taken in NICE TA614, is arbitrary and not supported by evidence, and is not aligned with our individual patients/carer level simulation modelling approach (as explained in our response document to the ACD, Issue #15).

We therefore believe our approach using carer utilities is a superior approach using superior evidence. The carer utilities were applied in our model until the carer's patient died. This is aligned with the general principle that when patients die in any other model, they do not continue to accrue any additional resource use, costs or quality of life benefits or impairments, and so patients who die in our model should not continue to accrue carer utility. To continue to include carer utility beyond the patient's death would also introduce a number of undesirable consequences and arbitrary assumptions and uncertainties:

- By retaining carer quality of life in the model when patients die retains a benefit of the discontinued treatment but none of the costs, which favours the least effective treatment in the model. As fenfluramine is superior in reducing convulsive seizure frequency (and so would plausibly reduce the risk of death) compared with cannabidiol plus clobazam or continued standard of care this approach biases the model in favour of the comparators and against fenfluramine.
- It is unclear at what level the carers' quality of life should be retained at in the model once the patient dies; increasing the carer's quality of life in the model once the patient dies (e.g. towards population norms, as was suggested in a scenario by the ERG) would have the (unintended) effect in the model of rewarding the patient's death. A strong arbitrary assumption is therefore required.
- It is unclear how long the carer's quality of life should be retained in the model following the patient's death; imposing an ongoing carer utility beyond the patient's death is incompatible with a patient lifetime time horizon, and requires a further arbitrary strong assumption.

Given these issues, we believe our base case is appropriate and internally consistent with the available data and our simulation model. However, to address the Committee's concerns with our approach we have undertaken a scenario analysis in which we retain a carer utility in the model once the patient dies. As this approach is associated with the above mentioned uncertainties and biases it is important to limit these as far as possible. For this scenario analysis we have therefore included a retained carer utility equal to lowest quality of life that the carer experienced while the patient was alive, which it should be noted still favours the least effective therapies over a prolonged time horizon, and whilst hypothetical, it would also be entirely hypothetical to assume an alternative, higher level of carer utility in the model following the death of a carer's child.

Table 24. Scenario analysis – fenfluramine vs cannabidiol + clobazam (both + SoC) – merged population - carer QoL retained when patient dies

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
5	Cannabidiol +clobazam	£227,384	14.71	6.08	23.08	29.16	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,247**

Interpretation: As expected, including carer utility in the model beyond the point at which the patients dies has the effect of rewarding the arm of the model with least effective therapy, as this therapy arm accrues QALYs without accruing costs for a longer period of time. In contrast, the most effective therapy arm accrues QALYs but also accrues ongoing cost for longer. This exemplifies the unintended consequences of assuming ongoing carer utility in the model following the death of their child.

9. Plausible alternative doses of cannabidiol

In our base case models we assume that the dose of cannabidiol is 12mg/kg/day as per the dose assumed in NICE TA614, which is towards the lower end of its licensed dose range. We also assume the maximum doses of fenfluramine. As there is mounting evidence that doses used in practice are plausibly greater than 12mg/kg/day (see our response to the ACD, Issue #18), we have explored alternative cannabidiol dose assumptions of 15mg/kg/day (the mid-point of its recommended dose range) and 20mg/kg/day (its maximum recommended dose).

Table 25. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population - cannabidiol dose 15mg/kg/day

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
11	Cannabidiol +clobazam	£242,407	14.71	6.08	11.84	17.92	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£16,779**

Table 26. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population - cannabidiol dose 20mg/kg/day

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
12	Cannabidiol +clobazam	£267,344	14.71	6.09	11.87	17.95	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**-£8,219 (Fenfluramine dominates cannabidiol)**

Interpretation: It is plausible that the dose of cannabidiol in practice could increase to more than the 12mg/kg/day dose assumed by NICE and adopted in our base case model. An increase in dose from 12mg/kg/day to 15mg/kg/day significantly reduces the ICER. Assuming the maximum dose (as is done for fenfluramine), results in fenfluramine dominating cannabidiol plus clobazam. Our base case analysis is therefore plausibly conservative.

10. Alternative stopping rules

In our base case we have adopted a stopping rule that ensures that fenfluramine is only continued to be used in patients who achieve at least a 30% reduction from baseline in convulsive seizure frequency 6 months after starting treatment. We have explored alternative stopping rules of 40% and 50% (whilst maintain the NICE-approved 30% stopping rule for cannabidiol), which would ensure that fenfluramine is continued only in those patients who are achieving these high reductions in seizure frequency.

Table 27. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population – 40% stopping rule for fenfluramine

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
8	Cannabidiol +clobazam	£227,384	14.71	6.08	11.84	17.92	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£26,436**

Table 28. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – merged population – 50% stopping rule for fenfluramine

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
9	Cannabidiol +clobazam	£227,384	14.71	6.08	11.84	17.92	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,474**

Interpretation: Increasing the stopping rule from 30% to 40% or 50% discontinues more patients from fenfluramine than in the base case. As fenfluramine is continued only in those achieving these high levels of response, the costs of fenfluramine are accrued only in those patients accruing higher levels of QALYs, leading to a reduction in the ICER as expected.

11. Conclusions of model analyses

Our revised base case implements 3 key assumptions in line with Committee members' preferences and uncertainties:

- Patients revert to placebo-based seizure frequencies upon treatment discontinuation
- Seizure frequency is constant throughout life (no change in seizure frequency in adulthood)
- An evidence-based relationship between reduction in convulsive seizure frequency and reduction in seizure days.

The resulting Revised base case ICER in the merged population (which was accepted in principle by the Committee as appropriate for the analysis), was marginally increased from £31,772/QALY to £31,841/QALY. Positioning analyses indicate that the estimates of cost effectiveness are consistent across different parts of the add-on pathway and therefore support the revised base case as suitable to estimate the cost effectiveness of fenfluramine across the whole pathway.

As requested by the Committee, we have:

- Explored alternative strengths of the relationship between convulsive seizure frequency and mortality as far as practically possible
- Explored an alternative approach to incorporation of carer utility in the model.
- Provided fully disaggregated results to demonstrate the influence of stiripentol and the contribution of carer vs patient QALY gains.

These and other analyses suggest our ICER estimates are robust but also demonstrate the challenges in modelling the cost effectiveness of a rare disease such as Dravet syndrome, due to natural heterogeneity on the patient populations and their disease course, and the treatments they receive.

Full details of the code, code changes analysis results have been provided.

We are happy to engage with the NICE team and ERG to address any questions or provide further information.

Additional supporting information

Bootstrapping method for the generation of seizures (Amended Appendix L from CS)

Defining the seizure and seizure-free endpoints within the trial period

In Study 1 and Study 1504 cohort 2, seizures were recorded in a daily diary by the patient or their carer. For each day during the trial period until end of study treatment on Day 99 and Day 106 in Study 1 and Study 1504 cohort 2, respectively (including 42 days of the baseline period, 14 days [Study 1] or 21 days [Study 1504 cohort 2] of the titration period and 84 days [12 weeks] of the maintenance period), the number of seizures, type of seizures, duration of each seizure, whether seizures were in a cluster and time of day of a seizure were recorded (ADXSALL dataset). These data include all patients that were randomised and received either fenfluramine or placebo, in addition to their standard of care (SoC) that excluded stiripentol (study 1) or included stiripentol (study 1504 cohort 2). Patients that experienced no seizures during the titration or maintenance period, or that discontinued during the titration or maintenance periods were included in the dataset. Patients that failed screening prior to randomisation (screen failures), or that discontinued before the maintenance period were however excluded from the analysed dataset. Upon discontinuation from the study, patients that discontinued/withdrew from the study were not required to complete the diary and so further data was not recorded.

For each patient, several types of information were recorded in the diary about each seizure episode:

- type of seizure:
    - convulsive seizure
        - hemiclonic
        - focal with clear observable motor signs
        - generalized tonic clonic convulsion
        - secondarily generalised tonic clonic
        - tonic
        - clonic
        - tonic/atonic)
    - non-convulsive seizure
        - absence or atypical absence
        - myoclonic

    - atonic
    - focal without clear observable motor signs
- time of day the episode occurred
    - early morning (12am – 7:59am)
    - morning (8am – 11:59am)
    - afternoon (12pm – 5:59pm)
    - evening (6pm – 11:59pm))
- duration
    - less than 2 minutes
    - 2-10 minutes
    - more than 10 minutes

A '**seizure day**' was defined as a 24 hour period (starting from 12:00am to 11:59pm on a given day) within which a patient experienced one or more convulsive seizures. Conversely, a '**seizure-free day**' was defined as a 24 hour period (starting from 12:00am to 11:59pm on a given day) upon which a patient experienced no convulsive seizures.

As highlighted in section B.3.3.2.2 of Document B, for the purposes of simplicity and conservatism, the cost-utility analyses have not incorporated the impact and treatment effect of fenfluramine on non-convulsive seizures.

The derivation of mean seizures per 28 days, and mean seizure-free days per 28 days are further detailed in section B.3.3.2 (Document B). The interval between sequential seizure-free days and total (cumulative) number of seizure-free days and/or seizure days have also been derived to facilitate a metric for characterising seizures.

Extrapolation of seizures and seizure free endpoints beyond the trial period

Given the lifetime time-horizon required by the NICE reference case [41], various methods for extrapolating seizures on a patient-level basis were explored to enable the clinical and economic impact of seizure events and their treatment over the patient's lifetime to be examined in the cost-utility analysis. As mentioned in section B.3.3.2 of Document B, individual patients' seizures were modelled as per their experience within the placebo arm of the respective fenfluramine studies (Study 1 and Study 1504 cohort 2). The seizure experience of the patients at the end of the trial period (Day 99 and

Day 106 in Study 1 and Study 1504 cohort 2, respectively) was simulated thereafter for all patients until they died, as no data existed past the end of the study.

Three methods were explored to simulate individual patient seizures that would generate a model that simulates Dravet patients as realistically as possible. The method which most closely replicated the trial data was chosen for the model and a population size equivalent to the population of Dravet syndrome patients inEngland.These methods are described below.

Within patient resampling

When examining the respective positioning of fenfluramine or its comparator, a cohort of representative patients were identified from the trial population (all patients on placebo and who met the inclusion for the trial results) and these representative patients were bootstrapped. Accordingly, the concomitant/prior medication patients were receiving was also adjusted for.

In order to extrapolate beyond the observed trial period, daily observations from within the maintenance period were randomly resampled within patients. Two methods were developed and described below. The extrapolation was run for each patient for 10 years, and those ten years repeated over the lifetime (as an assumption of no waning of treatment was made). The lifetime extrapolation was repeated 10 times for every patient to create a larger population and reduce random sampling variation associated with the extrapolation.

Within-Patient Resampling Method 1

For each patient, whilst continuing on their existing strategy (treatment or placebo), a day from the trial maintenance period was randomly sampled with replacement and the number of seizure events (including the possibility of no seizures) on that sampled day was used to synthesize the 'new day'. This was repeated for every day until the patient discontinued their existing treatment or died. Therefore, allowing for random variation within patients, the pattern of days with and without seizures, and the number of seizures on days with seizures, during the period of extrapolation would on average be the same as the maintenance period.

As described in section B.3.3.5 of Document B, patients may discontinue from their existing strategy for lack of efficacy, physician or patient decision, adverse events, implementation of a 'stopping rule' or death. For patients in both the treatment (intervention and comparator) and placebo strategies that discontinue their existing strategy for reasons other than death, the patient was returned to the frequency of seizure events observed in their baseline period. Therefore, for the day after their discontinuation, a day from their previous 42-day baseline period was randomly sampled and the number of seizure events on that sampled day was used to synthesise a 'new day'. This was repeated for subsequent days until the patient died. Patients that discontinue from either strategy are considered to be retained at their baseline level of seizures, without further deterioration in health (seizure related or otherwise) with the reduction in available treatment options available to them.

Within-Patient Resampling Method 2

A second bootstrapping method, which required two levels of bootstrapping was tested, in which we first sampled whether a day was a 'seizure day' (rather than a seizure-free day). If this was the case, then a second layer of sampling determined the number of seizures on that day.

Shared Frailty model

A fully parametric shared frailty approach to modelling individual seizure free intervals was explored. This was implemented using the parfm package in R with a Weibull survival function and a gamma frailty distribution. The model was not used in the final model as comparable treatment effects estimates were not available for Cannabidiol and the model did not appear to be a good fit to the empirical data.

Fitting a Poisson distribution for each patient

A zero inflated Poisson distribution was fitted to the number of seizures per day for each individual in the trial, and the distribution was sampled for each day. However, a number of patients (39) had too few seizures to fit a distribution to and therefore could not be considered with this method, limiting the size of the population to sample from.

Validation and method selection

The Poisson distribution method was not used, as too many patients failed to fit. Bootstrapping method 1 was selected as it fit the trial data better than method 2, and was therefore used in the final cost-utility model (comparison of mean seizure and seizure free days in Table 31).

The bootstrapping method 1 was validated by the following methods:

- The mean seizures per 28 days, and mean seizure-free days per 28 days for the actual trial data were calculated and compared against the simulated data for the placebo arm at baseline and over the 12 week maintenance period (Figure 3).
- The proportion of patients with a 25% or higher reduction in seizures from baseline was calculated for the placebo arm for the simulated and actual trial data and compared.
- The proportion of individuals having a seizure free interval of *n* days was plotted for the placebo arm for the actual trial data and the simulated data and compared (Figure 4).
- The number of seizures per day using actual trial data and the simulated data were plotted for each individual to look for anomalies (Figure 5 and Figure 6).

Following our submission, the ERG report (Figure 5.4, page 92-93,) referred to a "*seemingly implausible peak for patients with zero convulsive seizure-free days that seems to represent a cluster of outlier patients in terms of convulsive seizures*" in Study 1504, which it implied "*undermined the validity of the patent profiles used*". We have further explored the individual patient-level data used in the bootstrapping and can confirm that the

patient profiles match the underlying data. The peak in patients with zero convulsive seizure free days in Study 1504, referred to in Figure 5.4 of the ERG report, is actually due to just one patient who had a higher number of seizures at baseline and throughout the study compared with the other patients in the trial. We have replicated the ERG's Figure 5.4 for Study 1504 and provided a corresponding figure based on the actual trial data (see Figure 2). This demonstrates that the "cluster" in zero seizure free days referred to in Figure 5.4 of the ERG report is entirely consistent with the trial data and does not represent any form of error in the bootstrapping and generation of patient profiles. Given the limited size of the trial in this rare disease, we do not consider this patient to be an "outlier"; rather, it is an accurate reflection of the heterogenous nature of seizures in Dravet syndrome amongst the participants recruited to the trial, who have been confirmed to reflect patients in need of add-on therapy in clinical practice. The generated patient profiles are therefore plausible and consistent with the trial data, further validating out bootstrapping methods.

Clarification of implementation of the bootstrapping and application of treatment effects in the model

To aid the ERG we have detailed below how the bootstrapping is implemented, how treatment effects are applied and how patients return to placebo level seizures upon treatment discontinuation in our simulation model. Code changes for revision of our base case and all subsequent scenario analyses are details in the accompanying spreadsheet "Merged_disaggregated results_basecase v2_26_OCT".

Start of the model – for both Study 1 and Study 1504

Firstly, the data is split by seizures and seizure days into two seizure profiles, baseline (higher seizures) and trial (lower seizures). Each data set has the same patients (n=164) for 130 cycles. Via bootstrapping, each patient profile is built 10 times around the patient's original patient profile. For the modelled cohort only data for patients on placebo is used. Patients are then simulated according to the proportion of patients on stiripentol observed.

- Seizures.cycle$`131` <- Seizures.cycle$`130`
- Seizuredays.cycle$`131` <- Seizuredays.cycle$`130`
- Seizuresdiscon.cycle <- Seizuresdiscon.cycle[,-c(135)]
- Seizuredaysdiscon.cycle <- Seizuredaysdiscon.cycle[,-c(135)]

- This replaces cycle 131 for the trial's seizures and seizure days and removes the last column for the baseline seizures and seizure days. (There was an issue with the data sets where the baseline seizure data sets had an extra column). There are 4 additional columns at the start which contain information about the dataset. Each dataset now has 131 columns which represent 28-day cycles in the model.

Set cohort to 4920 profiles of 164 patients (30 profiles each)

- Seizures.cycle<- rbind(Seizures.cycle,Seizures.cycle,Seizures.cycle)
- Seizuredays.cycle<- rbind(Seizuredays.cycle,Seizuredays.cycle,Seizuredays.cycle)
- Seizuresdiscon.cycle<- rbind(Seizuresdiscon.cycle,Seizuresdiscon.cycle,Seizuresdiscon.cycle)
- Seizuredaysdiscon.cycle<- rbind(Seizuredaysdiscon.cycle,Seizuredaysdiscon.cycle,Seizuredaysdiscon.cycle)
  - This replicates the patients 3 times for each dataset in order to have enough patients on placebo. Now there are 164 patients, each with 30 profiles.

Set Time Horizon to 100 years

This section replicates the 10 year cycles by 10 so the patient have a lifetime horizon.

- Seizures.cycle1 <- Seizures.cycle1[, rep(seq_len(ncol(Seizures.cycle1)), each = 10)] #repeat all the columns
- Seizures.cycle <- cbind(Seizures.cycle, Seizures.cycle1) #Add the new cols to the old to keep the study data
- colnames(Seizures.cycle)[5:ncol(Seizures.cycle)] <- c(1:(ncol(Seizures.cycle)-4))
- remove(Seizures.cycle1)
  - This is done for the 4 datasets, only trial seizures are shown here for conciseness.

Filter for Placebo

- seizures.placebo.cycle <- Seizures.cycle %>%
- filter(tx == "Placebo") %>%
- filter(studyid %in% studyname) %>%
- filter(STP == stpexp)
  - This filters the trial seizures, currently containing 164 patients with 30 profiles (4920 rows). The Placebo filter filters only for patients who were on placebo treatment. The study filter filters for the study, and the final filter cuts the population in half, so all the remaining patients have 15 profiles. At this point there are 585 rows.
- seizures.placebo.cycle <- seizures.placebo.cycle[c(1:n.i),c(1:(n.t+1))]

- This final filter removes from the bottom the remaining profiles in order to reach the desired set population (n). In the base case we set this to be 480, so this final filter removes 105 profiles at random. We now have the population we use in the model, who are all patients that were on placebo.
- This same procedure is done for trial and baseline seizures and seizure days.
- This is repeated for each study (study 1 and study 1504)
- So currently, all 480 patients are on placebo and each has a data set from the trial and from baseline – so the only difference between those datasets is the the placebo effect.

Calculate placebo and treatment effect (CBD)

We calculate the placebo effect and add it to the treatment effects.

- placreduc <- (seizures.plac.discon.cycle1-seizures.placebo.cycle)/seizures.plac.discon.cycle1
  - This gets the placebo reduction. This is done by getting the percentage decrease from baseline to trial placebo. This is done for seizures and seizure days. This is an individual reduction for each patient and each cycle. Placebo response from trial data (bootstrapped).
- placreducCBD <- placreduc + CBDreduc
  - This adds the reduction we set for CBD (0.6) to the placebo reduction we have just calculated.
- seizures.plc.cycle1CBD <- placreducCBD * seizures.plac.discon.cycle1
  - This multiplies the baseline seizures of the patients by this reduction figure we have calculated to get the reduction in seizures we would see.
- seizures.plc.cycle1CBD <- seizures.plac.discon.cycle1 - seizures.plc.cycle1CBD
  - This takes the reduction in seizures we just calculated and takes it away from baseline seizures.
  - This same procedure is done for CBD seizure days.

Calculate placebo and treatment effect (FFA)

- placreduc <- (seizures.plac.discon.cycle1-seizures.placebo.cycle)/seizures.plac.discon.cycle1
  - This gets the placebo reduction. This is done by getting the percentage decrease from baseline to trial placebo. This is done for seizures and seizure days. This is an individual reduction for each patient and each cycle. Placebo response from trial data (bootstrapped).
- placreducCBD <- placreduc + ffareduc
  - This adds the reduction we set for CBD (0.3) to the placebo reduction we have just calculated.
- seizures.tx.cycle1ITC <- placreducITC * seizures.plac.discon.cycle1

    - This multiplies the baseline seizures of the patients by this reduction figure we have calculated to get the reduction in seizures we would see.
- seizures.tx.cycle1ITC <- seizures.plac.discon.cycle1 - seizures.plc.cycle1CBD
    - This takes the reduction in seizures we just calculated and takes it away from baseline seizures.
    - This same procedure is done for FFA seizure days.
    - These patient seizure profiles are then run through the microsimulation

Within the **microsimulation script**, the stopping rule is calculated with the following code.

Stopping Rule (lines 180-192)

m.discon[,] <- 0 # No one has discontinued to start (0 = not discontinued, 1 = discontinued)

- if (STOPPING.RULE == TRUE) {
    - This checks to see if the 30% stopping rule is turned on
- if(m.discon[i,1] == 0){
- if(Trt == 0){
- if(sum(m.S[i , c(1:6)]) > (1-percent.stopping) * sum(seizures.discon.cycle[i,c(1:6)])){
    - This checks to see if the sum of the seizures in the first 6 cycles for is greater than 0.7*the sum of the seizures in the first 6 cycles. This is for CBD.
- m.discon[i,7] <- 2
    - This puts in a tag to identify the patient should discontinue.
- } } else {
- if(sum(m.S[i , c(1:6)]) > (1-percent.stoppingffa) * sum(seizures.discon.cycle[i,c(1:6)])){
    - This checks to see if the sum of the seizures in the first 6 cycles for is greater than 0.7*the sum of the seizures in the first 6 cycles. This is for FFA.
- m.discon[i,7] <- 2
    - This puts in a tag to identify the patient should discontinue.

Discontinuation to placebo (lines 224-228) Microsimulation script.

- if (m.discon[i , t] != 0) {
    - if the person has discontinued then set their seizures to what it would be at baseline.

- m.discon[i , t + 1] <- 1
    - # if the person has discontinued, ensure they stay discontinued in the next cycle by adding a tag.
- m.M[i, t + 1] <- if{seizuredays.placebo.cycle[i , t + 1]}
    - This sets seizure days to placebo seizures days if the discontinue
- m.S[i, t + 1] <- {seizures.placebo.cycle[i , t + 1]}
    - This sets seizures to placebo seizures if when patients discontinue therapy.
    - Patients return to their own range of bootstrapped placebo seizures

Supporting information: Tables & Figures

Table 29. Bucher ITCs for convulsive seizure outcomes

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Comparison of model outputs for our model and the cannabidiol model in NICE TA614

In line with the discussions with ERG and NICE at our meeting 26th November 2021, we have provided an expanded description of differences in outputs between the current model and the model submitted by the manufacturer of cannabidiol in NICE TA614:

- The manufacturer of cannabidiol submitted a cohort model for NICE TA614. We have developed a patient-level micro-simulation model to account for the known heterogeneity in seizure frequencies and patients in Dravet syndrome. This is aligned with suggestions of the Appraisal Committee in NICE TA614, from which we reasonably infer that the Appraisal Committee considered that the cannabidiol cohort model used in NICE TA614 may not appropriately account for such heterogeneity.

- Given this, the other known issues with the cannabidiol model in TA614, and our fundamentally different modelling approach, there is no basis for assuming that the outputs from the model developed in TA614 are the benchmark against which the outputs of our model can or should be "validated". Furthermore, our model permits comparison of fenfluramine and cannabidiol in an internally consistent and relative way. Whilst acknowledging that all models have limitations, we maintain the view that cross comparison of our model outputs against those from with what we believe is an inferior model is not appropriate.

- Nonetheless, to accommodate the ERG's request, we have further explored the cannabidiol outputs of our model and those of the model used in TA614 as far as public data from TA614 allow.

- As demonstrated in Table 30 below, **differences in Costs, QALYs and ICERs** between our model and the cannabidiol model in NICE TA614 are fully expected. Such differences are likely to arise from not only the different modelling approach but also the data sources that are used in line with that modelling approach.

- **Costs and ICERs**: Key issues in comparing the Total costs estimates in the TA614 model and the current model include the use of different prices assumed for cannabidiol (i.e. list price [current model] versus confidential PAS price [TA614 model]); the patient simulation modelling approach vs a cohort modelling approach; and the adoption of an appropriate and clinically reasoned link between convulsive seizure frequency and mortality in the current model. There are no details of the relevant Total costs for cannabidiol in the TA614 model, nor of the relevant model itself , available in the public domain, which further hampers a full evaluation of the comparative differences in Total cost between models. .

    - The ERG report dated 13 October 2020 compared the outputs for cannabidiol from our model against those in the cannabidiol manufacturer's revised model following the ACD for TA614. The ERG report noted that the ICER for cannabidiol vs SoC in their revised model was £29,268/QALY (versus £69,469/QALY in our current merged base case), and total costs were £393,521 for cannabidiol (versus £227,384 in our current merged base case).

    - The cannabidiol model in TA614 uses the confidential PAS discounted price of cannabidiol. As we are not privy to the confidential agreed discount on the price of cannabidiol, our model appropriately uses the list price of cannabidiol. As the cost of cannabidiol is likely to be a significant driver of its Total costs and ICER estimate, this will contribute an unknown proportion to any discrepancy in Total costs and ICER estimates between the two models. In our original CS we provided a scenario analysis exploring different discounts on the list price of cannabidiol, but as we do not know the actual discount level we are unable to comment on this further.

- As a patient-level simulation that takes into account the expected heterogeneity in seizure frequencies, our model uses more granular data on HCRU and costs, and accrues costs in a more granular nature than in the arbitrarily defined cohort model in TA614. It is not possible for us to replicate the accrual of HCRU and costs from TA614 in our model without changing the fundamental structure and modelling approach, which would defeat the purpose of comparing the outputs of the two different modelling approaches. We maintain that the patient-level simulation approach is superior to the arbitrarily defined cohort model used in TA614.
- Our model adopts an appropriate and clinically reasoned link between convulsive seizure frequency and mortality. By including mortality associated with seizure frequency in our model, there would be a faster attrition of patients from our model versus excluding mortality associated with seizure frequency (as in TA614), resulting in lower accrual of ongoing costs of care. All else being equal, we would therefore expect that Total costs in our model would be lower than those in the TA614 model. This is indeed what has been observed by the ERG.
- Upon discontinuation of cannabidiol, patients returned to baseline seizure frequencies in the model in TA614. However, the Appraisal Committee preferred that in our model patients return to placebo rates of seizure frequency. Seizure frequency determines HCRU and costs in the model (and indirectly determines mortality). The actual seizure frequencies to which cannabidiol recipients return upon discontinuation are therefore different, which would lead to the accrual of different ongoing HCRU and costs.
- Differences in time horizon (90 years in the TA614 model versus 100 years in our model) could also contribute marginally to differences in accrued Total costs and the ICER.
- It is therefore clear that there are several components of our model that contribute to the observed differences in Total costs. Isolating the effects of each component, even where feasible, would not result in comparable estimates of Total costs, and it is not possible to implement all changes in line with the model in TA614 without fundamentally changing our model structure and approach, which would defeat the purpose of the exercise.

- **QALYs and ICERs:** Key issues in comparing the QALY estimates in the TA614 model and our model include the patient micro-simulation vs cohort modelling approach, adoption of an appropriate and clinically reasoned link between convulsive seizure frequency and mortality in our model, and the method used to estimate utility values. Details of the relevant QALYs and LYG for cannabidiol in the TA614 model, against which to make a comparison, are also lacking.
  - Our patient-level simulation model uses seizure frequencies to inform mortality and also the number of seizure free days, which drives utility values for patients and carers. Our approach using patient level seizure frequency data in a continuous time model better reflects the expected heterogeneity in seizure frequencies and patients with Dravet syndrome than does the arbitrarily specified health states used in the cohort model in TA614. The treatment effect of cannabidiol is appropriately applied from the ITC to patient-level data from the placebo arms of the fenfluramine trials. The actual seizure frequencies experienced with cannabidiol will therefore not be exactly the same as those experienced with cannabidiol in the TA614 model, by nature of the patient simulation modelling approach. This is not a limitation of our model; it is entirely expected and justified based on the modelling approach and robust methods adopted in the ITC.

- QALYs are composed of LYG and a quality of life adjustment. Any comparison of QALYs is an implicit comparison of the combined effect of mortality and quality of life. Both mortality and quality of life are implemented in different ways in the two models, making any comparison of QALYs challenging to interpret. This is all the more challenging because there are no LYG estimates available in the public domain for the model in TA614.
- Our model adopts an appropriate and clinically reasoned link between convulsive seizure frequency and mortality. By including mortality associated with seizure frequency in our model, there would be a faster attrition of patients from our model versus excluding mortality associated with seizure frequency (as in TA614), resulting in lower accrual of LYG. All else being equal, we would therefore expect the resulting incremental QALYs in our model to be lower than those in the TA614 model. This is indeed what has been observed by the ERG.
- We are unable to provide a comparison of survival between the two models as there are no publicly available LYG estimates for the TA614 model with which to make a comparison.
- Quality of life is implemented in our model via utility values derived from regression analysis of patient- and carer-level data from the fenfluramine trials. These data, based on empirical trial evidence, are internally consistent with our patient-level modelling approach and are aligned with the NICE reference case. In contrast, the utility values used in the TA614 model were based on a vignette study that was not aligned with the NICE reference case and derived utility values for 4 arbitrarily defined convulsive seizure health states. To implement this approach in our model would require us to adapt the model based on the same arbitrarily defined health states to accommodate these clearly inferior, non-evidence linked utility values. As the underlying differences in mortality would remain between the models, any comparison of resulting QALYs would not be informative.
- Upon discontinuation of cannabidiol, patients returned to baseline seizure frequencies in the model in TA614. However, the Appraisal Committee preferred that in our model patients return to placebo rates of seizure frequency. Seizure frequency indirectly determines mortality and quality of life in our model. The actual seizure frequencies to which cannabidiol recipients return upon discontinuation are therefore different between the two models, which would lead to different accrual of LYG and QALYs.
- Differences in time horizon (90 years in the TA614 model versus 100 years in our model) could also contribute marginally to differences in accrued LYG and QALYs.
- It is therefore clear that there are several components of our model that contribute to the observed differences in QALYs. Isolating the effects of each component, even where feasible, would not result in comparable estimates of QALYs, and it is not possible to implement all changes in line with the model in TA614 without fundamentally changing our model structure and approach, which would defeat the purpose of the exercise.

- It should be noted that, although the ERG is referring to the TA614 model results with an ICER of £29,268/QALY (based on the cannabidiol manufacturer's results post the ACD for TA614), the FAD for TA614 actually refers to an ICER of £32,471/QALY. Whilst the FAD lists a range of assumptions that contribute to this "final" ICER (including assumptions that would influence costs and efficacy, and hence QALY and ICER estimates), the actual direction of the influence of these assumptions, and the main driver of this difference in the ICER for cannabidiol reported by the ERG versus that reported in their FAD is not stated. No information on the Total or incremental costs or QALYs or LYG for this "final" ICER are provided in the FAD or elsewhere. Please note: The FAD for TA614 does, however, indicate that this ICER of £32,471/QALY is likely to have been an underestimate. It is therefore unclear if the ERG has compared the Total costs, QALYs or ICER for

cannabidiol based on our model outputs against the most relevant Total costs, QALYs or ICER estimates for cannabidiol in TA614. In the absence of public information on the costs, QALYs and LYG contributing to this "final" ICER from the model in NICE TA614, or the model itself, it is not possible to draw any meaningful comparisons beyond noting the differences in the costs and modelling approach discussed above.

- **In summary, differences in Total costs, QALYs and ICERs are fully expected based on the justifiably different modelling approach we have taken in our model versus the TA614 model. There are insufficient data on the Total costs, QALYs and LYG for cannabidiol in TA614 with which to compare the outputs of our model. Based on the data that are available, the Total Costs, incremental QALYs and ICER estimates for cannabidiol in our model seem to be in line with expectations given the underlying modelling of the costs of cannabidiol (based on its list price), the justifiable inclusion of a mortality effect, and the use of internally consistent evidence in our patient-level simulation model. Fenfluramine, cannabidiol and standard of care AEDs are all compared within this internally consistent model, and there is no basis for assuming that the differences in headline Total costs, QALYs or ICERs for cannabidiol observed by the ERG challenge the validity of our model**.

Table 30. Differences between the Cannabidiol model in TA614 and Fenfluramine model in the current appraisal

Characteristics and assumptions	**Cannabidiol model in TA614 (final model)**	**Fenfluramine model in current appraisal (revised base case)**	**Differences expected between models for cannabidiol outputs**
Model type	• Cohort model with 4 health states arbitrarily defined by different seizure frequencies (with substates based on different number of seizure-free days) • Does not appropriately account for heterogeneity in this rare disease population	• Individual patient state transition model using trial individual patient-level data (including seizures and patient / carer QoL) from the fenfluramine trials. • Developed in line with suggestions of CCommittee in TA614 FAD • Takes account of natural heterogeneity in this rare disease population	• Possible - given the cannabidiol cohort model does not account for natural clinical heterogeneity • There would be no benefit to the TA614 CCommittee's suggestion of a simulation type model to better account for heterogeneity if the model outputs are expected to be the same
Comparisons	• Cannabidiol plus clobazam + SoC vs SoC	• Fenfluramine + SoC vs Cannabidiol plus clobazam + SoC • Fenfluramine + SoC vs SoC	• n/a
Efficacy data	• Cannabidiol trial data vs placebo (SoC)	• Indirect Treatment Comparison (ITC) of fenfluramine and cannabidiol trial data vs common placebo (SoC) comparator • Fenfluramine trial data vs placebo (SoC)	• Possible - given that the ITC appropriately adjusts for the common comparator effects • An ITC is appropriate to provide adjusted relative treatment effects vs placebo • Seizure frequencies with cannabidiol would be slightly different when the ITC based cannabinol treatment effect is applied to the patient-level seizure frequencies derived from the placebo arms of the fenfluramine trials vs when the cannabidiol treatment

Characteristics and assumptions	Cannabidiol model in TA614 (final model)	Fenfluramine model in current appraisal (revised base case)	Differences expected between models for cannabidiol outputs
			effect is based only on the cannabidiol RCT data
Mortality assumption	• Link that cannabidiol extends life was removed	• Includes plausible link between convulsive seizure frequency and mortality based on the most robust evidence available in the literature. • Same approach adopted to both arms of the model. • (It is impossible to power a trial for mortality events in this rare disease, but the link between convulsive seizure frequency and mortality is well accepted, and the fact that fenfluramine substantially reduces convulsive seizure frequency is well accepted)	• Yes – the inclusion of mortality is appropriate and would be expected to have an impact on the QALYs and costs accrued with each treatment.
Seizure frequency upon treatment discontinuation	• Patients who discontinue cannabidiol are assumed to revert to baseline seizure rates	• Patients who discontinue fenfluramine or cannabidiol treatment are assumed to revert to placebo seizure frequency (as requested by the Committee, and updated from the original company submission, where patients were assumed to revert to their baseline level of seizures)	• Probably – the Committee's preference that patients in our model return to a placebo "on-treatment" convulsive seizure frequency would result in different accrual of QALYs and costs compared with return to baseline convulsive seizure frequency accepted in NICE TA614. • This is compounded by the fact that placebo frequencies in the model are derived from the ITC, which provides an adjusted estimate based on the placebo arms of both the fenfluramine and cannabidiol arms. The seizure frequencies upon treatment discontinuation therefore differ between the two models, which would influence costs, QALYs and ICER estimates obtained from the two models.

Characteristics and assumptions	Cannabidiol model in TA614 (final model)	Fenfluramine model in current appraisal (revised base case)	Differences expected between models for cannabidiol outputs
Patient utility	• Based on a vignette study (not aligned with NICE reference case) • Applied to the arbitrarily defined categorical health states	• Based on patient (carer proxy)-level clinical trial quality of life data mapped to EQ-5D-Y (as per the NICE reference case) • Applied in our continuous time model in line with this empirical evidence	• Yes – our use of empirical QoL data from the fenfluramine trials to derive utility values based on seizure frequency would generate different utility values to the inferior vignette approach adopted in TA614 • Our continuous time model, using empirical evidence of patient quality of life based on seizure frequency, would better reflect the accrual of QALYs than the arbitrarily defined health states in the cannabidiol cohort model, contributing to QALY differences between the two approaches
Carer utility	• Based on a vignette study (not aligned with NICE reference case) • Assumes 1.8 carers and disutility applied to the 2 "worst" arbitrarily defined categorical health states	• Based on carer-level clinical trial quality of life (EQ-5D-5L) data mapped to EQ-5D-3L (as per the NICE reference case) • Assumed 1.8 carers and utility applied in line with the empirical evidence from the trial and patient-carer opinion • (There is no agreed method for incorporation of carer QoL into models. Our approach ensures internal consistency based on empirical evidence from the trials)	• Yes – our use of empirical QoL data from the fenfluramine trials to derive utility values based on seizure frequency would generate different utility values to the inferior vignette approach adopted in the cannabidiol model • Our continuous time model, using empirical evidence of carer quality of life based on seizure frequency, would better reflect the accrual of QALYs than the arbitrarily defined health states in the cannabidiol cohort model, contributing to QALY differences between the two approaches
Drug costs	• Cannabidiol based on confidential PAS discount to its list price	• Cannabidiol based on list price (as PAS discount price is confidential and not known to us) • Fenfluramine based on confidential PAS discount to its anticipated list price	• Yes – the use of a far lower discounted price of cannabidiol in the cannabidiol model will result in different total costs compared with the higher list price of cannabidiol it was necessary to use in our model
Other costs / Health care resource use	• Based on clinical expert opinion of resource use related to the 4 arbitrarily defined health states in the model across 2 age categories	• Based on clinical expert opinion of resource use related to clinician-defined high/medium/low seizure frequencies across 7 different age groups.	• Possible – Greater granularity in HCRU to populate our continuous time model vs the cohort model in TA614 may theoretically lead to different non-drug lifetime costs • Differences in mortality assumptions in the model will also influence the accrual of SoC AED costs and other HCRU costs.

Characteristics and assumptions	Cannabidiol model in TA614 (final model)	Fenfluramine model in current appraisal (revised base case)	Differences expected between models for cannabidiol outputs
Stopping rule and treatment discontinuation	• Stopping rule: Convulsive seizure reduction of less than 30% from baseline assessed at 6 months and every 6 months • Long-term discontinuations based on the cannabidiol open-label extension study, and extrapolations based on assumptions for each arbitrarily defined health state	• Stopping rule: Convulsive seizure reduction of less than 30% from baseline assessed at 6 months (as no waning of effect assumed, and long-term discontinuation accounts for any other loss of efficacy) • Long-term discontinuations based on the fenfluramine and cannabidiol open-label extension studies, extrapolated	• Unlikely – given assumption of no waning of effect with either fenfluramine or cannabidiol – the first stopping rule at 6 months removes those with insufficient response, and the discontinuation rates taken from the open-label extension studies account for any other discontinuations, including lack of efficacy
Time horizon	• Adopted a 15 year time horizon that was then amended to 90 years in revised model	• Adopted a lifetime horizon of 100 years	• Possible – the 10 year difference in time horizon will marginally influence the long term discounting of costs and outcomes.

Table 31. Comparison of mean seizure and seizure free days per cycle between the trial and two different bootstrapping methods

		On treatment period		Baseline period	
Arm	Method	Mean seizure free days per cycle	Mean seizures per cycle	Mean seizure free days per cycle	Mean seizures per cycle
1504 placebo	Trial date	[redacted]	[redacted]	[redacted]	[redacted]
1504 placebo	Modelling method 1	[redacted]	[redacted]	[redacted]	[redacted]
1504 placebo	Modelling method 2	[redacted]	[redacted]	[redacted]	[redacted]
1 placebo	Trial date	[redacted]	[redacted]	[redacted]	[redacted]
1 placebo	Modelling method 1	[redacted]	[redacted]	[redacted]	[redacted]
1 placebo	Modelling method 2	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1. ICERs are stable across various population sizes (based on revised model provided to NICE/ERG 12th May 2021)

Figure 2. Comparison of bootstrapped data vs actual trial data in Study 1504

Figure 3 Mean seizure-free days and seizure days in simulated patients versus trial data using bootstrapping method 1, for patients on placebo

Figure 4. Mean seizure-free day interval in simulated patients vs trial data using bootstrapping method 1, for patients on placebo

Figure 5. Simulated versus trial data: number of seizures per day per individual patient in study 1 placebo arm at baseline

Figure 6. Simulated versus trial data: number of seizures per day per individual patient in study 1504 cohort 2, placebo arm at baseline

Figure 7 Patterns of individual seizure events in Study 1 and Study 1504

******

Figure 8. Regression analysis of change in convulsive seizure frequency vs change in days with seizures based on combined data from all arms of Study 1 and Study 1504

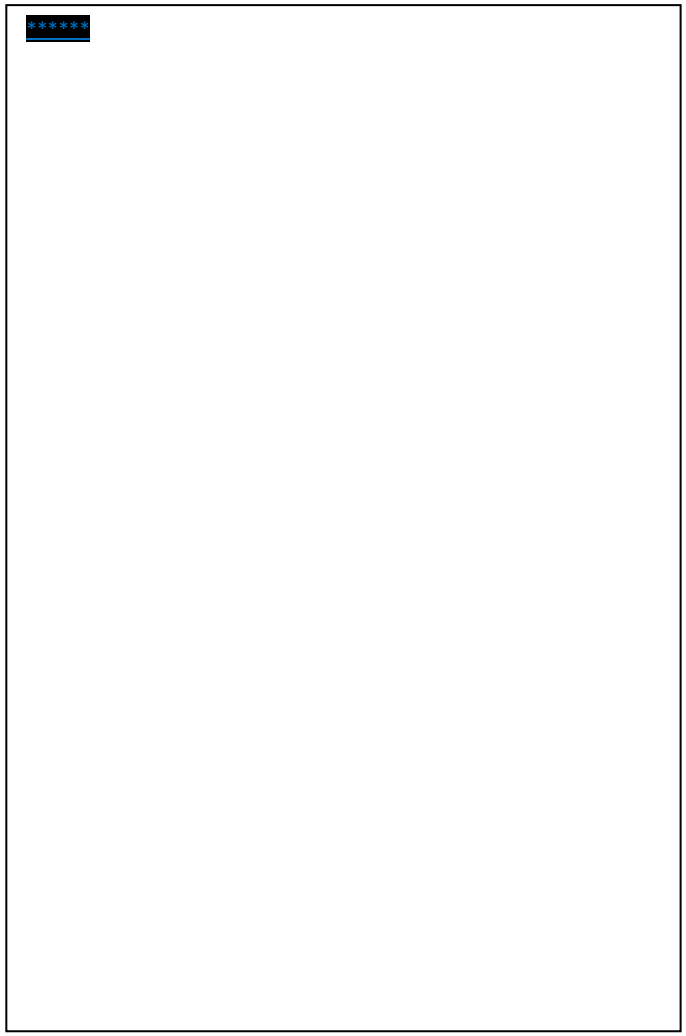
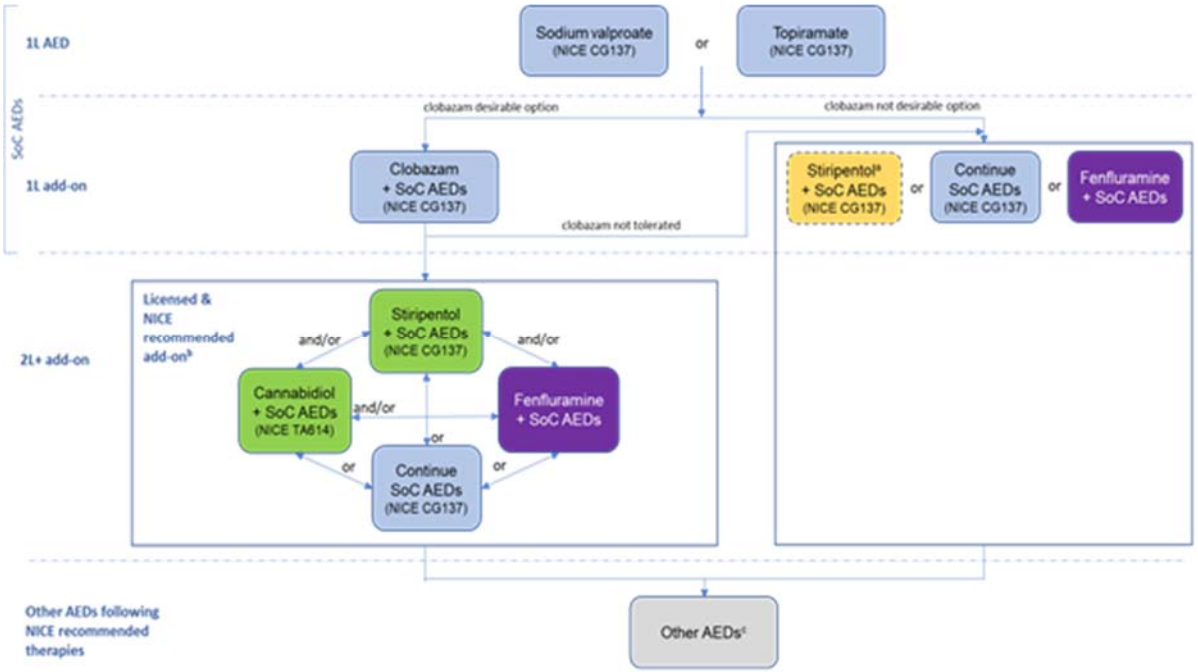


Figure 9. Bayesian probabilities of fenfluramine and cannabidiol being ranked 1st, 2nd, 3rd, 4th, 5th, 6th most effective therapy in the NMA

Figure 10. Proposed positioning of fenfluramine in the clinical pathway (Revised Figure 2 in the CS)



Additional scenario analysis: Trial-based discontinuations equal for fenfluramine and cannabidiol

As requested by the ERG, we have provided a scenario analysis in which the discontinuation probabilities for cannabidiol+ clobazam during the trial titration and maintenance phases are set equal to those for fenfluramine, with probabilities as reported in Table 30 of the CS.

Table 32. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) - merged population – same trial based discontinuations

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
34	Cannabidiol +clobazam	£224,010	14.71	6.08	11.81	17.89	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,291

Table 33 Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1 population (without concomitant stiripentol) – same trial based discontinuations

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
34	Cannabidiol +clobazam	£110,437	13.97	5.80	10.98	16.78	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,799

Table 34. Scenario analysis – fenfluramine vs Cannabidiol + clobazam (both + SoC) – Study 1504 population (with concomitant stiripentol) – same trial based discontinuations

Scenario #	Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. Patient QALYs	Incr. Carer QALYs	Incr. Total QALYs	ICER (£/QALY)
34	Cannabidiol +clobazam	£306,253	15.24	6.27	12.42	18.69	-	-	-	-	-	-
	Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,250

Interpretation of the results:

Setting the trial-based (i.e. titration + maintenance period) discontinuations for the cannabidiol + clobazam arm to be equal to those in the fenfluramine arm leads to patients discontinuing cannabidiol+clobazam sooner than in the current base case. This has minimal impact on the accrual of LYG and QALYs but nonetheless reduces the total costs of the cannabidiol+clobazam arm, as patients revert to the considerably less costly SoC AEDs sooner. The net result is a small increase in the incremental costs and incremental QALYs, with a resulting small increase to the ICER, compared to current base case. As the clinical aim is usually to maintain a patient's treatment to control their seizure frequencies, this leads to a clinically perverse scenario in which the ICER for fenfluramine vs cannabidiol+clobazam increases when treatment with cannabidiol+clobazam is assumed to be shorter. This situation, which was also observed in NICE TA614, penalises fenfluramine as the more clinically effective therapy.

(Note: the negligible discrepancy in the Total costs and QALY estimates for fenfluramine in this scenario versus in the revised base case (Tables 2 to 4) is due to the use of rounded figures for discontinuations taken from Table 30 of the CS).

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Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 10 May 2021 email: NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
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.	No links to tobacco industry. Honoraria received for educational activities from Eisai, Fidia, Lincoln and UCB pharma, not considered relevant for the current appraisal.
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this recommendation will lead to a potentially very effective drug not being available for this highly treatment refractory group of patients.
2	Regarding the committee's concern about long-term efficacy of treatment, data suggests that treatment effect can be maintained over at least a 3-year period. We appreciate that patients continuing in the open label studies are those who have had a benefit, but this is going to be the case for any drug and as clinicians, we regularly discontinue drugs if there is no benefit, or a beneficial effect is lost. Further, even if effects were to wear off after three years, we do not consider that a valid reason to withhold an effective treatment or not to use the treatment to reduce seizure and carer burden during this time and discontinue it once it is no longer effective. Additionally, 3 years of improvement would count as a long time for most in this patient group.
3	We note the committee's concern regarding where QALY gains come from and what factors contribute to them. We also note that the committee has previously appraised and approved CBD for the same indication and it is not clear to us why the committee is not using the same factors as taken into account for that treatment. Reviewing the modelling in the TA for CBD, that appears to be different to the current modelling and the committee seems to have used Markov multistate model to compare fenfluramine to CBD, when the original CBD approval was not actually based on this level of modelling. Similarly, seizure free days were not included in the CBD modelling and the criteria for continuing prescription is 30% reduction of seizure frequency. Overall, we are concerned that the level of scrutiny of data and modelling appears to be different for fenfluramine compared with that for CBD.
4	We are concerned that the committee is putting so much emphasis on whether treatment should be used with or without Stiripentol or if Stiripentol is a treatment modifier. Data supports benefit for Fenfluramine with and without concomitant use of Stiripentol and there are interactions between the drugs (resulting in higher serum levels of Fenfluramine if used with Stiripentol), is the likely reason lower dose of Fenfluramine can be used when taken in combination with Stiripentol.
5	We strongly disagree with the statement that "it is unclear if fenfluramine meets the criteria for an innovative treatment". The mode of action is different to previously used drugs and it is clear from clinical experience and trials that the same benefits have not been seen in other drugs.
6	We are concerned about the reports of valvopathies when the drug was uses in higher doses for other indications previously and would therefore recommend that cardiac monitoring (cost of echocardiogram) is included in the economic modelling.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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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.	This year, our charity, Dravet Syndrome UK, will receive some funding (unrestricted educational grant) from Zogenix to support educational projects. We also receive funding from various other pharma and non-pharma companies
Name of commentator person completing form:	[redacted]

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Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

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Comment number	Comments
1	Dravet Syndrome UK (DSUK) is very disappointed with the recommendation given in the Appraisal Consultation Document (ACD) not to recommend fenfluramine. Dravet Syndrome is a highly intractable and devastating condition, and there remains an urgent need for new treatment options. Seizure control is extremely rare with currently available treatments. This has a huge impact on quality of life, not only for the individual living with Dravet Syndrome, but also their entire family. Given this background of very poor quality of life for the majority of families and the high levels of unmet need, we urge the NICE committee to reconsider its recommendation, with particular reference to the points outlined below.
2	We feel the NICE committee hasn't fully taken into account the testimony previously submitted by DSUK in December 2020, which describes Dravet Syndrome as a spectrum disorder that is highly unpredictable (see our response to key issue 2). Not all children/adults with Dravet Syndrome respond in the same way to treatments. While fenfluramine may not work for all individuals with Dravet Syndrome, and their response to the treatment may change over time, it is important to recognise that this is to be expected due to the spectrum nature of the condition and its intractability. However, as stated in our previous submission, we have heard from many families in the UK and Europe for whom fenfluramine has worked, and some for whom it has been transformative. It is clear from the lived experience of our patient community that even small improvements in seizure control can lead to a dramatic improvement in quality of life for families. We submitted evidence to support this statement as an appendix to our submission - a survey conducted by the Dravet Syndrome European Federation (DSEF) among 118 patient caregivers in 8 European countries (including the UK). We are providing a summary of this research, which includes verbatim caregiver testimonies, as an appendix and ask that the NICE Committee read this document again in full.
3	Regarding the statement in the ACD that there is uncertainty about fenfluramine's treatment effect in adults. We feel that given expert clinician testimony and data now available from several real-world/open label studies, any exclusion of adults would be discriminatory. We refer the NICE committee to the evidence DSUK previously submitted in December 2020 (see our response to key issue 1) which describes how the adult Dravet population which has been under-recognised for many years. Historically, there is little data on adults living with Dravet Syndrome, compared to the paediatric population. Because adults are under-diagnosed, it is often a lot harder to gather data on adults. This situation should not lead to adults being disadvantaged. We urge the committee not to exclude adults living in the UK from the opportunity for better seizure control and better quality of life.

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Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

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4	Numerous other statements in the ACD (e.g., 'It is unclear if fenfluramine meets the criteria for an innovative treatment', 'The relationship between convulsive seizure frequency and mortality is not clear') are surprising to read because they do not correspond with the experience of our patient community or with what we have read and heard to date from the medical community. We are concerned that the experience and views of clinical experts have not be represented and taken into account as fully as they might be in the submissions and consultation. The anticipation for fenfluramine in the Dravet community has not been driven by the manufacturers but by grassroots experience and the excitement we have heard from the medical community involved in trials to date. We understand it is the company's responsibility to make the submission for approval of fenfluramine, but we also urge the NICE committee to take into account evidence from independent clinicians who have consistently expressed their view that fenfluramine represents a significant step change for a significant number of patients, who have not responded to currently available treatments. These patients, and their families, are desperately in need of new, effective and well-tolerated treatments for this absolutely devastating condition.

Insert extra rows as needed

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Patient perspective on the benefit of fenfluramine for the treatment of Dravet syndrome

A project of the Dravet Syndrome European Federation

Background

Fenfluramine (hydrochloride) is a potential promising new treatment for Dravet syndrome currently under regulatory review. Clinical trials with fenfluramine in this population documented treatment efficacy in terms of seizure reduction, and achieved primary endpoints, which focus on seizure-related outcomes. Seizures are very important for the daily life of patients with Dravet syndrome and their caregivers, but the disease is more complex and seizures represent only part of the disease burden. Instead, **the overall impact of the disease arises from the combination of seizures and other symptoms and comorbidities**.

The Dravet Syndrome European Federation (DSEF) is the umbrella patient organization that brings together seventeen national patient organizations across Europe. As part of our mission, we want to **bring the patient voice into regulatory decisions** using Patient Reported Outcomes and documenting the patient experience.

There are two treatments approved in Europe for the treatment of Dravet syndrome, stiripentol (Diacomit, 2007) and cannabidiol oral solution (Epidyolex, 2019). As the EMA reviews the efficacy of fenfluramine and the benefit that the medicine provides, it is important that it also considers the patient voice and the patient perspective. To facilitate this process, **we have captured structured data directly from Dravet syndrome caregivers to document the broader impacts of treatment with fenfluramine in this population**. It is our hope that these data will help the regulatory committees take into consideration the patient perspective.

Objectives

1. **Document the patient experience with fenfluramine** through an online survey to patient organization affiliated families to collect Patient Reported Outcomes and perspectives.
2. Share the survey outcomes with the EMA to **support the inclusion of the patient's perspectives within EMA benefit-risk considerations for fenfluramine**.

Methodology

1) Survey design

The survey was designed by Ana Mingorance (Scientific Advisor) and Julian Isla (Scientific Director) and reviewed by Simona Borroni (Board Member) and Silke Flege, all members of the Dravet Syndrome European Federation. All four authors analyzed the data and prepared this report for the EMA.

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 sponsor. **Instead, the focus remained on the patient experience**. It contained 13 questions, with the last one being open text. The entire survey text is attached to this letter. The data captured included demographic questions, information on previous treatments, and several aspects of the patient experience with fenfluramine.

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 was also **reviewed by a group of patient caregivers** to make sure the questions and in particular the possible answers were understandable for parents.

2) Survey distribution

The final list of questions and potential answers was then translated into 6 languages and loaded into SurveyMonkey for data collection.

The targets of the survey were **Dravet syndrome patients in Europe who have taken fenfluramine** during a clinical trial or who had access through compassionate use or open label study. Because patients with Dravet syndrome are unable to complete this type of survey, the questions and the communication was addressed to their caregivers.

The survey was only run on the European countries that had access to clinical trials or open label studies with fenfluramine: Belgium, Italy, France, Netherlands, Germany, Spain, United Kingdom. Patients from Switzerland who participated in the clinical trials in Germany were also included. Two responders indicated their current country as the US.

To ensure that the responders were Dravet syndrome caregivers while keeping the survey anonymous (and therefore not requesting any registration or verification step), the survey link was only distributed through the patient affiliation lists of the different EU national patient organizations and was not shared through social media. Caregivers were instructed to not share the link so as to preserve the communication within only verified Dravet syndrome families.

Responses were collected during 15 days (July 31 to August 14 2020). A total of 118 responses were obtained during this period, **equivalent to the size of Phase 3 studies in Dravet syndrome**.

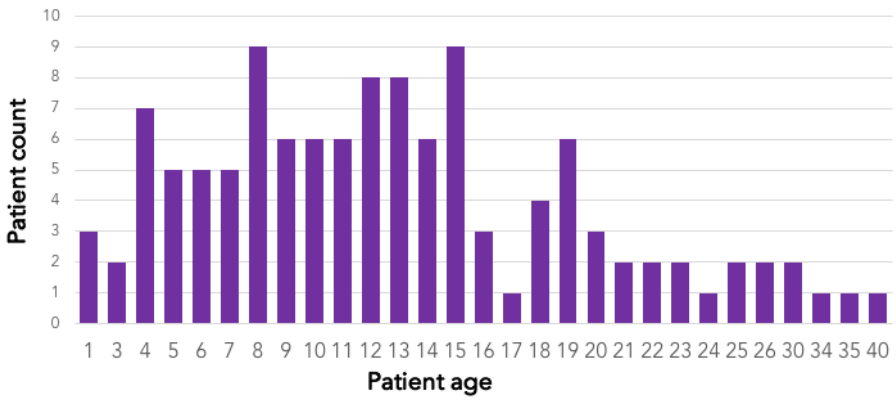
Results.

1) Demographic aspects

The survey received a total of 118 participants. 107 were complete responses, while 10 entries were partial responses not replying to all questions and 1 only replying the demographic and access to fenfluramine questions. The actual number of responses is indicated for each question of the survey throughout this report. Patient ages were 1 to 40 years old, with 29 patients being adult (18 years old and older) at the time of the survey.

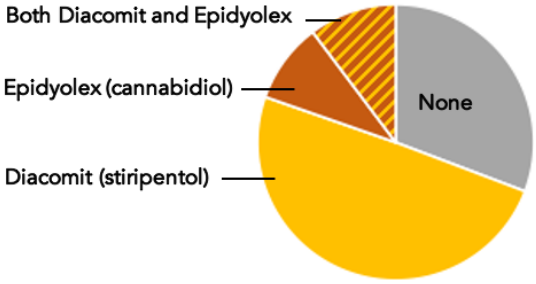
Country	Participants*	Complete responses
Germany	33	29
Italy	31	30
Netherlands	13	12
United Kingdom	12	12
Belgium	11	9
Spain	6	4
Switzerland	6	6
France	4	4
United States	2	1
Total responders	**118**	**107**

(*) Including patients with partial responses.



2) Experience with prior treatments

In line with Dravet syndrome being notoriously drug-resistant, participants had taken from 1 to 22 anti-epileptic drugs before trying fenfluramine, with 56 patients out of 117 having tried **more than 6 treatments before fenfluramine**.



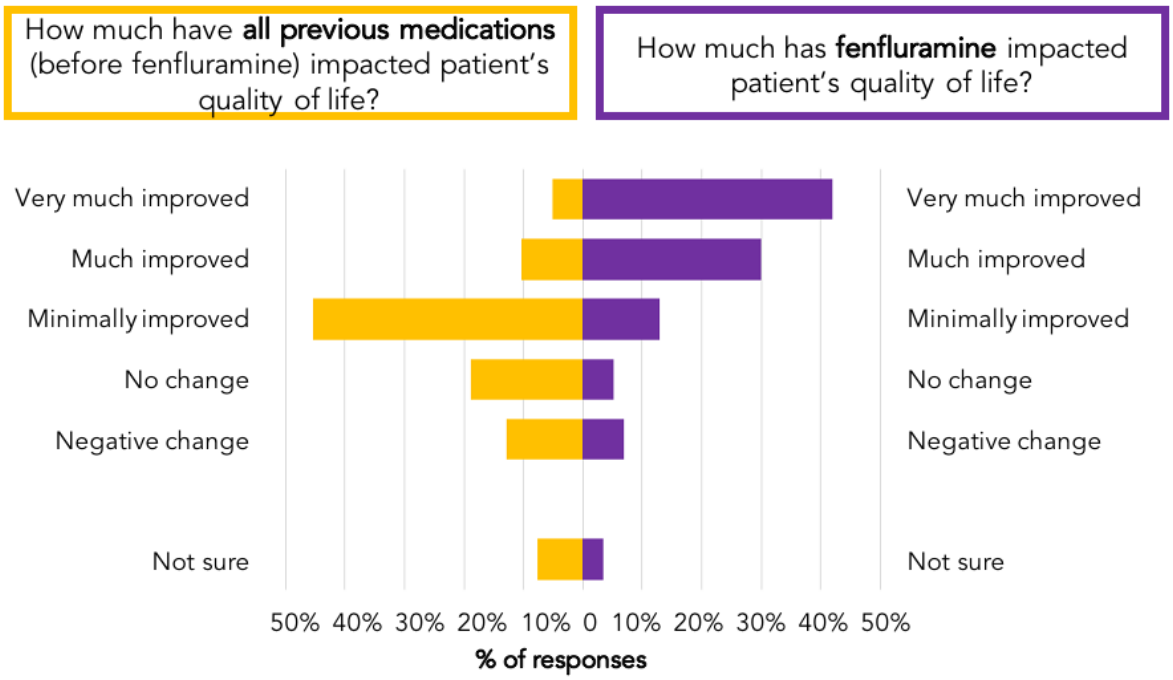
In response to whether the patient is taking or has taken the only two EMA-approved treatments for Dravet syndrome, (117 responses) 30,7% of participants reported not having tried these treatments while **69,3% had tried one or both** (49,6% only stiripentol, 9,4% only cannabidiol, and 10,3% both).

Asked to score on a 6-point scale the collective **impact of all these prior treatments** 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.

3) Experience with fenfluramine

When asked about how they had access to treatment 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 is 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 (see figure below). Again, responders were asked to report on global impact, and not only on seizure changes.



59% of the 117 participants 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%). Some caregivers reported eliminating treatment with stiripentol in order to access to treatment with fenfluramine, which was a requirement in some early studies. Participants were allowed to select multiple options.

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. This might lead families to introduce changes in their lifestyle as a response to better seizure control that can afford them to get closer to that normal life. **We asked caregivers whether a better seizure control would lead them to change their lifestyle.** Out of 107 responses, the majority reported to introduce changes in their lifestyle as a response to better seizure control to enjoy a more "normal" life at the risk of triggering some seizures:

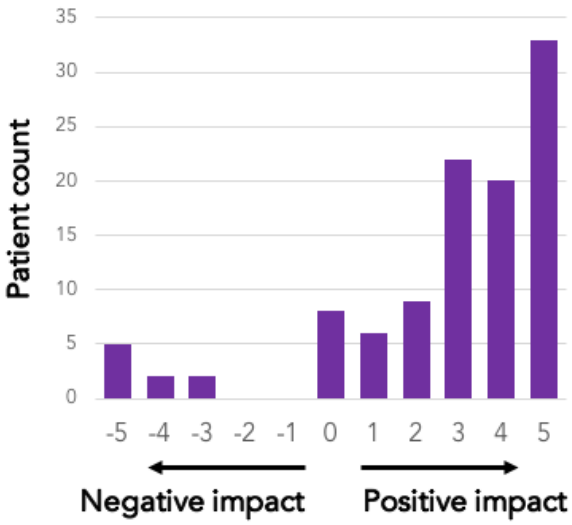
72%	"A better seizure control encourages us to enjoy a more 'normal' life, even with activities that could potentially trigger seizures"
24,3%	"Not sure. Both seizure frequency and enjoy a more normal life are equally important to us"
3,7%	"A better seizure control does not encourage us to enjoy a more 'normal' life, because we don't want to risk seizures by doing activities that could trigger them"

To explore these additional disease impacts, caregivers were asked in 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 (see table next page).

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. The questions around this one in the survey where replied by 107 participants so we estimated the percentage of patients seeing improvements in non-seizure diseases impacts relative to the number of actual responders (n=87) and the number of patients in fenfluramine or potential responders (n=107) to account for the survey inadvertently missing an option for “no other improvements or not sure”.

Improvements observed in patients with Dravet syndrome while taking fenfluramine	Total count	Percentage of those reporting improvements (n=87)	Percentage of all patients in fenfluramine (n=107)
Behavior	52	60%	49%
Overall happiness	42	48%	39%
Sleep	29	33%	27%
Autonomy	39	45%	36%
Ability to leave the house	26	30%	24%
Ability to attend school	23	26%	21%
Ability to enjoy activities such as outdoor playing and going to the beach or the pool	43	49%	40%
It improved my family's ability to travel with patient	41	47%	38%
It improved patient's opportunities for social interactions	45	52%	42%
It improved patient's cognitive skills	55	63%	51%
It improved my (parent/caregiver) capacity to work (fewer work absences)	41	47%	38%

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.



Last caregivers were asked 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 of the

testimonies received have been translated into English and are included in the next pages. Most were very positive including mentions of gained autonomy in adult patients, while some indicate no change, or even report a change to worse quality of life leading to withdrawing the medication.

While highlighting the importance of considering the impact of drug treatment in non-seizure disease aspects, we don't want to downplay the critical role that seizures play in limiting quality of life in Dravet syndrome and the resulting relief that comes with good seizure control. This is reflected in many of the testimonies attached. In the words of the parents of a 5-year-old boy with Dravet syndrome:

> *"The drug has honestly been life changing for not only him 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."*

The entire list of testimonies collected, as well as a copy of the survey, are attached to this report.

* * * * * * * *

Attachment: Caregiver testimonies of how fenfluramine has impacted the quality of life of the patient and their family (ordered by patient age, from youngest to oldest; translated into English; names redacted)

"We were able to do more activities that would have otherwise led to seizures, such as going to the pool"

"Our daughter is more alert and receptive, which means more understanding for us in everyday life"

"Our son had a lot of problems with light, pattern and stimulus-sensitive epilepsy (because of this we kept the house dark and went outside at least). **After using fenfluramine there is no more light sensitivity and the response to patterns is greatly reduced. This allows our son to play outside again, even on sunny days.** 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"

"We went swimming on vacation. We are trying to gradually send our child more hours to kindergarten so that I can work more again."

"Fenfluramine currently is one of our son's AED's that offers a level of seizure control. [Our son] has shorter and less frequent seizures that we managed at home. Prior to fenfluramine [our son] attended hospital much more frequently with longer seizures. There is an element of him getting older possibly improving his seizure control however we do think the fenfluramine has been a key factor."

"Minimally fewer seizures, otherwise more consistent quality of life."

"Better seizure control gives us the opportunity to do more things as a family: we now dare to go to the sea or to the pool. **We dare to go to a location more than fifteen minutes away from a hospital, and also abroad**, for example. We also dare to bring our son to a babysitter and call PGB, which is a must with his difficult behavior. "

"Unfortunately, fenfluramine had no effect on our daughter."

"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."

"Our main problem, apart from the frequency of seizures, is food. [Our daughter] only ate one brand of yogurt and spent long periods of eating absolutely nothing, just drinking water.

She had no strength or energy at all. Right now she is eating something better, accepting fruits, vegetables and pureed meats, so she is more active and energetic. She is having longer periods without seizures, during the first month with fenfluramine she only had 6 and none lasted more than 1 min or was convulsive, but when we eliminated topiramate her seizures got a bit out of control, although they are still short and non-convulsive they are appearing more frequently. We have barely spent two months on Fenfluramine so we have to keep adjusting doses. What amazes us and keeps us hopeful is that on a cognitive and motor level she is showing small improvements every day."

"No improvement occurred."

"**Prior to starting the drug trial my child was housebound due to photosensitivity.** We were house bound for over 4 months. He had such extreme photosensitivity that he seized at any sight of day light. This led to a very lonely existence at home with all blinds drawn to keep him safe. The first dose of the drug saw a significant reduction in photosensitivity, prolonged use and his photosensitivity has completely gone. We still have daily seizures (which we can cope with) however **our biggest achievement was that he no longer suffers the photosentive seizures that plagued him for over a year. He can go outside and enjoy everyday activities, he can play like a normal child, he is now a very happy, busy little boy who we take everywhere.** We have been to Disneyland twice, we have travelled across the country visiting all places that used to be off limits we have even had him up Ben Nevis with no issues. The drug has honestly been life changing for not only him 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."

"There is nothing I can assert at this point that we are doing differently than before."

"We do not necessarily do more, but have a slightly more 'normal' life because there are fewer attacks. **We are less tense / it feels like we don't have to be hyper alert all the time. That saves a lot of energy**. We are also less often in the hospital, which means that our daily life is less disrupted, we are more rested and can also work better. We also worry less when our child is at school."

"Seizures are well controlled, so we took a trip abroad last year."

"Difficult initial impact due to weight loss, but 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**."

"We are more flexible, as there is no longer any need for sleep breaks, around which everything was previously planned. Seizures were often sleep-bound, now seizure-free. So we can also spend the night with the grandparents. Our child takes part in life much more actively."

"**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."

"We were finally able to get out of the house with him, even in warm weather (over 25C), playground, swimming pool, vacation ..... everything is possible with fenfluramine !!! However, behaviorally and cognitively, linguistically .... no improvement!"

"**Fenfluramine did not improve our son who was 5 at the time**. But we are aware of how the disease is evolving and that a drug, taken at a different time, can be effective."

"For us initially there was a reduction in seizures even if after a few months the situation has worsened again, now we are waiting to reduce diacomit in order to get to a full dose of fenfluramine. On a general level of attention, behavior, etc. instead the improvement was evident, if before he was absent, apathetic, he did not respond to stimuli after he had a rebirth"

"Photosensitivity improved by 70%. Myoclonias decreased by 80%. Generalized crises decreased by 80%. Improved sleep. Much worse appetite. The management and the quality of life of the family have also been greatly improved"

"Seizure improvement, disappeared (apart from moments of high fever). Behavioral cognitive improvement, movement improvement, improvement in autonomy in socialization and language. Very significant overall improvement."

"Fenfluramine has had a positive impact on my son and the family in general, because **apart from not having a crisis, we can lead a much more normal life in every way**."

"Our life has completely changed. We can travel with our daughter, enjoy the summer, give her the opportunity to move without having to worry about her having a seizure. Temperatures above 25 ° no longer mean having to be afraid of a seizure, but rather looking forward to a day in the outdoor pool. Visiting friends and relatives has become a regular thing to do. The emergency medication stays at home more and more often."

"**Before fenfluramine, the playground and swimming pool would have been unthinkable** - Family life has become easier, siblings also benefit - Travel abroad is now possible - the patient is immensely happy to do activities such as splashing around in the pool or doing club sports or visiting the amusement park. None of this would have been possible before."

"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!**"

“Seizures are not as prolonged meaning no need for rescue meds to be given. Also more time between seizures going from weekly seizures to every couple of weeks.”

“It has only had drawbacks. **[Our son] stopped eating completely and only slept.** He was seriously weakened after two weeks. Therefore stopped.”

“Having fewer crises, we are able to lead a more or less "normal" life”

“**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.”

“My daughter had few seizures before fenfluramine. But now she has gotten really bad. I am very afraid. She takes a lot of medication, but not better. She gets a big seizure every 2 days. Lasts about 45 minutes. She gets over 100 tonic-clonic and absence seizures every day. I don't know what I can do.”

“The patient is sociable since we reduced the bromide. He treats his siblings better. He's slowly starting to write a little more.”

“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.”

“**Unfortunately, fenfluramine caused our child to become drowsy and completely lose strength.** This caused a sharp deterioration in quality of life”

“As we mentioned in the questionnaire, fenfluramine has so far slightly improved both the number of seizures and the quality of life. Indeed, the child has difficulty eating. His weight has remained the same for the past two years. For now, we don't see a future that can further improve with fenfluramine.”

“The introduction of Fenfluramine certainly had a positive impact on the quality of life for [our daughter], having fewer epileptic seizures, but it is much more oppositional.”

“[Our son] has improved in everything, in addition to the seizures reduced by 80%, the oppositional behavior has improved. **Our life has changed a lot, for the better**.”

“**Fenfluramine has been a game changer.** Seizures reductions is 50% and now all seizures are nocturnal. This allow us to do more activities outside without fear to seizures.”

“Unfortunately, not at all. **Our daughter was significantly sedated at the start of the study.** That changed only after reducing the dose. We could not establish any effect on the frequency of attacks.”

“The most important **benefits coming out of cannabidiol and transitioning into fenfluramine was that it improved her cognitive capacity, it stopped her stuttering and it reduced somewhat the frequency of seizures.** However it has not managed to control her seizures and when seizures now happen they are longer stop with emergency medication most of the times which was not the case before.”

“My son lost 10 kg in the short time with fenfluramine, became extremely aggressive and had behavioral problems, could barely walk, neither played nor did puzzles, etc. he no longer had any quality of life.”

“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”

“Better seizure control leads to a calmer feeling in parents if we leave him with others (babysitter, school)”

“A little less nocturnal seizures (very few daytime attacks in recent years) so less fatigue and less stress but still seizures regularly so that did not solve everything”

“On a cognitive level and much more active.”

“It greatly reduced number of seizures in our daughter due to fenfluramine, **giving us breathing space to be able to undertake activities outside the home as a family and to have social contact again**. It also contributes to our daughter's development as she can go back to school and participate in social activities due to fenfluramine intake. It also gives us confidence to hand her over to the school or a babysitter. And lastly, it also promotes our night's sleep, which before taking fenfluramine was disrupted every night due to our daughter not sleeping through and became unbearable due to the watch out for risk of a bigger attack or status.”

“Improved cognition, being more alert and ‘in the room’. My son is much happier in himself. Seizures have been cut by a half as well.”

“**Since we introduced fenfluramine we can go on vacation, travel longer (12 hours flying),** we can go to parties, play with other children, play outside longer. We can do more than 1 activity per day. The stress and the feeling of anxiety as a parent is also reduced.”

“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!"

"Greater alertness"

"Now it is easier to leave the house with the child because she is much calmer and more manageable, and also more communicative and present. **A big improvement**"

"Cognitive abilities significantly improved - myoclonus disappeared completely more attentive to the environment / more fun-loving / more on foot - that was otherwise not too strenuous"

"It is possible for us to let him sleep in the car during a trip without having a seizure. Overall he has better balance and he manages to tandem with his father. He can bathe without having a seizure. There are no more whole days of seizures and then regression in his learning. **He can enjoy life more and as a result his family too**."

"Unfortunately, fenfluramine made the situation even worse"

"It triggered more seizures than before, so the nights were restless."

"Seizures do still happen but the frequency and severity has been reduced enabling better focus and development."

"**Because the tonic-clonic seizures have decreased by 80% and only occur at night, we can let our son move much more freely at home and outside.** No longer having to stay within 1 meter of him each time in case he suddenly has a seizure and falls and gets hurt"

"We still do what we used to before, but those things no longer cause as many crises as before"

"**As a rule, we no longer need emergency medication** as the seizures stop on their own. Our daughter is much more alert and talks more. She no longer has the lack of satiety. She has lost weight. However, she has developed special preferences; she no longer likes bread and pasta. Sometimes it is also a bit problematic if she has no drive to eat herself."

"With the inclusion of fenfluramine and especially with the elimination of Diacomit, we were able to see an improvement from the cognitive point of view that allowed us to have a better social life"

"**The drug worked for a while but unfortunately the seizures have crept back up** so weaning off now sadly."

"She had no more seizures. Changed her behavior into very happy. But her body doesn't take it well."

“Our daughter can now stand without falling over, she can walk without tripping, she can sit up straight without the assistance of support cushions. She can eat by herself, drink by herself. She learns and retains information, she is engaged in play, painting, learning. She is happy and full of energy and joy and is growing and thriving. She sleeps and even dreams, she actually was laughing in her sleep a few nights ago. We can have days out as a family , we are not always tired and afraid or stressed out. **I feel like a mum again, not a caregiver**.”

“At the beginning of the study, the frequency of seizures decreased. The patient is then more active and can organize everyday life differently. There is an increase in concentration and receptivity. Regular attendance at the school was possible. Everyday family life is more relaxed, but after a while the number of seizures increased. An attempt was made to reduce the other drugs, but it was not effective and worsened the overall situation.”

“[our son] since coming on Fenfluramine from start of initial double blind trial had a very favourable reaction. We knew that [he] was on the drug during the double blind part as the change was instant. His seizures reduced month on month - and only when the first part of the trial was over we had to reduce him down and off it completely before starting again on a rising dose the seizures did come back with a vengence. **The biggest impact to taking fenfluramine was the reduction in numbers and also intensity of the tonic clonics and length. Also** a reduction in the number of doses of midazolam per month reduced. Virtually all non-convulsive and partial complex seizures vanished on fenfluramine. We have been on the drug as part of open trial now for nearly 3 years. We have no intention of bringing him off as yet as we feel the overall impact is very positive for him in many ways. He is more alert, more personality coming out , behaviours etc lol attitude stubbornness etc . we dont mind this at all as this means his true self is not being suppressed .in the last year we have seen clusters of seizures occur but the pattern has moved from one that was a recurring cycle of good week, worse week to shitty week and needing often more than 1 to 4 doses of midazalam to flip him out /reset his switch. and recovery was much longer, tiredness, lethergy etc. We still have seizures per month - TCs are reduced - depending on time of year - avg single figures some months to most 20 per month (if illness, viral, etc time of year) seizures in general are short lived - under 30 secs (less intense) and recovery is much better. very rarely does he need midazolam and only if the tonic clonic (during sleep) is more intense he may go into a 2nd part) post ictal /seizure complex partial ?? where he struggles to come down from it. We did reduce zonisamide because we felt it was a good time to try while in a better seizure control this was in 2019 and the primary reason for this was because of the fact he was on 3 aeds of which 2 were appetite suppressent. He was full dose of fenfluramine as per the trial restriction and on a dose of 6ml bd of zonisamide and 300 ml bd of epilim chromospheres. this has been his combo for the last 3 years. **diet and weight has been a small concern - and we have been referred a couple times for a peg assessment.** (when he has had clusters he tends to go off food, tiredness, lethargy and feeling very off) this impacts his ability to attend school) this in turn has caused problems with school and their ability to get food into him. we have this year been under supervision of dietician and using supplements Paedisure etc we add these into his diet and he eats really well and has put weight on again. and the feeling is that a peg is not valid option or needed as yet. while he is eating well and able to maintain weight and also make small increases. he is stunted anyway (previous trials he has been on include the ketogenic diet (5 years with Alderhey) and also has been through epidiolex trial before starting Fenfluramine. Of all the trials this one

has had the most impact in a favorable and longer lasting. We would highly recommend any Dravet family to consider this drug as part of their regime if they are struggling with high levels of seizure activity."

"Fewer seizures means being more awake and cognitively aware, both for patient and for parents/care givers. In turn this means a better quality of life all round."

"**Her drastic reduction of crisis has made her general condition improve dramatically, improving her quality of life and that of the whole family.** The patient convulsed every night, and in the morning she was so tired that on many occasions she could not lead a normal life. Her general condition was so bad that our lives were affected by the anguish that seeing her like this produced us, although we tried to lead a life as "normal" as possible."

"The only way to escape a bad moment is to keep walking until you find another moment. Fenfluramine was our moment"

"Seizure situation is a little better, however extreme tiredness and loss of appetite is a big problem."

"**Had no effect but no side effects either**"

"Due to a significant decrease in seizures, illness is somewhat more in the background. sometimes no attacks for months, which gives confidence. - Fenfluramine allows more action, before the start of fenfluramine, any exertion / excitement meant having a seizure."

"Behavior / opposition improved a lot more serenity in making him participate in activities with peers having night crises and every 2 or three months"

"Since due to the coronavirus situation our daughter does not go to school, the improvement in terms of participation in everyday life cannot really be assessed. A clear improvement is that the seizure frequency has decreased somewhat and that recovers again more quickly after the seizures. i.e. can probably go back to school after just one day and not need 3 days to be ok again as before. As part of the discontinuation of Diacomit and the introduction of fenfluramine, our daughter had a hormonal and physical development boost, and her period started promptly."

"We can move more freely thanks to better seizure control, **and my daughter can now be a little more independently by doing small household chores on her own.** Although there is no change in the permanent monitoring obligation, it is more relaxed (risk reduced from up to 50 to currently around 8-12 generalized tonic-clonic seizures per month)."

"Thanks to fenfluramine, the tonic-clonic clusters converge less quickly and there are fewer seizures per cluster. This improves the well-being of our child, he is fit faster and can go to school more often. Less hospital admissions. Less stress for us as parents"

Testimonies about adult patients:

“**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.”

“The better seizure control ensures that our daughter can gain more autonomy. For example, she can now stay home alone for half an hour or go to the physiotherapist independently. **This gives her a more positive self-image** so that she has less angry moods.”

“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.”

“**Return to normal after a descent into hell.** He holds himself better posture, he expresses his desires better. Hold on better. And he learns”

“Number of attacks halved, autonomic dysfunction significantly less, much clearer ..... more good periods so that more outings can be enjoyed together”

“No change”

“**The 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. Going to the pool, to the sea or anywhere else and being calmed is the most beautiful feeling that exists”

“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.”

“”**So far Fenfluramine has worked extremely well and has given our family much needed respite from the fear of impending doom of seizures**! Quality of life has improved in that we have been more relaxed and felt a little safer and have been able to sleep easier. Holidays and outdoor activities have been made possible. Cognition has improved. Happiest we’ve been!

“Speaks a lot more, is more active in the daily structure, more independent, still a fraction of the attacks than before fenfluramine”

“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”

“The patient is more independent, less aggressive. And in general more cheerful and lively.”

“**Thanks to greatly reduced attacks, she can do more** and she is not nearly as tired!”

“I don’t have to constantly think about him when he is not with me”

“The seizure frequency is currently still high. The first 10 weeks after starting it were great. **Although the patient had absolutely no more seizures, he developed a form of psychosis** (extreme sleep disorder and extreme "tunnel behavior"). The only subject he was interested in was shoes. He could no longer eat, drink, sleep, have a conversation, he could no longer perceive anything. His thoughts always revolved around shoes. The treatment with fenfluramine therefore had to be briefly interrupted. After the interruption, fenfluramine was started again at the absolutely lowest dose. The dosage level today is still extremely low and therefore may not be effective. But the fear of a new mental disorder is still great. The patient lives in a residential group and the management and support team there is rather negative about fenfluramine. However, our goal is to greatly reduce the frequency of the seizures without negative effects on psyche and behavior.”

“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.”

“In general, the important reduction in epileptic seizures has allowed the whole family to live daily life with more serenity and the patient to acquire greater self-awareness. For example, it has greatly improved the aspect of communication, even through telephone messages that it was previously unable to compose. Furthermore, **the current situation opens up new perspectives on the improvement of the patient's autonomy**.”

“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. We hope it will be approved soon.”

“The significant reduction of crises allows to leave **much more freedom of movement and therefore to improve autonomy**. We experience traveling outside the home with much more serenity.”

“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'."

"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 !!!"

"The first 6.5 years he had constant seizures including many statuses. He was always drowsy, could not make himself heard, could not stand on his feet .... **The day the seizures were under control started his life** (now 28 years ago). Despite some limitations, we now lead an ordinary life. We travel a lot (within Europe but also intercontinental) he goes to daytime activities, does a lot of sports (cycling, netball, swimming, indoor football), sings in an inclusive choir, goes to the drawing academy, goes to camp ..... All activities that we could not dream of before" *[Note: patient in Belgium, now 35 years old, on treatment with fenfuramine for 28 years]*

"He always has crises but much more manageable and therefore also a faster recovery"

NICE National Institute for Health and Care Excellence

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 10 May 2021 email: NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Epilepsy Action**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

Fenfluramine for treating seizures associated with Dravet syndrome [ID1109]

Consultation on the appraisal consultation document – deadline for comments 5pm on Monday 10 May 2021 email: NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Epilepsy Action is concerned that this recommendation may imply that fenfluramine is not an effective add-on therapy for treating seizures associated with Dravet syndrome despite available clinical evidence and lived experience to the contrary. Concerns raised in the appraisal consultation document (ACD) around economic modelling are valid and need to be addressed. However, these technicalities should be assessed against the clinical benefits of the proposed treatment and the severe impact of this severe condition. It is our view that the impact of uncertainties and limitations in both the company modelling and that of the ERG on cost-effective considerations should not prevent an effective and much needed additional add-on treatment option for seizures associated with Dravet from being recommended. We would encourage the company and NICE to work together at pace to address the issues highlighted in the ACD for an informed decision to be taken on the basis of rigorous data and evidence.
2	While due consideration should be given to whether treatment effect will stay the same in the long term it is not uncommon for antiepileptic drugs to reduce in effectiveness over time for some patients. There is some evidence that currently recommended add-on treatments for seizures associated with Dravet syndrome such as cannabidiol can reduce in effectiveness in the long term. Uncertainties around longer-term treatment effect should be compared against the severe and often life limiting nature of Dravet syndrome. If a treatment option can provide a reduction in frequency of convulsive seizures even for a short time the associated quality of life benefits for the patient and others involved with their care are likely to be significant.
3	Epilepsy Action is concerned about the proposed date for review of the treatment and would recommend a process of iterative review as and when modelling issues have been addressed or more high-quality data is made available. Given that the decision not to recommend at this stage is largely based on economic modelling considerations rather than concerns around safety and efficacy the proposed three-year review period is overly restrictive. We would encourage NICE to engage with the company and other experts to address the issues identified in the ACD as a matter of urgency and seek a review of the appraisal as soon as possible.
4	Given the intractable nature of Dravet syndrome, a treatment such as fenfluramine that offers significant benefits for some in terms of reductions in convulsive seizures and associated improvements in quality of life should be recognised as an innovative treatment. Epilepsy Action would echo the comments of the clinical expert in the ACD and encourage NICE to appraise fenfluramine as an “innovative treatment” offering a potential step change in the treatment of Dravet syndrome.
5	
6	

Insert extra rows as needed

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NICE National Institute for Health and Care Excellence

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures
Name of commentator person completing form:	Professor J Helen Cross

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am concerned that this recommendation may deny individuals with Dravet syndrome a step change state of the art treatment, for which there is evidence for significant clinical efficacy, in a condition where current standard treatments offer little prospect for seizure control
2	Section 3.3 Stiripentol is usually added to valproate and then ultimately a small dose of clobazam added, as if stiripentol is added to maximal doses of valproate and clobazam there will be drowsiness. The dose of clobazam needs to be individually titrated
3	Section 3.8 There is comment about a significant benefit in Quality of Life being seen with fenfluramine over placebo in study 1, but the difference not reaching significance in study 1504, albeit over 14 weeks. The company submission (B1.4.2) highlights the need for weighting of Quality of Life to prevent underestimation of the true impact of convulsive seizures
4	Section 3.9 I challenge that although it is usual for efficacy to be quoted vs placebo, rather than as a difference from placebo and therefore has led to concern about interpretation of the inclusion of placebo effect, the difference in effect relative to placebo is still very significant, a degree of effect not seen in any other clinical trials of anti seizure medication
5	Section 3.10 The document states that it is unclear as to whether stiripentol is an effect modifier of fenfluramine. Previous pharmacokinetic studies suggested the need for a lower dose of fenfluramine in view of the interaction with stiripentol (due to inhibition of the CYP 450 system in the liver), and consequent effect on fenfluramine metabolism. I would challenge there is any evidence of a modifier effect; the dose in combination with stiripentol was lower, but still showed significant benefit.
6	Section 3.11 I would suggest that any 'honeymoon' effect with a waning of effect of fenfluramine over time would be seen sooner than 3 years – at less than a year. I acknowledge the concern about lack of data on 'long term' effect, but minimal drop out was seen over a 3 year period suggesting good retention and maintenance of benefit
7	Section 3.18 It is stated that it is incorrect to assume that patients stopping treatment will return to the baseline seizure frequency rather than that seen on placebo, the placebo effect not taken into consideration. Where individuals are taken off the treatment it would be presumed in the majority to be lack of effect- in only a very small number this was due to poor tolerability.
8	Section 3.24 Non convulsive seizures; there is no question that these remain difficult to count securely and therefore numbers are less reliable. However, on the data submission there is a reduction in nonconvulsive seizures (and total seizures) compared to placebo. It is therefore less certain it would be detrimental rather than supportive to include the data in comparison with that of cannabidiol.
9	There is a concern about the high level of uncertainty in the relationship between convulsive seizure frequency and mortality and the assumption that reducing the frequency of seizures prolongs life. The mortality rate and rate of Sudden Unexpected Death in Epilepsy (SUDEP) in Dravet syndrome is high; the highest association is with ongoing convulsive seizures, so an assumption that reduction of convulsive seizures will reduce the risk of SUDEP is not inappropriate. *academic / commercial in confidence information removed* 'This said another marker of success of treatment would be reduction of hospital admissions (for prolonged seizures or exacerbation of seizure frequency).
10	It appears that the main concern within this report is one of uncertainties about the modelling put forward for cost effectiveness of the use of fenfluramine. I hope that the data required to amend this can be reviewed. There appears little question about the efficacy of fenfluramine in Dravet syndrome. I would like to emphasise that lack of access to fenfluramine for the Dravet population in the UK may be seen as discriminatory against this population when considering standard of care now acknowledged worldwide.

Insert extra rows as needed

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	None
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

See below for animal data

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

See below for my view of this statement

Are the recommendations sound and a suitable basis for guidance to the NHS?

I would argue not, which I mention in my statement

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not to my reading

Comments

NICE have determined that fenfluramine not be recommended for the management of Dravet syndrome: I disagree with this, and would urge NICE to review the information they have used.

The most relevant line of evidence I would submit that the committee should review is from figure 2 in Brunklaus, et al 'Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome' Brain 2012: 135; 2329-2336 which depicts the inexorable progression of this disorder. No disease-modifying agents exist to manage this process, but it does seem, to me, that fenfluramine might be considered to be an useful agent in modifying this process. First, it does have a novel mechanism (and in this I disagree with section 3.31), as it works via agonism of 5-HT(1D) and 5-HT(2C) receptors, as well as its blockade of sigma1 receptors. I would argue that this is distinct from other anti-convulsant drug activities, and I would submit that this makes it an attractive agent to use in concert with other (more conventional) agents in the management of this disorder (Sourbron, et al 'Pharmacological Analysis of the Anti-epileptic Mechanisms of Fenfluramine in scn1a Mutant Zebrafish' Front Pharmacol 2017: 8; 191 1-13). Second, there is a suggestion that fenfluramine might contribute to a disease-modifying activity through the restoration of neuronal cytoarchitecture, which might alter the trajectory I mentioned earlier (Tiraboschi, et al 'New insights into the early

mechanisms of epileptogenesis in a zebrafish model of Dravet syndrome' Epilepsia 2020: 61; 549-560)
I would appreciate your considering these findings, and their potential, when reconsidering your decision (it has also rendered the children with Dravet syndrome whom I manage, significantly seizure-free in comparison to their seizure burden prior to starting fenfluramine).

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fenfluramine for treating Dravet syndrome

Second response to company's ACD comments (December 2021)

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Correspondence to	Robert Wolff, Kleijnen Systematic Reviews Ltd. Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	21/12/2021

Following the Appraisal Committee (AC) meeting, discussions on 4th March 2021 and the resulting preliminary negative recommendation for the use of fenfluramine in the treatment of seizures associated with Dravet syndrome, the company submitted additional information in May 2021. In response to the ERG's response to this additional information, the company again submitted additional information (in agreement with the ERG and NICE) in November 2021. An updated model was submitted that incorporated several changes in response to the ACD. See below for the ERG comments on the submission of November 2021.

However, the ERG would like to note that there are some outstanding issues that have not been addressed by the company (as detailed below).

Clinical evidence

Preliminary recommendations

The ERG has no specific comments on the points made by the company regarding the ACD.

Effectiveness of fenfluramine compared to cannabidiol plus clobazam

The ERG refers to sections 4.2.5 and 4.4 of the ERG report.

Indirect treatment comparison – request for additional analysis using absolute change from baseline in seizure frequency

The ERG refers to section 4.4 of the ERG report.

Clarification of the effect of stiripentol as a treatment modifier

The ERG refers to section 5.2.3 of the ERG report.

Innovation

The ERG has no specific comments on this point which relates to the ACD.

Cost effectiveness evidence

Overall, the ERG considers that the original ERG report and accompanying (and submitted) ERG model files are not fully considered by the company, as reflected in the ACD responses. This is particularly worrisome given the committee's conclusion *"that the company should explore the ERG's concerns and clearly present and explain how it addresses those validity issues in its model"*.

Long-term effectiveness data for fenfluramine

The ACD stated that *"long-term treatment effect of fenfluramine while on treatment remains uncertain"*, also highlighting that there are no data beyond 3 years regarding the treatment effects of fenfluramine. However, in the ACD response the company states that *"there is little uncertainty in the long-term effectiveness of fenfluramine, and little risk that any residual uncertainty in the long-term effectiveness of fenfluramine biases the economic model"*. According to the ERG, the company did not provide compelling arguments and/or evidence to support this statement. Moreover, the arguments provided in section 5.2.6 of the ERG report regarding long-term effectiveness are still applicable.

In addition, in the ACD response the company stated *"the model implements treatment discontinuation rates observed in the open-label extension study, which includes discontinuations for all reasons, including loss of efficacy, over the model lifetime. This ensures only those with sustained clinical benefit*

are maintained on treatment in the long-term". Thus, the company assumes that treatment waning is fully captured through the discontinuation probabilities applied in the model (which are assumed treatment-dependent and constant over time post-maintenance). This assumes 1) that patients would immediately discontinue treatment after waning of treatment effect/loss of relative effectiveness; 2) that the post-maintenance discontinuation probabilities reflect long-term treatment waning. The implication of these assumptions is that the discontinuation probabilities and thus treatment waning would be more favourable [redacted] (see ERG report Table 5.10). The plausibility of these assumptions and thus the modelling of long-term treatment effectiveness, including treatment waning, are unclear to the ERG.

Proposed discontinuation criteria (stopping rules) for fenfluramine

In the ACD, the committee states that stopping rules at 6 months and every 6 months thereafter would be appropriate. The company agrees that it is appropriate to assess response to treatment every 6 months and stop fenfluramine if it is not effective. However, as also stated by the company, the economic model does not implement subsequent 6-month stopping rules. The company assumes that the discontinuation due to these subsequent stopping rules is reflected in the model by the ongoing discontinuation probabilities (see ERG report Table 5.10). The plausibility of this assumption is unclear to the ERG. The company did perform scenario analyses of alternative stopping rules: 40% stopping rule and 50% stopping rule at 6 months resulting in lower ICERs (£26,436 and £22,474 per QALY gained). However, both scenarios are not necessarily comparable to a situation in which stopping rules at 6 months and every 6 months thereafter are implemented.

Applicability of fenfluramine in all patients with Dravet syndrome

The committee concluded that the evidence in children and young people with Dravet syndrome is generalisable to adults in absolute terms, and the relative treatment effect is likely to be similar. However, given the lack of evidence on fenfluramine's treatment effect in adults, uncertainty remains. The company acknowledges that the committee agrees that the evidence from the trials is applicable to adults.

Model validity issues

The company helpfully submitted an adaptable model in which switches were included in order to reproduce the original CS base-case results using the newly submitted model file. While the ERG acknowledges that this is a substantial improvement, the adaptable model does not include the possibility to evaluate each scenario within the same model. The use of different model versions for each scenario analysis, instead of one adaptable model file (as is commonly done) hinders the validation of the scenarios submitted by the company.

Additionally, there were some remaining concerns about the validity of model given that the prior issues related to the validity of the model as highlighted in the ERG report that have now been addressed by the company:

1) *It is possible for individuals to improve both in terms of convulsive seizure frequency and convulsive seizure-free days after treatment discontinuation (ERG report section 5.2.2 and Figure 5.2 – resolved in ERG base-case)*; In the ACD response, the company states "we would expect some natural variation in convulsive seizures episodes (and therefore seizure-free days) for patients at 'baseline', 'on-treatment' and following 'treatment discontinuation". Hence, patients in the model can go on to have fewer convulsive seizures and more convulsive seizure-

free days after discontinuation. The ERG agrees that patients might potentially improve after discontinuation due to natural variation, however the degree of improvement after discontinuation, as illustrated in figure 5.2 of the original ERG report, might be larger than expected based on natural variation. This is particularly concerning given the committee discussion for TA614 where it was mentioned that "*the model generates more favourable results for patients that stop cannabidiol than would be expected*". Hence this issue remains unresolved.

2) *Patient profiles generated did contain seemingly inconsistent/ implausible patient profiles that could not be explored by the ERG (ERG report section 5.2.3 – unresolved)*; In its revised base-case the company has fixed the error regarding the number of seizures and seizure days in the 10-year bootstrapped data relating to the 131st 28-day cycle in line with the ERG. Furthermore, the company provided addition validation based on the trial data to validate a seemingly implausible peak for patients with zero convulsive seizure-free days that seemed to represent a cluster of outlier patients in terms of convulsive seizures. The ERG therefore considers this issue to be resolved.
3) *Several issues in the model that impacted usability and possibly threatened the internal validity and transparency of the model which included random draws that were not similar for both treatments, causing a difference in for example overall survival solely related to different random draws unrelated to any efficacy estimates in the model (ERG report section 6.4 – unresolved)*; in the ACD response, the company stated that random draws are not causing a difference in mortality or other outputs.

Lastly, one minor issue that was labelled by the ERG as fixing error was not addressed by the company in its revised base-case. As mentioned in the ERG report, 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. In the "Appendix to ACD response for ID1109" (updated version from 1st December 2021), the company did provide a scenario analysis in which the discontinuation probabilities for cannabidiol+ clobazam during the trial titration and maintenance phases were set equal to those for fenfluramine, with probabilities as reported in Table 30 of the CS. This analysis resulted in an increased ICER of £34,291 per QALY gained (compared to £31,841 in the company's revised base-case).

Overall, the ERG believes the model results are valid. However, one should keep in mind that the revised base-case (and corresponding scenario analyses) from the company do not include the change in discontinuation probabilities.

Adjusting for placebo effects

The company very helpfully provided a MS Excel file with the disaggregated results for the adjustment made to the company base-case *"revert to placebo at discontinuation"*. However, it remains unclear how the implementation differs exactly from the ERG's implementation of this adjustment (see original ERG report and the accompanying model files).

Proportionality between convulsive seizure frequency and convulsive seizure days

The company amended the proportionality between change in CSF and change in seizure days by using [redacted] times the reduction in convulsive seizure frequency. It is unclear how this value was exactly

derived. For example, in their response, the company refers to Figure 1 of the "*Appendix to ACD response"*. This Figure presents the output of a regression analysis of change in convulsive seizure frequency vs. change in days with seizures based on combined data from Study 1 and Study 1504. However, it is unclear whether data from all fenfluramine dosages as well as the placebo arms were used. It is also unclear which other regression functions were tested and whether the presented regression function had the best fit to the data. The ERG would have preferred to also see the relevant estimates stratified by trial(s) as well as treatment in order to judge to plausibility of the company's revised estimate.

In the ERG report, the ERG emphasised that it was deemed unrealistic that the company assumed the same percentage reduction for convulsive seizure days as was estimated, based on the NMA, for convulsive seizure frequency, i.e. % reduction from baseline in seizure days cannot be assumed to be the same as % reduction from baseline in convulsive seizure frequency. The ERG acknowledges that the numbers presented in CS Table 10 which were used to derive an alternative relationship by the ERG were not optimal to provide an estimate of the correct relationship. However, using data from the CSR, the ERG was able to provide a better estimate (see Table 1 below). This would result in a markedly smaller relationship of [redacted] for fenfluramine 0.7 mg/kg instead of [redacted]. Moreover, this highlights that the proportionality might be treatment dependent. This supports the point made in the ERG report (section 5.2.6) that assuming treatment independent proportionality probably favours 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. This is particularly likely 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). Similarly, the assumed proportionality % might be higher for placebo than for fenfluramine and thus assuming treatment independent proportionality probably favours fenfluramine when compared with SoC as well.

Given the above, the ERG would embrace the committee's suggestions (in the ACD) to avoid the problem of determining the most appropriate relationship by basing the model on convulsive seizure frequency only (rather than including convulsive-seizure-free days). It is not possible to determine to what extent results based on a model using seizure frequency would differ from the current model. However, in the current model, results assuming a relationship of [redacted] or [redacted] are only marginally different (£34,291 per QALY gained when assuming [redacted] and £36,465 per QALY gained when assuming [redacted]).

Table 1: Combining data from the CSR data and CS table 10 to consider the proportionality between convulsive seizure frequency and convulsive seizure days

	Seizure-free days			Seizure days (28-SFDs)		
	Placebo	**FFA 0.2 mg/kg**	**FFA 0.7 mg/kg**	**Placebo**	**FFA 0.2 mg/kg**	**FFA 0.7 mg/kg**
baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% difference from baseline in SFDs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Seizure-free days			Seizure days (28-SFDs)		
	Placebo	**FFA 0.2 mg/kg**	**FFA 0.7 mg/kg**	**Placebo**	**FFA 0.2 mg/kg**	**FFA 0.7 mg/kg**
% difference from baseline CSF (source: table 10 CS)				[redacted]	[redacted]	[redacted]
% difference from baseline in SFD/% difference from baseline in CSF				[redacted]	[redacted]	[redacted]

Relationship between convulsive seizures and mortality applied in the model

The company did not provide compelling arguments to change the ERG's view on this issue. Therefore, the arguments provided in the ERG report (section 5.2.6) and the ERG preference to remove the link between convulsive seizures and mortality are still applicable.

Non-convulsive seizures

The company did not provide compelling arguments to change the ERG's view on this issue. Therefore, the arguments provided in the ERG report (section 5.2.6) and the ERG statement that excluding non-convulsive seizures in the economic model not necessarily a conservative assumption are still applicable. The impact on the ICER of this assumption is unclear.

Adverse events applied in the model

As stated in the ACD, the ERG noted that the impact of adverse events and additional monitoring were not reflected in event costs or corresponding disutilities. The committee concluded that those should be accounted for in the model. As stated in the ERG report, the main concern of the ERG relates to not explicitly including adverse events into the economic model, despite Study 1 reporting 12.5% of patients with adverse events leading to discontinuation. This was not adjusted by the company. Although the exact impact of this assumption is unclear, it is likely to have a minor impact on the cost-effectiveness results.

Carer utility applied in the model

In their response to ACD the company mentions that, regarding caregivers QALYs, the approach suggested by the ERG to implement disutilities in line with the approach taken in NICE TA614 would *"irrationally penalise a therapy for being highly effective in reducing seizure frequency"*. This statement is based on an incorrect interpretation of the ERG's implementation by the company and the example provided by the company (in an additional appendix) is flawed. Hence, as mentioned in the ACD, which states that *"incorporating carers' utilities in the model is appropriate but overestimated by the company"*, the ERG acknowledges that this issue is still unresolved. Moreover, the implementation of the ERG approach (incorporated in the model files submitted with the ERG report) is to a large degree consistent with TA614. Additionally, the company provided a scenario analysis in which carer utilities were retained in the model once the patient dies. In this scenario, the company retained a carer utility equal to lowest quality of life that the carer experienced while the patient was alive. This scenario resulted in an ICER of £45,247 per QALY gained. The company notes that this approach favours the least effective therapies over a prolonged time horizon. The ERG believes this is debatable, particularly

assuming the carer utility to be equal to the lowest quality of life that the carer experienced, increasing this carer utility is not implausible and thus it potentially favours the most effective therapies. Moreover, the ERG would like to emphasize that the company's base-case approach probably favours the most effective therapies (i.e. given the additional "penalty" of losing the full carer utilities when a patient dies) and probably reflects, according to the ACM, "implausible assumptions for carers' utilities".

Conservatism in our approach to modelling

As discussed above and highlighted in more detail in the ERG report, the statement that the company's base-case is conservative is not applicable to all aspects of the economic model.

Other ERG comments

Although the company referred to NICE TA614 for several methodological assumptions, a cross-validation to that appraisal when looking at estimated outcomes of both models is lacking. When comparing total costs of cannabidiol in NICE TA614 to the total costs for cannabidiol as estimated in the CS a large discrepancy can be observed. 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. 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 was estimated for the current appraisal (see also section 6.4 of the ERG report for further details). 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 (as mentioned in the original ERG report) that it cannot be certain that the costs and QALY gains associated with cannabidiol are in line with TA614.

Updates to the company's base case following the ACD

See below an overview of the company's adjustments along with ERG comments.

Table 2. Updates to the company's base case following the ACD (source company submission)

#	Company update	ACD Response	ERG comment
1	Corrected outputs for FFA strategy	NA (company initiated)	The company corrected an error in the original base-case regarding reporting errors in the FFA strategy (the total cost calculation for the FFA strategy had a rounding error). Minor impact on ICER.
2	Corrected outputs for comorbidities	NA (company initiated)	The company corrected an error in the original base-case regarding co-morbidities ("minor error in the specification of co-morbidities in the model which had not been updated with data from the FFA registration studies"). This change entailed the implementation of a different distribution of motor impairments in the base-case analysis. Instead of assuming 30% ataxia, 20% severe motor issues, and 50% no issues; the following was implemented: 43.2% ataxia; 3.8% severe motor issues, and 52.9% no issues. It is not fully clear to the ERG how these estimates were derived.

#	Company update	ACD Response	ERG comment
			Minor impact on ICER.
3	Cycle 131 correction	NA (highlighted in ERG report)	This scenario changes the last cycle of the data sets. In the Seizures and Seizuredays variable, the last cycle (131) is replaced with the preceding cycle. This change is consistent with the preferences of the ERG.
4	Patients revert to placebo at discontinuation	3.18	Upon discontinuing their index intervention (existing SoC [placebo effect], FFA or CBD), patients receive a seizure profile equivalent to their "placebo effect", rather than reverting patients back to their baseline seizure profile as previously implemented in the original CS base case. This change is consistent with the preferences of the committee according to the ACD and the ERG.
5	No change in seizures at adulthood	3.12	Patients' seizure frequency remains constant throughout life. This change is consistent with the preferences of the committee according to the ACD and the ERG.
6	Amendment to proportionality between change in CSF and change in seizure days	3.21	The reduction in convulsive seizure days is [redacted] times the reduction in convulsive seizure frequency (based on regression model provided in Figure 1), rather than a 1:1 relationship used in the original base case. Although the ERG welcomes the revision of this assumption, the ERG is certain regarding the implemented strength of this assumption. It is also not fully clear how the [redacted] was derived (see section "Proportionality between convulsive seizure frequency and convulsive seizure days"). In addition, the ERG would have preferred the company to remove convulsive seizure-free days from the model in line with the ACD which stated that "basing the model on convulsive seizure frequency rather than convulsive-seizure-free days would avoid the problem of determining the most appropriate relationship between them.". However, the ERG acknowledges that the currently used relationship is probably a better reflection of reality compared to the original CS base-case which assumed a 1:1 relationship.

Additional ERG analyses

The ERG provided a scenario analysis in an attempt to explore the impact of a different relationship between the % reduction from baseline in seizure days and the % reduction from baseline in convulsive seizure frequency ([redacted] instead of [redacted]; see Table 1). It should be emphasized that this different relationship was implemented in the model in which the discontinuation probabilities for cannabidiol+ clobazam during the trial titration and maintenance phases were set equal to those for fenfluramine (as reported in Table 30 of the CS). This assumption is in line with the original ERG base-case.

This provides more insight in the impact of this assumption on the resulting cost-effectiveness estimates. Other analyses were not performed given that implementing alternative scenarios is particularly challenging and time consuming due the opaqueness of the economic model. This hampered the ERG's ability to thoroughly validate the model and explore some assumptions within the model.

The additional scenario provided by the ERG resulted in an increase of the ICER from £31,841 per QALY gained in the revised company base-case (Table 3) to £36,465 per QALY gained (Table 4). These ICERs, however, should be seen in light of the above mentioned comments.

Table 3. Company base-case after ACD (source company submission)

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Cannabidiol +clobazam	£227,384	17.92			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£31,841

Table 4. Company base-case after ACD + ERG scenario exploring the impact of an alternative relationship between the % reduction from baseline in seizure days and the % reduction from baseline in convulsive seizure frequency (0.584 instead of 0.81464)

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Cannabidiol +clobazam	£224,010	17.82			
Fenfluramine	[redacted]	[redacted]	[redacted]	[redacted]	£36,465

Conclusion

Although the company did implement some changes in accordance with the ACD, there remains uncertainty related to the estimated cost effectiveness (as highlighted above).