NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cannabidiol with clobazam for treating seizures associated with Dravet syndrome [ID1211]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cannabidiol with clobazam for treating seizures associated with Dravet syndrome [ID1211]

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.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>1</td><td>Consultee (company)</td><td>GW Pharma</td><td>
Clinical-effectiveness evidence
<table>
<tr><th>Committee Conclusion(s) from ACD</th></tr>
<tr><td>3.4 The committee has not seen data to assess whether the patients in the clinical trials reflect those who would have cannabidiol in the NHS.
The company’s submission included the baseline characteristics of the full trial population, but not the baseline characteristics of the subgroup that had cannabidiol with clobazam. Therefore, the committee concluded that it was unable to determine whether this subgroup reflected patients with Dravet syndrome who would have cannabidiol in the NHS.</td></tr>
</table>
The baseline characteristics from the GWPCARE2 and GWPCARE1 trials for patients who were taking clobazam at baseline (the ‘on-clobazam’ group) are reproduced in the tables below.
The company has discussed these baseline characteristics in interviews with UK clinical experts, who have confirmed that the on-clobazam patient population baseline characteristics are representative of patients with DS in their clinical practice and in the UK NHS clinical setting in general.
Baseline Characteristics for patients in the on-clobazam subgroup (GWPCARE2):
<table>
<tr><th rowspan="2">Baseline characteristic</th><th colspan="3">In conjunction with clobazam</th></tr>
<tr><th>CBD 10 mg/kg/day</th><th>CBD 20 mg/kg/day</th><th>Placebo</th></tr>
<tr><td>Number randomised</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Age, mean (SD)</td><td>[redacted]
Range [redacted]</td><td>[redacted]
Range [redacted]</td><td>[redacted]
Range [redacted]</td></tr>
<tr><td>Gender</td><td>[redacted] male
female</td><td>[redacted] male
female</td><td>[redacted] male
female</td></tr>
<tr><td>Baseline total seizure frequency per 28 days: median (range)</td><td>Total [redacted]</td><td>Total [redacted]</td><td>Total [redacted]</td></tr>
<tr><td>Baseline convulsive seizure frequency per 28 days: median (range)</td><td>Convulsive [redacted]</td><td>Convulsive [redacted]</td><td>Convulsive [redacted]</td></tr>
</table>
</td><td>Thank you for your comments.

Comments noted.

The committee concluded that the patients in the clinical trials reflected those who would have treatment in the NHS. Please see section 3.4 of the final appraisal document.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Prior AED treatments</td><td>Median 4
Range 0 to 12</td><td>Median 4
Range 1 to 11</td><td>Median 4
Range 0 to 9</td></tr>
<tr><td>Concurrent AED use</td><td>Median 3 (Range 1 to 5)

Valproate
Clobazam
Levetiracetam
Topiramate
Stiripentol</td><td>Median 3 (Range 2 to 4)

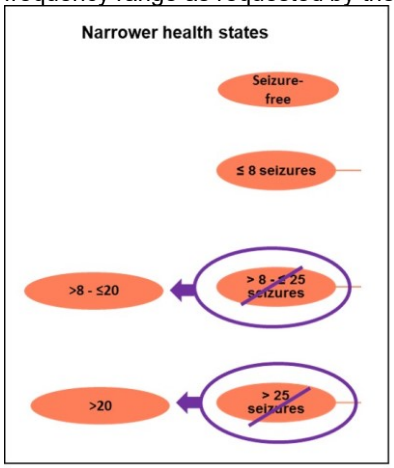
Valproate
Clobazam
Levetiracetam
Topiramate
Stiripentol</td><td>Median 3 (Range 1 to 5)

Valproate
Clobazam
Levetiracetam
Topiramate
Stiripentol</td></tr>
</table>
Baseline Characteristics for patients in the on-clobazam subgroup (GWPCARE1):
<table>
<tr><th rowspan="2">Baseline characteristic</th><th colspan="2">In conjunction with clobazam</th></tr>
<tr><th>CBD 20 mg/kg/day</th><th>Placebo</th></tr>
<tr><td>Number randomised</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Age, mean (SD)</td><td>[redacted]
Range [redacted]</td><td>[redacted]
Range [redacted]</td></tr>
<tr><td>Gender</td><td>[redacted] male
female</td><td>[redacted] male
female</td></tr>
<tr><td>Baseline total seizure frequency per 28 days: median (range)</td><td>Total [redacted]
[redacted]</td><td>Total [redacted]
[redacted]</td></tr>
<tr><td>Baseline convulsive seizure frequency per 28 days: median (range)</td><td>Convulsive [redacted]
[redacted]</td><td>Convulsive [redacted]
[redacted]</td></tr>
<tr><td>Prior AED treatments</td><td>Mean 4.4; SD 3.6</td><td>Mean 5.1; SD 3.4</td></tr>
<tr><td>Concurrent AED use</td><td>Mean: 3.0; SD 1.0

Clobazam
Valproate
Levetiracetam
Topiramate
Stiripentol</td><td>Mean: 3.1; SD 0.8

Clobazam
Valproate
Levetiracetam
Topiramate
Stiripentol</td></tr>
</table>
</td><td></td></tr>
<tr><td>2</td><td>Consultee (company)</td><td>GW Pharma</td><td>Clinical-effectiveness evidence
Committee Conclusion(s) from ACD</td><td>Comments noted.</td></tr>
</table>

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
			3.5 The committee concluded that cannabidiol with clobazam reduces seizure frequency compared with usual care, but that the long-term efficacy is uncertain. The company stated that the interim results of the open-label extension study (GWPCARE5) showed sustained efficacy with cannabidiol over 48 weeks of follow up. The committee noted that the company had not presented it with detailed methods or results for the open-label extension study in the subgroup of patients taking cannabidiol with clobazam. Detailed methods and results (up to 156 weeks) from interim analysis of data from the open-label extension study (GWPCARE5) for the subgroup of patients with DS taking cannabidiol with clobazam are shown in Appendix 1. These interim results from GWPCARE5 showed sustained efficacy with cannabidiol over 156 weeks of follow up.	The additional evidence submitted by the company was considered by the committee. Please see section 3.5 of the final appraisal document.
3	Consultee (company)	GW Pharma	***Stopping treatment*** **Committee Conclusion(s) from ACD** 3.7 The committee concluded that the stopping rule proposed by NHS England is appropriate, but that response to treatment should be assessed after 3 months of treatment. The committee was aware that the company implemented the stopping criteria proposed by NHS England in its model after 6 months of treatment with cannabidiol. However, during technical engagement, clinical experts reported that they review patients every 3 months in the first year then annually. The committee considered that applying the stopping rule at 3 months would be appropriate and aligned with the follow up in the clinical trials. The NHS England stopping rule applied from 3 months has been implemented as a scenario in the model. In the base case, stopping rules at two further timepoints have been implemented: CBD can now be stopped in the model at 6 months (as previously) and also at 12 and 24 months. At all these timepoints, the stopping rule is based on that specified by NHS England, and estimated from the patient level data in the GWPCARE5 trial. Specifically, it is a “one-off” discontinuation rate that is calculated based on the percentage of non-withdrawn patients in each health state at each timepoint in the trials who did not achieve a ≥30% reduction in convulsive seizures, but who did achieve this outcome at the last timepoint. The 12 and 24 month stopping points have been added to the model following guidance from NHSE at the committee meeting that treating clinicians would have to attest (e.g. via Blueteq) that CBD continues to meet the NHS England efficacy requirement at annual timepoints following treatment initiation, or else stop treatment with CBD. Please refer to the model and the separate document provided by the company: “ID1211 DS economic outcomes after ACD”.	Comment noted. Stopping rules were considered by the committee. Please see section 3.7 of the final appraisal document.

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
4	Consultee (company)	GW Pharma	***Company's economic model*** **Committee Conclusion(s) from ACD** 3.8 The committee concluded that the modelled health states did not adequately represent Dravet syndrome The committee was concerned that the health states based on seizure frequency had been arbitrarily derived because they were not based on any clinical rationale and represented wide ranges of seizure frequencies. It would have preferred to see scenario analyses categorising the health states differently. In particular, the committee would have preferred to see narrower seizure frequency ranges to better capture the effect of changes in this parameter on costs and benefits. There is no clinical consensus in DS, a heterogeneous and ultra-orphan disease, on what the seizure thresholds for the health state categories should be with regard to quality of life, so it would be extremely challenging to have a clinical rationale based only on seizure numbers. The original health state categories were therefore derived by dividing the original ITT population into three equal groups, mathematically, in order to avoid bias in any group. The company has retained the original health state definitions in its base case, as this maintains the validity of the utility estimates from the vignette study. However, further to discussions with the NICE technical team and clinical experts, the company has also run a scenario that lowers the upper threshold in order to narrow the middle health state seizure frequency range as requested by the NICE committee (see diagram below).  The clinical rationale for the new health state thresholds (≤8 convulsive seizures per month; >8 to ≤20; and >20) is that in the 'middle' seizure category (>8 to ≤20), most patients who have either a 50% decrease or a doubling in the number of convulsive seizures they have per month (clinical experts confirm that both of these are clinically-relevant and patient-relevant events) will move health state in the model, i.e. they will experience either an increase or a decrease in quality of life.	Comments noted. The structure of the company's model was considered by the committee. Please see section 3.8 of the final appraisal document.

<table>
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<tr><td></td><td></td><td></td><td>This approach was deemed plausible by the NICE technical team.

The company has also validated this approach with UK clinical experts, who concurred that it was a practical and plausible approach to narrowing the seizure frequency ranges in the health states, given the lack of clinical consensus in DS, a very rare disease.

Narrowing the seizure frequency ranges in the health states as described above, has a slight impact on the cost-effectiveness, decreasing the ICER by a small amount.
Please refer to the model and the separate document provided by the company: “ID1211 DS economic outcomes after ACD”.</td><td></td></tr>
<tr><td>5</td><td>Consultee (company)</td><td>GW Pharma</td><td>Company’s economic model
<table><tr><th>Committee Conclusion(s) from ACD</th></tr><tr><td>3.8 The committee also noted the company did not model the benefits associated with reducing non-convulsive seizures because it considered convulsive seizures to be more important to people with Dravet syndrome and their families and carers. However, it acknowledged that these may be challenging to include in the model.</td></tr></table>
The company appreciates the committee’s acknowledgement that it may be challenging to include non-convulsive seizures in the model.
As the company has indicated previously, data from the CBD Phase 3 trials shows that the average number of non-convulsive seizures is lower in health states with fewer convulsive seizures. Furthermore, CBD has a treatment effect versus placebo on non-convulsive seizures in GWPCARE2, and the reduction from baseline is maintained over the GWCPARE5 study. Therefore, there is “hidden upside” in terms of QALY gain that was not captured in the previous model from improving outcomes in these seizure types.
The contribution of non-convulsive seizures to quality of life has now been included in the company’s base case. Please refer to the model and the separate document provided by the company: “ID1211 DS economic outcomes after ACD”.
Although there is a dearth of utility data relating to non-convulsive seizures in the literature, in order to address the committee’s concerns, the company conducted a further literature search and has identified a suitable analogue (de Kinderen, RJ et al, Epilepsy Res. 2016 Sep;125:24-31) to estimate the contribution of non-convulsive seizures in the base case. The de Kinderen study reports an algorithm estimating the independent utilities of non-convulsive seizure types, which are derived from a regression model using data from a TTO study in the general population.
Using this algorithm, the company has calculated disutility estimates for the contribution of non-convulsive seizures to HRQoL for each of the convulsive-seizure defined health states in the model. As a conservative measure, these disutility values were reduced by 25% relative to the figures estimated from the de Kinderen study (see tables below).
These disutilities were then assigned to the model’s convulsive-seizure health states, based on the mean number of non-convulsive seizures per health state observed in the treatment period of the GWPCARE2 study (see tables below).

<table><tr><th># seizures per 28</th><th>Utility estimate</th><th>Disutility estimate**</th><th>75% of disutility</th></tr></table></td><td>Comments noted.

The benefits of reducing non-convulsive seizures were considered by the committee. Please see section 3.10 of the final appraisal document.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><th>days*</th><th></th><th></th><th>estimate</th></tr>
<tr><td>0</td><td>0.857</td><td>0</td><td>0</td></tr>
<tr><td>4</td><td>0.752</td><td>-0.105</td><td>-0.079</td></tr>
<tr><td>8</td><td>0.695</td><td>-0.162</td><td>-0.122</td></tr>
<tr><td>28</td><td>0.684</td><td>-0.173</td><td>-0.130</td></tr>
<tr><td>56</td><td>0.647</td><td>-0.21</td><td>-0.158</td></tr>
</table>
*Zero seizure utility is that for a state of 1 absence seizure per week
**Based on zero-seizure health state as a reference point

<table>
<tr><th>Convulsive seizure health state</th><th>Mean number of non-convulsive seizures* per month (GWPCARE2)</th><th>Disutility estimate from de Kinderen</th></tr>
<tr><td>Seizure free</td><td>0</td><td>0</td></tr>
<tr><td>≤8</td><td>4</td><td>-0.079</td></tr>
<tr><td>>8 to ≤25</td><td>10</td><td>-0.122</td></tr>
<tr><td>>25</td><td>12</td><td>-0.122</td></tr>
</table>
* Partial seizures</td><td></td></tr>
<tr><td>6</td><td>Consultee (company)</td><td>GW Pharma</td><td>
Company's economic model
<table>
<tr><th>Committee Conclusion(s) from ACD</th></tr>
<tr><td>3.8 The committee was also concerned that, in the usual-care arm, after cycle 2, some patients stayed in the highest seizure frequency health state for the rest of the model. It considered this was not clinically plausible.</td></tr>
</table>

In DS, the number of seizures an individual patient experiences may fluctuate over time. In addition, this is already a refractory population and there is no reason to assume that there is an underlying progression of the disease, such that patients get generally worse. Thus, in a cohort of patients for modelling purposes, on average, for every patient whose seizures increase at a given timepoint, there will be another whose seizures decrease, and it is reasonable to assume that the distribution of patients across heath states will be consistent over time.
From cycle 2 in the company's model, the distribution of health states at the end of cycle 1 in the usual-care arm was applied statically (i.e. without re-transitioning). This was defined by the distribution observed in the usual-care (placebo) arm at the end of the GWPCARE2 study, from which transition probabilities in cycle 1 of the usual-care arm were derived. As such, some patients on usual-care remained in the highest health state for the duration of the model but, importantly, others remained in the lowest (and all other) health states.
There are no longitudinal natural history data available in this very rare condition. Therefore, the company feels that the "snapshot" of health states in the usual-care/placebo arm at the end of GWPCARE2 Phase 3 trial represents the best data available to approximate how patients not treated with CBD will, on average, be distributed across health states.
As further evidence for the validity of this assumption, seizure outcomes versus baseline are very stable over time in the GWPCARE5 study (see Appendix 2). Therefore, any method to "reverse calculate" health state distributions in the usual-care arm over the open-label extension period would</td><td>Comments noted.

The company's approach to modelling patients on usual care or who stop cannabidiol was considered by committee. Please see section 3.13 of the final appraisal document.</td></tr>
</table>

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
			give a very stable result that would be unlikely to improve on the accuracy of the company's assumption above. Based on these considerations, the company has continued with its original approach (i.e. from cycle 2, the distribution of health states at the end of cycle 1 is applied statically in the usual-care arm and to discontinued CBD patients). In the company's base case following ACD, this assumption is applied to lifetime, meaning that the relative treatment effect for CBD is applied for the full time horizon. The company is not aware of a more accurate way of modelling the untreated course of the disease, given the absence of natural history information in this very rare condition.	
7	Consultee (company)	GW Pharma	***Company's economic model*** **Committee Conclusion(s) from ACD** 3.9 The committee concluded that it was appropriate to capture the benefits of having more convulsive seizure-free days. However, it was concerned that the company's approach to modelling these increased the complexity of the model. The committee considered it unusual to firstly categorise into numbers of seizures, and then subdivide these into number of seizure-free days. It considered that this may have resulted in 'double-counting' the benefits of reducing the frequency of seizures. It therefore noted that an alternative model structure may have better reflected the condition and captured the benefits of both convulsive seizure-free days and convulsive seizure frequency. One such model structure would be a discrete event simulation model examining the effect of different convulsive seizure rates on individual patients. The company welcomes the recognition from the committee that it is appropriate to capture the benefits of having both convulsive seizure reduction and more convulsive seizure-free days. The company felt that it had maybe not fully explained how the model allocates patients between seizure frequency and seizure-free days, such that it is not 'double-counting'. In a call with the NICE technical team and the ERG on 10th September 2019, the company had the opportunity to explain how the model is actually allocating patients between *mutually exclusive* health states, which are defined by the number of seizures and the number of seizure-free days per 28 days. Please refer to the diagram below, which shows the mutually exclusive health states (and no 'double-counting'). Note: this example (used during the call with the ERG and the NICE technical team) is for LGS, but exactly the same principle applies for DS. There is no 'double-counting'.	Comments noted. The company's approach to modelling the number of seizure-free days was considered by committee. Please see section 3.9 of the final appraisal document.

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			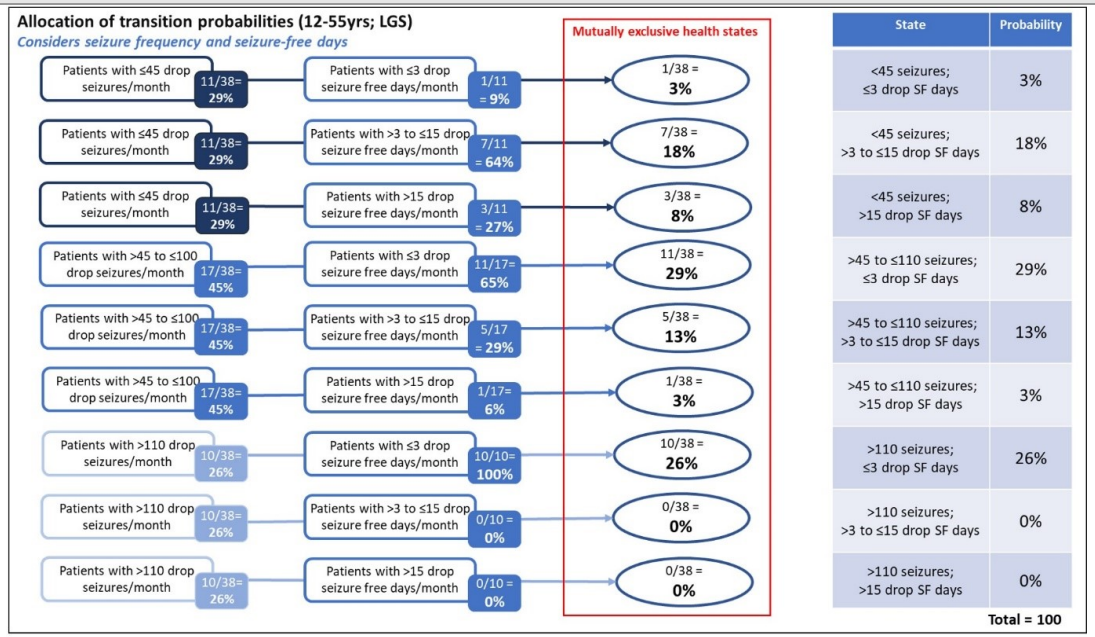 During a call with the NICE technical team on 28th August 2019, the company explained that, based on expert advice on when it may be methodologically appropriate to select a patient-level simulation in preference to a Markov simulation, the company does not believe that a discrete event simulation would improve the accuracy of outcomes versus a Markov model. Based on the above, the company plans to continue with a Markov model. It should be noted that the standard Markov model has been widely used in other epilepsy HTAs in the UK (e.g. SMC/AWMSG) and in the literature.	
8	Consultee (company)	GW Pharma	***Company's economic model*** **Committee Conclusion(s) from ACD** 3.10 The usual care arm should be modelled in the same way as the cannabidiol arm. The committee concluded that it would have preferred the outcomes in the usual care arm to be based on trial data up to cycle 9, as in the cannabidiol arm. The trial data for cannabidiol used in cycles 2-9 was taken from the GWPCARE5 *open-label* extension study (i.e. no placebo arm). In the absence of a comparator arm in GWPCARE5 (an open-label study), in the usual-care arm of the model the company has maintained the distribution of patients between health states at the end of cycle 1 for the lifetime of the model. This distribution is derived from the *placebo arm* in GWPCARE2. As per the explanation in 3.8 above, in the absence of natural history data, this is the most appropriate	Comments noted. The company's approach to modelling the usual care arm was considered by committee. Please see section 3.13 of the final appraisal document.

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
			way of approximating the seizure distribution in the usual-care arm. The relative treatment effect is applied to *lifetime* in the company's new base case (see Appendix 3). However, this approach clearly *over-estimates the benefit of usual-care*, as it assumes that the large improvement from baseline on seizure frequency in the placebo arm of the blinded, randomised controlled GWPCARE2 trial would be present in the open-label GWPCARE5 study. This is improbable, as any "trial effect" is likely to be higher in a blinded controlled trial than in an open-label study. This is supported by the observation that the reduction in convulsive seizures for carrying-over placebo patients re-baselined at the start of the GWPCARE5 study are in the range of those observed from baseline in the US Early Access Programme real world study (Laux et al 2019), in which there is unlikely to be a large "trial effect. Maintaining this benefit for usual-care for the duration of the model *biases the model considerably in favour of usual-care* and underestimates the cost-effectiveness of cannabidiol. This was noted in the NICE technical report: "The technical team notes that there is no comparative data beyond 14 weeks (i.e. the first cycle of the model) and that assuming the placebo effect is maintained in subsequent cycles may *overestimate the treatment effect of current clinical management*." Assuming that the large placebo effect observed over 3 months in the blinded GWPCARE2 trial would be of the same magnitude over 2 years in the open-label GWPCARE5, and carried indefinitely in this highly refractory population of patients when treated with existing therapies is unrealistic and significantly penalises cannabidiol in terms of its benefit and value to patients. Therefore, the company has also implemented a scenario in which the end-of-cycle-1 health state distribution in the usual-care arm is maintained from cycles 2-9 for usual-care and discontinuing CBD patients, who then revert to the distribution of health states at baseline. The company considers that this provides a scenario which avoids significantly overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	
9	Consultee (company)	GW Pharma	***Company's economic model*** **Committee Conclusion(s) from ACD** 3.11 The committee concluded that the results from the company's model were not valid. i) The ERG was concerned that the results of the company's model were not valid. The ERG explained that, when it set all the clinical inputs in the model as equal for both cannabidiol and usual care, it expected that the estimated quality-adjusted life years (QALYs) would be the same for both treatments. However, the model produced higher QALYs for cannabidiol. The company stated that the model produced equal QALYs only under certain conditions. The committee did not consider this sufficient. It agreed with the ERG that the model was flawed, and that this test of validity should hold for the base-case settings. ii) The committee recalled that patients receiving each treatment took different paths through the model and considered that this may have biased the results in favour of cannabidiol. iii) It was also concerned that there may have been unidentified flaws in the model coding.	Comments noted. The company's approach to modelling patients who stop cannabidiol was considered by the committee. Please see section 3.11 of the FAD

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<tr><td></td><td></td><td></td><td>
In a call with the NICE technical team and the ERG on 10th September 2019, the company had the opportunity to address the ERG's concerns about model validity.
i) and ii) In a series of demonstrations, the company demonstrated the model's validity in real time. Specifically, the company showed that under the conditions for 'Test 2' (see table below and Appendix 4), which set the clinical efficacy and safety parameters to be equal between cohorts and made CBD discontinuation rates equal across health states at all time points, a null QALY gain is returned.
The model does not return a null QALY gain in the base case if discontinuation rates are not set to be equal between health states ('Test 1'; see table below and Appendix 4). This is expected. It occurs because patients can discontinue CBD, but not usual-care (logically, it is not possible in practice to discontinue 'usual care'). Patients will discontinue CBD at faster rates when they have more seizures (as observed in the trials). Variable CBD discontinuation rates cause asymmetry in the health state distributions for CBD and usual-care patients in the model, even when clinical parameters are set to be equal. This effect is demonstrated in the simulated patient trace for the first 3 cycles for the younger age group in DS (Appendix 4).
Of note, patients do *not* take different paths through the model depending on their treatment allocation. It is possible in the model to move discontinuing CBD and usual-care patients back to the baseline distribution of health states at the same rate over time. This is shown in Test 3 in the table below. In these circumstances, an artificial "usual-care discontinuation rate" is set up; usual-care patients are maintained in the end-of-cycle-1 split of health states until they "discontinue", at which point they revert to the baseline split of health states. CBD patients go straight back to the baseline split at discontinuation. In Test 3, these rates are equalised, and a null QALY gain is achieved even when CBD discontinuation rates are aligned to the base case (i.e. not uniform across health states).
Test 3 is not a clinically-relevant scenario, but serves to demonstrate model symmetry and validity.
<table>
<tr><th>Test</th><th>Changes on base case</th><th>Tabs in model</th><th>QALY Gain</th></tr>
<tr><td>1. Clinical efficacy and safety set equal between arms</td><td>○ Transition probabilities for the CBD arm are changed to those for the usual care arm
○ Probability allocations for convulsive seizure-free days for the CBD arm are set to those for the usual care arm
○ Severe adverse event rates on CBD set to 0.00%
○ Mortality risk ratio for the convulsive seizure-free health state set to 1.0</td><td>SEIZURES "Cycle 1" D21:G24, D44:G47
"Subsequent cycle" O14:BA17, O37:BA40
DAYS D21:F24, D44:F47

SAFETY H35

MORTALITY E16, E20, E29, E33</td><td>0.5579</td></tr>
</table>
</td><td></td></tr>
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2. Clinical efficacy and safety set equal between arms CBD discontinuation rates uniform across health states	As per scenario 1, plus: ○ Discontinuation rates for all health states in subsequent and long-term cycles set to those for cycle 1 (5.56%) ○ Stopping rules for CBD switched off	DISCONTINUATION G21:G24, I21:I24, G44:G47, I44:I47 GLOBAL SETTINGS E24	0.0000
3. Clinical efficacy and safety set equal between arms Discontinuing CBD and usual care patients go back to the baseline health state split at the same rate in every cycle	As per scenario 1, plus: ○ Usual care "reversion to baseline" rates set equal to the CBD discontinuation rates for each health state in each cycle ○ CBD Stopping rule and "Placebo stopping rule" switched on	DISCONTINUATION E28:I31, E51:I54 GLOBAL SETTINGS E24, E28 (Stopping rates can be seen in DISCONTINUATIONS E81:I84, E88:I91, E128:I131, E135:I138)	0.0000

In Test 1, there is a residual QALY gain that is in favour of CBD. This is a result of seizure control being a key reason to discontinue CBD (as observed for AEDs in clinical practice), and CBD being studied adjunctively to its comparator.
As explained above, the distribution of health states at the end of cycle 1 in the usual-care cohort (which is derived from the placebo arm of the GWPCARE2 trial) is assumed to approximate the average distribution in the treated history of the condition (without adjunctive use of CBD), and is applied statically from cycle 2 onwards for all usual-care and discontinuing CBD patients. This assumption is appropriate because there is: no natural history data in this rare condition; no reason to assume that the distribution of usual-care patients across health states on average would change over time in a population highly refractory to existing medications; no data on seizure outcomes in patients for whom CBD was withdrawn in the trials; no reason to assume an enduring treatment effect for CBD once stopped.
It is thus not clinically relevant to "discontinue" usual-care within the model. This means that linking CBD discontinuation rates to seizure control has the effect of "enriching" the population of patients on CBD who have good seizure outcomes, which will give a residual HRQoL gain. This is a consequence of observation in a cost effectiveness analysis: the purpose of an economic model is to estimate outcomes for a cohort started on a technology versus a cohort on a comparator.
In clinical practice, patients whose seizure control naturally deteriorates on existing treatments over time would progressively be eligible to start adjunctive CBD, off-setting patients on CBD who discontinue due to poor seizure control and regress to being managed only with the mix of existing treatments.
iii) During the call with the NICE technical team and the ERG on 10th September 2019, a third party

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			agency (with significant expertise in health economic modelling and VBA coding) testified that it has performed comprehensive QC and validity testing on the company's model, outlined the tests it has conducted and confirmed that the model had passed all tests. The experts found no 'unidentified flaws' in the model coding.	
10	Consultee (company)	GW Pharma	***Assumptions in the economic model*** **Committee Conclusion(s) from ACD** 3.12 The committee concluded that the mean weight from the clinical trials should be used to model the weight-based dose of cannabidiol. The weight distribution at baseline of patients with DS (aged 2-11 and 12-18) in the on-clobazam subgroup is shown below.   It can be seen that there are heavier-weight outliers in both age groups that skew the mean weight upwards disproportionately. The median weight is more representative of the group as a whole. For this reason, the *median* weights have been used in the company's base case model. A scenario analysis using the *mean* weights has also been implemented.	Comments noted. The committee did not change its conclusion that mean weight should be used in the model. Please see section 3.12 of the final appraisal document.
11	Consultee (company)	GW Pharma	***Assumptions in the economic model*** **Committee Conclusion(s) from ACD** 3.13 The committee concluded that the combined placebo data from the clinical trials should only have been used in a scenario analysis, and that the company should use placebo data from GWPCARE2 in its base case. As requested by the committee, the base case model now includes data from the usual-care/placebo arm of GWPCARE2 only. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	Comment noted.
12	Consultee	GW Pharma	***Assumptions in the economic model***	Comments noted.

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	(company)		**Committee Conclusion(s) from ACD** 3.14 The company's approach does not appropriately account for the lack of comparator arm in the open-label extension study. Based on the data from the open-label extension study, the company assumed that, after cycle 2, patients in the usual-care arm returned to their baseline health states, while patients taking cannabidiol continued to benefit from cannabidiol...The company explained that it had modelled the treatment effect in this way because there are no data for placebo plus usual care after cycle 2 (everyone received cannabidiol in the open-label extension study). The committee concluded that it would have preferred the company to have accounted for the lack of a comparator arm in the open-label extension study rather than assuming patients would return to baseline. It suggested that one way of doing this would be to extrapolate the relative treatment effect from GWPCARE2 beyond the controlled part of the trial. The company would like to clarify that its intention in moving patients back to baseline in the usual-care arm was to avoid overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time (and not because there are no comparative data after cycle 1). Of note, in the technical report, the technical team also concluded that assuming the relative treatment effect is maintained in subsequent cycles may *overestimate the treatment effect of current clinical management* (usual-care). As per the company's response to 3.10 above, in the usual-care arm, the company has now maintained the distribution of patients between health states at the end of cycle 1 for the lifetime of the model. In the absence of natural history data, this is a reasonable way to extrapolate the relative treatment effect beyond the controlled phase of the trial (i.e. cycle 1). However, as also noted in 3.10 above, this approach clearly *over-estimates the benefit and value of usual-care*. Maintaining this benefit for usual-care for the duration of the model *biases the model considerably in favour of usual-care* and underestimates the cost-effectiveness of cannabidiol. In a scenario analysis, in the usual-care arm, the distribution of patients between health states at the end of cycle 1 is maintained until the end of the open-label extension period (cycles 2-9). The company considers that moving patients back to baseline in the usual-care arm after cycle 9 avoids overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	The company's approach to modelling the usual care arm was considered by committee. Please see section 3.13 of the final appraisal document.
13	Consultee (company)	GW Pharma	***Assumptions in the economic model*** **Committee Conclusion(s) from ACD** 3.15 The effectiveness of cannabidiol is likely to diminish over time. The committee concluded that it would have preferred to see scenario analyses in which the efficacy of cannabidiol diminished after 27 months. The clinical experts stated that they would expect the effectiveness of cannabidiol to diminish over time because this is seen with other antiepileptic drugs. The company considered that it had captured a reduction in efficacy over time in a scenario analysis in which it increased the	Comments noted. The company's assumptions on clinical effectiveness over time were considered by committee. Please see section 3.14 of the final appraisal document.

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			annual rate at which patients in the highest seizure-frequency health state stopped cannabidiol, increasing the rate from 5% to 10% a year. It argued that being in this health state implied that patients were no longer deriving benefit from cannabidiol and so would stop taking it. The clinical experts stated that the proportions of patients on cannabidiol at 3 and 5 years in the company's base-case analysis of the full trial population were plausible. However, the committee considered the rates at which people stopped treatment, and a reduction in treatment effect reflected separate issues. This was because a waning treatment effect would have applied to all patients, but not all of them would have moved to the health state with the highest seizure frequency and stopped cannabidiol. 3.23 In its summary, the committee also included some additional wording for this scenario as follows: "explores a diminishing treatment benefit of cannabidiol after 27 months, including a scenario in which the treatment effect is removed". The company would respectfully like to make a correction to the committee's conclusions in section 3.15. The ACD states that the company captured the effect of a reduction in efficacy over time in CBD by increasing the discontinuation rate from 5% to 10% in the *highest* health state. The committee concluded that the company's scenario analysis did not capture a waning effect, as they assumed that the company was simulating a situation in which patients who were receiving no benefit would move to the highest health state, and then discontinue at a greater rate. The committee considered that a waning effect should have applied to all patients, but not all of them would have moved to the health state with the highest seizure frequency and stopped cannabidiol. This is a misunderstanding of what was actually done in both the base case and in the scenario. The company assumed in its base case that 5% of patients in *all* health states (except seizure-free, 0.5%) would discontinue treatment per cycle, based on observations from the company's US early access programme (EAP), which is currently the best long-term real-world data set available. This 5% rate includes patients who discontinue due to a lack of continuing benefit, which was the major reason for withdrawal in the study. Similarly, in the scenario analysis, *all* health states (except seizure free, 0.5%) were assigned a 10% discontinuation rate to simulate the effect of *more* patients than observed in the US EAP discontinuing due to a lack of continuing benefit. For this reason, the company considered that it was not necessary to include a waning effect in the model, as the waning treatment effect described above already applied to *all* patients, not just those with the highest seizure frequency. There is currently no clinical evidence to support a loss of efficacy of CBD over time. In the GWPCARE5 long-term open-label study and in the US EAP, seizure outcomes were very stable to 3 years. Any assumption that further wanes the efficacy of CBD within the model is arbitrary, is only a hypothetical way of testing the responsiveness of the model mathematically, and is not based on clinical observation. The company has included recently available data that demonstrates that the treatment effect of CBD is continued to 156 weeks (see Appendix 1). The committee heard from clinical experts that they could not be confident that the treatment effect of CBD *would not* wane. This is a reasonable, professionally cautious response to the question asked based on their experience with other AEDs and limited experience with CBD. However, the converse is equally true. If the clinical experts had been asked instead "Are you absolutely confident based on	The committee acknowledged that the company's scenario analysis was based on applying a 10% discontinuation rate in all health-states and reconsidered the scenario based on this. Please see section 3.14 of the final appraisal document.

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			the evidence available that the effect of CBD *would* wane?", it is unlikely that they could have categorically stated that this was the case. What is more definitive is that, in the Committee meeting, both the patient and clinical experts attested to the timely stopping of treatment in DS if the patient/carer and/or clinician feels that the patient is not receiving benefit. As such, it seems more plausible that treatment waning would be better reflected in discontinuation rates, for which there is evidence, rather than in an arbitrary assumption for an unobserved outcome. However, notwithstanding the above, at the committee's request, a scenario to model an *additional* waning effect has been implemented. In this scenario, the discontinuation rate for long-term cycles (cycle 10 onwards) no longer discontinues patients; instead it reverts patients to the distribution of health states for usual-care patients, but carries the cost of CBD for another 3 months (1 cycle). This assumption is a proxy for waning, as it simulates a situation in which the efficacy of the drug is completely lost 3 months before the drug is discontinued. Interviews conducted with clinical experts have indicated that this is the maximum length of time a patient would be on an AED that is no longer considered effective before it is stopped. Given the very proactive approach to managing ineffective therapies by parents and clinicians in DS, this represents a clinically plausible means of modelling a progressive loss of efficacy over time. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD". 3.23. With regard to the committee's comment in 3.23 to include "a scenario in which the treatment effect is removed" after 27 months, the company respectfully considers that this is not a valid or viable scenario: • In the company's base case model, the relative treatment effect is now maintained to lifetime (such that the distribution of health states on placebo is maintained for usual-care patients indefinitely) • In the company's response to 3.15 above, we have explained the misunderstanding re discontinuations (which are occurring in *all* patients, not just those in the highest-seizure frequency health state) and we have also implemented a scenario to simulate an additional 'waning' effect as requested • A very recent additional interim data cut from the long-term GWPCARE5 study out to 156 weeks (see Appendix 1) shows that the treatment effect of CBD continues beyond 27 months • The company is aware from discussions with clinicians that LGS/DS are conditions with very motivated parents/carers/healthcare professionals, such that patients are not kept on drugs that are not working or not tolerated. Thus, it is unrealistic in this disease area to assume that a patient would be kept on a drug that is not working for the lifetime of the model (i.e. incurring no benefit, but incurring all costs). Given the above, the company feels that it makes little sense to include a scenario where the CBD treatment effect is removed completely at an arbitrary point where the GWPCARE5 data had	

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			previously run out. Furthermore, within the model structure, there is no evidence-based and timely way for the company to include a scenario where the treatment effect stops completely when the data run out. The company considers that this is already 'built in' via the long term discontinuation rates which cover *all* patients and reflect patients being stopped because the treatment is not working.	
14	Consultee (company)	GW Pharma	***Assumptions in the economic model*** **Committee Conclusion(s) from ACD** 3.16 The model may underestimate the mortality of people who are free from convulsive seizures. The committee was aware that relatively few patients in the model were free from seizures, so changing this assumption would likely have had a small effect on the cost-effectiveness results. It concluded that the model may have underestimated the mortality of patients free from convulsive seizures. It would have preferred to see scenario analyses in which the reduction in risk of death was smaller. The company has provided scenario analysis with regard to risk of death. The company has reduced the mortality benefit of being convulsive seizure-free in its base case. Previously the company assumed a risk ratio of 0.42 for the convulsive seizure-free health state relative to the mortality rate assigned to the >8 - ≤25 convulsive seizure health state (derived from Cooper MS, et al. Epil Res 2016;128:43-47). This risk ratio was based on an analogue identified in the literature in broader epilepsy types (Trinka E, et al. Epilepsia. 2013;54(3):495-501). The company has halved this risk reduction (it is now 0.71) in its revised base case following ACD. The company has further provided a scenario analysis with regard to risk of death in the convulsive seizure-free group, assuming no reduction in mortality from being convulsive seizure-free. Please refer to the model and the separate document provided by the company: "ID1211DS economic outcomes after ACD".	Comments noted. The company's approach to modelling mortality rates was considered by committee. Please see section 3.15 of the final appraisal document.
15	Consultee (company)	GW Pharma	***Costs in the economic model*** **Committee Conclusion(s) from ACD** 3.17 The company should model the costs of increasing the dose of cannabidiol. The committee concluded that the company should have included and justified the costs of increasing the dose of cannabidiol for some people in its base-case analysis. It noted that it would have preferred to see scenario analyses exploring how sensitive the cost-effectiveness results were to the proportion of people on higher doses. The company has provided scenario analyses to explore proportions of people on higher and lower doses. The recommended maintenance dose for cannabidiol in the Summary of Product Characteristics is 10 mg/kg/day, which is retained in the base case. The committee stated that clinical experts thought that ~20% of patients might respond well on this dose, and could thus be considered for escalation. Given the lack of a dose response, the worsening adverse event profile observed between the CBD 10mg and 20 mg arms in the clinical trials, and the cautious 'low and slow' approach taken by UK physicians when increasing the dose of AEDs, it is unlikely that many UK patients who are escalated would reach a dose of 20 mg/kg/day. The company has therefore assumed that 20% of patients would be maintained on 15 mg/kg/day, and tested a	Comments noted. The cost of increasing the dose of cannabidiol for some people was considered by committee. Please see section 3.16 of the final appraisal document.

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			scenario of an 11 mg/kg/day mean dose. Of note, in early real-world clinical practice, the company is also learning that some patients are not even escalated as far as 10 mg/kg/day. We have therefore also tested a scenario of a 9 mg/kg/day average dose. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	
16	Consultee (company)	GW Pharma	***Modelling adverse events*** **Committee Conclusion(s) from ACD** 3.18 The company should include the effect of adverse events on quality of life in the model. The committee concluded that the company should have included the effect of adverse events on quality of life in its model. It also concluded that the incidence of adverse events should have been based on data from the subgroup using cannabidiol with clobazam in the Dravet syndrome trials. The company has included the effect of adverse events on quality of life in its base case, using data from the subgroup taking cannabidiol with clobazam. A short-term (1 cycle) disutility for serious adverse events of special interest occurring in the CBD 10mg arm and not in the usual-care arm has now been included in the model. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	Comment noted.
17	Consultee (company)	GW Pharma	***Utility values in the economic model*** **Committee Conclusion(s) from ACD** 3.19 The utility values from the company's vignette study do not accurately reflect the health-related quality of life of people with Dravet syndrome. It noted that, among people with more than 24 convulsive seizure-free days per month, the utility values were similar whether they had, in total, more than 25 seizures per month or between 8 and 25 seizures per month. The committee considered this implausible because it had heard that convulsive seizures worsen quality of life. The company would like to highlight that the similar utility values seen between seizure frequency health states in this case would be expected, in the context of the *contribution of seizure-free days* to QoL. The company welcomes the Committee's acknowledgement of the importance of seizure-free days to QoL. When the number of seizures per month is higher, reductions in seizure number would not be expected to be the biggest driver of QoL (as patients are still experiencing many of them). The contribution of how seizures are spread over time becomes relatively more important. This is exactly what is observed. Based on this consideration, the company does not consider that there is a lack of face validity in these estimates	Comments noted.
18	Consultee (company)	GW Pharma	***Utility values in the economic model*** **Committee Conclusion(s) from ACD** 3.19 The committee was aware that the company had done a scenario analysis using values from a general population preference study in Lennox-Gastaut syndrome (Verdian et al. 2018).	Comments noted. The choice of utility values for patients was considered by committee. Please

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			The committee noted that, although not directly comparable, these values appeared lower than those in the company's vignette study. The company considers that the utility values from the vignette study are in line with analogues in the literature (including Verdian *et al*, 2018 which, although in LGS, is a good analogue for DS), and represent its best efforts to obtain HRQoL estimates in this very rare disease. • The estimates from the company's vignette study match almost exactly the relevant figures from the "anchor" state in Verdian (see Tables 1 and 2, Appendix 5). • The utility estimates measured cross sectionally in the large DISCUSS study for Dravet syndrome were comparable to those measured from the DS vignette study, both in European and UK populations (see Table 3, Appendix 5). • A further analogue supports the company's utility estimates in DS (Tritton T, et al. Epil & Behav. 20189;92:213-20). Tritton *et al* valued the QoL associated with seizures in 61 patients and 125 caregivers of people with Tuberous Sclerosis Complex (TSC), including in the UK. TSC is another highly refractory epilepsy condition characterised by heterogeneous seizures types, in which partial seizures predominate but convulsive seizures are also present (~ 30% of seizures in TSC are convulsive). Utilities for patients were assessed by seizure type in the last week using the EQ-5D and UK value set. As can be seen in Table 4 in Appendix 5, HRQoL estimates for patients experiencing convulsive seizures are similar to those for DS patients in the company's vignette study for the ≤8 seizure health state. Based on the above, the company considers that the utility estimates from Verdian are an appropriate analogue for the scenario analysis conducted previously. Therefore, the company proposes to keep the scenario analysis using Verdian as an analogue. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	see section 3.17 of the final appraisal document.
19	Consultee (company)	GW Pharma	***Utility values in the economic model*** **Committee Conclusion(s) from ACD** 3.20 It is appropriate to include the effect on carers' quality of life in the model, but the company's utility values may not accurately reflect this. The committee concluded that it was appropriate to include carers' quality of life in the model. However, it thought that the values from the company's vignette study may not have accurately reflected the effect of caring for someone in each of the health states in the model. It was concerned that the company had captured the effect on the quality of life of carers only for the 2 highest seizure-frequency health states. The company conducted a further literature search, but could find no further analogues (beyond Campbell *et al*, 2019) in the literature relevant to DS. This is to be expected given the very rare nature of this condition.	Comment noted. The choice of utility values was considered by committee. Please see section 3.18 of the final appraisal document.

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			In the previous model, the company measured disutilities for caregivers relative to the convulsive seizure-free state, rather than UK norms. Given recruitment constraints, only vignette profiles for the convulsive seizure-free and the two worst health states were performed. As a conservative measure, the company set the caregiver disutilities to zero for the seizure-free and ≤ 8 convulsive seizure health states. In the base case following ACD, the company has measured caregiver disutilities relative to UK VAS norms of 0.828 (Szende A, et al. 2014. DOI 10.1007/978-94-007-7596-1). See also 3.21 (below) - any small uncertainty in the disutility estimates is likely to be outweighed by not including disutilities for the many other carers/family members whose quality of life is impacted.	
20	Consultee (company)	GW Pharma	***Utility values in the economic model*** **Committee Conclusion(s) from ACD** 3.21 The company's approach to modelling carers' quality of life may overestimate the effect of caring for someone with Dravet syndrome. The committee was concerned that the company's approach meant that the caring burden increased linearly the more carers a patient had. However, for a patient with multiple carers, it expected there to be less effect on the quality of life of each carer because they would 'share' the burden. So, while the total burden for 1.8 carers may be greater than the burden for a sole care, it would likely not be 1.8 times greater. The committee acknowledged the substantial effect that caring can have on quality of life. However, it concluded that the company's approach to incorporating carers' quality of life in the model may have overestimated the effect. The company considers that applying the disutility to carers equally is appropriate: • In previous NICE submissions with a carer disutility included for more than one carer (e.g. ataluren for Duchenne Muscular Dystrophy (HST3); disutility applied for 2 and 3 carers), there is a precedent where each carer was allocated the same disutility. • The vignette study specifically asked respondents to evaluate their *own* perception of quality of life. The majority of respondents had a partner, so it is reasonable to assume that the disutility estimates are representative of an individual's quality of life decrement where another carer was present. • In a severe and life-threatening disease such as DS, where patients are at a significant ongoing risk of injury and death from their seizures, have multiple co-morbidities and often require lifelong round-the-clock care, it seems unlikely that a 'shared' burden reduces the disutility for each carer. This has been confirmed by the company in interviews with clinical experts. Since the date of the committee meeting, the company has conducted further interviews with clinical experts in order to understand the number of carers and the impact on their quality of life of caring for a patient with DS. The clinical experts interviewed stated that 2 carers is the minimum (this does not include 'paid-for' care outside the family), and 3 carers is more usual since round-the clock-care is often required. They considered that it is not just the primary carers such as the parent(s) who have their quality of life impacted, but also other carers/family members (e.g. siblings, grandparents, aunts and uncles).	Comments noted. The company's approach to applying utility decrements to carers was considered by committee. Please see section 3.19 of the final appraisal document. The committee did not change its conclusion on the number of carers to include in the model. Please see section 3.19 of the final appraisal document.

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			One clinician interviewed referred to a publication about the impact on siblings (Hames, A and Appleton, R; *Seizure* 18 (2009) 699-701). An extract from this publication clearly outlines this impact: "A few children commented on the responsibilities they felt for some of their sibling's care, irrespective of whether the parents were in or out of the house, almost as if they were the parent's extra 'eyes and ears': *'I need to be there quite often to look out for him'* (12-year-old sister) and *'I feel as though my parents sometimes depend on me when they go out shopping'* (16-year-old brother). Another commented that he felt that it was he and the other siblings in his family who encouraged his brother with epilepsy to lead as normal a life as possible because his parents were continually *'exhausted'* or *'shattered'* and *'couldn't think of anything else but his fits'* (12- year-old brother)." The company has been conservative in only including 2 carers in its base case, when clinicians and patient experts indicate that this severe and life-threatening form of epilepsy impacts other carers/ family members (e.g. siblings, grandparents, aunts and uncles). This was specifically referenced by clinical experts in the committee meeting, and in the committee slides. The company has run scenario analyses varying the number of carers (higher and lower numbers of carers: 3 carers and 1.8 carers) to demonstrate how this affects outcomes. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".	The committee considered the potential benefits for siblings of people with Dravet syndrome. Please see section 3.21 of the final appraisal document.
21	Consultee (company)	GW Pharma	***Cost-effectiveness results*** **Committee Conclusion(s) from ACD** 3.23 The committee would like to see a model that incorporates its preferred assumptions. The committee agreed that it would like to see a revised model that more adequately reflects Dravet syndrome and captures the costs and benefits of treatment with cannabidiol. The committee's preferred approach is for a model that: • has a structure that adequately reflects Dravet syndrome and captures the benefits of reducing both the number of convulsive seizures and the number of days free of convulsive seizures • explores scenarios around defining the health states by different seizure frequencies • models the usual care arm in the same way as the cannabidiol arm • passes all tests of validity and bias • maintains the relative treatment benefit of cannabidiol compared with usual care for the duration of the open-label extension study • explores a diminishing treatment benefit of cannabidiol after 27 months, including a scenario in which the treatment effect is removed • appropriately incorporates the effect on the quality of life of carers • explores the uncertainty in the utility values for patient and carers • uses mean, rather than median, body weight from the trials to calculate dosages and costs • includes the costs of increasing the dose of cannabidiol in some patients • includes disutilities for the most commonly observed cannabidiol-related adverse events • explores a smaller reduction in the risk of epilepsy-related death in the seizure-free health state accounting for confounding	Comment noted.

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			The company feels that its responses above and its revised economic analysis (see the updated model and the separate document "ID1211 DS economic outcomes after ACD") address all the points made in the summary of the committee's preferred assumptions/scenarios above.	
22	Consultee (company)	GW Pharma	***Other factors*** **Committee Conclusion(s) from ACD** 3.24 Cannabidiol does not meet the criteria for an innovative treatment but there are benefits that are not captured in the model. The committee concluded that cannabidiol did not meet the criteria for an innovative treatment. However, it noted there were additional gains in health-related quality of life that were not included in the QALY calculations. The company welcomes the committee's conclusion that there were additional gains in health-related quality of life that it was not able to include in the QALY calculation. In particular: • Seizure duration. Of note, although data on these outcomes could not be used in health state construction within the model, CBD did reduce seizure duration (as measured using the Subject and Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)) in GWPCARE2. • Co-morbidities, including long-term cognition, behaviour, mobility and learning difficulties o In the DISCUSS study in DS, comorbidity scores were better in patients with fewer versus more seizures o The SIGN guidelines (Epilepsies in children and young people: Investigative procedures and management. A national clinical guideline), when referring to LGS (a good analogue for DS), state that "Earlier and better seizure control may reduce associated comorbidity of LGS including significant long-term permanent cognitive impairment, and behavioural side effects, all of which significantly reduce quality of life for patients and their carers". The impact on siblings of better seizure control. The specific effect on the HRQoL of siblings was cited in the committee meeting. Although the company will test this impact in scenarios that vary the number of caregivers (see 3.21 above), the specific disutility for siblings cannot be accommodated in this analysis.	Comment noted. The committee considered factors not captured in the calculation of the quality-adjusted life years. Please see section 3.21 of the final appraisal document.
23	Consultee (Professional organisation)	ABN (endorsed by RCP)	Acknowledging limitations under which the ACD was prepared, we would like to note that for adults with Dravet Syndrome, clobazam may not be the antiepileptic drug with which cannabidiol will be used. This is for a variety of reasons. Whilst accepting that this is not the primary focus of the ACD, it is another important factor to consider in reviewing the evidence in order to come to a recommendation..	Thank you for your comments. Comment noted. The committee appraised the cost-effectiveness of cannabidiol within its marketing authorisation for "use as adjunctive therapy of seizures

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
				associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older."
24	Consultee (Professional organisation)	ABN (endorsed by RCP)	We consider that all the relevant evidence has been taken into account. The best quality evidence emerges from the limited number of randomised controlled trials undertaken and these have been taken into account.	Comment noted.
25	Consultee (Professional organisation)	ABN (endorsed by RCP)	We consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We are disappointed in the current limitations of the modelling undertaken by the company, as they limit confidence in the modelling and therefore adversely affect the possibility that the technology will be made available for people in great need of alternative treatments.	Comment noted. Cannabidiol is recommended for routine use in the NHS.
26	Consultee (Professional organisation)	ABN (endorsed by RCP)	We consider that the provisional recommendations are a sound and suitable basis for guidance to the NHS.	Comment noted. Cannabidiol is recommended for routine use in the NHS.
27	Consultee (NHS)	NHS England	Page 1 – the link to the committee papers take you to Lennox Gastaut committee papers rather than those with relation to Dravet syndrome	Thank you for your comments. The link has been corrected.
28	Consultee (NHS)	NHS England	This group of patients are at high risk of continuing seizures despite currently available AEDs. There is a high unmet need with regard to seizure control. There is high expectation that Cannabis based medicinal products will fulfil this unmet need. The current evidence available is only with regard to CBD; this shows evidence of short term efficacy compared to placebo. The committee have reviewed all evidence available.	Comment noted. Cannabidiol is recommended for routine use in the NHS.
29	Consultee (NHS)	NHS England	The EMA have ruled approval if in conjunction with clobazam. Many children will have trialled clobazam; if they no longer remain on clobazam it is likely they have experienced adverse effects	Comment noted. Committee appraised the cost-effectiveness of cannabidiol within its marketing authorisation for "use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older."
30	Consultee (NHS)	NHS England	It is difficult to follow the economic model utilised. Many of the data put forward would be speculative, without true data on which to work. NHS England acknowledge the criticisms of the modelling, but much of the data used would be tenuous whereas the data on efficacy is more reliable.	Comment noted.
31	Consultee (Patient organisation)	Epilepsy Action	Evidenced short term efficacy should be viewed in the context of the recognised severity of Dravet syndrome and the potential ongoing risks, including risks to life, of current seizure activity. In light of the often intractable nature of the condition, high levels of resistance to current NHS treatments and associated increased risks of premature mortality, available clinical evidence of short term efficacy and tolerability should carry more weight in the appraisal process.	Thank you for your comments. Comments noted. Cannabidiol is recommended for routine use in the NHS.

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
			In March, Epilepsy Action compiled a Patient Impact Report around cannabidiol for Dravet and Lennox-Gastaut syndrome (LGS) for the Clinical Priorities Advisory Group (CPAG). The report was informed by the feedback of parents/ carers' of people with Dravet syndrome and LGS, four and five respondents respectively. Question two of the patient impact report focused on the lived experience of people with these syndromes with specific attention paid to the impact of the condition on a person's daily life, physical capability and mental/ psychological wellbeing. Extract from CPAG Patient Impact Report, March 2019: *People with Dravet syndrome and LGS experience regular, often daily, seizures and many of these seizures can be prolonged and ultimately life threatening. In light of the frequency and severity of seizures associated with these syndromes, patients often have high care needs.* *One parent carer of a person with Dravet syndrome noted that their son experiences a variety of seizure types up to 50 times day. 'He experiences tonic clonic, focal, partial and absence seizures (sometimes 30-50 of these per day)'.* *They went on to highlight the severity of some of these seizures and the associated risks – '[their son] is hospitalised every 5 weeks on average due to a prolonged seizure'. During these hospitalisations, their son will often have to be intubated and placed in PICU at the children's hospital.* *Parents/ carers of people with LGS also noted the frequency and severity of seizures associated with the condition. One parent carer noted that 'We can go for days on end with continuous seizure activity and no rescue meds make any difference'. Another parent carer mentioned that their son continues to have weekly seizures, 'this has been the case for 34 years'. Another parent went on to list the type of seizures their son experiences, including 'atonic seizures…tonic seizures…myoclonic seizures' and noted that these seizures occur day and night. One parent carer went on to note that seizures happen day and night necessitating continuous one to one care.* *Another parent carer of a patient with LGS noted the impact of seizures on their son's heart rate and breathing highlighting that he could not be safely left alone. Two respondents highlighted the quantities of medications that many people with LGS are prescribed in an attempt to control or limit seizures. One parent carer noted that their son is currently taking five antiepileptic drugs (AEDs) without adequate seizure control. Another parent carer has to administer three AEDs, again with limited seizure control, along with other drugs and treatments: 'he needs medicating 6 times a day…he requires supplementary milk feeds through the tube due to weight loss and not willing to eat sufficiently'.* *People with Dravet syndrome and LGS often live with a range of comorbidities that can have a major impact on their day-to-day lives. Many also have a spectrum of learning disabilities with most being severe and many will be on the autistic spectrum.*	The unmet need for new treatment options for Dravet syndrome was considered by the committee

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
			Many people with Dravet will have difficulties with communication, some being non-verbal and unable to communicate at all. Sleep issues are a common problem with some having less than 2 hours a night. Those with Dravet syndrome have a spectrum of mobility issues, some have no mobility and use wheelchairs while others can have fairly good mobility but with balance issues. It is common to have a gait abnormality, which deteriorates over time. Feeding issues are also common with some patients eventually having to be tube fed. Other comorbidities include ADHD, behaviour issues and incontinence. *The prevalence of comorbidities in people with LGS was also highlighted by three of the five respondents in his cohort. One parent carer noted that their son also had 'severe learning difficulties' while another noted that their son had other complex health needs as well as his epilepsy. Another parent carer explained that their son was also 'significantly cognitively impaired'.* *These patient cohorts are often also at a significantly increased risk of associated injuries and ultimately death as a result of SUDEP or prolonged seizures. Injuries due to a fall during seizures can be severe, especially as patients get older. In relation to LGS, a parent carer noted that their son broke his leg after a drop seizure further exacerbating his care and support needs. They went on to succinctly note: 'LGS and the seizures it causes have major knock on effects on people lives, that severely exacerbate the already huge challenges that affect the individual and their family.'* *People with Dravet syndrome and LGS are also at high risk of SUDEP. This was succinctly noted by a parent carer of a child with Dravet syndrome, 'SUDEP is never far from our thoughts'. A parent carer of a son with LGS went on to say that their son 'continues to carry five risk factors around SUDEP. His doctor has said he places his risk at 1:100. This causes us untold anxiety and hinders recruiting paid support workers to care for him.'* *People with Dravet syndrome and LGS will require constant care throughout their lifetime. A parent carer of a child with Dravet syndrome noted that their son required '24 hour care and 24 hour monitoring for seizures'. In light of the current low rates of seizure control or management amongst people with Dravet and LGS these care needs are likely to be constant throughout their lifetimes. Two respondents highlighted that LGS prevents people with the condition from being able to look after themselves and denies them their independence.* *'My son is 16 with LGS, he is unable to do anything for himself so we have to provide 24 hour care'* *'He has no independence and requires continual supervision and support'*	
32	Consultee (Patient organisation)	Epilepsy Action	.20 – The inclusion of modelling to attempt to capture and reflect the potential impact of Dravet syndrome on carers' quality of life is very welcome. Severe and intractable epilepsies often have a profound impact of carers' and families. Whilst reductions in convulsive seizures and drop seizures are of most medical benefit, other changes in seizure activity, including altering patterns of seizures leading to increased seizure free days, should	Comments noted. The benefits of an increased number of seizure-days was considered by

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
			be viewed as clinically/ statistically significant for the purposes of this appraisal. For some carers' of people with severe and intractable epilepsies, the unpredictability of seizures can be as burdensome, and subsequently as important, as frequency and severity (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6546015/). As such, the treatment should be appraised with due consideration paid to the broadest definition of the seizure burden on patients and carers'. This will ensure relevant modelling accurately assesses the wider potential benefits of the treatment.	committee. Please see section 3.2 of the final appraisal document.
33	Consultee (Patient organisation)	Epilepsy Action	.21 – Dravet syndrome often has a profound impact beyond immediate carers', including on wider families. This should be recognised and reflected in this appraisal. In March, Epilepsy Action compiled a Patient Impact Report around cannabidiol for Dravet and Lennox-Gastaut syndrome (LGS) for the Clinical Priorities Advisory Group (CPAG). The report was informed by the feedback of parents/ carers' of people with Dravet syndrome and LGS, four and five respondents respectively. One of the questions in the report was focussed on the impact of these conditions on a patients' family, friends and caregivers. A full copy of the response to this question from the patient impact report is included below. The additional risk factors faced by people with Dravet syndrome feature heavily, including the increased prevalence of premature mortality, along with high care and support needs including administering multiple medications throughout the day and night and the prevalence of comorbidities. Extract from CPAG Patient Impact Report, March 2019: *People with Dravet syndrome and LGS often require round the clock care and most are fully dependent on parents and carers throughout their lives. The majority will never be able to live fully independent lives.* *Caring for someone with the condition is extremely isolating and affects every aspect of family life. There is usually a financial impact with one parent needing to give up their job/career to become a full time carer. One parent carer of a child with Dravet syndrome noted that 'the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially.'* *It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and relationships noting that 'it has been a real toll on our health and family life'. This was echoed by other respondents, 'we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up.'* *Many parents at some point will suffer from depression and anxiety and counselling is not readily offered to these families. The same parent carer quoted above went on to note that the burden of*	Comment noted. The impact on health-related quality of life of caring for someone with Dravet syndrome was considered by committee. Please see section 3.1 of the final appraisal document. The impact on health-related quality of life on siblings of people with Dravet syndrome was taken into account by the committee. Please see section 3.21 of the final appraisal document.

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
			caring for their son has made them suicidal. *The situation is very similar for families affected by LGS. The impact of the condition on parent carers and other family members was made clear by a number of LGS respondents. One parent carer noted 'the impact on our mental health and wellbeing has been significant. Without the respite we have been able to get, I doubt we would have managed at times.' Another parent carer mentioned that they had suffered a recent bout of serious ill health attributable in part to a weakened immune system they link to the exhaustion of caring for their son.* *There is also often a significant impact on siblings of people with these syndromes. Two parent carers of people with LGS highlighted the impact of their siblings condition on their other children's lives. One noted that while it was difficult to define the impact of the condition on their daughter, '[her brother's condition] has no doubt hugely impacted her life, the time we have been able to give her, the emotional and psychological pressures etc.'* *Another parent carer of a child with LGS highlighted that 'our eldest daughter won't have children for fear of having a child with an epilepsy. The other daughter feels the weight of caring for her brother' when her parents are no longer able to.* *The impact on siblings was also noted by a parent carer of a child with Dravet. In relation to their young daughter they said, 'helping with X [their son with Dravet syndrome] will undoubtedly have a huge impact on her in the future'.* *Beyond siblings, living with Dravet syndrome or LGS often affects the whole family. A parent carer of a child with Dravet felt compelled to move abroad to access support from grandparents.* *Parents/ carers of people with Dravet syndrome and LGS often struggle to receive support both practically and financially due in part to a lack of understanding and adequate support across most services. One parent carer whose son has LGS noted 'we struggle to get carers to help as he has complex health needs as well as his epilepsy. We struggle with professionals understanding how tiring it is'. This was echoed by a parent carer of a child with Dravet syndrome who also noted the complexities and challenges of coordinating professional care when it is available, 'X needs 24hr care and 24hr monitoring for seizures, we get help from Continuing health care for night support (waking nights 7-days a week) but we still have to manage lots of carers (interviews, people in our house, wages etc.). It has been a real toll on our health and family life. 14 years of it so far!'* *This experience was echoed by another family who cared for a child with Dravet syndrome 'as a family over the years we became social lepers, always trying to maintain respite given by LA [Local Authority] but it's exhausting.'* *Life for families affected by these conditions is extremely challenging and stressful with the constant daily fear and worry due to their child being at high risk of SUDEP and death due to prolonged seizures. A parent carer of a child with Dravet syndrome noted the intense medication regime that their child required and the potential consequences if a mistake is made with administering the medications.*	

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
			'Each morning, it's so important that we administer the correct AEDs as we are aware of the consequences if this doesn't happen. Having 3 AEDs, morning and night, plus a 3-day course of antibiotics each week, is now set as a routine'. *The additional risk factors that are prevalent amongst people with Dravet and LGS can make it harder for families to access professional care. A parent carer whose son has LGS noted '[our son] is significantly cognitively impaired and continues to carry five risk factors around SUDEP. His doctor has said he places his risk at 1:100 . This causes us untold anxiety and hinders recruiting paid support workers to care for him. After all who wants the responsibility of caring for him at £8.00 per hour.'*	
34	Consultee (Patient organisation)	Epilepsy Action	There is a strong case for cannabidiol to be appraised as an innovative treatment by NICE. Given the often intractable nature of Dravet syndrome and high levels of resistance to treatments currently available on the NHS, the available RCT evidence suggests that cannabidiol presents a potential 'step-change' in terms of outcomes for this patient group. Cannabis-based medicinal products (CBMPs), including cannabidiol, offer therapeutic potential as a new grouping of treatments. The potential of CBMPs, including cannabidiol, as a new category of antiepileptic drugs should be considered when assessing cannabidiols positioning as an innovative treatment. While the mechanism of action of cannabidiol as an antieplietpic drug is unknown, it is likely to be a novel pharmacological mechanism.	Comment noted. The committee considered the innovative nature of cannabidiol. Please see section 3.22 of the final appraisal document.
35	Web comment (Patient organisation)	Young Epilepsy	Neither the company's base-case analysis nor the ERG's scenarios give an accurate reflection of the cost effectiveness of cannabidiol We recommend that the guidance on this technology is considered for review 12 to 18 months after publication of the guidance, rather than after three years. Dravet syndrome has a significant impact on the lives of children and young people, as well as their families. As the evidence develops around cannabidiol use for treatment-resistant epilepsy, it is crucial that families have the earliest opportunity to benefit from new treatments. We note that further cannabidiol research is already underway and recommend that any relevant evidence should be reviewed at the earliest opportunity. Many families have received mixed messages regarding if and when their child might have access to cannabidiol as an NHS treatment. We urge NICE to ensure that the process and timescales for appraising cannabidiol are clearly communicated to families across the country on an ongoing basis. Yes, the relevant clinical evidence has been taken into account. Based on the information provided, the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We note that further interpretation of the evidence will be required once a revised economic model is provided by the company. Based on the information provided, the recommendations are sound and a suitable basis for guidance to the NHS. Young Epilepsy recognises the need for further research into the efficacy and safety of	Thank you for your comments. Comments noted. Cannabidiol is recommended for routine use in the NHS.

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
			cannabidiol for severe treatment-resistant epilepsy in children and young people, including: • Long term efficacy and safety of use in children and young people • Cognitive, psychological and emotional impact of use in children and young people • Impact of use in children and young people on structural and functional brain development We strongly recommend that specialist clinicians should still be able to prescribe cannabidiol on a case-by-case basis.	The committee concluded that the long-term efficacy and safety of cannabidiol was uncertain. See sections 3.5 and 3.6 of the final appraisal document.

ID1211 DS - GW ACD Responses 16th September 2019

This document contains the company's responses to the NICE ID1211 Appraisal Consultation Document (ACD), "Cannabidiol with clobazam for treating seizures associated with Dravet syndrome" issued on 16th August 2019.

This document should be read **in conjunction with the separate document** provided by the company: "ID1211 DS economic outcomes after ACD" and the cost-utility model.

Each of the key issues raised in the ACD are reproduced below (shown in boxes, each entitled "Committee Conclusion(s) from ACD"). The company's response to each issue follows immediately after each box.

Clinical-effectiveness evidence

Committee Conclusion(s) from ACD
3.4 The committee has not seen data to assess whether the patients in the clinical trials reflect those who would have cannabidiol in the NHS. The company's submission included the baseline characteristics of the full trial population, but not the baseline characteristics of the subgroup that had cannabidiol with clobazam. Therefore, the committee concluded that it was unable to determine whether this subgroup reflected patients with Dravet syndrome who would have cannabidiol in the NHS.

The baseline characteristics from the GWPCARE2 and GWPCARE1 trials for patients who were taking clobazam at baseline (the 'on-clobazam' group) are reproduced in the tables below.

The company has discussed these baseline characteristics in interviews with UK clinical experts, who have confirmed that the on-clobazam patient population baseline characteristics are representative of patients with DS in their clinical practice and in the UK NHS clinical setting in general.

Baseline Characteristics for patients in the on-clobazam subgroup (GWPCARE2):

Baseline characteristic	In conjunction with clobazam		
	CBD 10 mg/kg/day	CBD 20 mg/kg/day	Placebo
Number randomised	[redacted]	[redacted]	[redacted]
Age, mean (SD)	[redacted] Range [redacted]	[redacted] Range [redacted]	[redacted] Range [redacted]
Gender	[redacted] male female	[redacted] male female	[redacted] male female
Baseline total seizure frequency per 28 days: median (range)	Total [redacted]	Total [redacted]	Total [redacted]
Baseline convulsive seizure frequency per 28 days: median (range)	Convulsive [redacted]	Convulsive [redacted]	Convulsive [redacted]
Prior AED treatments	Median 4 Range 0 to 12	Median 4 Range 1 to 11	Median 4 Range 0 to 9
Concurrent AED use	Median 3 (Range 1 to 5) Valproate Clobazam Levetiracetam Topiramate Stiripentol	Median 3 (Range 2 to 4) Valproate Clobazam Levetiracetam Topiramate Stiripentol	Median 3 (Range 1 to 5) Valproate Clobazam Levetiracetam Topiramate Stiripentol

Baseline Characteristics for patients in the on-clobazam subgroup (GWPCARE1):

Baseline characteristic	In conjunction with clobazam	
	CBD 20 mg/kg/day	Placebo
Number randomised	[redacted]	[redacted]
Age, mean (SD)	[redacted] Range [redacted]	[redacted] Range [redacted]
Gender	[redacted] male female	male [redacted] female
Baseline total seizure frequency per 28 days: median (range)	Total [redacted]	Total [redacted]
Baseline convulsive seizure frequency per 28 days: median (range)	Convulsive [redacted]	Convulsive [redacted]
Prior AED treatments	Mean 4.4; SD 3.6	Mean 5.1; SD 3.4
Concurrent AED use	Mean: 3.0; SD 1.0 Clobazam Valproate Levetiracetam Topiramate Stiripentol	Mean: 3.1; SD 0.8 Clobazam Valproate Levetiracetam Topiramate Stiripentol

Clinical-effectiveness evidence

Committee Conclusion(s) from ACD
3.5 The committee concluded that cannabidiol with clobazam reduces seizure frequency compared with usual care, but that the long-term efficacy is uncertain. The company stated that the interim results of the open-label extension study (GWPCARE5) showed sustained efficacy with cannabidiol over 48 weeks of follow up. The committee noted that the company had not presented it with detailed methods or results for the open-label extension study in the subgroup of patients taking cannabidiol with clobazam.

Detailed methods and results (up to 156 weeks) from interim analysis of data from the open-label extension study (GWPCARE5) for the subgroup of patients with DS taking cannabidiol with clobazam are shown in Appendix 1.

These interim results from GWPCARE5 showed sustained efficacy with cannabidiol over 156 weeks of follow up.

Stopping treatment

Committee Conclusion(s) from ACD
3.7 The committee concluded that the stopping rule proposed by NHS England is appropriate, but that response to treatment should be assessed after 3 months of treatment. The committee was aware that the company implemented the stopping criteria proposed by NHS England in its model after 6 months of treatment with cannabidiol. However, during technical engagement, clinical experts reported that they review patients every 3 months in the first year then annually. The committee considered that applying the stopping rule at 3 months would be appropriate and aligned with the follow up in the clinical trials.

The NHS England stopping rule applied from 3 months has been implemented as a scenario in the model.

In the base case, stopping rules at two further timepoints have been implemented: CBD can now be stopped in the model at 6 months (as previously) and also at 12 and 24 months. At all these timepoints, the stopping rule is based on that specified by NHS England, and estimated from the patient level data in the GWPCARE5 trial. Specifically, it is a "one-off" discontinuation rate that is calculated based on the percentage of non-withdrawn patients in each health state at each timepoint in the trials who did not achieve a ≥30% reduction in convulsive seizures, but who did achieve this outcome at the last timepoint.

The 12 and 24 month stopping points have been added to the model following guidance from NHSE at the committee meeting that treating clinicians would have to attest (e.g. via Blueteq) that CBD continues to meet the NHS England efficacy requirement at annual timepoints following treatment initiation, or else stop treatment with CBD.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

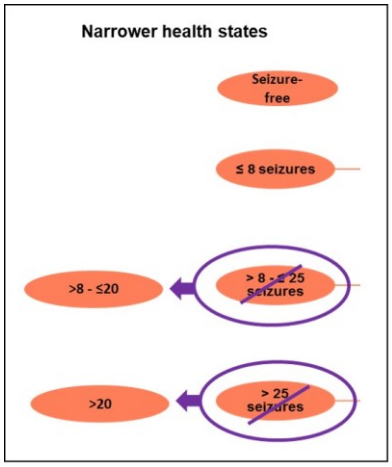
Company's economic model

Committee Conclusion(s) from ACD
3.8 The committee concluded that the modelled health states did not adequately represent Dravet syndrome The committee was concerned that the health states based on seizure frequency had been arbitrarily derived because they were not based on any clinical rationale and represented wide ranges of seizure frequencies. It would have preferred to see scenario analyses categorising the health states differently. In particular, the committee would have preferred to see narrower seizure frequency ranges to better capture the effect of changes in this parameter on costs and benefits.

There is no clinical consensus in DS, a heterogeneous and ultra-orphan disease, on what the seizure thresholds for the health state categories should be with regard to quality of life, so it would be extremely challenging to have a clinical rationale based only on seizure numbers. The original health state categories were therefore derived by dividing the original ITT population into three equal groups, mathematically, in order to avoid bias in any group.

The company has retained the original health state definitions in its base case, as this maintains the validity of the utility estimates from the vignette study.

However, further to discussions with the NICE technical team and clinical experts, the company has also run a scenario that lowers the upper threshold in order to narrow the middle health state seizure frequency range as requested by the NICE committee (see diagram below).



The clinical rationale for the new health state thresholds (≤8 convulsive seizures per month; >8 to ≤20; and >20) is that in the 'middle' seizure category (>8 to ≤20), most patients who have either a 50% decrease or a doubling in the number of convulsive seizures they have per month (clinical experts confirm that both of these are clinically-relevant and patient-relevant events) will move health state in the model, i.e. they will experience either an increase or a decrease in quality of life.

This approach was deemed plausible by the NICE technical team.

The company has also validated this approach with UK clinical experts, who concurred that it was a practical and plausible approach to narrowing the seizure frequency ranges in the health states, given the lack of clinical consensus in DS, a very rare disease.

Narrowing the seizure frequency ranges in the health states as described above, has a slight impact on the cost-effectiveness, decreasing the ICER by a small amount.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Company's economic model

Committee Conclusion(s) from ACD
3.8 The committee also noted the company did not model the benefits associated with reducing non-convulsive seizures because it considered convulsive seizures to be more important to people with Dravet syndrome and their families and carers. However, it acknowledged that these may be challenging to include in the model.

The company appreciates the committee's acknowledgement that it may be challenging to include non-convulsive seizures in the model.

As the company has indicated previously, data from the CBD Phase 3 trials shows that the average number of non-convulsive seizures is lower in health states with fewer convulsive seizures. Furthermore, CBD has a treatment effect versus placebo on non-convulsive seizures in GWPCARE2, and the reduction from baseline is maintained over the GWCPARE5 study. Therefore, there is "hidden upside" in terms of QALY gain that was not captured in the previous model from improving outcomes in these seizure types.

The contribution of non-convulsive seizures to quality of life has now been included in the company's base case. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Although there is a dearth of utility data relating to non-convulsive seizures in the literature, in order to address the committee's concerns, the company conducted a further literature search and has identified a suitable analogue (de Kinderen, RJ *et al*, Epilepsy Res. 2016 Sep;125:24-31) to estimate the contribution of non-convulsive seizures in the base case. The de Kinderen study reports an algorithm estimating the independent utilities of non-convulsive seizure types, which are derived from a regression model using data from a TTO study in the general population.

Using this algorithm, the company has calculated disutility estimates for the contribution of non-convulsive seizures to HRQoL for each of the convulsive-seizure defined health states in the model. As a conservative measure, these disutility values were reduced by 25% relative to the figures estimated from the de Kinderen study (see tables below).

These disutilities were then assigned to the model's convulsive-seizure health states, based on the mean number of non-convulsive seizures per health state observed in the treatment period of the GWPCARE2 study (see tables below).

# seizures per 28 days*	Utility estimate	Disutility estimate**	75% of disutility estimate
0	0.857	0	0
4	0.752	-0.105	-0.079
8	0.695	-0.162	-0.122
28	0.684	-0.173	-0.130
56	0.647	-0.21	-0.158

*Zero seizure utility is that for a state of 1 absence seizure per week
**Based on zero-seizure health state as a reference point

Convulsive seizure health state	Mean number of non-convulsive seizures* per month (GWPCARE2)	Disutility estimate from de Kinderen
Seizure free	0	0
≤8	4	-0.079
>8 to ≤25	10	-0.122
>25	12	-0.122

* Partial seizures

Company's economic model

Committee Conclusion(s) from ACD
3.8 The committee was also concerned that, in the usual-care arm, after cycle 2, some patients stayed in the highest seizure frequency health state for the rest of the model. It considered this was not clinically plausible.

In DS, the number of seizures an *individual patient* experiences may fluctuate over time. In addition, this is already a refractory population and there is no reason to assume that there is an underlying progression of the disease, such that patients get generally worse. Thus, in a *cohort* of patients for modelling purposes, on average, for every patient whose seizures increase at a given timepoint, there will be another whose seizures decrease, and it is reasonable to assume that the distribution of patients across heath states will be consistent over time.

From cycle 2 in the company's model, the distribution of health states at the end of cycle 1 in the usual-care arm was applied statically (i.e. without re-transitioning). This was defined by the distribution observed in the usual-care (placebo) arm at the end of the GWPCARE2 study, from which transition probabilities in cycle 1 of the usual-care arm were derived. As such, some patients on usual-care remained in the highest health state for the duration of the model but, *importantly*, others remained in the lowest (and all other) health states.

There are no longitudinal natural history data available in this very rare condition. Therefore, the company feels that the "snapshot" of health states in the usual-care/placebo arm at the end of GWPCARE2 Phase 3 trial represents the best data available to approximate how patients not treated with CBD will, on average, be distributed across health states.

As further evidence for the validity of this assumption, seizure outcomes versus baseline are very stable over time in the GWPCARE5 study (see Appendix 2). Therefore, any method to "reverse calculate" health state distributions in the usual-care arm over the open-label extension period would give a very stable result that would be unlikely to improve on the accuracy of the company's assumption above.

Based on these considerations, the company has continued with its original approach (i.e. from cycle 2, the distribution of health states at the end of cycle 1 is applied statically in the usual-care arm and to discontinued CBD patients).

In the company's base case following ACD, this assumption is applied to lifetime, meaning that the relative treatment effect for CBD is applied for the full time horizon. The company is not aware of a more accurate way of modelling the untreated course of the disease, given the absence of natural history information in this very rare condition.

Company's economic model

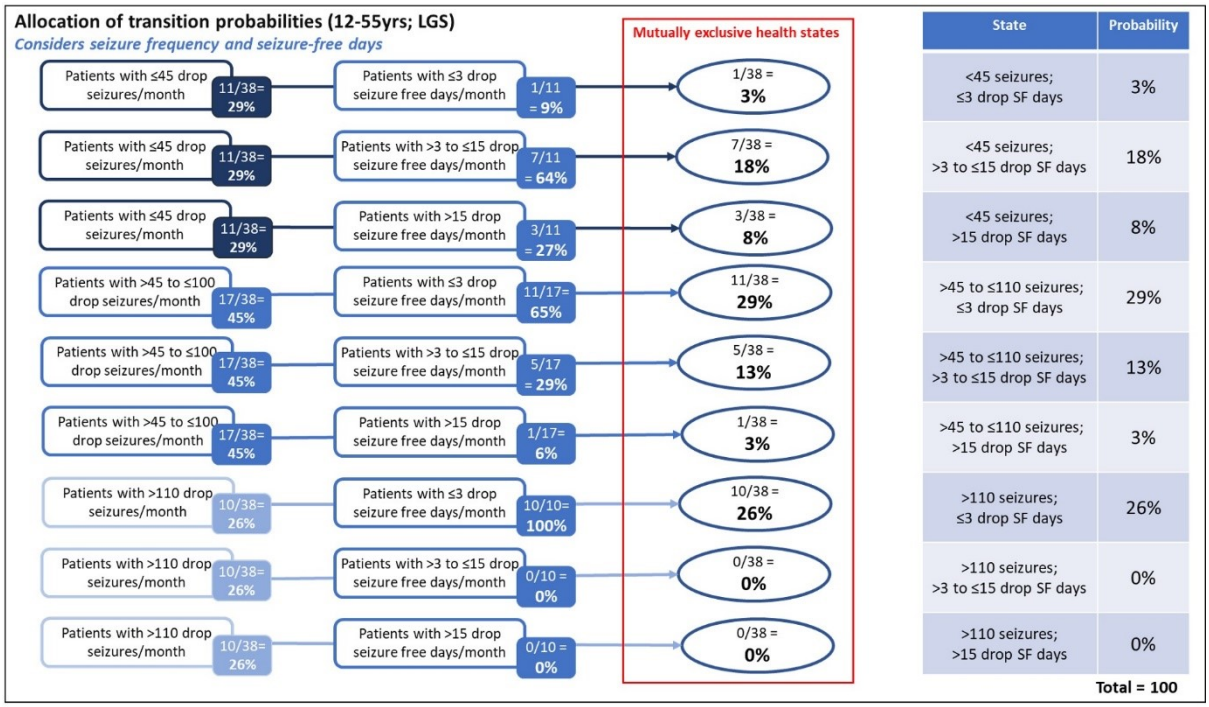
Committee Conclusion(s) from ACD
3.9 The committee concluded that it was appropriate to capture the benefits of having more convulsive seizure-free days. However, it was concerned that the company's approach to modelling these increased the complexity of the model. The committee considered it unusual to firstly categorise into numbers of seizures, and then subdivide these into number of seizure-free days. It considered that this may have resulted in 'double-counting' the benefits of reducing the frequency of seizures. It therefore noted that an alternative model structure may have better reflected the condition and captured the benefits of both convulsive seizure-free days and convulsive seizure frequency. One such model structure would be a discrete event simulation model examining the effect of different convulsive seizure rates on individual patients.

The company welcomes the recognition from the committee that it is appropriate to capture the benefits of having both convulsive seizure reduction and more convulsive seizure-free days.

The company felt that it had maybe not fully explained how the model allocates patients between seizure frequency and seizure-free days, such that it is not 'double-counting'.

In a call with the NICE technical team and the ERG on 10th September 2019, the company had the opportunity to explain how the model is actually allocating patients between *mutually exclusive* health states, which are defined by the number of seizures and the number of seizure-free days per 28 days.

Please refer to the diagram below, which shows the mutually exclusive health states (and no 'double-counting'). Note: this example (used during the call with the ERG and the NICE technical team) is for LGS, but exactly the same principle applies for DS. There is no 'double-counting'.



During a call with the NICE technical team on 28th August 2019, the company explained that, based on expert advice on when it may be methodologically appropriate to select a patient-level simulation in preference to a Markov simulation, the company does not believe that a discrete event simulation would improve the accuracy of outcomes versus a Markov model.

Based on the above, the company plans to continue with a Markov model. It should be noted that the standard Markov model has been widely used in other epilepsy HTAs in the UK (e.g. SMC/AWMSG) and in the literature.

Company's economic model

Committee Conclusion(s) from ACD
3.10 The usual care arm should be modelled in the same way as the cannabidiol arm. The committee concluded that it would have preferred the outcomes in the usual care arm to be based on trial data up to cycle 9, as in the cannabidiol arm.

The trial data for cannabidiol used in cycles 2-9 was taken from the GWPCARE5 *open-label* extension study (i.e. no placebo arm).

In the absence of a comparator arm in GWPCARE5 (an open-label study), in the usual-care arm of the model the company has maintained the distribution of patients between health states at the end of cycle 1 for the lifetime of the model. This distribution is derived from the *placebo arm* in GWPCARE2. As per the explanation in 3.8 above, in the absence of natural history data, this is the most appropriate way of approximating the seizure distribution in the usual-care arm.

The relative treatment effect is applied to *lifetime* in the company's new base case (see Appendix 3).

However, this approach clearly *over-estimates the benefit of usual-care*, as it assumes that the large improvement from baseline on seizure frequency in the placebo arm of the blinded, randomised controlled GWPCARE2 trial would be present in the open-label GWPCARE5 study. This is improbable, as any "trial effect" is likely to be higher in a blinded controlled trial than in an open-label study. This is supported by the observation that the reduction in convulsive seizures for carrying-over placebo patients re-baselined at the start of the GWPCARE5 study are in the range of those observed from baseline in the US Early Access Programme real world study (Laux et al 2019), in which there is unlikely to be a large "trial effect.

Maintaining this benefit for usual-care for the duration of the model *biases the model considerably in favour of usual-care* and underestimates the cost-effectiveness of cannabidiol. This was noted in the NICE technical report:

> "The technical team notes that there is no comparative data beyond 14 weeks (i.e. the first cycle of the model) and that assuming the placebo effect is maintained in subsequent cycles may *overestimate the treatment effect of current clinical management*."

Assuming that the large placebo effect observed over 3 months in the blinded GWPCARE2 trial would be of the same magnitude over 2 years in the open-label GWPCARE5, and carried indefinitely in this highly refractory population of patients when treated with existing therapies is unrealistic and significantly penalises cannabidiol in terms of its benefit and value to patients.

Therefore, the company has also implemented a scenario in which the end-of-cycle-1 health state distribution in the usual-care arm is maintained from cycles 2-9 for usual-care and discontinuing CBD patients, who then revert to the distribution of health states at baseline.

The company considers that this provides a scenario which avoids significantly overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Company's economic model

Committee Conclusion(s) from ACD
3.11 The committee concluded that the results from the company's model were not valid. i) The ERG was concerned that the results of the company's model were not valid. The ERG explained that, when it set all the clinical inputs in the model as equal for both cannabidiol and usual care, it expected that the estimated quality-adjusted life years (QALYs) would be the same for both treatments. However, the model produced higher QALYs for cannabidiol. The company stated that the model produced equal QALYs only under certain conditions. The committee did not consider this sufficient. It agreed with the ERG that the model was flawed, and that this test of validity should hold for the base-case settings. ii) The committee recalled that patients receiving each treatment took different paths through the model and considered that this may have biased the results in favour of cannabidiol. iii) It was also concerned that there may have been unidentified flaws in the model coding.

In a call with the NICE technical team and the ERG on 10th September 2019, the company had the opportunity to address the ERG's concerns about model validity.

i) and ii) In a series of demonstrations, the company demonstrated the model's validity in real time.

Specifically, the company showed that under the conditions for 'Test 2' (see table below and Appendix 4), which set the clinical efficacy and safety parameters to be equal between cohorts and made CBD discontinuation rates equal across health states at all time points, a null QALY gain is returned.

The model does not return a null QALY gain in the base case if discontinuation rates are not set to be equal between health states ('Test 1'; see table below and Appendix 4). This is expected. It occurs because patients can discontinue CBD, but not usual-care (logically, it is not possible in practice to discontinue 'usual care'). Patients will discontinue CBD at faster rates when they have more seizures (as observed in the trials). Variable CBD discontinuation rates cause asymmetry in the health state distributions for CBD and usual-care patients in the model, even when clinical parameters are set to be equal. This effect is demonstrated in the simulated patient trace for the first 3 cycles for the younger age group in DS (Appendix 4).

Of note, patients do *not* take different paths through the model depending on their treatment allocation.

It is possible in the model to move discontinuing CBD and usual-care patients back to the baseline distribution of health states at the same rate over time. This is shown in Test 3 in the table below. In these circumstances, an artificial "usual-care discontinuation rate" is set up; usual-care patients are maintained in the end-of-cycle-1 split of health states until they "discontinue", at which point they revert to the baseline split of health states. CBD patients go straight back to the baseline split at discontinuation. In Test 3, these rates are equalised, and a null QALY gain is achieved even when CBD discontinuation rates are aligned to the base case (i.e. not uniform across health states).

Test 3 is not a clinically-relevant scenario, but serves to demonstrate model symmetry and validity.

Test	Changes on base case	Tabs in model	QALY Gain
1. Clinical efficacy and safety set equal between arms	○ Transition probabilities for the CBD arm are changed to those for the usual care arm ○ Probability allocations for convulsive seizure-free days for the CBD arm are set to those for the usual care arm ○ Severe adverse event rates on CBD set to 0.00%	SEIZURES "Cycle 1" D21:G24, D44:G47 "Subsequent cycle" O14:BA17, O37:BA40 DAYS D21:F24, D44:F47 SAFETY H35 MORTALITY E16, E20, E29, E33	0.5579

Test	Changes on base case	Tabs in model	QALY Gain
	○ Mortality risk ratio for the convulsive seizure-free health state set to 1.0		
2. Clinical efficacy and safety set equal between arms CBD discontinuation rates uniform across health states	As per scenario 1, plus: ○ Discontinuation rates for all health states in subsequent and long-term cycles set to those for cycle 1 (5.56%) ○ Stopping rules for CBD switched off	DISCONTINUATION G21:G24, I21:I24, G44:G47, I44:I47 GLOBAL SETTINGS E24	0.0000
3. Clinical efficacy and safety set equal between arms Discontinuing CBD and usual care patients go back to the baseline health state split at the same rate in every cycle	As per scenario 1, plus: ○ Usual care "reversion to baseline" rates set equal to the CBD discontinuation rates for each health state in each cycle ○ CBD Stopping rule and "Placebo stopping rule" switched on	DISCONTINUATION E28:I31, E51:I54 GLOBAL SETTINGS E24, E28 (Stopping rates can be seen in DISCONTINUATIONS E81:I84, E88:I91, E128:I131, E135:I138)	0.0000

In Test 1, there is a residual QALY gain that is in favour of CBD. This is a result of seizure control being a key reason to discontinue CBD (as observed for AEDs in clinical practice), and CBD being studied adjunctively to its comparator.

As explained above, the distribution of health states at the end of cycle 1 in the usual-care cohort (which is derived from the placebo arm of the GWPCARE2 trial) is assumed to approximate the average distribution in the treated history of the condition (without adjunctive use of CBD), and is applied statically from cycle 2 onwards for all usual-care and discontinuing CBD patients. This assumption is appropriate because there is: no natural history data in this rare condition; no reason to assume that the distribution of usual-care patients across health states on average would change over time in a population highly refractory to existing medications; no data on seizure outcomes in patients for whom CBD was withdrawn in the trials; no reason to assume an enduring treatment effect for CBD once stopped.

It is thus not clinically relevant to "discontinue" usual-care within the model. This means that linking CBD discontinuation rates to seizure control has the effect of "enriching" the population of patients on CBD who have good seizure outcomes, which will give a residual HRQoL gain. This is a consequence of observation in a cost effectiveness analysis: the purpose of an economic model is to estimate outcomes for a cohort started on a technology versus a cohort on a comparator.

In clinical practice, patients whose seizure control naturally deteriorates on existing treatments over time would progressively be eligible to start adjunctive CBD, off-setting patients on CBD who discontinue due to poor seizure control and regress to being managed only with the mix of existing treatments.

iii) During the call with the NICE technical team and the ERG on 10th September 2019, a third party agency (with significant expertise in health economic modelling and VBA coding) testified that it has performed comprehensive QC and validity testing on the company's model, outlined the tests it has conducted and confirmed that the model had passed all tests.

The experts found no 'unidentified flaws' in the model coding.

Assumptions in the economic model

Committee Conclusion(s) from ACD
3.12 The committee concluded that the mean weight from the clinical trials should be used to model the weight-based dose of cannabidiol.

The weight distribution at baseline of patients with DS (aged 2-11 and 12-18) in the on-clobazam subgroup is shown below.

It can be seen that there are heavier-weight outliers in both age groups that skew the mean weight upwards disproportionately. The median weight is more representative of the group as a whole.

For this reason, the *median* weights have been used in the company's base case model.

A scenario analysis using the *mean* weights has also been implemented.

Assumptions in the economic model

Committee Conclusion(s) from ACD
3.13 The committee concluded that the combined placebo data from the clinical trials should only have been used in a scenario analysis, and that the company should use placebo data from GWPCARE2 in its base case.

As requested by the committee, the base case model now includes data from the usual-care/placebo arm of GWPCARE2 only.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Assumptions in the economic model

Committee Conclusion(s) from ACD
3.14 The company's approach does not appropriately account for the lack of comparator arm in the open-label extension study. Based on the data from the open-label extension study, the company assumed that, after cycle 2, patients in the usual-care arm returned to their baseline health states, while patients taking cannabidiol continued to benefit from cannabidiol...The company explained that it had modelled the treatment effect in this way because there are no data for placebo plus usual care after cycle 2 (everyone received cannabidiol in the open-label extension study). The committee concluded that it would have preferred the company to have accounted for the lack of a comparator arm in the open-label extension study rather than assuming patients would return to baseline. It suggested that one way of doing this would be to extrapolate the relative treatment effect from GWPCARE2 beyond the controlled part of the trial.

The company would like to clarify that its intention in moving patients back to baseline in the usual-care arm was to avoid overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time (and not because there are no comparative data after cycle 1).

Of note, in the technical report, the technical team also concluded that assuming the relative treatment effect is maintained in subsequent cycles may *overestimate the treatment effect of current clinical management* (usual-care).

As per the company's response to 3.10 above, in the usual-care arm, the company has now maintained the distribution of patients between health states at the end of cycle 1 for the lifetime of the model. In the absence of natural history data, this is a reasonable way to extrapolate the relative treatment effect beyond the controlled phase of the trial (i.e. cycle 1).

However, as also noted in 3.10 above, this approach clearly *over-estimates the benefit and value of usual-care*. Maintaining this benefit for usual-care for the duration of the model *biases the model considerably in favour of usual-care* and underestimates the cost-effectiveness of cannabidiol.

In a scenario analysis, in the usual-care arm, the distribution of patients between health states at the end of cycle 1 is maintained until the end of the open-label extension period (cycles 2-9). The company considers that moving patients back to baseline in the usual-care arm after cycle 9 avoids overestimating the benefit of usual-care by carrying the unusually large placebo effect seen in the GWPCARE2 study for an implausibly long period of time.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Assumptions in the economic model

Committee Conclusion(s) from ACD
3.15 The effectiveness of cannabidiol is likely to diminish over time. The committee concluded that it would have preferred to see scenario analyses in which the efficacy of cannabidiol diminished after 27 months. The clinical experts stated that they would expect the effectiveness of cannabidiol to diminish over time because this is seen with other antiepileptic drugs. The company considered that it had captured a reduction in efficacy over time in a scenario analysis in which it increased the annual rate at which patients in the highest seizure-frequency health state stopped cannabidiol, increasing the rate from 5% to 10% a year. It argued that being in this health state implied that patients were no longer deriving benefit from cannabidiol and so would stop taking it. The clinical experts stated that the proportions of patients on cannabidiol at 3 and 5 years in the company's base-case analysis of the full trial population were plausible. However, the committee considered the rates at which people stopped treatment, and a reduction in treatment effect reflected separate issues. This was because a waning treatment effect would have applied to all patients, but not all of them would have moved to the health state with the highest seizure frequency and stopped cannabidiol.
3.23 In its summary, the committee also included some additional wording for this scenario as follows: "explores a diminishing treatment benefit of cannabidiol after 27 months, including a scenario in which the treatment effect is removed".

The company would respectfully like to make a correction to the committee's conclusions in section 3.15.

The ACD states that the company captured the effect of a reduction in efficacy over time in CBD by increasing the discontinuation rate from 5% to 10% in the *highest* health state. The committee concluded that the company's scenario analysis did not capture a waning effect, as they assumed that the company was simulating a situation in which patients who were receiving no benefit would move to the highest health state, and then discontinue at a greater rate. The committee considered that a waning effect should have applied to all patients, but not all of them would have moved to the health state with the highest seizure frequency and stopped cannabidiol.

This is a misunderstanding of what was actually done in both the base case and in the scenario.

The company assumed in its base case that 5% of patients in *all* health states (except seizure-free, 0.5%) would discontinue treatment per cycle, based on observations from the company's US early access programme (EAP), which is currently the best long-term real-world data set available. This 5% rate includes patients who discontinue due to a lack of continuing benefit, which was the major reason for withdrawal in the study.

Similarly, in the scenario analysis, *all* health states (except seizure free, 0.5%) were assigned a 10% discontinuation rate to simulate the effect of *more* patients than observed in the US EAP discontinuing due to a lack of continuing benefit.

For this reason, the company considered that it was not necessary to include a waning effect in the model, as the waning treatment effect described above already applied to *all* patients, not just those with the highest seizure frequency.

There is currently no clinical evidence to support a loss of efficacy of CBD over time. In the GWPCARE5 long-term open-label study and in the US EAP, seizure outcomes were very stable to 3 years. Any assumption that further wanes the efficacy of CBD within the model is arbitrary, is only a hypothetical way of testing the responsiveness of the model mathematically, and is not based on clinical observation. The company has included recently available data that demonstrates that the treatment effect of CBD is continued to 156 weeks (see Appendix 1).

The committee heard from clinical experts that they could not be confident that the treatment effect of CBD *would not* wane. This is a reasonable, professionally cautious response to the question asked based on their experience with other AEDs and limited experience with CBD. However, the converse is equally true. If the clinical experts had been asked instead "Are you absolutely confident based on the evidence available that the effect of CBD *would* wane?", it is unlikely that they could have categorically stated that this was the case.

What is more definitive is that, in the Committee meeting, both the patient and clinical experts attested to the timely stopping of treatment in DS if the patient/carer and/or clinician feels that the patient is not receiving benefit. As such, it seems more plausible that treatment waning would be better reflected in discontinuation rates, for which there is evidence, rather than in an arbitrary assumption for an unobserved outcome.

However, notwithstanding the above, at the committee's request, a scenario to model an *additional* waning effect has been implemented.

In this scenario, the discontinuation rate for long-term cycles (cycle 10 onwards) no longer discontinues patients; instead it reverts patients to the distribution of health states for usual-care patients, but carries the cost of CBD for another 3 months (1 cycle). This assumption is a proxy for waning, as it simulates a situation in which the efficacy of the drug is completely lost 3 months before the drug is discontinued. Interviews conducted with clinical experts have indicated that this is the maximum length of time a patient would be on an AED that is no longer considered effective before it is stopped. Given the very proactive approach to managing ineffective therapies by parents and clinicians in DS, this represents a clinically plausible means of modelling a progressive loss of efficacy over time.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

3.23. With regard to the committee's comment in 3.23 to include "a scenario in which the treatment effect is removed" after 27 months, the company respectfully considers that this is not a valid or viable scenario:

- In the company's base case model, the relative treatment effect is now maintained to lifetime (such that the distribution of health states on placebo is maintained for usual-care patients indefinitely)

- In the company's response to 3.15 above, we have explained the misunderstanding re discontinuations (which are occurring in *all* patients, not just those in the highest-seizure frequency health state) and we have also implemented a scenario to simulate an additional 'waning' effect as requested
- A very recent additional interim data cut from the long-term GWPCARE5 study out to 156 weeks (see Appendix 1) shows that the treatment effect of CBD continues beyond 27 months
- The company is aware from discussions with clinicians that LGS/DS are conditions with very motivated parents/carers/healthcare professionals, such that patients are not kept on drugs that are not working or not tolerated. Thus, it is unrealistic in this disease area to assume that a patient would be kept on a drug that is not working for the lifetime of the model (i.e. incurring no benefit, but incurring all costs).

Given the above, the company feels that it makes little sense to include a scenario where the CBD treatment effect is removed completely at an arbitrary point where the GWPCARE5 data had previously run out.

Furthermore, within the model structure, there is no evidence-based and timely way for the company to include a scenario where the treatment effect stops completely when the data run out. The company considers that this is already 'built in' via the long term discontinuation rates which cover *all* patients and reflect patients being stopped because the treatment is not working.

Assumptions in the economic model

Committee Conclusion(s) from ACD
3.16 The model may underestimate the mortality of people who are free from convulsive seizures. The committee was aware that relatively few patients in the model were free from seizures, so changing this assumption would likely have had a small effect on the cost-effectiveness results. It concluded that the model may have underestimated the mortality of patients free from convulsive seizures. It would have preferred to see scenario analyses in which the reduction in risk of death was smaller.

The company has provided scenario analysis with regard to risk of death.

The company has reduced the mortality benefit of being convulsive seizure-free in its base case. Previously the company assumed a risk ratio of 0.42 for the convulsive seizure-free health state relative to the mortality rate assigned to the >8 - ≤25 convulsive seizure health state (derived from Cooper MS, et al. Epil Res 2016;128:43-47). This risk ratio was based on an analogue identified in the literature in broader epilepsy types (Trinka E, et al. Epilepsia. 2013;54(3):495-501). The company has halved this risk reduction (it is now 0.71) in its revised base case following ACD.

The company has further provided a scenario analysis with regard to risk of death in the convulsive seizure-free group, assuming no reduction in mortality from being convulsive seizure-free.

Please refer to the model and the separate document provided by the company: "ID1211DS economic outcomes after ACD".

Costs in the economic model

Committee Conclusion(s) from ACD
3.17 The company should model the costs of increasing the dose of cannabidiol. The committee concluded that the company should have included and justified the costs of increasing the dose of cannabidiol for some people in its base-case analysis. It noted that it would have preferred to see scenario analyses exploring how sensitive the cost-effectiveness results were to the proportion of people on higher doses.

The company has provided scenario analyses to explore proportions of people on higher and lower doses.

The recommended maintenance dose for cannabidiol in the Summary of Product Characteristics is 10 mg/kg/day, which is retained in the base case.

The committee stated that clinical experts thought that ~20% of patients might respond well on this dose, and could thus be considered for escalation. Given the lack of a dose response, the worsening adverse event profile observed between the CBD 10mg and 20 mg arms in the clinical trials, and the cautious 'low and slow' approach taken by UK physicians when increasing the dose of AEDs, it is unlikely that many UK patients who are escalated would reach a dose of 20 mg/kg/day. The company has therefore assumed that 20% of patients would be maintained on 15 mg/kg/day, and tested a scenario of an 11 mg/kg/day mean dose.

Of note, in early real-world clinical practice, the company is also learning that some patients are not even escalated as far as 10 mg/kg/day. We have therefore also tested a scenario of a 9 mg/kg/day average dose.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Modelling adverse events

Committee Conclusion(s) from ACD
3.18 The company should include the effect of adverse events on quality of life in the model. The committee concluded that the company should have included the effect of adverse events on quality of life in its model. It also concluded that the incidence of adverse events should have been based on data from the subgroup using cannabidiol with clobazam in the Dravet syndrome trials.

The company has included the effect of adverse events on quality of life in its base case, using data from the subgroup taking cannabidiol with clobazam.

A short-term (1 cycle) disutility for serious adverse events of special interest occurring in the CBD 10mg arm and not in the usual-care arm has now been included in the model. Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Utility values in the economic model

Committee Conclusion(s) from ACD
3.19 The utility values from the company's vignette study do not accurately reflect the health-related quality of life of people with Dravet syndrome. It noted that, among people with more than 24 convulsive seizure-free days per month, the utility values were similar whether they had, in total, more than 25 seizures per month or between 8 and 25 seizures per month. The committee considered this implausible because it had heard that convulsive seizures worsen quality of life.

The company would like to highlight that the similar utility values seen between seizure frequency health states in this case would be expected, in the context of the *contribution of seizure-free days* to QoL.

The company welcomes the Committee's acknowledgement of the importance of seizure-free days to QoL.

When the number of seizures per month is higher, reductions in seizure number would not be expected to be the biggest driver of QoL (as patients are still experiencing many of them). The contribution of how seizures are spread over time becomes relatively more important. This is exactly what is observed.

Based on this consideration, the company does not consider that there is a lack of face validity in these estimates.

Utility values in the economic model

Committee Conclusion(s) from ACD
3.19 The committee was aware that the company had done a scenario analysis using values from a general population preference study in Lennox-Gastaut syndrome (Verdian et al. 2018). The committee noted that, although not directly comparable, these values appeared lower than those in the company's vignette study.

The company considers that the utility values from the vignette study are in line with analogues in the literature (including Verdian *et al*, 2018 which, although in LGS, is a good analogue for DS), and represent its best efforts to obtain HRQoL estimates in this very rare disease.

- The estimates from the company's vignette study match almost exactly the relevant figures from the "anchor" state in Verdian (see Tables 1 and 2, Appendix 5).

- The utility estimates measured cross sectionally in the large DISCUSS study for Dravet syndrome were comparable to those measured from the DS vignette study, both in European and UK populations (see Table 3, Appendix 5).

- A further analogue supports the company's utility estimates in DS (Tritton T, et al. Epil & Behav. 20189;92:213-20). Tritton *et al* valued the QoL associated with seizures in 61 patients and 125 caregivers of people with Tuberous Sclerosis Complex (TSC), including in the UK. TSC is another highly refractory epilepsy condition characterised by heterogeneous seizures types, in which partial seizures predominate but convulsive seizures are also present (~ 30% of seizures in TSC are convulsive). Utilities for patients were assessed by seizure type in the last week using the EQ-5D and UK value set. As can be seen in Table 4 in Appendix 5, HRQoL estimates for patients experiencing convulsive seizures are similar to those for DS patients in the company's vignette study for the ≤8 seizure health state.

Based on the above, the company considers that the utility estimates from Verdian are an appropriate analogue for the scenario analysis conducted previously.

Therefore, the company proposes to keep the scenario analysis using Verdian as an analogue.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Utility values in the economic model

Committee Conclusion(s) from ACD
3.20 It is appropriate to include the effect on carers' quality of life in the model, but the company's utility values may not accurately reflect this. The committee concluded that it was appropriate to include carers' quality of life in the model. However, it thought that the values from the company's vignette study may not have accurately reflected the effect of caring for someone in each of the health states in the model. It was concerned that the company had captured the effect on the quality of life of carers only for the 2 highest seizure-frequency health states.

The company conducted a further literature search, but could find no further analogues (beyond Campbell *et al*, 2019) in the literature relevant to DS. This is to be expected given the very rare nature of this condition.

In the previous model, the company measured disutilities for caregivers relative to the convulsive seizure-free state, rather than UK norms. Given recruitment constraints, only vignette profiles for the convulsive seizure-free and the two worst health states were performed. As a conservative measure, the company set the caregiver disutilities to zero for the seizure-free and ≤ 8 convulsive seizure health states.

In the base case following ACD, the company has measured caregiver disutilities relative to UK VAS norms of 0.828 (Szende A, et al. 2014. DOI 10.1007/978-94-007-7596-1).

See also 3.21 (below) - any small uncertainty in the disutility estimates is likely to be outweighed by not including disutilities for the many other carers/family members whose quality of life is impacted.

Utility values in the economic model

Committee Conclusion(s) from ACD
3.21 The company's approach to modelling carers' quality of life may overestimate the effect of caring for someone with Dravet syndrome. The committee was concerned that the company's approach meant that the caring burden increased linearly the more carers a patient had. However, for a patient with multiple carers, it expected there to be less effect on the quality of life of each carer because they would 'share' the burden. So, while the total burden for 1.8 carers may be greater than the burden for a sole care, it would likely not be 1.8 times greater. The committee acknowledged the substantial effect that caring can have on quality of life. However, it concluded that the company's approach to incorporating carers' quality of life in the model may have overestimated the effect.

The company considers that applying the disutility to carers equally is appropriate:

- In previous NICE submissions with a carer disutility included for more than one carer (e.g. ataluren for Duchenne Muscular Dystrophy (HST3); disutility applied for 2 and 3 carers), there is a precedent where each carer was allocated the same disutility.
- The vignette study specifically asked respondents to evaluate their *own* perception of quality of life. The majority of respondents had a partner, so it is reasonable to assume that the disutility estimates are representative of an individual's quality of life decrement where another carer was present.
- In a severe and life-threatening disease such as DS, where patients are at a significant ongoing risk of injury and death from their seizures, have multiple co-morbidities and often require lifelong round-the-clock care, it seems unlikely that a 'shared' burden reduces the disutility for each carer. This has been confirmed by the company in interviews with clinical experts.

Since the date of the committee meeting, the company has conducted further interviews with clinical experts in order to understand the number of carers and the impact on their quality of life of caring for a patient with DS.

The clinical experts interviewed stated that 2 carers is the minimum (this does not include 'paid-for' care outside the family), and 3 carers is more usual since round-the clock-care is often required. They considered that it is not just the primary carers such as the parent(s) who have their quality of life impacted, but also other carers/family members (e.g. siblings, grandparents, aunts and uncles).

One clinician interviewed referred to a publication about the impact on siblings (Hames, A and Appleton, R; *Seizure* 18 (2009) 699-701). An extract from this publication clearly outlines this impact:

> "A few children commented on the responsibilities they felt for some of their sibling's care, irrespective of whether the parents were in or out of the house, almost as if they were the parent's extra 'eyes and ears': *'I need to be there quite often to look out for him'* (12-year-old sister) and *'I feel as though my parents sometimes depend on me when they go out shopping'* (16-year-old brother). Another commented that he felt that it was he and the other siblings in his family who encouraged his brother with epilepsy to lead as normal a life as possible because his parents were continually *'exhausted'* or *'shattered'* and *'couldn't think of anything else but his fits'* (12- year-old brother)."

The company has been conservative in only including 2 carers in its base case, when clinicians and patient experts indicate that this severe and life-threatening form of epilepsy impacts other carers/ family members (e.g. siblings, grandparents, aunts and uncles). This was specifically referenced by clinical experts in the committee meeting, and in the committee slides.

The company has run scenario analyses varying the number of carers (higher and lower numbers of carers: 3 carers and 1.8 carers) to demonstrate how this affects outcomes.

Please refer to the model and the separate document provided by the company: "ID1211 DS economic outcomes after ACD".

Cost-effectiveness results

Committee Conclusion(s) from ACD
3.23 The committee would like to see a model that incorporates its preferred assumptions. The committee agreed that it would like to see a revised model that more adequately reflects Dravet syndrome and captures the costs and benefits of treatment with cannabidiol. The committee's preferred approach is for a model that: • has a structure that adequately reflects Dravet syndrome and captures the benefits of reducing both the number of convulsive seizures and the number of days free of convulsive seizures • explores scenarios around defining the health states by different seizure frequencies • models the usual care arm in the same way as the cannabidiol arm • passes all tests of validity and bias • maintains the relative treatment benefit of cannabidiol compared with usual care for the duration of the open-label extension study • explores a diminishing treatment benefit of cannabidiol after 27 months, including a scenario in which the treatment effect is removed • appropriately incorporates the effect on the quality of life of carers • explores the uncertainty in the utility values for patient and carers • uses mean, rather than median, body weight from the trials to calculate dosages and costs • includes the costs of increasing the dose of cannabidiol in some patients • includes disutilities for the most commonly observed cannabidiol-related adverse events • explores a smaller reduction in the risk of epilepsy-related death in the seizure-free health state accounting for confounding

The company feels that its responses above and its revised economic analysis (see the updated model and the separate document "ID1211 DS economic outcomes after ACD") address all the points made in the summary of the committee's preferred assumptions/scenarios above.

Other factors

Committee Conclusion(s) from ACD
3.24 Cannabidiol does not meet the criteria for an innovative treatment but there are benefits that are not captured in the model. The committee concluded that cannabidiol did not meet the criteria for an innovative treatment. However, it noted there were additional gains in health-related quality of life that were not included in the QALY calculations.

The company welcomes the committee's conclusion that there were additional gains in health-related quality of life that it was not able to include in the QALY calculation. In particular:

- Seizure duration. Of note, although data on these outcomes could not be used in health state construction within the model, CBD did reduce seizure duration (as measured using the Subject and Caregiver Global Impression of Change in Seizure Duration (CGIC-SD)) in GWPCARE2.

- Co-morbidities, including long-term cognition, behaviour, mobility and learning difficulties
    - In the DISCUSS study in DS, comorbidity scores were better in patients with fewer versus more seizures
    - The SIGN guidelines (Epilepsies in children and young people: Investigative procedures and management. A national clinical guideline), when referring to LGS (a good analogue for DS), state that "Earlier and better seizure control may reduce associated comorbidity

of LGS including significant long-term permanent cognitive impairment, and behavioural side effects, all of which significantly reduce quality of life for patients and their carers".

- The impact on siblings of better seizure control. The specific effect on the HRQoL of siblings was cited in the committee meeting. Although the company will test this impact in scenarios that vary the number of caregivers (see 3.21 above), the specific disutility for siblings cannot be accommodated in this analysis.

Appendix 1

Methods and results for the subgroup of patients with DS taking cannabidiol with clobazam in GWPCARE5

Overview

GWPCARE5 is an ongoing open-label extension (OLE) study to investigate the safety of cannabidiol in children and adults with inadequately controlled DS or LGS.

The primary objective of this OLE study was to evaluate the long-term safety and tolerability of adjunctive CBD treatment, based on treatment-emergent adverse events (AEs), vital signs, 12-lead electrocardiograms, and clinical laboratory parameters, including serum levels of hepatic enzymes; drug-induced liver injury was assessed as per Hy's law.

Secondary objectives included the evaluation of the efficacy of CBD as determined by changes in convulsive seizure and total seizure frequency, seizure-reduction responder rates, and patient-reported outcomes based on changes in the Subject/Caregiver Global Impression of Change (S/CGIC) scale.

Methods

Patients with DS who completed the treatment period in trials GWPCARE1 (Part A and Part B) or GWPCARE2 were eligible for enrolment in GWPCARE5. All patients had a clinical diagnosis of DS, confirmed by the Epilepsy Study Consortium, that was inadequately controlled by ≥1 current AED. Patients from GWPCARE1 Part B and GWPCARE2 were 2-18 years of age with ≥4 convulsive seizures in the 4-week baseline period, whereas patients from the dose-ranging study GWPCARE1 Part A were 4-10 years of age with <4 convulsive seizures during the 4-week baseline period.

Patients received CBD in addition to their existing AEDs. Investigators could decrease the dose of CBD and/or concomitant AEDs if a patient experienced intolerance or could increase the dose if thought to be of benefit by the physician.

Caregivers completed a daily paper diary to record adverse events and daily usage of CBD, concomitant AEDs and rescue medications. Information on seizure number and type was collected through an interactive voice recording system telephone diary completed weekly. Blood and urine sampling for clinical laboratory assessments was carried out at all clinic visits. The 7-point S/CGIC scale was assessed at clinic visits at week 24, 38, and 48.

No formal sample size calculations were performed; all patients who wished to continue from the original placebo-controlled studies were eligible for inclusion. Seizure frequencies (per 28 days) were determined for each 12-week period of treatment. Percentage change in seizure frequency was calculated relative to the pre-randomisation baseline period from the parent placebo-controlled trials. Analyses were repeated using inclusion of a last observation carried forward (LOCF) step. Analyses were descriptive, and no formal hypothesis testing was conducted.

Analyses for the on-clobazam subpopulation have been carried out using Negative Binomial Regression effect modification analysis.

Results

GWPCARE5 is an ongoing OLE study. Interim analysis of the data (up to 156 weeks) for the subgroup of patients with DS taking CBD in conjunction with clobazam is presented in the tables below:

- Percentage reduction in convulsive seizures
- Percentage reduction in non-convulsive seizures
- Percentage reduction in total seizures
- Percentage of patients with ≥ 50% reduction in convulsive seizures
- Proportion of patients convulsive seizure free.

Percentage reduction in convulsive seizures (on-clobazam group)

[redacted]

Weeks since baseline	N	As observed	LOCF
1-12	[redacted]	[redacted]	[redacted]
13-24	[redacted]	[redacted]	[redacted]
25-36	[redacted]	[redacted]	[redacted]
37-48	[redacted]	[redacted]	[redacted]
49-60	[redacted]	[redacted]	[redacted]
61-72	[redacted]	[redacted]	[redacted]
73-84	[redacted]	[redacted]	[redacted]
85-96	[redacted]	[redacted]	[redacted]
97-108	[redacted]	[redacted]	[redacted]
109-120	[redacted]	[redacted]	[redacted]
121-132	[redacted]	[redacted]	[redacted]
133-144	[redacted]	[redacted]	[redacted]
145-156	[redacted]	[redacted]	[redacted]

Percentage reduction in non-convulsive seizures (on-clobazam group)

Weeks since baseline	N	As observed	LOCF
1-12	[redacted]	[redacted]	[redacted]
13-24	[redacted]	[redacted]	[redacted]
25-36	[redacted]	[redacted]	[redacted]
37-48	[redacted]	[redacted]	[redacted]
49-60	[redacted]	[redacted]	[redacted]
61-72	[redacted]	[redacted]	[redacted]
73-84	[redacted]	[redacted]	[redacted]
85-96	[redacted]	[redacted]	[redacted]
97-108	[redacted]	[redacted]	[redacted]
109-120	[redacted]	[redacted]	[redacted]
121-132	[redacted]	[redacted]	[redacted]
133-144	[redacted]	[redacted]	[redacted]
145-156	[redacted]	[redacted]	[redacted]

Percentage reduction in total seizures (on-clobazam group)

Weeks since baseline	N	As observed	LOCF
1-12	[redacted]	[redacted]	[redacted]
13-24	[redacted]	[redacted]	[redacted]
25-36	[redacted]	[redacted]	[redacted]
37-48	[redacted]	[redacted]	[redacted]
49-60	[redacted]	[redacted]	[redacted]
61-72	[redacted]	[redacted]	[redacted]
73-84	[redacted]	[redacted]	[redacted]
85-96	[redacted]	[redacted]	[redacted]

Weeks since baseline	N	As observed	LOCF
97-108	[redacted]	[redacted]	[redacted]
109-120	[redacted]	[redacted]	[redacted]
121-132	[redacted]	[redacted]	[redacted]
133-144	[redacted]	[redacted]	[redacted]
145-156	[redacted]	[redacted]	[redacted]

Percentage of patients with ≥ 50% reduction in convulsive seizures (on-clobazam group)

Weeks since baseline	N	As observed	LOCF
1-12	[redacted]	[redacted]	[redacted]
13-24	[redacted]	[redacted]	[redacted]
25-36	[redacted]	[redacted]	[redacted]
37-48	[redacted]	[redacted]	[redacted]
49-60	[redacted]	[redacted]	[redacted]
61-72	[redacted]	[redacted]	[redacted]
73-84	[redacted]	[redacted]	[redacted]
85-96	[redacted]	[redacted]	[redacted]
97-108	[redacted]	[redacted]	[redacted]
109-120	[redacted]	[redacted]	[redacted]
121-132	[redacted]	[redacted]	[redacted]
133-144	[redacted]	[redacted]	[redacted]
145-156	[redacted]	[redacted]	[redacted]

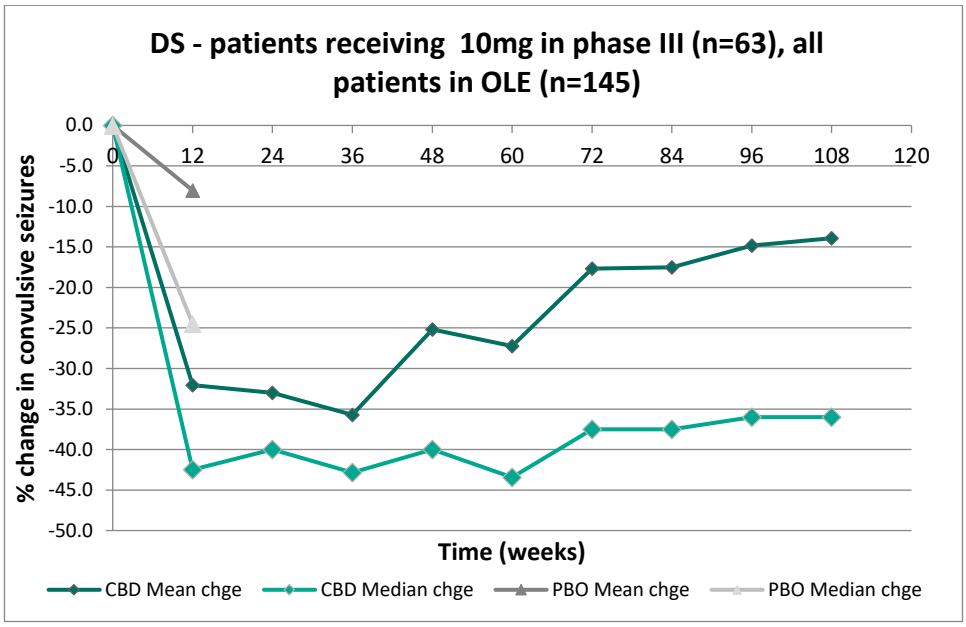
Proportion of patients who are convulsive seizure free (on-clobazam group)

Weeks since baseline	N	As observed
1-12	[redacted]	[redacted]
13-24	[redacted]	[redacted]
25-36	[redacted]	[redacted]
37-48	[redacted]	[redacted]
49-60	[redacted]	[redacted]
61-72	[redacted]	[redacted]
73-84	[redacted]	[redacted]
85-96	[redacted]	[redacted]
97-108	[redacted]	[redacted]
109-120	[redacted]	[redacted]
121-132	[redacted]	[redacted]
133-144	[redacted]	[redacted]
145-156	[redacted]	[redacted]

Appendix 2

Percentage change in convulsive seizure frequency over time in the GWPCARE2 and GWPCARE5 studies

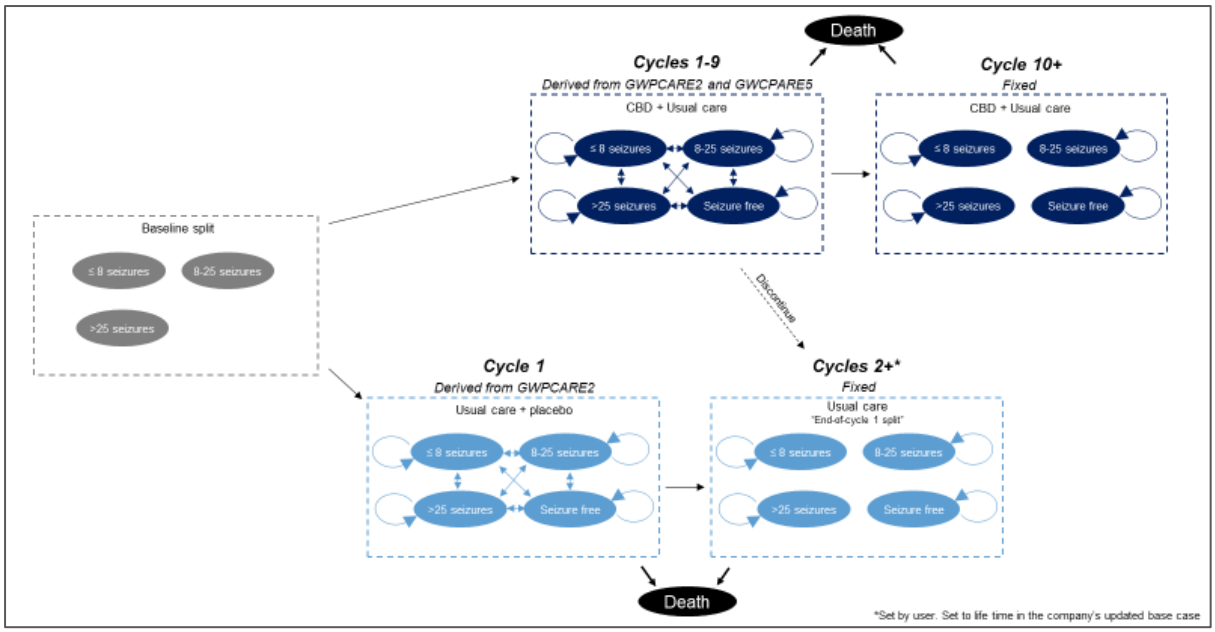
Descriptive analysis



[redacted]

Appendix 3

Model structure: health state distributions used over cycles in the model



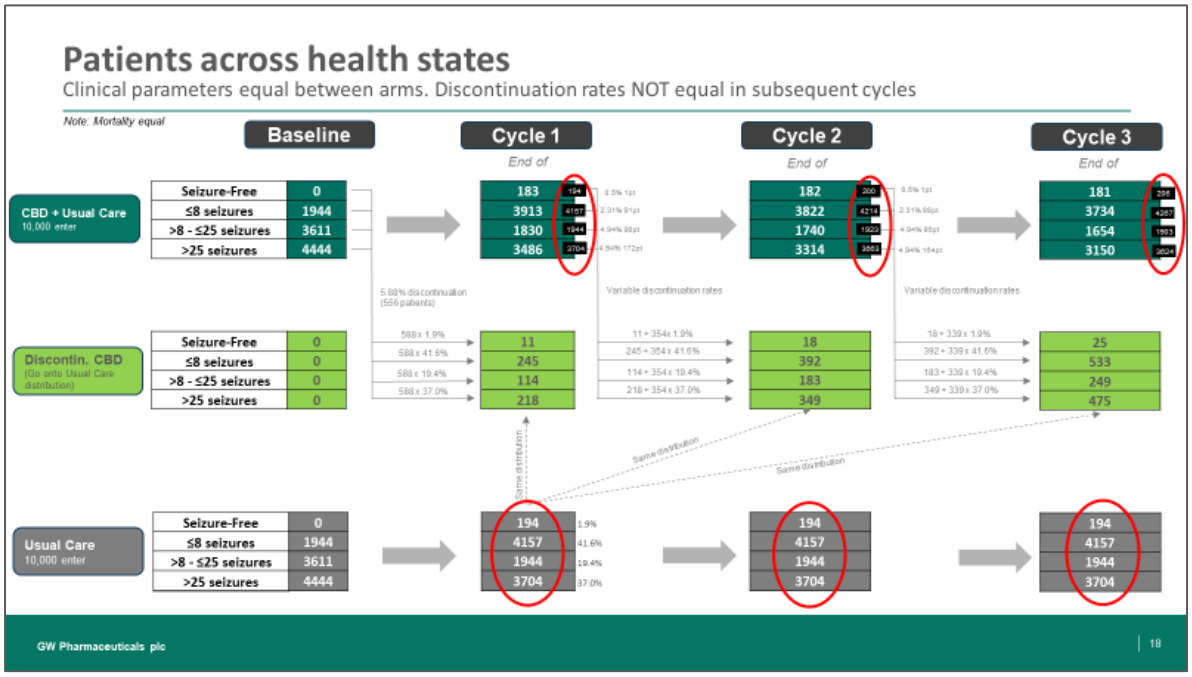
Appendix 4

Validity tests

"Test 1": Distribution of patients across health states for cycles 1-3 when clinical efficacy and safety are set equal

- Example from DS for age group 2-11 years
- Clinical efficacy set equal between CBD and usual-care arms by applying the transition probabilities for usual-care to the CBD arm (Tab #SEIZURES O14: BA17)
- Discontinuation rates set to the base case (no treatment stopping)

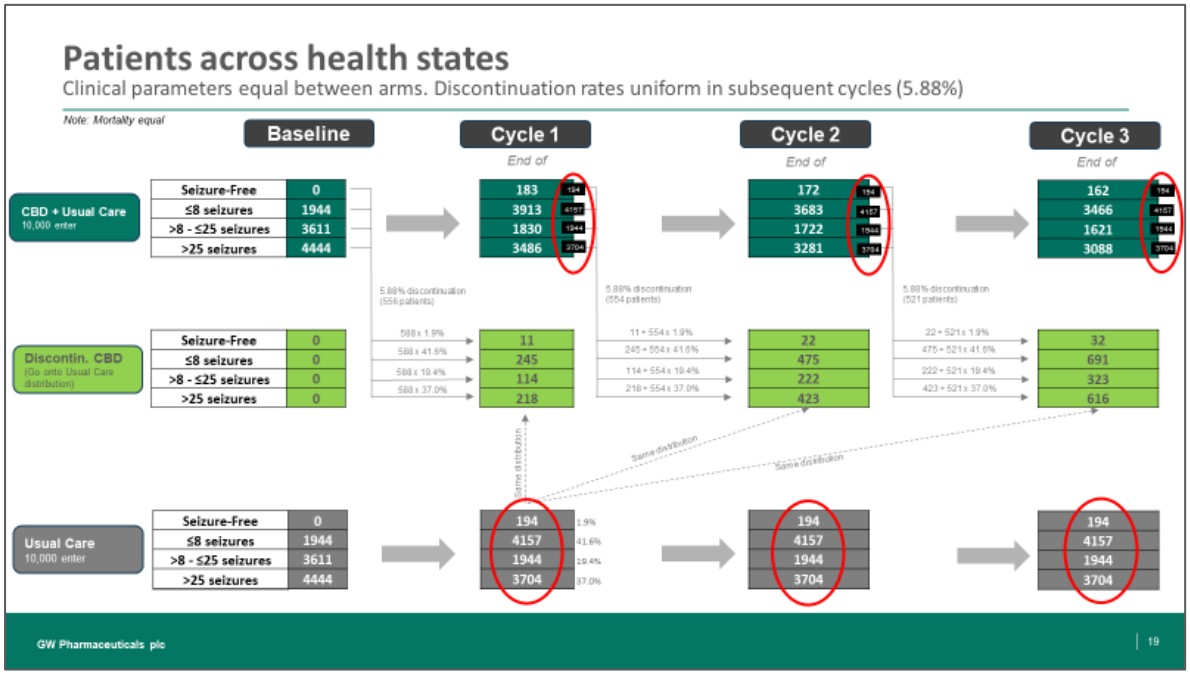
Note: total CBD patient numbers (dark and light green boxes) differ across health states versus usual care (grey boxes) in cycles 2-3 (red circles)



"Test 2": Distribution of patients across health states for cycles 1-3 when clinical efficacy and safety are set equal, and discontinuation rates are uniform across health states

- Example from DS for age group 2-11 years
- Clinical efficacy set equal between CBD and usual care arms by applying the transition probabilities for usual care to the CBD arm (Tab #SEIZURES O14: BA17)
- Subsequent cycle discontinuation rates for CBD set equal to those for cycle 1 - 5.88% (Tab DISCONTINUATION G21:G24, G44:G47). No stopping rules

Note: total CBD patient numbers (dark and light green boxes) are the same across health states versus usual care (grey boxes) in cycles 2-3 (red circles)



Appendix 5

Tables 1 and 2: Quality of life estimates from vignettes and analogues

Verdian et al 2010 QoL values			
Number of drop seizures per 28 days	**TTO**	**EQ-5D VAS**	**EQ-5D Index**
84-112 seizures ("anchor" state)	0.393	0.02	0.02
< 50% reduction	0.461	0.414	0.100
≥50% and <75% reduction	0.605	0.556	0.500
≥75% reduction	0.699	0.677	0.596

Number of convulsive seizures / 28 days	Number of seizure free days (SFD)	Mean quality of life scores*
No seizures (HS1)	(SFD3) No seizures	[redacted]
≤ 8 seizures (HS2)	(SFD1) ≤ 18 convulsive seizure-free days	[redacted]
	(SFD2) > 18 to ≤24 convulsive seizure-free days	[redacted]
	(SFD3) > 24 convulsive seizure-free days	[redacted]
> 8 to ≤25 seizures (HS3)	(SFD1) ≤ 18 convulsive seizure-free days	[redacted]
	(SFD2) > 18 to ≤24 convulsive seizure-free days	[redacted]
	(SFD3) > 24 convulsive seizure-free days	[redacted]
> 25 seizures (HS4)	(SFD1) ≤ 18 convulsive seizure-free days	[redacted]
	(SFD2) > 18 to ≤24 convulsive seizure-free days	[redacted]
	(SFD3) > 24 convulsive seizure-free days	[redacted]

*Mean QoL scores in this table are all academic in confidence
** Included for completeness; no values were obtained as this is not a possible state

Table 3: Analogues from the large DISCUSS Study in DS

Study	Methods	Instrument	Utility
Lagae L, et al. Dev Med & Child Neurol 2018;60:63-72	DS Caregiver survey. Multinational (mainly Europe). N=584	EQ5D-5L. UK value set	0.42 +/-0.29) [<0 to 1]
Pegano 2019, et al. Dev Med Child Neurol 2019;61(S1):62	UK cohort DISCUSS (N=72) DS. 78% paediatric, 22% adult	EQ5D-5L Index	0.382+/-0.27 [0.17 to 0.88]

Table 4: Analogue from TSC

EQ-5D VAS scores for patients with TSC base on seizure types experienced in the last week

Seizure frequency	N	Mean	SD	Median	95% CI
Focal: simple partial	92	68.89	17.1	0.72	65.40-72.38
Generalized: absence	36	57.28	21.1	0.60	50.39-64.17
Focal: complex partial	83	65.48	17.0	0.67	61.83-69.14
Secondary generalized: convulsive	43	58.65	19.6	0.56	52.80-64.50
Generalized: convulsive	40	58.28	18.1	0.57	52.68-63.87
Other (including infantile spasms)	18	65.33	18.8	68.5	56.63-74.04

The highlighted figures correspond to the estimates for convulsive seizures in the ≤8 seizure health state from the vignettes (0.57 and 0.61).
Tritton T, et al. Epil & Behav. 20189;92:213-20.

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]
Economic Outcomes – after ACD

This document provides cost-utility outcomes further to the issues raised in the NICE Appraisal Consultation Document (ACD).

It should be read in conjunction with the separate document containing the company's response to the ACD ("ID1211 DS - GW ACD responses").

This document includes the following information:

- Table 1 shows the updates to the company's base case as a result of the ACD
- Tables 2-3 show the company's base case after the ACD
- Table 4 shows scenario analyses on the company's base case after the ACD
- Table 5 provides a summary of the features and parameters in the model that have been updated since that provided for the on-clobazam population on 25th July 2019
- Table 6 and Figure 1 show the deterministic sensitivity analysis inputs and results
- Tables 7-8 and Figures 2-3 show the inputs and outcomes of the probability sensitivity analysis.

Economic Outcomes – after ACD

Table 1. Updates to the company's base case following the ACD

Update	ACD Response	See Table 5	Tab in model
90-year (lifetime) time horizon	N/A	Parameter 1	**GLOBAL SETTINGS** G10
The relative treatment effect applied to lifetime in the usual-care arm and for discontinued CBD patients	3.10, 3.14	Parameter 2	**GLOBAL SETTINGS** G19 (shown G22)
Stopping rules applied at 12 and 24 months, in addition to 6 months, based on NHS England Guidelines (derived from the GWPCARE5 dataset)	3.7	Parameter 4	**GLOBAL SETTINGS** D26 **DISCONTINUATION** E65:I108
Probability allocations and transition probabilities for clinical parameters at baseline and in cycle 1 derived only from the subpopulation of patients on clobazam in the 10 mg/kg/day and placebo arms of GWPCARE2. Transition probabilities for cycles 2-9 in the CBD arm derived only from GWPCARE5.	3.13	Parameter 6	**COHORT DEFINITION** C46:E46, G46:I46, C53:E55, G53:I55. **#SEIZURES** "Cycle 1" D21:G31, D44:G54, "Subsequent cycles" O14:BA31, O37:BA54 **#DAYS** D21:F31, D44:F54
Discontinuation rates in cycles 2-9 for the two most severe health states estimated from withdrawers using pooled estimates from the patient level data in the GWPCARE5 study.	N/A	Parameter 7	**DISCONTINUATION** G23:G24, G46:47.
Disutility applied for 1 cycle for adverse events of special interest rated as severe on CBD	3.6 3.18	Parameter 9	**SAFETY** H33:J51 **UTILITY** D54:D72
Risk ratio for death in the convulsive seizure-free health state set to 0.71	3.16	Parameter 10	**MORTALITY** E16, E20, E29, E33
Caregiver disutilities calculated from the EQ-5D VAS norms for the UK population for each health state (using utility outcomes from the Vignette study)	3.20 3.21	Parameter 13	**UTILITY** D24:F27
An average of 2 caregivers per patient	3.21	Parameter 14	**UTILITY** C33
Disutilities applied to each health state for non-convulsive seizures, estimated from de Kinderen 2016	3.8	Parameter 9	**UTILITY** D42:F45

Table 2. Company's Base Case after ACD

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)		Patients still on CBD at:	
						2 years	5 years	50 years
CCM	£359,041	-0.0389	-	-	-	-	-	-
CCM + CBD	£393,521	1.1391	**£34,479**	**1.1781**	**£29,268**	44.22%	26.32%	4.48%

*Note: the QALY changes are spread across the patient and an average of 2 caregivers, and a time horizon of 90 years. They do not represent a worse-than-death outcome for any one individual in the cohorts.

This base case assumes that the relative treatment effect observed in the GWPCARE2 trial is applied until lifetime in the usual-care arm (see response to 3.10/3.14 in the separate document "ID1211 DS - GW ACD responses").

However, this approach clearly *over-estimates the benefit and value of usual-care*, since the treatment effect from a blinded, randomised controlled trial (GWPCARE2, used for the usual-care arm in the model from cycle 2 onwards) is likely to be higher than the treatment effect from an open-label study (GWPCARE5, used for the CBD arm in the model from cycle 2 onwards).

Maintaining this benefit for usual-care for the lifetime duration of the model *biases the model considerably in favour of usual-care* and underestimates the cost-effectiveness of cannabidiol. This was noted in the NICE technical report (Issue 9):

> "The technical team notes that there is no comparative data beyond 14 weeks (i.e. the first cycle of the model) and that assuming the placebo effect is maintained in subsequent cycles may *overestimate the treatment effect of current clinical management*."

Assuming that the large placebo effect observed over 3 months in the blinded GWPCARE2 trial would be of the same magnitude over 2 years in the open-label GWPCARE5, and carried indefinitely in this highly refractory population of patients when treated with existing therapies is unrealistic and significantly penalises cannabidiol in terms of its benefit and value to patients. Therefore, the company has also implemented a scenario that applies the relative treatment effect up to 27 months, before usual-care and discontinued CBD patients revert to the distribution of health states at baseline (see Scenario 4 below).

Table 3. Costs in the Company's Base Case after ACD

Cost categories	CCM + CBD	CCM	Difference
Total costs per patient	£373,415	£339,561	£33,854
Treatment costs per patient	£193,920	£143,216	£50,704
Adverse Events costs per patient	£332	£223	£109
Management costs per patient	£178,036	£194,977	-£16,941
SUDEP cost per patient	£0	£0	£0
Non-SUDEP cost per patient	£1,128	£1,146	-£17

Table 4. Scenario analyses on the Company's Base Case after ACD

Scenarios on base case	ACD Section	Tab in model	Inc. Costs	Inc. QALYs	ICER
Company's base case	N/A	N/A	£34,479	1.1781	£29,268
1. NHSE stopping rule applied first at 3 months instead of 6 months	3.7	GLOBAL SETTINGS D26	[redacted]	[redacted]	[redacted]
2. Narrower seizure thresholds	3.8	Separate model: "ID1211 Narrower Seizure Thresholds Model.xls"	£31,537	1.1678	£27,006
3. Relative treatment effect applied to 9 cycles (usual-care and discontinued CBD patients then revert to the baseline distribution of health states)	3.10, 3.14	GLOBAL SETTINGS G18	[redacted]	[redacted]	[redacted]
4. Mean instead of median weights	3.12	COHORT DEFINITION D20:J20	[redacted]	[redacted]	[redacted]
5. Waning applied to the CBD treatment effect	3.15	GLOBAL SETTINGS G48	[redacted]	[redacted]	[redacted]
6. Mortality risk ratio for the convulsive seizure-free health state 1.0 (instead of 0.71 in the base case)	3.16	MORTALITY E16, E20, E29, E33	[redacted]	[redacted]	[redacted]
7. Average dose of 9 mg/kg/day	3.17	COHORT DEFINITION G37, I37	[redacted]	[redacted]	[redacted]
8. Average dose of 11 mg/kg/day	3.17	COHORT DEFINITION G37, I37	[redacted]	[redacted]	[redacted]
9. Utility estimates using Verdian *et al* 2008	3.19	UTILITIES F4	[redacted]	[redacted]	[redacted]
10. 1.8 caregivers (average derived from Lagae 2017)	3.21	UTILITIES C33	[redacted]	[redacted]	[redacted]

Scenarios on base case	ACD Section	Tab in model	Inc. Costs	Inc. QALYs	ICER
Company's base case	N/A	N/A	£34,479	1.1781	£29,268
11. 3 caregivers (in line with HST3 ataluren for DMD; reflecting the sum of other family members affected)	3.21	UTILITIES C33	[redacted]	[redacted]	[redacted]
12. Concomitant AED doses reduced for patients on CBD, as observed in Laux *et al* 2017*)	Existing scenario	COSTS H84, J84, H86, J86, H90, J90, H112, J112, H114, J114, H118, J118.	[redacted]	[redacted]	[redacted]
13. Incident population only (age 2-5 years at model entry). This reflects the cost effectiveness in the incident population, which the age mix of patients will progress to over time.	Existing scenario	COHORT DEFINITION D16	[redacted]	[redacted]	[redacted]

*46%, 52% and 16% of patients experience a 33% reduction in the dose of concomitant clobazam, valproate and levetiracetam respectively. The proportion of patients was reported in Laux *et al* 2017; the percentage reduction is based on clinical experts' estimation of a minimally clinically meaningful change.

Laux LC, *et al*. Poster presented at the American Epilepsy Society Meeting 2017.
Tritton T, et al. Epil & Behav. 20189;92:213-20.

Table 5. Parameter updates for the model

The following table lists the features added to, and inputs that have changed in, the model since the committee meeting on 30th July 2019. These follow the recommendations/requests in the NICE ACD.

Parameter	ACD	Tab and cell	Description
1. Time horizon	N/A	**GLOBAL SETTINGS** G10	The model computes costs and outcomes up to 90 years (considered as lifetime, as the survival rate is close to 0%)
2. Duration of relative treatment effect (placebo effect)	3.10 3.14	**GLOBAL SETTINGS** G19 (shown G22)	The model applies the relative treatment effect to lifetime in the base case. This means that the distribution of health states at the end of cycle 1 in the usual-care arm is maintained statically until lifetime from cycle 2 onwards for usual-care and discontinued CBD patients who have not died. The number of cycles over which the relative treatment effect is applied can be varied from 1-9 cycles and to lifetime. Where lifetime is not selected (e.g. 9 cycles), usual-care and discontinued CBD patients are maintained statically in the health state distribution at the end of cycle 1 in the usual-care arm until (e.g. cycle 9), and then revert back to the baseline distribution of health states. This function allows the impact of the large placebo effect in the phase 3 studies for CBD to be investigated in scenarios. Due to this large placebo effect, the cost effectiveness of CBD is underestimated in the base case, and the company suggests that the ICER is lower as per scenario 4 in Table 4, (which applies the relative treatment effect to 9 cycles).
3. Waning effect	3.15	**GLOBAL SETTINGS** G48	This function allows for a waning effect in the effectiveness of CBD to be applied. When activated, the long-term discontinuation rates (from cycle 10) set in in tab **DISCONTINUATIONS** (I21:24, I44:47) no longer discontinue, but instead revert to the health state distribution at the end of cycle 1 in the usual-care arm (see Parameter 2 above). They do not stop CBD, however, and the cost of the drug is applied for another cycle (3 months). This assumption is a proxy for waning, as it simulates a situation in which the efficacy of the drug is completely lost 3 months before the drug is discontinued. Interviews conducted with clinical experts have indicated that this is the maximum length of time a patient would be on an AED that is no longer considered effective before it is withdrawn.
4. CBD stopping rule	3.7	**GLOBAL SETTINGS** D26 **DISCONTINUATION** E65:I108	The user has the option to apply a stopping rule to CBD patients at 3 time points; 3, 6 or 12-months for the 1st time point; and then 1-year and 2-years for the 2nd and 3rd time point respectively. (Note if "1 year" is chosen for the 1st time point, then only a 2nd time point at 2 years applies). The stopping rule is based on that specified in the draft NHS England Guidelines, and estimated from the patient level data in the GWPCARE5 trial. Specifically, it is a "one-off" discontinuation rate that is calculated based on the percentage of non-withdrawn patients in each health state at each time point in the trials who did not achieve a ≥30% reduction in convulsive seizures, but who did achieve this outcome at the last time point. 2nd and 3rd stopping points using this stopping rule have been added to the model following guidance at the committee meeting that treating clinicians would have to attest that CBD continues to meet the NHSE efficacy requirement at annual timepoints following treatment initiation, or else stop treatment with CBD.

Parameter	ACD	Tab and cell	Description
			Patients who stop treatment are managed in the same way as discontinued CBD patients (see Parameter 2).
5. CBD dose	3.17	**COHORT DEFINITION** G37, I37	A 10 mg/kg/day dose is applied to all patients in cycle 1 (months 1-3). Transitions probabilities derived from patient-level data in the 10mg arm of the GWPCARE2 study are thus also applied to all patients in cycle 1. (Outcomes from the 20 mg/kg/day arms in GWPCARE studies are no longer applied). This reflects the draft NHS England Guidelines, which recommend that dose escalation above the recommended maintenance dose of 10 mg/kg/day be considered at a minimum of 3 months after drug initiation. Therefore, all patients can be considered to be on a 10 mg/kg/day dose for the first cycle of the model. Subsequent to cycle 1, an average CBD dose is applied to all patients. Transition probabilities are derived from the patient level data in the GWPCARE5 study for all patients.
6. Treatment efficacy – transition matrices for cycle 1 and subsequent cycles	3.13	**COHORT DEFINITION** C46:E46, G46:I46, C53:E55, G53:I55. **#SEIZURES** "Cycle 1" D21:G31, D44:G54 "Subsequent cycles" O14:BA31, O37:BA54 Range PLB_Age1_TP1 & PLB_Age2_TP1 **#DAYS** D21:F31, D44:F54 Range PLB_Age1_Days & PLB_Age2_Days	The clinical data that inform probability allocations and transition probabilities for health states in the model include only data from the 10mg and placebo arms of the GWPCARE2 study in cycle 1, and from the GWPCARE5 study in cycles 2-9 (for the CBD cohort only).
7. Discontinuation rates – subsequent cycles	N/A	**DISCONTINUATION** G23:G24, G46:47. Ranges CBD10_Age1_Disc2 & CBD10_Age2_Disc2	Discontinuation rates in cycles 2-9 (6-27 months) for the two most severe health states are estimated from withdrawers using pooled estimates from the patient level data in the GWPCARE5 study.
8. Safety – adverse events	3.6 3.18	**SAFETY** H6:J26	The incidence rates for adverse events of special interest are now specific to the DS on-clobazam population, and not derived from the pooled data for LGS and DS.
9. Safety – severe adverse events	3.6 3.18	**SAFETY** H33:J51 **UTILITY** D54:D72	A table has been added reporting adverse events of special interest graded as severe. These are used to calculate utility decrements associated with adverse events. Disutilities attached to these adverse events are derived from de Kinderen, *et al* 2016.

Parameter	ACD	Tab and cell	Description
10. Mortality rates for convulsive seizure-free patients	3.16	**MORTALITY** E16, E20, E29, E33	The risk ratio for convulsive seizure-free patients is now 0.71, versus 0.42 in the previous base case. This assumes that the risk ratio is half that observed in the analogue used to set this assumption (Trinka 2013).
11. Disease-specific utility values for patients	3.19	**UTILITY** F4, D9:F12	The model now allows the user to select between the scores elicited from the company's vignette study, and the TTO values published by Verdian *et al* (Verdian 2008). The TTO values are chosen because the utility estimates in this analogue using EQ-5D and EQ-5D VAS lack face validity in the "anchor state".
12. Decrements of utilities (caregivers)	3.20 3.21	**UTILITY** D24:F27	The user has the option to select caregiver decrements determined using the EQ-5D VAS UK norms (Szenda 2014) as the reference case, and the seizure-free health state utility value elicited from the vignette study as the reference case. The base case now uses UK norms.
13. Number of caregivers	3.21	**UTILITY** C33	The number of caregivers has been set at 2 in the company's base case. This number can be changed by the user.
14. Decrements of utilities (other seizure types)	3.8	**UTILITY** D42:F45	The user can select the option to include additional decrements associated with other seizure types in DS. Disutilities for each health state in the base case were estimated from the regression model published in de Kinderen 2016 (see response to 3.8 in the separate document ("ID1211 DS - GW ACD responses")).
15. DSA	N/A	**DSA** E205:I229	The DSA includes the new parameters added in the UTILITY tab (caregiver number, decrements of utilities for other seizure types)
16. PSA	N/A	**PSA** E114:Q138	The PSA includes the new parameters added in the UTILITY tab (caregiver number, decrements of utilities for other seizure types)

Trinka E, *et al*. Epilepsia. 2013;54(3):495-501.
Verdian L, *et al*. Abstract 1.3.52 presented at the 62nd meeting of the American Epilepsy Society 2008.
de Kinderen RJA, *et al*. Epil Res 2016;125:24-31.
Szende A, *et al*. 2014. DOI 10.1007/978-94-007-7596-1

Table 6: Parameter variations in the DSA

Parameter	Base Case	Lower Bound	Upper Bound	References
Discount Rates				
Costs	3.5%	0.0%	6.0%	NICE recommendation
Outcomes	3.5%	0.0%	6.0%	
Weight (kg)				
2 - 5 years	[redacted]	[redacted]	[redacted]	Based on the patient level data from the GWPCARE1 & 2 studies, using 40th and 60th percentiles
6 - 11 years	[redacted]	[redacted]	[redacted]	
12 - 17 years	[redacted]	[redacted]	[redacted]	
18 - 55 years	[redacted]	[redacted]	[redacted]	
Dose reduction concomitant valproate and clobazam				
All age groups	0%	0%	-100%	Assumption
Discontinuation rates				
All cycles	As below	-10%	+10%	Assumption
Subsequent cycles	As observed in GWPCARE5	-50%	+50%	Assumption
Long-term	0.5% / 5%	-50%	+50%	Assumption
Stopping rules				
% patients stopping at 6 months per health state	As observed in GWPCARE5	-20%	+20%	Assumption
% patients stopping at 12 months per health state	As observed in GWPCARE5	-20%	+20%	Assumption
% patients stopping at 24 months per health state	As observed in GWPCARE5	-20%	+20%	Assumption

Parameter	Base Case	Lower Bound	Upper Bound	References
Management Unit Costs				
Visits Costs	Between £106 and £3,529	-20%	+20%	Assumption
Hospitalisation Costs	Between £0 and £5,817	-20%	+20%	Assumption
Rescue Med Costs	Between £0 and £408	-20%	+20%	Assumption
Institutionalisation Costs	Between £0 and £1,604	-20%	+20%	Assumption
Daily Cost ICU				
Adults	£1,299	£643	£4,482	Tables 32 & 38 of Document B
Paediatric	£1,583	£784	£5,867	
Daily Cost General Ward				
Adults	£460	£402	£807	Tables 32 & 38 of Document B
Paediatric	£597	£560	£760	
Phone Call Follow-up				
Neurologist	£107	£57	£153	Tables 32 & 38 of Document B
Paediatric neurologist	£258	£55	£234	
Emergency Department Visit				
Per episode	£237	£56	£838	Tables 32 & 38 of Document B
Non-SUDEP costs, days in ICU				
2 - 11 years	7.00	-20%	+20%	Tables 32 & 38 of Document B
12 - 55 years	7.00	-20%	+20%	
% of institutionalisation				
Seizure-Free	2.00%	1.60%	2.40%	Table 32 of Document B
≤8 seizures	10.00%	8.00%	12.00%	
>8 - ≤25 seizures	10.00%	8.00%	12.00%	

Parameter	Base Case	Lower Bound	Upper Bound	References
>25 seizures	10.00%	8.00%	12.00%	
CBD average dosage per patient (mg/kg/day)				
All age groups	10.0 mg	N/A	11.0 mg	Assumes 80% of patients are dosed at 10 mg/kg/day, and 20% at 15 mg/kg/day (See response to 3.12 in the separate document ("ID11211 DS - GW ACD responses").
Epilepsy-related Mortality				
SUDEP – RR				
Seizure-Free				
2 - 11 years	0.71	-10%	+10%	Assumption
12 - 55 years	0.71	-10%	+10%	
≤8 seizures				
2 - 11 years	1.00	-10%	+10%	Assumption
12 - 55 years	1.00	-10%	+10%	
>25 seizures				
2 - 11 years	1.00	-10%	+10%	Assumption
12 - 55 years	1.00	-10%	+10%	
SUDEP – Probabilities				
>8 - ≤25 seizures				
2 - 11 years	0.23%	0.11%	0.49%	Based on 98% CIs in Cooper MS, *et al*. 2016 Epil Res 128:43-7.
12 - 55 years	0.23%	0.11%	0.49%	
Non-SUDEP – RR				
Seizure-Free				
2 - 11 years	0.71	-10%	+10%	Assumption
12 - 55 years	0.71	-10%	+10%	
≤8 seizures				
2 - 11 years	1.00	-10%	+10%	Assumption
12 - 55 years	1.00	-10%	+10%	
>25 seizures				
2 - 11 years	1.00	-10%	+10%	Assumption
12 - 55 years	1.00	-10%	+10%	

Parameter	Base Case	Lower Bound	Upper Bound	References
Non-SUDEP – Probabilities				
>8 - ≤25 seizures				
2 - 11 years	0.16%	0.11%	0.21%	Based on 98% CIs in Cooper MS, *et al*. 2016 Epil Res 128:43-7.
12 - 55 years	0.16%	0.11%	0.21%	
Utilities				
Patient utilities				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study Table 25 of Document B
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>18 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Caregiver utility decrements				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Based on standard errors from vignette study
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Decrement of utilities for other seizure types				
Seizure-Free; >24 days	[redacted]	[redacted]	[redacted]	Assumption
≤8 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	

Parameter	Base Case	Lower Bound	Upper Bound	References
≤8 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>8 - ≤25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; ≤18 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >18 - ≤24 days	[redacted]	[redacted]	[redacted]	
>25 seizures; >24 days	[redacted]	[redacted]	[redacted]	
Adverse Events Disutilities				
All adverse events	[redacted]	[redacted]	[redacted]	Based on standard errors from de Kinderen

de Kinderen RJA, *et al*. Epil Res 2016;125:24-31.

Figure 1: DSA Tornado Diagram

Table 7: Parameter variations in the PSA

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
Transition probabilities								
Transition probabilities		Trial data	Bootstrap from trial data					
Weight								
2 - 5 years		[redacted]	N/A	N/A	0.53	1113.66	0.02	Gamma
6 - 11 years		[redacted]	N/A	N/A	1.14	576.31	0.05	Gamma
12 - 17 years		[redacted]	N/A	N/A	2.27	544.10	0.10	Gamma
18 - 55 years		[redacted]	N/A	N/A	2.27	544.10	0.10	Gamma
Subsequent cycle discontinuation								
2 - 11 years	Seizure-Free	0.50%	0.25%	0.75%	N/A	N/A	N/A	Uniform
	≤8 seizures	2.31%	1.16%	3.47%	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	4.94%	2.47%	7.41%	N/A	N/A	N/A	Uniform
	>25 seizures	4.94%	2.47%	7.41%	N/A	N/A	N/A	Uniform
12 - 55 years	Seizure-Free	0.50%	0.25%	0.75%	N/A	N/A	N/A	Uniform
	≤8 seizures	2.75%	1.38%	4.31%	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	3.90%	1.95%	5.85%	N/A	N/A	N/A	Uniform
	>25 seizures	3.90%	1.95%	5.85%	N/A	N/A	N/A	Uniform
Long-term discontinuation								
Seizure-Free		0.50%	0.25%	0.75%	N/A	N/A	N/A	Uniform
≤8 seizures		5.00%	2.50%	7.50%	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures		5.00%	2.50%	7.50%	N/A	N/A	N/A	Uniform
>25 seizures		5.00%	2.50%	7.50%	N/A	N/A	N/A	Uniform
Stopping rules								
2 - 11 years	Seizure-Free	0.00%	0.00%	0.00%	N/A	N/A	N/A	Uniform
	≤8 seizures	17.50%	14.00%	21.00%	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	71.43%	57.14%	85.71%	N/A	N/A	N/A	Uniform
	>25 seizures	80.00%	64.00%	96.00%	N/A	N/A	N/A	Uniform
12 - 55 years	Seizure-Free	0.00%	0.00%	0.00%	N/A	N/A	N/A	Uniform
	≤8 seizures	18.75%	15.00%	22.50%	N/A	N/A	N/A	Uniform
	>8 - ≤25 seizures	25.00%	20.00%	30.00%	N/A	N/A	N/A	Uniform
	>25 seizures	57.14%	45.71%	68.57%	N/A	N/A	N/A	Uniform
Management Unit Costs								
Visits Costs								
2 - 11 years	Seizure-Free	£275	£138	£413	70.15	15.37	17.90	Gamma
	≤8 seizures	£971	£486	£1,457	247.71	15.37	63.19	Gamma
	>8 - ≤25 seizures	£2,008	£1,004	£3,011	512.13	15.37	130.65	Gamma
	>25 seizures	£3,529	£1,764	£5,293	900.14	15.37	229.63	Gamma
12 - 55 years	Seizure-Free	£106	£53	£160	27.14	15.37	6.92	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
	≤8 seizures	£311	£155	£466	79.31	15.37	20.23	Gamma
	>8 - ≤25 seizures	£560	£280	£839	142.74	15.37	36.42	Gamma
	>25 seizures	£1,192	£596	£1,788	304.15	15.37	77.59	Gamma
Hospitalisation Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£1,454	£727	£2,181	370.98	15.37	94.64	Gamma
	>8 - ≤25 seizures	£2,908	£1,454	£4,363	741.96	15.37	189.28	Gamma
	>25 seizures	£5,817	£2,908	£8,725	1483.92	15.37	378.56	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£188	£94	£282	48.02	15.37	12.25	Gamma
	>8 - ≤25 seizures	£376	£188	£565	96.04	15.37	24.50	Gamma
	>25 seizures	£753	£376	£1,129	192.08	15.37	49.00	Gamma
Rescue Med Costs								
2 - 11 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>8 - ≤25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
	>25 seizures	£408	£204	£612	104.08	15.37	26.55	Gamma
12 - 55 years	Seizure-Free	£0	£0	£0	0.00	N/A	N/A	Gamma
	≤8 seizures	£51	£26	£77	13.01	15.37	3.32	Gamma
	>8 - ≤25 seizures	£102	£51	£153	26.02	15.37	6.64	Gamma
	>25 seizures	£204	£102	£306	52.04	15.37	13.28	Gamma
Institutionalisation Costs								
18 - 55 years	Seizure-Free	£321	£160	£481	81.86	15.37	20.88	Gamma
	≤8 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>8 - ≤25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
	>25 seizures	£1,604	£802	£2,407	409.29	15.37	104.41	Gamma
Daily Cost ICU								
Adults		£1,299	£643	£4,482	979.49	1.76	738.39	Gamma
Paediatric		£1,583	£784	£5,867	1296.58	1.49	1061.73	Gamma
Daily Cost General Ward								
Adults		£460	£402	£807	103.43	19.78	23.26	Gamma
Paediatric		£597	£560	£760	51.01	137.00	4.36	Gamma
Emergency Department Visit								
Per episode		£237	£56	£838	199.33	1.41	167.64	Gamma
Epilepsy-related Mortality – SUDEP								
2 – 11 years (>8 - ≤25 seizures)		0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
12 – 55 years (>8 - ≤25 seizures)		0.23%	0.11%	0.49%	0.00	5.80	0.00	Gamma
Epilepsy-related Mortality – Non-SUDEP								
2 – 11 years (>8 - ≤25 seizures)		0.16%	0.11%	0.21%	0.00	43.86	0.00	Gamma
12 – 55 years (>8 - ≤25 seizures)		0.16%	0.11%	0.21%	0.00	43.86	0.00	Gamma

Parameters		Base case	Min	Max	SE	Alpha	Beta	Distribution
% of institutionalization								
Seizure-Free		2.00%	1.60%	2.40%	N/A	N/A	N/A	Uniform
≤8 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
>25 seizures		10.00%	8.00%	12.00%	N/A	N/A	N/A	Uniform
Utilities								
Patient utilities - Values estimated based on SE								
No seizures	>24 days	0.753	N/A	N/A	0.049	57.46	18.82	Beta
≤8 seizures	≤18 days	0.000	N/A	N/A	0.000	N/A	N/A	Beta
	>18 - ≤24 days	0.572	N/A	N/A	0.041	82.25	61.65	Beta
	>24 days	0.611	N/A	N/A	0.046	67.51	42.92	Beta
>8 - ≤25 seizures	≤18 days	0.361	N/A	N/A	0.033	75.56	133.56	Beta
	>18 - ≤24 days	0.443	N/A	N/A	0.039	73.17	91.89	Beta
	>24 days	0.466	N/A	N/A	0.052	42.76	49.06	Beta
>25 seizures	≤18 days	0.235	N/A	N/A	0.024	76.04	247.54	Beta
	>18 - ≤24 days	0.374	N/A	N/A	0.033	77.95	130.22	Beta
	>24 days	0.445	N/A	N/A	0.048	46.36	57.78	Beta
Caregiver utility decrements – values based on SE								
>8 - ≤25 seizures	≤18 days	-0.294	N/A	N/A	0.052	31.989	0.009	Gamma
	>18 - ≤24 days	-0.294	N/A	N/A	0.052	31.989	0.009	Gamma
	>24 days	-0.294	N/A	N/A	0.052	31.989	0.009	Gamma
>25 seizures	≤18 days	-0.337	N/A	N/A	0.054	39.440	0.009	Gamma
	>18 - ≤24 days	-0.337	N/A	N/A	0.054	39.440	0.009	Gamma
	>24 days	-0.337	N/A	N/A	0.054	39.440	0.009	Gamma
Caregivers								
Number of caregivers		2.0	1.0	2.5	N/A	N/A	N/A	Uniform
Decrements of utilities (other seizure types)								
≤8 seizures	>18 - ≤24 days	-0.079	-0.087	-0.071	N/A	N/A	N/A	Uniform
	>24 days	-0.079	-0.087	-0.071	N/A	N/A	N/A	Uniform
>8 - ≤25 seizures	≤18 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
	>18 - ≤24 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
	>24 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
>25 seizures	≤18 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
	>18 - ≤24 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
	>24 days	-0.122	-0.134	-0.109	N/A	N/A	N/A	Uniform
Adverse Events Disutilities								
All age and seizure groups		-0.120	N/A	N/A	0.004	900	0.00013	Gamma

Table 8: PSA results compared to base case (1000 simulations)

	Inc. Costs	Inc. QALYs	ICER
Base Case	£34,479	1.1781	£29,268
PSA	£35,757	1.1645	£32,338

Figure 2: Cost-effectiveness plane

Figure 3: Cost-effectiveness acceptability curve

NICE National Institute for Health and Care Excellence

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome [ID1211]

Consultation on the appraisal consultation document – deadline for comments 5pm on **16 September 2019**

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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.	N/A
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	Evidenced short term efficacy should be viewed in the context of the recognised severity of Dravet syndrome and the potential ongoing risks, including risks to life, of current seizure activity. In light of the often intractable nature of the condition, high levels of resistance to current NHS treatments and associated increased risks of premature mortality, available clinical evidence of short term efficacy and tolerability should carry more weight in the appraisal process. In March, Epilepsy Action compiled a Patient Impact Report around cannabidiol for Dravet and Lennox-Gastaut syndrome (LGS) for the Clinical Priorities Advisory Group (CPAG). The report was informed by the feedback of parents/ carers' of people with Dravet syndrome and LGS, four and five respondents respectively. Question two of the patient impact report focused on the lived experience of people with these syndromes with specific attention paid to the impact of the condition on a person's daily life, physical capability and mental/ psychological wellbeing. Extract from CPAG Patient Impact Report, March 2019: *People with Dravet syndrome and LGS experience regular, often daily, seizures and many of these seizures can be prolonged and ultimately life threatening. In light of the frequency and severity of seizures associated with these syndromes, patients often have high care needs.* *One parent carer of a person with Dravet syndrome noted that their son experiences a variety of seizure types up to 50 times day. 'He experiences tonic clonic, focal, partial and absence seizures (sometimes 30-50 of these per day)'.* *They went on to highlight the severity of some of these seizures and the associated risks – '[their son] is hospitalised every 5 weeks on average due to a prolonged seizure'. During these hospitalisations, their son will often have to be intubated and placed in PICU at the children's hospital.* *Parents/ carers of people with LGS also noted the frequency and severity of seizures associated with the condition. One parent carer noted that 'We can go for days on end with continuous seizure activity and no rescue meds make any difference'. Another parent carer mentioned that their son continues to have weekly seizures, 'this has been the case for 34 years'. Another parent went on to list the type of seizures their son experiences, including 'atonic seizures…tonic seizures…myoclonic seizures' and noted that these seizures occur day and night. One parent carer went on to note that seizures happen day and night necessitating continuous one to one care.* *Another parent carer of a patient with LGS noted the impact of seizures on their son's heart rate and breathing highlighting that he could not be safely left alone. Two respondents highlighted the quantities of medications that many people with LGS are prescribed in an attempt to control or limit seizures. One parent carer noted that their son is currently taking five antiepileptic drugs (AEDs) without adequate seizure control. Another parent carer has to administer three AEDs, again with limited seizure control, along with other drugs and treatments: 'he needs medicating 6 times a day…he requires supplementary milk feeds through the tube due to weight loss and not willing to eat sufficiently'.* *People with Dravet syndrome and LGS often live with a range of comorbidities that can have a major impact on their day-to-day lives. Many also have a spectrum of learning disabilities with most being*

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	severe and many will be on the autistic spectrum. *Many people with Dravet will have difficulties with communication, some being non-verbal and unable to communicate at all. Sleep issues are a common problem with some having less than 2 hours a night. Those with Dravet syndrome have a spectrum of mobility issues, some have no mobility and use wheelchairs while others can have fairly good mobility but with balance issues. It is common to have a gait abnormality, which deteriorates over time. Feeding issues are also common with some patients eventually having to be tube fed. Other comorbidities include ADHD, behaviour issues and incontinence.* *The prevalence of comorbidities in people with LGS was also highlighted by three of the five respondents in his cohort. One parent carer noted that their son also had 'severe learning difficulties' while another noted that their son had other complex health needs as well as his epilepsy. Another parent carer explained that their son was also 'significantly cognitively impaired'.* *These patient cohorts are often also at a significantly increased risk of associated injuries and ultimately death as a result of SUDEP or prolonged seizures. Injuries due to a fall during seizures can be severe, especially as patients get older. In relation to LGS, a parent carer noted that their son broke his leg after a drop seizure further exacerbating his care and support needs. They went on to succinctly note: 'LGS and the seizures it causes have major knock on effects on people lives, that severely exacerbate the already huge challenges that affect the individual and their family.'* *People with Dravet syndrome and LGS are also at high risk of SUDEP. This was succinctly noted by a parent carer of a child with Dravet syndrome, 'SUDEP is never far from our thoughts'. A parent carer of a son with LGS went on to say that their son 'continues to carry five risk factors around SUDEP. His doctor has said he places his risk at 1:100. This causes us untold anxiety and hinders recruiting paid support workers to care for him.'* *People with Dravet syndrome and LGS will require constant care throughout their lifetime. A parent carer of a child with Dravet syndrome noted that their son required '24 hour care and 24 hour monitoring for seizures'. In light of the current low rates of seizure control or management amongst people with Dravet and LGS these care needs are likely to be constant throughout their lifetimes. Two respondents highlighted that LGS prevents people with the condition from being able to look after themselves and denies them their independence.* *'My son is 16 with LGS, he is unable to do anything for himself so we have to provide 24 hour care'* *'He has no independence and requires continual supervision and support'*
2	3.20 – The inclusion of modelling to attempt to capture and reflect the potential impact of Dravet syndrome on carers' quality of life is very welcome. Severe and intractable epilepsies often have a profound impact of carers' and families. Whilst reductions in convulsive seizures and drop seizures are of most medical benefit, other changes in seizure activity, including altering patterns of seizures leading to increased seizure free days, should be viewed as clinically/ statistically significant for the purposes of this appraisal. For some carers' of people with severe and intractable epilepsies, the unpredictability of seizures can be as burdensome, and subsequently as important, as frequency and severity (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6546015/). As such, the treatment should be appraised with due consideration paid to the broadest definition of the seizure burden on patients and carers'. This will ensure relevant modelling accurately assesses the wider potential benefits of the treatment.

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3	3.21 – Dravet syndrome often has a profound impact beyond immediate carers', including on wider families. This should be recognised and reflected in this appraisal. In March, Epilepsy Action compiled a Patient Impact Report around cannabidiol for Dravet and Lennox-Gastaut syndrome (LGS) for the Clinical Priorities Advisory Group (CPAG). The report was informed by the feedback of parents/ carers' of people with Dravet syndrome and LGS, four and five respondents respectively. One of the questions in the report was focussed on the impact of these conditions on a patients' family, friends and caregivers. A full copy of the response to this question from the patient impact report is included below. The additional risk factors faced by people with Dravet syndrome feature heavily, including the increased prevalence of premature mortality, along with high care and support needs including administering multiple medications throughout the day and night and the prevalence of comorbidities. Extract from CPAG Patient Impact Report, March 2019: *People with Dravet syndrome and LGS often require round the clock care and most are fully dependent on parents and carers throughout their lives. The majority will never be able to live fully independent lives.* *Caring for someone with the condition is extremely isolating and affects every aspect of family life. There is usually a financial impact with one parent needing to give up their job/career to become a full time carer. One parent carer of a child with Dravet syndrome noted that 'the first thing I had to do on [his son's] diagnosis (at 8 months) was give up work. My wife had to extend her maternity leave. Immediately we took a huge hit financially.'* *It is not just financial pressures, another parent carer highlighted the impact of caring for a child with Dravet on their own health and relationships noting that 'it has been a real toll on our health and family life'. This was echoed by other respondents, 'we haven't had a night out in over two years, we live in darkness, and communicate in whispers for fear of waking [their son] up.'* *Many parents at some point will suffer from depression and anxiety and counselling is not readily offered to these families. The same parent carer quoted above went on to note that the burden of caring for their son has made them suicidal.* *The situation is very similar for families affected by LGS. The impact of the condition on parent carers and other family members was made clear by a number of LGS respondents. One parent carer noted 'the impact on our mental health and wellbeing has been significant. Without the respite we have been able to get, I doubt we would have managed at times.' Another parent carer mentioned that they had suffered a recent bout of serious ill health attributable in part to a weakened immune system they link to the exhaustion of caring for their son.* *There is also often a significant impact on siblings of people with these syndromes. Two parent carers of people with LGS highlighted the impact of their siblings condition on their other children's lives. One noted that while it was difficult to define the impact of the condition on their daughter, '[her brother's condition] has no doubt hugely impacted her life, the time we have been able to give her, the emotional and psychological pressures etc.'* *Another parent carer of a child with LGS highlighted that 'our eldest daughter won't have children for fear of having a child with an epilepsy. The other daughter feels the weight of caring for her brother' when her parents are no longer able to.* *The impact on siblings was also noted by a parent carer of a child with Dravet. In relation to their young daughter they said, 'helping with X [their son with Dravet syndrome] will undoubtedly have a*

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	huge impact on her in the future'. *Beyond siblings, living with Dravet syndrome or LGS often affects the whole family. A parent carer of a child with Dravet felt compelled to move abroad to access support from grandparents.* *Parents/ carers of people with Dravet syndrome and LGS often struggle to receive support both practically and financially due in part to a lack of understanding and adequate support across most services. One parent carer whose son has LGS noted 'we struggle to get carers to help as he has complex health needs as well as his epilepsy. We struggle with professionals understanding how tiring it is'. This was echoed by a parent carer of a child with Dravet syndrome who also noted the complexities and challenges of coordinating professional care when it is available, 'X needs 24hr care and 24hr monitoring for seizures, we get help from Continuing health care for night support (waking nights 7-days a week) but we still have to manage lots of carers (interviews, people in our house, wages etc.). It has been a real toll on our health and family life. 14 years of it so far!'* *This experience was echoed by another family who cared for a child with Dravet syndrome 'as a family over the years we became social lepers, always trying to maintain respite given by LA [Local Authority] but it's exhausting.'* *Life for families affected by these conditions is extremely challenging and stressful with the constant daily fear and worry due to their child being at high risk of SUDEP and death due to prolonged seizures. A parent carer of a child with Dravet syndrome noted the intense medication regime that their child required and the potential consequences if a mistake is made with administering the medications. 'Each morning, it's so important that we administer the correct AEDs as we are aware of the consequences if this doesn't happen. Having 3 AEDs, morning and night, plus a 3-day course of antibiotics each week, is now set as a routine'.* *The additional risk factors that are prevalent amongst people with Dravet and LGS can make it harder for families to access professional care. A parent carer whose son has LGS noted '[our son] is significantly cognitively impaired and continues to carry five risk factors around SUDEP. His doctor has said he places his risk at 1:100 . This causes us untold anxiety and hinders recruiting paid support workers to care for him. After all who wants the responsibility of caring for him at £8.00 per hour.'*
4	There is a strong case for cannabidiol to be appraised as an innovative treatment by NICE. Given the often intractable nature of Dravet syndrome and high levels of resistance to treatments currently available on the NHS, the available RCT evidence suggests that cannabidiol presents a potential 'step-change' in terms of outcomes for this patient group. Cannabis-based medicinal products (CBMPs), including cannabidiol, offer therapeutic potential as a new grouping of treatments. The potential of CBMPs, including cannabidiol, as a new category of antiepileptic drugs should be considered when assessing cannabidiols positioning as an innovative treatment. While the mechanism of action of cannabidiol as an antieplietpic drug is unknown, it is likely to be a novel pharmacological mechanism.
5	
6	

Insert extra rows as needed

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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.
- Do not include medical information about yourself or another person from which you or the person could be identified.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[**Insert your name here**]

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

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Example 1	
1	Acknowledging limitations under which the ACD was prepared, we would like to note that for adults with Dravet Syndrome, clobazam may not be the antiepileptic drug with which cannabidiol will be used. This is for a variety of reasons. Whilst accepting that this is not the primary focus of the ACD, it is another important factor to consider in reviewing the evidence in order to come to a recommendation. .
2	We consider that all the relevant evidence has been taken into account. The best quality evidence emerges from the limited number of randomised controlled trials undertaken and these have been taken into account.
3	We consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We are disappointed in the current limitations of the modelling undertaken by the company, as they limit confidence in the modelling and therefore adversely affect the possibility that the technology will be made available for people in great need of alternative treatments.
4	We consider that the provisional recommendations are a sound and suitable basis for guidance to the NHS.
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UCL-GOS-Institute of Child Health & Great Ormond Street Hospital for Children NHS England Specialised Commissioning: Neurosciences CRG
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I was [redacted]. All remuneration went to the department I am [redacted]
Name of commentator person completing form:	[redacted]

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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	Page 1 – the link to the committee papers take you to Lennox Gastaut committee papers rather than those with relation to Dravet syndrome
2	This group of patients are at high risk of continuing seizures despite currently available AEDs. There is a high unmet need with regard to seizure control. There is high expectation that Cannabis based medicinal products will fulfil this unmet need. The current evidence available is only with regard to CBD; this shows evidence of short term efficacy compared to placebo. The committee have reviewed all evidence available.
3	The EMA have ruled approval if in conjunction with clobazam. Many children will have trialled clobazam; if they no longer remain on clobazam it is likely they have experienced adverse effects.
4	It is difficult to follow the economic model utilised. Many of the data put forward would be speculative, without true data on which to work. NHS England acknowledge the criticisms of the modelling, but much of the data used would be tenuous whereas the data on efficacy is more reliable.

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	Young Epilepsy
Location	
Conflict	
Notes	

Comments on the ACD:

Neither the company's base-case analysis nor the ERG's scenarios give an accurate reflection of the cost effectiveness of cannabidiol

We recommend that the guidance on this technology is considered for review 12 to 18 months after publication of the guidance, rather than after three years. Dravet syndrome has a significant impact on the lives of children and young people, as well as their families. As the evidence develops around cannabidiol use for treatment-resistant epilepsy, it is crucial that families have the earliest opportunity to benefit from new treatments. We note that further cannabidiol research is already underway and recommend that any relevant evidence should be reviewed at the earliest opportunity.

Many families have received mixed messages regarding if and when their child might have access to cannabidiol as an NHS treatment. We urge NICE to ensure that the process and timescales for appraising cannabidiol are clearly communicated to families across the country on an ongoing basis.

Yes, the relevant clinical evidence has been taken into account.

Based on the information provided, the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We note that further interpretation of the evidence will be required once a revised economic model is provided by the company.

Based on the information provided, the recommendations are sound and a suitable basis for guidance to the NHS. Young Epilepsy recognises the need for further research into the efficacy and safety of cannabidiol for severe treatment-resistant epilepsy in children and young people, including:

• Long term efficacy and safety of use in children and young people
• Cognitive, psychological and emotional impact of use in children and young people
• Impact of use in children and young people on structural and functional brain development

We strongly recommend that specialist clinicians should still be able to prescribe cannabidiol on a case-by-case basis.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Cannabidiol with clobazam for treatment of seizures associated with Dravet syndrome - Addendum

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Marie Westwood, Reviews Manager, Kleijnen Systematic Reviews Ltd, U Bram Ramaekers, Health Economist, Maastricht UMC Willem Witlox, Health Economist, Maastricht UMC Ben Wijnen, Health Economist, Maastricht UMC Debra Fayter, Systematic Reviewer, KSR Ltd Steve Ryder, Health Economist, KSR Ltd Nigel Armstrong, Health Economist, KSR Ltd Titas Buksnys, Health Economist, KSR Ltd Gill Worthy, Statistician, KSR Ltd Kate Misso, Information Specialist, KSR Ltd Manuela Joore, Health Economist, Maastricht UMC Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University
Correspondence to	Marie Westwood, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	24/09/2019

Following the EMA licence of cannabidiol, the company provided evidence from a subgroup of the trial population (patients treated also with clobazam). The company provided an additional submission following the first appraisal committee (AC) meeting. An updated model was submitted that incorporated several changes in response to the ACD. See below for the ERG comments on this submission.

Clinical evidence

Baseline data for the new subgroup (with clobazam) seem unbalanced, with respect to seizure frequency and convulsive seizure frequency, between the CBD 10mg/kg/day and placebo arms. The ERG consider that it is unclear what, if any, effect this may have on the treatment effect.

Validity of the economic model

The ERG was able to verify that the company's model produced a null QALY gain under the conditions set out by the company (removing discontinuation of CBD) and agrees that the company was able to demonstrate the symmetry of the model in both arms. It is furthermore reassuring that the company, together with a third party, undertook a significant number of internal validity tests that the model passed. However, there are some remaining concerns about the face validity of model assumptions surrounding the health states that patients return to upon treatment discontinuation. On discontinuation from CBD, it is assumed that patients would transit to the seizure frequency distribution as assumed for placebo (i.e. cycle 2 of the comparator arm). This assumption is viewed as particularly problematic because patients discontinue from all health states, but with higher probabilities in the severe health states, and hence patients' health states might improve upon CBD discontinuation. ERG did provide a scenario analysis in an attempt to explore the impact of this structural assumption (see Table 3). Implementing alternative scenarios is particularly challenging and time consuming due the opaqueness of the economic model. Transparency issues include many hidden worksheets, hidden cells, and coding most of the model in VBA which may not have been necessary and which had changed substantially in producing the latest version of the model. This hampered the ERG's ability to thoroughly validate the model, and explore some assumptions within the model.

Updates to the company's base case following the ACD

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

Table 1. Updates to the company's base case following the ACD (source company submission)

#	Company update	ACD Response	ERG comment
1	The relative treatment effect applied to lifetime in the usual-care arm and for discontinued CBD patients	3.10, 3.14	Consistent with ERG preferences (see also ERG report section 5.2.2)
2	Stopping rules applied at 12 and 24 months, in addition to 6 months, based on NHS England Guidelines (derived from the GWPCARE5 dataset)	3.7	This is inconsistent with the committee preferences which preferred applying the stopping rule at 3 months. Moreover, the evidence used to derive the input parameters for the stopping rules is unclear to the ERG. Additionally, it is unclear whether the 2nd and

			3rd stopping points are also included in the company's scenario using a 3 months (instead of 6 months) stopping rule.
3	Probability allocations and transition probabilities for clinical parameters at baseline and in cycle 1 derived only from the subpopulation of patients on clobazam in the 10 mg/kg/day and placebo arms of GWPCARE2. Transition probabilities for cycles 2-9 in the CBD arm derived only from GWPCARE5.	3.13	This update is consistent with the subpopulation of patients on clobazam.
4	Discontinuation rates in cycles 2-9 for the two most severe health states estimated from withdrawers using pooled estimates from the patient level data in the GWPCARE5 study.	N/A	It is unclear to the ERG why this was adjusted.
5	Disutility applied for 1 cycle for adverse events of special interest rated as severe on CBD	3.6 3.18	Incorporating disutilities related to adverse events is in line with ERG preferences. However, the value used (i.e. [redacted] for all adverse events) might be questionable.
6	Risk ratio for death in the convulsive seizure free health state set to 0.71	3.16	The mortality risk is halved. The ERG critiqued the appropriateness of this risk ratio (ERG report section 5.2.6). In short, the initially reported risk ratio of 0.42 reflects the risk ratio for being seizure-free: presumably this is not restricted to convulsive-seizures only. Hence, it is unclear to what degree this evidence supports the association between number of convulsive seizures and increased epilepsy-related mortality. Halving this risk ratio does not resolve this issue.
7	Caregiver disutilities calculated from the EQ-5D VAS norms for the UK population for each health state (using utility outcomes from the vignette study)	3.20 3.21	It is unclear to the ERG how the updated caregiver disutilities are calculated by the company.
8	An average of 2 caregivers per patient	3.21	As mentioned before, if multiple carers are involved, the ERG is not convinced that utility decrements are on an additive scale (e.g., if you would consider the whole family, not everyone will have the same disutility). According to the recent DSU report on caregiver QALYs, there is uncertainty on how caregiver (dis)utilities are best incorporated, and the ERG wishes to highlight that this addition is therefore subject to some uncertainty.

9	Disutilities applied to each health state for non-convulsive seizures, estimated from de Kinderen 2016	3.8	The main ERG concerns relate to input parameters used for the convulsive-seizure free health state that may reflect that patients are also non convulsive-seizure free (which was not the case). Particularly input parameters related to mortality (both SUDEP and non-SUDEP) and utility values (see also ERG report section 5.2). Therefore, separately capturing non-convulsive seizures likely results in double counting. Moreover, the ERG could not reproduce the utility values retrieved from Kinderen et al (the disutility values retrieved by the ERG were smaller). Furthermore, there may be another issue with double counting as the study of De Kinderen et al. assumed seizure reduction from all seizures (not restricted to non-convulsive seizures).

Additional ERG comments

Dosing of CBD is calculated based on patients' weight. The company used the median instead of mean weight to inform this calculation, arguing that the weight distribution was skewed. However, in clinical practice, outlier patients will also be encountered and therefore the ERG, in line with the committee, considers the mean weight more relevant than the median weight (as explored by the company in a scenario).

As mentioned before, the plausibility of the company's the assumptions for longer-term discontinuation (from cycle 10 onwards), adjusting these parameters to 5% per cycle in all 'seizure' health states, is unclear to the ERG. The ERG would prefer to use identical longer-term discontinuation probabilities as was used for cycles 2-9 (i.e. based on the GWPCARE5 trial).

The company performed a 'waning effect' scenario. This scenario assumes that patients after long-term discontinuation (from cycle 10) incur an additional cycle (3 months) of CBD treatment cost. The ERG would have preferred the treatment waning scenarios as implemented by the ERG (see ERG report).

Additional ERG analyses

Due to the lack of time and model transparency, the ERG was only able to perform a specific explorative analyses related to particular issues discussed during the NICE pre-meeting briefing.

Table 2. Company base-case after ACD (source company submission)

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	£359,041	-0.0389	-	-	-
CCM + CBD	£393,521	1.1391	£34,479	1.1781	£29,268

Table 3. Company base-case after ACD + ERG scenario exploring the impact of assuming patients would transit to the seizure frequency distribution as assumed for placebo after CBD discontinuation*

Technologies	Total costs (£)	Total QALYs*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
CCM	£359,041	-0.04	-	-	-
CCM + CBD	£402,254	0.96	£43,212	1.00	£43,126

* In this scenario the discontinuation rate for CBD is set equal across all health states (mentioned by the company to fix the abovementioned issue) and then calibrated so that the time on CBD is equal to that in the company base-case (with discontinuation rate varying with severity). The calibrated CBD discontinuation rate is 2.19%

Conclusion

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