Single Technology Appraisal

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from AbbVie**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Parkinson's UK
   b. Association of British Neurologists, endorsed by the Royal College of Physicians

3. **Comments on the Draft Guidance from experts:**
   a. Marc van Grieken - patient expert, nominated by Cure Parkinson's

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 03 August 2023. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	N/A
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. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Summary

AbbVie would like to thank the committee for its considered discussion during the Appraisal Committee Meeting (ACM). AbbVie is disappointed, however, by the draft recommendation from NICE not to recommend foslevodopa-foscarbidopa for patients with advanced levodopa-responsive Parkinson's disease (henceforth referred to as advanced Parkinson's, as this is generally the preferred term by patients with the condition) with severe motor fluctuations and hyperkinesia or dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results.

The committee heard from patient and clinical experts about the considerable challenges faced daily by patients with advanced Parkinson's, who experience worsening motor and non-motor symptoms, and the significant burden associated with these. Patients at advanced stages of the disease face a particularly high unmet need, as acknowledged by the committee, with limited treatment options, often requiring highly invasive surgery, and impractical administration. According to National Health Service England (NHSE), as of August 2022, 49% of patients referred for neurosurgical services were waiting over 18 weeks to start treatment, further highlighting the substantial unmet need associated with current advanced Parkinson's therapies.[1,2] Foslevodopa-foscarbidopa represents a novel treatment formulation, capable of maintaining good symptom control without the need for invasive and burdensome administration. In support of this, the committee heard the direct experience of a patient who described the transformative improvement in quality of life (QoL) they observed following treatment with foslevodopa-foscarbidopa.

AbbVie is grateful for the opportunity to respond to the Draft Guidance Document (DGD) to address the committee's key areas of uncertainty surrounding the Company's submission.

In this response to the DGD, AbbVie have provided detailed comments to each of the following topics summarised in Section 3.18 of the DGD:

Issue	DGD section	Response
Limitations with the original modelling approach, including the large number of health states	Sections 3.10 and 3.11	A supporting grouped OFF state model (with five health states) is presented
Uncaptured benefits of foslevodopa–foscarbidopa	Section 3.21	Additional sleep benefits of foslevodopa–foscarbidopa are now captured within the economic analyses. Additional benefits other than sleep that were not possible to robustly incorporate have been detailed qualitatively in Responses 1, 2 and 7.
The utility values and costs associated with health states in the model	Section 3.16 and 3.17	Utility values and health state costs are now capped at OFF10

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Use of M15-736 trial data to model best medical therapy (BMT) treatment effect	Section 3.7	BMT treatment effect is now modelled using M15-736 data
Treatment effect following discontinuation	Section 3.13	Patients discontinuing treatment are redistributed to baseline, which AbbVie maintain is most reflective of long-term improvements associated with active treatment
Uncertainty in the indirect treatment comparison	Sections 3.8 and 3.9	AbbVie maintain that foslevodopa-foscarbidopa offers improved efficacy over levodopa-carbidopa intestinal gel (LCIG) for patients
The generalisability of the M15-736 trial population to the population of interest in this submission and reliability and magnitude of the treatment effect	Section 3.5	AbbVie maintain that the M15-736 population is generalisable to the population of interest
Data source of discontinuation	Section 3.14	M15-736 data now informs discontinuation rates for the first model cycle
Approach to modelling long-term natural disease progression	Section 3.12	AbbVie maintain that their approach to extrapolating data from Palmer et al. (2002) is most appropriate

Alongside these comments, AbbVie have provided a revised base case in light of committee preferences, including capturing additional benefits of foslevodopa-foscarbidopa, 'capping' the utilities and health state costs used in the model which effectively reduces the number of unique health states, and updating the approach to long-term treatment benefits associated with foslevodopa-foscarbidopa. The new base case analysis using the Company's original model yields incremental cost-effectiveness ratios (ICERs) against both comparators within the range for which a new treatment is considered a cost-effective use of NHS resources.

In addition, AbbVie have presented a separate supporting economic model to address committee concerns surrounding the large number of health states in the original model. This supporting model has been aligned to the updated base case of the original model, and reduces the number of health states from 17 to five, through grouping patients into health states based on four-hour increments in OFF time. This additional supporting model yields results similar to the Company's original model structure, with both models showing foslevodopa-foscarbidopa to be a cost-effective use of NHS resources at a willingness-to-pay (WTP) threshold of £30,000 per QALY. This supportive model therefore provides reassurance that the results can be considered a reliable basis from which to inform decision-making. The original model remains more representative of patients' daily fluctuations in OFF time, as it is able to capture clinically

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	meaningful hourly changes in OFF time, and has therefore been retained as the principle source of evidence for the cost-effectiveness for foslevodopa-foscarbidopa in advanced Parkinson's. Further scenario analyses demonstrate the results from both models to be robust to outstanding uncertainty. AbbVie therefore consider that these updated economic analyses offer reliable evidence of foslevodopa-foscarbidopa's cost-effectiveness, and request the committee to consider the evidence presented to enable this novel treatment and its associated benefits to be available under routine commissioning.
1	**AbbVie have reduced the number of health states informing the model through adopting a grouped OFF model structure as part of a supporting analysis, in order to reduce uncertainty associated with the Company's original model structure.** The committee commented in the DGD that the large number of health states in the model led to cost-effectiveness results associated with uncertainties relating to a lack of data to reliably inform patient transitions, utility and cost estimates (DGD sections 3.10 and 3.11). The committee noted this as a key issue with the Company's model, affecting other areas of the modelling. Indeed, this issue was discussed at Technical Engagement, with the External Assessment Group (EAG) suggesting to adopt a model structure driven by both OFF and Hoehn & Yahr (H&Y) states. AbbVie maintain that the inclusion of H&Y states to the model structure is not appropriate for a number of reasons. The committee's concerns surrounding the large number of health states would not be resolved by the EAG's suggested approach, which would yield 25 health states, with patients distributed across 17 of these health states at baseline; the outcomes of such a model would therefore remain subject to much larger uncertainty, with a larger number of health states each being informed by fewer data. The previous Chaudhuri et al. (2022)[3] model which utilised this structure could better justify the increased health states given there were a larger number of patients to inform the transition probabilities and utilities from available trial data (N=196, versus [redacted] in the Company's model); however, it is noted by Chaudhuri et al. (2022) that even with this larger sample size, the model is still subject to uncertainty due to limited data. For health state costs derived from the Adelphi 2017–2019 dataset, there would be [redacted] direct observations in at least [redacted] of the 10 highest OFF states if H&Y health states were included, which would further amplify concerns of limited data informing the health states. Further to the increased uncertainty described above, the inclusion of H&Y states in the model would not address the committee's concerns that additional benefits of foslevodopa-foscarbidopa are not captured by modelling OFF time alone (DGD section 3.11). For example, the patient expert at the ACM noted almost immediate improvements in daily functioning, symptom control and sleep following initiation of treatment with foslevodopa-foscarbidopa. AbbVie have retained OFF time as the principal outcome informing the modelling, and have instead addressed the

	committee's concerns regarding additional benefits of foslevodopa-foscarbidopa not being captured without the need to incorporate H&Y outcomes in the model (see Response 2 below). AbbVie's understanding that OFF time is the most suitable outcome to use in the modelling of Parkinson's is informed by clinical expert discussion during the committee meeting and by feedback previously obtained on this issue; a survey of 38 UK healthcare professionals (HCPs) regarding the classification of advanced Parkinson's found that [redacted]% of HCPs consider that the number and length of OFF periods are among the most important classification criteria, while only [redacted]% believed that the H&Y scale was.[4] OFF time captures a breadth of health effects, including motor symptoms such as tremors (described by 50% of patients during OFF periods), gait changes (25%), and rigidity (17%), and also captures non-motor symptoms such as fatigue (19%), anxiety (15%), and cognitive symptoms (16%).[5] AbbVie maintain that the granularity of modelling 1-hour increments in OFF time is the best way to account for the more stable hour-to-hour symptom control associated with foslevodopa-foscarbidopa's 24-hour continuous administration. One-hour increments in OFF time have been demonstrated to be clinically meaningful for patients, with analyses of two clinical trials concluding that the minimal clinically important change (MCIC) for changes in OFF time was one hour.[6] Foslevodopa-foscarbidopa is a novel treatment and represents the first treatment to be administered by 24-hour continuous daily infusion, and the first for Parkinson's to be evaluated by NICE. Therefore, a *de novo* model structure which reflects this and better captures clinically meaningful changes to patients' daily lives is most appropriate. Notwithstanding the above, AbbVie recognise the limitations noted by the committee relating to data availability associated with the original modelling approach. To address the committee's preference for a model with fewer health states (section 3.11), and to provide reassurance that the cost-effectiveness results provided by the Company's economic model are robust for decision-making, AbbVie have 'capped' health state costs and utilities at 10 hours of OFF time to mitigate uncertainty derived from sparse data between OFF health states 11–16 (as a result, reducing the number of unique health states from 17 to 11; see Responses 3 and 4 below). In addition and separately, a supporting model has been developed with a reduced number of health states, in which greater granularity of OFF time has been forgone to allow for transitions, utilities and costs informed by larger numbers of patients. In this revised approach, OFF health states have been grouped into 4-hour quartiles, representing patients experiencing 1–4 (OFFI), 5–8 (OFFII), 9–12 (OFFIII) and 13–16 (OFFIV) hours of daily OFF respectively, based on a 16-hour waking day (Figure 9 and Figure 10 in Appendix 3). A separate health state, OFF0, captures patients who are experiencing no OFF time. This therefore reduces the number of OFF time health states from 17 in the original Company model to five, in line with the number of health states used in previous 'grouped OFF' model approaches;[3, 7] this revised approach also corresponds with the same groupings used in

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	the MDS-UPDRS scale (item 4.3).[8] Details of this supporting model and the conversion of health states and corresponding inputs are provided in Appendix 3. The results of this analysis are presented alongside the results of the revised base case analysis from the original Company model in Appendix 1, with matching base case settings. Scenario analyses explored in the original Company model were recreated in the supporting grouped OFF model, with results presented alongside the original model scenario analyses in Appendix 3. As shown in Appendix 1, cost-effectiveness results comparing foslevodopa-foscarbidopa to each comparator are similar across both models. The results provided by this analysis are consistent with those of the original Company model, and both models behave in a similar fashion when equivalent scenario analyses are tested in each (see Appendix 2). Small differences in ICERs should be noted however, with smaller differences in incremental costs and QALYs seen in the comparison with BMT. This is expected, given that the grouped OFF model is not able to fully capture the benefits associated with foslevodopa-foscarbidopa's greater hourly improvements in OFF time, which leads to reduced improvement in utility and health state cost savings. Minor differences in incremental costs and QALYs are observed in the comparison with LCIG across both models, however foslevodopa-foscarbidopa yields marginally more QALYs than LCIG in the base case analysis using the grouped OFF model, as opposed to marginally fewer in the hourly model. Nevertheless, both models predict foslevodopa-foscarbidopa to be cost-effective in the base case analysis, and across a range of relevant scenarios explored and presented in Appendix 2. The results of the grouped OFF model therefore provide reassurance that the results predicted by the original hourly model structure are robust to uncertainty surrounding limited patient numbers. Overall, AbbVie still consider the hourly model to be the most appropriate approach, given the reasons outlined above and as 1-hour reductions in OFF time have been shown to be clinically meaningful. The findings of the original Company model are corroborated by the supporting grouped OFF model, thereby alleviating the uncertainty surrounding the cost-effectiveness results.
2	**Additional benefits of foslevodopa-foscarbidopa have been accounted for in the Company's revised economic analysis, in the form of sleep benefits captured by use of treatment-specific utility values and health state costs adjusted for sleep using M15-736 trial data.** As previously noted, the approach of modelling PD based solely on OFF time was chosen in large part due to the fact that it is the most clinically relevant measure for patients with Parkinson's. OFF time was chosen as it is considered to be the best source of evidence for treatments' ability to control symptoms in a predictable manner on a daily basis, the outcome of most importance to patients.

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	However, AbbVie recognise that this approach is unable to fully capture the multifaceted nature of Parkinson's, and by extension additional benefits associated with foslevodopa-foscarbidopa compared with currently available treatments. In particular, and as noted by the committee in the DGD, benefits related to sleep and foslevodopa-foscarbidopa's 24-hour method of administration may not have been fully captured in the Company's 16-hour model structure (DGD section 3.21). As noted in the DGD, clinical experts highlighted that unpredictability of motor symptoms can make day-to-day life very difficult for people with advanced Parkinson's, and good dopamine control can confer benefits beyond motor symptoms. The patient expert at the ACM emphasised the sleep benefits that foslevodopa-foscarbidopa can provide due to its continuous 24-hour infusion; indeed, foslevodopa-foscarbidopa was shown to significantly improve sleep as measured in the M15-736 trial by the Parkinson's Disease Sleep Scale-2 (PDSS-2), a reliable and validated tool for measuring sleep disorders in PD.[9, 10] Foslevodopa-foscarbidopa also reduced the presence of morning akinesia compared with BMT in the M15-736 trial. At Week 12, a smaller proportion of patients receiving foslevodopa-foscarbidopa (8/47 [17%]) reported being OFF at the time of waking, compared with patients receiving BMT (38/60 [63%]; LS mean of Odds Ratio [SE]: [redacted]). This was despite patients in the BMT arm being allowed to receive night-time oral dosing. Incorporating sleep-related outcomes in the model would allow for a broader range of health effects relevant to patients with advanced Parkinson's to be taken into account in the committee's decision-making, reducing uncertainty expressed by the committee around OFF time being the only outcome accounted for in the model (DGD section 3.21). In order to better reflect the important impact on sleep associated with the symptoms of Parkinson's, AbbVie have explored adjusting for sleep-related outcomes in the modelling of health state utility estimates used in the model. In the base case analysis, an additional utility benefit reflecting avoidance of sleep disturbance has been applied to foslevodopa-foscarbidopa in the model. This analysis is based on the comparison of patients experiencing sleep disturbance in each arm of the M15-736 trial, defined as a PDSS-2 score ≥18 at Week 12 of the trial. PDSS-2 score ≥18 is a previously validated threshold that defines clinically relevant Parkinson's-specific sleep disturbances.[11] [redacted] of patients receiving foslevodopa-foscarbidopa reported a lack of sleep disturbance, defined as a PDSS-2 score <18 at Week 12 of the trial, compared with [redacted] in the BMT arm. Utility values based on PDSS scores above and below 18 reported in Xiao et al. (2022) were then used to derive weighted utility values associated with sleep disturbance in each arm.[12] The difference between these values ([redacted]) was then applied as an additive adjustment to the utility value in the foslevodopa-foscarbidopa arm until treatment discontinuation. As LCIG is only administered during patients' waking day before being halted prior to sleep, it was assumed to be associated with the same sleep disturbance as BMT, with no additional utility applied to the LCIG arm of the model. Further details of the methodology used to derive this additional sleep-related utility are

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	presented in Appendix 4. The impact of adopting this approach in both the original Company model and the supportive grouped OFF model are presented in Appendix 1. In addition to adjustments to the health state utility values, in the base case analysis, health state costs have also been adjusted for to account for sleep benefits of foslevodopa-foscarbidopa treatment, whereby yearly cost savings of [redacted] are applied to the foslevodopa-foscarbidopa arm, derived using the proportion of patients reporting sleep disturbance (PDSS-2 ≥18) from the M15-736 trial detailed above, and costs relating to excessive sleepiness reported in the Adelphi dataset (see 'Cost regression output' of the model). The preferred base-case has been informed by clinician interviews, whereby clinicians noted that resource-use is expected to be greater in patients who have poor sleep outcomes. Furthermore, excessive sleepiness was noted as the most relevant outcome resulting in excess resource use; it has also been associated with increased cognitive impairment, and found to be correlated with worsening QoL in patients with Parkinson's.[13] A scenario analysis has been conducted in which yearly savings of [redacted] are applied to the foslevodopa-foscarbidopa arm derived from costs relating to sleep disturbance, rather than excessive sleepiness, from the Adelphi dataset to inform this cost-saving. Details of how these costs were derived are provided in Appendix 4. Foslevodopa-foscarbidopa's novel 24-hour continuous method of administration represents a clear benefit to patients, most notably due to its ability to control symptoms of Parkinson's during patients' sleep, and experience good symptom control when waking. This was observed in the M15-736 trial where [redacted] patients ([redacted]) receiving foslevodopa-foscarbidopa reported morning akinesia at baseline while only 8 (17%) did so at Week 12.[9] As noted by the patient expert invited to the ACM, poor sleep represents one of the most important challenges of living with Parkinson's, which improved dramatically following their treatment with foslevodopa-foscarbidopa. AbbVie therefore agree with the committee that such benefits should be incorporated into the economic analysis, which AbbVie have conducted in the analyses described above. Whilst these analyses attempt to capture the most important additional clinical benefits associated with foslevodopa-foscarbidopa, it should be noted that, in the absence of appropriate data, many other benefits are unable to be fully captured and the presented analysis may be considered conservative as a result of this. For instance, the model does not account for differences in mortality; a meta-analysis has demonstrated that sleep disorders are associated with cognitive deficits, and in turn cognitive impairments have been associated with increased mortality.[14, 15] Patients with Parkinson's with rapid eye movement (REM) sleep behaviour disorder have also been found to have an increased risk of mortality.[16] Additionally, dementia, which is highly prevalent in patients with Parkinson's and associated with cognitive decline and sleep disorders, has also been found to significantly increase mortality in Parkinson's.[17, 18] The clinical evidence presented throughout this appraisal process suggest that clinically important sleep

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	benefits reported following treatment with foslevodopa-foscarbidopa may well lead to a downstream reduction in mortality. Further to this, the patient expert present at the ACM noted general aspects of wellbeing which cannot be quantified in an economic analysis: the patient expert vividly described having to abandon activities and hobbies due to their disease, the burden of having to schedule meals around administration of numerous oral medications, and the anxiety induced by the unpredictability of being 'ON' or 'OFF'. Whilst all efforts have been made to capture as many aspects of Parkinson's most relevant to patients' quality of life, many of these cannot be captured in a robust, quantitative manner, yet are likely to be improved following treatment with foslevodopa-foscarbidopa, as witnessed by the patient expert's own experience of treatment. The impact of modelling sleep-related benefits of foslevodopa-foscarbidopa on the base case cost-effectiveness estimates is shown in Appendix 1, and leads to an increase of 0.14 QALYs and a reduction of £[redacted] in the total costs associated with foslevodopa-foscarbidopa. Whilst these additional benefits have been informed by robust sources of evidence, AbbVie acknowledge that some uncertainty over this additional analysis may remain. A scenario in which neither costs nor utilities are adjusted for sleep-related benefits has therefore been presented in Appendix 2. Results show that foslevodopa-foscarbidopa remains cost-effective in the comparison to both comparators when the additional benefits associated with sleep are not accounted for.
3	**AbbVie have considered the committee's concerns with both the Company's original health state costs assumptions and those in the EAG's preferred analyses, and have therefore taken a conservative approach utilising the original regression analysis, with costs capped at OFF 10. OFF 10 represents the [redacted] observable data from the Adelphi dataset that informed the original analysis. AbbVie consider this approach to be conservative given patients with 11 to 16 hours of OFF time are expected to incur higher costs than patients with 10 hours of OFF time.** The committee considered both the EAG and the Company's approach to modelling health state costs to be associated with uncertainty, indicating that the health state costs are likely to lie between the EAG and Company estimates (DGD section 3.17). As noted in the Company's response to Technical Engagement, AbbVie consider the trend in costs yielded by the EAG's analysis using direct observed cost data including patients with all stages of Parkinson's to be clinically implausible. For instance, the highest costs are associated with OFF 4, while OFF 7–9 are associated with the lowest costs. Moreover, OFF 0 is associated with three times greater costs than OFF 16, bringing into question the face validity of these data: worsening symptoms of Parkinson's are anticipated to be associated with greater healthcare resources use costs, in line with previous cost-effectiveness studies in Parkinson's and clinical opinion.[3 7] This implausible

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	analysis additionally then results in substantially reduced health state costs, which lack clinical validity. Taking this into account, AbbVie consider the most appropriate approach to be a conservative one, which attempts to find a middle-ground between previous estimates. The economic model base case has been updated to include the original Company's health state costs up to OFF 10, following which the costs for higher OFF states have been capped as the same cost as OFF 10. The approach of also capping utilities at OFF 10 (Response 4) effectively reduces the number of unique health states in the base-case model from 17 to 11, as patients incur the same utility and costs, regardless of their occupation of health states 10–16. The cost-effectiveness results of this change to the base case model are presented in Appendix 1. This approach is aligned with a suggestion made in the EAG report and is a conservative approach aimed to overcome concerns surrounding the lack of patient numbers and data at higher OFF states. This approach is also aligned with the scenario of capping at OFF Group III in Chaudhuri et al. (2022),[3] and is consistent with Thach et al. (2021), whereby predicted costs were only generated up to OFF 10.[19] This approach of capping at OFF 10 may be considered conservative, given costs would be expected to be higher for a patient with close to 16 hours of OFF time. For the committee's reference, a scenario analysis has been presented in which no capping of health state costs is applied, and is presented in Appendix 2. This scenario predicts foslevodopa-foscarbidopa to be dominant against BMT, and leading to cost savings per QALY forgone above a WTP threshold of £30,000 versus LCIG.
4	**Utility values used in the updated Company base case are now capped at OFF 10, in order to reduce uncertainty associated with limited patient numbers in higher OFF health states.** AbbVie have taken steps to address the EAG and committee's concerns regarding utility values informing the Company base case (DGD section 3.16). In particular, the EAG have noted the small number of patients informing the utility values in health states OFF 10 and above. In order to reduce uncertainty owing to the sharp drop off in patient numbers available for the highest health states, the utility values have been capped at OFF 10. This approach is aligned with a previous suggestion from the EAG, and is aligned with the approach taken to health state costs in Response 3 above. The results of applying these updated utility values to the base case are shown in Appendix 1. As noted in the Company's response to Technical Engagement, pooled utility values across the four foslevodopa-foscarbidopa trials were used to maximise patient numbers informing the analysis of utility values in the model. AbbVie maintain the validity of this approach as it is a better-fitting model than the EAG's proposed approach and improves the precision of the utility estimates. However, for completeness, a scenario analysis aligned with the EAG's preference of

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	using utility data from M15-736 only, with data from both trial arms used in the analysis is presented in Appendix 1. This represents a smaller overall sample size ([redacted] patients were included in the utility analysis of M15-736, compared with [redacted] in the pooled trial data), which may lead to increased uncertainty. Additionally, the EAG noted that it is unclear as to why age and gender were not tested as variables in the regressions. As highlighted in the Company's response to Technical Engagement, age and gender have been tested for, and it was concluded that these are unlikely to have a significant impact on health state utility values. These analyses are presented in Appendix 4, where adjustment of the utility values derived from the pooled trial data shows little impact; therefore, these were not explored further in the cost-effectiveness model. To align with the EAG's preference, a scenario analysis has been conducted in which the M15-736 utility data is used, and an additional scenario in which these are capped at OFF 10 (see Appendix 2). The company's previous approach to utilities has also been explored within the updated base case, in which pooled trial are used and not capped at OFF10. These scenarios show largely congruent results, showing the model to be robust to assumptions surrounding utility values.
5	**The treatment effect for BMT has been modelled using trial data, to resolve committee uncertainty in the relative treatment effect versus foslevodopa-foscarbidopa. AbbVie maintain that this approach is likely to overestimate the benefits of patients receiving BMT in a population of patients uncontrolled on their current therapy in UK clinical practice.** The committee expressed concerns surrounding the estimation of the treatment effect of foslevodopa-foscarbidopa relative to comparators, particularly for the comparison with BMT (DGD section 3.7). AbbVie maintain that, whilst associated with limitations, the assumption that patients receiving BMT in the model receive no treatment benefit is most appropriate given the population of interest for this submission: patients with Parkinson's whose symptoms are not adequately controlled by their current medical therapy (i.e. BMT). This is supported by an interim analysis from the ongoing PROSPECT study, which is a 24-month observational, international study evaluating the disease progression and burden of patients with Parkinson's who are inadequately controlled by BMT and not receiving a device-aided therapy.[20] Despite BMT optimisation, this interim analysis found that at Month 12, the average (SD) change in daily OFF time from baseline was only −0.3 (1.8) hours, which is not a clinically meaningful change in OFF time.[6, 21] However, in order to resolve the committee's uncertainty relating to the relative treatment effect of foslevodopa-foscarbidopa versus BMT (DGD section 3.7), AbbVie have updated their economic analysis to model BMT treatment effect using M15-736 trial data for the first model cycle, after which patients return to baseline following loss of the trial effect in Cycle 2, and natural disease progression is assumed from Cycle 3 onwards. Whilst AbbVie consider this approach to represent an overestimation of both BMT's absolute and relative effect in Cycle 1, the subsequent return to baseline is supported by outcomes from the PROSPECT study, whereby despite

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	optimisation, patients remained uncontrolled with BMT in practice. This continues to align with clinical feedback received throughout the appraisal process in which it was noted that patients with advanced Parkinson's receiving medication constituting BMT would not be anticipated to experience material improvements in OFF time, and any trial benefit observed for BMT would not last. Additionally, a clinical expert has noted in an interview conducted as part of this appraisal, that patients returning to baseline may be a conservative assumption; while a patient could be expected to return to baseline following the trial period, some patients may have deteriorated further beyond their baseline OFF time at treatment initiation. Nevertheless, AbbVie have adopted this approach in order to mitigate the uncertainty surrounding the treatment effect of BMT in relation to foslevodopa-foscarbidopa. The results of this change to the base case are presented in Appendix 1. Two scenario analyses relating to BMT efficacy are presented in Appendix 2; a scenario in which BMT efficacy is modelled using natural history of disease based on Palmer et al. (2002) (as per the previous Company base case), and another in which BMT is modelled using M15-736 trial data for the first cycle then natural disease progression is assumed from Cycle 2 onwards (rather than returning to baseline, as in the latest Company base case).
6	**AbbVie maintain that the current approach to modelling treatment efficacy upon discontinuation reflects long-term improvements in patients' quality of life following active treatment.** Patient and clinical experts indicated that it is plausible that other treatment benefits, beyond improvements in OFF time, may continue following discontinuation. For example, as indicated by clinical experts, while a patient with Parkinson's is being well managed by treatment, they may age with a similar trajectory to a person without Parkinson's. Clinical feedback noted that better control of motor symptoms whilst receiving treatment would lead to patients experiencing greater functioning, mobility, as well as mental wellbeing. Clinicians noted that such improvements in daily functioning, including the ability to exercise and maintain better physical and mental health would have long term benefits for patients and may result in some improvement in OFF time being retained, despite discontinuation of active treatment. Indeed, studies have found that factors such as exercise and an active lifestyle are associated with decreased cognitive decline, disease progression, and even mortality (over a 32–34-year follow-up).[22, 23] The Company-preferred approach to modelling treatment discontinuation, whereby patients are redistributed according to baseline OFF time, attempts to account for potential maintenance of some treatment benefit in the long term.. The EAG notes that this approach could lead to improvements in OFF time upon discontinuation, if patients discontinue from higher OFF states than baseline. The EAG instead proposed redistributing patients according to BMT health states in the cycle following discontinuation. As noted in the Company's response to Technical Engagement, this assumes that all treatment effect (i.e. reduction in OFF time) experienced by patients whilst

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	receiving treatment would be lost. This is in contradiction to clinical feedback received by AbbVie, and heard from clinical experts present at the ACM. As BMT is now modelled using M15-736 trial data in the first model cycle, patients discontinuing in the first model cycle (presumably having not experienced substantial treatment benefit at this stage) would discontinue to health states above baseline, a situation which appears clinically implausible in practice. AbbVie have therefore not adopted the EAG's suggested approach to modelling long-term benefits of treatment following discontinuation in the base case model, and have retained the approach to redistributing discontinuing patients to baseline health states. A scenario analysis has however been conducted in which the EAG's approach of modelling discontinuing patients according to BMT heath states has been presented in Appendix 1. Whilst acknowledging EAG criticism that this approach may overestimate long-term treatment benefit upon discontinuation, AbbVie maintain that, on balance, this approach is most in line with anticipated long-term benefits of treatment. As highlighted above, in the Company's response to technical engagement, and by clinical and patient expert feedback heard at committee, this approach retains the ability of the model to capture long-term health benefits patients experience despite discontinuation from active treatment.
7	**Whilst AbbVie acknowledge the uncertainty in the indirect treatment comparison of foslevodopa-foscarbidopa versus LCIG, AbbVie maintain that foslevodopa-foscarbidopa provides improved efficacy for patients with Parkinson's.** The committee considered that both the Company and the EAG's approaches to estimating relative treatment effect via a network meta-analysis (NMA) were associated with limitations (DGD section 3.8). Whilst acknowledging uncertainty associated with the Company's NMA, AbbVie maintain that foslevodopa-foscarbidopa provides improved efficacy over LCIG for patients with Parkinson's. As noted in the response to Technical Engagement, expert clinical feedback obtained as part of this appraisal indicated that it is not justified to simply assume equivalence between the two treatments, and there are benefits of foslevodopa-foscarbidopa that could not be modelled, that can plausibly translate into improved efficacy. Importantly, foslevodopa-foscarbidopa can provide capacity-sparing benefits for the NHS which can translate into improved outcomes for patients compared with LCIG. As highlighted in the summary above, wait times for neurosurgical services in NHS England are long due to postponements, cancellations, and capacity-related issues. Many patients waiting for LCIG surgery will be maintained on BMT for up to 4 months (or 6–9 months, according to one clinical expert). As a result, these patients are being maintained on treatment that is insufficient to adequately control their motor fluctuations, and as a result have their QoL impacted until they receive surgery: 21% of surgical postponements and cancellations have been ascribed to NHS

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	workforce issues; 4% ascribed to no beds being available; and a further 2% due to issues with gastric services.[1,2] Additionally, approximately 42% of surgical postponements and cancellations are due to "clinical issues"; the majority due to inability to place the percutaneous endoscopic gastrostomy (PEG) tube required for treatment.[2] There are challenges to quantitatively incorporating these factors into the economic model, and therefore these are not captured as additional benefits of foslevodopa-foscarbidopa. The lack of requirement for surgical intervention for foslevodopa-foscarbidopa is an important benefit, and can translate into improved outcomes for patients compared with LCIG through avoiding risk of associated surgical complications, as well as providing capacity and resource savings to the NHS with there being no need for a multidisciplinary team to initiate treatment. In addition, as has been highlighted throughout the appraisal, the 24-hour infusion of foslevodopa-foscarbidopa versus the non-continuous nature of LCIG can also translate into improved efficacy. Patients receiving LCIG can experience biphasic dyskinesia on starting or ending a dose (atypical biphasic dyskinesia),[24, 25] something which is avoided by the continuous overnight administration of foslevodopa-foscarbidopa. Clinical expert opinion has indicated that this biphasic dyskinesia can greatly impact patients' QoL, therefore providing further support for the improved efficacy of foslevodopa-foscarbidopa over LCIG. Overall, based on clinician feedback indicating plausibility for an improved efficacy profile for foslevodopa-foscarbidopa, and ongoing constraints for neurosurgical services in the NHS impacting the optimisation of LCIG treatment benefit, AbbVie consider it inappropriate to assume clinical equivalence between the treatments, and have therefore retained the approach to modelling the efficacy of LCIG based on the relative risk derived from the observed means NMA. However, a scenario analysis has been presented in Appendix 2, in which equal efficacy has been assumed between foslevodopa-foscarbidopa and LCIG, as per the EAG's preferred approach. Foslevodopa-foscarbidopa remains cost-effective against LCIG in this scenario.
8	**Outcomes from the pivotal trial for foslevodopa-foscarbidopa, M15-736, are representative of those patients anticipated to receive treatment in NHS clinical practice, and are informed by patient diaries which accurately reflect treatment effect on patients' lives.** ***The patient population from the pivotal clinical trial is generalisable to the population of interest in this submission.*** The committee concluded that the M15-741 and M15-736 trials represented a broader patient population than foslevodopa-foscarbidopa was being positioned in, as these trials enrolled patients with prior apomorphine and DBS use (DGD section 3.5). It should be noted that the patient population in which foslevodopa-foscarbidopa is anticipated to be used in NHS clinical practice covers patients for whom apomorphine and DBS are unsuitable,

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	or no longer providing adequate symptom control. The proposed positioning therefore does not preclude prior use of apomorphine or DBS, and the inclusion of patients having received prior treatments does not inherently represent a broader patient population that the proposed indication. *Post hoc* subgroup analyses of the M15-741 trial have demonstrated that patients who received prior DBS (N=24) had similar improvements in OFF and ON times to patients who had not received prior DBS (N=220).[26] No statistically significant differences in OFF time and ON time without troublesome dyskinesia were shown between the subgroups based on prior DBS treatment. Patients who had received prior DBS had a mean change from baseline in OFF time of −1.96 hours (SD=3.44), compared with −2.45 hours (SD=3.82) for patients who had no prior DBS; similarly, patients who had received prior DBS had a mean improvement in ON time without troublesome dyskinesia of 2.57 hours, compared with 2.71 hours for patients who had not received prior DBS. Overall, regardless of prior treatment the efficacy and safety profile appeared similar between the patient groups, although it should be noted that the statistical comparisons between the two groups are limited by the sample size imbalance. Additionally, as previously presented in Table 1 (Page 3) of the clarification questions document, and Section B.2.3.1.2 (Table 5, Page 36) and Section B.2.4.1.2 (Table 18, Page 55) of the Company submission (CS), patients who received prior apomorphine or DBS in M15-741 were similarly matched to the full trial populations who were enrolled in M15-736 and M15-741 study. It is therefore not expected that outcomes for these patients would differ between the population in M15-736 and the population the Company is focusing on. AbbVie therefore maintain that the results of the M15-736 trial are generalisable to the population of patients anticipated to receive foslevodopa-foscarbidopa in NHS practice. Furthermore, AbbVie propose that this patient population represents the greatest unmet need, as noted by the committee (DGD section 3.4), and where the introduction of foslevodopa-foscarbidopa will offer the most value for the NHS. ***Parkinson's diaries are the gold standard measure for Parkinson's clinical trials, and accurately reflect patients' experience of treatments' impact on their disease.*** The committee additionally noted the EAG's concerns that OFF times were recorded by patients in the M15-736 trial via a Parkinson's diary, and may therefore be subject to bias, particularly if they had been able to "guess" treatment allocation, causing unblinding (DGD section 3.7). A number of strategies were employed in the design of M15-736 to minimise bias and uncertainty related to the Parkinson's diaries. Most notably, a concordance evaluation was conducted during Visit 1. During this period, the patient had to experience at least one transition from OFF to ON or from ON to OFF, which had to be observed by the investigator or a qualified rater; there was a

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	requirement for at least 75% concordance between the patient's diary and the diary completed by the investigator or qualified designee. In addition to Parkinson's diaries in M15-736, MDS-UPDRS Part IV includes OFF time as one outcome, and these assessments were conducted by a separate independent rater; MDS-UPDRS Part IV was [redacted] AbbVie therefore maintain that any treatment effect observed in the foslevodopa-foscarbidopa arm of the M15-736 trial is reflective of treatment effect, and does not lead to uncertainty when used to model foslevodopa-foscarbidopa's efficacy.
9	**To ensure consistency across data sources used within the economic model for efficacy and discontinuation, AbbVie have aligned with the EAG's preference of using M15-736 data to inform discontinuations for the first three months.** The committee noted that two different sources of discontinuation rates for foslevodopa-foscarbidopa were proposed by the EAG and the Company (DGD section 3.14). AbbVie consider that data from Cohort 2 of the M15-741 trial are most representative of clinical experience of foslevodopa-foscarbidopa in NHS practice. As highlighted previously, this cohort benefitted from use of the new infusion set, whereby training was provided on the correct use and application of the infusion set cannula, including aseptic technique. Whilst the new infusion set was also used in the M15-736 trial, enrolment data from both trials indicate that investigators were more familiar with the device in the M15-741 trial, and as a result fewer discontinuations were observed. More investigators in the M15-741 trial enrolled a higher number of patients than investigators in M15-736; [redacted] ([redacted]) of triallists in M15-741 enrolled more than three patients, compared with [redacted] ([redacted]) of triallists in M15-736 who enrolled more than three patients in the foslevodopa-foscarbidopa arm. As such, investigators were likely more familiar with the infusion set in the M15-741 trial, using it with higher frequency, thereby more closely resembling expected real-life clinical use. This was corroborated by clinical expert feedback submitted ahead of the first ACM, which indicated that data from Cohort 2 of the M15-741 study is possibly more reflective of the likelihood of stopping treatment if foslevodopa–foscarbidopa was delivered in NHS practice. However, AbbVie acknowledge that there is an inconsistency in the data sources used in the model to inform efficacy and discontinuation. Therefore, to address the uncertainty resulting from that inconsistency, AbbVie have aligned with the EAG's suggestion and the data sources for discontinuation have been updated to: • M15-736: 0–3 months • M15-741 cohort 2: 3–12 months • M15-737: 12–24 months

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	The results of this change to the model base case are presented in Appendix 1.
10	**AbbVie maintain that the Company's approach to extrapolating data from Palmer et al. (2002) to derive natural disease progression is the most appropriate method, and has retained this approach in the base case economic analysis.** The EAG, whilst agreeing with the use of Palmer et al. (2002) to estimate long term natural disease progression, noted in its response to Technical Engagement that the midpoints of the data for over and under 25% OFF time should be used in the extrapolation of the data. This is instead of the Company's approach, in which all data points are used in the regression analysis. Whilst noting uncertainty associated with both approaches, on balance the committee favoured the EAG's approach (DGD section 3.12). AbbVie consider the approach using all data points to be more appropriate. The use of all data points represents a more realistic fit of the data than taking two average data points, which does not account for variability in levodopa duration based on OFF time. Furthermore, this approach is aligned with previous economic models in Parkinson's.[3, 7] These transitions are associated with slower disease progression at higher OFF states, which is more reflective of disease progression observed in real-life, and is supported by clinical opinion. Further, in patients who are uncontrolled by BMT, there is an expectation that they will transition through the time horizon in a similar manner to the base-case approach in the Company model, when contrasted with the EAG's approach. AbbVie have therefore retained the original Company approach to extrapolating Palmer et al. (2002) data in the base case analysis. However, in order to explore the impact of using the committee's preferred approach, AbbVie have recreated the EAG's approach to extrapolating the Palmer et al. (2002) data, and incorporated this in the economic models presented as part of this DGD response. Scenario analyses using the EAG's method of extrapolation have been presented for both the original Company model and the grouped OFF model (see Appendix 1 below).

Appendix 1 Updates to Company base case

Original company model

Table 1 below shows the impact in isolation of individual changes made to the company base case cost-effectiveness in response to the above issues, as well as the revised base case cost-effectiveness results, using the company's original model. All results shown include 3.5% discounting of both costs and QALYs as per the NICE reference case, with the patient access scheme (PAS) included for foslevodopa-foscarbidopa and LCIG. The additional supporting grouped OFF state model has also been aligned to this updated base case, with resulted presented below, and details of the model presented in Appendix 3.

Table 1: Updated base case results, with-PAS

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)
Company's original base case (deterministic)	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Company's base case following clarification questions (deterministic)	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	−0.10	[redacted]	[redacted]
Company's base case following technical engagement (deterministic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	−0.11	[redacted]	[redacted]
Updates to the base case (applied cumulatively, deterministic)						

	BMT			LCIG		
	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)
Response 2: Capturing additional sleep benefits of foslevodopa–foscarbidopa	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	0.03	[redacted]	Foslevodopa-foscarbidopa dominant
Response 3: Original fitted health state costs, capped at OFF10	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	0.03	[redacted]	Foslevodopa-foscarbidopa dominant
Response 4: Utility values derived from pooled trial data capped at OFF10	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	0.07	[redacted]	Foslevodopa-foscarbidopa dominant
Response 5: BMT treatment effect modelled using M15-736 data	0.38	[redacted]	Foslevodopa-foscarbidopa dominant	0.07	[redacted]	Foslevodopa-foscarbidopa dominant
Response 9: Updated sources of discontinuation rates: • M15-736: 0–3 months • M15-741 cohort 2: 3–12 months • M15-737: 12–24 months	0.30	[redacted]	Foslevodopa-foscarbidopa dominant	–0.01	[redacted]	[redacted]

	BMT			LCIG		
	Incremental QALYs	**Incremental costs**	**ICER (change from technical engagement ICER)**	**Incremental QALYs**	**Incremental costs**	**ICER (change from technical engagement ICER)**
Company's revised base case (deterministic)	0.30	[redacted]	Foslevodopa-foscarbidopa dominant	–0.01	[redacted]	[redacted]
Company's revised base case (probabilistic)	**0.30**	[redacted]	Foslevodopa-foscarbidopa dominant	–0.02	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

[redacted]

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Probabilistic sensitivity analyses

Figure 1: Updated cost-effectiveness plane for foslevodopa-foscarbidopa versus comparators, with-PAS

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 2: Updated cost-effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, with-PAS

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year.

Deterministic sensitivity analysis

Figure 3: Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus LCIG, with-PAS

ABBV-951 = foslevodopa-foscarbidopa. Duodopa = LCIG.
Abbreviations: LCIG: levodopa-carbidopa intestinal gel; NHB: net health benefit; NMA: network meta-analysis; PAS: patient access scheme; RR: relative risk.

Figure 4: Updated tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus BMT, with-PAS

ABBV-951 = foslevodopa-foscarbidopa.
Abbreviations: BMT: best medical therapy; NHB: net health benefit; PAS: patient access scheme.

Supportive grouped OFF model

Table 2: Base-case cost-effectiveness results in grouped OFF model structure, with-PAS price (deterministic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)	ICER incremental (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.32	–			
LCIG	[redacted]	5.29	[redacted]	0.03	Foslevodopa-foscarbidopa dominant	Strictly dominated by foslevodopa-foscarbidopa
BMT	[redacted]	5.08	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	Strictly dominated by foslevodopa-foscarbidopa

[a]SW quadrant ICER: costs saved per QALY forgone.
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LYG: life years gained; QALY: quality-adjusted life year; SW: south-west.

Table 3: Base-case cost-effectiveness results in grouped OFF model structure, with-PAS (probabilistic)

Technologies	Total costs (£), 95% CI	Total QALYs, 95% CI	Incremental costs (£)	Incremental QALYs	ICER for foslevodopa-foscarbidopa versus comparator (£/QALY)	ICER incremental (£/QALY)
Foslevodopa-foscarbidopa	[redacted]	5.32 (5.11, 5.53)	–			
LCIG	[redacted]	5.29 (5.09, 5.50)	[redacted]	0.03	Foslevodopa-foscarbidopa dominant	Strictly dominated by foslevodopa-foscarbidopa
BMT	[redacted]	5.08 (4.87, 5.30)	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	Strictly dominated by foslevodopa-foscarbidopa

[redacted]

Abbreviations: BMT: best medical therapy; CI: confidence interval; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; LYG: life years gained; NHS: National Health Service; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Probabilistic sensitivity analyses

Figure 5: Cost-effectiveness plane for foslevodopa-foscarbidopa versus comparators, grouped OFF model with-PAS

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 6: Cost-effectiveness acceptability curve for foslevodopa-foscarbidopa versus comparators, grouped OFF model with-PAS

Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year.

Deterministic sensitivity analysis

Figure 7: Tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus LCIG, grouped OFF model with-PAS

ABBV-951 = foslevodopa-foscarbidopa. Duodopa = LCIG.
Abbreviations: LCIG: levodopa-carbidopa intestinal gel; NHB: net health benefit; NMA: network meta-analysis; PAS: patient access scheme; RR: relative risk.

Figure 8: Tornado diagram for the drivers of NHB – top ten most influential parameters for foslevodopa-foscarbidopa versus BMT, grouped OFF model with-PAS

ABBV-951 = foslevodopa-foscarbidopa.
Abbreviations: BMT: best medical therapy; NHB: net health benefit; PAS: patient access scheme.

Appendix 2 Additional scenario analysis results

Table 4: Probabilistic scenario analysis results, with-PAS (original Company model)

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
Base case (probabilistic)	[redacted]	5.17	[redacted]	0.30	Foslevodopa−foscarbidopa dominant	[redacted]	−0.02	[redacted]
Equal efficacy assumed between foslevodopa-foscarbidopa and LCIG	[redacted]	5.17	[redacted]	0.30	Foslevodopa−foscarbidopa dominant	[redacted]	−0.05	[redacted]
Patients redistributed to BMT health states following discontinuation	[redacted]	5.17	[redacted]	0.30	Foslevodopa−foscarbidopa dominant	[redacted]	0.03	Foslevodopa−foscarbidopa dominant
EAG method of extrapolating Palmer et al. (2002)	[redacted]	5.22	[redacted]	0.30	Foslevodopa−foscarbidopa dominant	[redacted]	−0.02	[redacted]
BMT efficacy modelled using natural history	[redacted]	5.16	[redacted]	0.37	Foslevodopa−foscarbidopa dominant	[redacted]	−0.02	[redacted]
BMT efficacy modelled using M15−736, immediately followed by natural history	[redacted]	5.16	[redacted]	0.27	[redacted]	[redacted]	−0.02	[redacted]
Fitted health state costs not capped at OFF 10	[redacted]	5.17	[redacted]	0.38	Foslevodopa-foscarbidopa dominant	[redacted]	−0.02	[redacted]

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
M15−736 utilities	[redacted]	5.78	[redacted]	0.35	Foslevodopa-foscarbidopa dominant	[redacted]	−0.01	[redacted]
M15−736 utilities capped at OFF 10	[redacted]	5.92	[redacted]	0.27	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa−foscarbidopa dominant
Pooled trial utilities not capped at OFF 10	[redacted]	4.95	[redacted]	0.39	Foslevodopa-foscarbidopa dominant	[redacted]	-0.08	[redacted]
Pooled trial utilities and health state costs not capped at OFF 10	[redacted]	4.94	[redacted]	0.39	Foslevodopa-foscarbidopa dominant	[redacted]	-0.09	[redacted]
Sleep-related cost savings based on sleep disturbance	[redacted]	5.17	[redacted]	0.30	Foslevodopa-foscarbidopa dominant	[redacted]	-0.02	[redacted]
No sleep-related benefits modelled	[redacted]	5.05	[redacted]	0.19	Foslevodopa-foscarbidopa dominant	[redacted]	-0.13	[redacted]

[a]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: BMT: best medical therapy; ICER: incremental cost−effectiveness ratio; LCIG: levodopa−carbidopa intestinal gel; QALY: quality−adjusted life year; SW: south−west.

Table 5: Probabilistic scenario analysis results, with-PAS (supportive grouped OFF model)

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
Base case (probabilistic)	[redacted]	5.32	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
Equal efficacy assumed between foslevodopa-foscarbidopa and LCIG	[redacted]	5.32	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	−0.01	[redacted]

Description	Foslevodopa-foscarbidopa		BMT			LCIG		
	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICERs (£)	Inc. costs (£)	Inc. QALYs	ICERs (£)
Patients redistributed to BMT health states following discontinuation	[redacted]	5.32	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	0.07	Foslevodopa-foscarbidopa dominant
BMT efficacy modelled using natural history	[redacted]	5.32	[redacted]	0.30	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
BMT efficacy modelled using M15−736, immediately followed by natural history	[redacted]	5.32	[redacted]	0.23	[redacted]	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
Fitted health state costs not capped at OFFIII	[redacted]	5.32	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
Observed health state costs (Adelphi overall PD set)	[redacted]	5.33	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
M15−736 utilities	[redacted]	5.98	[redacted]	0.17	Foslevodopa-foscarbidopa dominant	[redacted]	0.06	Foslevodopa-foscarbidopa dominant
M15−736 utilities capped at OFFIII	[redacted]	6.02	[redacted]	0.16	Foslevodopa-foscarbidopa dominant	[redacted]	0.07	Foslevodopa-foscarbidopa dominant
Pooled trial utilities not capped at OFFIII	[redacted]	5.25	[redacted]	0.27	Foslevodopa-foscarbidopa dominant	[redacted]	0.01	Foslevodopa-foscarbidopa dominant
Pooled trial utilities and health state costs not capped at OFFIII	[redacted]	5.25	[redacted]	0.27	Foslevodopa-foscarbidopa dominant	[redacted]	0.01	Foslevodopa-foscarbidopa dominant
Sleep-related cost savings based on sleep disturbance	[redacted]	5.32	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	0.03	Foslevodopa-foscarbidopa dominant
No sleep-related benefits modelled	[redacted]	5.21	[redacted]	0.12	Foslevodopa-foscarbidopa dominant	[redacted]	-0.09	[redacted]

[a]SW quadrant ICER; costs saved per QALY forgone.
Abbreviations: BMT: best medical therapy; ICER: incremental cost−effectiveness ratio; LCIG: levodopa−carbidopa intestinal gel; QALY: quality−adjusted life year; SW: south−west.

Appendix 3 Grouped OFF model

As outlined in Comment 1 of the DGD response, a supportive model with a structure based on grouped OFF time health states has been explored. This model was adapted from the original model structure comprising health states of one-hour increments in OFF time, which were combined in the supporting model to reduce the total number of health states (including death) from 18 to six. As the change only affected health states, all other model inputs, settings and assumptions not relating to health states are the same as those in the original Company model; detailed descriptions of these can be found in the Company submission and the Company responses to clarification questions, technical engagement and the DGD. This appendix therefore only details changes to the model structure and inputs relating to the newly implemented model heath states.

Model Structure

The grouped OFF approach utilises a transition-state Markov model, consisting of 5 health states, and one absorbing 'Death' state. Each health state is defined by the number of daily 'Off' hours - normalised to a 16-hour day - experienced by patients, ranging from 1 to 16 hours, in four-hour increments, with a separate OFF state representing patients experiencing no OFF time. This yields the OFF time health states shown in Table 6, and align with the groupings used in the MDS-UPDRS (Part 4.3) and previous models where OFF time had been grouped.[3, 7, 8]

Table 6: Grouped OFF model health states

Health state	Description	% of the day[a]	MDS-UPDRS[8]
OFF 0	0 hours OFF	0%	0: Normal
OFF I	1–4 hours OFF	≤25%	1: Slight
OFF II	5–8 hours OFF	26-50%	2: Mild
OFF III	9–12 hours OFF	51-75%	3: Moderate
OFF IV	13–16 hours OFF	>75%	4: Severe

[a]Normalised to a 16-hour waking day

As with the original modelling approach, the model is divided into two distinct periods: the within trial period and beyond trial period, which are described in detail in Document B, Section B.3.2.2 of the Company submission. Briefly, the within trial model period applies to the first three months of the model time horizon, during which patients can transition freely between any of the model health states, as shown diagrammatically in Figure 9. This is aligned with trial data for foslevodopa-foscarbidopa from M15-736, in which substantial improvements in OFF time were observed. The beyond trial period models efficacy from the end of the first model cycle (Month 3) to the end of the model time horizon. In this beyond trial period, patients could only transition to the adjacent worsening health state, as shown diagrammatically in Figure 10.

Figure 9: Model structure for within trial period

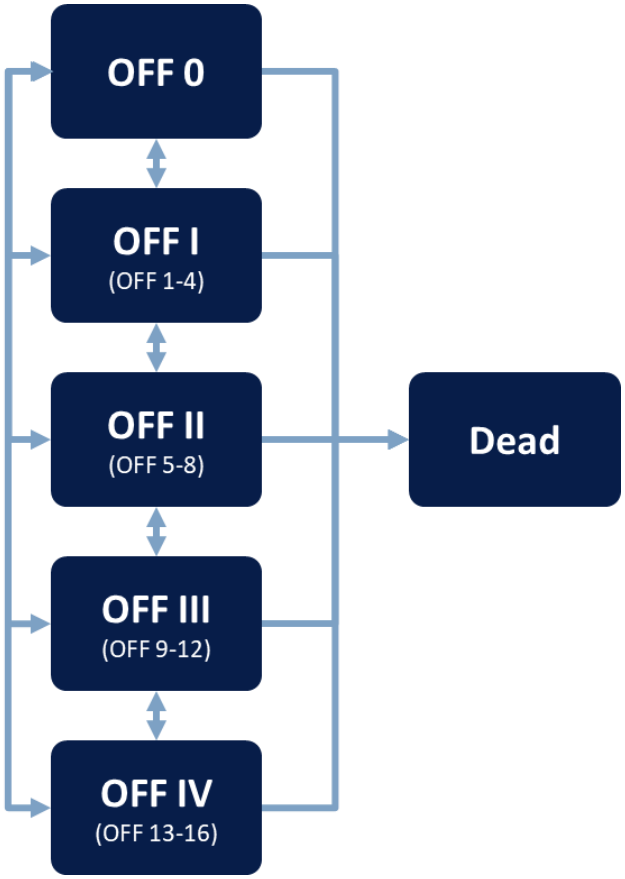
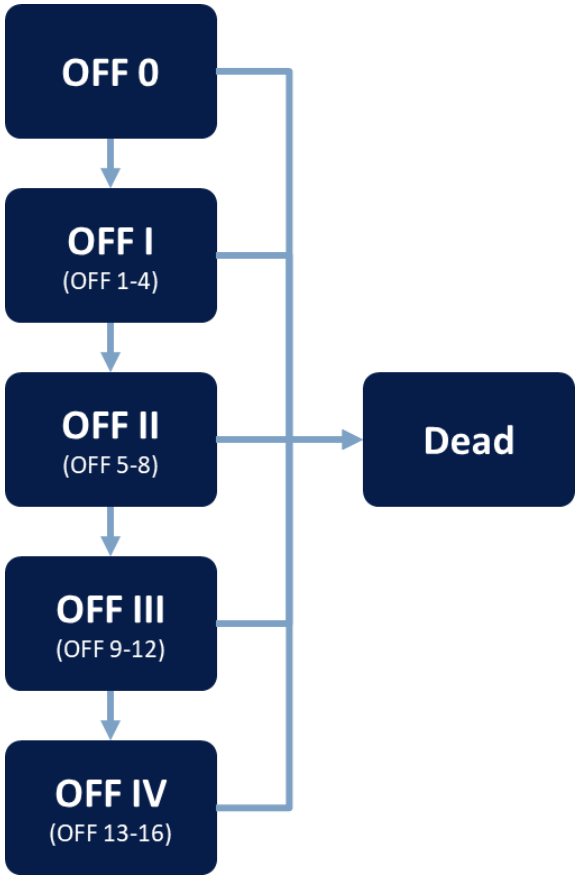


Figure 10: Model structure for beyond trial



Baseline distribution of patients

Baseline characteristics were the same as in the original Company approach (Table 52 of CS), based on the M15-736 trial population. The baseline distribution of patients entering the grouped OFF model are shown in Table 7. These represent aggregate values of the respective grouped OFF times.

Table 7: Baseline distribution of patients entering the grouped OFF model

Health state	Starting distribution (M15-736 ITT population)
OFF 0	[redacted]
OFF I	[redacted]
OFF II	[redacted]
OFF III	[redacted]
OFF IV	[redacted]
Death	0.0%
Total	100.0%

Abbreviations: ITT: intention-to-treat.

Within trial period transitions

As in the original model, foslevodopa-foscarbidopa treatment effect for the first three months was modelled based on transition probabilities derived from the initial three-month effect observed in the ITT population of the M15-736 trial. In line with the revised base case analysis in the original Company model (see Response 5 above), BMT treatment effect in the trial period is also modelled using Month 3 trial data from the M15-736 trial. Patient OFF time was reported in one-hour increments in the trial, and were therefore aggregated to the

corresponding four-hour OFF time health states. The distribution of patients at the end of Month 3 in both arms of the M15-736 trial are shown in Table 8 below.

Table 8: Distribution of patients at the end of the grouped OFF model trial period

Health state	Distribution at Month 3 (M15-736 ITT population)	
	Foslevodopa-foscarbidopa	BMT
OFF 0	[redacted]	[redacted]
OFF I	[redacted]	[redacted]
OFF II	[redacted]	[redacted]
OFF III	[redacted]	[redacted]
OFF IV	[redacted]	[redacted]
Death	0.0%	0.0%
Total	100.0%	100.0%

Abbreviations: BMT: best medical therapy; ITT: intention-to-treat.

As in the original economic analysis, the treatment effect for LCIG was modelled using the relative risk output from the observed means NMA presented at technical engagement, both in the within and beyond trial model periods.

Beyond trial period transitions

In response to technical engagement, AbbVie updated the original modelling approach to the beyond trial period, to avoid long-term extrapolation of the treatment effect seen for foslevodopa-foscarbidopa in the M15-736 trial. As a result, patients would now remain in the health states at the end of the trial period, for a subsequent six model cycles (33 months), following which patients followed the BMT arm transition probabilities based on natural disease progression. The natural history transition probabilities based on Palmer et al. (2002) were sourced from the Chaudhuri et al. (2022) model.[3, 28]

Health state utility values

In line with the revised base case presented using the original company model, utility values applied to the five health states (OFF0 and OFFI to OFFIV) in the model were estimated by fitting linear mixed models to EQ-5D values from patients in both arms of the M15-736 trial. Details of the regression analysis are presented in Appendix 4 below. As with the economic analysis using the original model structure, the base case using the grouped OFF model accounts for sleep benefits of foslevodopa-foscarbidopa by applying a utility increment to the utility values of the foslevodopa-foscarbidopa arm, based on the avoidance of sleep disturbance reported in the M15-736 trial. This utility increment of [redacted] is derived in exactly the same way as described in Response 2 above, and further detailed in Appendix 4 below.

The base case using the original model structure additionally caps utility values beyond OFF10, in order to account for the sharp drop-off in patient numbers available beyond the OFF10 heath state, and in line with a suggestion made by the EAG. Given that 10 hours OFF time represents the mid-point of the OFFIII health state (9–12 hours OFF time) in the grouped OFF model, a choice of either the OFFII or OFFIII could reasonably be made to represent such a cap in the grouped OFF model. OFFIII was chosen, as it was deemed that modelling all patients experiencing greater than five hours of OFF time to have the same utility lacked clinical validity, and capping at OFFII would omit a substantial amount of data available in the OFFIII health state.

The base case utility values for each model health state are shown in Table 9. As with the original model structure analysis, scenarios were explored in which sleep disturbance and morning OFF time were accounted for via regression analysis of EQ-5D reported in the M15-736 trial, as detailed in Appendix 4.

Table 9: Utility values based on a linear mixed model regression used in the grouped OFF model base case (including sleep-related incremental benefits for foslevodopa-foscarbidopa)

Health state	Utility value foslevodopa-foscarbidopa (SE[a])	Utility value BMT/LCIG (SE[a])
OFF0	[redacted]	[redacted]
OFFI	[redacted]	[redacted]
OFFII	[redacted]	[redacted]
OFFIII	[redacted]	[redacted]
OFFIV[b]	[redacted]	[redacted]
Dead	0	0

[a]In the absence of an observed SE, an estimate of ±20% of the mean is utilised in the model.
[b]Utility values are capped at OFFIII. Utility values from the regression analysis of OFF time predicts OFFIV utility values of [redacted] and [redacted] for foslevodopa-foscarbidopa and BMT/LCIG, respectively.
Abbreviations: BMT: best medical therapy; LCIG; levodopa-carbidopa intestinal gel; SE: standard error.

Health state costs

The health state costs for the relevant one-hour OFF states in the original model structure were averaged to derive health state costs associated with the grouped OFF health states. As with the approach to utility value described above and in line with the approach in the original model structure base case, the health state costs associated with the OFFIV health state were capped at the health state costs for OFFIII. This is because the [redacted] observable data point in the Adelphi dataset was at OFF 10. The resulting health state costs informing the grouped OFF model are presented in Table 10.

Table 10: Total health state specific costs included in the grouped OFF model base case

Health state	Total yearly costs
OFF0	[redacted]
OFFI	[redacted]
OFFII	[redacted]
OFFIII	[redacted]
OFFIV[a]	[redacted]
Dead	£0

[a]Health state costs are capped at OFFIII. Average grouped health state costs from the regression analysis of OFF time predicts total yearly costs of [redacted] associated with OFFIV.

Appendix 4 Sleep-related utility and cost benefits

Additional utility and cost benefits associated with avoidance of sleep disturbance for patients treated with foslevodopa-foscarbidopa has been incorporated into the model in the form of incremental benefits applied directly to all health states in the foslevodopa-foscarbidopa arm.

Utility increment due to avoidance of sleep disturbance

As outlined in Response 2 above, the base case analysis in both models accounts for the sleep benefits of foslevodopa-foscarbidopa by applying a utility increment to the health states utility values for patients receiving foslevodopa-foscarbidopa only (patients experience BMT utility upon discontinuation).

Xiao et al. (2022) reports statistically significantly lower utility values for patients experiencing Parkinson's sleep-related problems, defined as reporting a PDSS value ≥18, than those not reporting sleep problems.[12] PDSS-2 score <18 is a previously validated threshold that defines clinically relevant Parkinson's-specific sleep disturbances.[11] A linear regression model was applied to EQ-5D-5L index values reported by 380 patients with multiple system atrophy (MSA), and mapped to utility values using the EQ-5D-5L value set for China. The study reports utility values of 0.669 and 0.431 for patients with and without sleep-related problems, respectively.[12] Whilst acknowledging limitations with this study, particularly around its generalisability to the relevant population, it represents the only study AbbVie are aware of reporting utilities based on this threshold, which was also then used in the M15-736 trial to define sleep disturbance.

These utility data were used in combination with incidence data for sleep-related problems experienced by patients in the M15-736 trial to derive a utility increment associated with the avoidance of sleep disturbance. In the M15-736 trial, [redacted]% of patients having received foslevodopa-foscarbidopa reported a PDSS score <18 at week 52, compared with [redacted]% in the BMT arm.[27] These values were used in combination with the utility values for patients reporting PDSS scores above and below 18, as reported in Xiao et al. (2022), to produce a weighted average sleep-related utility value for each arm, as shown in Table 11.

Table 11: Derivation of sleep-related increment associated with foslevodopa-foscarbidopa in the base case

Treatment	Patients reporting PDSS < 18 at Week 12	Patients reporting PDSS ≥ 18 at Week 12	Weighted sleep-related utility[a]
Foslevodopa-foscarbidopa	[redacted]%	[redacted]%	[redacted]
BMT	[redacted]%	[redacted]%	[redacted]

[a]Based on utility values reported in Xiao et al. (2022):[12] 0.669 in patients with PDSS < 18 and 0.431 in patients with PDSS ≥ 18.
Abbreviations: BMT: best medical therapy; PDSS: Parkinson's Disease Sleep Scale.
Source: AbbVie Data on File: M15-736 CSR;[27] Xiao et al. (2022).[12]

The sleep-related utility increment was then taken as the difference between the weighted sleep-related utility values associated with each model arm, [redacted], and subsequently applied to the foslevodopa-foscarbidopa utility values. In the absence of equivalent sleep-related utility data for LCIG, it was assumed that it would be associated with the same sleep-related utility value as BMT, and therefore no sleep-related utility adjustment was made to LCIG arm. This is in line with the clinical expectation that patients receiving LCIG, which is not routinely administered overnight, would not experience additional sleep-related benefits beyond those experienced by patients receiving BMT.

Sleep-related cost benefits

In line with the above approach, sleep-related costs benefits were calculated by using costs relating to excessive sleepiness reported in the Adelphi dataset; this resulted in an incremental cost benefit of £[redacted]

per year that was consequently subtracted from all health-state costs in the foslevodopa-foscarbidopa arm (Table 12).

Table 12: Calculation of sleep-related cost benefit (per year)

	PDSS-2 <18	PDSS-2 ≥18	
Treatment arms			**Weighted average cost**
Foslevodopa-foscarbidopa	[redacted]	[redacted]	[redacted]
BMT	[redacted]	[redacted]	[redacted]
Sleep-related incremental cost benefit with foslevodopa-foscarbidopa			[redacted]

Abbreviations: BMT: best medical therapy; PDSS: Parkinson's Disease Sleep Scale.
Source: AbbVie Data on File. M15-736 Clinical Study Report;[27] Adelphi 2017-2019.[29]

Equivalent calculations were performed for the scenario analysis in which yearly savings derived from costs relating to sleep disturbance, rather than excessive sleepiness, from the Adelphi dataset were used to inform a cost-saving of £[redacted] applied to the foslevodopa-foscarbidopa arm (Table 13).

Table 13: Calculation of sleep-related cost benefit (per year) – scenario analysis

	PDSS-2 <18	PDSS-2 ≥18	
Treatment arms			**Weighted average cost**
Foslevodopa-foscarbidopa	[redacted]	[redacted]	[redacted]
BMT	[redacted]	[redacted]	[redacted]
Sleep-related incremental cost benefit with foslevodopa-foscarbidopa			[redacted]

Abbreviations: BMT: best medical therapy; PDSS: Parkinson's Disease Sleep Scale.
Source: AbbVie Data on File. M15-736 Clinical Study Report;[27] Adelphi 2017-2019.[29]

Appendix 5 Health state utility values scenario analyses

Treatment-dependent sleep-related utility values in original Company model

The application of a utility increment to the foslevodopa-foscarbidopa arm of the model is supported by additional analyses accounting for sleep-related benefits associated with foslevodopa-foscarbidopa. Linear mixed models were applied, adjusting for two sleep-related variables reported in the pooled trial data: PDSS-2 score and morning OFF time. An additional scenario was explored in which a combination of PDSS-2 score and morning OFF time were adjusted for in the linear mixed model. The resulting utility values for each scenario are presented in Table 14–Table 16, with the outputs of each regression analysis presented in Table 17–Table 19.

Table 14: Treatment-dependent utility values derived from patient utility model based on number of 'OFF' hours and PDSS-2 score (pooled trial data)

Health state	Utility value	
	Foslevodopa-foscarbidopa	BMT/LCIG
OFF 0	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]
OFF2	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]

OFF 6	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]
OFF 11[a]	[redacted]	[redacted]
OFF 12[a]	[redacted]	[redacted]
OFF 13[a]	[redacted]	[redacted]
OFF 14[a]	[redacted]	[redacted]
OFF 15[a]	[redacted]	[redacted]
OFF 16[a]	[redacted]	[redacted]
Dead	0.000	0.000

[a]Scenario analyses using sleep-related utility values were aligned with the base case approach, in which utility values were capped at OFF10. Utility values for OFF11–16 derived from the regression analysis are presented for reference.
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PDSS: Parkinson's Disease Sleep Scale.

Table 15: Treatment-dependent utility values derived from patient utility model based on number of OFF hours and morning OFF (pooled trial data)

Health state	Utility value	
	Foslevodopa-foscarbidopa	BMT/LCIG
OFF 0	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]
OFF2	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]
OFF 11[a]	[redacted]	[redacted]
OFF 12[a]	[redacted]	[redacted]
OFF 13[a]	[redacted]	[redacted]
OFF 14[a]	[redacted]	[redacted]
OFF 15[a]	[redacted]	[redacted]
OFF 16[a]	[redacted]	[redacted]
Dead	0.000	0.000

[a]Scenario analyses using sleep-related utility values were aligned with the base case approach, in which utility values were capped at OFF10. Utility values for OFF11–16 derived from the regression analysis are presented for reference.
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PDSS: Parkinson's Disease Sleep Scale.

Table 16: Treatment-dependent utility values derived from patient utility model based on number of 'OFF' hours, PDSS-2 score and morning OFF (pooled trial data)

Health state	Utility value	
	Foslevodopa-foscarbidopa	BMT/LCIG
OFF 0	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]
OFF 2	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]
OFF 11[a]	[redacted]	[redacted]
OFF 12[a]	[redacted]	[redacted]
OFF 13[a]	[redacted]	[redacted]
OFF 14[a]	[redacted]	[redacted]
OFF 15[a]	[redacted]	[redacted]
OFF 16[a]	[redacted]	[redacted]
Dead	0.000	0.000

[a]Scenario analyses using sleep-related utility values were aligned with the base case approach, in which utility values were capped at OFF10. Utility values for OFF11–16 derived from the regression analysis are presented for reference.
Abbreviations: BMT: best medical therapy; LCIG: levodopa-carbidopa intestinal gel; PDSS: Parkinson's Disease Sleep Scale.

Table 17: Regression coefficients for the patient utility model based on number of 'OFF' hours and PDSS-2 score

Parameter	Value	SE	AIC	BIC
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
NROFF	[redacted]	[redacted]		
PDSSTOS	[redacted]	[redacted]		

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; NROFF: number of 'OFF' hours per day; PDSS: Parkinson's Disease Sleep Scale; SE: standard error.

Table 18: Regression coefficients for the patient utility model based on number of 'OFF' hours and morning OFF

Parameter	Value	SE	AIC	BIC
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
NROFF	[redacted]	[redacted]		

Parameter	Value	SE	AIC	BIC
MorningOFF	[redacted]	[redacted]		

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; NROFF: number of 'OFF' hours per day; SE: standard error.

Table 19: Regression coefficients for the patient utility model based on number of 'OFF' hours, PDSS−2 score and morning OFF

Parameter	Value	SE	AIC	BIC
Intercept	[redacted]	[redacted]	[redacted]	[redacted]
NROFF	[redacted]	[redacted]		
PDSSTOS	[redacted]	[redacted]		
MorningOFF	[redacted]	[redacted]		

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; NROFF: number of 'OFF' hours per day; PDSS: Parkinson's Disease Sleep Scale; SE: standard error.

Summary of utility value regression analyses explored

A summary of the regression models and model fit statistics explored for the utility values in the pooled trial dataset and reported in the M15-736 trial for the original Company model structure are presented in Table 20 and Table 21, respectively. The regression models and model fit statistics for the supportive grouped OFF model are shown in Table 22 and Table 23, respectively. The utility values resulting from selected models in the original Company model structure and grouped OFF model are presented in Table 24 and Table 25, respectively.

These regression outputs and resulting utility values indicate that the chosen model has limited impact on predicted utility values.

Table 20: Model Fit for Utilities from the Pooled Trials for the Hourly Cost-Effectiveness Model

Model	Utility Regression Adjustments								Statistical fit	
	OFF	Age	Sex	Treatment Duration	Disease Duration	Treatment Arm	PDSS-2	Morning Symptoms	AIC	BIC
1	X								[redacted]	[redacted]
2	X			X		X			[redacted]	[redacted]
3	X			X					[redacted]	[redacted]
4	X	X	X	X					[redacted]	[redacted]
5	X	X		X					[redacted]	[redacted]
6	X		X	X					[redacted]	[redacted]
7	X					X			[redacted]	[redacted]
8	X						X		[redacted]	[redacted]
9	X					X	X		[redacted]	[redacted]
10	X							X	[redacted]	[redacted]
11	X					X		X	[redacted]	[redacted]
12	X						X	X	[redacted]	[redacted]
13	X					X	X	X	[redacted]	[redacted]
14	X		X						[redacted]	[redacted]
15	X	X	X						[redacted]	[redacted]
16	X	X	X			X			[redacted]	[redacted]
17	X	X	X				X		[redacted]	[redacted]
18	X	X	X			X	X		[redacted]	[redacted]
19	X	X	X					X	[redacted]	[redacted]

20	X	X	X			X		X	[redacted]	[redacted]
21	X	X	X				X	X	[redacted]	[redacted]
22	X	X	X			X	X	X	[redacted]	[redacted]
23	X	X	X		X				[redacted]	[redacted]
24	X	X	X		X	X			[redacted]	[redacted]
25	X	X	X		X		X		[redacted]	[redacted]
26	X	X	X		X	X	X		[redacted]	[redacted]
27	X	X	X		X			X	[redacted]	[redacted]
28	X	X	X		X	X		X	[redacted]	[redacted]
29	X	X	X		X		X	X	[redacted]	[redacted]
30	X	X	X		X	X	X	X	[redacted]	[redacted]

Table 21: Model Fit for Utilities from the M15-736 Trial for the Hourly Cost-Effectiveness Model

Model	Utility Regression Adjustments							Statistical fit	
	OFF	Age	Sex	Treatment Duration	Treatment Arm	PDSS-2	Morning Symptoms	AIC	BIC
1	X							[redacted]	[redacted]
2	X				X			[redacted]	[redacted]
3	X					X		[redacted]	[redacted]
4	X				X	X		[redacted]	[redacted]
5	X						X	[redacted]	[redacted]
6	X				X		X	[redacted]	[redacted]
7	X					X	X	[redacted]	[redacted]

8	X				X	X	X	[redacted]	[redacted]
9	X		X					[redacted]	[redacted]
10	X	X	X					[redacted]	[redacted]
11	X	X	X		X			[redacted]	[redacted]
12	X	X	X			X		[redacted]	[redacted]
13	X	X	X		X	X		[redacted]	[redacted]
14	X	X	X				X	[redacted]	[redacted]
15	X	X	X		X		X	[redacted]	[redacted]
16	X	X	X			X	X	[redacted]	[redacted]
17	X	X	X		X	X	X	[redacted]	[redacted]
18	X			X				[redacted]	[redacted]

Table 22: "Grouped OFF" Model Fit for Utilities from the Pooled Trials

Model	Utility Regression Adjustments							Statistical fit	
	OFF	Age	Sex	Treatment Duration (/ Visit Date)	Treatment Arm	PDSS-2	Morning Symptoms	AIC	BIC
1	X							[redacted]	[redacted]
2	X				X			[redacted]	[redacted]
3	X					X	X	[redacted]	[redacted]
4	X				X	X	X	[redacted]	[redacted]
5	X			X				[redacted]	[redacted]
6	X	X	X	X				[redacted]	[redacted]
7	X	X		X				[redacted]	[redacted]
8	X		X	X				[redacted]	[redacted]
9	X				X			[redacted]	[redacted]
10	X	X	X	X	X			[redacted]	[redacted]
11	X	X		X	X			[redacted]	[redacted]
12	X	X	X		X			[redacted]	[redacted]

Table 23: "Grouped OFF" Model Fit for Utilities from the M15-736 Trial

Model	Utility Regression Adjustments				Statistical fit	
	OFF	Treatment Arm	PDSS-2	Morning Symptoms	AIC	BIC
1	X				[redacted]	[redacted]
2	X	X			[redacted]	[redacted]
3	X		X	X	[redacted]	[redacted]

4	X	X	X	X	[redacted]	[redacted]
5	X		X		[redacted]	[redacted]
6	X			X	[redacted]	[redacted]
7	X	X	X		[redacted]	[redacted]
8	X	X		X	[redacted]	[redacted]

Table 24: Utility Values for the Hourly Cost-Effectiveness Model Across Pooled Trials

Health State	Utility Regression Adjustments			
	OFF[a]	OFF + Age + Treatment Duration	OFF + Sex + Treatment Duration	OFF + Age + Sex + Treatment Duration
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]

[a]Utilities available in the cost-effectiveness model

Table 25: Utility Values for the "Grouped OFF" Cost-Effectiveness Model Across Pooled Trials

Health State	Utility Regression Adjustments				
	OFF[a]	OFF + Treatment Duration	OFF + Age + Treatment Duration	OFF + Sex + Treatment Duration	OFF + Age + Sex + Treatment Duration
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OFF IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]Utilities available in the cost-effectiveness model

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NICE National Institute for Health and Care Excellence

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 21 June 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Parkinson's UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	£13,093.75 in 2021 - to speak at 2 events and to fund a leaflet to help Parkinson's UK local groups transition back to face-to-face meetings post pandemic. • We have not published a position on this technology or a comparator in the last 12 months • We do not have any other interests relevant to the technology or a comparator.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. 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	• Has all of the relevant evidence been taken into account? We would suggest that NICE reflects a recent paper published by The National Institute of Health Research to give this section greater context on the challenges of living with Parkinson's. (https://evidence.nihr.ac.uk/alert/helping-people-cope-with-the-changing-nature-of-parkinsons/) We welcome the inclusion of the patient perspective, but would encourage NICE to represent the perspective of care partners too, as their lives are impacted by the intervention as well. We would encourage NICE to add some of the comments from our previous submission from care partners, a selection are provided below.

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	"He can drive again which is great as he can get out and about. I don't monitor him as much, but keep an ear out for when he's active as sometimes I worry he's doing too much." "It frees me up a lot, I don't have to chase my husband to take his tablets." "It's great not to have to constantly clock watch to make sure [my husband]l has taken his tablets. It is lovely to see him able to get up and move around at night without pain. Having a 24/7 therapy makes a huge difference." "His quality of life has improved a lot. He forgets a lot less, if he comes in from the garden he used to stand there and needs to be reminded what he was doing .I don't have to watch him as carefully, before I felt like I needed to keep an eye all the time. [Him] being on the therapy has enabled me to have a bit more time to myself. I've been able to get out in the garden and do some work." "Fosleveodopa has enabled my husband to reduce his Requip medication, which had stopped his impulse control disorder."
2	• Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? We believe so, however we welcome the recognition of the high unmet need for treatments to control motor symptoms and would encourage NICE to explore an interim ruling to allow relevant data to be collected, if the company is not able to provide suitable data. This could be similar to the One Wales approach that allows a treatment or therapy to be prescribed for 12 months while data is collected to demonstrate its efficacy. We are also aware that Individual Funding Requests are lengthy to complete for professionals and can be a barrier to an innovative treatment being trialled.
3	• Are the recommendations sound and a suitable basis for guidance to the NHS? We reiterate the transformative nature of foslevodopa-foscarbidopa which we believe has been demonstrated by comments from people with Parkinson's and care partners. And would urge NICE to to explore an interim ruling to allow relevant data to be collected, if the company is not able to provide suitable data.
4	• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We believe the committee's recommendation not to offer foslevodopa-foscarbidopa could mean that older people with Parkinson's, especially those over 75 and who are unsuitable for deep brain stimulation and less likely to have surgery for LCIG will be disadvantaged.

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	This transformative treatment could help manage their symptoms and improve their quality of life as it is less invasive. We support the position argued by clinical experts that foslevodopa-foscarbidopa might be a preferred treatment option, as the intervention is less invasive and easier to use. Comments from people with Parkinson's in our latest submission reiterate this. "My sleep pattern was very erratic, but on the therapy it has started to improve as the meds are being delivered 24 hrs, which is a positive key aspect of this drugs delivery compared to some other medication." "Before Foslevodopa I took multiple medicines during the day - up to 28 tablets. I had real issues with being 'on and off' throughout the day. This had an impact on my motivation, my movement and also sometimes my thinking. Overall this therapy has significantly decreased the feeling of swinging from either on or off, which was proving a major problem for me on the previous oral meds." "I feel like I've been able to press the pause button on Parkinson's. I know the condition is progressing, but I'm much more in control of it and how I can help myself. I'm still trying to be active and the therapy enables me to do that. My energy levels stay fairly static throughout the day (in a good way), this helps me to prepare and plan activities." "This therapy isn't massively invasive, yes you have to carry a pump round, but you're still able to get out and about and be active. I'd like there to be a longer tube from the pump to the needle as it makes it difficult when I go out cycling. I have to put the pump in a specific place, which can sometimes result in the pump falling or pulling on the tubing."
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association of British Neurologists Movement Disorder Advisory Group

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Pathikonda U Nath

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	3.1 A very minor point – dyskinesia and hyperkinesia are mentioned in the draft guidance as distinct. They mean the same thing in practice. Usually the term dyskinesia is preferred and indicates abnormal, involuntary and excessive movements
2	3.1 One of the clinical experts referred to brain fog which is a term commonly used by patients. It is very non specific and could be better termed "difficulties with concentration".
3	3.2 Motor fluctuations should include dyskinesias as well as off periods
4	Section 3.3 levodopa is taken with a dopa decarboxylase inhibitor as standard so could omit the term "usually"
5	Section 3.3 The statement relating to "30 tablets a day" refers to all the patient's medications both for Parkinson's and non Parkinson's medications. Patients with Parkinson's maytake up to 15 tablets or capsules per day.

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6	Please note that we are not expert statisticians and do not have an economics background, so our comments relate primarily to the clinical interpretation of the evidence. We cannot comment definitively on cost effectiveness.
7	3.3 - "Dopamine agonists given orally can be associated with impulse control so apomorphine is given by injections or infusion (subcutaneously)". Please amend this sentence to two separate sentences. ie dopamine agonists, particularly when given orally, can be associated with impulse control problems. Apomorphine is given by subcutaneous injections or continuous infusions.
8	3.3 "DBS is more suitable for patients with stiffness and tremor" – please amend to: "effective for people with significant motor fluctuations with good levodopa responsiveness, as well as for people with levodopa-resistant tremor"
9	3.3 There are criteria for using LCIG which are generally used as guides: we suggest removing the phrase "strict criteria" as the tertiary centres do offer flexibility. Both DBS and LCIG are only available in tertiary neuroscience centres and therefore not readily available for the majority of patients with Parkinson's – this is related to geographical challenges, clinician awareness and patient preferences.
10	3.12 Could other sources of data such as for example, from the Critical Path data set and look at data for advanced Parkinson's. eg PPMI,Tracking, Discovery. This may give useful data on natural history and progression. Currently the only such data the company have used is from Palmer et al 2002 the only such study available.
11	3.13 Even when Parkinson's motor symptoms are well controlled, the trajectory is not really going to be like someone without PD (as the committee states in the draft). For this to be true they would have to have no comorbidities and no non-motor complications.
12	3.15 The draft states that "Troublesome dyskinesia is felt to be less problematic to patients than off periods of immobility or freezing". It is likely that troublesome dyskinesias occur only in a minority of patients with PD. Even so if there is data on troublesome dyskinesias available to the company it would be useful to be able to review it.
13	3.16 Re: effect of gender and age on PD - If the model assumes linear progression that is similar in all patients, irrespective of age, gender and disease severity, then this is incorrect. We know that older age, male sex and more advanced disease are associated with higher rates of disease progression, and therefore it is likely that patients will transition between health states faster than in the Palmer paper.
14	All of the relevant evidence has been taken into account The summaries of clinical effectiveness are reasonable interpretations of the evidence, in particular: • 3.4 the patient population unsuitable for apomorphine or DBS might well be frailer with possibly worse treatment outcomes than the study populations • 3.4 we agree with the suggestion for evaluation in all people within the scope of the marketing authorisation • 3.9 we agree with the conclusion of equal efficacy for foslevodopa foscarbidopa and levodopa carbidopa intestinal gel • 3.11 we agree that there is insufficient data to support the large number of health states used in the company model; moreover, the clinical significance of differentiating between such a large number of health states is not clear

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	However: • 3.9 the oral comparator arm in the 736 study may not be equivalent to standard of care, as additional efforts would have been spent to ensure optimisation of the regime as per protocol, which does not reflect standard care; additionally the 12 week duration of the 736 study may not be long enough duration to allow any meaningful progression in terms of disease burden related to the increasing duration of off time (Please note that we are not expert statisticians and do not have an economics background, so our comments relate primarily to the clinical interpretation of the evidence. We cannot comment definitively on cost effectiveness) The provisional recommendations form sound and a suitable basis for guidance to the NHS
15	3.14 it is not unreasonable to suggest, as the company does, that experienced sites may have better retention rates for infusion therapies than less experienced sites and we suggest the model takes this experience into account.
16	3.17 it would be helpful to define terms such as early or advanced Parkinson's so that there could be a better shared understanding of their meaning
17	Importantly, we agree with EAG comments relating to scope of approval for foslevodopa-foscarbidopa. This drug could potentially be used in preference to LCIG or DBS as it is much easier to start/stop and in that sense is more easily reversible, not requiring any form of surgery. Therefore the positioning should ideally be wider, so that it is in line with its marketing authorisation ie for use in advanced PD, with severe motor fluctuations, where currently available treatments are not providing adequate symptom control.
18	There is a high unmet need for effective treatments in advanced PD and there are many potential benefits of foslevodopa-foscarbidopa. We agree that an improved economic model will help inform NICE committee's final decision.

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):	

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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:	Marc van Grieken

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Thank you for the opportunity to comment on the draft guidance report which I have read several times. The draft guidance document is complex which makes the report fairly impenetrable. This may be illustrated by the following quote taken from paragraph 3.5: *the company also provided supporting evidence from non-comparative safety studies of foslevodopa-foscarbidopa, Including M15-741 and M15-737. The committee noted that because people in M15-736 could have previously had apomorphine, the study population was broader than that in the company's submission.* It may be the case that experienced people will recall the differences between the three trials (M15-741, -737 and -736) referred to, but a lay person certainly would not. Perhaps even greater effort should be made to write these reports in plain language that can be understood by all people.

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	Turning now to the purpose of the committee meeting, may I put it this way? Stripping the process down to its bare minimum, the assessment committee is required to answer 2 or 3 basic questions: • Does the medicine or intervention work? • can the cost be justified? And, • if the answers to the questions above are qualified, what additional information or evidence is required?
2	There is reference in the report to the experience of people living with Parkinson's. Everyone's Parkinson's is unique albeit that the overarching effects are very similar: for all of us living with Parkinson's, managing the condition becomes increasingly difficult, ineffective and unpleasant. The relentless progression of Parkinson's severely affects our quality of life which for many leads to losing one's dignity. That is not a particularly attractive prospect. Parkinson's is the fastest growing neurological condition in the world and 60 years since levodopa was first identified no significant new treatments have been identified. The unique nature of everyone's Parkinson requires a unique, holistic care plan suitable for the individual. The report however is based on a general population or might I say 'a generic person with parkinson's'. I know from personal experience gained over 3.5 year using foslevodopa – foscarbidopa that it has transformed my life. I also know that others did not experience the benefits. "We do not know what causes it Parkinson's (Idiopathic Parkinson's), comprises approximately 90% of cases and genetic causes (faulty gene causes) the remaining 10%. The high percentage of 'unknown causes' further underpins the unique and individual nature of our PD. I hazard a guess that this diversity could be one of the factors why research has made so little progress. Whilst on the face of it applying the same outline methodology to assess efficacy and value for money/cost etc of medicines and or treatments for different conditions (eg Parkinson's – certain cancers) seems appropriate, the lack of informed qualitative analysis is extremely disappointing and not only that, I think it does not meet NICE's own principles. I don't think there is any ambiguity about the efficacy of the treatment. It is frustrating therefore to note that the scientific committee considers there not to be sufficient evidence (of its efficacy) because of the errors in use and relevance of data et cetera. I would suggest that when the people in a double-blind trial conclude that they must be receiving the drug being trialled (because their condition improves so much), then that should not be seen as a failure of the methodology but merely as evidence of efficacy. With respect to economics I understand the need to consider cost and value for money in comparison with current best medical treatment and the potential implication of these costs on other treatments. Around 2014-15, working became more difficult for me because of symptoms associated with Parkinson's. I could see the professional world around me thinking: 'he's not quite right'. In order to make it possible to continue to work longer, I resigned from my post as Director of a large environmental consultancy which required daily commuting and in its

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

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	place established MVGLA, a small landscape practice. Thanks to the, what I have called, transformational effect of Foslevodopa-Foscarbidopa which I have been trialling since December 2019, I have been able to continue working full time and presently employ five people. In fact, I have increased professional activity. Very importantly it has also greatly improved my mental state and this is in itself of course an important aspect of treatment. The economic case therefore should be made in a much more rounded way and explain how the different types of calculations are combined to reach an overall conclusion.
3	To finish my opinion, I will briefly refer to some of the principles guiding the work by NICE that in my view are most relevant to this case. Principle 4. I accept that NICE takes into account the advice and experience of people using services and their carers or advocates et cetera. Indeed there are some patient representatives on the committee but it is unclear how they influence the decision making. I am especially interested in the decision-making process and think that the people who are effectively at the heart of the assessment process, eg people with Parkinson's, should actively participate and be co-responsible for the results/effects of the decision.
4	Principle 5: there is plenty evidence of NICE's approach to providing opportunities for commenting and influencing, and I like the reference to requiring to be accountable to the public and taking decisions in a clear and transparent way. But as I stated above, patients should be party to decision making?
5	Principle 6: I note the reference to a comprehensive approach to assessment and to qualitative as well as quantitative assessment. In my view the draft guidance before us is almost exclusively limited to quantitative appraisal only and much more qualitative analysis is required. It is not just the ICER and QaLy of the person living with Parkinson's, it is also the loss of economic activity of the Person with Parkinson's and effects on family and carers, the ever-increasing burden of the growing numbers and the effect on mental health that should be considered.
6	Principle 7: The ICER and Qaly gained are mostly impenetrable. Parkinson's, the world's fastest neurological condition, almost guarantees that they will end up needing extensive and expensive care. The relentless progression will continuously adversely and continuously affect their quality of life and the quality of life of their family and friends. I find it very hard to see any qualitative reasoning. There are many similar comments I could make about the next three principles but considered the above as most important.
7	In conclusion: Foslevodopa-foscarbidopa has, at least for what I believe to be sizeable contingent, led to substantial increases in quality of life with secondary effects such as improved mental state and ability to make economic contributions. I believe this would easily and clearly be evidenced had a thorough qualitative assessment be undertaken also. This is a serious and substantial shortcoming of the

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	report of the draft guidance. I would hope that this shortcoming might be rectified by the committee requesting a qualitative assessment from the company whereby it is the responsibility of the committee to phrase the questions (what are the desired outcomes and how can be measured qualitatively. Company and committee will need to work in partnership if they truly wish to help improve our quality of life. Anything short of that will in my opinion fail our collective duty to the Parkinson's community.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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

Single Technology Appraisal

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Not specified
Location	Not specified
Conflict	Not specified
Notes	Not specified

Comments on the DG:

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes - I believe the current model doesn't take account of the range of symptoms and improvements in QoL that will be achieved with this drug

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

Based on the current model yes, but this drug is likely to be transformative for patients, caregivers and clinicians managing PD

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

No

- Draft guidance consultation

There is clear evidence from the clinical studies that this drug improves on time, reduces 'off' time, improves sleep (with likely positive effects on daytime symptom control and QoL) and morning akinesia.

I agree that the best comparator is standard care, but also worth noting that this drug may play an important role where other device aided therapies are not tolerated or declined by patients. It may also be effectively used as bridging

therapy and in situations when oral treatment may not be possible (such as when a patient is NBM)

Foslevodopa-foscarbidopa for treating Parkinson's disease with motor symptoms [ID3876]

EAG response to company ACD comments

August 2023

Source of funding

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1 Introduction

This document provides the Evidence Assessment Group (EAG)'s critique of the company's response to the appraisal consultation document (ACD) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of foslevodopa-foscarbidopa for treating Parkinson's disease (PD) with motor symptoms (ID3876).

Section 2 presents the EAG's critique of the comments made by the company in response to the ACD, the company's updated results are presented in Section 3 and Section 4 presents the EAG's updated base case and scenarios. Comments by the company are discussed according to comment number as per the company's response document to ACD. Table 1 below summarises these comments, including which area of the ACD they relate to and the EAG response.

Table 1. Summary of issues covered in company's response to ACD

Comment in company ACD response	Issue	Relevant sections of ACD	Company response	EAG comment
1	Limitations with the original modelling approach, including the large number of health states	Sections 3.10 and 3.11	A supporting grouped OFF state model (with five health states) is presented	EAG maintains there is uncaptured benefit. Accepts company's 5 state model and cap on utility/cost.
2	Uncaptured benefits of foslevodopa–foscarbidopa	Section 3.21	Additional sleep benefits of foslevodopa–foscarbidopa are now captured within the economic analyses. Additional benefits other than sleep that were not possible to robustly incorporate have been detailed qualitatively in Responses 1, 2 and 7.	The EAG considers the company's cost and utility benefit are inappropriate.
3	The utility values associated with health states in the model	Section 3.16 and 3.17	Utility values and health state costs are now capped at OFF10	The EAG maintains that there is evidently external influence on utility. Prefers use of 736 regression analysis.
4	The cost values associated with health states in the model			Update to EAG costing. EAG maintains that using observed values is most appropriate.

5	Use of M15-736 trial data to model best medical therapy (BMT) treatment effect	Section 3.7	BMT treatment effect is now modelled using M15-736 data	Error in application of reversion to baseline. EAG adopted BMT trial values into base case in an alternative way to company.
6	Treatment effect following discontinuation	Section 3.13	Patients discontinuing treatment are redistributed to baseline, which AbbVie maintain is most reflective of long-term improvements associated with active treatment	EAG maintains that patients following discontinuation should revert to BMT efficacy.
7	Uncertainty in the indirect treatment comparison	Sections 3.8 and 3.9	AbbVie maintain that foslevodopa-foscarbidopa offers improved efficacy over levodopa-carbidopa intestinal gel (LCIG) for patients	Uncertainty remains and the EAG maintains its view that the company should update the NMAs of OFF time and ON time without troublesome dyskinesia to consistently include LS mean data and MMRM to account for missing data.
8	The generalisability of the M15-736 trial population to the population of interest in this submission and reliability and magnitude of the treatment effect	Section 3.5	AbbVie maintain that the M15-736 population is generalisable to the population of interest	Uncertainty remains and EAG advises caution should be taken in drawing any conclusions from the prior DBS subgroup results.
9	Data source of discontinuation	Section 3.14	M15-736 data now informs discontinuation rates for the first model cycle	Issue resolved.
10	Approach to modelling long-term natural disease progression	Section 3.12	AbbVie maintain that their approach to extrapolating data from Palmer et al. (2002) is most appropriate	EAG maintains that the company's method is inappropriate.

Abbreviations: ACD, appraisal consultation document; BMT, best medical therapy; EAG, External Assessment Group; LS, least squares; LCIG, levodopa-carbidopa intestinal gel; MMRM, mixed model repeated measures; NMA, network meta-analyses.

2 EAG's critique of company response to ACD

2.1 *Comment 1. Limitations with the modelling approach*

In the EAG report, and at technical engagement, OFF time alone was identified as not adequately representing the heterogeneity of Parkinson's disease. In addition, the data available for informing efficacy, utility, and costs for 17 health states was considered insufficiently powerful for so many health states, given the shortage of patients in many of the health states. The EAG advised that the company utilise a model structure similar to previous models Kalabina *et al.* 2019,[2] Walter and Odin 2015,[3] Chaundhuri *et al.* 2022,[4] Lowin *et al.* 2011[5] and Lowin *et al.* 2017,[6] which utilised fewer health states driven by OFF time and H&Y (Hoehn & Yahr) state. The EAG advised the company to adopt a model that utilised a similar structure.

The company maintains that use of H&Y would be inappropriate as it fails to address concerns around the large number of health states as it would increase the number of states from 17 OFF states to 25 (5 defined by OFF time and 5 defined by H&Y). They consider that this would remain subject to larger uncertainty as there would be more health states informed by less data. Previous models which used this structure, such as Chaundhuri *et al.* 2022[4] had access to a greater amount of data to inform the model transition probabilities and utilities (N=196, versus [redacted] in the Company's model). In addition, the Adelphi 2017-2019 would lack a significant number of observations in higher health states to inform costs.

The company also considered that the addition of H&Y states to the model wouldn't address the concerns regarding the potential benefits of foslevodopa-foscarbidopa that go beyond reducing OFF time. The company claims benefits such as improvements in daily functioning, symptom control, and sleep after starting foslevodopa-foscarbidopa treatment will not be captured by H&Y. The company has attempted to capture unaccounted benefits of the treatment without incorporating H&Y outcomes in the model. In order to better reflect one unaccounted for aspect of Parkinsons, brought up by patient experts at ACM1, the company has updated the model to account for sleep benefits of treatment. This would not be captured in the previous model which only accounts for OFF time in waking hours. This addition and any issues with it has been separated into its own section and is further discussed in 2.2.

Recognising the limitations of the data available, the company have capped health state costs and utilities at 10 hours of OFF time in order to limit uncertainty from the small number of patients in

high OFF states in their base case model. Furthermore, they have provided a model with a reduced number of OFF health states as requested. OFF health states have been grouped into 5 health states, representing patients experiencing 0 (OFF0), 1–4 (OFFI), 5–8 (OFFII), 9–12 (OFFIII) and 13–16 (OFFIV) hours of daily OFF time, respectively. However, the company maintain that modelling 1-hour increments in OFF time is most appropriate modelling technique to capture all clinically relevant benefits and the results.

EAG response

The concern over the large number of health states informed by too few patients is because this health state data is mutually exclusive to the patient. However, a single patient can provide data on OFF time and H&Y, the outcomes are not mutually exclusive.

The company correctly identify that [redacted] of the 10 highest OFF states would lack cost data to inform them if H&Y was used as shown in Figure 1. However, this is primarily the result of a lack of data for higher OFF states not for higher H&Y state and therefore would remain an issue whether H&Y were to be included or not. In addition, it is the EAG's understanding that very few patients would be expected to occupy these lower H&Y states if they had advanced Parkinsons and a high OFF time.

Figure 1. H&Y and OFF - Advanced Parkinson's Disease Adelphi 2017-2019 dataset

It is not clear how the company derived the new transition rates. The EAG expectation is that the transition probability of OFF 0-> OFF I in the 5 health state model would have the same transition probability as OFF 0->OFF 1 in the 17 health state model but this is not the case. In addition, since patients can only improve or get worse the EAG would expect that the probability of going from OFF I to OFF II would be OFF 1->2, 2->3, 3->4 and 4->5 multiplied together (since a patient would need to qualify for all of these probabilities to transition to OFF II). Where the EAG has calculated 5 HS model transition probabilities this method has been used. EAG expectations vs the 5 HS transition rates are shown in Table 2.

Table 2. EAG expectation of TP conversion to 5 HS model

Health state	17 HS model TP (6 month)	5 HS model TP (6 month)	EAG expectation 5 HS model TP (6 month)
OFF 0	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]
OFF2	[redacted]		
OFF 3	[redacted]		
OFF 4	[redacted]		
OFF 5	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]		
OFF 7	[redacted]		
OFF 8	[redacted]		
OFF 9	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]		
OFF 11	[redacted]		
OFF 12	[redacted]		
OFF 13	[redacted]		
OFF 14	[redacted]		
OFF 15	[redacted]		
OFF 16	[redacted]		

Abbreviations: EAG, external assessment group; HS, health state; TP, transition probabilities;

The EAG agrees with the company's decision to cap utility and cost data at OFF 10 due to lack of available data. The EAG believes the 5-state model to be the most appropriate for use in the evaluation of cost-effectiveness. The EAG maintains the position that the current model structure may not accurately reflect the diversity of health effects from this disease.

2.2 Comment 2: Uncaptured benefits of foslevodopa-foscarbidopa

In the company response to the draft guidance, the company has highlighted sleep benefits associated with foslevodopa-foscarbidopa including that foslevodopa-foscarbidopa significantly improved sleep as measured in the M15-736 trial by a Parkinson's Disease Sleep Scale-2 (PDSS-2) ≥18 at Week 12 of the trial.[7-9] A total of [redacted] of patients receiving foslevodopa-foscarbidopa reported a lack of sleep disturbance, defined as a PDSS-2 score <18 at Week 12 of the M15-736 trial, compared with [redacted] in the BMT arm. In addition, fewer patients on foslevodopa-foscarbidopa experienced morning akinesia compared with BMT in the M15-736 trial at week 12 (foslevodopa-foscarbidopa 8/47 [17%] patients reported being OFF at the time of waking, compared with 38/60 [63%] patients receiving BMT; LS mean of Odds Ratio [SE]: [redacted]). The EAG notes that this was despite patients in the BMT arm being allowed to receive night-time oral dosing. The EAG also notes that [redacted] patients [redacted] receiving foslevodopa-foscarbidopa reported morning akinesia at baseline while only 8 (17%) did so at Week 12.

The company has added a utility and cost benefit reflecting avoidance of sleep disturbance. Patients experiencing sleep disturbance are defined as having a PDSS-2 score ≥18 at Week 12 of the M15-736 trial. Utility values based on PDSS scores above and below 18 reported in Xiao *et al.* 2022[10] were used to derive utility associated with lack of sleep disturbance of [redacted] LCIG was assumed to provide no benefit, as with BMT.

Yearly cost savings of [redacted] are applied to the foslevodopa-foscarbidopa arm, derived using the proportion of patients reporting sleep disturbance (PDSS-2 ≥18) from the M15-736 trial detailed above, and costs relating to excessive sleepiness reported in the Adelphi dataset (see 'Cost regression output' of the model). A scenario analysis has been conducted in which yearly savings of [redacted] are applied to the foslevodopa-foscarbidopa arm derived from costs relating to sleep disturbance, rather than excessive sleepiness, from the Adelphi dataset to inform this cost-saving.

EAG comment

The company's method for deriving utility benefit for [redacted] from the Xiao *et al.* 2022[10] paper is likely to overestimate the benefit from lack of sleep disturbance. The paper registers the median utility of patients with PD-SP (Parkinsons disease-related sleep problems) and patients without and the company applies these utility values to the proportion of patients with PDSS-2 ≥18 and PDSS-2 < 18 in the foslevodopa-foscarbidopa and BMT arms. The company then takes the difference in utility

between these two utilities to derive the sleep benefit from foslevodopa-foscarbidopa vs BMT and LCIG.

[redacted]

The issue with this method is the data used is a simple average of patients with sleep issues and patients who do not have these issues, it has not isolated sleep as the cause of the difference. This would only provide an appropriate estimate of sleep-related utility if the two groups (those with/without Parkinsons related sleep issues) are assumed to have equal OFF time, which seems unlikely.

The company also provided additional analysis that added PDSS-2 and morning OFF time to the utility regression for NROFF (number OFF hours per day). Of these analyses, NROFF and PDSS-2 appears the most appropriate to account for sleep related benefit, as morning OFF time will likely introduce significant multicollinearity issues with NROFF as the two variables are inherently linked. This method of deriving utility is more appropriate and may also contribute to resolving the issue of the inconsistency in the reporting of utility relating to OFF time between trials; referenced in section 2.3. However, without "trial" being a variable in the regression this cannot be confirmed. Furthermore, there are a number of 'on treatment' benefits that foslevodopa-foscarbidopa provide over BMT, outside of OFF time and sleep, such as reduced dyskinesia. It is possible that PDSS in the regression may be acting as a proxy for patients successfully treated and therefore some of the benefit may also apply to LCIG.

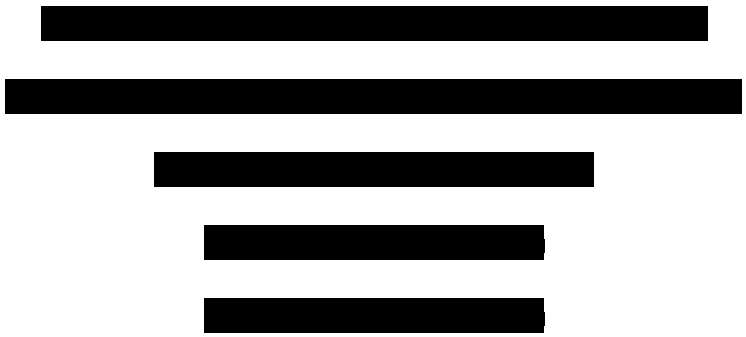
The calculations, provided by the company, for the sleep related cost saving of [redacted] is shown in Table 3.

Table 3.Calculation of sleep-related cost benefit (per year) (reproduced from table 12 in company response document)

	PDSS-2 <18	PDSS-2 ≥18	
Treatment arms			**Weighted average cost**
Foslevodopa-foscarbidopa	[redacted]	[redacted]	[redacted]
BMT	[redacted]	[redacted]	[redacted]
Sleep-related incremental cost benefit with foslevodopa-foscarbidopa			[redacted]

The company states that the same approach was used for deriving cost as utility benefit. Therefore, we can derive the cost to an individual patient from lack of sleep:

[redacted]



This means the company is suggesting a patient with PDSS-2 ≥ 18 will cost over £20,000 a year more, which appears implausibly high.

While the company does provide a lower scenario analysis cost associated with sleep disturbance, as opposed to excessive sleepiness, the company's method for deriving the cost benefit appears to have the same flaw as the utility benefit. While the company has only provided an overview of the Adelphi data collected and not the relevant dataset itself, it seems from the "Cost regression output" worksheet that the company has taken a simple difference in average resource use between those with excessive sleepiness (or those with sleep disturbance for their scenario analysis) and those without and used this to derive the cost. This likely double counts costs from OFF time as these costs are not specific to sleep and the excessive sleepiness and sleep disturbance are likely correlated with inadequately controlled patients with higher OFF time.

The EAG acknowledges that there are likely quality of life related benefits from improved sleep from foslevodopa-foscarbidopa. Yet, uncertainty around both the cost and QoL benefit provided lead the EAG to consider that the cost saving benefit be removed, and the PDSS-2 regression utility be used in scenarios where this benefit is applied. The EAG has not applied this benefit in the update EAG base case but has provided it as a scenario. The company should demonstrate that any QoL or cost benefit is related only to sleep if it wishes to include these potential benefits so that it does not double count other benefits from treatment.

2.3 *Comment 3 . The utility values associated with health states in the model*

The EAG disagreed, in the EAG report and at technical engagement, with combining the utility data in studies M15-736; M15-741; M20-098; and M15-737 due to the lack of comparability across mean utility values for the same OFF states at baseline. This was considered strong supporting evidence that OFF time alone is an insufficient measure of patient efficacy. In addition, the EAG noted that few observations were present to validate predicted declines in utility above OFF 10 and the

company regression models failed to test for age, sex, baseline OFF hours and treatment duration as relevant covariates.

As with health state costs, the company has opted to address the lack of data in the higher OFF states by making a conservative assumption in assuming utilities are capped at OFF 10. The company maintain that using pooled utility values across the four trials, although they provided a scenario using M15-736 trial data. In addition, as previously stated, the company have now provided the option to use a 5 OFF state model to account for limited available data.

Furthermore, the company stated that age and sex along with a number of other items have been tested for in regressions and were thought to be unlikely to have a significant impact on health state utility values.

EAG comment

The EAG maintains that the best use of the available data is the alternative modelling approach utilising fewer OFF states. In addition, as stated at TE, the issue with pooling data across multiple trials remains as the values shown in Table 4 show a clear inconsistency in QoL across these trials. As the company has not provided a plausible rationale for why the inconsistency would be expected or accounted for it in any way in their analysis, the EAG maintains that the M15-736 trial data alone should be used to inform utilities in the base case, as this is the key trial that informs efficacy and baseline OFF state.

However, as the EAG is no longer presenting an "illustrative" base case, the regression results of the M15-736 trial utility have been used in order to ensure inputs have clinical validity. The EAG still maintains there is evidently a significant external influence on utility, resulting in such high utilities for patients with high OFF states in the M15-736 trial. Scenario analyses have been conducted in Section 4.2 to show the substantial impact of using the observed trial utilities over the regression.

Table 4. Mean utility values at baseline in all studies used by the company

OFF hours	M15-736		M20-098		M15-741		M15-737	
	Frequency (n=71)	Mean (SD)	Frequency (n=59)	Mean (SD)	Frequency (n=222)	Mean (SD)	Frequency (n=73)	Mean (SD)
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3	[redacted]							
4	[redacted]							
5	[redacted]							
6	[redacted]							
7	[redacted]							
8	[redacted]							
9	[redacted]							
10	[redacted]							
11	[redacted]							
12	[redacted]							
13	[redacted]							
14	[redacted]							
15	[redacted]							
16	[redacted]							
Abbreviations: n, number; SD, standard deviation.								

2.4 *Comment 4. Costs associated with health states in the model*

In the EAG report, and at technical engagement, the company's approach to estimation of health state costs is noted as being flawed and overestimating costs. The regression analyses used by the company to estimate health state costs demonstrate a poor fit to the underlying cost data and show an overestimation of the costs observed in the Adelphi study. Aside from OFF 0 and OFF 1, the company's regression model appeared to significantly overestimate costs relative to the data and the company lacked any data beyond OFF 10 and yet estimated increasingly higher costs. For this reason, the EAG replaced the health state costs with the raw data from the Adelphi study as an illustrative base case.

The company have responded to this issue by opting to cap the regression analysis at OFF 10, using the costs at OFF 10 to represent OFF 11-16. They consider this a conservative approach as they consider it to be reasonable to expect patients with 11-16 hours of OFF time should incur higher costs. The company considers the EAG trend in costs clinically implausible, as the highest costs are associated with OFF 4 and OFF 0 has higher costs than patients with OFF 5 to OFF 16.

EAG comment

The EAG has updated its exploratory analysis to now include the observed values for all health state cost components; previously only professional care, hospitalisation costs and respite care observed values were used, the company's regression was used for all other resource use components. In

addition, professional care costs have been updated to be appropriately weighted by the percentage of patients likely requiring professional care. This is assumed to be the number of observations for rates of professional care use in an OFF state divided by the number of patients in health state included in Adelphi study. Previously OFF state professional care costs were weighted by the percentage of all patients in professional care.

This has significantly changed the costs as shown in Table 5 due to the difference in multiplier with 100% of patients estimated to in OFF 10 + and only 3% of patients in OFF 0.

Table 5. Update to EAG approach to health state cost calculation

Health state	Total yearly costs in EAG's previous exploratory analysis	Total yearly costs in EAG's updated exploratory analysis
OFF 0	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]
OFF2	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]

*taken from the previous OFF state with available observed data

With the EAG update, the observed data appears to fit expectations, particularly when separated out into the 5 health states as shown in Table 7.

However, the health state costs are subject to substantial uncertainty due to being driven largely by a very small number of patients professional care costs, as shown in Table 6.

Table 6. Estimated observed professional care costs and number of observations

Health state	Total observations of patients requiring professional care	Estimated professional care cost by health state
OFF 0	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]
OFF2	[redacted]	[redacted]
OFF 3	[redacted]	[redacted]
OFF 4	[redacted]	[redacted]
OFF 5	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]
OFF 7	[redacted]	[redacted]
OFF 8	[redacted]	[redacted]
OFF 9	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]
OFF 11	[redacted]	[redacted]
OFF 12	[redacted]	[redacted]
OFF 13	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]
OFF 15	[redacted]	[redacted]
OFF 16	[redacted]	[redacted]

The EAG and company health state costs for the 5 and 17 health state model are shown in Table 7.

The EAG maintains that the estimated observed cost values should be preferred.

Table 7. Total health state specific costs included in the EAG's exploratory analysis

Health state	Total yearly costs in company's base case	Total yearly costs in EAG's exploratory analysis	5 HS company	5 HS EAG exploratory analysis
OFF 0	[redacted]	[redacted]	[redacted]	[redacted]
OFF 1	[redacted]	[redacted]	[redacted]	[redacted]
OFF2	[redacted]	[redacted]		
OFF 3	[redacted]	[redacted]		
OFF 4	[redacted]	[redacted]		
OFF 5	[redacted]	[redacted]	[redacted]	[redacted]
OFF 6	[redacted]	[redacted]		
OFF 7	[redacted]	[redacted]		
OFF 8	[redacted]	[redacted]		
OFF 9	[redacted]	[redacted]	[redacted]	[redacted]
OFF 10	[redacted]	[redacted]		
OFF 11	[redacted]	[redacted]		

OFF 12	[redacted]	[redacted]		
OFF 13	[redacted]	[redacted]	[redacted]	[redacted]
OFF 14	[redacted]	[redacted]		
OFF 15	[redacted]	[redacted]		
OFF 16	[redacted]	[redacted]		

Abbreviations: EAG, external assessment group; HS, Health state.

2.5 *Comment 5. Use of the M15-736 trial data for BMT*

The EAG previously questioned the validity of not utilising the M15-736 trial data to inform the BMT arm. The company maintain that patients receiving no benefit is most appropriate given the population of interest. In addition to previous arguments, discussed after technical engagement, the company cites interim analysis from the PROSPECT study, which shows clinical and economic outcomes of Parkinsons patients with symptoms inadequately controlled with their current therapy and not on DAT (device aided therapies). This analysis found that the average (SD) change in OFF time from baseline was -0.3 (1.8) hours at 12 months.[11] This is not a statistically significant change in OFF time and is lower than the change predicted by the M15-736 trial.

Despite this, the company have updated their base case economic analysis to include M15-736 trial data for the BMT arm. Patients are assumed to return to baseline in cycle 2 and natural disease progression is used from cycle 3. The company claims this return to baseline is supported by the PROSPECT study and clinical expert feedback.

EAG comment

An error has been identified with the company's application of the company's application of the M15-736 trial data. Despite there being no intended difference in mortality between treatment arms life years (Lys) are higher in the BMT arm in both the grouped and 1-hour incremental models. This is caused by the company's application of the reversion to baseline in the "Patient distribution" worksheet CJ7:CZ8. The model appears to have not taken into account mortality when it reverts patients back to baseline health states, meaning in the company's base case effectively no mortality is applied to BMT arm patients between cycle 2 and 3.

It should be noted, that PROSPECT demonstrated the average patient who remains inadequately controlled on oral anti-Parkinsons medication will experience a decline in OFF time (even if not statistically significant), and this suggests that the company's previous assumption that patients decline immediately following the trial period, underestimated the relative efficacy of BMT.

Furthermore, the company claims PROSPECT validates their modelling assumptions and this does not appear to be accurate, since the company's assumption is that patients return to baseline in cycle 2 (6 months) and natural disease progression returns by cycle 3 (12 months). This means the company is assuming increases in OFF time at 12 months as opposed to a small decline. In addition, there is no suggestion from the available M15-736 trial data that OFF time for patients in the BMT arm is trending towards baseline after 3 months, as shown in Figure 2.

Figure 2. Plot of mean change in average daily normalised OFF time from M15-736 trial

The EAG reiterates that it accepts the benefit seen in BMT may be a "trial effect", but that this should equally apply to foslevodopa-foscarbidopa as well as BMT. Given the supplemental evidence of continued efficacy of foslevodopa-foscarbidopa long term and the PROSPECT evidence that there is little change in OFF time at 12 months for patients who remain on oral treatment, the EAG's have applied the same assumptions regarding treatment effect and LOCF to the BMT arm as the foslevodopa-foscarbidopa arm.

2.6 Comment 6. Treatment effect following discontinuation

The company reiterated their case for some retained benefit following discontinuation as both patient and clinical experts accepted its plausibility. This is assumed to be caused by legacy benefits from having improved motor symptoms allowing patients to have healthier lifestyles than counterparts on BMT. To account for this, benefit the company has assumed that patients who discontinue resort to baseline OFF states. The EAG notes that this approach would result in patients

who discontinue after a certain period of time obtaining an improvement in OFF time, as demonstrated in the illustrative scenario in Figure 3.

Figure 3. EAG scenario to demonstrate issue with company's implementation of discontinuation assumption

Despite this, the company maintain that this approach is most in-line with expected long-term benefits. Furthermore, as a result of the inclusion of M15-736 data in the modelling of the BMT arm, the company believe the EAG's approach of having patients redistributed according to BMT health states in the cycle following discontinuation to be implausible. This is because patients in the first cycle would discontinue to an improved health state despite not receiving any substantial treatment benefit.

EAG comment

The EAG maintains that the assumption that patients resort to the equivalent OFF state outcomes as the BMT arm is the most reasonable assumption given the available data. For the company to include an extended quality of life (QoL) benefit from a more active lifestyle while on treatment, the company would need to be able to support this assumption with evidence. The company has taken a plausible benefit and applied an unrelated benefit to represent this. There remains no justification provided for why the retained QoL benefits of a healthier lifestyle will result in patient OFF time declining to only baseline and the issue of patients OFF time improving if they discontinue beyond a specific point still remains.

2.7 *Comment 7. Uncertainty in indirect treatment comparisons of foslevodopa-foscarbidopa and LCIG*

The EAG does not consider that the company has presented any new clinical evidence in their response to the appraisal consultation document (ACD) but notes that the company consider it inappropriate to assume clinical equivalence between the treatments.

EAG comment

The EAG maintains its view that the company should update the network meta-analyses (NMAs) of OFF time and ON time without troublesome dyskinesia to consistently include least squares (LS) mean data and mixed model for repeated measures (MMRM) to account for missing data for all three included trials: M15-736,[7] Olanow 2014[12] and DYSCOVER.[13] Additionally, the EAG considers it important to highlight that the results from both the EAG and the updated company NMA are associated with high levels of uncertainty. The EAG considers the assumption of similar efficacy for foslevodopa-foscarbidopa and levodopa-carbidopa intestinal gel (LCIG), as applied in the EAG base case, is not unreasonable until the aforementioned more appropriate analysis is conducted.

2.8 *Comment 8. Generalisability of M15-736 trial population and reliability and magnitude of the treatment effect*

The committee raised concerned that the M15-741[14] and M15-736[7] trials represented a broader patient population than foslevodopa-foscarbidopa was being positioned in due to the enrolment of patients with prior apomorphine and deep brain stimulation (DBS) use in the trials. In the company response to the ACD, the company reported that the population in which foslevodopa-foscarbidopa is anticipated to be used in NHS clinical practice covers patients for whom apomorphine and DBS are unsuitable, or no longer providing adequate symptom control. The company therefore considered that the proposed positioning doesn't preclude prior use of apomorphine or DBS, and therefore the trials do not necessarily represent a broader patient population than the proposed indication.

In addition, the company reported that *post hoc* subgroup analyses of the M15-741 trial demonstrated that patients who received prior DBS (N=24) had similar improvements in OFF and ON times to patients who had not received prior DBS (N=220). Patients who had received prior DBS had a mean change from baseline in OFF time of −1.96 hours (SD=3.44), compared with −2.45 hours (SD=3.82) for patients who had no prior DBS. Patients who had received prior DBS had a mean

improvement from baseline in ON time without troublesome dyskinesia of 2.57 hours, compared with 2.71 hours for patients who had not received prior DBS.

The EAG also notes that in the company response to the ACD the company reported that, "*a number of strategies were employed in the design of M15-736 to minimise bias and uncertainty related to the Parkinson's diaries*". The EAG notes that one of these strategies involved a concordance evaluation during Visit 1 where a patient had to experience at least one transition from OFF to ON or from ON to OFF that was observed by the investigator or a qualified rater. The trial required at least 75% concordance between the patient's diary and the diary completed by the investigator or qualified rater. The company also reported that in the Movement Disorders Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS) Part IV assessment, OFF time was assessed as a single outcome with assessments conducted by a separate independent rater. The MDS-UPDRS Part IV assessment was [redacted][7]

EAG comment

The EAG notes that the sample size for the prior DBS subgroup is small and that these are *post hoc* subgroup analyses were not appropriately powered to detect a difference in treatment effect contingent on prior DBS. The EAG, therefore, considers caution should be taken in drawing any conclusions from these results.

As discussed during TE, the EAG remains concerned that for M15-736 the key efficacy outcome, OFF time, was captured in patient reported Parkinson's disease diaries which are subjective, and at higher risk of bias than objective outcome assessments. The EAG's clinical experts agreed with the company's clinical experts view that the use of patient diaries as an instrument to collect 'Off' time data is standard in Parkinson's disease trials.

The EAG agrees with the company and the company's clinical experts that M15-736 is a well conducted double blind randomised controlled trial (RCT), that takes reason steps to minimise bias, and which provides the best available evidence for the relative clinical effectiveness of foslevodopa-foscarbidopa compared with oral carbidopa/levodopa (CD/LD). However, the EAG still considers that it is likely that patients on foslevodopa-foscarbidopa may overestimate the efficacy of their treatment and that patients on best medical therapy (BMT) may underestimate the efficacy of treatment as a result of patients correctly deducing which treatment they were randomised to.

2.9 *Comment 9. Data source of discontinuation*

The company and EAG used different sources of discontinuation rates for foslevodopa-foscarbidopa. The company considers that Cohort 2 of the M15-741 trial best represents real-world experience with the treatment, benefiting from a new infusion set and reflecting familiarity of investigators, leading to fewer discontinuations. However, the company have acknowledged data inconsistency and, to tackle the uncertainty arising from this, has followed the EAG's advice and updated the discontinuation data sources.

EAG comment

Since the company has accepted the EAG base case this issue is considered resolved.

2.10 *Comment 10. Approach to modelling long-term natural disease progression*

The company and EAG disagreed on how to apply the Palmer *et al.* 2002 data[15]. This paper contained two datapoints; time on oral levodopa for patients under 25% OFF time and time on oral levodopa for patients with over 25% OFF time (maximum OFF time of any patient in the dataset was 12). Based on this information the company's approach to deriving a formula for the change in OFF time with time on therapy is shown in Figure 4 and the EAG's in Figure 5.

Figure 4. Company base case exponential model fitted to the two datapoints taken from Palmer *et al.* 2002

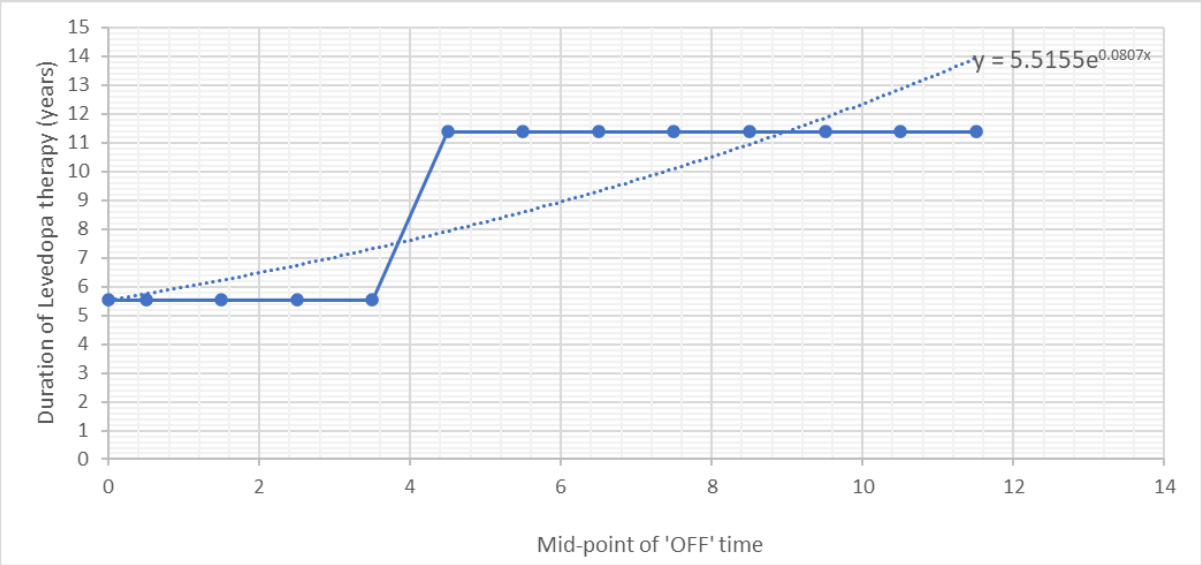
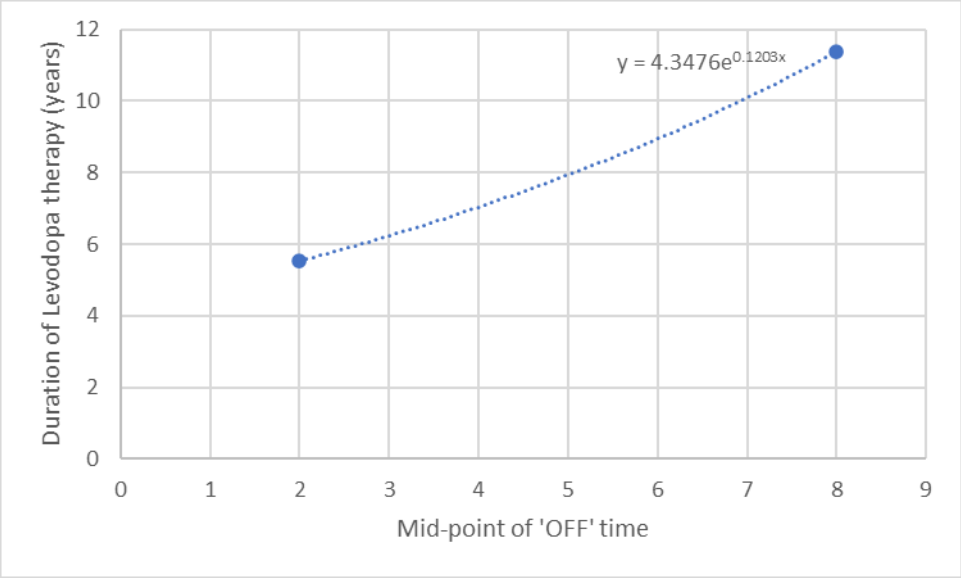


Figure 5. EAG alternative exponential model fitted to the two datapoints taken from Palmer *et al.* 2002



The company stated that they maintain that using their approach is more appropriate, since use of all data points provides a more realistic fit that considers variability in levodopa duration based on OFF time. The company also stated there is an expectation that they will transition through the time horizon in a similar manner. They also make note that this is aligned with previous economic models in Parkinsons.

The company also stated that these transitions are associated with slower disease progression at higher OFF states, which is more reflective of disease progression observed in real-life, and is supported by clinical opinion.

EAG comment

The company appears to have misunderstood the graph. As duration of levodopa (or time) is the Y axis as opposed to the X axis the EAG's steeper curve means it is associated with slower disease progression at higher OFF states. The company stated that there is an expectation for patients to transition in a similar way to their model but provide no information on where this expectation comes from. Both models consider variability in levodopa duration based on OFF time since that is the only source of data represented.

While the EAG acknowledge that the company's method has been used in prior models, it is still an inappropriate way of estimating OFF time given treatment duration using the data available. The

EAG is unclear what the 11 “fabricated datapoints” used to produce the graph in Figure 4 are intended to represent. For example, if they represent an estimation of potential patients then there is a strong assumption that within the two health states, time on levodopa does not correlate with OFF time, while also assuming duration on levodopa and OFF time are exponentially linked. This is a contradictory assumption and the EAG consider it clinically implausible that patients would have the same time on levodopa between 0 and 3.5 hours of OFF time or between 4.5 and 11.5 hours of OFF time.

3 Company's revised cost-effectiveness results

3.1 Company revisions as a result of ACM1

In response to ACM1, the company presented updated base case analyses. The updates are listed in Table 8. Note that these results contain a minor error referenced in Section 2.5.

Table 8. Changes to the company's cost-effectiveness model (reproduced from table 1 of the company's ACM response)

	BMT					LCIG				
	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)
Company's original base case (deterministic)	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.10	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case following clarification questions (deterministic)	0.80	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.10	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case following technical engagement (deterministic)	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.11	[redacted]	[redacted]	[redacted]	[redacted]
Updates to the base case (applied cumulatively, deterministic)										
Response 2: Capturing additional sleep benefits of foslevodopa–foscarbidopa	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	0.03	[redacted]	Foslevodopa - foscarbidopa dominant	[redacted]	[redacted]

	BMT					LCIG				
	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)
Response 3: Original fitted health state costs, capped at OFF10	0.60	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	0.03	[redacted]	Foslevodopa - foscarbidopa dominant	[redacted]	[redacted]
Response 4: Utility values derived from pooled trial data capped at OFF10	0.46	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	0.07	[redacted]	Foslevodopa - foscarbidopa dominant	[redacted]	[redacted]
Response 5: BMT treatment effect modelled using M15-736 data	0.38	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	0.07	[redacted]	Foslevodopa - foscarbidopa dominant	[redacted]	[redacted]
Response 9: Updated sources of discontinuation rates: • M15-736: 0–3 months • M15-741 cohort 2: 3–12 months • M15-737: 12–24 months	0.30	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.01	[redacted]	[redacted]	[redacted]	[redacted]
Company's revised base case (deterministic)	0.30	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.01	[redacted]	[redacted]	[redacted]	[redacted]

	BMT					LCIG				
	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)	Incremental QALYs	Incremental costs	ICER (change from technical engagement ICER)	NHB (£20k /QALY)	NHB (£30k /QALY)
Company's revised base case (probabilistic)	**0.30**	[redacted]	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]	−0.02	[redacted]	[redacted]	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone
Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

3.2 Company's updated base case

The company's updated probabilistic base case results are given in this section. For the model using one-hour increments in OFF time probabilistic results are shown in

Table 9 and deterministic in Table 10. For the grouped OFF state model Table 11 contains the probabilistic and Table 12 for the deterministic. In the company's updated base case foslevodopa-foscarbidopa remains associated with lower costs and lower quality-adjusted life years (QALYs) compared to levodopa-carbidopa intestinal gel (LCIG), resulting in a dominant incremental cost-effectiveness ratio (ICER). Best medical therapy (BMT) is dominated by foslevodopa-foscarbidopa.

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.17	-	-	-	-	-
LCIG	[redacted]	5.19	[redacted]	-0.02	[redacted]	[redacted]	[redacted]
BMT	[redacted]	4.87	[redacted]	0.30	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]

*LYG is not available in the PSA results

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

The EAG presents deterministic and probabilistic ICERs for the company's updated based case results and the EAG's base case results incorporating all relevant PAS discounts in the confidential appendix.

Table 9. Company's probabilistic base case results (1 hour increment OFF state model)

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.17	-	-	-	-	-
LCIG	[redacted]	5.19	[redacted]	-0.02	[redacted]	[redacted]	[redacted]
BMT	[redacted]	4.87	[redacted]	0.30	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]

*LYG is not available in the PSA results

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 10. Company's deterministic base case results (1 hour increment OFF state model)

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.17	-	-	-	-	-
LCIG	[redacted]	5.18	[redacted]	-0.01	[redacted]	[redacted]	[redacted]
BMT	[redacted]	4.87	[redacted]	0.30	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 11. Company's probabilistic base case results (grouped OFF state model)

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.32	-	-	-	-	-
LCIG	[redacted]	5.29	[redacted]	0.03	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]
BMT	[redacted]	5.08	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]

*LYG is not available in the PSA results

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 12. Company's deterministic base case results (grouped OFF state model)

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.32	-	-	-	-	-
LCIG	[redacted]	5.29	[redacted]	0.03	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]
BMT	[redacted]	5.08	[redacted]	0.24	Foslevodopa-foscarbidopa dominant	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

4 EAG's cost-effectiveness results

4.1 EAG base case

In this section of the report, the EAG also presents its base case ICER. Key differences between the company's base case ICER and EAG's base case ICER are given in Table 13.

- Assumed equal efficacy between LCIG and foslevodopa-foscarbidopa;
- Health states are minimised to 5 OFF states rather than 17;
- Patients who discontinue have equivalent outcomes to natural disease progression arm;
- Alternate implementation of Palmer *et al.* 2002 data using only the available data from the paper;
- Use M15-736 placebo arm benefit for BMT arm, this benefit is maintained for 2 cycles before natural disease progression occurs; reversion to baseline removed;
- Use M15-736 placebo arm benefit for BMT arm in the same way the intervention arm benefit is used;
- Use direct data to inform resource use for health state cost 5
- Use only the M15-736 trial to inform utilities;
- Remove sleep benefit.

Table 13. EAG's preferred assumptions

#	Assumptions	Company approach	EAG approach
1	Efficacy between ABBV-951 and duodopa	Updated technical engagement NMA relative risk between 951 and duodopa (RR = 1.16)	Efficacy between foslevodopa-foscarbidopa and LCIG assumed equal
2	Health states are minimised to 5 OFF states rather than 17	Company has preference for 17 health state model	EAG has a preference for 5 OFF state model
3	Patients who discontinue are assumed to have a significant change in efficacy	Patients who discontinue have equivalent outcomes to baseline	Patients who discontinue have equivalent outcomes to natural disease progression arm
4	Implementation of Palmer *et al.* 2002, how to extrapolate the two data points	Implementation of Palmer *et al.* 2002 data using 13 data points (2 observed, 11 assumed)	Alternate implementation of Palmer *et al.* 2002 data using 2 data points

5	Remove reversion to baseline following M15-736 placebo arm benefit for BMT arm	Patients revert to baseline OFF states after cycle 2. This includes an error whereby no mortality is applied to patients in this cycle	Patients are not forced to revert to baseline OFF time and instead follow natural disease progression
6	Use LOCF assumption on BMT arm	Company assumes reversion to baseline after first cycle	EAG aligns assumption of BMT to treatment arms
7	Use either regression or direct data to inform costs of health states	Use regression	Use direct data to inform resource use for health state cost
8	Use combined or single trials to inform utility	Use combined trial data	Use only the M15-736 trial to inform utilities
9	Remove sleep benefit	Keep sleep related benefit	Remove sleep related benefit

Abbreviations: BSC, best supportive care; EAG, External Assessment Group;

Table 14 shows the cumulative impact of each assumption for the EAG base case (deterministic results). The final EAG probabilistic results are presented in Table 15 with the deterministic in Table 16. EAG's deterministic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.99	-	-	-	-	-
LCIG	[redacted]	6.02	[redacted]	-0.03	[redacted]	[redacted]	[redacted]
BMT	[redacted]	5.94	[redacted]	0.05	[redacted]	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west

. Fully incremental analysis ordering treatments from the lowest to highest total cost is presented in Table 17 for probabilistic and Table 18 for deterministic.

Table 14. EAG's base case (deterministic cumulative impact)

	Results per patient	Intervention	BMT	LCIG	Incremental value BMT	Incremental value LCIG
0	Company's updated base case					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.17	4.87	5.18	0.30	-0.01
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]

1	Assumed equal efficacy LCIG and foslevodopa-foscarbidopa					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.17	4.87	5.23	0.30	-0.06
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
2	Health states are minimised to 5 OFF states rather than 17					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.32	5.08	5.33	0.24	-0.01
	ICER (£/QALY)	-	-	-	Dominant	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
3	Patients who discontinue have equivalent outcomes to natural disease progression arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.32	5.08	5.29	0.24	0.03
	ICER (£/QALY)	-	-	-	Dominant	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
4	Alternate implementation of Palmer *et al.* 2002 data using only the available data from the paper					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.45	5.24	5.40	0.21	0.05
	ICER (£/QALY)	-	-	-	Dominant	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
5	Remove reversion to baseline following M15-736 placebo arm benefit for BMT arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.46	5.24	5.41	0.22	0.05
	ICER (£/QALY)	-	-	-	[redacted]	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
6	Apply LOCF assumption to BMT arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.47	5.26	5.42	0.21	0.05
	ICER (£/QALY)	-	-	-	[redacted]	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
7	Use direct data to inform resource use for health state cost					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.47	5.26	5.42	0.21	0.05

	ICER (£/QALY)	-	-	-	[redacted]	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
8	Use only the M15-736 trial to inform utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	6.10	5.94	6.02	0.16	0.09
	ICER (£/QALY)	-	-	-	[redacted]	Dominant
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
9	Remove sleep related benefit					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.99	5.94	6.02	0.05	-0.03
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

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

Table 15. EAG's probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.99	-	-	-	-	-
LCIG	[redacted]	6.02	[redacted]	-0.03	[redacted]	[redacted]	[redacted]
BMT	[redacted]	5.94	[redacted]	0.05	[redacted]	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 16. EAG's deterministic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
Foslevodopa-foscarbidopa	[redacted]	5.99	-	-	-	-	-
LCIG	[redacted]	6.02	[redacted]	-0.03	[redacted]	[redacted]	[redacted]
BMT	[redacted]	5.94	[redacted]	0.05	[redacted]	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west

Table 17. EAG's fully incremental probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
BMT	[redacted]	5.94	-	-	-	-	-
Foslevodopa-foscarbidopa	[redacted]	5.99	[redacted]	0.05	[redacted]	[redacted]	[redacted]
LCIG	[redacted]	6.02	[redacted]	0.03	[redacted]	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west.

Table 18. EAG's fully incremental deterministic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k/ QALY)	NHB (£30k/ QALY)
BMT	[redacted]	5.94	-	-	-	-	-
Foslevodopa-foscarbidopa	[redacted]	5.99	[redacted]	0.05	[redacted]	[redacted]	[redacted]
LCIG	[redacted]	6.02	[redacted]	0.03	[redacted]	[redacted]	[redacted]

Abbreviations: BMT: best medical therapy; ICER: incremental cost-effectiveness ratio; LCIG: levodopa-carbidopa intestinal gel; PAS: patient access scheme; QALY: quality-adjusted life year; SW: south-west

4.2 EAG scenario analyses

In Section 2, the EAG has described several scenarios that warrant further exploration. The scenarios that the EAG has produced are applied to the EAG's revised base case and include:

- Apply regression PDSS-2, NROFF regression analysis to account for sleep benefit (additional issue 2);
- Add sleep benefit in same way as company (additional issue 2);
- M15-741 directly observed trial data used for utilities;
- M15-736 directly observed trial data utilities;
- Use of regression derived costs (same as the company base case);
- LOCF assumption not applied to BMT arm.

Results of the EAG's scenarios are given in Table 19.

Table 19. Results of EAG scenarios (deterministic)

	Results per patient	Intervention	BMT	LCIG	Incremental value BMT	Incremental value LCIG
0	EAG's updated base case					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.99	5.94	6.02	0.05	-0.03
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
1	Apply regression PDSS-2, NROFF regression analysis to account for sleep benefit					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.96	5.90	5.97	0.07	-0.01
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
2	Add sleep benefit in same way as company					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	6.10	5.94	6.02	0.16	0.09
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
3	M15-741 directly observed trial data used for utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.27	5.23	5.30	0.0462	-0.03
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
4	M15-736 directly observed trial data used for utilities					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	6.56	6.56	6.55	0.00	0.01
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]
5	Use of regression derived costs.					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.99	5.94	6.02	0.05	-0.03
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]

6	LOCF assumption not applied to BMT arm					
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	5.98	5.93	6.02	0.05	-0.03
	ICER (£/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£20k/QALY)	-	-	-	[redacted]	[redacted]
	NHB (£30k/QALY)	-	-	-	[redacted]	[redacted]

[a]SW quadrant ICER: costs saved per QALY forgone.

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

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